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Стелара® (устекинумаб)

СТЕЛАРА® – баланс эффективности системного биологического препарата и безопасности как у селективного

Скорость наступления эффекта

Уменьшение боли в животе и частоты дефекаций **уже на 1-й неделе** терапии препаратом Стелара® у пациентов с болезнью Крона[1] и **уменьшение** частоты дефекаций **на 1-й неделе** терапии при язвенном колите[2, 3]

Долгосрочная клиническая ремиссия

3 из 4 пациентов на терапии препаратом Стелара® **сохраняют ремиссию** в течение не менее 3 лет при болезни Крона[4] и в течение не менее 2 лет при язвенном колите[5]

Благоприятный профиль безопасности

Профиль **безопасности** устекинумаба в отношении риска возникновения инфекций, в том числе туберкулёза, и малигнизации **сопоставим с плацебо** и препаратами селективного механизма действия[6]

Самая высокая выживаемость терапии

Стелара® демонстрирует **самую высокую выживаемость терапии** по сравнению с другими ГИБП при болезни Крона в любой линии – **75%** пациентов за 2 года наблюдения остаются на терапии[7, 8]

Препарат Стелара® входит в российские и международные клинические рекомендации для терапии 1-й и 2-й линий БК и ЯК[9–12]

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БК – болезнь Крона. ЯК – язвенный колит. ГИБП – генно-инженерные биологические препараты.
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КРАТКАЯ ИНСТРУКЦИЯ ПО МЕДИЦИНСКОМУ ПРИМЕНЕНИЮ ПРЕПАРАТА СТЕЛАРА®, ЛП-001104, ЛСР-006465/09

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Краткая инструкция по медицинскому применению препарата Стелара®. Перед применением ознакомьтесь с полной версией инструкции по применению. Регистрационный номер – ЛП-001104, ЛСР-006465/09. Торговое наименование препарата – Стелара®. **Международное непатентованное наименование** – устекинумаб. **Лекарственная форма** – раствор для подкожного введения. **Показания к применению. Бляшечный псориаз.** Препарат Стелара® показан для лечения бляшечного псориаза средней или тяжёлой степени у взрослых пациентов при отсутствии ответа или при наличии противопоказаний, или при непереносимости других методов системной терапии, в том числе циклоспорина, метотрексата или ПУВА-терапии (псорален и ультрафиолет А). **Бляшечный псориаз у детей.** Препарат Стелара® показан для лечения бляшечного псориаза средней или тяжёлой степени у детей и подростков в возрасте от 6 лет и старше при отсутствии адекватного ответа или непереносимости других методов системной терапии или фототерапии. **Псориатический артрит.** Лечение взрослых пациентов с активным псориатическим артритом (ПсА) в качестве монотерапии или в комбинации с метотрексатом при отсутствии адекватного ответа на предыдущую стандартную терапию. **Псориатический артрит у детей.** Лечение детей в возрасте 5 лет и старше с активным ювенильным псориатическим артритом. Препарат Стелара® может применяться в качестве монотерапии или в комбинации с метотрексатом. **Болезнь Крона.** Лечение взрослых пациентов с активной болезнью Крона средней или тяжёлой степени с неадекватным ответом, утратой ответа или непереносимостью стандартной терапии или терапии ингибиторами ФНО, или имеющих медицинские противопоказания к проведению такой терапии. **Язвенный колит.** Лечение взрослых пациентов с активным язвенным колитом умеренной и тяжёлой степени с неадекватным ответом, утратой ответа или непереносимостью стандартной или биологической терапии, или имеющих медицинские противопоказания к проведению такой терапии. **Противопоказания.** Повышенная чувствительность к устекинумабу или любому вспомогательному веществу препарата; детский возраст до 6 лет (по показанию «бляшечный псориаз»), до 5 лет (по показанию «псориатический артрит»), до 18 лет (по показаниям «болезнь Крона» и «язвенный колит»); беременность и период грудного вскармливания; серьёзные инфекционные заболевания в острой фазе, в том числе туберкулёз; злокачественные новообразования. **С осторожностью.** Хронические или рецидивирующие паразитарные и инфекционные заболевания вирусной, грибковой или бактериальной природы, злокачественные опухоли в анамнезе, пожилой возраст (≥65 лет). **Способ применения и дозы.** Препарат Стелара® «раствор для подкожного введения» предназначен для подкожных инъекций. **Взрослые пациенты. *Бляшечный псориаз.*** Рекомендованная доза составляет 45 мг. Вторую инъекцию делают 4 недели спустя после первого применения, затем каждые 12 недель. У пациентов с массой тела более 100 кг препарат рекомендуется использовать в дозе 90 мг. При неэффективности терапии в течение 28 недель рекомендуется рассмотреть целесообразность применения препарата. Коррекция дозы. Пациентам, у которых клиническая эффективность препарата при применении каждые 12 недель выражена недостаточно, следует увеличить дозу препарата до 90 мг каждые 12 недель. В случае если такой режим дозирования неэффективен, дозу препарата 90 мг следует вводить каждые 8 недель. Возобновление лечения. Было показано, что возобновление терапии по схеме: вторая инъекция через 4 недели спустя после первого применения, а затем каждые 12 недель, является эффективным и безопасным. ***Псориатический артрит.*** Рекомендованная доза: 45 мг. Вторую инъекцию делают 4 недели спустя после первого применения, затем каждые 12 недель. У пациентов с массой тела более 100 кг препарат рекомендуется использовать в дозе 90 мг. **Болезнь Крона и язвенный колит.** Пациентам с болезнью Крона или язвенным колитом рекомендовано однократное, инициирующее терапию внутривенное введение препарата Стелара® «концентрат для приготовления раствора для инфузий» в дозе, рассчитанной на основании массы тела, с последующим подкожным введением дозы 90 мг через 8 недель (первое подкожное введение) и 1 раз каждые 12 недель в дальнейшем. Подробная информация о внутривенном введении препарата Стелара® указана в инструкции по медицинскому применению препарата Стелара®, концентрат для приготовления раствора для инфузий. Пациенты, у которых через 8 недель после первого подкожного введения не удалось получить достаточный ответ, в это время могут получить вторую подкожную инъекцию. У пациентов с потерей ответа при введении 1 раз в 12 недель положительный результат может быть получен при увеличении частоты введений до 1 раза в 8 недель. В дальнейшем препарат пациентам можно вводить 1 раз в 8 недель или 1 раз в 12 недель, в зависимости от клинической ситуации. При прерывании терапии болезни Крона или язвенного колита возобновление её посредством подкожных инъекций каждые 8 недель является безопасным и эффективным. **Дети (6 лет и старше).** ***Бляшечный псориаз.*** Рекомендованная доза зависит от массы тела пациента. При массе тела менее 60 кг рекомендованная доза составляет 0,75 мг/кг, от 60 кг до 100 кг – 45 мг, при массе тела более 100 кг – 90 мг. Для расчёта необходимого объёма препарата (мл) для пациентов с массой тела менее 60 кг используется следующая формула: масса тела (кг) 0,0083 (мл/кг). Рассчитанный объём препарата округляется до сотой доли мл (0,01 мл). Инъекция осуществляется градуированным шприцем вместимостью 1 мл. Вторую инъекцию делают 4 недели спустя после первого применения, затем каждые 12 недель. Детям препарат применяется в условиях стационара. При неэффективности терапии в течение 28 недель рекомендуется рассмотреть целесообразность применения препарата. **Дети (5 лет и старше).** ***Псориатический артрит.*** Вторую инъекцию делают 4 недели спустя после первого применения, затем каждые 12 недель. Рекомендованная доза препарата Стелара® у детей с массой тела менее 60 кг составляет 0,75 мг/кг. Рекомендованная доза препарата Стелара® у детей с массой тела 60 кг и более составляет 45 мг. Рекомендованная доза препарата Стелара® у детей с сопутствующим бляшечным псориазом средней или тяжёлой степени и массой тела более 100 кг составляет 90 мг. Детям препарат применяется в условиях стационара. При неэффективности терапии в течение 28 недель рекомендуется рассмотреть целесообразность применения препарата. **Побочное действие.** Инфекции и инвазии (инфекции верхних дыхательных путей, назофарингит, синусит, воспаление подкожной жировой клетчатки, одонтогенные инфекции, опоясывающий лишай, вирусные инфекции верхних дыхательных путей, вульвовагинальные грибковые инфекции), нарушения со стороны психики (депрессия), нарушения со стороны нервной системы (головокружение, головная боль), нарушения со стороны дыхательной системы, органов грудной клетки и средостения (орофарингеальная боль, заложенность носа), нарушения со стороны ЖКТ (диарея, тошнота, рвота), нарушения со стороны кожи и подкожной клетчатки (зуд, акне), нарушения со стороны опорно-двигательного аппарата и соединительной ткани (боль в спине, миалгия, артралгия), общие нарушения и реакции в месте введения препарата (усталость, эритема в месте введения, боль в месте введения, реакции в месте введения (в том числе кровотечение, гематома, уплотнение, припухлость и зуд), астения). **Пострегистрационные сообщения.** Нарушения со стороны иммунной системы (реакции гиперчувствительности (в том числе сыпь, крапивница), серьёзные реакции гиперчувствительности (в том числе анафилаксия и ангионевротический отёк), инфекции и инвазии (инфекции нижних отделов дыхательных путей), нарушения со стороны нервной системы (паралич лицевого нерва), нарушения со стороны дыхательной системы, органов грудной клетки и средостения (аллергический альвеолит, эозинофильная пневмония, организующаяся пневмония), нарушения со стороны кожи и подкожной клетчатки (пустулёзный псориаз, шелушение кожи, эритродермический псориаз, эксфолиативный дерматит, лейкоцитокластический васкулит). **Особые указания. Инфекции.** Препарат Стелара® является селективным иммунодепрессантом, и потенциально может увеличивать риск возникновения инфекций и реактивации латентных инфекций. В ходе клинических исследований у пациентов, получавших препарат Стелара®, наблюдались случаи возникновения серьёзных бактериальных и вирусных инфекций. Препарат Стелара® не следует применять у пациентов с клинически значимой активной инфекцией. Следует с осторожностью применять препарат Стелара® у пациентов с хронической инфекцией или рецидивирующей инфекцией в анамнезе. **Злокачественные новообразования.** Препараты-иммунодепрессанты могут способствовать увеличению риска развития злокачественных новообразований. У некоторых пациентов, получавших препарат Стелара® в рамках клинических исследований, наблюдалось развитие кожных и некожных злокачественных новообразований. Следует проявлять осторожность при назначении препарата Стелара® пациентам со злокачественными новообразованиями в анамнезе, а также при рассмотрении возможности продолжения терапии препаратом Стелара® у пациентов с диагностированными злокачественными новообразованиями. **Реакции гиперчувствительности.** В ходе пострегистрационного наблюдения были зарегистрированы серьёзные реакции гиперчувствительности, включая анафилаксию и ангионевротический отёк. **Вакцинация.** Не рекомендуется применять живые вирусные или живые бактериальные вакцины одновременно с препаратом Стелара®. **Сопутствующая иммуносупрессивная терапия.** В исследованиях у пациентов с болезнью Крона и язвенным колитом совместное применение препарата Стелара® с иммуномодуляторами или с кортикостероидами не влияло на безопасность и эффективность препарата Стелара®. **Иммунотерапия.** Безопасность и эффективность применения препарата Стелара® у пациентов, прошедших иммунотерапию аллергических заболеваний, не установлены.

Общероссийская общественная организация
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том 22, № 1, 2023

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РЕДАКЦИОННАЯ КОЛЛЕГИЯ ЖУРНАЛА «КОЛОПРОКТОЛОГИЯ»

РЕДАКЦИОННЫЙ СОВЕТ ЖУРНАЛА «КОЛОПРОКТОЛОГИЯ»

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ЦЕЛИ И ЗАДАЧИ

Целью журнала «Колопроктология» является освещение современных тенденций и научно-практических достижений в колоректальной хирургии.

Заболевания толстой кишки, заднего прохода, тазового дна и промежности являются одними из наиболее распространённых, а колопроктология — наиболее динамично развивающейся хирургической специальностью.

Колоректальный рак занимает одну из ведущих позиций в структуре онкологических заболеваний, наблюдается неуклонный рост воспалительных заболеваний кишечника, дивертикулярной болезни. Постоянно изменяются диагностические и лечебные подходы при лечении геморроидальной болезни, свищей заднего прохода, анальной трещины, анальной инконтиненции.

Колопроктологи в России, как и во всем остальном мире, интенсивно взаимодействуют с онкологами, гастроэнтерологами, общими хирургами, эндоскопистами, патофизиологами и специалистами других научно-практических направлений врачебной деятельности.

Целевой аудиторией журнала являются колопроктологи, а также врачи других специальностей, интерес которых сконцентрирован на заболеваниях толстой кишки, заднего прохода, тазового дна и промежности.

Журнал «Колопроктологии» объединяет колопроктологов России в тесном сотрудничестве с профессиональными объединениями мира и ведущими международными экспертами в области колоректальной хирургии.

В журнале публикуются оригинальные статьи, результаты фундаментальных исследований, направленные на изучение общепатологических процессов с целью улучшения лечения больных, описание клинических наблюдений, метаанализы и обзоры литературы по широкому спектру вопросов колопроктологии, а также результаты клинических и экспериментальных исследований.

AIM AND SCOPE

The purpose of the journal *Koloproktologia* (Russian Journal of Coloproctology) is to highlight current trends and scientific achievements in colorectal surgery.

Diseases of the colon, anus, pelvic floor, and perineum are among the most common; and coloproctology is the most dynamically developing surgical specialty.

Colorectal cancer occupies one of the leading positions in the structure of oncological diseases. There is a steady increase in inflammatory bowel diseases, diverticular disease, stoma patients.

Diagnostic and treatment options for hemorrhoid disease, anal fistula, anal fissure, and anal incontinence are constantly changing.

Coloproctologists in Russia, as in the rest of the world, intensively interact with oncologists, gastroenterologists, general surgeons, endoscopists, pathophysiologists, and specialists in other scientific and practical areas of medical activity.

The target audience of the journal is coloproctologists, as well as doctors of other specialties, whose interest is focused on diseases of the colon, rectum, anus, pelvic floor and perineum.

The journal *Koloproktologia* (Russian Journal of Coloproctology) unites coloproctologists of Russia in close cooperation with professional associations of the world and leading international experts in the field of colorectal surgery.

The journal publishes original articles, the results of basic research aimed at studying general pathological processes in order to improve the treatment of patients, clinical cases, meta-analyses, and literature reviews on a wide range of coloproctology issues, as well as the results of clinical and experimental studies.

Журнал включен в перечень рецензируемых научный изданий, рекомендуемых ВАК, для публикации основных научных результатов диссертаций на соискание ученой степени кандидата наук, на соискание ученой степени доктора наук по научным специальностям (по состоянию на 07.12.2022)

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LIST OF ABBREVIATIONS

ALT — alanine aminotransferase
AST — aspartate aminotransferase
5-ASA — 5-aminosalicylic acid
AZA — azathioprine
Anti-TNF — antibodies to tumor necrosis factor alpha
CD — Crohn's disease
BFB — biofeedback
IBD — inflammatory bowel diseases
gamma-GT — gamma-glutamyltranspeptidase
GEBD — genetically engineered biological drug
GCS — glucocorticosteroids
CI — coincidence interval
GIT — gastrointestinal tract
IPAA — ileal pouch anal anastomosis
BMI — body mass index
CT — computed tomography
LDH — lactate dehydrogenase
MMS — multimatrix shell
MP — mercaptopurin
MRI — magnetic resonance imaging
NSAIDs — nonsteroidal anti-inflammatory drugs
RCT — randomized controlled trial
ESR — erythrocyte sedimentation rate
CRP — C-reactive protein
TIS — targeted immunosuppressors
TNF-alpha — tumor necrosis factor-alpha
UC — ulcerative colitis

TERMS AND DEFINITIONS

Ulcerative colitis (UC) is a chronic colorectal characterized by immune inflammation of its mucosa.

Exacerbation (relapse, attack) of UC is the appearance of typical symptoms of the disease in patients with UC in the stage of clinical remission, spontaneous or medically supported.

In practice, signs of clinical exacerbation are an increase in the frequency of bowel movements with blood excretion and/or characteristic changes detected during colonoscopy.

UC remission is the disappearance of the main clinical symptoms of the disease [1] and healing of the colorectal mucosa ("deep remission") [2].

UC remission, clinical — absence of blood admixture in the stools, absence of imperative/false urges at a frequency of defecation no more than 3 times per 24 hours.

UC remission, endoscopic — absence of visible macroscopic signs of inflammation during endoscopic examination of the large bowel.

UC remission, histological — absence of microscopic signs of inflammation.

Steroid resistance — in the case of a severe attack — the absence of positive changes on the part of clinical and laboratory indicators, despite the use of systemic GCS at a dose equivalent to 2 mg/kg of body weight of prednisolone ** per 24 hours, for more than 7 days;

In the case of a moderate attack, the activity of the disease is maintained with oral administration of GCS at a prednisolone ** dose equivalent to 1 mg/kg of body weight for 2 weeks [3,4].

Steroid addiction is an increase in the activity of the disease that occurred when the dose of GCS was reduced after the initial improvement

was achieved within 3 months from the start of treatment.
The relapse of the disease within 3 months after the end of treatment with GCS.
A bionaïve patient is a patient who has not previously received genetically engineered biological drugs (GEBD) or targeted immunosuppressors (TIS).
Colectomy is a surgery to remove caecum and the entire colon from ilecaecal valve to rectosigmoid.

1. BRIEF INFORMATION ON THE DISEASE OR CONDITION (GROUP OF DISEASES OR CONDITIONS)

1.1 Definition of the Disease or Condition (Group of Diseases or Conditions)

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucosa.
In UC, only the large intestine is affected (with the exception of retrograde ileitis), the rectum is necessarily involved in the process, inflammation is most often limited to the mucous layer (with the exception of acute severe colitis) and is diffuse.

1.2 Etiology and Pathogenesis of the Disease or Condition (Group of Diseases or Conditions)

The etiology of IBD, including UC, has not been clarified. The disease develops as a result of a combination of several factors, including genetic predisposition, defects in congenital and acquired immunity, intestinal microflora disorders and the influence of environmental factors. About 100 genetic polymorphisms associated with UC have been described. Genetic determinism leads to changes in the congenital immune response, autophagy, violation of the mechanisms of recognition of microbes, lesion of the epithelial barrier and, as a result, perversion of adaptive immunity. A key defect predisposing to the development of IBD is a violation of the recognition of bacterial molecular markers (patterns) by dendritic cells, which leads to hyperactivation of signaling proinflammatory pathways. Also, with IBD, there is a decrease in the diversity of intestinal microflora due to a decrease in the proportion of anaerobic bacteria, mainly *Bacteroidetes* and *Firmicutes*.
Against this background, the development of IBD occurs under the influence of triggering factors, which include smoking, nervous stress, vitamin D deficiency, a diet with a low content of dietary fiber and an increased content of animal protein, intestinal infections, especially *Clostridioides* difficile infection and cytomegalovirus infection.
The result of the mutual influence of genetic and predisposing factors is the activation of various subpopulations of T-lymphocytes: T-helper 1,2,17 types and regulatory T-lymphocytes at different stages of inflammation, which leads to over expression of proinflammatory cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukins 1, 12, 23, 17 (IL1, IL12, IL23, IL17) and others and cell adhesion molecules.
As a result of these disorders, inflammatory lymphoplasmocytic infiltration and destruction of the colorectal mucosa with macroscopic changes characteristic of UC are formed.

1.3 Epidemiology of the Disease or Condition (Groups of Diseases or Conditions)

The maximum prevalence of UC in the world is currently 505/100,000 of the population (in Europe), and the incidence in different regions ranges from 0.6 to 24.3 per 100,000 population. The highest incidence of UC 24.3/100,000 was noted in Europe, 19.2/100,000 in North America [4–8].
Data on the prevalence of UC in Russia are limited [9,10]. The prevalence of UC is higher in northern latitudes and in western regions. The incidence and prevalence of UC in Asia is lower; however, it is currently increasing. Caucasians suffer from the disease more often than people of the Negroid and Mongoloid races. The peak of morbidity occurs in the age range of 20–30 years, in some countries the second peak of morbidity is observed at the age of 60–70 years. The incidence among males and females is approximately the same.

1.4 Features of Coding the Disease or Condition (Group of Diseases or Conditions) According to the International Statistical Classification of Diseases and Health-Related Problems

K51.0 — Ulcerative (chronic) enterocolitis
K51.1 — Ulcerative (chronic) ileocolitis
K51.2 — Ulcerative (chronic) proctitis
K51.3 — Ulcerative (chronic) rectosigmoiditis

Table 1. *Montreal classification of UC by lesion extent [12]*

The extent of inflammation	Designation according to the Montreal Classification	Characteristic
Proctitis	E1	Distal UC, limited to the rectum
Left-sided colitis	E2	Affected mucosa from the anal sphincter to the left flexure
Total colitis (pancolitis)	E3	The lesion spreads proximally to the left flexure, capturing the entire large intestine, sometimes in combination with retrograde ileitis (involvement of 10–15 cm of the ileum in the inflammatory process)

Table 2. *Severity of UC attack according to Truelove-Witts criteria [3,4]*

Indicator	Mild attack	Moderate attack	Severe attack
Frequency of stools with blood per 24 hours	< 4	⩾ 4, if:	⩾ 6 and:
FS per 1 minute	< 90 /min.	⩽ 90 /min.	> 90 /min. or
Temperature	< 37.5°C	⩽ 37.8°C	> 37.8°C or
Hemoglobin	> 115 g/l	⩾ 105 g/l	< 105 g/l or
ESR or CRP	⩽ 20 mm/h Norm	⩽ 30 мг/л	> 30 mm/h or > 30 mg/l

K51.4 — Pseudopolyposis of the colon
K51.5 — Mucosal proctocolitis
K51.8 — Other ulcerative colitis
K51.9 — Ulcerative colitis, unspecified

1.5 Classification of the disease or condition (groups of diseases or conditions)

The existing classification of UC by the extent of the lesion, the course, the severity of the attack and the presence of complications determines the choice of drug therapy, indications and the choice of the type of surgery, as well as the frequency of screening for colorectal cancer [11].

To describe the extent of the lesion, the Montreal Classification is used (Table 1), which estimates the extent of macroscopic changes during colonoscopy.

It should be particularly noted that proctosigmoiditis is included in the concept of left-sided UC, and total colitis also includes subtotal large intestine lesion proximal to the left flexure.

According to the course of the disease, there are:

1. Acute (less than 6 months from the onset of the disease);
2. Chronic continuous (duration of remission less than 6 months on the background of adequate therapy);
3. Chronic recurrent (duration of remission is more than 6 months).

For the correct formulation of the diagnosis and determination of treatment approach, the severity of the current attack should be assessed, for which simple Truelove-Witts criteria are used, usually used in common practice, and the UC activity index (Mayo index; DAI), usually used in clinical trials.

However, to assess the prognosis of the disease and determine the social status of the patient, including disability, preferential supply by medical agents, free rehabilitation and other social benefits, it is necessary to take into account the comprehensive severity of the disease, which is determined by the severity of the current attack, the presence of extra-intestinal manifestations and complications, refractory to treatment, in particular, the development of steroid addiction and resistance.

There are mild, moderate and severe attacks of UC (Tables 2, 3).

In clinical practice, the so-called “extremely severe or extremely severe attack” of UC is often found, characterized by diarrhea more than 10–15 times per 24 hours, a crucial drop of hemoglobin, fever above 38°C, severe hypoproteinemia and electrolyte downshifts, high levels of C-reactive protein (CRP) [13–15]. Approaches to the treatment of such colitis differ from the usual ones. In English-language literature, this condition is called “acute severe UC” [16].

The Schroeder mucosal assessment scale used in the Mayo Index is shown in Table 4 and is used to assess the endoscopic activity of UC.

The classification of UC depending on the response to glucocorticosteroids (GCS) facilitates the

Table 3. *Severity of the attack according to the UC activity index (Mayo index)*

Index value (points)	0	1	2	3
Stools frequency	Usual	1–2 more per day than usual	3–4 more per day than usual	5 more per day than usual
Blood in the stools	No	Blood Streaks	Visible blood	Mostly blood
The condition of the mucous layer	Norm	Minimum activity (1 point according to Schroeder)	Moderate activity (2 points according to Schroeder)	Pronounced activity (3 points according to Schroeder)
General assessment of the condition by a doctor	Norm	Satisfactory condition	Condition of moderate severity	Severe condition
The severity of the UC attack is determined by the sum of the points of 4 parameters from the table: 0–2 points: remission (while the assessment of the parameters of rectal bleeding and the endoscopic state of the mucosa = 0 points); 3–5 points: mild UC attack; 6–9 points: moderate UC attack 10–12 points: severe UC attack				
Partial (incomplete) Mayo index without endoscopy data: 0–1 points: clinical remission (with the parameter “rectal bleeding” = 0 point) 1–2 points: mild attack 3–5 points: moderate attack ⩾ 6 points: severe attack				

Table 4. *Classification of UC depending on endoscopic activity (according to Schroeder) [17]*

0	1 (minimal activity)	2 (moderate activity)	3 (pronounced activity)
Norm or inactive disease	Slight hyperemia, blurred vascular pattern. Easy contact vulnerability	Pronounced hyperemia, absence of vascular pattern, moderate contact vulnerability, erosion)	Spontaneous vulnerability, ulceration

choice of rational therapeutic approach, since the goal of conservative treatment is to achieve stable remission with discontinuation of GCS therapy. For these purposes, [3,4] are distinguished as follows:

1. Steroid resistance:

a. In the case of a severe attack, there is no positive changes on the part of clinical and laboratory parameters, despite the use of systemic GCS at a prednisolone dose equivalent to 2 mg/kg of body weight per 24 hours for more than 7 days;

b. In the case of a moderate attack — the preservation of the activity of the disease with oral administration of GCS at a dose of prednisolone equivalent to 1 mg/kg of body weight for 2 weeks.

2. Steroid addiction:

a. An increase in the activity of the disease that occurred when the dose of GCS was reduced after the initial improvement was achieved within 3 months from the start of treatment;

b. The occurrence of a relapse of the disease within 3 months after the end of treatment with GCS.

When formulating a diagnosis, it is necessary to reflect the nature of the course of the disease, the extent of the lesion, the severity of the current attack or the presence of remission, the presence of steroid addiction or resistance, as well as the presence of extra-intestinal manifestations or intestinal complications of UC. Below are examples of formulations of the diagnosis:

1. “Ulcerative colitis, chronic recurrent course, proctitis, moderate attack”.
2. “Ulcerative colitis, chronic continuous course, left-sided lesion, moderate attack. Steroid addiction. Extra-intestinal manifestations (peripheral arthropathy)”.
3. “Ulcerative colitis, chronic recurrent course, total lesion, severe attack. Steroid resistance. Toxic megacolon”.

1.6 Clinical picture of the disease or condition (group of diseases or conditions)

The clinical picture of UC includes four clinical syndromes:

Intestinal syndrome. Typical intestinal symptoms include diarrhea, mainly at night (65% of cases), blood in the stools (95–100% of cases), tenesmus (more often with proctitis and proctosigmoiditis), sometimes tenesmus in combination with

Table 5. *The main extra-intestinal (systemic) manifestations of ulcerative colitis*

Autoimmune, associated with the activity of the disease	Autoimmune, non-activity-related diseases	Caused by prolonged inflammation and metabolic disorders
Arthropathies (arthralgia, arthritis) Skin lesion (erythema nodosum, gangrenous pyoderma) Mucosal lesion (aphthous stomatitis) Eye damage (uveitis, iritis, iridocyclitis, episcleritis) Liverdamage (autoimmunehepatitis)	Primarysclerosingcholangitis Ankylosing spondylitis (sacroiliitis) Osteoporosis, osteomalacia Psoriasis, psoriatic arthritis	Cholelithiasis Liver steatosis, steatohepatitis Peripheral vein throm BFB is, pulmonary embolism Amyloidosis

constipation with distal limited lesion. With proctitis and proctosigmoiditis, diarrhea may be absent, tenesmus predominate in the clinical picture. For UC, unlike CD, abdominal pain is not characteristic. There may be a moderately pronounced abdominal pain syndrome of a spastic nature, more often before the stools.

Endotoxemia is signs of systemic inflammation due to the high activity of the inflammatory process in the colon. Endotoxemia accompanies moderate and severe forms of UC to varying degrees. The main symptoms are general intoxication, fever, tachycardia, anemia, increased ESR, leukocytosis, thrombocytosis, increased levels of acute phase proteins: CRP, fibrinogen.

Metabolic disorders are the result of diarrhea, toxemia, excessive loss of protein with feces due to exudation and impaired absorption of water and electrolytes. Clinical symptoms are typical: weight loss (sometimes to the point of exhaustion), dehydration, hypoproteinemia, hypoalbuminemia with the development of edematous syndrome, hypokalemia and other electrolyte disorders, hypovitaminosis.

Extra-intestinal systemic manifestations (EISM) occur in 20–25% of cases of UC and usually accompany severe forms of the disease [18] (Table 5).

Autoimmune manifestations associated with the activity of the inflammatory process appear together with the main intestinal symptoms of exacerbation and disappear with them during treatment. Autoimmune manifestations that are not associated with the activity of the process (in the English literature they are often called "concomitant autoimmune diseases") tend to progress regardless of the phase of the underlying disease (exacerbation or remission) and often determine a negative prognosis of the disease.

Intestinal complications of UC include intestinal bleeding, toxic dilation and perforation of the large intestine, as well as colorectal cancer. Since these complications require surgery, they are discussed in detail in Section 3.2 "Surgical treatment".

2. DIAGNOSIS OF THE DISEASE OR CONDITION (GROUP OF DISEASES OR CONDITIONS), MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF DIAGNOSTIC METHODS

Criteria for establishing a diagnosis/condition *based on pathognomonic data:*

1) anamnesis;
2) clinical examination;
3) laboratory tests;
4) instrumental tests.

There are no unambiguous diagnostic criteria for UC. The diagnosis is made based on a combination of anamnesis, clinical picture and typical endoscopic and histological changes.

2.1 Complaints and Anamnesis

• In all patients with suspected UC, it is **recommended** to collect anamnesis and complaints to verify the diagnosis [19–22].

Grade of recommendation — C (Level of evidence is 4)

• In particular, when collecting anamnesis, it is **recommended** to clarify the presence of the fact of smoking in order to narrow the circle of diagnostic search and verification of the diagnosis [23].

Grade of recommendations is C (Level of evidence is 5)

Comment. *It is necessary to pay attention to the frequency and structure of stools (liquid multiple stools, tenesmus), evaluate the 24-hour volume of stools, the duration of these symptoms, the presence of blood in the stools, the type of abdominal pain;*

trips to southern countries; medications taken (in particular, antibiotics and nonsteroidal anti-inflammatory drugs (NSAIDs)); smoking; the presence of inflammatory and malignant intestinal diseases in relatives [24,25].

2.2 Physical Examination

• Physical examination is **mandatory** for all patients with suspected UC in order to narrow the circle of diagnostic search and verification of the diagnosis: — inspection of the perianal area; — digital rectal examination [26].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Physical (clinical) examination may reveal various manifestations of UC, including fever, peripheral edema, nutritional deficiency, signs of perforation or toxic dilatation of the large bowel, as well as extra-intestinal manifestations.*

2.3 Laboratory Diagnostic Tests

• A detailed general (clinical) blood test is **recommended** for all patients with suspected UC to diagnose anemia, comorbidities, as well as to determine the degree of UC activity [27–32].

Grade of recommendations is C (Level of evidence is 4)

Comment. *During a clinical blood test, anemia (iron deficiency, anemia of chronic disease, B_{12}- or folic deficiency anemia), leukocytosis (against the background of chronic inflammation or against the background of steroid therapy), thrombocytosis, an increase in ESR can be diagnosed.*

• It is **recommended** for all patients with suspected UC to do biochemical blood analysis (total protein, albumin, glucose, ALT, AST, total bilirubin, gamma-GT, cholesterol, LDH, K+, Na+, Cl–, C-reactive protein, alkaline phosphatase, fibrinogen) for the diagnosis of comorbidities [29,32–36].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Biochemical test reveals electrolyte disorders, hypoproteinemia (in particular, hypoalbuminemia), as well as an increase in alkaline phosphatase, which is a possible manifestation of primary sclerosing cholangitis associated with UC.*

• It is **recommended** for patients with acute UC (the first attack of the disease) to differentiate diagnosis with acute intestinal infection [37].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with acute UC to check stools for toxins A and B *Cl. difficile* to exclude clostridial infection [38–41].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** to perform a laboratory test of the feces of toxigenic *Cl. difficile* by methods: enzyme immunoanalysis with the determination of toxins A and B and/or immunochemiluminescence analysis with the determination of toxins A and B and/or polymerase chain reaction.

Grade of recommendations is C (Level of evidence is 4)

• **B**iopsies and/or PCR in the biopsy material of the colorectal mucosa (from lesions) for the presence of cytomegalovirus (CMV) is **recommended** for all patients with suspected UC, moderate and severe UC attacks, with steroid resistance or resistance to biological therapy [42,43].

Grade of recommendations is C (Level of evidence is 4)

2.4 Instrumental Diagnostic Studies

• It is **recommended** that all patients with mild to moderate UC activity undergo ileocolonoscopy to verify the diagnosis. Sigmoidoscopy is **recommended** for patients with pronounced UC activity [25,44].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Colonoscopy is mandatory to establish the diagnosis of UC and assess the activity of UC, as well as to resolve the issue of colectomy. Colonoscopy is the main method of diagnosing UC, but there are no specific endoscopic signs. The most peculiaris diffuse inflammation, limited by the mucous layer, starting in the rectum and spreading proximally, with a clear border of inflammation. The endoscopic activity of the UC is best reflected by contact vulnerability (the release of blood in contact with the endoscope), the absence of a vascular pattern and the presence of erosions and ulcerations. Detection of persistent narrowing of the intestine against the background of UC requires mandatory exclusion of colorectal cancer.*

• Abdominal X-ray is **recommended** for patients with severe UC attack to exclude perforation of the large intestine [45].

Grade of recommendations is C (Level of evidence is 4)

•Abdominal X-ray is **recommended** that patients with severe UC attack have an to exclude toxic dilatation [25].

Grade of recommendations is C (Level of evidence is 5)

• For all patients with suspected UC at the initial diagnosis, in case of doubts about the correctness of the previously made diagnosis, it is **recommended** to perform a biopsy in order to verify the diagnosis [46,47].

Grade of recommendations is C (Level of evidence is 5)

Comment. *With a long history of UC (more than 7–10 years), chromoendoscopy with a targeted biopsy or a step biopsy (from each part of the large intestine) is advisable to exclude epithelial dysplasia.*

The recommended standard of biopsy for diagnosis is to take biopsies of the mucous layer of the rectum and from at least 4 other areas of the large intestine, as well as the mucous layer of the ileum.

Microscopic signs of UC include crypt deformation (branching, multidirection, the appearance of crypts of different diameters, a decrease in crypt density, "shortening of crypts", crypts do not reach the underlying layer of the muscle plate of the mucosa), "uneven" mucosal surface in the biopsy of the mucous membrane, a decrease in the number of goblet cells, basal plasmocytosis, infiltration of its own plate of the mucosa mononuclear cells with an admixture of segmented leukocytes and eosinophils, the presence of crypt abscesses and basal lymphoid clusters. The degree of inflammatory infiltration usually decreases with distance from the rectum.

• It is **recommended** for all patients with suspected UC at the initial diagnosis, in case of doubts about the correctness of the previously made diagnosis, with a long history of UC, with suspected complications of UC, as well as to exclude pathology of other abdominal organs, to make abdominal ultrasound, ultrasound of retroperitoneal space and pelvis [48,49].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients with suspected UC, as a screening diagnosis, as well as to evaluate the effectiveness of therapy, to conduct an ultrasound of the intestine to assess the extent and severity of colorectal lesions [50].

Grade of recommendations is B (Level of evidence is 2)

• It is **recommended** for all patients with suspected UC, if differential diagnosis is necessary or if it is impossible to perform aileocolonoscopy, one of the following imaging methods of examination:

– magnetic resonance imaging (MRI) of the large bowel with contrast [51];

Grade of recommendations is C (Level of evidence is 4)

– computed tomography (CT) with intestinal contrast (in case of unavailability of expert assessment or impossibility of performing MRI) [52,53].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended** that patients with suspected UC, if differential diagnosis is necessary or if it is impossible to perform a colonoscopy, MRI and CT, undergo double-contrast barium enema to assess the extent of colorectal lesions, clarify the presence of tumors, strictures, etc. [26,54,55].

Grade of recommendations is B (Level of evidence is 2)

Comment. *It is also possible for patients with suspected UC to perform additional studies, depending on the clinical situation.*

2.5 Other Diagnostics

Additional instrumental and laboratory studies are performed mainly for the purpose of differential diagnosis with a number of diseases. These are infectious, vascular, drug, toxic and radiation lesions, as well as diverticulitis, etc. At the next stage of differential diagnosis, verification of clinical diagnoses of UC and CD belonging to the IBD group is carried out. Thus, the differential diagnosis of UC is carried out with colorectal CD, acute intestinal infections (dysentery, salmonellosis, campylobacteriosis, yersiniosis, amoebiasis), parasitoses, intestinal lesions associated with Cl. difficile, including those caused by antibiotics [56], intestinal tuberculosis, systemic vasculitis, colorectal cancer, diverticulitis, microscopic colitis (collagen and lymphocytic) [56], radiation proctitis.

For the purpose of differential diagnosis and selection of therapy for extra-intestinal manifestations of UC and comorbidities, consultation may be required:

– *a psychotherapist or a medical psychologist (neurosis, planned surgery with the presence of a stoma, etc.);*
– *an endocrinologist (steroid diabetes mellitus, adrenal insufficiency in patients on long-term therapy of GCS);*
– *dermatovenerologist (differential diagnosis of erythema nodosum, pyoderma, etc.);*
– *rheumatologist (arthropathy, sacroiliitis, etc.);*
– *obstetrician-gynecologist (pregnancy).*

3. TREATMENT, INCLUDING DRUG AND NON-DRUG THERAPY, DIET THERAPY, ANESTHESIA, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF TREATMENT METHODS

3.1 Conservative Treatment

3.1.1 Goals and Principles of Therapy

Therapeutic measures for UC include prescribing medications, surgery treatment, psychosocial support and dietary recommendations.

Globally, the goals of UC treatment are currently defined by the "Treat-to-target (T2T)" strategy, which means "Treatment until the goal is achieved". This concept is aimed at achieving a long-term effect of treatment, prevention of complications, reducing the incidence of hospitalizations, reducing the risk of surgery and colorectal cancer, improving the quality of life and reducing the incidence of disability in patients with chronic diseases [57,58]. From the point of view of common practice, the goals of UC therapy are to achieve and maintain long-term steroidal clinical and endoscopic remission (discontinuation of GCS within 12 weeks after the start of therapy) [59].

In accordance with the "T2T" strategy for UC, the primary goal of therapy should be the complete relief of clinical symptoms (absence of blood in the stools and normalization of the stools), which are reported by the patient him/herself. It is mandatory to achieve endoscopic remission.

With the progression of the process and/or the development of life-threatening complications, the specific goal is timely surgical treatment.

As part of the "T2T" strategy, continuous monitoring of the effectiveness of treatment is provided through regular biological markers (CRP, FC) and endoscopy [58].

The choice of the type of conservative or surgical treatment is determined by the severity of the attack, the extent of the colorectal lesion, the presence of EIM (extra-intestinal manifestations), the duration of the anamnesis, the effectiveness and safety of previous therapy, as well as the risk of complications of UC [59,60] and the presence of risk factors for a negative prognosis of UC [61–64].

Risk Factors for a Negative Prognosis of the Course of UC

Predictors of Aggressive Course and Predictors of Colectomy Risk

- Age of diagnosis ⩽ 40 years (associated with a more severe disease, a short period of remission and a higher risk of colectomy);
- Age ⩾ 65 years at the time of diagnosis (associated with the risk of early colectomy);
- extensive lesion;
- high activity according to endoscopy (large and/or deep ulcers);
- presence of extra-intestinal manifestations;
- early need for systemic GCS (prescription at the onset of the disease) or the need for at least one course of GCS;
- severe attack according to Truelove-Witts (the number of criteria in addition to the frequency of stools with blood ⩾ 6 times/24 hours correlates with the prognosis: the incidence of colectomy in the outcome of the current attack) [65];
- Extremely severe attack of UC with diarrhea more than 10–15 times per 24 hours, progressive anemia, fever above 38°C, hypoalbuminemia ⩽ 27 g/l, high levels of CRP and deep extensive ulcers of the colorectal mucosa is associated with a high risk of colectomy in the first days of attack [13,15];
- Elevated levels of inflammatory markers;
- Non-smokers and former smokers tend to have a longer duration of inflammation and slower healing.

Smokers have more rare acute attacks and hospitalizations.

Since the complete cure of UC patients is achieved only by removal of large intestine (proctocolectomy), when remission is achieved, the non-operated patient must remain on constant maintenance (anti-relapse) therapy.

It should be particularly noted that GCS cannot be used as a maintenance therapy.

Below are recommendations on the choice of drugs for induction and maintenance of remission, depending on the extent of the lesion and the severity of the attack [26].

3.1.2 Proctitis. Mild and Moderate Attack

• Local treatment is **recommended** for this group of patients.

Grade of recommendations is A (Level of evidence is 1)

Comment. *In this situation, it is advisable to prescribe suppositories with mesalazine** (1 g/24-hr, if necessary, the dose can be increased to 2 g/24-hr) or rectal mesalazine foam (1 g 1 time/24-hr, if necessary, the dose can be increased to 2 times/24-hr) [26,66,67]. Evaluation of the therapeutic response is carried out after 2 weeks [66], with a positive response, treatment at these doses is prolonged to 6–8 weeks.*

• It is **recommended** for patients with ineffective treatment with rectal mesalazine to prescribe rectal forms of GCS.

Grade of recommendations is A (Level of evidence is 1)

Comment. *In this situation, it is advisable to prescribe rectal budesonide foam 2 mg per 24 hours, suppositories with prednisolone 10 mg (extempore) 2 times per 24 hours with an assessment of the response after 2 weeks to achieve remission [26,68,69].*

• When remission is achieved, maintenance therapy is **recommended** — rectal mesalazine (suppositories or rectal foam) 1 g 3 times a week in the form of monotherapy for at least 2 years to maintain remission [26,70].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended**, if local treatment is ineffective, to add oral forms of mesalazine (granules, tablets **, tablets in a multimatrix shell (MMX**) at a therapeutic dose according to the instructions for use to achieve remission [71].

Grade of recommendations is A (Level of evidence is 2)

Comment. *It is permissible to prescribe sulfasalazine** instead of mesalazine** [74,77].*

• It is **recommended** for patients in the absence of the effect of oral forms of mesalazine to prescribe GCS to achieve remission [26,69].

Grade of recommendations is C (Level of evidence is 5)

Comment. *In this clinical situation, GCS is prescribed in tablets at a dose equivalent to prednisolone 0.5–0.75 mg/kg of body weight per day to achieve remission.*

• It is **recommended** to combine GCS with azathioprine** (AZA) or mercaptopurine** (MP) in case of relapse requiring repeated administration of GCS to achieve remission [26,72].

Grade of recommendations is C (Level of evidence is 5)

Comment. *AZA is prescribed 2–2.5 mg/kg, and MP — 1.5 mg/kg. Local therapy (rectal budesonide foam 2 mg per 24 hours, suppositories with prednisolone 10 mg × 1–2 times per 24 hours) can be continued.*

• It is **recommended** to carry out maintenance therapy of AZA 2–2.5 mg/kg (or MP 1.5 mg/kg) for at least 2 years to maintain remission when GCS-induced remission is achieved [71,72].

Grade of recommendations is A (Level of evidence is 1)

• It is **recommended** for patients who have cytomegalovirus DNA in the colorectal mucosa to be treated with ganciclovir** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days to eliminate the pathogen [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.3 Proctitis. Severe Course (Develops Extremely Rarely)

• It is **recommended** for patients with severe ulcerative proctitis intravenous administration of GCS at a dose equivalent to prednisolone ** 1–1.5 mg/kg of body weight per 24 hours in combination with local mesalazine therapy ** (suppositories, rectal foam) or in combination with GCS rectally (budesonide foam 2 mg per day, suppositories with prednisone 10 mg × 2 times per 24 hours) to achieve remission [26,69].

Grade of recommendations is C (Level of evidence is 5)

• In the case of the first attack of UC, when remission is achieved, to maintain it, patients are **recommended** to be treated with local forms of mesalazine preparations (suppositories, rectal foam) 1 g × 3 times a week in the form of

monotherapy or in combination with oral mesalazine (granules, tablets, MMX tablets) at a dose of 2–2.4 g — at least 2 years to maintain remission [26,67,70,71,74,75,76].

Grade of recommendations is A (Level of evidence is 1)

Comment. *It is permissible to prescribe sulfasalazine ** 2 g/24-hr instead of mesalazine ** [74,77].*

• It is **recommended** in case of relapse requiring repeated administration of GCS (systemic or topical), simultaneously with GCS, to prescribe AZA 2–2.5 mg/kg (or #MP 1.5 mg/kg) and then continue maintenance therapy with immunosuppressants (AZA or #MP) for at least 2 years to maintain remission [72].

Grade of recommendations is C (Level of evidence is 5)

• Ganciclovir therapy** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days for the elimination of the pathogen is **recommended** for patients who have cytomegalovirus DNA in the colorectal mucosa [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.4 Left-sided and Total Ulcerative Colitis. Mild Attack

• It is **recommended** for patients with the first attack or relapse to administer mesalazine orally (granules, tablets, MMX tablets) in maximum therapeutic doses in accordance with the instructions for use in combination with mesalazine** in enemas of 4 g/24-hr to achieve remission [26,70,78,79].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The therapeutic response is evaluated after 2 weeks. With an improvement in the clinical picture and positive laboratory changes, therapy lasts up to 6–8 weeks.*

• It is **recommended** in the absence of the effect of combination therapy with mesalazine preparations** the administration of rectal forms of GCS [79,80].

Grade of recommendations is A (Level of evidence is 2)

Comment. *It is advisable to prescribe rectal budesonide foam 2 mg per 24 hours or a suspension of hydrocortisone acetate with lidocaine 125–250 mg once per 24 hours in the form of enemas or rectal drip to achieve remission.*

• It is **recommended** that patients, upon reaching remission, undergo maintenance therapy with oral mesalazine** (granules, tablets, MMX tablets) 2–2.4 g/24-hr to maintain remission [81].

Grade of recommendations is A (Level of evidence is 1)

Comment. *Additional administration of mesalazine ** in enemas of 2 g × 2 times a week ("weekend therapy") increases the likelihood of long-term remission.*

• It is **recommended** for patients in the absence of a response to combined treatment with oral mesalazine preparations** in combination with any rectal drug, the administration of topical corticosteroids (budesonide MMX) or systemic corticosteroids (see section 3.1.4) to induce remission [82].

Grade of recommendations is B (Level of evidence is 3)

• Ganciclovir therapy** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days for the elimination of the pathogen is **recommended** for patients who have cytomegalovirus DNA in the colorectal mucosa [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.5 Left-sided and Total Ulcerative Colitis. Moderate Attack

• It is **recommended** for patients with the first attack or relapse of UC to prescribe oral mesalazine (granules, tablets **, tablets ** MMX) at the maximum therapeutic dose (in accordance with the instructions for use) in combination with mesalazine ** in enemas of 4 g/24-hr to achieve remission [26,75,76].

Grade of recommendations is A (Level of evidence is 1)

Comment. *The therapeutic response is evaluated after 2 weeks. With an improvement in the clinical picture and positive laboratory dynamics, therapy lasts up to 6–8 weeks.*

• It is **recommended** that patients achieve remission with maintenance therapy with mesalazine** (granules, tablets, MMX tablets) 2.0–2.4 g/24-hr orally + mesalazine ** in enemas of 4 g × 2 times a week to maintain remission [26,75,76,79].

Grade of recommendations is A (Level of evidence is 1)

Comment. *It is permissible to prescribe sulfasalazine** 2 g/24-hr instead of mesalazine** [74,77].*

• It is **recommended** for patients without a response to mesalazine for 2 weeks, but in the absence of signs of systemic inflammation, the administration of topical GCS (budesonide MMX). Topical GCS is prescribed at a dose of 9 mg/24-hr. After 10 weeks of taking budesonide MMX, dose reduction is carried out every other day for 1–2 weeks until complete withdrawal [46,83,84,85].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients with the ineffectiveness of mesalazine for 2 weeks and with signs of systemic inflammation, the administration of systemic GCS to achieve a therapeutic effect [46,82,86,87,88].

Grade of recommendations is A (Level of evidence is 1)

Comment. *Systemic GCS is prescribed at a dose equivalent to prednisolone * * 1 mg/kg body weight per24 hours until a clinical response is achieved, followed by a decrease of 5 mg in 5–7 days until complete withdrawal, for no more than 12 weeks.*

• It is **recommended** for patients, when reducing the dose of GCS to the equivalent of 35–45 mg of prednisolone **, to additionally prescribe mesalazine ** (granules, tablets, MMX tablets) at the maximum therapeutic dose in accordance with the instructions for the drugs to maintain the therapeutic effect (if the patient does not receive immunosuppressants and GEBD) [78].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Further reduction of GCS should be carried out against the background of mesalazine ** followed by the transition to maintenance therapy with mesalazine** (granules, tablets, MMX tablets) 2.0–2.4 g per24 hours.*

• It is **recommended** for patients in case of intolerance to mesalazine preparations ** or, if necessary, to re-prescribe GCS for a year or less, combine GCS with AZA** 2.0–2.5 mg/kg or MP 1.5 mg/kg to achieve a therapeutic effect [72,89].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** that patients, upon reaching remission, continue maintenance therapy with AZA 2.0–2.5 mg/kg/24-hr or MP 1.5 mg/kg for at least 2 years to maintain remission [72,89].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients in the absence of the effect of GCS for 2 weeks prescription of GEBD (infliximab **, adalimumab **, golimumab**, vedolizumab**, ustekinumab**) or TIS (tofacitinib**, upadacitinib** or ozanimod **) to achieve remission in the form of induction (initiating) course and maintenance therapy [90–96].

Grade of recommendations is A (Level of evidence is 2)

Regimens and doses of drugs for GEBD and TIS as part of the induction course and the maintenance therapy:

• for infliximab, the induction course provides for three intravenous injections at 0, 2 and 6 weeks at dose of 5 mg/kg of bode weight, then the same dose for maintenance therapy every 8 weeks.

• for adalimumab, the induction course consists of the first subcutaneous injection at dose of 160 mg, afterwards the second subcutaneous injection after 2 weeks at dose of 80 mg, then maintenance therapy at dose of 40 mg every 2 weeks.

• for golimumab, the induction course consists of the first subcutaneous injection of 200 mg, the second subcutaneous injection after 2 weeks at dose of 100 mg, then maintenance therapy is carried out at 100 mg subcutaneously every 4 weeks.

• for vedolizumab, the induction course provides for three-time administration at 0, 2 and 6 weeks intravenously at dose of 300 mg, then maintenance treatment of 300 mg intravenously every 8 weeks.

• for ustekinumab, the induction dose is administered intravenously on the first day at dose of 6 mg/kg of body weight, then after 8 weeks the first subcutaneous injection at dose of 90 mg and afterwards maintenance therapy at dose of 90 mg subcutaneously every 8 or 12 weeks (depending on the course of the disease).

• for tofacitinib, 8-week induction course at dose of 10 mg × 2 times a day, then 5 mg × 2 times a day as a maintenance therapy.
• for upadacitinib, 8-week induction course at dose of 45 mg in tablets once a day and then 30 mg or 15 mg in tablets once a day as a maintenance therapy.
• for ozanimod, the induction course is 7 days with a gradual increase in the dose orally according to the instructions for use, on the 8th day and further, the full dose is 0.92 mg once a day.

Grade of recommendations is A (Level of evidence is 2)

Comment. *In bio-naive patients, any of these drugs can be used as the first line of therapy [203].*
It should be borne in mind that vedolizumab is more effective than adalimumab in the first line of therapy [210].

• It is **recommended** that patients receiving infliximab** combine it with immunosuppressants (AZA** 2.0–2.5 mg/kg) to increase the effectiveness of treatment [72,97,98].

Grade of recommendations is A (Level of evidence is 2)

Comment. *It is permissible to use #MP 1.5 mg/kg instead of AZA due to the fact that MP is a metabolite of AZA. For other GEBD, the effectiveness of the combination with immunosuppressants has not been proven. The combined use of azathioprine and tofacitinib is contraindicated [99,100].*

• It is **recommended** for patients with the effectiveness of the induction course of GEBD and TIS to carry out anti-relapse therapy with the same drug for at least 2 years to maintain remission [91,92,93,101,102].

Grade of recommendations is A (Level of evidence is 2)

• It is **recommended** for patients with primary ineffectiveness or loss of response to any of the anti-TNF drugs to change therapy to vedolizumab**, tofacitinib**, ustekinumab**, upadacitinib** or ozanimod** to achieve remission [93,95,96,103,104].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Any of these drugs can be prescribed as the 2nd and subsequent lines of therapy with or without GCS. When choosing vedolizumab after anti-TNF, it should be borne in mind that its effectiveness as a 2nd-line drug is lower than in the 1st line [211].*
The choice of ustekinumab as a second line of GEBD with the ineffectiveness of the first anti-TNF is associated with better results (achievement of clinical response and clinical remission) compared to switching to another anti-TNF or vedolizumab [225,226].

• It is **recommended** for patients with loss of response to anti-TNF drugs in the 1st line of therapy (recurrence of UC on the background of previously achieved remission) optimization of therapy in the form of increasing the dose of the drug (10 mg/kg of infliximab ** every 8 weeks, 100 mg of golimumab ** every 4 weeks, 80 mg of adalimumab every 2 weeks) or shortening the intervals between injections (infliximab ** up to 4–6 weeks, adalimumab **40 mg every week) or prescribing drugs of a different mechanism of action: vedolizumab**, tofacitinib**, ustekinumab**, upadacitinib** or ozanimod** to achieve a therapeutic effect [91,92,93,101,102,104,105].

Grade of recommendations is A (Level of evidence is 2)

Comment. *Switching to another anti-TNF drug is possible, but its effectiveness is lower than when switching to drugs of other classes (vedolizumab**, tofacitinib**, ustekinumab**, upadacitinib** or ozanimod**).*

• It is **recommended** for patients with loss of response to vedolizumab** at a standard dose of 300 mg every 8 weeks to optimize therapy in the form of shortening the intervals between injections to 4 weeks or change to a biological drug of another class (anti-TNF, ustekinumab**, tofacitinib**, upadacitinib**, ozanimod**) [106,211].

Grade of recommendations is C (Level of evidence is 4)

Comment. *The effectiveness of anti-TNF in the 2nd line of therapy after loss of response to vedolizumab does not decrease compared to their effectiveness in the 1st line, i.e. the use of vedolizumab does not affect the subsequent effectiveness of anti-TNF [211,212].*

• It is **recommended** for patients with loss of response to ustekinumab** in the standard mode of administration every 12 weeks, optimization of therapy in the form of shortening the intervals between injections to 8 weeks or changing to a drug of another class (GEBD or TIS) [104].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with loss of response to tofacitinib** at a standard dose of 10 mg per day to optimize therapy to 20 mg per day [107].

Grade of recommendations is C (Level of evidence is 4)

Comment. *The evidence basis on the possibility of switching from tofacitinib to biological drugs is insufficient.*

The change of drugs is possible and remains at the discretion of the attending physician. When stable clinical and endoscopic steroidal remission is achieved, the duration of biological therapy is determined by the attending physician.

In most countries, treatment has been carried out for many years. Early withdrawal of drugs, as a rule, leads to a relapse of UC in a short time.

If prolonged use of GEBD and TIS is not possible, maintenance therapy is carried out only with immunosuppressants.

• It is **recommended** for patients with relapse that occurred against the background of maintenance therapy with thiopurines to prescribe GEBD (infliximab**, adalimumab**, golimumab**, vedolizumab ** or ustekinumab **) or TIS tofacitinib **, upadacitinib** or ozanimod ** (with the cancellation of thiopurines according to the instructions for medical use) [91,92,93,95,96,101].

Grade of recommendations is A (Level of evidence is 2)

Comment. *Any of these drugs can be prescribed as a first-line therapy (see section 3.1.5).*

• It is **recommended** for patients who have cytomegalovirus DNA detected in the colorectal mucosa, ganciclovir therapy** at a dose of 5 mg/kg 2 times per 24 hours for 14–21 days to eliminate the pathogen [26,73].

Grade of recommendations is C (Level of evidence is 4)

Comment. *For the period of treatment with ganciclovir **, the cancellation of basic therapy is not required.*

3.1.6 Left-sided and Total Ulcerative Colitis. Severe Attack

• Intravenous administration of GCS is **recommended** for patients as the first line of therapy to achieve remission [26,108].

Grade of recommendations is A (Level of evidence is 1)

Comment. *The use of GCS is advisable at a dose equivalent to prednisolone ** 2 mg/kg of body weight intravenously (with a high body weight, 1.5 mg/kg may be prescribed) for 7 days or the use of hydrocortisone ** at an equivalent dose.*

The equivalence of doses and duration of action of GCS is shown in Table 6. The response is estimated in the range from 3 to 7 days. If the condition is stable for three days, then therapy is continued for up to 7 days. If the patient's condition worsens within three days, the question of "rescue therapy" or colectomy is raised.

If clinical improvement is noted after 7 days, then GCS therapy can be continued until stable improvement and then switch to oral medication and slowly reduce the dose of 5 mg every 5–7 days.

If there is no significant clinical improvement after 7 days, the condition is regarded as steroid resistance.

• It is **recommended** for patients to additionally prescribe local therapy with enemas with mesalazine ** 4 g per 24 hours or a suspension of hydrocortisone acetate with lidocaine 250 mg × 1 time per 24 hours in the form of enemas or rectal drip to achieve remission [79,80].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with metabolic disorders to carry out infusion therapy in order to rehydrate, correct protein-electrolyte disorders [59].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Hypokalemia and hypomagnesemia increase the risk of toxic dilation of the colon.*

• It is **recommended** for patients with hemoglobin levels below 80 g/l to correct anemia in the form of hemotransfusion (erythromass), with hemoglobin levels from 80 to 100 g/l — parenteral iron therapy: sucrose hydroxide complex **, iron (III) dextran hydroxide, iron (III) hydroxide oligoisomaltosate, iron carboxymaltosate** [109].

Grade of recommendations is C (Level of evidence is 5)

• It is **recommended** for patients to reduce the risk of thrombosis to carry out preventive therapy with low molecular weight heparins (ATC B01AB),

Table 6. *Comparative characteristics of GCS*

Drug	Duration of action ($t_{1/2}$)	Equivalent dose (mg)
Cortisol (hydrocortisone)	8–12 hours	20
Prednisone	12–36 hours	5
Prednisolone	12–36 hrs	5
Methylprednisolone	12–36 hrs	4

unfractionated heparin**, fondaparinux sodium** [204,205].

Grade of recommendations is B (Level of evidence is 2)

• It is **recommended** for patients with a body weight deficit (BMI less than 18) to prescribe additional enteral nutrition, including tube feeding, to improve the trophological status [110].

Grade of recommendations is C (Level of evidence is 2)

Comment. *Complete parenteral nutrition and/or temporary restriction of oral nutrition is impractical.*

• With the development of signs of systemic inflammation in patients, it is **recommended** to prescribe antibiotics to prevent septic complications:
1 line — #metronidazole** + fluoroquinolones (ciprofloxacin**, ofloxacin**) [111];
Line 2 — cephalosporins [112,113].

Grade of recommendations is A (Level of evidence is 1)

• It is **recommended** for patients with a clinical response to GCS after 7 days to change to oral prednisolone ** followed by a reduction to complete withdrawal of 5–10 mg of prednisolone ** in 5–7 days to maintain remission [59].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The scheme of transition from intravenous GCS to oral forms is considered individually by the attending physician, depending on the speed of achieving the effect and the severity of the therapeutic response.*

With the development of steroid resistance, if there is no immediate life-threatening or severe complications requiring immediate surgery, "rescue therapy" is indicated, against the background of continuing treatment of GCS, i.e. strengthening of conservative therapy, which is carried out with infliximab (at a dose of 5 mg/kg as part of an induction course at 0, 2 and 6 weeks) or cyclosporine A i/v (2–4 mg/kg for 7 days with monitoring of renal function and determination of the concentration of the drug in the blood) or tofacitinib (20 mg/24-hr as part of an induction course for 8 weeks) [103,206,207,208]. The clinical result of such therapy is evaluated after 7 days. Studies have shown that the effectiveness of both regimens (with infliximab and cyclosporine) on day 8 of treatment is identical, therefore, currently infliximab is mainly used in foreign practice, as drug is safer and does not require time-consuming and expensive concentration determination. If there is no effect after 7–8 days, surgical treatment options are considered. If it is impossible to prescribe infliximab, it is permissible to prescribe tofacitinib taking into account the speed of achieving the effect [207, 208] in accordance with the instructions for use.(see section 3.1.5).

• It is **recommended** that patients who achieve remission on infliximab** continue supportive anti-relapse therapy with the same drug according to the standard scheme in combination with AZA** 2–2.5 mg/kg (or #MP 1.5 mg/kg) or without it [98,102,114].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended** that patients with a positive response to i/v #cyclosporine ** after 7 days switch to oral administration of the drug at a dose of 2 mg/kg of body weight with the additional administration of AZA ** 2 mg/kg (against the background of a therapeutic dose of GCS) with the gradual abolition of GCS for 12 weeks until the therapeutic concentration is reached and the beginning of the action of AZA** to increase the duration of remission in the patient.

When remission is achieved, oral cyclosporine can be canceled, leaving the patient on the maintenance therapy of AZA** for at least 2 years [72,89,115,116].

Grade of recommendations is C (Level of evidence is 5)

Comment. *A significant drawback of such a treatment regimen is due to the simultaneous use of three immunosuppressive drugs at once with an increased risk of adverse events.*

3.1.7 Extremely severe Ulcerative Colitis of Any Extent

In this form, both the first attack of the UC and any of the subsequent acute attacks can occur (for a description, see the section "Classification of the UC"). The patient must be hospitalized in a multidisciplinary (specialized) hospital for conservative treatment, followed by mandatory supervision by a gastroenterologist and a coloproctologist (surgeon) to decide on the feasibility of performing surgery within 24 hours.

• It is **recommended** for patients with aextremely severe attack of UC to prescribe intravenous corticosteroids at a dose equivalent to prednisolone ** 2 mg/kg of body weight to achieve a therapeutic effect [117].

Grade of recommendations is C (Level of evidence is 4)

Comment. *The effectiveness of conservative therapy in extremely severe UC attack does not exceed 50%. At the same time, the clinical picture and laboratory parameters are evaluated every 24 hours, and more often if necessary. With the worsening of the clinical picture and laboratory parameters, the only way to save a patient's life in anextremely severe attack of UC is colectomy. With significant positive changes on the part of the clinical picture and laboratory parameters, with a sufficient degree of caution, it is possible to continue intravenous therapy with GCS for up to 14 days. If there is no positive changes within 3 days, then this condition is regarded as steroid resistance.*

• In the case of steroid resistance, if there is no immediate threat to the patient's life or the development of severe complications requiring urgent surgery, for this group of patients it is **recommended** to prescribe "second-line" therapy (in the English literature, "rescue therapy"), which includes the following treatment options:
infliximab** 5 mg/kg (administered as part of an induction course at 0, 2 and 6 weeks) [118,119] or #cyclosporine** (preferably intravenous) 2–4 mg/kg for 7 days with monitoring of renal function [120,121] ortofacitinib 20 mg/24-hr as part of an induction course for 8 weeks [103,206,207,208].

Grade of recommendations is A (Level of evidence is 2)

Comment. *Other biological drugs are not used as "rescue therapy". Surgery is indicated for this group of patients with negative shifts or in the absence of a response on day 7 of therapy with infliximab**, cyclosporine** or tofacitinib** [122].*

• It is **recommended** that patients who achieve remission on infliximab** continue supportive anti-relapse therapy with the same drug according to the standard scheme in combination with AZA** 2–2.5 mg/kg (or #MP 1.5 mg/kg) or without it [98,102,114].

Grade of recommendations is B (Level of evidence is 3)

• It is **recommended** that patients who achieve remission on tofacitinib ** continue maintenance therapy with the same drug 10 mg/24-hr. [103].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** that patients with a positive response to i/v #cyclosporine ** after 7 days switch to oral administration of the drug at a dose of 2 mg/kg of body weight with the additional administration of AZA ** 2 mg/kg (against the background of a therapeutic dose of steroids) with the gradual abolition of steroids for 12 weeks until the therapeutic concentration is reached and the beginning of the action of AZA** to increase the duration of remission in the patient.
When remission is achieved, oral cyclosporine can be canceled, leaving the patient on the maintenance therapy of AZA** for at least 2 years [72, 89,115,116].

Grade of recommendations is C (Level of evidence is 5)

3.1.8 Biosimilars (Bio-analogues)

Biosimilars are biological medicinal products containing a version of the active substance already approved by the original biological medicinal product (reference drug) [213]. Currently, the biosimilar market is constantly expanding. In relation to IBD, this still applies to biosimilars based on monoclonal antibodies to TNF-alpha. In Europe alone, 21 biosimilars have been registered in the last decade, of which 14 are based on adalimumab and 4 are based on infliximab [214]. Biosimilars of infliximab and adalimumab have also been registered in the Russia, analogues of tofacitinib have recently appeared. The use of biosimilars reduces the economic burden on the healthcare system and, thereby, significantly expands the

possibilities of using and accessibility of GEBD. Now there is a sufficient evidence for the effectiveness and safety of biosimilars, but among clinicians there remains a prejudice against them as drugs with lower efficacy [215].

The European Organization for the Study of IBD (ECCO) in 2017 declared a position on the use of biosimilars in IBD, which emphasizes that after registration, a biosimilar is considered to be as effective a drug as the original product, and large observational studies are required to assess its long-term effectiveness and safety [216]. It is from these positions that a systematic review of 90 studies in various immuno-inflammatory diseases in 2018 showed that in the vast majority of studies there were no differences in safety, efficacy or immunogenicity between biosimilars and the corresponding original drugs, which indicates the preservation of a good benefit-risk profile when switching from the original drug to a biosimilar [217]. Real clinical practice in European countries and the USA demonstrates similar efficacy, safety and immunogenicity when switching IBD patients from the original infliximab to its biosimilars [218–222]. Only in one study, in 9.9% of cases, the need for reverse switching from a biosimilar to a reference drug was recorded due to undesirable manifestations from the skin, gastrointestinal tract or due to loss of response to the drug. In the vast majority of patients, the response to treatment after the reverse switch restored [220]. Comparison of adalimumab and its two analogues in patients with IBD in Italy showed no significant difference in efficacy, safety and immunogenicity between the drugs after the induction course and after 6 months of maintenance treatment [223]. The results of long-term post-marketing monitoring of the efficacy and safety of biosimilars based on monoclonal antibodies for 7 years did not reveal any side effects specific to biosimilars [224]. The ECCO consensus emphasizes that the decision to switch from an original drug to a biosimilar for non-medical reasons should be carried out in accordance with national clinical guidelines and all information should be brought to the attention of the patient and explained to him [216]. Despite the clearly formulated statements about biosimilars, there are certain contradictions in this matter, according to which the adopted provisions are based on studies with different methodological approaches and an insufficient number of observations, which limits their reliability [227].

Russian publications indicate that frequency of secondary loss of response and adverse events in IBD patients when switching from the original infliximab to its biosimilar is about 30%, which is significantly higher than in patients who regularly receive the original drug. In addition, the frequency of adverse events is significantly higher in patients receiving the drug according to INN, which leads to unjustified and unregulated alternation of the original drug and bioanlogs compared with patients receiving drugs by trade name [228].

The provision on biosimilars is being introduced for the first time in the Russian clinical guidelines for UC. Because Russian biosimilars are not represented on the foreign market, international data on successful switching experience will have limited applicability for Russia. Therefore, it is necessary to extrapolate these data with caution to domestic clinical practice.

• It is **recommended** to use both the original drug and its biosimilars as equivalent medicines when indications for the administration of a GEBD class of TNF-alpha inhibitors (infliximab and adalimumab) [215,216].

Comment. *This provision applies equally to the primary administration of anti-TNF drugs in bio-naive patients, and switching from the original drug to a biosimilar for non-medical indications. However, it should be aware that frequent switching from the original drug to a biosimilar or different biosimilars and back according to INN can lead to a worsening of course of the disease, a rapid loss of response and adverse events [228].*

Switching from one anti-TNF drug to another within the same class with a loss of response to the first drug is not recommended either for original drugs or for biosimilars (see section 3.1.5). There is not yet a sufficient evidence basis for the use of biosimilars of drugs of other classes for the treatment of UC.

3.2 Surgical Treatment

3.2.1 Indications for Surgical Treatment of UC: Ineffectiveness or Impossibility to Continue Conservative Treatment

Indications for surgical treatment of UC are the ineffectiveness of conservative treatment (steroid

resistance, inefficiency of GEBD) or the impossibility of their continuation (steroid addiction, intolerance or contraindications for conservative treatment), intestinal complications of UC (toxic dilation, intestinal perforation, intestinal bleeding), as well as colorectal cancer or a high risk of its occurrence.

The ineffectiveness of conservative therapy is evidenced (see section 1.5):

- Steroid resistance;
- Steroid addiction.

Steroid addiction can be effectively overcome with the help of GEBD and/or immunosuppressants (AZA**, MP**) in 40–55% of cases [78,116], and with steroid resistance, the administration of cyclosporine** or infliximab** allows to induce remission in 43–80% of cases [118,119,120].

However, in some patients with a high risk of complications and ineffectiveness of conservative therapy with the development of steroid resistance or addiction, surgical treatment is possible without attempting to use GEBD or immunosuppressants.

3.2.2 Indications for Surgical Treatment of UC: Intestinal Complications of UC

- Patients with complications of UC (intestinal bleeding, perforation of the large intestine, toxic dilation on the background of adequate infusion therapy) are **recommended** to undergo subtotal colectomy or total colectomy or proctocolectomy (with severe rectal activity) to increase the patient's life expectancy [123,124,125].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Toxic dilation of the colon (toxic megacolon) is an expansion of the colon 6 cm or more unrelated to obstruction with intoxication phenomena. Risk factors for toxic dilation include hypokalemia, hypomagnesemia, bowel cleansing for colonoscopy using osmotic laxatives and antidiarrheal medications. Indirectly, the development of toxic dilatation is indicated by a sudden decrease in the frequency of stools against the background of existing diarrhea, bloating, as well as a sudden decrease or disappearance of pain syndrome and an increase in symptoms of intoxication (an increase in tachycardia, a decrease in blood pressure). Perforation of the large intestine is the most dangerous complication of UC with almost 50% mortality.*

3.2.3 Indications for Surgical Treatment of UC: Colorectal Cancer

In patients with a long history of UC, the risk of colorectal cancer is significantly increased, which necessitates regular check-up to detect dysplasia in the epithelium of the colorectal mucosa. The probability of cancer is influenced by the following factors:

a) The duration of the history of UC: the risk of colorectal cancer is 2% at 10-year-old, 8% at 20-year-old and 18% at 30-year-old history [126];

b) The onset of the disease in childhood and adolescence, although this factor can only reflect the duration of the anamnesis and is not an independent predictor of colorectal cancer [127];

c) The extent of the lesion: the risk is most elevated in patients with total UC, while in patients with proctitis the risk does not differ from the average in the population;

d) The presence of primary sclerosing cholangitis [128];

e) Family history of colorectal cancer;

f) Severe attacks of UC in the anamnesis or continuous course of UC. The consequence of high UC activity may be inflammatory polyposis, which is also a risk factor for colorectal cancer [129].

A control colonoscopy should be performed in conditions of good preparation of the intestine and, preferably, during remission, since active inflammation makes it difficult to detect dysplasia.

Clarifying endoscopic techniques are used for screening neoplastic changes in the mucous membrane: video colonoscopy with chromoscopy in combination with dye or virtual (optical) chromoscopy with targeted biopsy [130, 131, 132]. When using clarifying endoscopic techniques, a search biopsy is not required.

The results of the screening biopsy affect the approach for further treatment and follow-up.

- Surgical treatment in the scope of total colectomy is **recommended** for patients with UC when a high degree of dysplasia is detected in the biopsy from a macroscopically unchanged mucosa [126].

Grade of recommendations is C (Level of evidence is 5)

Comment. *It is possible to perform a proctocolectomy with permanent terminal ileostomy or a proctocolectomy with the simultaneous ileal pouch with protective loop ileostomy.*

The presence of dysplasia in the epithelium of the colorectal mucosa should be confirmed by a second independent pathologist. The type of surgery is discussed together with the patient, thereby taking into account his/her desire for the preservation of anal defecation or the permanent ileostomy.

• It is **recommended**, when mild dysplasia is detected in the epithelium of a macroscopically unchanged mucosa, to discuss individually with the patient two options for surgical treatment — total colectomy (or proctocolectomy) with the permanent terminal ileostomy and proctocolectomy with the simultaneous formation of ileal pouch under the guise of a loop ileostomy to improve the patient's quality of life or continuation of regular endoscopic screening with a reduction in the interval between studies in the period from 6 to 12 months [126].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The type of surgery should be discussed with the patient, thereby taking into account his desire for the preservation of anal defecation or the formation of a permanent ileostomy.*

The patient has the right to refrain from surgical treatment, in which case endoscopic screening is offered.

• It is **recommended** for patients with UC remission, upon confirmation of the presence of an adenomatous polyp (endoscopically and according to the results of a pathomorphology), to perform a standard polypectomy for secondary cancer prevention [128].

Grade of recommendations is C (Level of evidence is 4)

Comment. *In patients with remission of UC in the presence of large neoplastic lesions of the large intestine and the absence of dysplasia in the epithelium of the mucosa outside of these lesions, it is possible to perform mucosectomy or dissection in the submucosal layer [133,134].*

• Colectomy is **not recommended** for patients with UC in the presence of an adenomatous polyp with severe dysplasia, if there is no dysplasia in the epithelium of the mucosa in other parts of the large intestine or corresponds to a mild degree [128].

Grade of recommendations is C (Level of evidence is 4)

• It is **recommended** for patients with ulcerative colitis in the presence of a narrowing area in the large intestine to conduct an endoscopic examination with a biopsy from the narrowing area to exclude colorectal cancer [129].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Dysplasia in the epithelium of the mucous membrane should be confirmed by a second pathologist, and then the treatment program should be discussed by a multidisciplinary medical consultation.*

If the colonoscopy is not total due to the presence of narrowing, CT with intravenous and intraluminal contrast is necessary to assess the nature of changes in the large intestine wall proximal to the narrowing [135].

All patients with colorectal cancer on the background of ulcerative colitis, after an oncological consultation, are shown surgical treatment in the scope of total colectomy with abdominal-anal resection of the rectum to eliminate the risk of malignant transformation in the remaining parts of the large intestine.

3.2.4 Surgery Types

In most patients with UC, modern conservative treatment allows controlling the inflammatory process. However, in 10–30% of patients, due to the ineffectiveness of drug treatment, it is necessary to resort to surgery aimed at removing the large intestine [123,124]. Until the early 1980s, the standard of surgical treatment was proctocolectomy with terminal ileostomy, despite the episodic formation of ileorectal anastomosis.

Over the past 20 years, reconstructive surgery has become the new gold standard — total colectomy with pouch (proctocolectomy with IPAA) [136,137] (Table 7). In the absence of complications, this surgery provides the possibility of controlled defecation through the anus with a satisfactory quality of life [136]: the frequency of defecation after the formation of IPAA is 4–8 times per 24 hours [138–140], and the average 24-hour volume of semi-formed/liquid stools is about 700 ml per 24 hours (compared with 200 ml/24-hr in a healthy person).

All patients who are going to undergo surgery (total or subtotal colectomy or colectomy with intersphincter resection of the rectum) due to the

Table 7. *Methods of surgical treatment of UC*

With the formation of a permanent ileostomy	With the restoration of defecation through the anus		
Colectomy with abdominal-anal resection of the rectum and the formation of a permanent terminal ileostomy	With the formation of IPAA, in 2 stages:	With the formation of IPAA, in 3 stages:	Subtotal colorectal resection with ileorectal anastomosis (in exceptional cases)
	1. Colectomy with rectal resection, IPAA, loop ileostomy; 2. Closure of the loop ileostomy	1. Subtotal colorectal resection (subtotal colectomy), terminal ileostomy; 2. Proctectomy, IPAA formation, loop ileostomy; 3. Closure of the loop ileostomy	

ineffectiveness of conservative treatment, with the exception of intestinal complications, it is preferable to use laparoscopic technologies to reduce the rate of intraoperative and postoperative morbidity, faster recovery, reduce the risk of adhesions in the abdominal cavity, reducing the risk of fertility decline and improving the cosmetic result [141–146].

3.2.5 Choosing the Type of Surgery

Reconstructive surgery with IPAA, despite its obvious attractiveness to the patient, is not possible in all cases, since a number of factors worsen the functional outcome of the surgery and increase the risk of complications, leading to the need to remove the pouch in 3.5–10% of patients [147–149].

In patients of older age groups with UC, despite the higher incidence of concomitant diseases, the surgery itself with ileal pouch is safe [150]. The anal sphincter function, which plays a key role for the normal functioning of IPAA, as a rule, worsens in older age groups [151].

In addition, patients over 60 years old are more likely to develop complications, in particular, pouch and anastomotic stricture [152, 153]. At the same time, no specific age threshold for refusing to form IPAA has been determined.

The IPAA by 30–70% increases the risk of infertility in women of childbearing age with UC [154–158].

The risk of infertility is associated with the adhesive process involving the fallopian tubes. Planned pregnancy and the young age of a woman are not contraindications to the IPAA. However, the patient should be warned about the potential risk of infertility. In some cases, it is possible to consider the formation of an ileorectal anastomosis as an intermediate stage of surgical treatment (see below).

In all patients with UC, when indications for surgery arise, the use of laparoscopic technologies reduces the risk of infertility by 90% [158].

In approximately 10% of patients, even with a pathomorphological study of the surgical specimen after colectomy, it is not possible to make a differential diagnosis between CD and UC, and therefore they are diagnosed with unspecified colitis. The decision on the formation of IPAA in such cases is made individually, while the patient should be warned about the risks of ineffectiveness of reconstructive plastic surgery and other complications associated with CD.

In patients with UC in the presence of concomitant diseases such as rectal cancer and severe anal incontinence of the 2nd or 3rd degrees, the IPAA is impractical.

- It is **recommended** that patients with severe UC attack who did not respond to conservative treatment, as well as patients with UC who, by the time indications for surgery were established, had hormone therapy with prednisolone for more than 6 weeks** at a dose of at least 20 mg per 24 hours for more than 6 weeks, undergo three-stage surgical treatment (colectomy with ileostomy at the first stage, the ileal pouch and a loop ileostomy at the second stage, and the closure of a loop ileostomy at the third stage) to reduce the risk of postoperative complications [159–161].

Grade of recommendations is C (Level of evidence is 4)

Comment. *In all patients with severe or extremely severe attack of ulcerative colitis, if indications for surgery arise, surgical intervention should be at least colectomy with end ileostomy, which allows to improve the general condition of the patient, eliminate metabolic disorders, and pathomorphology of the removed specimen excludes CD. Colectomy is a relatively safe surgery even in patients in critical condition [159–161]. With sufficient qualification of the surgeon, it is safe to use laparoscopic technologies [162, 163].*

The ileorectal anastomosis does not lead to a cure of the patient and does not exclude the possibility of recurrence of inflammation in the rectum and the development of cancer [164–166]. This surgery in UC

can be performed only in exceptional cases in women planning pregnancy. A prerequisite is the presence of remission in the rectum and the patient's consent to a regular rectal examination with a mucosal biopsy [165, 167].

3.2.6 Surgery Features in the Formation of Ileal Pouch

In patients with UC who have undergone colectomy, reconstructive plastic surgery with IPAA is performed in specialized hospitals, since the morbidity rate and the functional outcome of such procedures significantly depends on the personal experience of the surgeon [165].

The Length of the Preserved Rectum and/or Sigmoid Colon

For patients with UC, when performing colectomy for urgent indications, which are planned for ileal pouch in the future, it is advisable to preserve the entire rectum and low mesenteric vessels to improve the quality of life. It is advisable to cross the rectum at the level of promontorium or additionally preserve the distal sigmoid colon (the decision is made by the operating surgeon). While maintaining the distal part of the sigmoid colon, it is displayed on the anterior abdominal wall in the form of aendsigmostomy. The latter option is the safest, since at the same time there is no stump of the intestine in the abdominal cavity. When crossing the rectum at the level of promontoriumfor several days, drainage of the stump through the anus is recommended to prevent the leakage due to the collection of mucus. In case of preservation of the diverted rectum or rectum and sigmoid colon, the development of secondary inflammatory changes of the mucosa (diversion colitis) is possible. Controlled trials of drugs in patients after colectomy have not been done yet. Empirical treatment consists in topical application of mesalazine [168], steroids, washing of the diverted rectum with antiseptic solutions.

The IPAA

For patients with UC who are planning surgical treatment with ileal pouch, in order to improve functional results, it is advisable to keep the distal rectum no longer than 2 cm above the dentate line. The preservation of an extended rectal stump (more than 2 cm above the dentate line) may cause chronic inflammation in it with pouch dysfunction, and also contributes to the preservation of the risk of dysplasia and (very rarely) cancer [164]. If it is impossible to form a pouch-rectal anastomosis using a stitching device, abdominal-anal resection of the rectum should be performed and a manual ileoanal anastomosis should be applied.

Morphological changes in the epithelium of the pouch usually develop 12–18 months after the closure of the ileostomy and are characterized by flattening and reduction of the number of villi, and are often accompanied by the development of colorectal metaplasia [169,170], which is potentially associated with the risk of malignant transformation of the mucosa of the pouch. In addition, when applying stapler IPAA, a small area of the rectal mucosa ("cuff") is preserved. The risk of developing pouch cancer is increased in patients operated for cancer or dysplasia against the background of UC (and when dysplasia is detected in removed specimen), as well as in patients with primary sclerosing cholangitis (PSC). Scientific substantiation of the frequency of control check-up of patients with IPAA has not been performed; however, in patients with the presence of the above risk factors, it is advisable to conduct control pouch endoscopy with a mucosal biopsy at least once every 2 years.

3.2.7 Medications during Surgical Treatment

The effect of drug therapy on the risk of operation.

- It is **recommended** to carry out drug therapy (hormonal, immunosuppressive, GEBT) with caution during surgical treatment to reduce the risk of postoperative complications [171–176].

Grade of recommendations is C (Level of evidence is 4)

Comment. *Taking prednisolone** at a dose of more than 20 mg for more than 6 weeks increases the rate of postoperative complications [171, 172]. Preoperative administration of AZA and MP does not worsen the outcome of surgical treatment [173], while the administration of infliximab** and cyclosporine**# shortly before surgery may increase the frequency of postoperative complications [174, 175], although data on infliximab** remain contradictory [176]. Abrupt discontinuation of GCS therapy can cause withdrawal syndrome (acute adrenal insufficiency, the so-called Addison crisis), which necessitates the temporary continuation of hormone therapy after surgery until complete withdrawal. At the moment, there is no reliable scientific basis to substantiate any scheme for stopping hormone therapy after colectomy for UC. The dose of GCS for*

further oral administration during the withdrawal of hormone therapy is determined by the duration of previous therapy and the value of doses used.

*According to the recommendations of the European Society for the Study of UC and CD (ECCO) [26], if hormone therapy was carried out no more than a month before surgery, it is possible to stop taking GCS immediately after surgery.If the patient received GCS for more than a month before surgery, after surgery it is advisable to switch from the above-described high parenteral dose to oral administration of GCS at a dose not lower than the upper limit of the 24-hour stress production of cortisol, that is, not lower than 20 mg of prednisolone **.*

3.2.8 Pouchitis and Other Complications of Surgical Treatment in the Formation of a Small Intestine Pouch

Pouchitis is a nonspecific inflammation of the ileal pouch and the most common complication of IPAA.

Its incidence varies in a wide range from 15% to 50% within 10 years after the IPAA in large specialized centers [177–179]. Such differences may be due to a significantly higher risk of pouchitis in UC, exceeding the rate of this complication in IPAA for other diseases (in particular, familial adenomatous polyposis) [180–181].

In patients with picture of pouchitis, intestinoscopy (pouch endoscopy) should be performed to assess the degree of inflammatory changes in the pouch mucosa with biopsy.

Pouchitis is accompanied by abscesses, fistulas, stenosis of the IPAA and the risk of developing cancer in the pouch. The latter complication is extremely rare and almost always occurs when severe dysplasia or cancer is detected in the removed specimen after colectomy.

Differential diagnosis of suspected pouchitisis performed with irritable pouch syndrome (IPS), ischemic lesions, CD and other rare causes of pouch dysfunction, such as collagenose, cytomegalovirus and Clostridioides difficile-associated pouchitis. The possibility of the development of nonspecific ileitis caused by taking NSAIDs and the syndrome of excessive bacterial growth should be taken into account.

The main drugs used for the treatment of pouchitis remain antibiotics, which makes it possible to classify pouchitis as antibiotic-sensitive, antibiotic-dependent and antibiotic-resistant.

• For patients with pouchitis, first-line therapy, including a 14-day course of oral metronidazole** (15–20 mg/kg/24-hr) or ciprofloxacin** (1,000 mg/24-hr) is **recommended** to achieve a therapeutic effect [182].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Adverse events are much more common when taking metronidazole.*

In cases of antibiotic-resistant pouchitis, oral budesonide (9 mg) may be prescribed for 8 weeks.

• It is **recommended** for patients with pouchitis in the absence of an effect or with the development of dependence on taking these drugs, to prescribe reserve drugs — rifaximin (2,000 mg/24-hr) and tinidazole (1,000–1,500 mg/24-hr), including in combination with ciprofloxacin (1,000 mg/24-hr), rectal corticosteroids, rectal drugs mesalazine **, azathioprine** to achieve a therapeutic effect [182].

Grade of recommendations is C (Level of evidence is 5)

• It is **recommended** for patients with chronic therapy-resistant pouchitis in case of ineffectiveness of first-line therapy and reserve medications, to prescribe #TNF-α blockers [183], #vedolizumab [184] or #ustekinumab [185] for induction and maintenance of remission.

Grade of recommendations is C (Level of evidence is 5)

Inflammation of the Mucosa of the Preserved Area of the Rectum

Another potential complication of IPAA is inflammation of the mucosa of the rectum, preserved during the application of a stapler anastomosis.

• It is **recommended** for patients with proctitis after ileal pouch, to conduct treatment with mesalazinesuppositories ** 500 mg 2 times per 24 hours and/or rectal corticosteroids to achieve a therapeutic effect [68].

Grade of recommendations is A (Level of evidence is 1)

3.2.9 Ileostomy Dysfunction after Surgical Treatment of UC

Ileostomy dysfunction refers to an increase in the volume of intestinal discharge through the ileostomy of more than 1,000 ml per 24 hours. This condition is also accompanied by rapidly progressing metabolic and water-electrolyte disorders [186, 187].

• It is **recommended** for patients with ileostomy dysfunction to use an algorithm for laboratory diagnosis of *Clostridioides difficile* –associated diarrhea, including molecular biological fecal test for the pathogen *Cl. difficile* or immunochromatographic rapid fecal test for toxins A, B and binary toxin *Cl. difficile* [186,188].

Grade of recommendations is C (Level of evidence is 5)

Comment. *In addition to abundant liquid discharge through the stoma, the clinical picture also shows an increase in body temperature to 39^{0}C, flatulence, rarely complaints of nausea, vomiting, abdominal spastic pain. In laboratory tests: anemia, hypoproteinemia, hypoalbuminemia, hypokalemia, an increase in the level of CRP, rarely an increase in creatinine concentration.*

• It is **recommended** for patients with mild ileostomy dysfunction to prescribe a diet therapy, antispasmodics and drugs that slow down the passage through the gastrointestinal tract to achieve a therapeutic effect and improve the patient's quality of life [186–188].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The mild form of the disease is characterized by an increase in the volume of intestinal discharge by ileostomy, without signs of systemic inflammation.*

• It is **recommended** for patients with a moderate form of ileostomy dysfunction, when confirming the diagnosis of clostridial infection, to prescribe metronidazole at a dose of 500 mg orally three times a day for 10 days. In the absence of a clinical effect from metronidazole ** after 5–7 days, the drug is changed to vancomycin ** at a dose of 1,000 mg per day *per os* for 10 days to achieve a therapeutic effect and improve the patient's quality of life [186,187,189,190].

Grade of recommendations is C (Level of evidence is 5)

Comment. *The moderate form is characterized by an increase in the volume of intestinal discharge by ileostomy, an increase in body temperature and changes in laboratory parameters: with an increase in the level of leukocytes in the blood more than 15 × 10^9/l, serum creatinine above 115 mmol/l, a rise in body temperature above 38^{0}C and a decrease in albumin less than 25 g/l, patients should receive treatment in a 24h hospital. In case of confirmation of clostridial infection, the administration of vancomycin ** at a dose of 1,000 mg orally per day for 10 days is indicated.*

• It is **recommended** for patients with severe ileostomy dysfunction when confirming the diagnosis of clostridial infection, along with infusion therapy, to prescribe vancomycin orally at a dose of 500 mg 4 times a day in combination with metronidazole ** at a dose of 500 mg 3 times a day intravenously [187,191].

Grade of recommendations is C (Level of evidence is 5)

Comment. *A severe form of ileostomy dysfunction, in addition to an increase in the volume of intestinal discharge through the ileostomy, is manifested by abdominal pain of a spastic nature, the development of fever up to hectic values, leukocytosis, hypoalbuminemia. If it is impossible to administer the drug through the mouth, vancomycin ** is prescribed intramuscularly — while the drug at a dose of 500 mg is diluted in 500 ml of 0.9% sodium chloride solution and injected into the intestinal lumen four times a day. Deterioration of the patient's condition with the occurrence of hypotension, hyperthermia above 38.5° C, stools retention, pronounced bloating, change of consciousness, leukocytosis above 15 × 10^9 or leukopenia below 2 × 10^9, increased serum lactate levels above 2.2 mmol/L, the development of multiple organ failure syndrome requires his/her transfer to the intensive care unit for further treatment.*

4. MEDICAL REHABILITATION, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF REHABILITATION METHODS

There are no specific rehabilitation measures for patients with UC.

Since in some cases UC therapy is associated with the use of immunosuppressants, the main method of rehabilitation of patients is the prevention of opportunistic infections described in section 5.

In patients who required surgical treatment of ulcerative colitis, rehabilitation is possible in three stages.

The 1st stage is early rehabilitation, carried out immediately after surgical treatment from the 2nd to the 14th day. The main task of the 1st stage of

rehabilitation is to restore the normal functioning of the gastrointestinal tract after surgery.

It is at this stage that urination disorders are most often detected and should be corrected. An important role is also assigned to the control of homeostasis, measures aimed at healing postoperative wounds, relief of postoperative pain syndrome, activation of the patient. During this period, laboratory parameters are monitored by prescribing a general blood test, a biochemical blood test, a blood coagulogram, and a general urine test.

The 2nd stage of rehabilitation begins after 15 days and continues as necessary in the future. It is aimed at the final healing of postoperative wounds with control over the activity of the gastrointestinal tract and other body systems. This stage can be carried out both on an outpatient basis and in a day- or 24h hospital.

The 3rd stage of rehabilitation is carried out in the late rehabilitation period in patients with both permanent ileostomy and before reconstructive and restorative surgery. The main task at this stage is to normalize the function of the gastrointestinal tract, measures aimed at identifying and correcting violations of the function of the rectal occlusion apparatus.

Anal Sphincter Incontinence

Rehabilitation is possible in stages 2 and 3. In a number of patients whose surgery for UC resulted in ileal pouch, there is a decrease in the anal function. In patients with UC with anal sphincter incontinence, before reconstructive and restorative treatment, it is advisable to study the function of the rectal occlusion apparatus (sphincterometry, profilometry, sacral nerve latency), followed by consultations with a physiotherapist for treatment aimed at improving the function of holding [192].

In patients with UC, when detecting anal sphincter incontinence of the 2nd-3rd degrees, it is advisable to conduct a 10-day cycle of electrostimulation, BFB therapy and tibial neuromodulation in a daytime or 24h hospital, aimed at improving the contractility of the muscles of the external sphincter and pelvic floor by increasing both the strength and duration of voluntary contraction [192,193].

BFB therapy is a non-invasive method involving the body's own resources in the rehabilitation process with the development of the right skills at the level of creating new conditioned reflex connections. The method of tibial neuromodulation is also effective. Neuromodulation is a process in which an electric current through one nerve pathway modulates pre-existing activity in other nerve pathways or centers. Percutaneous electrical stimulation of the posterior tibial nerve is used in functional diseases of the pelvic organs, since fibers from the II and III sacral segments of the spinal cord pass through the posterior tibial nerve, which play a significant role in the innervation of the rectum, bladder and their sphincters. It has been proved that the muscle structures of the disabled anal sphincter can respond to the right therapy, increasing both the tone and the strength of volitional contractions [192,193]. Stimulation of the tibial nerve is carried out using a cutaneous stimulating electrode, which allows the patient to continue the course of treatment independently at home after a course of preliminary training. In this case, the course of treatment with daily stimulation sessions can be extended up to 1–3 months. The effectiveness of BFB therapy is monitored before and at the end of each course of procedures by a comprehensive physiological test of the function of the anal sphincter. With the improvement of the tone and contractility of the anal sphincters, it is possible to raise the question of performing reconstructive and restorative surgery aimed at resuming the natural passage through the gastrointestinal tract.

5. PREVENTION AND DISPENSARY SURVEILLANCE, MEDICAL INDICATIONS AND CONTRAINDICATIONS TO THE USE OF PREVENTION METHODS

*Ulcerative colitis is characterized by a chronic recurrent course. Dispensary surveillance for UC is carried out for life. The purpose of dispensary follow up is, first of all, the prevention of colorectal cancer. In most patients in clinical remission, colonoscopy should be performed at least every 3 years. In some patients, the frequency of dispensary follow-up with colonoscopy may be different. The specifics of monitoring patients receiving immunosuppressants and/or biological drugs include the prevention of opportunistic infections. Risk factors for the development of opportunistic infections include: taking prednisolone ** 20 mg per 24 hours or more for 2 weeks, taking immunosuppressants (AZA**, MP**, MT**) and biological drugs, age over 50 years, concomitant*

diseases (chronic lung diseases, alcoholism, organic brain diseases, diabetes mellitus).

Patients should be explained the need for constant medication, since compliance with the prescriptions for therapy significantly (2–2.5 times) reduces the frequency of exacerbations, and the therapy itself is a method of chemoprophylaxis of colorectal cancer.

• Mandatory vaccination is **recommended** for all patients in accordance with the European Consensus on the Prevention, Diagnosis and Treatment of opportunistic infections in IBD for their prevention. The necessary minimum of vaccination is [194]:

• Recombinant vaccine against HBV;
• Polyvalent inactivated pneumococcal vaccine;
• Trivalent inactivated influenza virus vaccine;
• For women under 26 years old, if there is no virus at the time of screening, vaccination against human papillomavirus is recommended.

Grade of recommendations is C (Level of evidence is 5)

Comment. *Patients during the period of GCS therapy need to monitor the level of glycemia (study of blood glucose levels) to prevent the side effects of glucocorticoids.*

Patients also need monthly monitoring of leukocyte levels (general blood test) and liver enzymes (ALT, AST, bilirubin, alkaline phosphatase, GGT) at the beginning of treatment once every two weeks, then once a month during the first 6 months of therapy, then once every three months to prevent side effects from therapy.

• It is **recommended** for patients, before taking GEBD or TIS and further every 6 months, to consult a phthisiatrician and do screening for tuberculosis (quantiferon test, and if it is impossible, an intradermal test with a tuberculosis allergen — Mantoux test, diaskin test) for the diagnosis of tuberculosis [195].

Grade of recommendations is C (Level of evidence is 5)

Comment. *Female patients with UC need an annual consultation with a gynecologist and screening of cervical cancer (Papanicolau cytology) to diagnose intraepithelial neoplasia of the cervix [209].*

• It is **recommended** that patients before the administration of immunosuppressive therapy, including GEBD or TIS, and against the background of treatment, make a screening for the diagnosis of comorbidities in accordance with professional clinical recommendations:

1) For the markers of viral hepatitis (Determination of antibodies to hepatitis C virus in the blood; Determination of antibodies to the surface antigen (HBsAg) of hepatitis B virus in the blood) [194].
2) For human immunodeficiency (Determination of antibodies of classes M, G (IgM, IgG) to the human immunodeficiency virus HIV-1 in the blood; Determination of antibodies of classes M, G (IgM, IgG) to the human immunodeficiency virus HIV-2 in the blood) [194].
3) For syphilis (Determination of antibodies to pale treponema in non-treponema tests (RPR, RMP) (qualitative and semi-quantitative study) in blood serum).

Grade of recommendations is C (Level of evidence is 5)

• It is **recommended** for all patients to perform a stools test for calprotectin level and/or proctoscopy every 6 months in order to evaluate the effectiveness of the therapy [197–202].

Grade of recommendations is C (Level of evidence is 4)

Comment. *From the point of view of the long-term prognosis of the course of UC, it is advisable to regularly assess the presence of endoscopic remission (healing of the mucous membrane).*

6. ORGANIZATION OF MEDICAL CARE

Medical care, with the exception of medical care within the framework of clinical testing, in accordance with Federal Law No. 323-FL of 21.11.2011 (ed. of 25.05.2019) "On the basics of protecting the health of citizens in the Russian Federation", Decree of the Government of the Russian Federation No. 1968 of 17.11.2021 "On approval of the rules for the phased transition of medical organizations to medical care based on clinical recommendations developed and approved in accordance with parts 3, 4, 6–9 and 11 of article 37 of the Federal Law "On the basics of protecting the health of citizens in the Russian Federation" is organized and provided:

1) In accordance with the regulations on the organization of medical care by type of medical

care, which is approved by the authorized federal executive authority;
2) In accordance with the procedures for providing assistance in the profiles "gastroenterology", "coloproctology", mandatory for execution on the territory of the Russian Federation by all medical organizations;
3) Based on the present clinical recommendations;
4) Taking into account the standards of medical care approved by the authorized federal executive authority.

Primary specialized medical and sanitary care for patients with UC is provided by a gastroenterologist, a coloproctologist and other specialist doctors in medical organizations licensed to provide appropriate types of medical activities.

In case of suspicion or detection of ulcerative colitis in a patient, internists, district internists, general practitioners (family doctors), specialist doctors, secondary medical workers, in accordance with the established procedure, refer the patient for consultation to a medical organization that has an office of a gastroenterologist, a coloproctologist, and/or an outpatient gastroenterology center (unit), and/or outpatient coloproctology center (unit), and/or center for the diagnosis and treatment of inflammatory bowel diseases (if present in the subject, organized on a functional basis) to provide him/her with primary specialized health care. Consultation in the specified structural divisions of the medical organization should be carried out no later than 15 working days from the date of issuance of the referral for consultation, and in cases of severe ulcerative colitis no later than 3 working days from the date of issuance of the referral for consultation.

A gastroenterologist, a coloproctologist of a medical organization that includes an office of a gastroenterologist, a coloproctologist, an outpatient gastroenterology center (unit), an outpatient coloproctology center (unit), a center for the diagnosis and treatment of inflammatory bowel diseases, organizes timely qualified examination and treatment of the patient, including determining the severity of the inflammatory process, the extent of the lesion, the presence of intestinal and extra-intestinal manifestations, including the taking of biopsy material.

If treatment and in-depth examination in inpatient conditions are necessary, the patient is referred by the attending physician to the gastroenterology unit, coloproctology unit, the center for diagnosis and treatment of inflammatory bowel diseases or another medical organization that provides medical care in inpatient conditions to patients in the profile "gastroenterology", "coloproctology".

If ulcerative colitis is suspected and (or) detected in a patient during the provision of emergency medical care, such patients are transferred or referred to medical organizations providing medical care in the profile of "gastroenterology", "coloproctology" to determine the tactics of management and the need to additionally use other methods of specialized treatment, including targeted biological therapy.

A gastroenterologist, a coloproctologist of a medical organization that includes an office of a gastroenterologist, a coloproctologist, an outpatient gastroenterology center (unit), an outpatient coloproctology center (unit), a center for the diagnosis and treatment of inflammatory bowel diseases directs the patient to medical organizations that have inpatient medical care in their as part of the gastroenterology unit and/or coloproctology unit, and/or a center for the diagnosis and treatment of inflammatory bowel diseases to clarify the diagnosis (in case it is impossible to establish a diagnosis in the provision of primary specialized medical care) and the provision of specialized, including high-tech, medical care.

The deadline for the start of specialized, with the exception of high-tech, medical care is determined by the decision of the commission for the selection of patients for hospitalization, depending on the severity of ulcerative colitis, the nature of the course, the prevalence of the inflammatory process, should not exceed 30 calendar days from the date of the referral for hospitalization.

Specialized, including high-tech, medical care for ulcerative colitis is provided by gastroenterologists, coloproctologists in medical organizations that have a gastroenterology unit and/or a coloproctology unit, and/or a center for the diagnosis and treatment of inflammatory bowel diseases, licensed, the necessary material and technical base, certified specialists, in inpatient and daytime

hospital conditions and includes prevention, diagnosis, treatment of ulcerative colitis, requiring the use of special methods and complex unique medical technologies, as well as medical rehabilitation.

Indications for hospitalization in a 24h or daytime hospital of a medical organization providing specialized, including high-tech medical care for ulcerative colitis are determined by a gastroenterologist and/or a coloproctologist with a multidisciplinary consultation, if necessary.

The indication for hospitalization to a medical organization in an emergency or urgent form is:

1) The presence of complications of ulcerative colitis that require specialized medical care in an emergency and urgent form;
2) The presence of complications of treatment (surgery, biological therapy, hormonal and cytostatic therapy, etc.) of ulcerative colitis.

The indication for elective hospitalization to a medical organization:

1) The need to perform complex interventional diagnostic medical interventions that require follow-up in a 24-hour or daytime hospital;
2) The presence of indications for specialized treatment of ulcerative colitis (surgery, hormonal and cytostatic therapy, biological and targeted therapy), requiring observation in a 24h or daytime hospital.

The indication for the patient's discharge from the medical organization is:

1) Completion of a course of treatment, or one of the stages of providing specialized, including high-tech medical care, in a 24h or daytime hospital, provided there are no complications of treatment requiring medical correction and/or medical interventions in a hospital setting;
2) Refusal of the patient or his/her legal representative from specialized, including high-tech medical care in a 24h or daytime hospital, established by the council of a medical organization providing treatment for ulcerative colitis, provided there are no complications of the underlying disease and/or treatment requiring medical correction and/or medical interventions in inpatient conditions;
3) The need to transfer the patient to another medical organization according to the appropriate profile of medical care. The conclusion on the expediency of transferring the patient to a specialized medical organization is carried out after a preliminary consultation on the provided medical documents and/or a preliminary examination of the patient by doctors-specialists of the medical organization to which the transfer is planned.

7. ADDITIONAL INFORMATION AFFECTING THE COURSE AND OUTCOME OF THE DISEASE

The risk of severe attack of UC during life is 15%, while the probability of a severe attack is higher in patients with total affected large intestine. If adequate anti-relapse therapy is carried out within 5 years, attacks can be avoided in half of patients, and within 10 years — in 20% of patients. During the first year after diagnosis, the probability of colectomy is 4–9% (with a severe attack — about 50%), in the future, with each year of the disease, the risk of colectomy increases by 1%. Risk factors for the aggressive course of UC are the progression of the lesion from distal (proctitis) to total, primary sclerosing cholangitis, as well as childhood and adolescence at the time of the onset of the disease. Pregnancy planning should be carried out during the period of IBD remission, which makes it possible to improve pregnancy outcomes. The use of most drugs for the treatment of IBD by pregnant women is associated with a low risk of adverse effects on the fetus, with the exception of methotrexate and 5-ASA preparations containing dibutyl phthalate. The abolition of anti-TNF or the transition to monotherapy is possible only in a limited number of patients with a low risk of IBD reactivation. Treatment with genetically engineered biological drugs that are not contraindicated during pregnancy (see the instructions for use) can be continued if the benefits to the mother exceed the potential risks to the fetus.

Reducing the risks associated with the administration of GCS is achieved by strict adherence to the principles of hormone therapy. GCS cannot be used as a maintenance therapy.

When prescribing hormone therapy, the following should be taken into account:

- Gradual reduction of the dose of steroids until complete withdrawal is strictly mandatory;
- The total duration of hormone therapy should not exceed 12 weeks;

• Concomitant intake of calcium and vitamin D preparations is mandatory;
• During the treatment period, regular monitoring of blood glucose levels is necessary.

Patients who have had an intestinal stoma formed as a result of surgical treatment may require consultation and supervision by a specialist in the rehabilitation of stomatized patients.

CRITERIA FOR ASSESSING THE QUALITY OF MEDICAL CARE

Criteria for assessing the quality of primary health care for adults with ulcerative colitis

№ п/п	Quality assessment criteria	Performance assessment
1.	An administration (examination, consultation) of a gastroenterologist and/or a coloproctologist with mandatory transrectal digital examination (at diagnosis) was performed	Yes/No
2.	Colonoscopy or rectosigmoidoscopy was performed (upon diagnosis)	Yes/No
3.	Ultrasound examination of abdominal organs (complex) was performed (at diagnosis)	Yes/No
4.	Fecal examination for the presence of the toxin *Clostridioides difficile* or immunochromatographic rapid examination of feces for toxins A and B of *Clostridioides difficile* or determination of the DNA of the pathogen *Clostridioides difficile* in fecal samples by PCR (in acute ulcerative colitis and/or suspected of this pathology) was performed	Yes/No
5.	Therapy with drugs of the aminosalicylic acid group and similar drugs or glucocorticosteroids for topical use has been prescribed	Yes/No

Criteria for assessing the quality of specialized medical care for adults with ulcerative colitis

№ п/п	Quality assessment criteria	Performance assessment
1.	An administration (examination, consultation) of a gastroenterologist and/or a coloproctologist with mandatory transrectal digital examination (at diagnosis) was performed	Yes/No
2.	Colonoscopy was performed (if it was not performed on an outpatient basis earlier during the previous 12 months)	Yes/No
3.	Ultrasound examination of the abdominal cavity organs (complex) was performed (at diagnosis, if it was not performed on an outpatient basis)	Yes/No
4.	A biopsy of the colorectal mucosa in the affected area was performed (upon diagnosis, if it was not performed on an outpatient basis or if the previously established diagnosis is doubtful, except for the stage of very high activity of the disease)	Yes/No
5.	Therapy was performed with drugs of the 5-aminosalicylic acid group and similar drugs and/ or systemic glucocorticosteroids and/or other immunosuppressants and/or inhibitors of tumor necrosis factor alpha (TNF-alpha) or ustekinumab or vedolizumab or tofacitinib or upadacitinib or ozanimodomi / or surgical intervention (depending on medical indications and in the absence of medical contraindications)	Yes/No

Clinical recommendations on the diagnosis and treatment of ulcerative colitis were discussed at a meeting of the profile commission on the specialty “Coloproctology” on October 8, 2022 within the framework of the All-Russian Scientific and Practical conference with international participation of “Congress of Coloproctologists of Russia”, at a meeting of the Commission in surgical sciences of the Scientific Council of the OMedS RAS on November 25, 2022 within the XVI All-Russian conference with international participation of “Levitan Readings”

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Results of multicenter observational study «predictors of colectomy in patients with «extremely severe» ulcerative colitis

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ABSTRACT *AIM: to improve the results of treatment of "extremely severe" ulcerative colitis (UC).*
PATIENTS AND METHODS: a multicenter observational prospective "case-control" study was conducted. The study included 71 patients with "extremely severe" UC from June 2019 to October 2021. All patients underwent conservative treatment in accordance with current clinical guidelines. Evaluation of the effectiveness of treatment was carried out on the 3rd and 7th days of therapy, a "response" or "no response" to steroid therapy was stated.
RESULTS: a total of 48 (68%) patients underwent surgery during hospital stay. Twenty-three (32%) patients "responded" to conservative treatment and were discharged without colectomy. A reliable independent predictor of colectomy at the time of hospital stay was the level of albumin less than 29 g/l (OR = 8.6; 95% CI: 2.5–39.9; p = 0.002). On day 3, the reliable predictors were the level of C-reactive protein over 40 mg/l (OR = 9; 95% CI: 2.4–46.1; p = 0.003) and the Mayo index above 7 points (OR = 13.3; 95% CI: 3.3–75.7; p = 0.0009).
CONCLUSION: the study demonstrated that the only reliable and independent predictor of colectomy at admission to the clinic is the level of albumin less than 29 g/l. Reliable factors that make it possible to evaluate and predict the effectiveness of therapy are the level of C-reactive protein more than 40 mg/l and the Mayo index above 7 points on the 3rd day of therapy, as well as the level of C-reactive protein above 30 mg/l on the 7th day.

KEYWORDS: *ulcerative colitis, acute severe ulcerative colitis, colectomy, predictors of colectomy*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

According to a systematic review of the literature by Zhao M. et al., in 2021, the incidence of ulcerative colitis (UC) continued to grow and reached 44 cases per 100 000 people in developed countries. The authors of the review also note that approximately 30% of patients with the onset of the disease have a severe attack and develop a total lesion of the mucosal layer of the large intestine [1]. During the first year after the manifestation, 35% of patients are admitted for potentially life-threatening severe UC attack [2]. At the same time, up to 23% of such patients undergo radical surgery — colectomy within the first two years after the onset of the disease [2].

Surgery for patients with severe UC attack, according to a cohort study by Leeds L., et al., is associated with a high rate of postoperative complications, reaching 60% [3]. This is largely due to metabolic disorders, and, above all, to hypoalbuminemia [4]. Thus, with an albumin level of less

than 30 g/l, postoperative mortality can reach 6% [5]. Due to the high risk of adverse outcomes in patients with severe UC attack, it is advisable to select a group of patients whose surgery should be performed earlier than provided for by clinical guidelines.

In this regard, in 2017, the Russian Association of Coloproctology and the Russian Association of Gastroenterology proposed to distinguish out an "extremely severe" UC attack [6].

As a retrospective study conducted earlier in our center showed, the presence of a characteristic endoscopic picture of extensive ulcers with "islands" of mucosal layer of the large intestine, the level of albumin less than 31 g/l and hemoglobin less than 107 g/l can be objective criteria for an "acute severe" UC attack. With the combination of these predictors, the risk of colectomy was 100% [7].

AIM

The purpose of this study is to improve the results of treatment of patients with "extremely severe" UC attack.

PATIENTS AND METHODS

A multicenter observational prospective case-control study was initiated at the Ryzhikh National Medical Research Center of Coloproctology.

Two regional centers participated: the Coloproctology Unit of Samara State Medical Clinic at Samara Medical University and Alexandro-Mariinsky Regional Clinical Hospital (Astrakhan). The incidence of colectomy and acute intestinal complications of UC, and total mortality were studied. It was also planned to identify predictors of colectomy.

From June 2019 to October 2021, 71 patients over the age of 18 were included in the study in the presence of acute severe UC attack diagnosed at the prehospital stage (Table 1). To this end, all patients with a clinical picture of severe UC attack at the time of admission underwent sigmoscopy without bowel cleansing. Upon detection of extensive, merging ulcerative defects with the formation of "islands" of the mucosal layer, at least in one anatomical part of the large intestine, a diagnosis of "acute severe" UC attack was concluded. The criteria for non-inclusion were:

1) Acute intestinal complications of UC (toxic dilation, perforation of the colon, profuse intestinal bleeding);
2) Ineffectiveness of conservative treatment (hormonal resistance and dependence, loss of the effect of biological therapy).

Among all the patients included in the study, patients with total colitis were mainly registered — 65 (91.0%). At the same time, 30 (42.0%) patients had the onset of the disease, and the median duration of the history of UC was 12 (2.5) months. Treatment with systemic steroids previously received 45 (63.0%) patients, thiopurines — 23 (32.0%) patients, and biological therapy was performed in 11 (16.0%) cases.

Association of ulcerative colitis with cytomegalovirus infection (CMV) verified in 23 (35.0%) cases. The presence of CMV infection was detected by PCR in biopsies of the mucosa of the large intestine taken during the first sigmoscopy. The median of the UC severity Mayo index at the admission to the clinic was the maximum value of 9 points (9.9). It is worth noting that the Mayo severity index was calculated in an abbreviated version, without taking into account the endoscopic picture. The medians and mean values of laboratory parameters estimated at the admission of patients to the clinic and at different stages of treatment are presented in Table 1.

Statistical Analysis

Descriptive variables are presented as absolute values for categorical data. Numerical variables with the correct distribution are presented as an arithmetic mean with the standard deviation (± SD). In cases of incorrect distribution, the values are represented by medians indicating interquartile intervals (25%, 75%).

After dividing the patients into 2 groups: surgical (case) and conservative (control), a comparative analysis of all variables was performed using t-test, nonparametric Mann-Whitney test and the Fisher exact test. Before factor analysis, a ROC analysis was performed for numerical variables, as a result of which critical diagnostic values of

Table 1. *Descriptive statistics*

Variables	Value
Male Female	43 (61%) 28 (39%)
Me of age, years	35 (29, 48)
Me of Body Mass Index, kg/m^2	21 (19, 25)
The nature of the lesion of the mucosal layerof the large intestine: Total colitis Left-sided colitis	 65 (91%) 6 (9%)
The nature of the UC course: Acute Chronic (continuous and recurrent)	 30 (42%) 41 (58%)
Me of duration of anamnesis of UC, months	12 (2, 50)
Drug therapy in the anamnesis: Systemic glucocorticosteroids Thiopurines Inhibitor of tumor necrosis factor α Integrin a4ß3 inhibitor	 45 (63%) 23 (32%) 9 (13%) 2 (3%)
Association of colitis with cytomegalovirus infection	25 (35%)
Me of the number of copies of PCR CMV infection	0 (0, 8300)
Me of the Mayo index at admission, points	9 (9, 9)
Average hemoglobin level at admission, g/l	104 (± 22)
Me of albumin level at admission, g/l	30 (26, 31)
Me of level of C-reactive protein upon admission, mg/l	100 (48, 142)
The average value of the Mayo index on the 3rd day of therapy, points	6 (± 1.5)
Me of albumin level on the 3rd day of therapy, g/l	29 (25, 31)
Me of hemoglobin level on the 3rd day of therapy, g/l	99 (88, 115)
Me of C-reactive protein level on the 3rd day of therapy, mg/l	34 (12, 62)
Me of stool frequency on the 7th day of therapy	2 (0, 5)
Average albumin level on the 7th day of therapy, g/l	29 (± 4.3)
Average hemoglobin level on the 7th day of therapy, g/l	107 (± 17)
Me of C-reactive protein level on day 7 of therapy, mg/l	11 (6, 35)

**Me — Median*

predictors were obtained, and the data were converted to binary (yes/no).

Predictors were selected for a factor analysis based on the results of comparative and ROC analyses: age, albumin and C-reactive protein levels at admission; albumin, C-reactive protein levels and the value of the Mayo index on day 3 of the therapy; stool with blood, albumin, hemoglobin and C-reactive protein levels on day 7 of prednisolone treatment. A univariate analysis was performed, the values of the odds ratio for all predictors were obtained. A multivariate analysis was performed using the logistic regression for the identified predictors at the time of admission. Also, a multivariate analysis was carried out separately for predictors on the 3rd and 7th days of steroid therapy. Statistical significance was assumed at $p < 0.05$. Given the observational nature of the study, no preliminary calculation of the sample size was made. Statistical analysis was performed using the software "GraphPadPrism 9.2.0".

RESULTS

To all patients ($n = 71$) included in the study was initiated the steroid therapy with prednisolone at a dosage of 2 mg/kg per 24 hours in accordance with clinical recommendations. To assess the effectiveness of the steroid therapy, a reduced Mayo index of UC activity was used, without taking into account the endoscopic picture. Prior to evaluating the effect of the prednisolone treatment, 2 (3.0%) patients were operated on urgently on day 3 due to the development of acute intestinal complications (toxic dilation and perforation of the colon).

Table 2. *Results of comparative analysis of variables in groups*

Variables	Surgical Treatment n = 48	Conservative Therapy n = 23	Value p
Male gender Female gender	29 (60%) 19 (40%)	14 (61%) 9 (39%)	0,9 0.9
Me of age, years	37 (29, 51)	30 (25, 38)	0.02*
Me of body mass index, kg/m^2	21,5 (18, 26)	21 (20, 24)	0.9
Total lesion of UC	44 (92%)	21 (91%)	0.9
Acute course of UC	23 (48%)	7 (30%)	0.3
Me of duration of anamnesis, months	8 (2, 46)	13 (3, 50)	0.3
Therapy in anamnesis: Systemic steroids Thiopurines Biological therapy	 30 (62%) 13 (27%) 6 (12%)	 15 (65%) 10 (43%) 3 (13%)	 0.9 0.2 0.9
Me of PCR CMV infection, copies × 10^5	0 (0–9500)	0 (0–0)	0.05*
Me of the Mayo index at admission, 9 points	9 (9, 9)	9 (8, 9)	0.05*
Average hemoglobin level at admission, g/l	103 (± 22)	105 (± 22)	0.7
Me of albumin level at admission, g/l	28 (25, 31)	31 (30, 34)	0.0002*
Me of level of C-reactive protein at admission, mg/l	95 (51, 139)	106 (16, 160)	0.8
"Response" on day 3	8 (17%)	14 (61%)	0.0007*
The average value of the Mayo index on day 3, 9 points	7 (± 1)	5 (± 1)	0.0001*
Me of albumin level on day 3, g/l	28 (23, 30)	30 (27, 32)	0.009*
Average hemoglobin level on day 3, g/l	100 (± 19)	103 (± 18)	0.5
Me of C-reactive protein level on day 3, mg/l	36 (19, 67)	13 (7, 61)	0.03*
Meof incidence of stool with blood on day 7	4 (1, 5)	0 (0, 2)	0.0001*
Average albumin level on day 7, g/l	28 (± 4)	32 (± 3)	0.0002*
Average hemoglobin level on day 7, g/l	102 (± 19)	112 (± 13)	0.03*
Me of C-reactive protein level on day 7, mg/l	22 (9, 49)	8 (2, 11)	0.0003*
2nd line therapy: Infliximab	 1 (2%)	 4 (17%)	 0.03*
Tofacitinib	1 (2%)	11 (48%)	0.0001*

**Me –p < 0.005*

In this regard, the effectiveness of the treatment on day 3 was evaluated in 69 patients. A decrease in the Mayo index by 30% or more, indicating the effectiveness of prednisolone on the 3rd day of the treatment, was registered in 22/69 (32%) patients and they all continued therapy at the same dosage. A decrease in the Mayo index by less than 30% from the initial one, or its retention at the same level or increase, was interpreted as a "lack of response" to the prednisolone and was noted in 47/69 (68%) patients.

Among 47 patients who were found to have "no response" to the steroid therapy on day 3, 35/47 (75%) patients continued treatment with prednisolone in the previous dosages, and in the remaining 12/47 (25%) cases, colectomy was performed urgently due to the worse of the patients' status.

Further, in the interval between the 3rd and 7th days, 9 more patients were subjected to colectomy for urgent indications, also due to the aggravation of clinical manifestations. In total, in 21/71 (30%) cases, the revaluation on day 7 was not carried out due to surgical treatment before the specified period.

Thus, among all the patients, the effectiveness of the therapy was evaluated on day 7 in 50 (70%) patients based on the calculation of the frequency of stool with blood, as well as a reassessment of the endoscopic picture and laboratory parameters. The positive effect of the treatment on day 7 was registered in 28/50 (56%) patients, and the absence of effect was observed in 22/50 (44%) cases.

It is worth noting that 8/50 (16%) patients were discharged after reducing the dose of prednisolone on maintenance therapy with salicylates, thiopurines. Line 2 therapy was initiated in 17/50 (34%) patients: infliximab in 5 (10.0%)

Table 3. *ROC analysis for continuous variables*

Predictor	AUC (95% CI)	Value p	Sensitivity (95% CI)	Specificity (95% CI)	Critical level
Age	0.66 (0.53–0.79)	0.03	31 (20–45)	87 (68–95)	> 47 years
PCR of CMV (copies)	0.62 (0.49–0.75)	0.09	–	–	–
Albumin level at admission	0.76 (0.64–0.83)	0.0004	56 (42–60)	87 (68–95)	< 29g/l
Hemoglobin level at admission	0.53 (0.39–0.68)	0.63	–	–	–
The level of C-reactive protein at admission	0.52 (0.36–0.67)	0.8	–	–	–
Mayo Index at admission	0.6 (0.46–0.75)	0.1	–	–	–
Albumin level on day 3	0.69 (0.56–0.82)	0.001	26 (16–40)	95 (79–99)	< 24 g/l
Hemoglobin level on day 3	0.55 (0.4–0.69)	0.5	–	–	–
The level of CRP on day 3	0.66 (0.5–0.81)	0.03	83 (69–91)	61 (41–78)	> 40 mg/l
Mayo index on day 3	0.78 (0.67–0.88)	0.0002	43.5 (30–58)	100 (86–100)	> 7 points
Incidence of stool with blood on day 7	0.8 (0.68–0.92)	0.0002	46 (29–64)	100 (86–100)	> 4 times
Albumin level on day 7	0.78 (0.66–0.9)	0.0006	37 (21–56)	100 (86–100)	< 26 g/l
Hemoglobin level on day 7	0.68 (0.53–0.84)	0.02	41 (24–59)	95 (79–99)	< 94 g/l
CRP level on day 7	0.79 (0.66–0.92)	0.0004	44 (28–63)	95 (79–99)	> 30 mg/l

cases, and tofacitinib in 12 (24.0%) patients. After 7 days of therapy, surgery was carried out in another 27/50 (54%) cases due to "loss of response", futility of further drug therapy or the worse patient status.

Among all the patients, acute intestinal complications developed in 7 (10%) cases, steroid resistance in 39 (55.0%) patients, and ineffectiveness of the 2ndline therapy in 2 (3.0%) patients. In total, 48 (68.0%) patients underwent surgery. The fatal outcome occurred in 2 (3.0%) cases: one patient developed pulmonary embolism after colectomy, the other — postoperative secondary peritonitis and sepsis.

A comparative analysis of categorical and numerical data was carried out between the group of surgical (48 patients) and conservative treatment (23 patients). By gender, extent of the lesion, the nature of the course of UC, body mass index — the groups did not differ statistically significantly (Table 2). The "response" on the 3dday of the therapy was significantly less in the surgical group — 17%, compared with the conservative group — 61% (p = 0.0007), respectively. Also, on the 7th day of the therapy, the effect of the therapy in the colectomy group was observed in 30%, compared with the conservative treatment group in 87% (p = 0.0001), respectively. The biological therapy was significantly more often prescribed in the conservative treatment group: tofacitinib — 2% in the colectomy group, compared with the drug therapy group — 48%, p = 0.0001 and infliximab — 2% in the surgical group, compared with the drug treatment group — 17%, p = 0.03, respectively.

When comparing laboratory parameters, the median albumin level at the time of admission was significantly lower in the surgical group — 28 g/l than in the conservative therapy group — 31 g/l (p = 0.002). On the 3rd day of the steroid therapy, the median albumin level was also lower in the surgical group — 28 g/l compared with the conservative group — 30 g/l (p = 0.009). The median level of C-reactive protein was significantly higher in the surgical group — 36 mg/l than in the conservative group — 13 mg/l (p = 0.03), respectively.

On day 7, the same trend persisted as on day 3 of the therapy. Thus, the average albumin level was significantly lower in the surgical group — 28 g/l, compared with 32 g/l in the conservative group (p = 0.0002). The average hemoglobin level was significantly lower in the surgical group — 102 g/l than in the conservative group — 112 g/l (p = 0.03). The median of C-reactive protein, as well as on day 3, was significantly higher in the surgical group — 22 mg/l, compared with patients from the conservative group — 8 mg/l (p = 0.0003), respectively.

For the subsequent factor analysis, ROC curves are constructed and the critical values of the selected numerical variables are determined (Table 3).

The following variables had significant diagnostic value in predicting colectomy: the age of patients older than 47 years (p = 0.03) and the level of albumin at admission less than 29 g/l (p = 0.0004). On the 3rd day of the therapy: the level of albumin

Table 4. *Univariate and multivariate analyses for predictors of colectomy during steroid therapy*

Predictor	Univariate Analysis		Multivariate Analysis	
	OR (95% CI)	*p*-value	OR (95% CI)	*p*-value
At admission				
Age > 47years	3 (0.8–10.7)	0.1	–	–
Albumin less than 29 g/l	8.6 (2.4–29.3)	0.0007	8.6 (2.5–39.9)	0.002*
On the 3rd day of steroid therapy:				
Albumin less than 24 g/l	7.7 (1.2–86)	0.05	5.4 (0.6–134.8)	0.2
C-reactive protein more than 40 mg/l	7.4 (2.5–22)	0.0007	9 (2.4–46.1)	0.003*
The Mayo index more than 7 points	4.9 (1.8–13.2)	0.003	13.3 (3.3–75.7)	0.0009*
On the 7th day of steroid therapy:				
Stool with blood more than 4 times	6.6 (1.5–23.9)	0.007	3.4 (0.6–21.1)	0.1
Albumin less than 26 g/l	5.7 (1.4–28.2)	0.04	1.2 (0.1–11.9)	0.8
Hemoglobin less than 94 g/l	7.6 (1.6–36.5)	0.01	19 (2.5–120.6)	0.01*
C-reactive protein more than 30 mg/l	9.5 (2.1–45.4)	0.005	8.3 (1.5–68.5)	0.02*

less than 24 g/l ($p = 0.001$) and C-reactive protein above 40 mg/l ($p = 0.03$), as well as the value of the Mayo index above 7 points ($p = 0.0002$).

On the 7th day of the therapy, significant diagnostic value was demonstrated: the incidence of stool with blood more than 4 times per 24 hours ($p = 0.0002$), albumin level less than 26 g/l ($p = 0.0006$), hemoglobin level less than 94 g/l ($p = 0.02$), C-reactive protein level more than 30 mg/l ($p = 0.0004$). The presented variables were converted to a binary data type depending on the critical values obtained (yes/no), after which a univariate analysis was performed.

As a result of the univariate analysis aimed at identifying possible predictors of colectomy, a reliable predictor at admission was an albumin level of less than 29 g/l (OR — 8.6 95% CI: 2.4–29.4, $p = 0.0007$).

On the 3rd day of the therapy, the following were determined as predictors of colectomy: the Mayo index above 8 points (OR — 4.9 95% CI: 1.8–13.2, $p = 0.003$), albumin level less than 24 g/l (OR — 7.8 95% CI: 1.2–86.6, $p = 0.05$), C-reactive protein level above 40 mg/l (OR — 7.4 95% CI: 2.5–22.1, $p = 0.0007$).

For 7th day of the therapy, the following predictors of colectomy were revealed: stool with blood more often than 4 times per 24 hours (OR — 6.6 95% CI: 1.5–23.9, $p = 0.007$), albumin level less than 25 g/l (OR — 5.7 95% CI: 1.2–28.2, $p = 0.04$), the level of C-reactive protein above 30 mg/l (OR — 9.5 95% CI: 2.1–45.4, $p = 0.005$), hemoglobin level less than 94 g/l (OR — 7.6 95% CI: 1.6–36.5, $p = 0.01$).

Reliable predictors of colectomy determined in the univariate analysis were included in the multivariate analysis, and logistic regression was performed. It is important to note that the logistic regression formula is compiled separately for predictors of colectomy at admission, on the 3rd and 7th days of the therapy (Table 4).

The multivariate analysis revealed that a reliable independent predictor of colectomy at admission was the level of albumin less than 29 g/l (OR — 8.6 95% CI: 2.5–39.9, $p = 0.002$).

On day 3, independent predictors of colectomy were: the level of C-reactive protein more than 40 mg/l (OR — 9,95% CI: 2.4–46.1, $p = 0.003$) and the Mayo index value is above 7 points (OR — 13.3 95% CI: 3.3–75.7, $p = 0.0009$).

On the 7th day of the therapy, independent predictors of colectomy are the level of C-reactive protein more than 30 mg/l (OR — 8.3, 95% CI: 1.5–68.5, $p = 0.02$), as well as the hemoglobin level less than 94 g/l (OR — 19, 95% CI: 2.4–120.6, $p = 0.01$).

DISCUSSION

This is the first Russian observational study of outcomes of treatment in patients with acute severe attack of UC. Since the isolation of “extremely severe attack” of UC in 2017, the rate of colectomy was determined for the first time for this group of patients — 68%, which is significantly more than described in the literature. In recent years, the incidence of colectomy in patients with severe UC attack in different studies varies from 10% to

46% [1,8,9,10]. This range of colectomy rate in the papers is mainly due to the heterogeneity of patients in terms of severity of the disease, history of drug therapy. Traditionally, all authors single out severe UC attack based on the Truelove &Witts criteria.

It is worth noting that according to the Russian clinical guidelines for the treatment and diagnosis of UC, "acute severe" attack is an extreme degree of severity, significantly exceeding the Truelove & Witts criteria [6]. However, in our opinion, such a classification does not allow predicting the outcomes in severe group of patients and, consequently, has no practical significance. In this regard, a combination of traditional the Truelove & Witts criteria with predictors of colectomy could solve the problem of stratification of a group of high-risk patients at the time of initiation of steroid therapy.

The study by Grant, R.C., et al. presents the ACE scale (albumin, C-reactive protein, endoscopy) as a way to objectify the selection of a group of patients at high risk of drug therapy inefficiency. As a result of the analysis, it was shown that with the ACE scale value of 3 points (albumin less than 30 g/l, C-reactive protein more than 50 mg/l and pronounced endoscopic activity), even without taking into account the Truelove & Witts criteria, the incidence of the absence of the effect of steroid therapy is significantly higher and amounted to 78%, compared with 47% ($p > 0.001$) under the traditional classification [9].

The study included patients exclusively with an "extremely severe" UC attack, established on the basis of the Truelove & Witts criteria in combination with an endoscopic picture of extensive ulcerative defects with the formation of mucosal layer "islands" and metabolic disorders. This is due to a significant difference in the rate of colectomy compared with the literature data, and a high incidence of acute intestinal complications of UC during therapy was recorded — 10% and total mortality — 3%.

The most discussed predictor of colectomy today is the level of albumin. It is known that the concentration of serum albumin decreases under the action of pro-inflammatory cytokines, which probably explains the development of adverse outcomes in severe UC attack and, accordingly, allows them to be predicted. So, in a study by a group of authors from Japan — Tanaka M., et al., the albumin level of less than 24.5 g/l was an independent predictor of colectomy (OR = 6.1, 95% CI: 1.83–20.3). Particular interest in the level of albumin is also due to the possibility of predicting the effectiveness of "rescue therapy" with the use of anti-TNF inhibitors. In the experiments by Kevans D., et al., it was demonstrated that a low serum albumin level leads to an acceleration of the clearance of infliximab and shortens the half-life of the drug from the blood, which causes the absence or loss of the effectiveness of the treatment [12]. Given the above, it becomes clear why the level of albumin is a significant predictor in predicting outcomes in patients with severe or acute severe UC attack.

In addition to the albumin level, our study revealed predictors of colectomy on the 3rd and 7th days of steroid therapy. On the 3rd day of prednisolone treatment, reliable predictors were the value of the Mayo index above 7 points and the level of C-reactive protein over 40 mg/l. These factors are of key importance in assessing the effectiveness of steroid therapy, on the basis of which a decision can be made to continue or discontinue drug treatment. Previous prospective studies have demonstrated that an increase in C-reactive protein on the 3rd day of steroid therapy is the most important independent predictor of colectomy in patients with severe UC [13]. The value of the Mayo index above 7 points corresponds to the fact of the lack of effectiveness of the therapy, which has also been repeatedly demonstrated earlier in various studies. In particular, the "Swedish Index" was previously presented, which is essentially a combination of the absence of a clinical response and a high level of C-reactive protein. Our results clearly demonstrate the need for stratification of patients with severe UC attack at the time of initiation of drug therapy. In our opinion, the allocation of a "acute severe attack" is advisable based on a combination of traditional criteria with an endoscopic picture and albumin level. The evidence value of the results obtained is certainly limited by its design. In order to obtain more convincing and highly evidence-based results, further work on this problem is necessary with the conduct of a cohort prospective study.

CONCLUSION

In the group of patients at high risk of adverse outcomes of "extremely severe" UC attack, the rate of colectomy was 68%, the incidence of acute intestinal complications reached 10%, and the overall mortality was much higher than in the population of patients with UC, and amounted to 3% when treated in a specialized institution. A reliable predictor of colectomy, which allows predicting outcomes before starting conservative treatment, is the level of albumin less than 29 g/l at admission to the clinic.

Reliable factors for evaluating the effectiveness of the therapy and predicting its prognosis are the level of C-reactive protein more than 40 mg/l and the value of the Mayo index above 7 points on the 3d day of the therapy, as well as the level of C-reactive protein above 30 mg/l on the 7th day.

AUTHORS CONTRIBUTION

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Efficacy and safety of ustekinumab in Russian patients with moderately to severely active ulcerative colitis: a subanalysis of global phase 3 induction and maintenance studies (UNIFI) up to 3 years

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ABSTRACT *AIM: to evaluate efficacy and safety of ustekinumab in Russian patients with ulcerative colitis in UNIFI study.*
PATIENTS AND METHODS: the UNIFI program (CNTO1275UC03001) consisted of two randomized placebo-controlled trials: an 8-week induction study and a 44-week maintenance study and long-term period. This analysis included patients from 14 Russian centers.
RESULTS: the induction study of the UNIFI program enrolled 74 patients from Russia, 89.2% patients (n = 66) were bionaive. The paper presents the results of bionaive patients. Sixty-six are included in the induction phase: 18 received ustekinumab 130 mg IV, 25 received ustekinumab 6 mg/kg IV, and 23 received a placebo. At week 8 in the groups of patients treated with ustekinumab at doses of 6 mg/kg and 130 mg, clinical remission was achieved in 24.0% and 16.7%, respectively, in the placebo group, the rate was 17.4%. The proportion of patients with clinical responses at week 8 was 68.0%, 50.0% and 39.1% in the ustekinumab 6 mg/kg, 130 mg and placebo groups, respectively. Mucosal healing at week 8 was achieved in 48.0% in the ustekinumab 6 mg/kg group, in 33.3% of patients in the ustekinumab 130 mg group, and in 21.7% of patients in the placebo group. Histoendoscopic mucosal healing at week 8 developed in 27.8% of patients in the ustekinumab 130 mg group, in 24.0% of patients in the ustekinumab 6 mg/kg group, and in 21.7% of patients in the placebo group. Forty bionaive patients were re-randomized for further participation in the maintenance phase: 13 patients received ustekinumab 90 mg subcutaneously every 12 weeks, 12 received ustekinumab every 8 weeks, and 15 received a placebo. At week 44, clinical remission was achieved in 46.2% of ustekinumab every 12 weeks, 75.0% of ustekinumab every 8 weeks (p = 0.054 compared with placebo), and 33.3% of placebo. Mucosal healing achieved in 46.2% of patients in the ustekinumab once every 12 weeks group, in 75.0% of patients in the ustekinumab once every 8 weeks group (p = 0.054 compared with. placebo), and in 33.3% of patients in the placebo group. Histoendoscopic mucosal healing achieved in 46.2% of patients in the ustekinumab once every 12 weeks group, while in the ustekinumab once every 8 weeks group, the percentage of such patients was 75.0% (p = 0.021 compared with placebo) and in the placebo group — 26.7%. Symptomatic remission at week 152 developed in 83.3% in the ustekinumab every 12 weeks group, 81.8% in the ustekinumab every 8 weeks group. In the induction phase decrease of CRP and FCP median levels detected in patients treated with ustekinumab, in the maintenance phase, median levels of laboratory inflammatory markers after induction were sustained by ustekinumab treatment. The rate of steroid-free symptomatic remission at week 152 was consistent with the rate of symptomatic remission. The safety profile of ustekinumab was generally consistent with placebo during all follow up period.
CONCLUSION: subanalysis confirmed short- and long-term efficacy and safety in Russian patients with moderate to severe active ulcerative colitis. The results of subanalysis are consistent with previously obtained data in the population of patients participating in the global UNIFI program.

KEYWORDS: *ulcerative colitis, ustekinumab, biologic therapy, genetically engineered biological agents, steroid-free remission*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease affecting the colon that is characterized by immune inflammation of the intestinal mucosa and usually requires life-long therapy due to its chronic, continuous, or relapsing nature [1–3].

To date, data on the incidence of ulcerative colitis in the Russian Federation are limited. Single epidemiologic studies indicate that the incidence of ulcerative colitis in Russia is 19.3–29.8 cases per 100,000 persons [4]. In real clinical practice, Russian patients with IBD, particularly ulcerative colitis, tend to have a late diagnosis (with the average time to diagnosis of 1.5 years) and initiate treatment, including biologic agents, late in the course of the disease. Moreover, Russian population demonstrates the prevalence of moderately severe and severe forms of ulcerative colitis as well as a high mortality rate [5].

More severe course of ulcerative colitis in Russian patients is evidenced by the data of the international multicenter retrospective and prospective non-interventional observational study INTENT (NCT03532932), which had been conducted in Russia, Belarus and Kazakhstan. According to the study 27,1% of patients with ulcerative colitis had a chronic, continuous disease (without periods of remission lasting for more than 6 months),frequency of complicated forms was 12.9%.[6,7].

Treatment of ulcerative colitis is aimed primarily at achieving and sustaining remission after glucocorticoid withdrawal, preventing UC complications, avoiding surgical intervention. Russian and international guidelines recommend that patients with active, moderate-to-severe ulcerative colitis and inadequate response or intolerability to conventional treatments are prescribed biologic agents [1,2].

When initiating biologic treatments for ulcerative colitis, possible treatment-related risks should be considered, such as the lack of primary response or loss of effectiveness associated with a possibility of disease progression and complications, as well as adverse events that comprise infections, including opportunistic infections, and malignancies, which may result in the withdrawal of a biologic agent [1,8,9]. All these factors underline the importance of a thoughtful choice of the first-line biologic agent.

Interleukins 12 and 23 (IL-12, 23) are two cytokines that play a significant role in inflammatory bowel disease; both promote T-cell differentiation and proliferation via Th-1, 2 and 17 pathways leading to the development of ulcerative colitis and Crohn's disease [10,11].

Ustekinumab is a monoclonal IgG1 antibody with the target the p40 subunit common to the Il-12/Il-23 proteins [12] approved for use in psoriasis, psoriatic arthritis, and Crohn's disease. In 2019, results from the UNIFI study (Study to Evaluate the Safety and Efficacy of Ustekinumab Induction and Maintenance Therapy in Participants With Moderately to Severely Active Ulcerative Colitis CNTO1275UCO3001) were published that demonstrated induction and maintenance therapy with ustekinumab to be safe and effective in patients with active, moderate-to-severe ulcerative colitis, which resulted in its approval for use in patients with ulcerative colitis [13].

AIM

Considering the clinical and epidemiological characteristics of Russian patients with ulcerative colitis and limited data on ustekinumab usage in early lines in ulcerative colitis the aim of this analysis was to assess the effectiveness and safety of ustekinumab in the Russian patients who participated in the UNIFI induction and maintenance studies and were predominantly naïve to treatment with biologics.

PATIENTS AND METHODS

Study population

The Phase 3 UNIFI program (CNTO1275UCO3001) consisted of two randomized, double-blind, placebo-controlled studies under the same protocol: an eight-week induction study and a forty-four-week maintenance study. It was conducted from August 2015 until August 2018 using the same protocol in 244 study sites worldwide. The program enrolled adult patients (aged ⩾ 18) with moderately severe or severe ulcerative colitis (defined as the total Mayo score of 6–12, including an endosciopic subscore ⩾ 2 as determined using central analysis of video endoscopy) that had been diagnosed at least 3 months before screening.

Totally 74 patients from 14 study sites in Russia participated in the UNIFI program, 66 (89.2%) of them were bionaive. The analyses in this paper focus on these bionaive patients.

At study entry, the patients showed inadequate response or intolerability to conventional nonbiologic treatment (i.e., corticosteroids and/or 6-mercaptopurine/azathioprine) or corticosteroid dependence. Key exclusion criteria were imminent risk of colectomy, recent gastrointestinal or intrabdominal surgery or a history of extensive bowel resectionmalignancies, and active infections (including tuberculosis). Aminosalicylates and immunomodulators at stable doses were allowed from induction baseline through week 44 of the maintenance phase. Oral corticosteroids at stable doses could be used during induction.For subjects who were receiving oral corticosteroids on entry into the maintenance study, the investigator was to taper the daily dose of corticosteroids beginning at Week 0 of the maintenance study(For definitions and for more details on the patients, randomization, assessments, and end points, see the Supplementary Appendix, available at NEJM.org.) [13].

Study design

A detailed description of the study design is provided in the articles by Sands B. et al. and Abreu M. et al. [13,14]. At week 0 of the induction study, the patients were randomized in a 1:1:1 ratio to receive a single intravenous (IV) infusion of ustekinumab 130 mg, a weight-range based dose that approxinmated 6 mg/kg of body weight, or placebo. Patients were stratified by previous biologic treatment results (treatment failure — yes or no) and their region of residence (Eastern Europe, Asia, or other countries) in randomization.

Patients who were in clinical response (defined asa decrease from induction baseline in the Mayo score by ⩾ 30% and ⩾ 3 points, with either a decrease from induction baseline in the rectal bleeding subscore ⩾ 1 or a rectal bleeding subscore of 0 or 1) at Week 8 were eligible to enter the maintenance study. Patients who were not in clinical response at Week 8 received either subcutaneous (SC) or IV ustekinumab in a blinded manner as follows: 1) those who initially received ustekinumab IV induction received a ustekinumab SC dose of 90 mg; and 2) those who initially received IV placebo induction received a ustekinumab IV dose of ~6 mg/kg. Patients who were in clinical response at Week 16 were also eligible to enter the maintenance study. Patients who failed to respond to ustekinumab treatment at week 16 were discontinued from further participation.

Patients who achieved clinical response to asingle IV induction dose of ustekinumab were randomized in a 1:1:1 ratio in the maintenance study, stratified by the induction treatment received (ustekinumab 130 mg, ustekinumab 6 mg/kg or placebo with consequent ustekinumab 6 mg/kg), clinical remission status (yes or no, defined as the Mayo score ⩽ 2 without any individual subscore of > 1) at baseline of the maintenance study, and use of oral corticosteroids (yes or no) at baseline of the maintenance study, to receive treatment with SC ustekinumab 90 mg every 12 weeks (q12w), 90 mg every 8 weeks (q8w), or placebo.

Patients who demonstrated a clinical response to placebo IV during the induction study received SC placebo, while those who had shown a delayed response to ustekinumab (at week 16) received SC ustekinumab at the dose of 90 mg q8w during the maintenance study. Patients in these two groups were not randomized. Subjects who completed the safety and efficacy

evaluations at Week 44 and who, in the opinion of the investigator, might benefit from continued treatment had the opportunity to participate in the long-term extension (LTE). The LTE began after the assessments listed for the maintenance Week 44 visit (M-44) were completed and will continue through Week 220.

Study unblinding occurred after the Week 44 analyses were completed. After unblinding, ustekinumab-treated patients continued in the LTE, whereas patients remaining on placebo were discontinued. Patients whose UC disease activity worsened [in the clinical opinion of the investigator] were eligible for a single dose adjustment (starting at Week 56) as follows: placebo SC to ustekinumab 90 mg SC q8w [prior to unblinding]; ustekinumab 90 mg SC q12w to ustekinumab 90 mg SC q8w; ustekinumab 90 mg SC q8w continued on ustekinumab 90 mg SC q8w [sham dose adjustment, prior to unblinding]. Efficacy assessments were conducted every 12 weeks until unblinding and then q8w or q12w at dosing visits.

The duration of the study was approximately one year of induction and maintenance therapy with further follow-up for 3 years in LTE. Study protocols at each study site were approved by the Independent Ethical Committee or the Review Board. Prior to study enrollment, all patients provided written informed consent.

Study endpoints

The primary endpoint in the induction study was clinical remission at week 8. Secondary endpoints at week 8 included mucosal healing (defined as the endoscopy Mayo subscore of 0 or 1), clinical response. Other endpoints included histologic healing (defined as < 5% neutrophils in the epithelium, absence of crypts and no evidence of erosions, ulcerations, or granulation tissue), histo-endoscopic mucosal healing (defined as the endoscopic and histologic healing combined) and faecal calprotectin and CRP levels during induction. [15].

The primary endpoint in the maintenance study was clinical remission at week 44. Secondary endpoints included sustained clinical response at week 44, mucosalhealing at week 44, clinical remission without corticosteroid use at week 44 (defined as clinical remission at week 44 without concomitant corticosteroid use at week 44). Other study endpoints included histo-endoscopic mucosal healing at week 44 and faecal calprotectin and CRP levels through 44 weeks.

Symptomatic remission (Mayo stool frequency subscore of 0 or 1 and a rectal bleeding subscore of 0) and steroid-free symptomatic remission (in symptomatic remission and not receiving corticosteroid) were evaluated in LTE.

Safety assessments included adverse events (AEs), serious AEs, infections and serious infections as assessed by the investigator, as well as infusion/injection-site reactions.

Immunogenicity

Antibodies to UST were evaluated by means of a drug-tolerant electrochemiluminescence assay over time during the study at scheduled visits.

Statistical methods

All analyses for Russian patients were performed as post hoc. Descriptive statistics were reported for baseline characteristics. Dichotomous endpoints were compared between each ustekinumab group and the placebo group using the Fisher exact test. For continuous efficacy endpoints, last observation carried forward was used for missing data, and induction baseline observation was carried forward from the time of first treatment failure (ie, a prohibited change of UC medication, a rescue medication for clinical flare, an ostomy or colectomy, discontinuation of study agent due to lack of efficacy or an AE of worsening of UC disease) onward. For dichotomous endpoints, nonresponder imputation were applied for patients who met treatment failure criteria or had missing data. Dose adjustment in LTE was not considered as a treatment failure. Safety was analyzed according to the period of reporting, ie, induction, maintenance Week 0 though Week 44, maintenance Week 0 through Week 156.

RESULTS

Patients

The induction study of the UNIFI program enrolled 74 patients from Russia: 22 patients received

Table 1. *Baseline characteristics of the Russian population of bionaive patients who were randomized during the induction study*

	Placebo IV	Ustekinumab IV 130 mg	Ustekinumab IV 6 mg/kg*	Combined	Total
Number of bionaive patients enrolled in the study (n)	23	18	25	43	66
UC duration (years)					
Mean (SD)	4,62 (5,26)	4,92 (3,45)	4,71 (4,50)	4,80 (4,045)	4,74 (4,47)
UC anatomy					
Left-sided	20 (87.0%)	11 (61.1%)	19 (76.0%)	30 (69.8%)	50 (75.8%)
Total	3 (13.0%)	7 (38.9%)	6 (24.0%)	13 (30.2%)	16 (24.2%)
UC severity					
Moderate disease (6 ⩽ Mayo score ⩽ 10)	22 (95.7%)	16 (88.9%)	21 (84.0%)	37 (86.0%)	59 (89.4%)
Severe disease (Mayo score > 10)	1 (4.3%)	2 (11.1%)	4 (16.0%)	6 (14.0%)	7 (10.6%)
Mayo Scale (0–12)					
Mean (SD)	8,3 (1,39)	8,7 (1,74)	9,0 (1,43)	8,9 (1,56)	8,7 (1,52)
C-reactive protein (mg/L)					
Mean (SD)	3,56 (5,04)	4,65 (4,66)	6,34 (10,15)	5,64 (8,29)	4,89 (7,31)
Fecal calprotectin (mg/kg)					
Mean (SD)	2428,95 (4863,88)	2637,53 (3726,70)	2176,08 (3191,23)	2367,41 (3385,86)	2388,26 (3908,30)

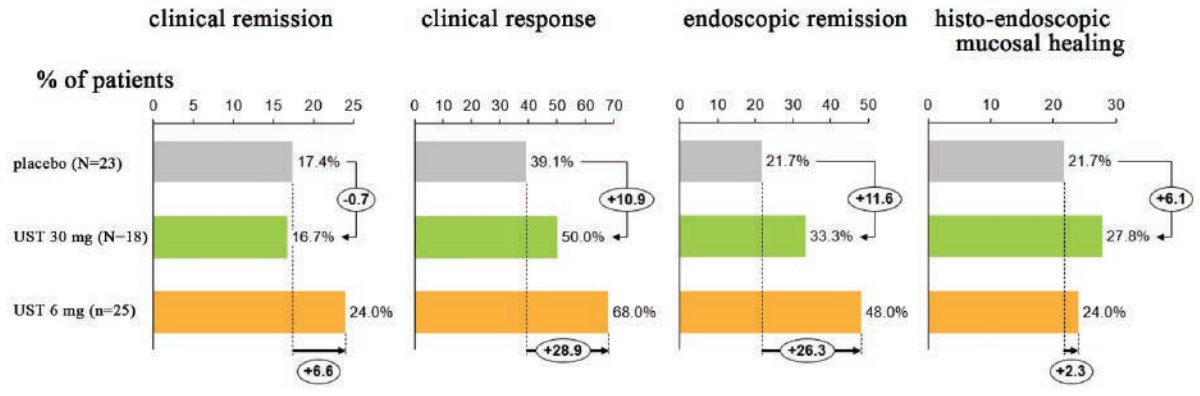

Figure 1. *Effectiveness measures at week 8 of the induction study in bionaive patients*

ustekinumab 130 mg intravenously, 26 patients received ustekinumab 6 mg/kg intravenously, and 26 patients received placebo at Week 0.

Among the study participants, 89.2% patients (n = 66) were bionaive, meaning that they had no history of previous biologic treatment: of these, 18 patients were allocated to the ustekinumab 130 mg group, 25 to the ustekinumab 6 mg/kg group, and 23 patients to the placebo group.

Disease characteristics of bionaive patients who were randomized during the induction study are provided in Table 1. At induction baseline, the mean age of patients was 38.9 years, 59.1% male, disease duration — 4.74 years. Most patients presented with left-sided ulcerative colitis — 75.8% (n = 50), moderately active disease (Mayo index 6–10 points) — 89.4% (n = 59) patients, the mean Mayo score was 8.7, CRP — 4.89 mg/L, faecal calprotectin — 2388.26 mg/kg. Demographics and disease characteristics were generally similar across treatment group in the induction study.

Induction study results

In ustekinumab 6 mg/kg and 130 mg groups clinical remission was observed in 24.0% and 16.7% of patients, respectively, while in the placebo group this outcome was reached by 17.4% of patients (Figure 1).

The proportion of patients with clinical response was 68.0%, 50.0%, and 39.1% for the ustekinumab 6 mg/kg, ustekinumab 130 mg and the placebo groups, respectively.

Mucosal healing was achieved by 48.0% of patients in the ustekinumab 6 mg/kg group, 33.3% of patients in the ustekinumab 130 mg, and 21.7% of patients in the placebo group.

Histo-endoscopic mucosal healing was observed in 27.8% of patients in the ustekinumab 130 mg group, 24.0% of patients in the ustekinumab 6 mg/kg group, and 21.7% of patients in the placebo group. Among Russian bionaive patients, the proportion of subjects in the ustekinumab 6 mg/kg group who achieved clinical remission, clinical response and mucosal healing at week 8 was numerically greater compared to both the placebo group and the ustekinumab 130 mg group.

MAINTENANCE STUDY RESULTS

Out of a total of 66 Russian bionaive patients who participated in the induction study, 40 patients were re-randomized in the maintenance study: 13 patients received 90 mg ustekinumab via subcutaneous injections every 12 weeks, 12 patients received ustekinumab every 8 weeks, and 15 patients were given placebo.

At week 44 of the maintenance study, clinical remission was achieved by 46.2% of patients who received ustekinumab every 12 weeks, 75.0% of patients who received ustekinumab every 8 weeks (p = 0.054 compared to placebo), and 33.3% of patients who received placebo (Figure 2). All patients who achieved clinical remission did not require treatment with corticosteroids.

Clinical response was observed in 84.6% and 83.3% of patients treated with ustekinumab every 12 and 8 weeks, respectively, and in 66.7% of patients in the placebo group.

Mucosal healing was observed in 46.2% in the ustekinumab q12w group, 75.0% in the ustekinumab q8w group (p = 0.054 compared to

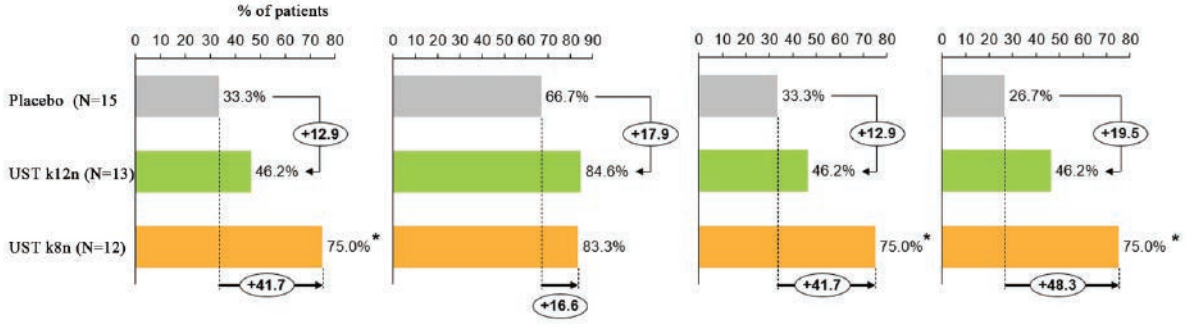

Figure 2. *Effectiveness measures at week 44 of the maintenance study in bionaive patients*

placebo), and in 33.3% of patients in the placebo group.

Histo-endoscopic mucosal healing was seen in 46% of patients in the ustekinumab q12w group, while in the ustekinumab q8w group the percentage of these patients was 75.0% (p = 0.021 compared to placebo), and in the placebo group — 26.7%.

The proportion of randomized patients in the ustekinumab q8w group who achieved clinical remission, clinical response, mucosal healing and histo-endoscopic mucosal healing at week 44 was numerically greater compared to both the placebo group and ustekinumab q12w [13].

Laboratory inflammatory markers over time

In the induction study decrease of median levels of CRP was demonstrated in patients treated with ustekinumab IV Median baseline CRP levels at the beginning of the maintenance study were 1.75 mg/L (IQ range 0.86; 2.62) for patients who received ustekinumab every 12 weeks, 0.68 mg/L (IQ range 0.34; 2.27) for patients who received it every 8 weeks, and 1.61(IQ range 0.86; 2.75) mg/L in the placebo group. In the maintenance phase median level of CRP after induction was sustained by ustekinumab SC treatments (Figure 3).

In the induction study decrease of median levels of faecal calprotectin was demonstrated in

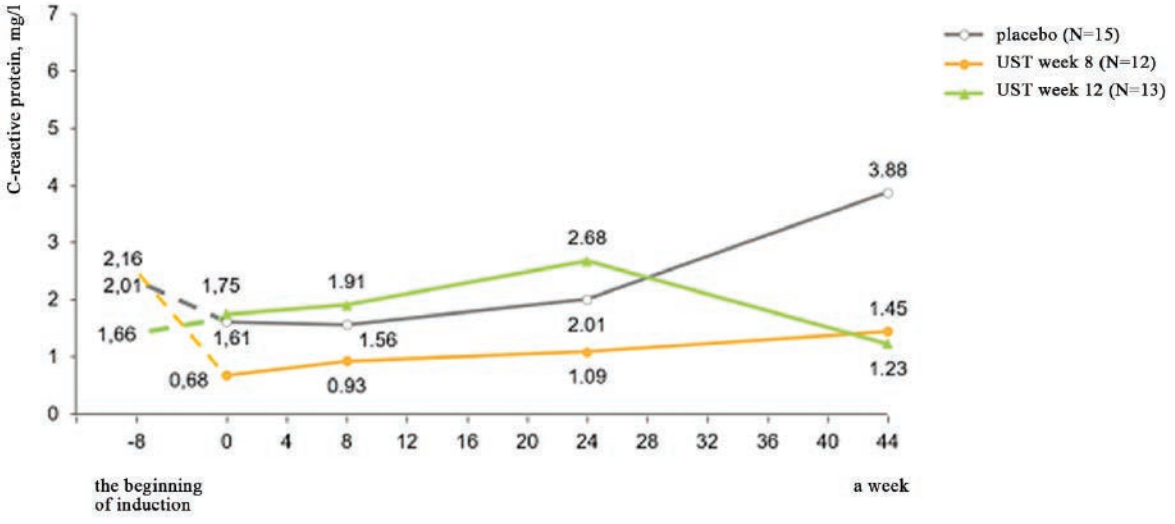

Figure 3. *Changes of median CRP levels over time during the maintenance study in bionaive patients through week 44*

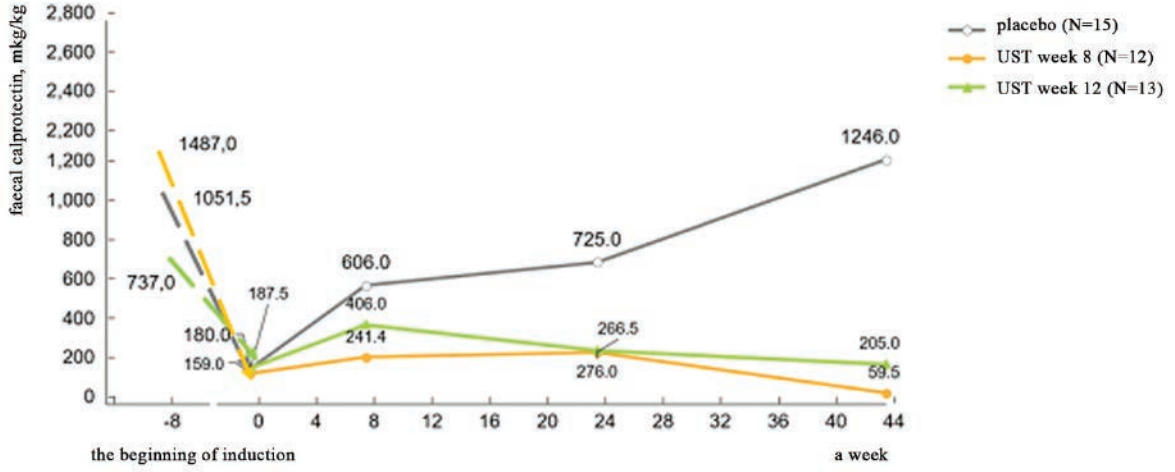

Figure 4. *Changes of median faecal calprotectin levels over time during the maintenance study in bionaive patients by treatment week 44*

patients treated with ustekinumab IV Median baseline faecal calprotectin levels at the beginning of the maintenance phase were 737.0 mg/kg (IQ range 142.5; 1464.5) in patients who received ustekinumab every 12 weeks, 1487.0 (IQ range 496.0; 4736.0) in those receiving it every 8 weeks, and 1051.5 (IQ range 600.0; 1553.0) in the placebo group. At week 8 of the maintenance phase, no meaningful differences in change from baseline values were noted between ustekinumab group and placebo, however, by weeks 24 and 44, faecal calprotectin levels were sustained in all ustekinumab groups as compared to placebo, where level increased($p < 0.004$ at week 24 and $p < 0.001$ at week 44) (Figure 4). Patients in the ustekinumab groups demonstrated persistent decreases in fecal calprotectin levels, while in the placebo groups these values appeared to increase over time from week 24 through 44.

Safety

Through the end of induction study the percentage of patients who reported at least one adverse event in the 130 mg ustekinumab group, 6 mg/kg ustekinumab group, and the placebo group was 22.2%, 40.0%, and 26.1%, respectively. No serious adverse events were reported in the ustekinumab groups; in the placebo group, 1 patient reported a serious adverse event. The proportion of patients with infections in the 130 mg and 6 mg/kg ustekinumab and the placebo groups was 5.6% (1 patients), 8.0% (2 patients) and 4.3% (1 patients) respectively.

The rate of adverse events from maintenance Week 0 through week 44 was comparable in the ustekinumab groups and the placebo group: 200.0, 164.9and 173.1 events per 100 patient-years in the ustekinumab q12w, ustekinumab q8w, and the placebo groups, respectively. The rate of serious adverse events reported in patients who received ustekinumab every 12 weeks was 0.0 events per 100 patient-years, 5.3 for patients who received ustekinumab every 8 weeks, and 19.2 in the placebo group.

The rates of infections as identified by the investigator through week 44 were: 0.0, 58.5, and 19.2 events per 100 patient-years in the ustekinumab q12w group, the ustekinumab q8w group, and the placebo group, respectively. In the ustekinumab q8w group, serious infections were reported at a rate of 5.3 (0.1, 29.6) events per 100 patient-years; no serious infections were reported in the ustekinumab q12w or placebo groups.

The rate of treatment discontinuation due to adverse events was 0.0 per 100 patient-years in the ustekinumab q12w group, 5.3 in the ustekinumab q8w group, and 19.2 in the placebo group.

No serious infections (including tuberculosis), malignancies or deaths were reported during the induction and maintenance studies.

Results from Long-term extension phase through 156 weeks

34 randomized bionaive patients from Russia were enrolled and treated in the long-term extension, 11 of whom received placebo, 12 received ustekinumab every 12 weeks, and 11 received ustekinumab every 8 weeks.

Symptomatic remission at week 152 was reported in 83.3% of patients in the ustekinumab q12w group, 81.8% in the ustekinumab q8w group. The proportion of patients in symptomatic remission and not receiving corticosteroids at week 152 was consistent with that of symptomatic remission.

Among all bionaive patients who were treated in LTE, from Week 0 of maintenance through Week 156, the rate of any adverse event was 142.00 in the ustekinumab q12w group, 125.35 in the ustekinumab q8w group, and 133.33 events per 100 patient-years in the placebo group. Infections were reported at a rate of 23.67 and 46.11 events per 100 patient-years for the q12w and q8w groups, respectively, and 40.74 events per 100 patient-years in the placebo group. Safety profile of ustekinumab was consistent with what was observed from Week 0 through Week 44, with the data reported for the Russian subpopulation through one year of exposure, including the induction and maintenance studies.

Immunogenicity

This study additionally evaluated the incidence of subjects who were positive for antibodies to ustekinumab. Among ustekinumab treated patients the majority were negative for antibodies

to ustekinumab. Among the 50 patients who entered the maintenance study. 8.0% (4 patients) were positive antibodies to ustekinumab through Week 44. Among 36 bionaive patients who were treated with ustekinumab during the LTE, from their first ustekinumab dose through Week 156, anti-ustekinumab antibodies were detected in 4 patients.

DISCUSSION

The additional analyses of the Russian patient population from the UNIFI study demonstrated that the patients with active, moderate-to-severe ulcerative colitis who were bionaive benefited from treatment with ustekinumab. Benefit was observed both during the induction and the maintenance studies as well as through the LTE. Patients who responded to induction therapy with intravenous ustekinumab, underwent a second randomization, q8w regimen of subcutaneous ustekinumab, achieved a clinical remission after 44 weeks of the maintenance period more often than those re-randomized to receive placebo treatment and q12w ustekinumab group.

It should be noted that all Russian patients who achieved clinical remission at week 44 of the maintenance period were not receiving glucocorticoids at Week 44, indicating that ustekinumab could be used to reduce patient's dependence on steroid agents. The majority of Russian bionaive patients treated with ustekinumab in the maintenance study achieved mucosal and histoendoscopic mucosal healing at Week 44.

In the induction phase decrease of CRP and faecal calprotectin median levels was demonstrated in patients treated with ustekinumab IV, in the maintenance phasemedian levels of laboratory inflammatory markers after induction were sustained by ustekinumab SC treatments.

Ustekinumab demonstrated a favourable safety profile in Russian patients. Rate of any adverse event among patients who received at least one dose of ustekinumab in the induction study or during 156 weeks of follow-up of the maintenance study was generally similar to that in the placebo group. Malignancy, active tuberculosis and death were not observed among these patients.

CONCLUSION

Taking into account limited global clinical practice data on the use of ustekinumab in early-line therapy for ulcerative colitis, this analysis was essential for choosing a biologic agent. The results of this analysis have allowed to confirm both the short- and the long-term effectiveness and safety of ustekinumab treatment in a Russian population of bionaive patients with active moderate-to-severe ulcerative colitis.

Overall, the results from the analysis of Russian patient population are consistent with earlier evidence from the overall patient population participating in the UNIFI program and allow us to consider ustekinumab asoptimal therapeutic option for early intervention in bionaive patients with ulcerative colitis.

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Clinical and Demographic Features and Treatment Approaches for Inflammatory Bowel Diseases (Crohn's Disease, Ulcerative Colitis) in the Russia. The Primery Results of the Analysis of the National Register

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ABSTRACT *The National Register of Patients with Inflammatory Bowel Disease (IBD) in the Russian Federation (RF) was established to study the epidemiological and clinical features and to evaluate the common conservative and surgical practice.*

AIM: to analyze the database of patients with IBD in the Russia including clinical and demographic features, medical status, the incidence of use of various classes of drugs and response to treatment, the survival rates of advanced therapy and the reasons for their cancellation.

METHODS: from May 2017 to August 2021, depersonalized data of 3,827 adult patients with IBD (ulcerative colitis (UC) — 2,358 pts, Crohn's disease (CD) — 1,469 pts) from 80 regions of the Russia were included in the register, both with previously and newly diagnosed UC or CD, who are in inpatient or outpatient care.

RESULTS: in Russian population, the ratio of UC:CD was 1.6:1. The distribution of patients by gender was the same.

The average age of patients in the register was 40.6 ± 13.1 (13–83 years) for UC and 38.5 ± 14.3 (15–75 years) for CD, the half of patients were in the age range of 21–40 years for both diseases. The average age of disease onset did not differ for UC and CD and was 35.3 years (12–75 years) and 31.2 years (14–72 years), respectively. The duration between the onset of symptoms and the establishment of a diagnosis was 13.2 months in UC, and significantly longer in CD — 34.8 months (P < 0.01). The proportion of smokers in CD was significantly higher than in UC (14.6% vs. 9.6%, respectively, P < 0.001). The incidence of disability was also significantly higher in CD than in UC patients (41.7% vs. 29.8%, P < 0.01). The diagnosis of mild UC was established in 36% of cases, moderate UC occurred in 48.9% of patients, severe UC in 14.2% of patients. For the first time, the incidence of acute severe UC (1%) was estimated. The majority of patients had total UC (56.8%), 33.0 had left-sided colitis, and 9.4% had proctitis. In CD ileocolitisoccurred in 55.9%, terminal ileitis — in 23.9%, colitis — in 20.2%, perianal lesions — in 32.5% of cases. The morbidity rate in CD was 46% (681 patients), the most common were strictures (48.0%) and fistulas (25.1%). The rate of extraintestinal manifestations did not differ in UC and CD was 20.1% (473 patients) and 24.5% (360 patients), respectively. Of these, musculoskeletal lesions were more common (41.6% in UC, 42% in CD), lesions of the skin, eyes, mucous membranes, liver, anemia were also noted. In the treatment of IBD, steroids were used most often (79.3% and 65% in UC and CD, respectively), followed by 5-ASA — 47% in UC, 32.4% in CD. Immunosuppressors in CD were prescribed significantly more often (28.4%) than in UC (11%) (p < 0.05). GEBDs (biotherapy) were used in 20.6% of UC patients and in 30% of CD patients. The highest 2-year survival of advanced therapy was noted for ustekinumab in CD (96%), tofacitinib in UC (89.3%), and vedolizumab in both UC and CD (92.5% and 88.4%, respectively). The survival rates of all TNF-α inhibitors were approximately the same and varied within 58.1–72.4% in UC and 60-70% in CD. The most common reasons for cancel of advanced treatment were lack of efficacy/loss of response in both UC and CD. The second common reason was achieving remission. Certolizumab pegol in CD was canceled for this reason most often (22.7%). A small number of cancelled treatment due to adverse events: for UC — 1 patient each on adalimumab, golimumab, and tofacitinib, and 7 patients on infliximab, for CD- 5 patients on infliximab and adalimumab (9.6% and 7.5%, respectively) and 2 patients (4.6%) on certolizumab. Unfortunately, the proportion of cancel for non-medical reasons was significant and varied from 7% to 50% for different agents. In some patients, the reason for therapy cancel remained unknown.

CONCLUSION: the difficulties of differential, often untimely diagnosis of CD and UC, the predominance of complicated and severe forms against the background of an increase in incidence and prevalence, and at the same time the lack of adequate statistical accounting of CD and UC, make it necessary to create a unified clinical register for patients with IBD. The register of IBD patients will provide a holistic picture of the IBD situation in the country, including optimizing the budget funds for the treatment of patients with CD and UC, ensuring their rational planning.

KEYWORDS: *Inflammatory bowel disease, ulcerative colitis, Crohn's disease, epidemiology, treatment options, biologics persistence (survival), national registry*

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INTRODUCTION

The study of inflammatory bowel diseases (IBD), which include ulcerative colitis (UC) and Crohn's disease (CD), has remained relevant for several decades. This is due to the steady increase in morbidity, the expansion of the geography of IBD, the lack of knowledge about their ethology and pathogenesis and the imperfection of treatment approaches, despite the constant increase in therapeutic capabilities. Both diseases have a clear social significance, since the main cohort of patients is of young, able-bodied, reproductive age, belonging to the category of "long-term disease", requiring often hospitalizations and having disabilities [1–3]. In all countries, IBD imposes a significant economic burden on national health systems due to the progressive course, expensive drugs, severe intestinal complications, hospitalizations and intestinal surgeries [4–6]. The maximum prevalence of IBD in Europe is 505/100,000 of the population for UC and 322/100,000 for CD. In North America, the prevalence of CD is higher than UC: 319 and

249 per 100 thousand, respectively. The highest incidence of UC 24.3/100,000 was noted in Europe, 19.2/100,000 in North America. For CD, these figures are 12.7/100,000 in Europe and 20.2/100,000 in North America. The incidence is increasing in Asia, the Middle East and China [7–11]. The number of epidemiological studies is increasing every year, of which 75% of studies on CD and 60% on UC demonstrate a constant increase in the incidence of IBD [3]. There are significant differences in the incidence and prevalence of IBD between northern and southern countries and between western and eastern countries in Europe with the predominance of the highest rates in the northern and western territories, but with their constant growth in the eastern direction [12,13]. Since Russia occupies a geographical position between the West and the East, it is extremely important to know the true basic epidemiological indicators for the country; however, at present information on the prevalence and incidence of IBD in the Russia is extremely limited, presented by partial data from Oblastal registers and largely differ from each other [14,15]. Thus, in the Moscow Oblast, the incidence of IBD is 5.1/1,000,000, and the prevalence is 60.7/100,000 [13,14]. In Irkutsk, the prevalence of IBD is 74.9/100,000, and in the Republic of Tatarstan 40/100,000 of the population [14,15]. A comprehensive study of Russian epidemiological indicators can be available within the framework of the permanent national Register of IBD.

Socio-demographic and clinical characteristics of IBD, as well as therapeutic approaches have already been studied in a number of large Russian studies, such as ESCApe, ESCApe-2, INTENT [16,17]. These were well-organized, multicenter, observational studies with a sufficient sample of patients that demonstrated a number of trends that coincide with global trends and a number of epidemiological features that differ from general patterns. Despite the convincing results, these studies do not reflect a detailed picture of the IBD in the country as a whole, because they were cross-sectional and were done on the basis of the leading specialized centers of the IBD only in some Oblasts. Thus, 17 Oblasts participated in the ESCApe study, ESCApe-2 and INTENT-7 Oblasts each. This, of course, is not enough to fully characterize the state of affairs and the problem of IBD on a national scale. Patient registers can provide a more complete picture of the state of any medical and social problem.

The register is an organized system for collecting, recording and storing unified information about patients, which makes it possible to evaluate real long-term data on the effectiveness and safety of therapy, late outcomes of the disease and treatment, cost-effectiveness and other parameters. Randomized and cohort clinical trials cannot provide a complete answer to these questions, as they are limited by design and endpoints, strict inclusion/exclusion criteria, and the target cohort of patients. This article presents the first results of the national Register of IBD in Russia.

AIM

Analysis of data from the national Register of patients with IBD in the territory of the Russia with the study of clinical and demographic characteristics, the medical status of patients, the incidence of use of various classes of drugs and the nature of the response to treatment, assessment of the survival of GEBD and the reasons for their cancellation.

PATIENTS AND METHODS

The Register included patients with IBD, both with a previously established diagnosis, and with newly diagnosed UC or CD, who are on inpatient or outpatient treatment.

To fill out the Register, a special patient registration form was developed with a list of key issues related to demographic and social characteristics, features of the course of diseases, complications and treatment options for UC and CD. Data collection and analysis was carried out in the period from May 2017 to August 2021 inclusive. The data of 3,827 patients (UC 2,358, BC 1,469) from 78 Oblasts of the Russia were entered into the Register.

Table 1. *Participants of the project "National Register of IBD in the Russia"*

Territorial District	Region	Number of Patients
Central	Moscow	1196
	Belgorod region	93
	Bryansk region	10
	Vladimir region	43
	Voronezh region	21
	Ivanovo region	8
	Kaluga region	17
	Kostroma region	8
	Kursk region	7
	Lipetsk region	61
	Moscow region	406
	Orlov region	9
	Ryazan region	10
	Smolensk region	25
	Tambov region	15
	Tver region	28
	Tula region	26
	Yaroslavl region	17
North-west	Arkhangelsk region	6
	Vologda region	15
	Kaliningrad region	20
	Leningrad region	23
	Murmansk region	9
	Novgorod region	11
	Pskov region	12
	Republic of Karelia	6
	Komi Republic	11
	St. Petersburg	653
South	Astrakhan region	10
	Volgograd region	26
	Krasnodarskiy Territory	14
	Rostov region	48
	Republic of Adygea	2
	Republic of Kalmykia	5
	Republic of Crimea	8
	Sevastopol	1
Siberian	Altai Territory	2
	Irkutsk region	3
	Kemerovo region	197
	Krasnoyarsk Territory	4
	Omsk region	5
	Republic of Tyva	2
	Republic of Khakassia	1
	Tomsk region	2
Uralsky	Kurgan region	7
	Sverdlovsk region	9
	Tyumen region	9
	Khanty-Mansi Autonomous District — Yugra	5
	Chelyabinsk region	60
	Yamalo-Nenets Autonomous District	10
Far-Eastern	Amur region	9
	Trans — Baikal Territory	1
	Kamchatka Territory	9
	Magadan region	1
	Primorsky Territory	1
	Republic of Buryatia	1
	Republic of Sakha (Yakutia)	2
	Sakhalin region	3
Privolzhsky	Kirov region	6
	Nizhny Novgorod region	188
	Orenburg region	4
	Penza region	9
	Perm Territory	4
	Republic of Bashkortostan	7
	Republic of Mari El	2
	Republic of Mordovia	17
	Republic of Tatarstan	24
	Udmurt Republic	5
	Republic of Chuvashia	62
	Saratov region	9
	Ulyanovsk region	6
North-Caucasian	Kabardino-Balkarian Republic	10
	Karachay-Cherkess Republic	3
	Republic of Dagestan	49
	Republic of Ingushetia	3
	Republic of North Ossetia-Alania	18
	Stavropol Territory	154
	Chechen Republic	8

Statistical Processing

Statistical data processing was performed in the IBM SPSS Statistics program. Methods of descriptive statistics were used to generalize and evaluate demographic continuous and discrete variables. Quantitative variables were described using averages, standard deviation, minimum, maximum and median. Qualitative variables were characterized by absolute and relative (%) incidence. Absolute figures and percentages were calculated for patients within each class of diseases. Comparison of qualitative variables in two independent groups was carried out using the χ^2 criterion.

All IBD patients signed an informed consent to include their depersonalized data in the national Register Technical support of the Register platform: The United System of Medical Informatization (РОСМЕД.ИНФО).

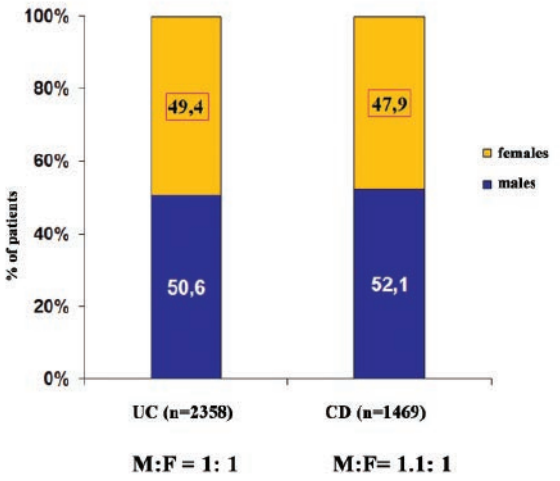


Figure 1. *The ratio of males and females with UC and CD according to the National Register*

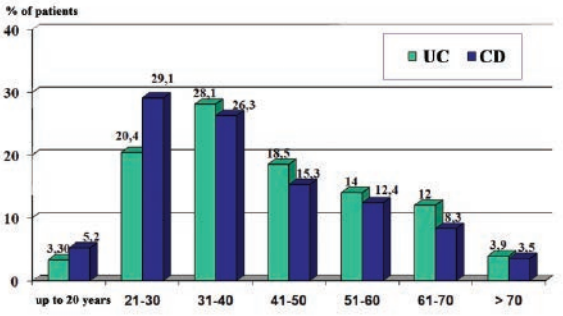


Figure 2. *Age of patients with IBD in the Russian Federation at the time of inclusion in the National Register*

Table 2. *Age characteristics of IBD patients (years)*

Indicator	UC	CD
Number of patients	2358	1469
Average age of patients	40.6	38.5
Standard deviation	13.1	14.3
Minimum	13	15
Maximum	83	75
Median	38	36

RESULTS AND DISCUSSION

Demographic and Socio-economic Characteristics

Incidence of IBD on Gender and Age

The Register included 2,358 patients with UC and 1,469 patients with CD (the ratio of UC:CD = 1.6:1). The distribution of patients by gender, shown in Figure 1, demonstrated an equal proportion of males and females in both diseases without the predominance of one of the genders, which corresponds to the data of previous studies in Russia [16,17,20] and epidemiological trends in the world [3,18,19].

The age of patients with UC and CD included in the Register are shown in Table 2 and Figure 2. It ranged significantly from 13–15 to 75–83 years in both UC and CD. The average age was 40.6 years with UC and 38.5 years with CD. The vast majority of IBD patients are represented by young people in the age of 21–30 and 31–40 years for both diseases, which is 48.5% in the UC group and 55.4% in the CD group.

There were no significant age differences between UC and CD in any age group.

Age of Disease Onset

It is this characteristic that determines the social component of the disease, because all over the world, the main contingent of patients is young people aged 20–40 years. This trend has been repeatedly confirmed in the countries of Europe, Asia and America, as well as in Russia in earlier studies [3,16–18,20]. The age of the

Table 3. *Age of the onset of IBD in Russia (years) in 2014 and 2021*

Indicator	Ulcerative Colitis		Crohn's Disease	
	Register (2021)	ESCApe-2 (2014)	Register (2021)	ESCApe-2 (2014)
Number of patients	2358	666	1469	333
Average age of onset of the disease	35.3	36.4	31.2	32.6
Minimum	12	2	14	10
Maximum	75	75	72	75
Median	33	32	29	34

onset of the disease predominantly determines the phenotype and prognosis of the disease, which is especially pronounced in CD, in which the early age of the onset of the disease is one of the factors for complications and negative prognosis [21–25].

In our national Register, the average age at the beginning of IBD was almost the same (34.2 years for CD and 36.1 years for UC) and corresponded to this general trend (Table 3).

We compared the average age of the onset of IBD according to the Register (2021) and according to the ESCApe-2 study (2014). Convincing data on age-related shifts in the onset of diseases over the past 7 years were not observed in either UC or CD (Table 3). Currently, in some countries, there is an increase in the incidence of IBD over the age of 60 years [3,9]. This is an important factor for the poor prognosis of UC, because this category of patients has an increased likelihood of early colectomies and the risk of colorectal cancer [21,24–26]. The data from our Register does not yet indicate such a trend in Russia.

Timing and Age of Diagnosis

According to the Register, the average age of diagnosis of UC and CD (36.1 and 34.2 years, respectively) did not differ from the age of onset of the disease (35.3 and 31.2 years, respectively) (Fig. 3).

These data suggest that the diagnosis of IBD is quite fast, i.e. a short time after the onset of symptoms.

At the same time, the analysis of the Register shows that the average time of IBD from the onset of symptoms to diagnosis in the whole country remains quite long and amounts to 2.9 years

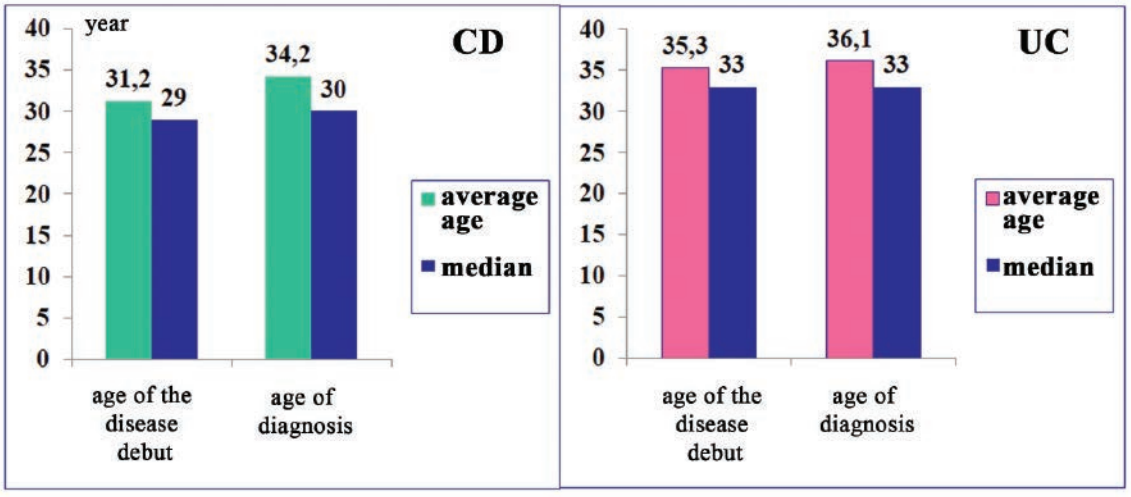
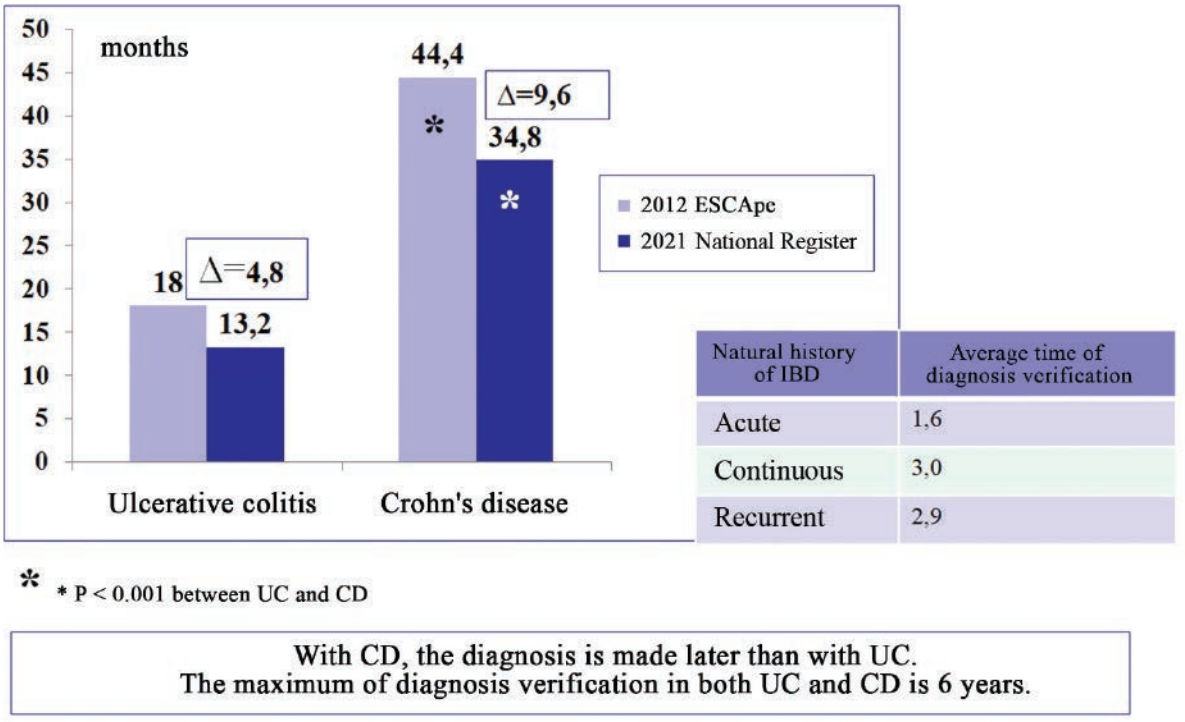


Figure 3. *Age of disease onset and age of diagnosis in IBD according to the National Registry*



Natural history of IBD	Average time of diagnosis verification
Acute	1,6
Continuous	3,0
Recurrent	2,9

Figure 4. *Duration of the disease from the first symptoms to diagnosis (months)*

(34.8 months) in CD and 1.1 years (13.2 months) in UC (Fig. 4).

Apparently, this contradiction of indicators requires clarification as the number of patients in the Register increases. When comparing the timing of diagnosis in the ESCApe study and in the Register, it was shown that this period decreased from 44.4 months to 34.8 months with CD and from 18 months to 13.2 months with UC (Fig. 4). Apparently, the decrease in the time of diagnosis was influenced by the improvement of doctors' awareness of IBD and the increase in diagnostic options. It is also likely that the diagnosis is made more quickly with a bright, manifest picture of IBD, which is not always the case. Thus, in the Register, the average time of diagnosis in the acute IBD, the same for UC and CD, was 1.6 years (19.2 months), which is unacceptably long for an acute attack, but less than in continuous and recurrent forms of diseases

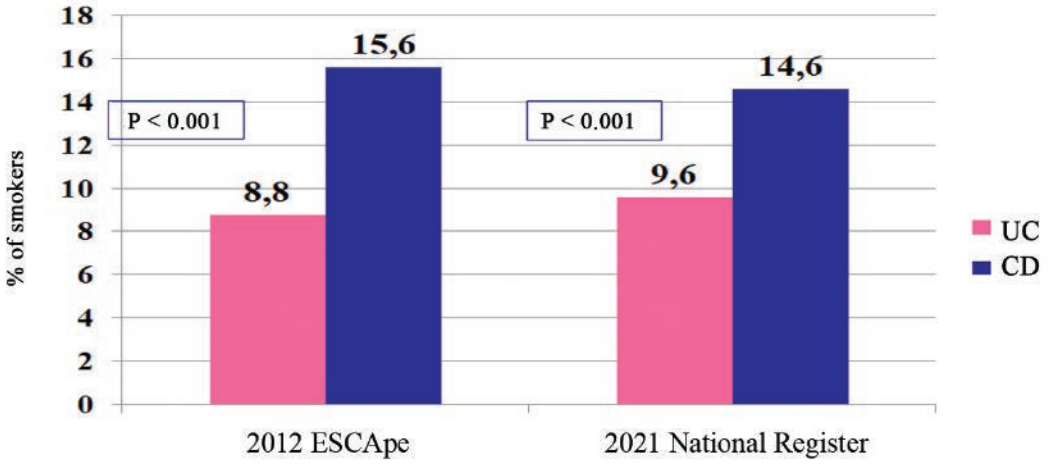


Figure 5. *Smoking status in IBD. The proportion of patients who smoke in UC and CD*

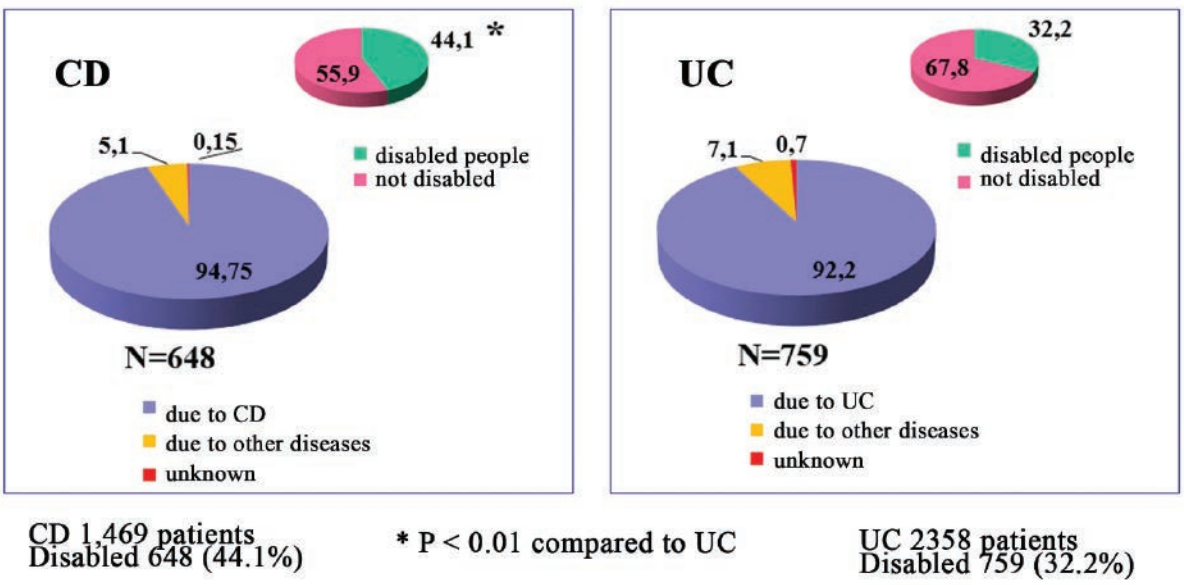


Figure 6. *Rate and cause of disability of IBD according to the National Register (%)*

(Fig. 4). There are still patients whose diagnosis is delayed for a long period. According to the Register, the maximum duration of the diagnostic period was 72 months (6 years) both with CD and with UC. It should be noted, however, that this period has also decreased in comparison with the 2012–2014 data. (Fig. 4) [16]. The task of evaluation of causes of late diagnosis of IBD in the analysis of the Register was not set. It can be assumed that this is due, on the one hand, insufficient knowledge of a wide range of doctors with an unusual clinical picture of IBD, and on the other hand, insufficient compliance of patients and their late access to a doctor with mild symptoms of the disease. In any case, late diagnosis can lead to of severe complications and surgery. It is interesting to note that a significant difference was revealed between the time of verification of CD and UC. The duration of the diagnostic period in CD is more than 2 times longer than in UC, and this trend continues to the present (Fig. 4). Similar data were obtained in a vast European study, where it was shown that 20% of CD patients do

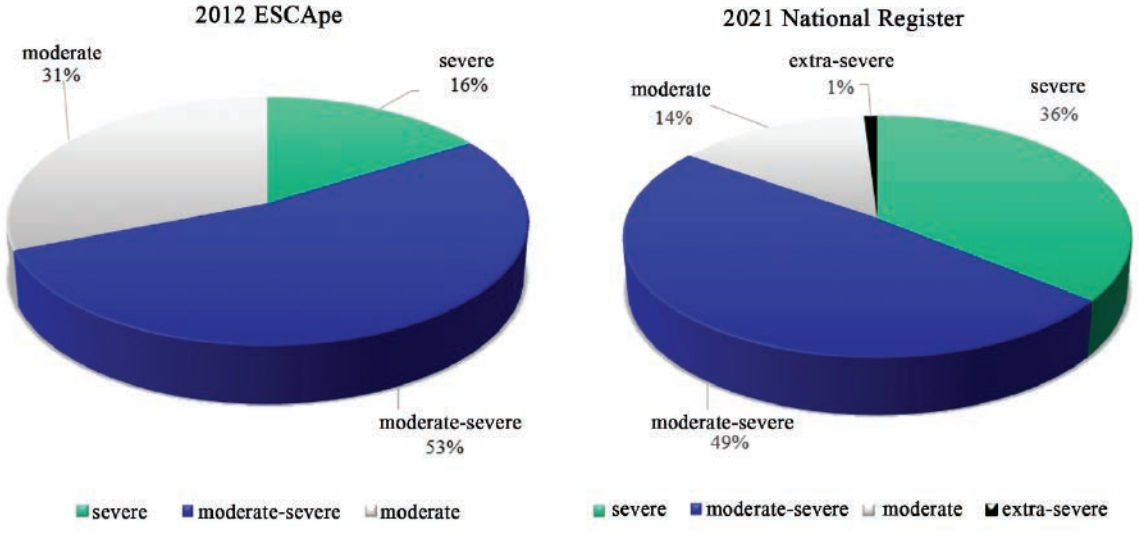


Figure 7. *The severity of the UC in Russia*

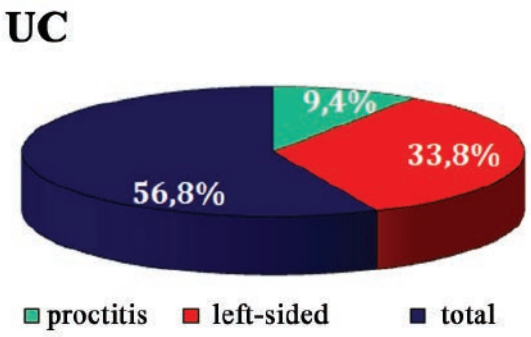


Figure 8. *The extent of UC according to the National Register*

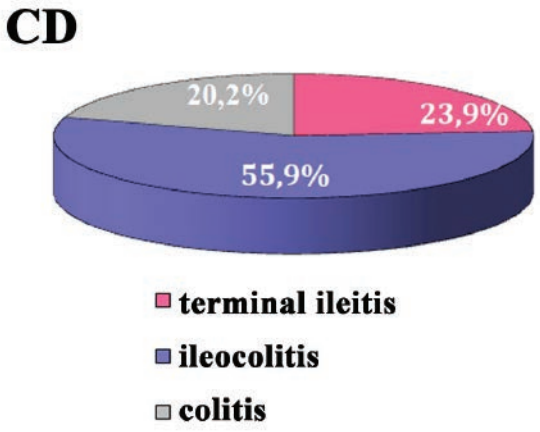


Figure 9. *Localization of Crohn's disease according to the National Register*

not have a diagnosis more than a year after the onset of symptoms, while only 9% of such UC patients [27].

Risk Factors for IBD (Smoking)

The effect of nicotine on the development of IBD has been well known for a long time, and this is a multidirectional effect in CD and UC. In CD, smoking is considered one of the most important risk factors for the development and poor prognosis of the disease. It was found that smoking increases the risk of CD formation by more than two times, and the number of smokers in the cohort of CD patients is significantly higher than in the general population [28–31]. In UC, nicotine not only does not have a negative effect on the disease, but on the contrary, it is a protective factor. The incidence of UC among smokers is lower than in the population, and the proportion of smokers among UC patients is less than in the population of patients without UC [28–31]. The Register data showed a similar trend among Russian patients: the proportion of smokers in CD was statistically significantly higher than in UC (14.6% vs. 9.6%, respectively) (Fig. 5). Similar data obtained in the ESCApe study [16] are also shown for comparison in Figure 5. The same results were obtained in the INTENT study [17]. Thus, the data of the Russian national Register on the status of smoking in patients and the effect of smoking on IBD generally correspond to international trends. The average smoking experience in our patients with UC and CD was the same: 16.5 and 17 years, respectively.

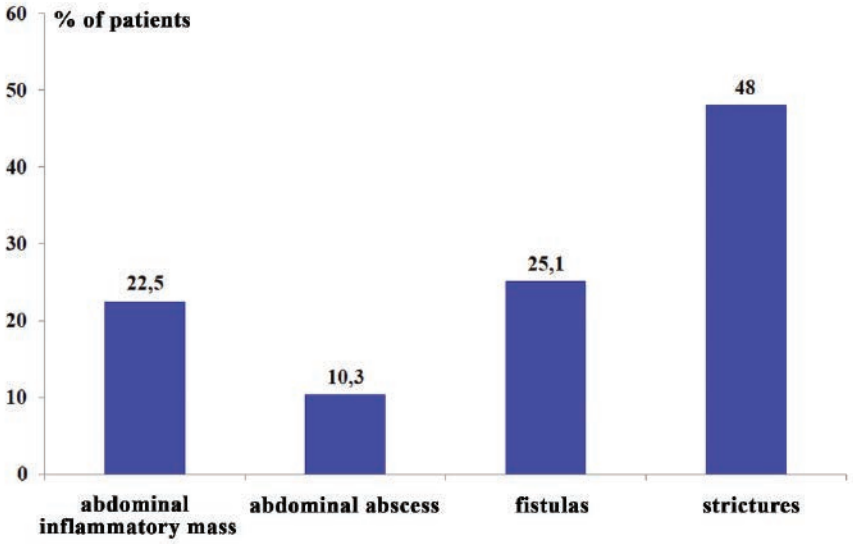


Figure 10. *The incidence and nature of complications in Crohn's disease*

Employment Status (Disability)

The rate of disability of IBD patients in Russia should be assessed not only for the Registration of severe complicated forms of the disease that require revision of the treatment, but also from the standpoint of the possibility of preferential drug provision, especially expensive genetically engineered biological drugs (GEBD). Among patients with CD, the proportion of disabled people was significantly higher — 44.1% (648 people) than in UC — 32.2% (759 people) (P < 0.001). However, some of these patients had disabilities due to other diseases unrelated or indirectly related to IBD (5.1% and 7.1%, respectively) (Fig. 6). Most often these were rheumatic and skin diseases, in some cases cardiovascular diseases and diabetes mellitus. There was no information on 0.15 and 0.7% of patients. Thus, 41.7% had a disability directly for CD, 29.8% for UC. It was these patients who could have a drug benefit.

Clinical Parameters of IBD

Severity of the IBD

To assess the severity (activity) of UC, the Mayo scale or the Truelove-Witts severity criteria recommended in Russia were used [32]. According to the Register, the severity assessment was available only for UC. The ratio of different forms of UC in severity is shown in Fig. 7. In accordance with the Russian National Guidelines and the Montreal Classification [33], mild UC (36%), moderate UC (48.9%), severe UC (14.2%) were distinguished. For the first time, the incidence of extra-severe UC (1%) was statistically estimated, which was included in National Guidelines only in 2020 [32]. It should be noted that the ratio of groups of patients with varying degrees of severity in the national Register and in the ESCApe study [16] was different: mild UC in the Register was 36% versus 16% in the ESCApe, the proportion of severe UC, on the contrary, was lower-14.2% versus 31%. The proportion of moderate UC was the same (Fig. 7). From our point of view, such a difference in the assessment of severity in the Register and in the ESCApe is interesting from two points: firstly, the diagnosis of mild forms of UC has improved over a 9-year period; secondly, we believe that these differences in data demonstrate the advantages of evaluating indicators for the Register with a significantly larger coverage of territories and populations compared to cohort studies. Our data coincide with the European data on the ratio of different forms of UC in severity [6]. Unfortunately, data on the severity of CD in the Register were not available.

The Extent of Inflammation in UC

The extent of inflammation in UC, estimated in accordance with the Montreal Classification, according to which distal colitis (proctitis), left-sided colitis and total colitis (pancolitis) are distinguished, is shown in Figure 8 [33]. The vast majority of patients had pancolitis (56.8%), left-sided colitis was diagnosed in more than a third of patients, proctitis occurred in only 9.4% of patients. Such a small proportion of patients with distal lesions indicates their insufficient diagnosis. For various reasons, these patients do not come to the attention of doctors, which can negatively affect the prognosis and outcomes of the disease, because it has been shown that over time, UC can progress with an increase in length [34]. Thus, in 15% of patients, after 9 years, the length of the lesion may increase, and proctitis passes into common forms of UC [35]. Statistical differences between total and left-sided colitis are significant, as well as differences between left-sided and distal colitis ($p < 0.001$). Thus, the results of processing the Register data showed that UC with a widespread nature of inflammation (left-sided and total) currently prevails in the Russia. The European population shows significantly higher rates of distal colitis, varying in different countries and different time intervals from 27% to 60% [6,36].

Lesion Site in CD

CD lesion site was also evaluated according to the Montreal Classification [33]. More than half of the patients (55.9%) were diagnosed with a combined lesion (ileocolitis) (Fig. 9). There were significantly more such patients ($p < 0.05$) than patients with terminal ileitis (23.9%) and colitis (20.2%). Other sites (jejunum, upper

Table 4. *Rate and nature of extraintestinal manifestations in IBD in the National Register (%)*

Type of EIM	UC *n* = 2358	CD *n* = 1469
All EIMs	20.1 (*n* = 473)	24.5 (*n* = 360)
Joints and spine	41.6	42.0
Skin and mucosa	16.1	17.3
Liver	17.0	13.3
Eyes	5.2	3.6
Blood	15.6	12.0

**In the table, the incidence of individual types of EIM is given in relation to the total number of EIMs.*

gastrointestinal tract) in the Register were not distinguished independently, but were found in combination with the three main ones. Perianal lesions were noted in 32.5% of CD patients, usually in combination with another locations, only in 8% of patients as the single lesion, which was included in the group of patients with colitis. In general, the results of the Register coincide with earlier data for the Russia [16,17].

Complications and Phenotype of CD

The overall incidence of complications in CD in the Register was registered in 676 (46.0%) patients, there were no complications in 793 (54.0%) patients in whom CD can be characterized as luminal (luminal, inflammatory). The fistulous form of CD (external and internal fistulas, of different location) was diagnosed in 25.1% of patients. Strictures showed 48% of patients, but it is not possible to establish the exact incidence of the stricturing phenotype of CD according to the Register, because in some patients both fistulas and strictures were registered simultaneously or sequentially (Fig. 10). The rate and nature of UC complications are not reflected in the Register.

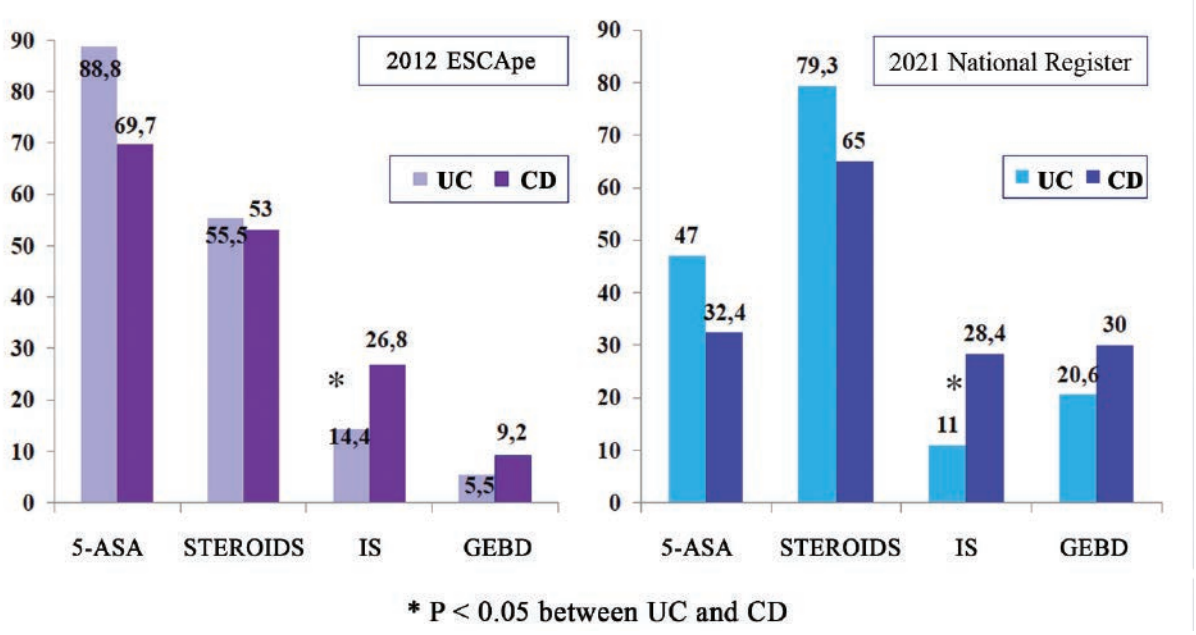


Рисунок 11. *Частота разных видов терапии ВЗК с разницей в 9 лет*
Figure 11. *The incidence of different types of IBD therapy with a difference of 9 years*

Table 5. *Survival of Biologics (GEBD) and tofacitinib therapy after 2 years of follow-up*

Drug	UC				CD			
	Prescribed	Stopped taking	Continue taking after 2 years		Prescribed	Stopped taking	Continue taking after 2 years	
	N	N	N	%	N	N	N	%
Infliximab	191	79	112	58.6	169	52	117	69.2
Adalimumab	86	36	50	58.1	223	67	156	70.0
Golimumab	105	29	76	72.4	–	–	–	–
Certolizumab pegol	–	–	–	–	110	44	66	60.0
Vedolizumab	93	7	86	92.5	86	10	76	88.4
Tofacitinib	178	19	159	89.3	–	–	–	–
Ustekinumab	5	2	3	60.0	25	1	24	96.0

Extraintestinal Manifestations

Extraintestinal manifestations (EIM) most often reflect an autoimmune component in the pathogenesis of IBD [37] and are usually observed in severe cases [34–36]. The European consensus provides data on a significantly higher rate of EIM in CD compared to UC and notes that at least one EIM occurs in 50% of IBD patients [37]. In contrast to Western countries, the incidence of EIM among patients in our national Register did not differ significantly in UC and CD and amounted to 20.1% (473 patients) and 24.5% (360 patients), respectively (Table 4). This is lower than the previous results for the Russia [16,17] and lower than the data of most foreign publications [38–41]. As in most studies, musculoskeletal lesions, including peripheral arthritis, ankylosing spondylitis, psoriatic arthritis (Table 4), were the most often among all EIMs, which completely coincides with data from foreign sources [37]. There were no significant differences in the rate of individual EIM in UC and CD.

Skin lesions in our population were typical (erythema nodosum, gangrenous pyoderma, psoriasis, atopic dermatitis) [42,43]. Involvement of the mucosa was represented by aphthous stomatitis, and the lesion was represented by ocular uveitis and iridocyclitis. Primary sclerosing cholangitis in UC, autoimmune hepatitis and cross syndrome were among the liver lesions. EIM of the blood system included anemia of various genesis. Knowledge of the nature of EIM is of great importance for the early diagnosis of IBD, when intestinal symptoms of the disease may be absent or subclinically occur, and the disease manifests EIM [37].

Treatment Characteristics

The incidence of use of different groups of drugs, including 5-ASAs, glucocorticosteroids (steroids), immunosuppressors (IS) and GEBD, was evaluated. In addition, the survival of GEBD therapy, the rate and causes of GEBD withdrawal were evaluated. The main results are shown in Fig. 11, where you can see how the actual practice of therapeutic approaches in the Russia has changed over 9 years, i.e. how the Register data differ from the results of the first ESCApe study of 2012 [16].

First of all, attention is drawn to the reduction in 5-ASA by almost half from 2012 to the present (from 88.7% to 47% in UC, from 69.7% to 32.4% in CD). Such shift is important to note for UC, since it is well known that 5-ASA are recommended for mild and moderate disease, but are not effective for severe one [32,44,45]. The proportion of patients with mild UC in the Register

Table 6. *Reasons for discontinuation of Biologics therapy*

Drug	Reasons for discontinuation of therapy (abs. and % of those who stopped treatment)									
	Medical Reasons						Non-medical Reasons		Unknown Reason	
	Inefficiency/Loss of Response		Achieving Remission		Side Effects					
	UC	CD	UC	CD	UC	CD	UC	CD	UC	CD
Infliximab	25/31.6	10/19.2	3/3.8	1/1.9	7/8.9	5/9.6	13/16.5	5/9.6	31/39.2	31/59.7
Adalimumab	8/22.2	19/28.4	0	5/7.5	1/2.8	5/7.5	3/8.3	17/25.4	24/66.7	21/31.2
Golimumab	5/17.2	–	0	–	1/3.4	–	2/7.0	–	21/72.4	–
Certolizumab pegol	–	22/50	–	10/22.7	–	2/4.6	–	10/22.7	–	0
Vedolizumab	3/42.8	4/40.0	0	0	0	0	1/14.3	1/10.0	3/42.8	5/50.0
Tofacitinib	15/78.9	–	0	–	1/5.3	–	3/15.8	–	0	–
Ustekinumab	1/50.0	0	0	0	0	0	1/50.0	1 patient	0	0

was 36%, and with moderate — about 49% (Fig. 7). From the comparison of these figures, it can be assumed that mesalazines were mainly received by patients with mild UC and a small part of patients with moderate UC. The formula is simple: 47% of administrationsis 5-ASA, of which 36% is mild UC and the remaining 11% was for moderate UC. Of course, it is categorical to say that the distribution was exactly like this is not entirely correct, but given the provisions of the National Guidelines, this is most likely. In any case, the differences in comparison with 2012 are clear and it can be stated that 5-ASA for UC began to be prescribed more correctly.

Unfortunately, this cannot be said about CD. Although the incidence of prescribing 5-ASA in CD has decreased more than twice in 9 years, the fact itself suggests that doctors still do not take into account the part of National Guidelines that clearly reflect the low effectiveness of 5-ASA in CD [45–49].

It is unknown whether 5-ASA was prescribed independently or in combination with other classes of drugs, in particular with steroids. This is also an important point, because patients who need steroids, as a rule, do not respond to 5-ASA. Such a combination is not advisable and increases the cost of treatment. It is possible that patients received a combination of 5-ASA and steroids, 5-ASA and IS, and even a combination of 5-ASA and GEBD. Such variants are often found in Russian clinical practice, which was shown in the INTENT study [17], although such combinations do not comply with National Guidelines [46–48]. In the future, it is advisable to include data on the practice of combination therapy in the Register.

With regard to steroids, we can only say that the rate of their use in IBD has not changed in 9 years, but has even increased somewhat (Fig. 11). It is not yet known from the Register data whether steroids were prescribed in repeated courses and for how long. In the INTENT study [17], it was demonstrated that patients in Russia received from 2 to 7 repeated courses of steroids, which also does not comply with Russian and international guidelines. It is also advisable to include this section in the Register.

Attention is drawn to the almost identical incidence of use of IS (mainly thiopurines) in 2012 and 2021 and significant differences in the incidence of use of IS in UC and CD, and this trend has not changed over 9 years (Fig. 11).The reason for such differences is not clear, because

indications for the use of IS in UC and CD are the same: maintenance therapy after achieving remission on steroids. It will be important to understand why thiopurines are so rarely used in UC, in only 11% of cases.

As for GEBD, the incidence of their administration has increased significantly over 9 years (4 times for UC and 3 times for CD) (Fig. 11), which is quite natural, since the availability of GEBD has increased significantly throughout the country during this time. The positive changes is also explained by the increase in the educational level of gastroenterologists.

As part of the Register analysis, the "survival of therapy" with GEBD and selective immunosuppressants (tofacitinib) was evaluated. The survival rate of GEBD is an important parameter reflecting long-term therapeutic efficacy, safety and adherence to therapy in common clinical practice. The survival of therapy is a new term defined as the time from the moment of administration of GEBD to the moment of discontinuation of the drug or to the moment of switching to another drug [50]. In our analysis, the survival of GEBD was assessed by repeated visits of patients, the proportion of patients who continued to take biologics for 2 years from the date of administration was determined (Table 5). The highest 2-year survival was noted for ustekinumab in CD (96%), for tofacitinib in UC (89.3%) and for vedolizumab in both UC and CD (92.5% and 88.4%, respectively). It is not yet possible to assess the survival of ustekinumab in UC due to the small number of patients — only 5 people.

The survival rate of all TNF-α inhibitors was approximately the same and somewhat lower than other classes of drugs, and ranged from 58.1–72.4% in UC and 60–70% in CD (Table 5). There were no significant differences in the survival rate of different drugs in either UC or CD, as well as there were no significant differences between UC and CD for any of the drugs.

The data we have obtained on survival are generally comparable with the results given in the literature, although there are very few studies on this topic so far. So, in a Korean study, the 2-year survival rate of infliximab and adalimumab therapy for CD was the same and amounted to about 80% (in our Register, about 70%), and in UC for both drugs 54% (in our Register, 58%) [50]. An Australian study demonstrated a higher survival rate of ustekinumab in CD (more than 70%) and vedolizumab in UC (more than 60%) compared to other drugs [51].

In the Khan systematic review, the reasons for discontinuation of GEBD therapy in IBD were assessed by three main parameters: loss of response/insufficient response, side effects, and insufficient adherence to treatment [52]. It should also be borne in mind that the reasons for the drug cancel may not be medical, related to organizational and financial issues, violation of the auction schedule, etc. We analyzed the reasons for the cancel of GEBD and janus kinase inhibitors, focusing on the data entered in the Register. An additional reason for the cancellation/refusal of treatment was the achievement of remission and improvement of the patient's status. Refuse of therapy for this reason can be regarded as a violation of treatment compliance. However, there is no information in the Register about whether the withdrawal of the drug was the initiative of the doctor or the patient. The reasons for the withdrawal of all drugs in patients of our population are indicated in Table 6. The most common reasons were insufficient efficacy or secondary loss of response. However, it should be noted that there were few such patients compared to those who continued therapy (Tables 5,6). For an unclear reason, cancel due to the achievement of remission in a high percentage of cases was noted during treatment with certolizumab pegol in CD (22.7%). Due to the side effects of the drugs, only a small number of patients stopped treatment. Unfortunately, non-medical reasons for withdrawal accounted for a significant proportion, this is especially noticeable for infliximab and adalimumab. In a large number of patients, the reason for discontinuation of therapy remained unknown. This section of the Register should be given more attention in the future.

CONCLUSION

The difficulties of differential, often untimely diagnosis of CD and UC, the predominance of complicated and severe forms against the background of an increase in morbidity and prevalence, and at the same time the lack of adequate statistical accounting of CD and UC, make it necessary to create a unified clinical register of patients with IBD. The National Register of IBD Patients will provide a holistic picture of the IBD situation in the country, including optimizing the use of budget funds for the treatment of patients with CD and UC, ensuring their rational planning.

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Does the type of anastomosis affect the risk of recurrence in Crohn disease?

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ABSTRACT *AIM: to evaluate the effect of intestinal anastomosis type on risk of Crohn's disease (CD) recurrence.*
PATIENTS AND METHODS: the retrospective cohort study included 130 patients with CD who underwent surgery for a complicated CD in 2012–2017. Ileocecal resection with anastomosis was performed in 112/130 (86.2%) patients. Resection of the terminal ileum with resection of the right side of the colon with the formation of an ileo-transverse anastomosis. In 18/130 (13.2%) cases. Stapled "side-to-side" anastomosis was formed in 57/130 (43.8%) patients, while hand sewn "end-to-end" — in 73/130 (56.2%) patients. Post-op complications occurred in 21/130 (16.2%) cases. After surgery, most patients were treated by azathioprine as an anti-recurrence therapy — 112/130 (86.2%) patients, while in 31/112 (23.8%) cases, additional biological therapy was done. In 14/130 (10.7%) patients, anti-recurrence therapy was carried out in mono mode with a biological drug.
RESULTS: mean follow-up was 28.5 (1.9–95.4) months. Recurrence occurred in 54/130 (41.5%) patients on average 18 ± 5 (12–41) months after surgery. Thus, the operative time exceeding 200 minutes was significantly associated with an increase in the recurrence rate ($p = 0.03$). It was found that the type of anastomosis does not affect the recurrence risk. Moreover, among the significant factors was the operative time. It increases the chance of recurrence by 2.9 times in the univariate model ($p < 0.05$), and in the multivariate model — by 6.3 times, when exceeding 155 minutes.
CONCLUSION: the type of anastomosis does not affect the recurrence risk. The operation time exceeding 155 minutes increases the chance of recurrence by 6 times ($p < 0.01$).

KEYWORDS: *Crohn's disease, recurrence, anastomosis*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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INTRODUCTION

Crohn's disease is a chronic inflammatory disease of the gastrointestinal tract that requires surgery in 80% of cases, regardless of the type of conservative treatment [1]. At the same time, the surgery does not completely cure patients and the recurrence rate remains high: a year after the surgery, endoscopic recurrence develops in 35–85% of patients, and clinical recurrence — in 10–38% of cases. By the third year of follow-up, the recurrence rate increases to 85–100% and 34–86%, respectively [2]. According to the literature, the CD recurrence detected during endoscopy develops either in the "neoterminal" ileum, or directly in the anastomosis [3,4]. This fact has caused concern among surgeons as to which type of anastomosis is accompanied by a low risk of ischemia, minimizes reflux of intestinal contents into the small intestine and prevents excessive bacterial growth in the ileum [5,6]. A number of studies have been published in which it is claimed that stapled "side-to-side" anastomosis is associated with a low incidence of postoperative recurrence [7–9]. In a retrospective study by Scarpa M., et al., 141 patients with CD were presented. No significant differences in recurrence rate was detected between the stapled and hand sewn method of anastomosis [10]. The results obtained were confirmed in a randomized controlled trial of McLeod R.S. Among 139 patients after 12 months, endoscopic recurrence occurred in 42.5% of patients after hand sewn anastomosis and in 37.9% after

Table 1. *Clinical criteria in patients with remission and recurrence*

	Recurrence (*n* = 54)	Remission (*n* = 76)	*P*
Stapled anastomosis	25 (46.3%)	32 (42.1%)	0.2
Hand sewn anastomosis	29 (53.7%)	44 (57.9%)	0.3
Gender (male)	31 (57.4%)	41 (53.9%)	0.18
Age, years (median, min-max)	28.5 (18–68)	28 (18–70)	0.5
CDIC[1]	10 (18.5%)	8 (10.5%)	0.2
Anamnesis, months (median, min-max)	48 (4–168)	33 (3–360)	0.11
Previous treatment	26 (48.1%)	33 (43.4%)	0.2
H-B[2] index (average point, min-max)	5 (3–10)	5 (2–14)	0.5
Laparoscopy	21 (38.8%)	25 (32.9%)	0.2
Operation time, minutes (median, min-max)	200 (120–390)	190 (90–450)	**0.03**
Lesion extent, cm (median, min-max)	20 (5–100)	20 (8–150)	0.3
Lesion of the jejunum	9 (16.6%)	6 (7.9%)	0.2
Abdominal mass	39 (72.2%)	60 (78.9%)	0.1
Abscess	8 (14.8%)	23 (30.2%)	**= 0.059**
Post-opcomplication	8 (14.8%)	13 (17.1%)	0.2
AZA[3]	44 (81.5%)	68 (89.5%)	0.1
BIO[4]	18 (33.3%)	27 (35.5%)	0.2

(CDIC[1] — Crohn's disease in the form of ileocolitis; H-B[2]– Harvey-Bradshaw index; AZA[3] — Azathioprine; BIO[4] — Biological therapy)

stapled anastomosis ($p = 0.55$) [11]. However, an earlier work by Muñoz-Juárez M., et al., based on an analysis of 138 patients operated on for CD, clearly indicates a significant decrease in the recurrence rate after a stapled anastomosis [12].

Taking into account these disagreements, we analyzed results in 130 patients with CD.

PATIENTS AND METHODS

The retrospective cohort study included 130 patients with CD who underwent surgery for a complicated CD in 2012–2017. Males were 72/130 (55.3%), females — 58/130 (44.7%). The median age was 28 (18–70) years. In 112/130 (86.2%) cases there was CD in the form of terminal ileitis, in the remaining 18/130 (13.2%) cases — in the form of ileocolitis. In 7 (5.4%) cases, there was an additional lesion of the jejunum.

Abdominal mass before surgery was detected in 99/130 (76.2%) cases, and intra-abdominal abscess — in 31/130 (23.8%) patients. The median disease history was 36 (3–360) months. In 112/130 (86.2%) cases, ileocecal resection with anastomosis was performed, in 18/130 (13.8%) cases — resection of the terminal ileum with the right colon and ileo-transverse anastomosis. The extent of the surgery volume was associated with the involvement of the colon in the inflammation. The extent of the lesion averaged 25 ± 1.6 (5–150) cm. 59/130 (45.4%) patients had previous prolonged conservative treatment for Me = 3 (1–7) months, including antibiotics (in 55/59 (93.2%) cases) and steroids (in 26/59 (44.1%) cases). In the remaining 71/130 (54.6%) patients, preoperative treatment, including antibacterial and steroid therapy, was carried out for Me = 7 (1–14) days. The Harvey-Bradshaw disease activity index, immediately before surgery, was Me = 5 (2–14) points. Laparoscopic procedures were performed in 46/130 (35.4%)

cases. The average operation time was 200 (90–450) minutes. Stapled "side-to-side" anastomosis was done in 57/130 (43.8%) patients, while hand sewn "end-to-end" anastomosis — in 73/130 (56.2%).

Post-op complications occurred in 21/130 (16.2%) cases. After surgery, azathioprine — 112/130 (86.2%) was used as anti-recurrence therapy for most patients, while biological therapy — in 31/112 (23.8%) patients. In 14/130 (10.7%) patients, anti-recurrence therapy was carried out in a single mode with a biological drug.

RESULTS

Follow-up had a median of 28.5 (1.9–95.4) months. Recurrence developed in 54/130 (41.5%) patients in 18.5 (12–41) months after surgery.

It should be noted that the groups were comparable by the type of the anastomosis ($p = 0.08$). Initially, we compared various clinical criteria in patients with recurrence and remission. The following signs were assessed: type of anastomosis, gender, age, presence of ileocolitis, duration of the disease, the fact of conservative treatment before the first surgery, Harvey-Bradshaw index, laparoscopic procedures, operation time, extent of lesion before primary surgery, presence of jejunum lesion in the anamnesis, abdominal mass or abscess before surgery in abdominal cavity, early postoperative complications, anti-recurrence therapy with azathioprine or biological drugs (Table 1).

It is interesting to note that in the group of patients with remission, cases with diagnosed abdominal abscess prevail, while there is a borderline reliability of the results ($p = 0.05$). This fact will be separately verified with further multivariate analysis. Moreover, unexpected

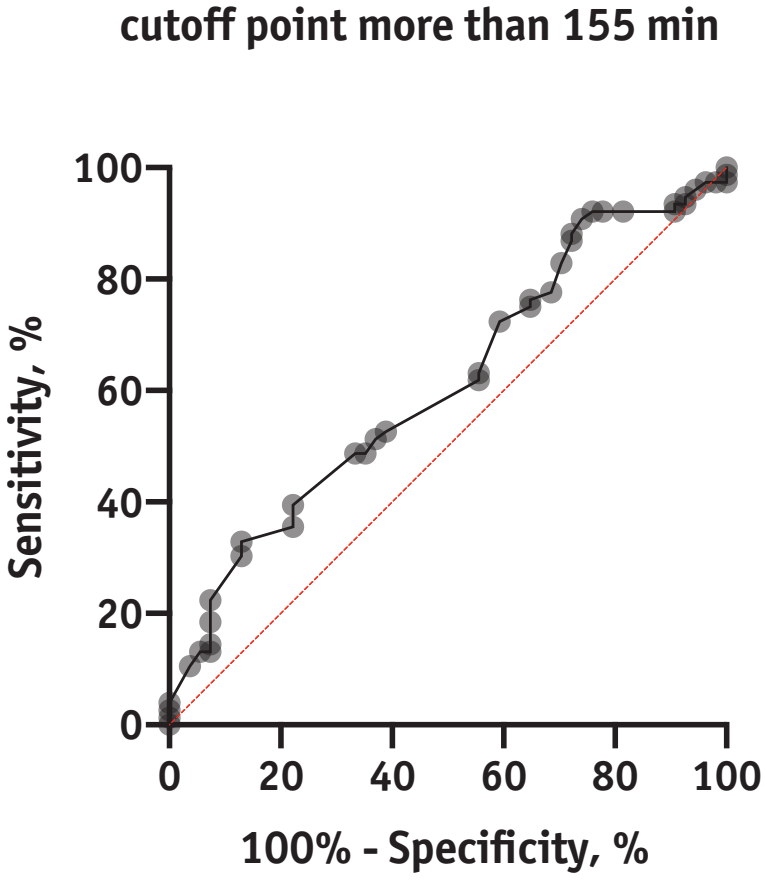

Figure 1. *ROC curve for determining the cut-off point for the duration of operations*

Table 2. *Odds ratio and confidence interval for risk factors for CD recurrence*

Predictors	Column A	Column B	Column C
	Univariate models (each variable is included separately) OR (CI)	**Multivariate model (all variables are included simultaneously) OR (CI)**	**Multivariate model (some variables are excluded) OR (CI)**
Stapled anastomosis	(0.587–2.393)	1.468 (0.576–3.744)	
Gender	1.151 (0.570–2.324)	1.955 (0.791–4.835)	
Age, years	1.000 (0.969–1.032)	1.005 (0.965–1.046)	
CDIC[1]	1.932 (0.708–5.273)	3.102* (0.842–11.43)	
Anamnesis, months	1.001 (0.994–1.007)	1.000 (0.991–1.008)	
Previous treatment	1.210 (0.601–2.438)	1.592 (0.644–3.937)	1.168 (0.541–2.521)
H-B[2]index	1.033 (0.872–1.224)	1.041 (0.841–1.290)	1.055 (0.881–1.264)
Laparoscopy	1.339 (0.646–2.776)	1.135 (0.412–3.128)	
Operation time, minutes	1.005* (1.000–1.010)		
Surgery duration over average (200 minutes)	1.371 (0.674–2.792)		
Operation time over 155 minutes	**2.914** (1.146–7.405)**	**6.278*** (1.799–21.91)**	
Lesion extent, cm	0.990 (0.970–1.011)	0.994 (0.969–1.019)	
Lesion of the jejunum	2.333 (0.778–7.001)	1.938 (0.514–7.312)	
Abdominal mass	0.693 (0.308–1.561)	0.501 (0.155–1.615)	0.872 (0.360–2.112)
Abscess	**0.401** (0.164–0.982)**	**0.293** (0.0945–0.909)**	**0.415* (0.156–1.108)**
Post-opcomplication	0.862 (0.330–2.251)	1.126 (0.351–3.619)	1.206 (0.424–3.435)
AZA[3]	0.518 (0.190–1.413)	0.504 (0.138–1.838)	0.428 (0.137–1.341)
BIO[4]	0.907 (0.435–1.893)	0.524 (0.192–1.433)	0.674 (0.289–1.573)

(CDIC[1] — Crohn's disease in the form of ileocolitis; H-B[2]– Harvey-Bradshaw index; AZA[3] — Azathioprine; BIO[4] — Biological therapy)
*(*p > 0.05; ** p < 0.05; ***p < 0.01)*

results were obtained when comparing the operative. Thus, the surgery duration exceeding 200 minutes was significantly associated with an increase in the recurrence rate of the disease ($p = 0.03$). Since the difference between the two groups is 10 minutes, we made additional analysis to identify the cut-off point using the ROC curve and the Yuden index (Fig. 1). As a result, the value of the point < 155 minutes was obtained, which will be used in further analysis.

To identify the predictors of recurrence, univariate and multivariate analysis was carried out.

The first step was to consider each of the above factors separately in univariate models, then all the factors in one model.

The odds ratio and coincidence intervals with confidence can be seen in Table 2. Figure 2 shows the results of univariate (each coefficient is included in turn) and multivariate (coefficients are included all together) models.

As a result of this analysis, it was revealed that the type of anastomosis does not affect the risk of the disease recurrence. Moreover, among the significant factors is the operation time.

Its exceeding 155 minutes in the univariate model increases the chance of recurrence by 2.9 times ($p < 0.05$), and in the multivariate model — by 6.3 times. In addition, in the univariate model (Table 2, column A), the presence of an abscess reduces the chances of recurrence by about 2.5 times (1/OR = 1/0.4), and in the multivariate model (Table 2, column B) — by about 3.4 times (1/OR = 1/0.29). On the conjugacy table, the presence of an abscess is less common in patients with recurrence ($p = 0.05$). We assumed that due to the inclusion of a large number of signs, this factor is most likely associated with other characteristics and therefore gives a contradictory result. In this regard, we conducted another multivariate analysis (optimized), in which we excluded several variables and left only the fact of previous therapy and other characteristics of the patient indicated in Table 2 in column B (Fig. 3). At the same time, the significance of the presence of an abscess

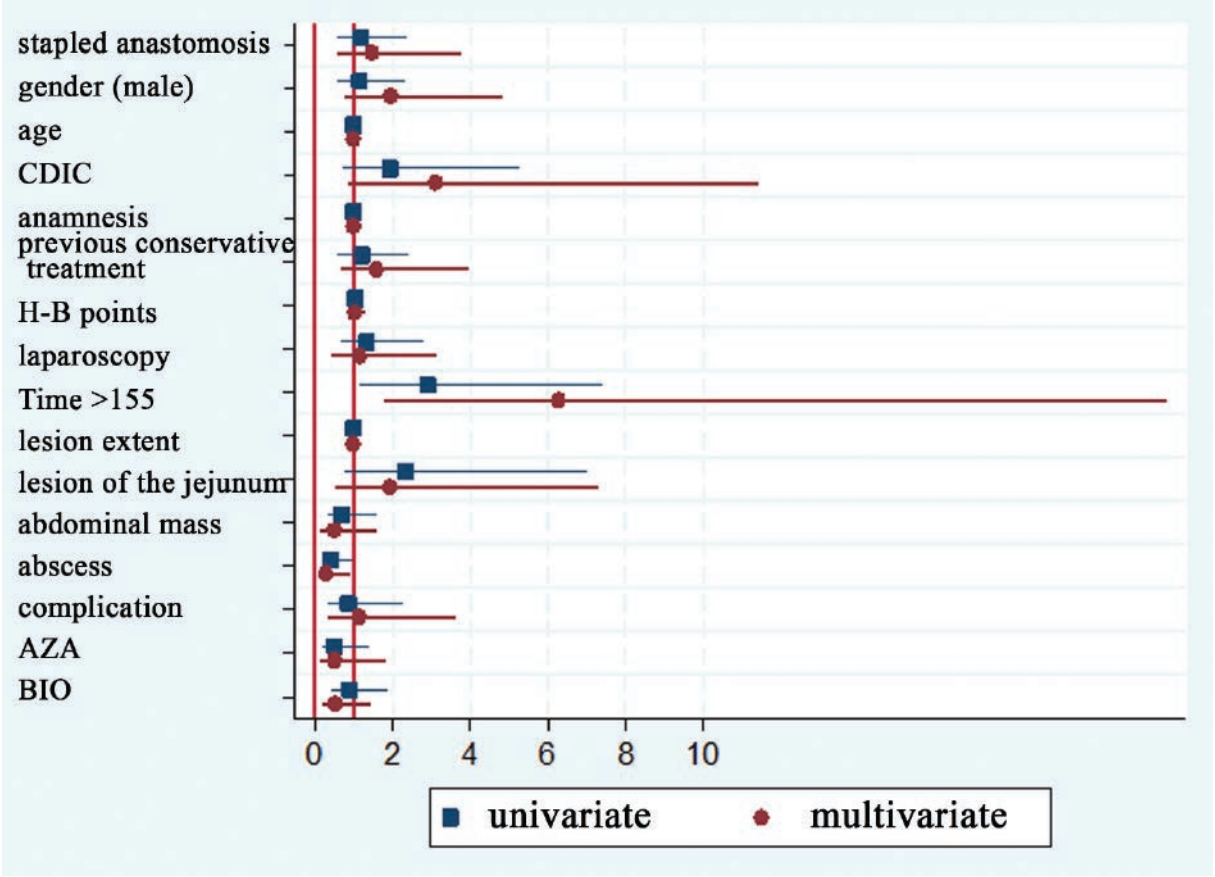

Figure 2. *Univariate and multivariate model for analyzing risk factors for the likelihood of CD recurrence*

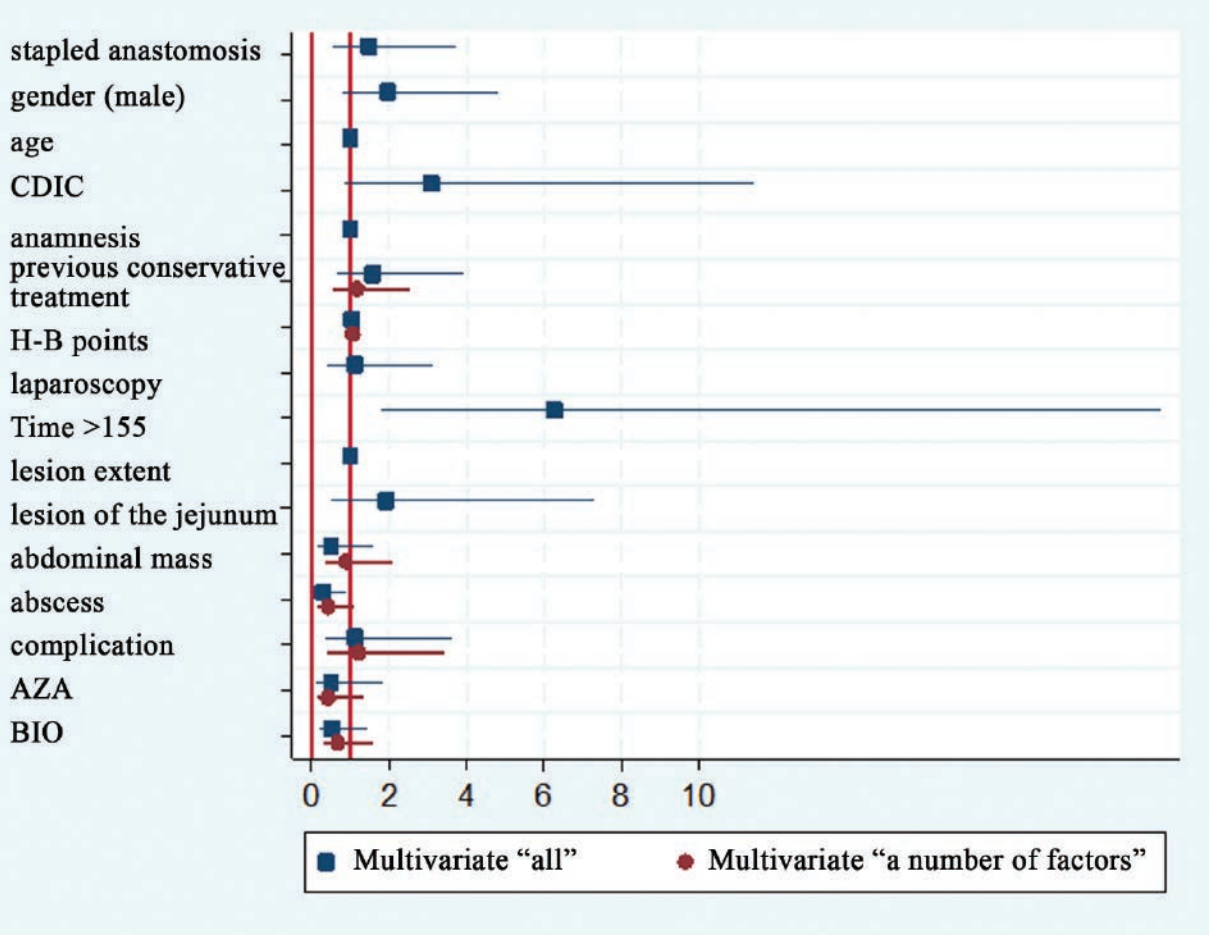

Figure 3. *Optimized univariate and multivariate model for analyzing risk factors for the likelihood of CD recurrence*

decreases ($p > 0.05$). This conclusion proves the connection of this criterion with other characteristics, which leads to a false increase in the probability of recurrence.

DISCUSSION

In 2014, a team of authors from China published a meta-analysis on the comparison of two types of anastomosis in ileocecal resection. The work included 8 studies summarizing the results of treatment in 821 patients, among whom in 396 (48.2%) cases the stapled anastomosis was performed and in 425 (51.8%)–hand sewn anastomosis. It is interesting to note that 3 out of 8 studies were randomized. A 5-fold reduction in the risk of the disease recurrence after "side-to-side" stapled anastomosis was found. It is extremely important to emphasize that after analyzing the isolated results of three randomized trials, our colleagues did not reveal any significant differences in the incidence of CD recurrences ($p = 0.2$) and re-operations for CD recurrence ($p = 0.12$) in the groups of patients with hand sewn or stapled anastomoses [13]. Another meta-analysis was done by Simillis C., et al. in 2007, which included 8 papers analyzing the effect of the type of anastomosis on the late results of CD treatment [14]. A total of 661 patients who underwent 712 intestinal resections were analyzed. In 383 (53.8%) cases, hand sewn anastomosis was formed, and in 329 (46.2%) – stapled anastomosis. When analyzing the late results, no correlation was found between the CD recurrence rate and the anastomosis type. It should be emphasized that the meta-analysis included 5 retrospective studies. McLeod R.S., et al., in their multicenter randomized study, analyzing the late results of surgery for CD for 12 months who had "end-to-end" and "side-to-side" anastomoses, demonstrated an equal CD

recurrence rate as for endoscopic signs (42.5% vs. 37.9%; $p = 0.55$), and by clinical manifestations (21.9% vs. 22.7%; $p = 0.92$) [11].

In a meta-analysis published in 2018, Feng J.S., et al. cautiously concluded that a stapled "side-to-side" anastomosis is preferable to hand sewn one [15]. However, the authors themselves noted in conclusion that the number of selected controlled studies was small, more than half of the studies were retrospective, and the follow-up time between the groups was different, which indicates the heterogeneity.

It turned out to be very interesting that on the issue of comparing different types of anastomoses in CD, a total of 4 meta-analyses were published from 2007 to 2018 [13–16]. In almost all works, the implementation of stapled "side-to-side" anastomosis is promoted, accompanied by both a lower postoperative complications rate and a CD recurrence.

However, many studies were not comparable, the groups of patients were heterogeneous, which has a negative impact on the reliability of the conclusions.

In this study, despite the retrospective nature, the lack of advantages of the stapled anastomosis in relation to the probability of postoperative recurrence was also demonstrated. It is interesting to note that the operation time, as an independent risk factor for the CD recurrence, has not been found in the available literature. The revealed pattern can be explained by the fact that longer procedures were associated with more severe and extensive complications of CD. In other words, patients with a developed recurrence initially had a more aggressive disease. Most likely, it is necessary to continue research in this area, giving preference to randomized trials.

CONCLUSION

The type of anastomosis does not affect the risk of the disease recurrence. The operation time exceeding 155 minutes increases the chance of recurrence by 6 times ($p < 0.01$).

AUTHORS CONTRIBUTION

Concept and design of the study: *Armen V. Vardanyan*

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Clinical and laboratory markers of the pre-test probability of inflammatory bowel diseases

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ABSTRACT *AIM: to distinguish clinical and laboratory markers that could help to diagnose irritable bowel syndrome (IBS) and forms of inflammatory bowel diseases (IBD) — Crohn`s disease (CD) and ulcerative colitis (UC), before colonoscopy.*
PATIENTS AND METHODS: the retrospective study included 712 patients (CD — 39.2%, UC — 37.8%, IBS — 23%). Clinical (complaints, anamnesis) and laboratory data from medical histories of patients with confirmed flare of IBD and IBS analyzed.
RESULTS: Patients with IBS had significant direct correlations with female gender, constipation, abdominal pain, presence of concomitant functional pathology, absence of extra-intestinal (EIM) and perianal (PAM) manifestations, weight loss due to food restriction ($p < 0.001$), hemoglobin ($p < 0.001$) and total protein levels ($p = 0.002$), and inverse correlations with levels of leukocytes, fecal calprotectin (FC) and C-reactive protein (CRP) ($p < 0.0001$). Patients with IBD had significant direct correlations with night symptoms ($p = 0.045$ for CD, $p = 0.023$ for UC) and diarrhea (up to 2 times per 24 hours in CD, $p = 0.018$; ⩾ 5 times per 24 hours in UC, $p < 0.001$) and FC ($p < 0.001$). CD was categorized by the presence of PAMs and EIMs, young age, fever, surgery in anamnesis ($p < 0.001$), weight loss ($p = 0.032$), elevated CRP levels, anemia ($p < 0.001$) and hypoproteinemia ($p = 0.032$). Patients with UC had direct correlations with male gender ($p = 0.008$), stool with blood and leukocytosis ($p < 0.001$) and had inverse correlation with abdominal pain ($p < 0.001$).
CONCLUSION: the identified clinical and laboratory markers can be used as criteria to distinguish IBD from IBS in routine clinical practice. However, further prospective studies are required for validation.

KEYWORDS: *Crohn`s disease, ulcerative colitis, inflammatory bowel diseases, clinical and laboratory markers, differential diagnostic criteria*

CONFLICT OF INTEREST: *The authors declare no conflict of interest.*

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INTRODUCTION

Inflammatory bowel diseases (IBD) are chronic progressive diseases that represent two main nosologies — ulcerative colitis (UC) and Crohn's disease (CD) [1,2]. All over the world, including Russia, there is an increase in new cases and the prevalence of these diseases [3,4]. Diagnosis of IBD often takes months from the onset of the first symptoms of the disease [5–7] due to insufficient data for diagnosis verification and often long-term management of patients as irritable bowel syndrome (IBS) [8].

At the same time, patients with IBS and IBD may have a similar clinical manifestation, which creates difficulties in diagnosing these nosologies [9]. Up to 50% of patients with IBD have symptoms that are criteria for the diagnosis of IBS [9], which leads to untimely verification of the correct diagnosis.

The clinical assessment of disease activity using indices is not always objective and does not allow to distinguish between the

Table 1. *Assessed clinical and laboratory characteristics*

Clinical indicators					
Gender			Age		
Incidence of liquid stool	**The presence of constipation**	**Blood impurity in stool**	**Abdominal pain**	**Nocturnal symptoms**	**Weight loss**
Extra-intestinal manifestations (EIM)					
Arthropathy	Ankylosing spondylitis	Skin lesion	Mucosal lesion	Eyes lesion	Involvement of the gastrointestinal tract
The presence of fever	Perianal manifestations (PAM)	Strictures	Fistulas	Abscess	Abdominal mass
Surgery on the small/large intestine					
Comorbidities					
Primarysclerosingc holangitis	Primary biliary cholangitis	Autoimmune hepatitis	Rheumatoid arthritis	Other rheumatological diseases	Functional pathologies
Family history of IBD, autoimmune diseases					
Laboratory indicators					
Hemoglobin	Leukocytes	Total protein	C-reactive protein (CRP)	Fecal calprotectin (FC)	

symptoms of IBD and IBS [10]. In a study by Lahiff et al., when comparing Best's indices (Crohn's Disease Activity Index (CDAI)) in individuals with CD and IBS, 62% of patients from the group with functional diseases had a CDAI level of more than 150 points [10], which indicates the presence of activity. Moreover, serological studies in patients with typical IBS symptoms without the presence of "red flags" have low diagnostic accuracy [11]. Due to the common presence of nonspecific complaints in IBD [1,2,12] and the absence of increased markers of systemic inflammation in the mild disease [1,2] before performing colonoscopy, it is necessary to search for new clinical and laboratory markers for the differentiation of IBD and IBS.

THE AIM OF THE STUDY

Determination of the clinical and laboratory symptoms that will allow to differentiate IBS and nosological forms of IBD before the videocolonoscopy is performed.

PATIENTS AND METHODS

We retrospectively analyzed the medical histories of 840 patients with UC, CD and IBS. The study included patients over 18 years of age with clinical exacerbation: 2 or more points on the Mayo index without evaluation of the endoscopic part for UC and more than 150 points on the Best index (CDAI) for CD [8,13], as well as patients with typical IBS complaints (abdominal pain associated with defecation, frequency change and/or forms of stool ⩾ 1 time per week for the last 3 months with a total duration of symptoms of more than six months) [14]. The study excluded patients with identified intestinal infections, comorbidities that could lead to gastrointestinal complaints (diverticular disease, adhesive disease), as well as in the presence of endoscopic remission in IBD.

The analysis evaluated patient complaints, anamnesis data and laboratory parameters (Table 1). The presence of strictures, fistulas, inflammatory infiltrates and abscesses was assessed both at the initial visit and in the anamnesis. Stool disorders (⩾ 25% of type 1–2 defecations

Table 2. *Characteristics of patients included in the study*

Characteristic	CD (*n* = 278)	UC (*n* = 270)	IBS (*n* = 164)	
Male gender — number (%)	124 (44.6%)	137 (50.7%)	53 (32.3%)	
Age — years				
Median	33	36	43	
IQR	26–44	29–49	33–60	
Hemoglobin — g/l				
Median	125 (*n* = 273)	126 (*n* = 255)	**Arithmetic mean**	133.42 ± 13.618 (*n* = 121)
IQR	112–134	109.5–140	**95% CI**	130.96–135.88
Leukocytes — 109/l				
Median	6.9 (*n* = 271)	7.3 (*n* = 255)	5.4 (*n* = 120)	
IQR	5.25–9.35	5.7–10.2	4.7–6.7	
Total protein — g/l				
Median	70 (*n* = 208)	72 (*n* = 194)	75 (*n* = 86)	
IQR	67–76	67–76	69–77	
C-reactive protein — mg/l				
Median, (min, max)	5.93 (*n* = 250)	3.4 (*n* = 237)	1 (*n* = 110)	
IQR	2.16–16.5	1.38–9.43	0.5–2.4	
Fecal calprotectin — mcg/g				
Median	600 (*n* = 158)	800 (*n* = 109)	26.18 (*n* = 77)	
IQR	221–1000	362–1800	25.0–64.16	

IQR — Interquartile range; CI — coincidence interval.

according to the Bristol Scale (BS) for constipation and ⩾ 25% of type 6–7 defecations according to BS for diarrhea), the presence of blood impurities, abdominal pain syndrome, weight loss (⩾ 5% of the original body weight), the presence of a temperature increase of more than 37.0°C were evaluated for 3 months prior to seeking medical help. Body weight loss was assessed in two variants: unintentional and against the background of compliance with dietary restrictions by the patient.

All patients subsequently underwent a video colonoscopy and other studies, if necessary, to confirm the main diagnosis.

The study was approved by the local Ethics Committee and was a part of a PhD thesis on the development of a program for the diagnosis and differential diagnosis of IBD using artificial intelligence.

Statistical processing was carried out with the StatSoft Statistica 12 program. Spearman's rank correlation coefficient was used as a measure to assess the relationship between variables. The choice of the criterion was determined by the fact that the analyzed data array contained both quantitative and categorical variables.

RESULTS

At the initial screening, the study included 840 patients, out of whom 128 patients were excluded due to the detection of comorbidities leading to similar clinical and laboratory picture, and endoscopic remission in patients with IBD. The characteristics of 712 patients included in the study are presented in Table 2.

Table 3. *Correlation analysis of clinical and laboratory parameters*

Indicators	Number of patients	Crohn's disease			Ulcerative colitis			Irritable bowel syndrome		
		Spearman's Coefficient	t(N-2)	*p*-level	Spearman's Coefficient	t(N-2)	*p*-level	Spearman's Coefficient	t(N-2)	*p*-level
Gender	712	–0.010099	–0.2691	0.787928	–0.099975	–2.6773	0.00759*	0.12683	3.407	< 0.001*
Age	712	–0.197422	–5.36608	< 0.001*	0.021571	0.57491	0.56554	0.204052	5.554	< 0.001*
Constipation	712	–0.143552	–3.86509	< 0.001*	–0.237563	–6.5166	< 0.001*	0.439989	13.0555	< 0.001*
Liquid stool 1–2 times/24hr	712	0.088808	2.37576	0.017777*	–0.125662	–3.3751	< 0.001*	0.041736	1.1131	0.266063
Liquid stool3-4ts/24hr	712	0.071478	1.90947	0.056604	0.001176	0.03132	0.97502	–0.08423	–2.2523	0.024611*
Liquid stool ⩾ 5 ts/24hr	712	–0.022625	–0.60302	0.546691	0.250339	6.88987	< 0.001*	–0.26204	–7.2349	< 0.001*
Blood impurity in stool	712	–0.152077	–4.09991	< 0.001*	0.560594	18.0385	< 0.001*	–0.46921	–14.1576	< 0.001*
Abdominal pain	711	0.007158	0.19061	0.848886	–0.200639	–5.4533	< 0.001*	0.22252	6.0774	< 0.001*
Nocturnal symptoms	711	0.0752	2.00804	0.045018*	0.085475	2.28431	0.02265*	–0.18551	–5.0269	< 0.001*
Weight loss	712	0.091214	2.44064	0.014905*	0.029321	0.78161	0.43471	–0.13952	–3.7542	< 0.001*
Weight loss on a diet background	712	–0.110161	–2.95331	0.003248*	–0.091083	–2.4371	0.01505*	0.232604	6.3727	< 0.001*
Absence of EIM	712	–0.272905	–7.5587	< 0.001*	0.020189	0.53806	0.5907	0.293158	8.17042	< 0.001*
Fever	712	0.156293	4.2164	< 0.001*	0.01085	0.28911	0.77258	–0.1937	–5.26093	< 0.001*
Absence of PAM	712	–0.403901	–11.7646	< 0.001*	0.280978	7.80116	< 0.001*	0.144737	3.89767	< 0.001*
Surgical treatment	712	0.328751	9.2754	< 0.001*	–0.199131	–5.4144	< 0.001*	–0.15185	–4.09376	< 0.001*
Functional pathology	712	–0.131001	–3.52097	< 0.001*	–0.103511	–2.773	0.0057*	0.271076	7.50402	< 0.001*
Family history of autoimmune diseases	710	0,015435	0.41075	0.681378	0.062023	1.65351	0.09867	–0.08925	–2.38437	0.017371*
Hemoglobin	649	–0.149972	–3.85834	< 0.001*	–0.022671	–0.5768	0.56427	0.219322	5.7179	< 0.001*
Leukocytes	646	0.035479	0.90092	0.367965	0.188648	4.87489	< 0.001*	–0.28198	–7.4584	< 0.001*
Total protein	488	–0.097088	–2.15051	0.032007*	–0.009991	–0.2203	0.82576	0.138778	3.0893	0.002121*
CRP	597	0.275101	6.97974	< 0.001*	0.007887	0.19238	0.84751	–0.3615	–9.4576	< 0.001*
FC	344	0.217022	4.11143	< 0.001*	0.337025	6.61999	< 0.001*	–0.63566	–15.2279	< 0.001*

** Changes in indicators are statistically significant ($p < 0.05$)*

IBS revealed a significant direct correlation with female sex, constipation, abdominal pain syndrome, the presence of concomitant functional pathology, absence of extra-intestinal and perianal manifestations, family history of autoimmune diseases ($p < 0.001$), and this category of patients tended to lose weight against the background of dietary restriction ($p < 0.001$) (Table 3). When analyzing laboratory parameters, there was an inverse correlation with the level of leukocytes, FC and CRP ($p < 0.001$), and a positive correlation with the level of hemoglobin ($p < 0.001$) and total protein ($p = 0.002$).

For the group of patients with IBD, significant positive correlations were found with nocturnal symptoms ($p = 0.045$ in CD, $p = 0.023$ in UC), FC ($p < 0.001$), as well as diarrheal syndrome (up to 2 times/24-hrwithCD, $p = 0.018$; ⩾ 5 times/24-hr with UC, $p < 0.001$). CD was characterized by: young age, the presence of perianal and extra-intestinal manifestations, fever, a history of surgery ($p < 0.001$), weight loss ($p = 0.015$), increased CRP, anemia ($p < 0.001$), and hypoproteinemia ($p = 0.032$). UC is characterized by: male sex ($p = 0.008$), the presence of blood in the stool ($p < 0.001$) and leukocytosis ($p < 0.001$), as well as an inverse correlation with abdominal pain ($p < 0.001$).

DISCUSSION

According to global statistics, IBS symptoms are detected in almost 50% of patients seeking help from a gastroenterologist [15]. Even if there are clear diagnostic criteria for IBS [14], some patients do not have a typical clinical picture, and functional disorders are regarded as unclassified IBS [16]. At the same time, the increasing incidence of IBD [5–7] requires careful identification of "red flags" in all patients with symptoms of intestinal dyspepsia.

Due to the fact that IBD can manifest itself with various clinical symptoms, we tried to include in the assessed signs the most frequent and characteristic complaints of patients according to clinical guidelines [1,2,14].

According to the results of our study, significant correlations with clinical and laboratory indicators were revealed, which, after further studies, can be used in routine clinical practice for effective differential diagnosis between UC, CD and IBS until the endoscopic examination. So, to distinguish between functional and organic pathology, there were significant correlations with such indicators as female sex, constipation, abdominal pain syndrome, weight loss against the background of predominant dietary restriction, concomitant functional pathology, absence of autoimmune diseases in relatives of the 1st line for IBS, and increased FC, nocturnal symptoms, diarrheal syndrome for IBD. Abdominal pain was predominantly a characteristic symptom for IBS, more likely due to the fact that this sign is a mandatory diagnostic criterion [14].

In turn, for further differentiation between types of IBD, age, the presence of perianal and extra-intestinal manifestations, fever, surgical treatment, weight loss, anemia, increased CRP and a decrease in total protein characteristic of CD, and blood impurities in the stool, male sex and the presence of a more pronounced diarrheal syndrome for UC should be taken into account.

The search for simple and affordable markers has been going on for a long time all over the world. Thus, Danese et al. developed and validated a questionnaire of the pre-test probability of Crohn's Disease (Red flag score), including 21 questions, for its differential diagnosis with IBS [17]. By multivariate analysis, 8 independent signs were identified that significantly correlate with CD and were included in this questionnaire: non-healing or complex perianal fistula, abscess or perianal lesions; a 1st-line relative with confirmed IBD; weight loss over the last 3 months (5% of body weight); chronic abdominal pain (for over 3 months); nocturnal diarrhea; subfebrility for 3 months; absence of abdominal pain for 30–45 minutes after eating, especially vegetables; absence of imperative urges [17]. Patients who scored 8 or more points as per the questionnaire had the highest probability of detecting CD compared to the population (OR 290, 95% CI 77–1086), sensitivity and specificity were 0.94 (95% CI 0.88–0.99) and 0.94 (95% CI 0.90–0.97), respectively [17]. The data obtained by us are similar to the results by Danese et al. However, according to the results of our study, there was no correlation with the presence of a burdened hereditary history for CD and abdominal pain syndrome.

Serological markers also have their place in the differentiation between functional disorders of the gastrointestinal tract and IBD. The CRP and erythrocyte sedimentation rate (ESR) used in routine practice are indicators of the presence and severity of systemic inflammation, but they are not specific to IBD and in many cases do not reflect histological inflammation [18]. Fecal calprotectin (FC) is an accurate marker of inflammation of the intestinal mucosal layer and one of the most convenient due to its noninvasiveness [19].

The FC level, which should be used to distinguish functional and organic pathology of the gastrointestinal tract, is still being discussed: many studies indicate that its values characteristic of IBS can range from 45 [20] to 188 mcg/g [21]. However, there are studies that reveal a range of FC in IBS of 16–294 mcg/g [22], which once again indicates the need for a comprehensive assessment of the clinical and laboratory parameters of the patient. The international consensus on standardization of FC measurements has not come to a consensus on the threshold value of FC, but at the same time it is emphasized that its level correlates with endoscopic and histological activity in IBD [19]. In our study, an increase in the FC level was considered to be a reference laboratory value of more than 50 mcg/g, and its increase had

a positive correlation with the presence of CD or UC in the patient.

When conducting a correlation analysis between laboratory parameters, data were obtained on a negative correlation for the levels of hemoglobin and total protein in CD, and on a positive correlation with the levels of CRP and FC. At the same time, the highest correlation values were noted for CRP and FC (0.275 and 0.217, respectively). In UC, a significant correlation was found only for leukocytes and FC (correlation coefficient 0.189 and 0.337, respectively, $p < 0.001$). The values of hemoglobin and total protein had an inverse correlation at values $p > 0.05$, which shows the lack of reliability of the results obtained. The increase in the level of CRP also showed no significant correlation ($p = 0.84$).

It should be noted that the diagnosis of IBD requires a lot of experience and knowledge of a number of details when collecting and evaluating the patient's anamnesis and laboratory parameters. A doctor who has had little experience in the management of patients with IBD may not focus on mucosal lesions or joint syndrome, which, in our opinion, should be attributed to differential diagnostic tools when verifying IBD. However, despite this, at the same time there is a tendency to increase the number of "falsely" diagnosed IBD, which increases the burden on the healthcare system due to increased visits to various specialists and repeated endoscopic interventions.

All of the above shows that it is necessary to develop questionnaires or programs that will already contain targeted questions and will help doctors identify a focus group of patients for further examination, which will allow timely diagnosis of these diseases.

Our research has a number of features and limitations that should be taken into account when using the results in practical work. Firstly, patients' complaints were evaluated retrospectively, and the quality of anamnesis collection depended on the qualifications and communication skills of the doctor. Secondly, there are difficulties in calculating the sample of patients. Thus, the estimated number of patients in St. Petersburg for UC is 293 people, for CD — 126 people [3,23,24]. However, it is not possible to calculate the IBS sample for St. Petersburg, given the limited data on morbidity, which makes it possible to use only a "global" sample. Thirdly, we did not conduct correlation studies depending on the extent of the pathological process (in UC and CD), the nature of the disease course in CD (stricturing, penetrating, inflammatory) and IBS (with a predominance of constipation, diarrheal syndrome and a mixed variant), as well as the severity of exacerbation of IBD. Fourth, a prospective study is required to validate the data obtained.

CONCLUSION

The identification of IBD among gastroenterological patients is a difficult task for many doctors due to the low prevalence and polymorphism of their manifestations, which leads to the diagnosis at a late stage against the background of the development of extra-intestinal manifestations and complications.

In the course of the study, clinical and laboratory indicators were identified that were more characteristic of IBD and IBS, which can help clinicians to pay attention to such patients in a timely manner and send them for a deep check-up. In our opinion, it is advisable to create and introduce questionnaires into the practice of primary care physicians to identify focus groups of patients suspicious of IBD, which will allow them to further conduct targeted follow-up tests and ensure the diagnosis of IBD at early stages.

It seems that the creation of questionnaires for early diagnosis of IBD will be possible during a prospective study.

AUTHORS CONTRIBUTION

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Predictors of steroid dependence and resistance in patients with ulcerative colitis

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ABSTRACT *AIM: to detect predictors of steroid dependence (SD) and steroid resistance (SR) in ulcerative colitis (UC).*
PATIENTS AND METHODS: a retrospective study was done. The medical documentation of 1,105 patients, who underwent inpatient treatment from 2018 to 2021, were analyzed. Sixty-nine percent of patients (n = 762) received systemic steroid therapy for UC. In accordance with inclusion and non-inclusion criteria, the medical documentation of 170 patients was selected for statistical analysis. Depending on the steroid status of patients, three groups were identified: group 1 (n = 56) with steroid dependence, group 2 (n = 56) with steroid resistance and group 3 — controls (n = 58), who got systemic GCS without the further SD and SR.
RESULTS: the incidence of SD was 33.9% (259/762), and SR was 22.04% (168/762). We identified the following predictors and SD risk factors: age of the disease onset < 30 years old (AOR = 0.960; 95% CI = 0.928–0.993; p = 0.019), start dose of prednisolone < 60 mg (AOR = 2.369; 95% CI = 1.030–5.441; p = 0.042), prescription of systemic GCS ⩾ 2 courses per year (AOR = 2.988, 95% CI = 1.349–6.619, p = 0.007), Mayo Index Score < 10 points (AOR = 0.631; 95% CI = 0.492–0.809; p < 0.001). The risk of SR statistically significant when Mayo Index Score ⩾ 10 points (AOR = 2.573, 95% CI = 1.094–6.050, p = 0.030), albumin level < 37.1 g/l (AOR = 4.571; 95% CI = 1.567–13.330; p = 0.005), CRP ⩾ 47.1 mg/l (AOR = 2.641; 95% CI = 1.102–6.328; p = 0.029).
CONCLUSION: it is rational to predict an individual response to GCS in patients with UC. With a high risk of SD and SR, it is advisable to consider early administration of biological and target therapy, avoiding re-prescription of GCS.

KEYWORDS: *ulcerative colitis, steroid dependence, steroid resistance*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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LIST OF ABBREVIATIONS

IBD — inflammatory bowel diseases
GCS — glucocorticosteroids
SR — steroid resistance
SD — steroid dependence
CRP — C-reactive protein
UC — ulcerative colitis
OCED — optimal clinical effective dose

INTRODUCTION

Systemic glucocorticosteroids (GCS) have been widely used in the treatment of ulcerative colitis (UC) since the middle of the XX century [1]. Nowadays, despite the emergence of new classes of drugs for the treatment of inflammatory bowel diseases (IBD), systemic corticosteroids remain the basic therapy for the induction of remission in moderate, severe and acute severe forms of UC. More than 50% of patients with UC have at least one course of systemic therapy of GCS during their lifetime [2]. Having a wide range of pharmacological effects, GCS inevitably have an undesirable effects, and therefore their use as maintenance therapy is unacceptable. According to Russian and foreign guidelines for UC, achieving steroidal remission is one of the fundamental goals of conservative approach, and the duration of systemic steroid therapy should not exceed 12 weeks [3–5]. Nevertheless, according to real clinical practice, the duration of GCS courses in IBD is on average

13–30 weeks, which significantly exceeds the recommended duration [6]. And in 34% of patients, there is a need to re-prescribe GCS within a year [7].

In assessing the effectiveness of UC treatment, the main aspect is the clinical, laboratory and endoscopic response to systemic steroid therapy.

When describing the hormonal status, the concepts are distinguished:

- Steroid resistance (SR) — the absence of positive shifts in clinical and laboratory indicators in severe UC attack against the background of the use of systemic GCS at a dose equivalent to 2 mg/kg of prednisolone per 24 hours for more than 7 days; or in the case of a moderate attack — the preservation of the activity of the disease with oral administration of GCS at a dose equivalent to 1 mg/kg of prednisolone, for 14 days.
- Steroid dependence (SD) — an increase in the activity of the disease with a decrease in the dose of GCS against the background of achieving initial improvement within 3 months from the start of treatment; or the occurrence of the disease recurrence within 3 months after the end of systemic steroid therapy [5].

According to a large epidemiological study of ESCApe in Russia in 2011, the incidence of SR in UC was 23%, and SD — 21%, i.e. almost half of the patients had an absence or loss of response to GCS [8].

Currently, the use of immunosuppressors (azathioprine, mercaptopurine, cyclosporine), genetically engineered biological and targeted therapy is available for the treatment of steroid-dependent and steroid-resistant forms of ulcerative colitis [5]. According to the mechanism of action, the following groups of drugs for the treatment of UC are distinguished: blockers of tumor necrosis factor alpha (infliximab, adalimumab and golimumab), a selective antagonist of integrin receptors (vedolizumab), an inhibitor of IL12/23 (ustekinumab), a modulator of sphingosine-1-phosphate receptors (ozanimod), as well as small molecules — inhibitors of JAK kinases (tofacitinib and upadacitinib).

Over the past three decades, foreign and Russian researchers have been trying to identify factors and develop criteria that could predict the effectiveness of conservative therapy and the risks of colectomy in UC. At the same time, the authors study clinical, laboratory, endoscopic and radiological parameters [9]. The Oxford Index [10], the Swedish Index [11], the ACE (Albumin, CRP and Endoscopy) index [12], which mainly assess the risks of colectomy against the background of systemic steroid therapy in acute severe UC, received the greatest prevalence in clinical practice.

It is noteworthy that many indices and criteria [10,11,13] were developed in the era of pre-biological therapy, and the dosages of GCS in these studies differ from those prescribed today. It is also worth noting that there is limited data in the literature on predictors of the SD formation. For example, Skrzypczak-Zielinska M. [14] and colleagues studied the genetic predictors of the response to steroid therapy, and the association of polymorphism of the FKBP5 gene and deletion of the MAPK14 gene with the development of SD in patients with UC was revealed. In some studies, it was found that the positivity of the serological marker p-ANCA is associated with a high risk of developing SD [15,16]. However, the use of genetic and serological markers is difficult in real clinical practice due to their high cost and low availability. A work on clinical predictors of the SD formation has been published in the Russian literature. According to Koinova, I.A. and co-authors, SD in UC is combined with frequent recurrences, a high score as per the Mayo index and the presence of extra-intestinal manifestations [17].

Some Russian experts in IBD associate the lack of response to systemic steroid therapy with the prescribed doses of the drug. According to Kharitonov A.G., one of the reasons for SR is the administration of low doses of GCS, insufficient to relieve inflammation with high activity of UC [18]. Alekseeva O.P. and co-authors studied construction dose-effect relationship in the first and repeated courses of systemic steroid therapy in patients with moderate and severe attacks of IBD. The optimal clinical effective dose (OCED) of prednisolone with statistical parameters of 50.70 ± 0.65 mg (p = 0.05) during the first course of therapy was determined. For repeated courses of prednisolone, the OCED

Table 1. *Characteristics of the patients*

Factors	SD (*n* = 56)	SR (*n* = 56)	Control (*n* = 58)	*p*
Gender, abs. (%) – Male – Female	 38 (67.9%) 18 (32.1%)	 32 (57.1%) 24 (42.9%)	 36 (62.1%) 22 (37.9%)	 0.504 0.504
Age, years, Me (Q1–Q3)	35 (30–43)	36 (30–44)	39 (34–50)	**0.03**
Course of the disease, abs.(%) – Acute – Chronic recurrent – Chronic permanent	 2 (3.6%) 5 (8.9%) 49 (87.5%)	 10 (17.9%) 14 (25%) 32 (57.1%)	 11 (19%) 20 (34.5%) 27 (46.5%)	 0.029 < 0.001 0.005
Extent of lesion, abs.(%) – Left-sided – Total	 10 (17.9%) 46 (82.1%)	 8 (14.3%) 48 (85.7%)	 8 (13.8%) 50 (86.2%)	 0.807 0.807
Previous therapy, abs. (%) – 5-ASA – immunosuppressors – cyclosporine – biological ± immunosuppressors – without specific therapy	 27 (27.3%) 23 (41.1%) 0 (0%) 6 (10.7%) 0 (0%)	 31 (31.3%) 8 (14.3%) 1 (1.8%) 10 (17.9%) 6 (10.7%)	 41 (41.4%) 9 (15.5%) 0 (0%) 5 (8.6%) 3 (5.2%)	 0.045 < 0.001 0.359 0.423 0.040
Body Mass, kg, M ± SD	69 ± 16	64 ± 15	70 ± 14	0.122

was 51.43 ± 1.55 (48.24–54.61) mg (p = 0.05), but the effectiveness of the therapy was 42% lower, which, according to the authors, indicates an insufficient effect of repeated courses of systemic steroid therapy for a period of 3 to 12 months [19].

So, we started our own study, the purpose of which was to identify predictors of SD and SR in patients with UC.

PATIENTS AND METHODS

A retrospective single-center study included 1,105 patients with UC in 2018–2021. Of these, 69% of patients (n = 762) underwent systemic steroid therapy for UC during their lifetime, including repeated courses of GCS in history. When analyzing medical documents, in most cases there was no comprehensive information about the duration and doses of systemic steroids, which were previously prescribed to patients in other medical institutions. In accordance with the inclusion criteria (established diagnosis of UC and administration of systemic steroid therapy in anamnesis) and non-inclusion criteria (age < 18 years, absence in primary medical documentation of data on the number and duration of courses of systemic steroid therapy, prescribed doses of GCS, absence of clinical laboratory and endoscopic data at the time of administration of systemic steroid therapy, and also, the transformation of the main diagnosis in the anamnesis), we selected the medical documentation of 170 patients for further statistical processing. Depending on the steroid status of patients, three groups were identified: group 1 (n = 56) with SD, group 2 (n = 56) with SR, and group 3 — control (n = 58), who were prescribed systemic therapy of GCS without further development of SD and SR. The following factors were analyzed as possible predictors of SD and SR:

- Clinical and demographic (gender, age of the patient, including at the time of the onset of the disease, heredity, smoking status, extent of lesion, presence of extra-intestinal manifestations, Mayo index);
- Laboratory (erythrocytes, hemoglobin, platelets, leukocytes, neutrophils, rod-shaped and segmented, lymphocytes, monocytes, ESR, total protein, albumin, globulins, albumin/globulin ratio, CRP, fibrinogen);
- Schemes of systemic steroid therapy (administration of topical corticosteroids in anamnesis,

Table 2. *Regression analysis to identify predictors and risk factors for steroid dependence*

Indicators	SD is present (*n* = 56)	SD is absent (*n* = 114)	HR	95% CI	*p*
Males, abs. (%)	38 (67.9%)	68 (59.6%)	1.428	0.728–2.804	0.3
Females, abs. (%)	18 (32.1%)	46 (40.4%)	0.7	0.357–1.324	0.3
Age of patient, years, Me (Q1-Q3)	35 (30.00–43.25)	37 (31.25–48.00)	0.971	0.943–0.999	**0.044**
Disease debut age, years, Me (Q1-Q3)	26 (21.00–32.00)	31 (23.00–41.75)	0.959	0.931–0.989	**0.007**
Heredity, abs. (%)	3 (5.7%)	5 (5.1%)	1.094	0.281–4.764	0.905
Smoking, abs. (%)	12 (22.0%)	11 (12.4%)	2.026	0.824–4.983	0.124
Lesion extent, abs. (%) – Left-sided – Total	 10 (17.9%) 46 (82.1%)	 16 (14.0%) 98 (86%)	 1.331 0.751	 0.561–3.161 0.316–1.782	 0.516 0.516
Acute course, abs.(%)	2 (3.6%)	21 (18.4%)	0.164	0.037–0.727	**0.017**
Extra-intestinal manifestations, abs. (%)	13 (23.2%)	21 (18.4%)	1.339	0.613–2.921	0.464
Starting dose of prednisolone < 60 mg, abs. (%)	23 (42.6%)	19 (18.4%)	3.280	1.575–6.835	**0.002**
Total number of GCS courses, Me (Q1-Q3)	2 (2–4)	1 (1–2)	1.537	1.204–1.962	**0.001**
⩾ 2 courses of GCS per year, abs. (%)	30 (53.6%)	29 (25.4%)	3.382	1.725–6.633	**< 0.001**
Prednisolone administration < 1 mg/kg, abs. (%)	22 (39.3%)	23 (20.4%)	2.532	1.251–5.124	**0.01**
Prednisolone administration > 2 mg/kg, abs. (%)	4 (7.1%)	12 (10.6%)	0.647	0.199–2.106	0.470
The course of GCS < 4 weeks, abs. (%)	13 (23.2%)	28 (29.8%)	0.713	0.333–1.527	0.383
The course of GCS > 12 weeks, abs. (%)	15 (26.8%)	10 (8.8%)	3.768	1.565–9.070	**0.003**
Escalation of the dose of GCS, abs. (%)	23 (41.1%)	23 (20.2%)	2.758	1.366–5.562	**0.005**
Administration of topical GCS (budesonide MMX), abs. (%)	10 (17.9%)	16 (14%)	1.331	0.561–3.161	0.516
Mayo Index, points, Me (Q1-Q3)	9 (7–9)	10 (8–11)	0.648	0.524–0.802	**< 0.001**

the starting dose of the first course of corticosteroids in terms of prednisolone, the number of courses of systemic steroid therapy during the year, the duration and dose of systemic steroid therapy during the year, escalation of the dose of corticosteroids).

Statistical Processing

Statistical analysis was carried out using the StatTech v.2.8.4. program.

Quantitative indicators were evaluated for compliance with the normal distribution using the Shapiro-Wilk and Kolmogorov-Smirnov criteria. Indicators of descriptive statistics included: number of cases (n), mean (M), standard deviation (SD), 95% coincidence interval limits (95% CI), median (Me), lower and upper quartiles (Q1–Q3). Absolute values with percentages were used to describe categorical data. To compare groups by quantitative indicator, Student's t-test, Tukey's test, Mann-Whitney's U-test, Kraskel-Wallis' test, and Dann's test with Holme's correction were used. The comparison of percentages in the analysis of multipole conjugacy tables was performed using Pearson's χ^2 criterion. The search for significant differences was carried out, the critical value of the level of which (p) was assumed to be 0.05. To assess the diagnostic significance of quantitative signs in predicting a certain outcome, the method of analysis of ROC curves was used. The separating value of the quantitative feature at the cut-off point was determined by the highest value of Youden's index.

Table 3. *Regression analysis to identify predictors and risk factors for steroid resistance*

Indicators	SR is present (*n* = 56)	SR is absent (*n* = 114)	HR	95% CI	*p*
Males, abs. (%)	32 (57.1%)	74 (64.9%)	0.721	0.375–1.387	0.327
Females, abs. ((%)	24 (42.9%)	40 (35.1%)	1.387	0.721–2.670	0.327
Age of patient, years, Me (Q1–Q3)	36 (30.00–44.00)	37 (32.00–47.75)	0.993	0.966–1.019	0.585
Disease debut age, Me (Q1–Q3)	27 (22.75–35.25)	28.5 (22.25–41.75)	0.995	0.969–1.021	0.689
Heredity, abs. (%)	2 (4.1%)	6 (5.8%)	0.688	0.134–3.540	0.654
Smoker status, abs. (%)	5 (11.4%)	18 (20.5%)	0.499	0.172–1.446	0.2
Lesion extent, abs. (%) – Left-sided – Total	 8 (14.3%) 48 (85.7%)	 18 (15.8%) 96 (84.2%)	 0.889 1.125	 0.361–2.190 0.457–2.773	 0.798 0.798
Acute course, abs.(%)	10 (17.9%)	13 (11.4%)	1.698	0.690–4.133	0.251
Extra-intestinal manifestations, abs. (%)	9 (16.1%)	25 (21.9%)	0.682	0.294–1.579	0.371
Starting dose of prednisolone < 60 mg, abs. (%)	9 (18.8%)	33 (30.3%)	0.531	0.231–1.221	0.136
Total number of GCS courses, Me (Q1-Q3)	2 (1–3)	2 (1–3)	0.928	0.780–1.105	0.401
2 ⩾ GCS courses per year, abs. (%)	17 (30.4%)	42 (36.8%)	0.747	0.377–1.483	0.405
Prednisolone administration < 1 mg/kg, abs. (%)	10 (18.2%)	45 (39.5%)	0.502	0.227–1.107	0.088
Prednisolone administration > 2 mg/kg, abs. (%)	6 (10.9%)	10 (8.8%)	1.273	0.438–3.702	0.657
The course of GCS < 4 weeks, abs. (%)	25 (45.5%)	16 (16.8%)	4.114	1.933–8.758	**< 0.001**
The course of GCS > 12 weeks, abs. (%)	5 (9.1%)	20 (17.5%)	0.470	0.166–1.327	0.154
Escalation of the dose of GCS, abs. (%)	20 (35.7%)	26 (22.8%)	1.880	0.933–3.789	0.077
Administration of topical GCS (budesonide MMX), abs. (%)	5 (8.9%)	21 (18.4%)	0.434	0.154–1.220	0.114
Mayo Index, points, Me (Q1-Q3)	10 (9–11)	9 (8–10)	1.717	1.339–2.201	**< 0.001**

RESULTS

According to data obtained, the incidence of SD among 762 patients receiving systemic steroid therapy was 33.9% (259/762), and SR– 22.04% (168/762). When comparing the groups by gender, lesion extent and body weight, they were homogenous (Table 1). Among patients with SD and SR, younger people prevailed compared to the control group ($p = 0.03$). Chronic continuous course of the disease was characteristic for patients with SD ($p = 0.005$), and acute disease was significantly more common in patients with SR and in the control group ($p = 0.029$). When comparing the groups, depending on previous therapy, it was revealed that 5-ASA were significantly more often used in patients of the control group ($p = 0.045$), immunosuppressants — in patients with SD ($p < 0.001$), and patients with SR were significantly more often without specific therapy ($p = 0.04$), which occurred mainly in the acute disease.

Regression analysis was carried out to identify predictors and risk factors for SD and SR.

Reliable risk factors for the SD (Table 2), according to our data, are: the age of the patient < 52 years, the age of the disease onset < 30 years, the starting dose of prednisolone < 60 mg, the total number of courses of systemic steroid therapy ⩾ 2 during life, as well as the administration of ⩾ 2 courses of systemic steroid therapy during year, Mayo index < 10 points. The threshold values of the indicators were obtained by sequentially constructing the ROC curve at the cut-off point, which

Table 4. *Regression analysis to identify laboratory predictors and risk factors for steroid dependence and steroid resistance*

Indicator	SD (*n* = 56)	SR (*n* = 56)	Control (*n* = 58)	*p*
Erythrocytes, × 10^{12}/l	4.42 ± 0.76	3.98 ± 0.77	4.33 ± 0.60	**0.012**
Hemoglobin, g/l	111.92 ± 24.92	108.19 ± 23.71	116.87 ± 22.91	0.197
Platelets, × 10^9/l	339.00 (275.20–416.50)	382.00 (303.00–507.65)	378.50 (298.35–450.93)	0.164
Leukocytes, × 10^9/l	9.00 (6.84–12.50)	9.26 (6.83–12.50)	9.90 (7.51–12.80)	0.636
Rod-shaped neutrophils, × 10^9/l	0.18 (0.10–0.41)	0.19 (0.08–0.40)	0.23 (0.11–0.36)	0.859
Segmented neutrophils, × 10^9/l	5.66 (4.22–9.14)	6.50 (4.73–9.15)	6.73 (4.56–8.63)	0.532
Lymphocytes, × 10^9/l	1.73 (1.18–2.38)	1.41 (1.12–2.04)	1.97 (1.34–2.55)	0.182
Monocytes, × 10^9/l	0.60 (0.42–0.69)	0.47 (0.34–0.80)	0.65 (0.36–0.91)	0.718
ESR, mm/hour	22.00 (11.50–32.00)	23.00 (14.00–43.00)	23.00 (14.00–32.00)	0.463
Total protein, g/l	65.43 ± 7.96	63.25 ± 7.53	65.61 ± 7.17	0.243
Albumin, g/l	37.00 (34.00–40.00)	34.00 (30.00–36.00)	36.00 (32.00–41.00)	**0.005**
Globulins, g/l	30.44 ± 5.99	30.83 ± 4.68	29.28 ± 6.13	0.607
Albumin/globulinratio	1.24 (0.98–1.39)	1.11 (0.95–1.26)	1.25 (1.06–1.48)	0.133
CRP, mg/l	11.75 (4.83–31.98)	51.30 (11.60–89.00)	14.90 (5.00–40.30)	**0.014**
Fibrinogen, g/l	3.10 (2.70–4.00)	3.81 (3.25–4.60)	3.5 (3.00–4.10)	**0.019**

corresponded to the highest value of Youden's index. Prescribing prednisolone at a dose of < 1 mg/kg and duration of over 12 weeks significantly influenced the SD development. It was also found that the escalation of the dose of GCS in the anamnesis demonstrates significance in the SD formation.

During the multivariate analysis, the following predictors and risk factors for the SD were identified:

- age of onset < 30 years (COR = 0.960, 95% CI = 0.931–0.990, *p* = 0.010, AOR = 0.960, 95% CI = 0.928–0.993, *p* = 0.019);
- starting dose of prednisolone < 60 mg (COR = 2.924, 95% CI = 1.387–6.160, *p* = 0.005, AOR = 2.369, 95% CI = 1.030–5.441, *p* = 0.042);
- administration of ⩾ 2 courses of GCS during the year (COR = 3.663, 95% CI = 1.790–7.493, *p* < 0.001 AOR = 2.988, 95% CI = 1.349–6.619, *p* = 0.007);
- Mayo index < 10 points (COR = 0.645, 95% CI = 0.517–0.804, *p* < 0.001 AOR = 0.631, 95% CI = 0.492–0.809, *p* < 0.001).

It was revealed that gender, the lesion extent, heredity, smoking status, extra-intestinal manifestations, the administration of topical GCS in the anamnesis are not associated with the SD.

When assessing the risk of SR(Table3), we have found significance with Mayo's index of ⩾ 10 points. The threshold value of the indicator was obtained by constructing the ROC curve at the cut-off point, which corresponded to the highest value of Youden's index. It was revealed that the duration of systemic steroid therapy was < 4 weeks. It is a risk factor for the SR development. However, this is due to the fact that 48.2% (*n* = 27) of patients with SR were operated on, and therefore the therapy of GCS was terminated prematurely.

Other clinical and demographic factors, as well as the schemes of systemic steroid therapy, did not significantly affect the SR development.

In the regression analysis of laboratory parameters (Table 4) it was found that the level of albumin, as well as the level of inflammatory markers (CRP and fibrinogen) significantly affect the SR development.

Using the construction of ROC curves, threshold values of laboratory parameters were identified:

albumin (< 37.1 g/l), CRP (⩾ 47.1 mg/l), fibrinogen (⩾ 3.4 g/l).

During the multivariate analysis, the following predictors and risk factors for the SR were identified:

– Mayo's index ⩾ 10 points (COR = 3.391, 95% CI = 1.556–7.389, p = 0.002 AOR = 2.573, 95% CI = 1.094–6.050, p = 0.030);
– albumin < 37.1 g/l (COR = 5.320, 95% CI = 1.904–14.865, p = 0.001 AOR = 4.571, 95% CI = 1.567–13.330, p = 0.005);
– CRP ⩾ 47.1 mg/l (COR = 4.014, 95% CI = 1.800–8.953, p = 0.001 AOR = 2.641, 95% CI = 1.102–6.328, p = 0.029).

DISCUSSION

Predictors of aggressive UC and risk of colectomy are actively discussed by Russian and foreign authors [5,20–24]. In our work, we did not aim to evaluate the predictors of colectomy in UC, focusing on the predictors and risk factors for SD and SR.

The data we obtained on the risks of SD at the onset of the disease at the age of < 30 years correlate with the results of Reinisch W., who demonstrated that the age of ⩽ 40 years at the time of diagnosis is associated with a more severe disease and short periods of remission [20].

Inadequate courses of systemic steroid therapy significantly affect the SD development. The Russian clinical guidelines for the diagnosis and treatment of UC [5] strictly regulate the doses of prednisolone and the duration of courses of systemic steroid therapy. In case of UC recurrence, requiring repeated administration of GCS for a year or less, it is recommended to prescribe immunosuppressants (azathioprine or mercaptopurine) simultaneously with GCS. According to our data, conducting ⩾ 2 courses of GCS during the year with high reliability affects the SD development, which confirms the need for immunosuppressive therapy during the second course of GCS during the year. In case of UC exacerbation after two or more courses of systemic GCS carried out during the year, it is necessary to consider the administration of biological or targeted therapy. The initial administration of low doses of prednisolone (< 60 mg), as well as the subsequent escalation of the dose, contribute to the SD formation, and therefore it is advisable to recommend hospitalization to patients not only with a severe attack of UC, but also with a moderate attack to a hospital for the administration of an adequate dose of prednisolone in accordance with clinical recommendations.

Laboratory indicators (albumin and CRP levels), as well as the clinical and endoscopic Mayo's index can be routinely used in clinical practice to assess the risk of SR, allowing the doctor to be wary of the ineffectiveness of steroid therapy from the first days of treatment. It is advisable for this category of patients from the first days of admission to do a specific tests (Diaskin's — test, quantiferon test, T-SPOT) to exclude tuberculosis infection in order to timely prescribe genetically engineered biological and targeted therapy for the SR development.

CONCLUSION

In the era of personalized medicine, it is rational to predict an individual response to GCS. Predictors of a high risk of SD and SR in patients with ulcerative colitis have been identified, which can be used in clinical work. In this category of patients, it is advisable to consider the early administration of genetically engineered biological and targeted therapy, avoiding repeated use of GCS.

AUTHORS CONTRIBUTION

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Clinical and epidemiological aspects of ulcerative colitis in the Irkutsk region

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ABSTRACT *AIM: to study sociodemographic, clinical and epidemiological features in patients with ulcerative colitis in the Irkutsk region (Russia).*

PATIENTS AND METHODS: the database of the Irkutsk IBD Center included 1,122 patients with ulcerative colitis (UC) registered from 01.01.2006 to 31.12.2019. The study is retrospective with a focus on the results of follow-up, check up and treatment in different periods of their disease (acute attack, chronic course, remission). Statistical analysis was performed according to the principles of the International Committee of Medical Journal Editors (ICMJE).

RESULTS: the incidence of inflammatory bowel disease in the Irkutsk Oblast over the previous 14 years has increased by 2.7 times, of ulcerative colitis — by 3.1 times and was 3.91 person-years per 100,000 population. The prevalence of UC was 68.5 per 100,000 population. The annual increase in new UC cases was 46.6 ± 8.2. Most patients had total lesion (68.4%) and moderate-to-severe disease (46.9%). Extra-intestinal manifestations (13.6%) were represented by skin lesions (40.7%). Body weight deficiency occurred in 9.9% in females and in 5.1% in males. The probability of colectomy was 1.4/100 patient-years (follow-up period was 7049.5 patient-years; n = 1122). Patients underwent urgent operations in 76.3%. Postoperative mortality was 1.03/100 patient-years (exposition time — 291.6 years, n = 3). Total mortality for the entire follow-up period was 1.8% — 0.34/100 patient-years (exposition time — 4440.8 years).

CONCLUSION: objective epidemiological data, clinical features and treatment options for patients with ulcerative colitis in long-term follow-up in the Irkutsk Oblast are presented. The results of such studies on a national scale can serve as a platform for further scientific research and planning of socio-economic programs.

KEYWORDS: *ulcerative colitis, incidence, prevalence, non-surgical treatment, surgical treatment*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Ulcerative colitis (UC) refers to chronic inflammatory bowel diseases of unclear etiology, with lesions of the large intestine and suspected multifactorial trigger components with inadequate immune response in genetically predisposed individuals [1]. The annual incidence of UC varies and is observed in the range of 8.8–23.1 per 100,000 patient-years in North America; 0.6–44.0 in Europe and 7.3–17.4 in Oceania [2]. In the XXI century, the incidence of UC in developed Western countries has stabilized. At the same time, since the nineties of the XX century, according to an annual analysis, there has been an increase in the incidence in Asia, Africa, South America and Brazil by 14.9% [10.4–19.6], in Taiwan — by 4.8% [1.8–8.0]) [1,2]. In China, in the year of 2000, the diagnosis of UC was detected in 10,000 patients, and in 2010, the diagnosis of inflammatory bowel diseases (IBD) was already recorded in 266,394 [3]. In general, the first peak of morbidity occurs in the age

group of 20–40 years, and the second — after 60 years, with the same gender distribution [2]. It is noted that in developing countries, UC is a more common disease than Crohn's disease (CD). In India, the incidence of UC is 6.02 per 100,000 population, which is much lower than in the USA (8.8 per 100,000) and Sweden (20.0 per 100,000). Numerous studies have shown the predominance of the urban population among patients with UC [4,5]. Attention is drawn to the existing worldwide spread of data on morbidity (0.4–44.5 per 100,000 population) and the prevalence of UC (from 1.5 to 505.0 per 100,000 population) within and between geographical regions, reaching maximum values in the countries of Scandinavia, North America, Canada, Israel. The prevalence of IBD is expected to continue to increase in high-income countries, and is also likely to accelerate in developing countries. This is partly due to the growing number of cases of UC in old age and the aging of patients, as well as a decrease in mortality due to the introduction of genetically engineered biological therapy (GEBT) into practice and a change in the paradigm of both conservative and surgical treatment [6–8].

The indicators of mortality in UC are in a wide range of values and depend on the socio-economic level of the reporting country. According to a meta-analysis published in 2007 by Jess, T. et al., among patients with UC, the average percentage of deaths was 17% (11; 30). In this subgroup of patients, the most common causes of death were colorectal cancer (CRC) 37% (24; 44) and surgical or postoperative complications 44% (17; 100).

Other causes indicated by the authors were associated with a severe course of the disease (toxic megacolon, bowel perforation, mesenteric thrombosis, secondary myocardial infarction on the background of anemia and decompensated liver disease due to primary sclerosing cholangitis) [9].

The number of population-based studies of UC in Eastern Europe, including in the Russian Federation, is limited. The prevalence of UC in Russia consists of the results of individual epidemiological studies and data from the registers of individual healthcare institutions [10]. According to the Ministry of Health of Russia, the increase in UC from 2012 to 2015 was 31.7%. According to published data from the leading centers of IBD, the prevalence of UC in the Moscow region is 19.3 per 100,000 population; 40.0 in the Republic of Tatarstan; 49.0 — in the Novosibirsk region; 22.0 per 100,000 adult population in the Chelyabinsk region [11,12,13].

AIM

The purpose of this study is to evaluate the clinical and epidemiological indicators and sociodemographic characteristics of patients suffering from ulcerative colitis living in the Irkutsk region and Irkutsk city.

PATIENTS AND METHODS

The Irkutsk region is located in the southeastern part of the Siberian Federal District; the area of the territory is 774.8 thousand square kilometers. In the west, the region borders with the Krasnoyarsk Territory, in the northeast — with the Republic of Sakha (Yakutia), in the east — with the Trans–Baikal Territory, in the east and south — with the Republic of Buryatia, in the southwest — with the Republic of Tyva. The population of the region as of 2021 was 2,375,640 people. 78.8% of the region's population lives in urban areas. The population density is low — 3.07 people/km².

In connection with the data of Irkutsk Scientific Center of Surgery and Traumatology (ISCST), on the basis of the Irkutsk Regional Clinical Hospital (IRCH), since 1996, all patients of the city and region with an verified or suspected diagnosis of inflammatory bowel disease were sent to the outpatient unit for coloproctologist's consultation. By the order of the chief physician of the IRCH dated 01.03.2006, the IBD office was established on a functional basis. By that time, a separate registry for patients with IBD had been created, internal documentation had been developed, and an electronic unified database of patients had been created. This allowed the authors to analyze the incidence,

prevalence, and features of clinical manifestations of IBD in long-term follow-up. The present study is based on a prospective and retrospective analysis of the results of follow-up, tests and treatment of patients in different periods of the disease (acute, chronic, remission), with an established diagnosis of ulcerative colitis in accordance with the diagnostic criteria of the disease [14].

The unified database is constantly updated and includes personal data, information about the onset of the disease, severity of the course, extra-intestinal manifestations, concomitant pathology, medications received, surgical treatment and other indicators, a total of 126 parameters [15]. All the patients signed an informed consent to the use of depersonalized information for scientific purposes.

In the period from 01.01.2006 to 31.12.2019 in the database of the IBD center of Irkutsk city 1,122 patients suffering from UC were registered. The period of 2020–2021 was excluded from the epidemiological analysis due to the conversion of medical facilities to provide assistance to the population with the new COVID-19 coronavirus infection and restrictions in working with profile patients.

To calculate the epidemiological characteristics, the generally accepted indicators *"prevalence"* and *"morbidity"* per 100,000 inhabitants, the indicator *"person-years"/"patient-years"*, which most accurately reflects the real picture of the phenomenon under study and directly includes in the denominator the time of observation of a specific object, were used [16].

Statistical processing of the results of the study was carried out using the Statistica for Windows 10.0 program (StatSoft Inc., USA). The statistical analysis was performed according to the principles of the International Committee of Medical Journal Editors (ICMJE). Quantitative data are described using averages with the error of the mean, minimum, maximum and median with upper and lower quartiles, rate and fractions were calculated (in %). Descriptive statistics methods were used to generalize and evaluate demographic continuous and discrete variables. To describe qualitative indicators, rate and fractions (in%), a two-way 95% coincidence interval (95% CI) were calculated.

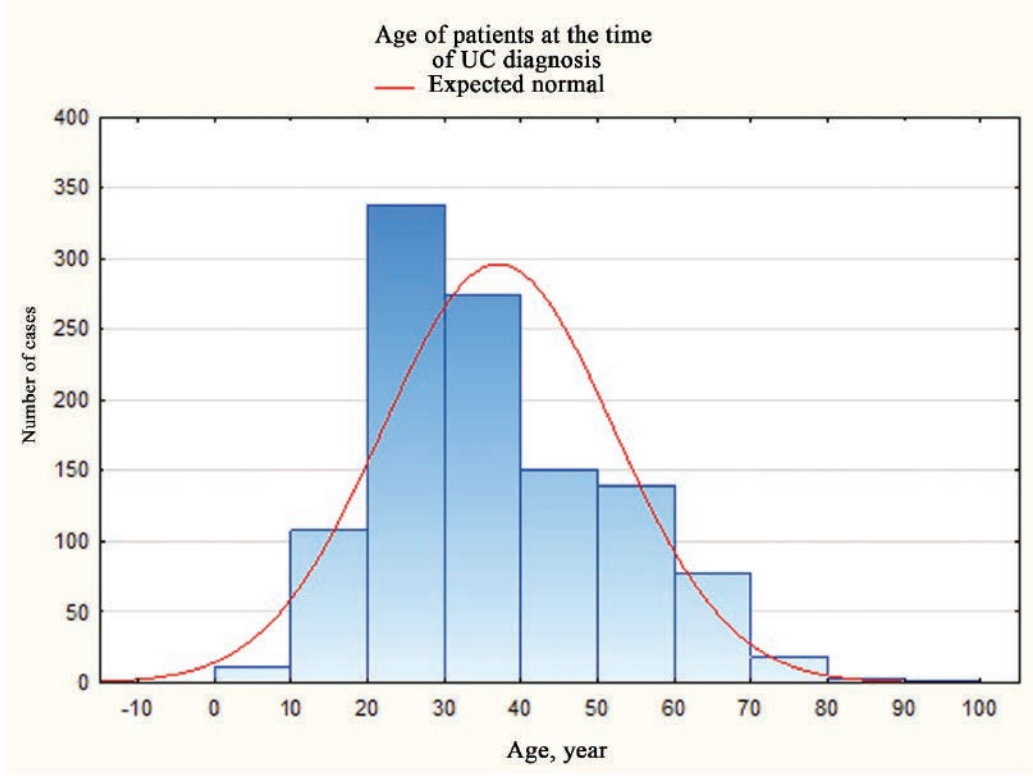

Figure 1. *Age of patients at diagnosis (years)*

Statistical hypotheses were tested at a critical significance level of $p < 0.05$.

The study was approved by the local Ethics Committee of ISCST within the framework of research No. 01201280993 (0543-2018-0018) State Registration, 2018.

RESULTS

Socio-Demographic Characteristics of Patients

In the period from 01.01.2006 to 31.12.2019, 1,122 people suffering from UC were registered in the database, of whom 619 (55.2%) were females, 503 (44.8%) were males; the ratio of females to males was 1.2:1.0. The average age of patients at the time of registration in the database was 43.1 ± 0.5 years (min–18.0; max–91.0). The maximum number of patients $n = 532$ (47.4%) was observed in the age group from 21 to 40 years, patients from 40 to 60 years were 32.7% ($n = 367$). The average age of the disease onset (the time of onset of UC symptoms) was recorded at 37.1 ± 0.5 years (min–3.0; max–87.0 years). The distribution of patients by age groups at the time of diagnosis of UC is shown in Figure 1 and falls on the young age from 20 to 30 years — 603 (54.4%) patients.

The median time from the appearance of the first symptoms to the diagnosis of UC was 6.5 months (0.3–12.4); on average, the diagnosis of UC was established after 1.2 ± 0.1 years. The minimum time from the onset of the disease to the diagnosis was 3 days, in single cases (the first super-severe or severe) acute attack of UC; the maximum time from the appearance of intestinal symptoms to the diagnosis of UC in our study was 38 years, when the patient was observed and treated throughout life with various diseases of the gastrointestinal tract. The median history of UC in the cohort of patients was 7.0 years (0.5–14.0). According to the survey, patients associated the onset of the disease and subsequent exacerbations with the following causes: psychological trauma, stress — 21.8%; viral infection — 18.2%; pregnancy — 16.4%; for no apparent reason — 14.5%; harmful

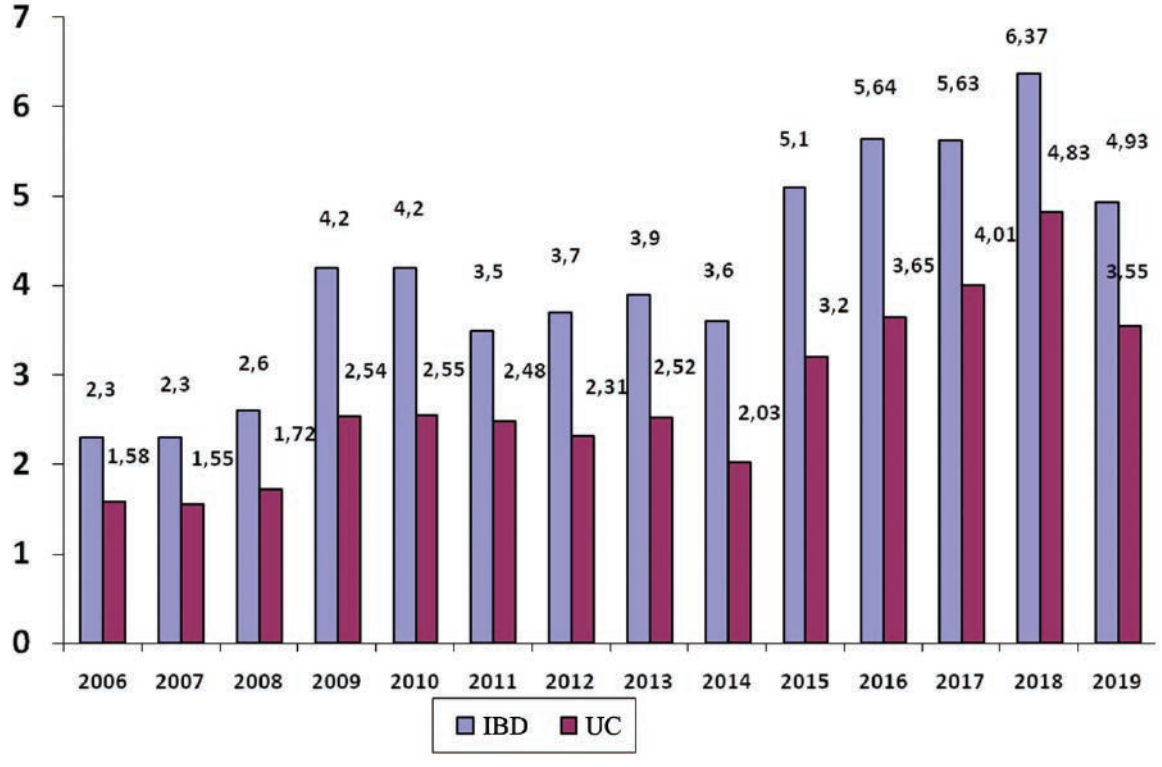

Figure 2. *Incidence of inflammatory bowel disease and ulcerative colitis per 100,000 population in the Irkutsk region (01.01.2006–31.12.2019)*

industries — 12.7%; climate change — 9.1%; intestinal infections in history — 7.3%

About a quarter of patients gave up smoking due to their illness, 63.7% never smoked on average and 7% of patients continued to smoke.

Disability due to the underlying disease was recorded in 24.2% (*n* = 269) of cases, and the overwhelming majority (85%) of patients were identified as group 3.

According to social status, patients were distributed as follows: most of them work — 61.5%, 22.6% do not work, pensioners — 11.8%, students — 4.0%, the share of military personnel is 0.1%. In the Irkutsk region, more than 38% of patients with ulcerative colitis live in the regional center, the incidence ratio "city/village" was 1.6:1.0.

Incidence and Prevalence of Ulcerative Colitis in Irkutsk city and Irkutsk region

Over a 14-year follow-up period, the average incidence rate corresponds to 2.75 ± 0.95 (min–1.55; max-4.83) per 100,000 population (Fig. 2) or 3.59 per 100,000 person-years. Every year we register 46.6 ± 8.2 new cases of the disease in the IBD center.

The UC prevalence in the Irkutsk region is 46.9 per 100 thousand population, in the city of Irkutsk — 68.5 (Fig. 3).

Phenotypic, Clinical Manifestations and Course of Ulcerative Colitis

Burdened heredity for ulcerative colitis was traced in our cohort of patients in 3.0% of cases (*n* = 23).

At the time of inclusion of patients in the database, acute UC attack/exacerbation was detected in 22.7% of cases (*n* = 225), chronic recurrent course during remission in 48.3% (*n* = 795), continuous course of the disease — 29.0% (*n* = 325). The prevalence of patients with total large intestine lesion (E3) was revealed in 68.4% (*n* = 768); left-sided colitis (E2) was recorded in 19.7% (*n* = 221); proctitis (E1) — in 11.9% (*n* = 133). The course of the disease was dominated by patients with moderate-severe UC — 46.9% (*n* = 526), a third of patients were diagnosed with severe course — 30.5% (*n* = 342), in 22.6% of cases (*n* = 254) — mild.

Steroid resistance and steroid dependence were detected in 10.4% (*n* = 115) and 18.1% (*n* = 201), respectively.

Average Body Mass Index (BMI) in females was 24.95 ± 0.19 (min–15.4; max–46.8); in 9.9% of cases, the body mass index was less than 18.0. The average BMI in males was 24.91 ± 0.22 (min–15.6; max–40.0); in 5.1% of cases, the BMI was less than 18.0.

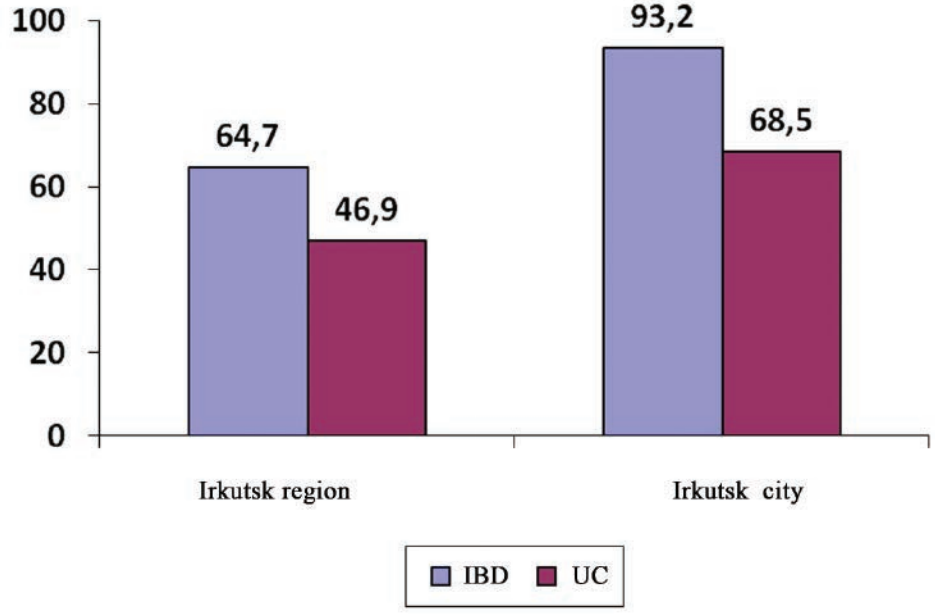

Figure 3. *Prevalence of inflammatory bowel disease and ulcerative colitis per 100,000 population in the Irkutsk region*

Extra-Intestinal Manifestations

Systemic extra-intestinal manifestations of IBD in patients with ulcerative colitis were detected in 13.6% (*n* = 152) of cases, which amounted to 2.1/100 patient-years (follow-up period 7,049.5 p/y, *n* = 1,122). In 77.6% (*n* = 118) there was an isolated lesion of one organ (skin, musculoskeletal system, eyes, oral mucosal layer and others), and in 22.4% of cases (*n* = 34) there was a combined lesion of 2 or more organs and systems.

In 40.7% of cases, skin lesions were noted (dermatitis, erythema nodosum, gangrenous pyoderma); arthropathies/arthritis were observed in 38.2% of cases; oral cavity lesions (aphthous stomatitis, glossitis) in 4.6%; the proportion of primary sclerosing cholangitis was 11.5%; eye lesions (uveitis, iridocyclitis, conjunctivitis, blepharitis) were observed in 5.3% of cases. Over 14 years of follow-up, 5 cases of colorectal cancer were detected, which amounted to 0.44% in the observed cohort of patients.

In 11.4% of cases (*n* = 127), patients with ulcerative colitis were diagnosed with other immune-mediated diseases: vasculitis, psoriasis, systemic scleroderma, myositis, autoimmune thyroiditis, rheumatoid arthritis, systemic lupus erythematosus, bronchial asthma, demyelinating diseases of the nervous system. Porphyria was observed in two patients. In 3.6% of cases (*n* = 40), oncological diseases of extra-intestinal localization were observed in the studied cohort of patients: cancer of the root of the tongue, uterus, ovaries, pancreas, lungs, bladder, retroperitoneal sarcoma, lymphoma, melanoma.

Conservative Therapy

The total cumulative exposure of drug treatment was 90.6% for 5-ASA drugs; 48.7% for systemic corticosteroids; 33.8% for immunosuppressants (azathioprine) and 10.0% for biological therapy during the follow-up period.

Treatment with azathioprine was received in the observed period by 374 patients (33.3%), in the course of observation, the drug was canceled for various reasons in 95 patients (8.5%). Biological therapy was received by 109 (9.71%) patients with ulcerative colitis, which amounted to 1.8/100 patient-years (follow-up period 7049.5 p/y, *n* = 1,122), in 27.9% of cases, GEBT (infliximab) was prescribed as a "rescue therapy". The reasons for the cancellation of drugs of the tumor necrosis factor alpha (TNFa) blocker group were: loss of response in 21.2% of cases, adverse events — 21.2% (infusion reactions, urticaria, dermatitis, alopecia, opportunistic infections, including tuberculosis, lymphoma, leukemoid reaction); discontinuation of therapy at the request of the patient occurred in 10.5%; in two cases (1.9%), the ineffectiveness of the initiated "rescue therapy" was found in super-severe forms of ulcerative colitis, patients were operated on.

Surgical Treatment

Total rate of colectomies by the end of the follow-up period (within 14 years) was 8.7% (*n* = 97). The need for surgical treatment was 1.4/100 patient-years (follow-up period 7049.5 p/y, *n* = 1,122).

In 76.3% of cases, patients underwent emergency and urgent surgery (complicated severe and super-severe forms of ulcerative colitis), in 23.7% surgery was elective (inefficiency of all types of basic therapy, malignancy). Post-op complications occurred in 10.6% of cases (*n* = 7). Postoperative mortality was 2.9% (*n* = 3) or, taking into account the time interval (exposure 291.6) 1.03/100 patient-years. All deceased patients were delivered from the districts in a serious condition with colon necrosis, peritonitis, multiple organ failure. In 2 cases, the cause of death was infectious complications (subtotal bilateral pneumonia, sepsis, DIC) and in one case, the cause of death was massive PE, on the background of sepsis.

Mortality

According to the summary data of the Irkutsk city and Irkutsk region medical institutions, 20 patients with ulcerative colitis died within 14 years in the observed cohort of patients. The following causes of death were determined: in the early postoperative period — 3 patients (52, 58, 84 years old); in 7 cases, death from malignant tumors of extra–intestinal localization (retroperitoneal sarcoma, tongue cancer, ovarian cancer — 2 cases, Klatsken tumor, pancreatic head cancer, lung cancer) of patients aged

27, 28, 33, 50, 57, 66, 70 years old, respectively; two patients died of colorectal cancer (27 and 62 years old); in two cases — cardiovascular events (43 and 73 years old); 2 patients (23 and 27 years old) with primary sclerosing cholangitis; (one patient died on the third day after liver transplantation; the second — against the background of progressive liver failure); in 1 case, the death of a 29-year-old patient occurred from respiratory failure (post-tracheostomy stricture trachea). Thus, the total mortality for the entire follow–up period was 1.8%; when converted to the "patient-time" indicator, the observation exposure was 4,440.8 years, the total mortality was 0.34/100 patient-years.

DISCUSSION

The incidence of IBD in the Irkutsk region over the previous 14 years has increased 2.7 times, ulcerative colitis — 3.1 times and amounted to 3.91 "person-years" per 100,000 population. It should be noted that these figures are much lower than the world data, but are comparable with the incidence in the countries of Central, Southern and Eastern Europe (Romania — 2.4, Cyprus — 2.9, Croatia — 3.1, Belgium — 3.6, Moldova — 3.9, Portugal — 4.4 person-years per 100,000 population) [17]. The prevalence of IBD on a global scale increased from 79.5 to 84.3 per 100,000 population from 1990 to 2017, in the UK it is 449.6, in Europe the prevalence of IBD varies significantly; in particular in Eastern European countries it is registered at 104.5 per 100,000 [18]. In the Irkutsk region, the UC prevalence was 68.5 per 100,000 population, IBD — 93.2, which is slightly higher than the values given in the Russian Federation. The present study was dominated by patients with total large intestine lesion (68.4%), which is twice as much as the data obtained both in foreign studies and in the ESCApe2 study — 55% [10]. Moderate-severe course of UC occurred in 46.9% of cases. The patients, both males and females, were of normal weight, the body mass index averaged 24.9 (norm 18.50–24.99). Body weight deficiency (< 18) was detected twice as often in females (9.9%). The dominant extra-intestinal manifestations in the Irkutsk region were skin lesions (40.7%), which in 22.4% of cases were combined with rheumatological or other. The proportion of immunosuppressive therapy prescribing, including GEBT, exceeded the indicators for Russia, due to the predominance of medium-severe and severe forms. The socio-demographic characteristics obtained in the study are comparable to global trends. The need for surgical treatment tends to decrease. Based on the analysis of the database of the unified IBD center of the Irkutsk region, objective epidemiological characteristics, clinical course features and treatment options for patients with ulcerative colitis in a long-term study were obtained.

CONCLUSION

The epidemic of immune-mediated diseases predicted in the world, in particular IBD, high treatment costs with extensive use of biological agents and small molecules, dictates the need to search for both etiopathogenetic mechanisms and features of ethnic cohorts of patients with a specific geographical reference. Filling information niches in the Russian Federation is a platform for further scientific research, with the possibility of forecasting and planning socio-economic programs.

AUTHORS CONTRIBUTION

Concept and design of the study: *Elena Yu. Chashkova, Evgeny G. Grigoryev, Vladislav E. Pak*
Collection and processing of the material: *Natalia S. Korotaeva, Elena Yu. Chashkova, Liudmila R. Shedoeva, Natalia V. Tungusova*
Statistical processing: *Natalia S. Korotaeva*
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Granulomatous bowel disease: Crohn's disease and tuberculosis. Difficulties in differential diagnosis (case report and review)

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ABSTRACT *Diagnosis of extrapulmonary forms of tuberculosis is still challenging. Abdominal tuberculosis has no pathognomonic signs, so most patients had various diagnoses. In this clinical case, the diagnostic difficulties are due to the absence of a history of tuberculosis and the manifestation of the isolated tuberculosis process in the intestine. This forced us for a wide differential diagnostic search to exclude inflammatory bowel diseases and neoplasms and required the multidisciplinary team. This approach, awareness and alertness of specialists regarding extrapulmonary forms of tuberculosis made it possible to achieve success in this patient.*

KEYWORDS: *abdominal tuberculosis, intestinal tuberculosis, Crohn's disease*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

Recently, despite the positive trends in the epidemic situation with tuberculosis worldwide, the incidence of extrapulmonary tuberculosis (EPT) is unstable [1]. Diagnosis of extrapulmonary tuberculosis is difficult, the disease can occur covertly, under the "mask" of other pathological processes (infectious, gastroenterological, surgical, oncological) [2].

Abdominal tuberculosis is an infectious disease caused by mycobacterium tuberculosis, related to extrapulmonary forms of tuberculosis and characterized by the presence of a specific inflammatory process in the abdominal organs [3]. According to epidemiological data, of the extrapulmonary forms of tuberculosis, abdominal tuberculosis accounts for 4.4–8.3% to 17–21% of cases, which does not allow it to be considered a rare disease [4]. The official clinical classification of abdominal tuberculosis includes tuberculosis of the intestine, peritoneum, mesenteric lymph nodes and other forms [5]. The intestine is most often involved in the pathological process, namely the ileocecal zone (70–89.5% of cases), distal forms are rare [6]. It is known that there are no screening methods for the detection of abdominal tuberculosis [7], and all laboratory and instrumental examinations carried out do not always allow to verify the diagnosis.

Clinical Case

Female patient K., 89 years old, with complaints of periodic cramping pain in the lower abdomen, weight loss, an increase in body temperature in the evening to 37.3°C, vomiting once every three days, a half-formed stool 1–2 times per 24 hours without pathological mixtures.

It is known from the anamnesis that in the summer of 2021, against the background of complete

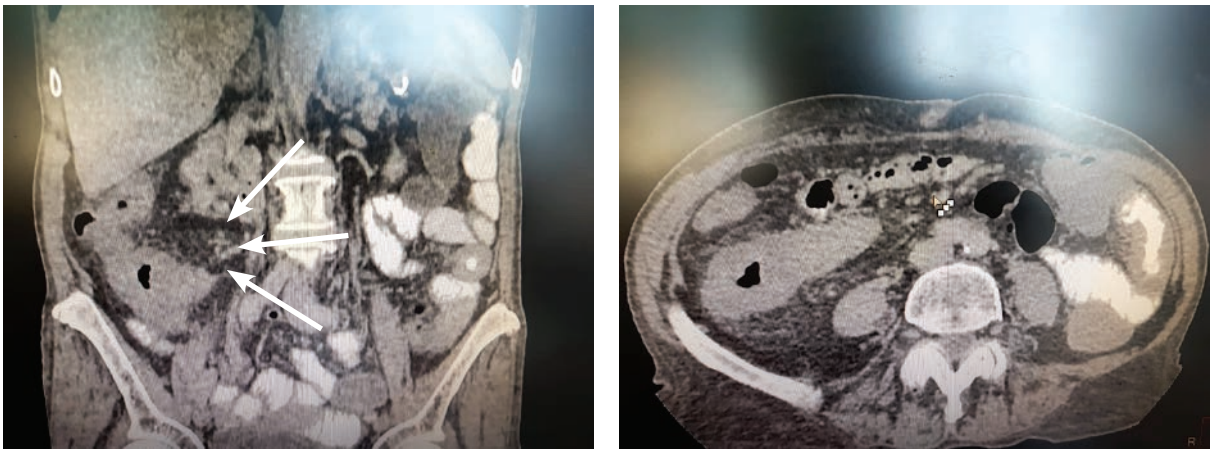

Figure 1. *CT scan. The arrows indicate the thickening of the wall of the ileum and ascending colon, inflammatory infiltrated tissue*

well-being, the patient began to notice episodes of fever up to 40°C. She turned to a therapist at her place of residence. An acute respiratory viral infection was suspected. The analysis for a new coronavirus viral infection was negative; systemic antibacterial therapy was prescribed (she could not specify the drugs) with a positive effect (no fever). Simultaneously she took probiotics.

In November 2021, abdominal pain without a definite site and episodes of unformed stool appeared. She applied to the outpatient clinic at her place of residence and was sent to one of the city hospitals for check-up. A colonoscopy performed in December 2021 revealed a circular narrowing of the lumen of the ascending colon — a tumor was suspected. Biopsies revealed no tumor.

She was sent to the RNMRC of Coloproctology of the Health Ministry of Russia for further examination and verification of the diagnosis.

The initial consultant was oncologist. Objectively: the general condition satisfactory, somewhat asthenized. Height of 158 cm, body weight of 50 kg (BMI = 20 kg/m^2).

The skin colored pale, pasty of the lower limbs was noted. No hemodynamic disorders were detected. The tongue was moist, overlaid with a white coating at the root. There was a postoperative scar on the anterior abdominal wall after cholecystectomy without signs of inflammation. The abdomen was not swollen, soft on palpation, painless in all parts. Digital examination of the rectum and proctoscopy were without pathology. The lab tests dated January 17, 2022: total protein — 59.5 g/l, hemoglobin — 91 g/l, platelets — 454x10^9/l.

According to compute tomography (CT) dated January 21, 2022: pulmonary pattern with signs of focal pneumosclerosis, no obvious focal and infiltrative changes were found. The ascending intestine to the area of the hepatic flexure and the terminal part of the ileum were changed for 5 cm, the wall was thickened to 1.0–1.5 cm due to all layers. The surrounding tissues were strongly compacted. The infiltration extended to the peritoneum of the right lateral canal. Along the course of the mesentery vessels, the lymph nodes were up to 0.6 cm. (Fig. 1). Conclusion:

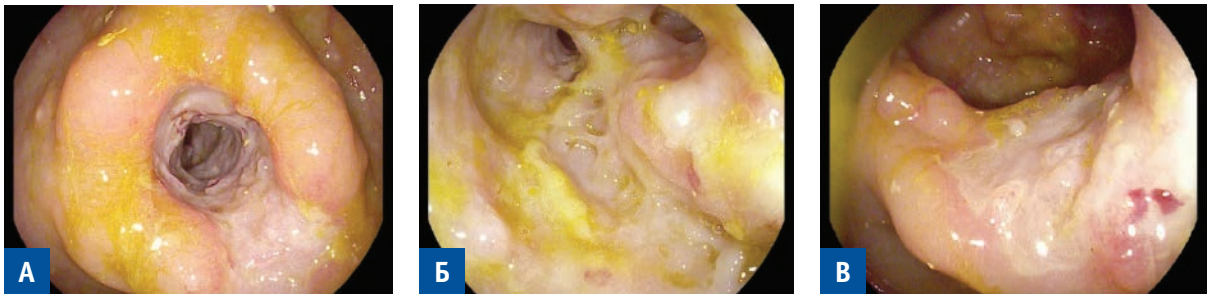

Figure 2 (а,б,в). *Endoscopic images of the ascending colon: а — distal edge of the circular ulcerative defect, б — fistulous openings of the ascending colon, в — ulcerative defect 1.0 cm in diameter.*

The CT picture of infiltrative changes in the ascending colon and ileum may correspond to the tumor process.

According to colonoscopy data dated February1, 2022: the device was carried out in the middle third of the ascending intestine, where the distal edge of the circular ulcerative lesion, elastic consistency is determined, the lumen is narrowed to 1.3 cm. The device was carried out proximally by 5–6 cm, the lumen narrowed to 0.6 cm and internal openings were visualized, which did not exclude the system of fistula tracks. The mucosa here was pale pink, represented by a circular ulcerative lesion, sometimes with a touch of fibrin, bleeding on contact. Distal to the haustra there is an ulcerative lesion occupying ½ of the circumference, bright red in color, with a touch of fibrin. In the hepatic flexure, there was an ulcer1.0 cm, bright red, with a touch of fibrin. In the distal third of the ascending colon — aphthae up to 0.2 cm in diameter with a corolla of hyperemia and a coating of fibrin, a biopsy was performed. The distal parts of the large intestine are not changed (Fig. 2).

Conclusion: the endoscopic picture is difficult to interpret, it is necessary to differentiate between the infiltrative tumor process, Crohn's disease in the stage of ulcers, lymphosarcoma and tuberculosis. The result of histological examination dated February 3, 2022: in the areas of the proper plate of the mucosal and submucosal layer, groups of histiocytic granulomas are determined, partially merging, with single giant multinucleated cells of the Pirogov-Langhans type (Fig. 3). Conclusion: signs of tumor growth (including lymphoproliferative processes) were not found, the morphological picture may correspond to Crohn's disease (differential diagnosis with tuberculosis).

The patient was consulted by a gastroenterologist. Taking into account the patient's age, anamnesis data, tests results, it was suggested that there was a high probability of the infectious nature of the disease. The diagnosis was established: Crohn's disease in the form of ileocolitis (?), intestinal tuberculosis (?). A phthisiologist's consultation was recommended, a study of the level of fecal calprotectin was prescribed, fecal analysis for toxins A and B *Clostridium difficile*, clinical infections. Prescribed treatment: mesalazine 3 grams per 24 hours, metronidazole 1 gram per 24 hours, ciprofloxacin 1 gram per 24 hours, antispasmodics for abdominal pain, a balanced mixture for enteral nutrition.

Against the background of the therapy, the condition remained stable, but the patient's initial complaints persisted. Tests for intestinal infections (yersiniosis, salmonellosis, shigellosis, giardiasis, amoebiasis) and toxins A and B of *Clostridium difficile* are negative. Fecal calprotectin dated February 25, 2022: 538 mcg/g (N = 0–150 mcg/g). At the place of residence, the patient was checked-up by a phthisiologist; the results of the chest CT dated January 21, 2022 were revised, a Mantoux test and sputum examination for the presence of acid-resistant mycobacteria (ARM) were performed, data for active tuberculosis were not received. Lab tests dated March 1, 2022: hemoglobin — 84 g/l, platelets — $574x10^9$/l, total protein — 62 g/l, albumin — 30 g/l.

Taking into account ineffective treatment, negative laboratory changes (progression of anemia, thrombocytosis, hypoalbuminemia), it is recommended to perform magnetic resonance imaging (MRI) of the intestine with contrast.

According to the MRI data dated March 24, 2022: in the terminal part of the ileum for 4.8 cm, in the cecum and ascending colon for 6.2 cm, there is a circular thickening of the wall to 1.0 cm, the lumen is circularly narrowed to 0.5 cm (Fig. 4). In the distal third of the ileum there was a section of circular thickening of the intestinal wall up to 0.9 cm for 4.9 cm, the lumen was narrowed to 0.3 cm. The ileum was proximal to the constriction throughout expanded to 4.5 cm. In the middle third of the ileum there was a section of circular thickening of the intestinal wall up to 0.9 cm for 2.5 cm, the lumen was narrowed to 0.3 cm. The changes accumulated contrast. Conclusion: MR image of segmental lesions of the ileum and ascending colon (it should be differentiated between inflammatory and neoplastic processes). Expansion of the small intestine lumen.

The patient was consulted by a coloproctologist: taking into account the anamnesis, the patient's age, the results of tests, negative

laboratory shifts (decrease in hemoglobin, albumin), ineffectiveness of conservative treatment, preservation of inflammatory narrowing of the small and large bowel, prestenotic dilation, indications for surgery were set. The patient's consent to the surgery was obtained. The patient was admitted with a diagnosis of Crohn's disease (?) in the form of ileocolitis, complicated by inflammatory strictures of the ileum and right colon, with signs of partial small bowel obstruction. Tumor (?) in the right colon; intestinal tuberculosis (?); chronic iron deficiency anemia of moderate severity.

On April 6, 2022, laparoscopic surgery was performed. Intraoperatively (Fig. 5), a deformed scar-altered ileocecal part of the intestine with severe inflammatory changes and a dense endophytic component was found. Seven inflammatory sites with narrowing of the lumen were identified in the ileum, while there was no inflammation in the mesentery of the intestine. After the 3rd narrowing site, there was a prestenotic expansion of the

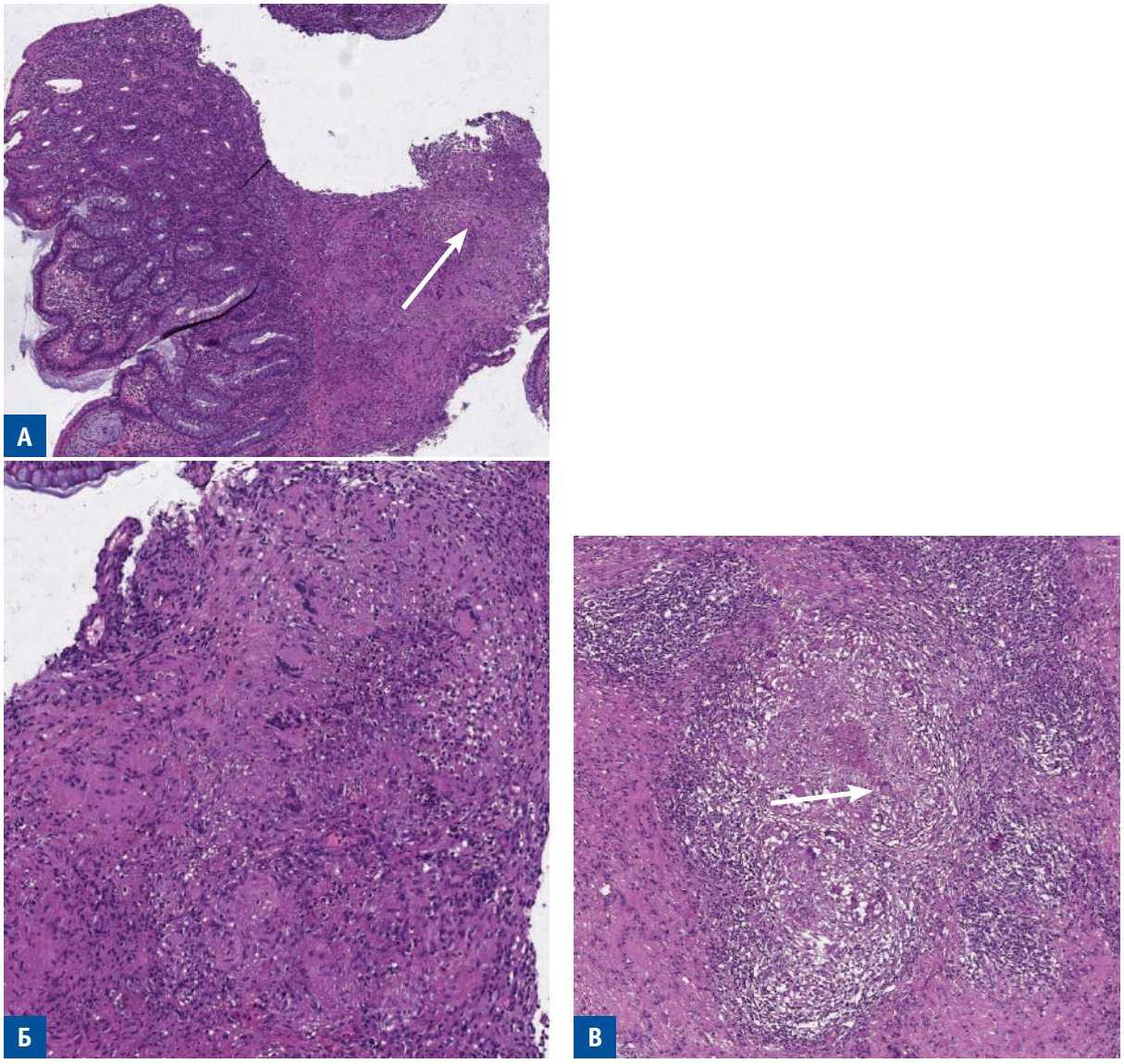

Figure 3. *A. The morphological picture in the biopsy from the edge of the ulcer: signs of chronic inflammation and granulation tissue with foci of necrosis, a large number of histiocytes that form granulomas with the presence of giant multinucleated cells of the Pirogov-Lankhgans type (magn. ×10). Б. Granulation tissue (detail, magn. ×100). B. Granuloma of epithelioid and lymphoid cells, Pirogov-Lankhgans cells and a necrosis focus in the center (detail, magn. ×100). Arrows indicate Pirogov-Langhans cells. А, Б, В — staining with hematoxylin and eosin.*

ileum. The picture was difficult to interpret. Visually, changes from the intestinal wall are not characteristic of Crohn's disease. Crohn's disease and tuberculosis should be placed in the differential series. Considering the lesion extent of the small intestine, taking into account the age of the patient, it was decided to refrain from extensive resection and stricturoplasty. A decision was made to resect the ileocecal part of the intestine (Fig. 6) with the ileo-ascendoanastomosis and bypass "side-to-side" ileo-ileoanastomosis between unchanged parts of the ileum of 40 cm from the proximal border of resection and the jejunum, thus "disabling" 3 areas of narrowing in the ileum with irreversible changes from the intestinal wall.

The result of a histology dated April 12, 2022: multiple merging histiocytic granulomas with a large number of giant multinucleated cells of the Pirogov-Langhans type are detected in all layers of the intestinal wall, in the adjacent fiber and lymph nodes. Part of granulomas was with fibrous changes in the center, isolated — with central small necrosis. Conclusion: the morphological picture highly likely corresponds to tuberculosis in the resected ileocecal part.

Thus, according to the results of histology of the removed specimen, the patient was verified with the final clinical diagnosis: Intestinal tuberculosis with lesions of the small and large bowel. Tuberculous mesadenitis.

The postoperative period was uneventful. The patient discharged with the supervision of a phthisiologist at the place of residence.

When trying to take combined anti-tuberculosis treatment, she noted the appearance of nausea, vomiting, diarrhea, and therefore the treatment stopped. Four months after surgery, the patient's condition was satisfactory, without complains, the phthisiologist continued follow-up.

DISCUSSION

Recently, despite various laboratory tests, the progress in endoscopic and radiation diagnostics, great difficulties arise in the differential diagnosis of two granulomatous intestinal diseases with different etiologies, but similar manifestations. These are intestinal tuberculosis and Crohn's disease, which is demonstrated by this clinical case.

Clinical signs of both diseases include abdominal pain, fever, weight loss, chronic diarrhea, hematocheesia, recurrent intestinal obstruction, extra-intestinal manifestations such as arthralgia, aphthous stomatitis, skin and eye lesions [8]. Due to its non-specificity, none of these signs alone or in combination, does not reliably suggest a particular disease.

Among the immunological tests for detecting a specific cellular immune response to mycobacterium antigens, the traditional Mantoux test with 2 TE PPD-L, a skin test with a recombinant tuberculosis allergen (DIASKINTEST®), as well as tests for the release of interferon-γ by T-lymphocytes (QuantiFERON® -TB Gold/ Gold Plus, T-SPOT®-TB). A positive result of the Mantoux test is registered in 50–100%

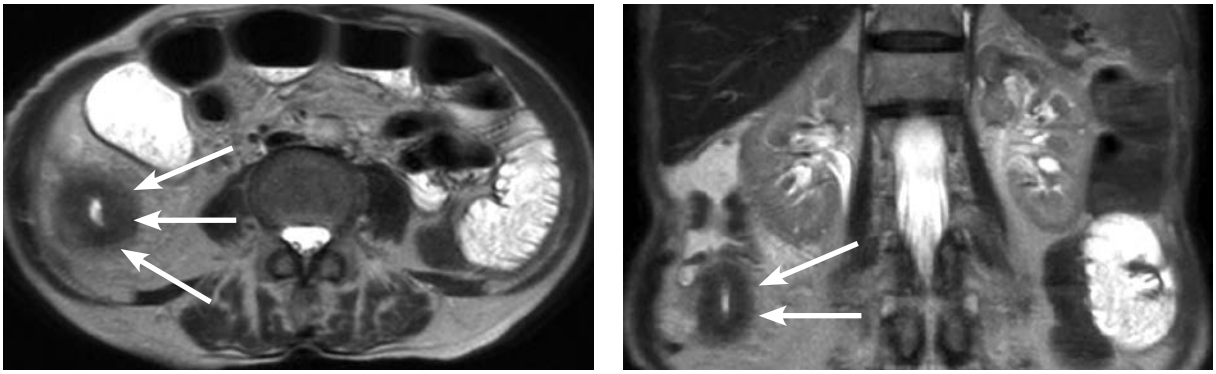

Figure 4. *MRI. The arrows indicate the circular narrowing of the ascending colon up to 5 mm, the circular thickening of the wall up to 10 mm, and the compaction of the surrounding tissue*

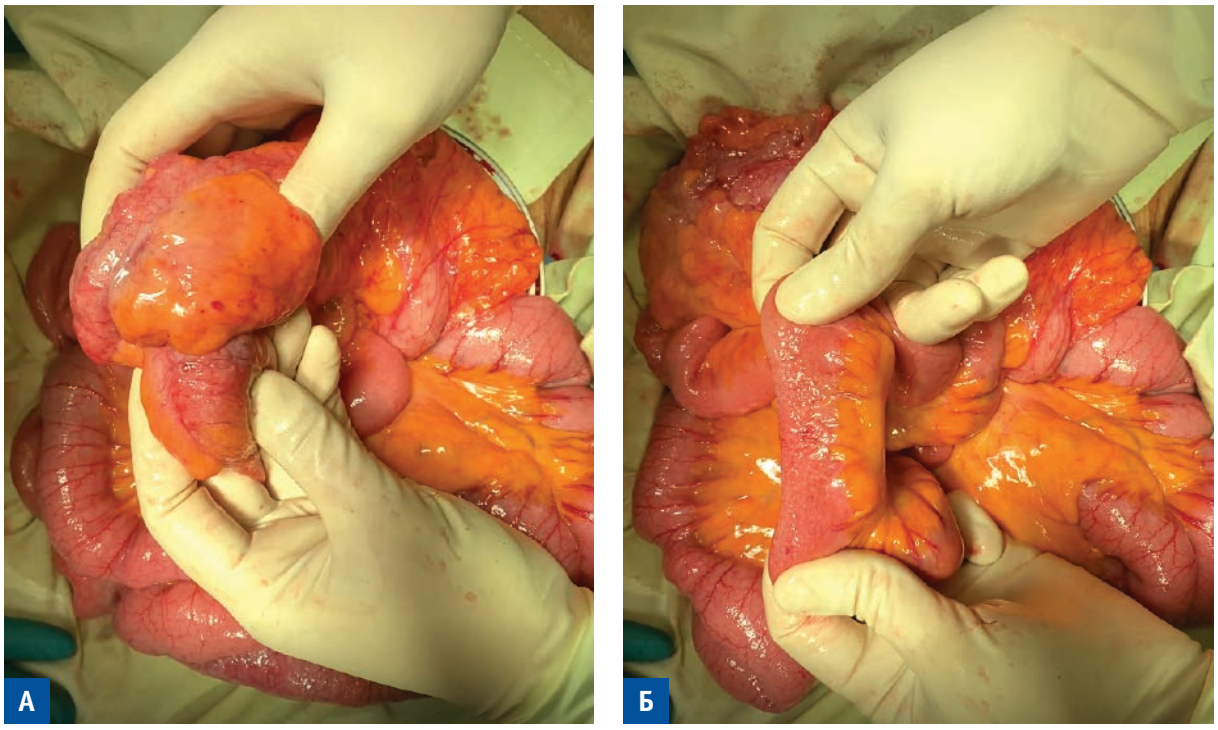

Figure 5(а,б). *Intraoperative photo: а — deformed ileocecal zone with inflammatory, б — one of the ileumstrictures.*

of patients with intestinal tuberculosis. However, according to the literature on the role of immunodiagnostics in the verification of pathology, several meta-analyses reported the sensitivity and specificity of about 80% of the Mantoux test [12]. This is due to the high percentage of false positive results of the Mantoux test in vaccinated and infected children [9–11], which makes this method ineffective for detecting tuberculosis infection.

Fecal mycobacteria test is not carried out due to the almost complete absence of positive results [5].

As with any other infectious disease, the detection of *M. tuberculosis* using microbiological methods in samples can be a diagnostic sign of tuberculosis, but since intestinal tuberculosis is

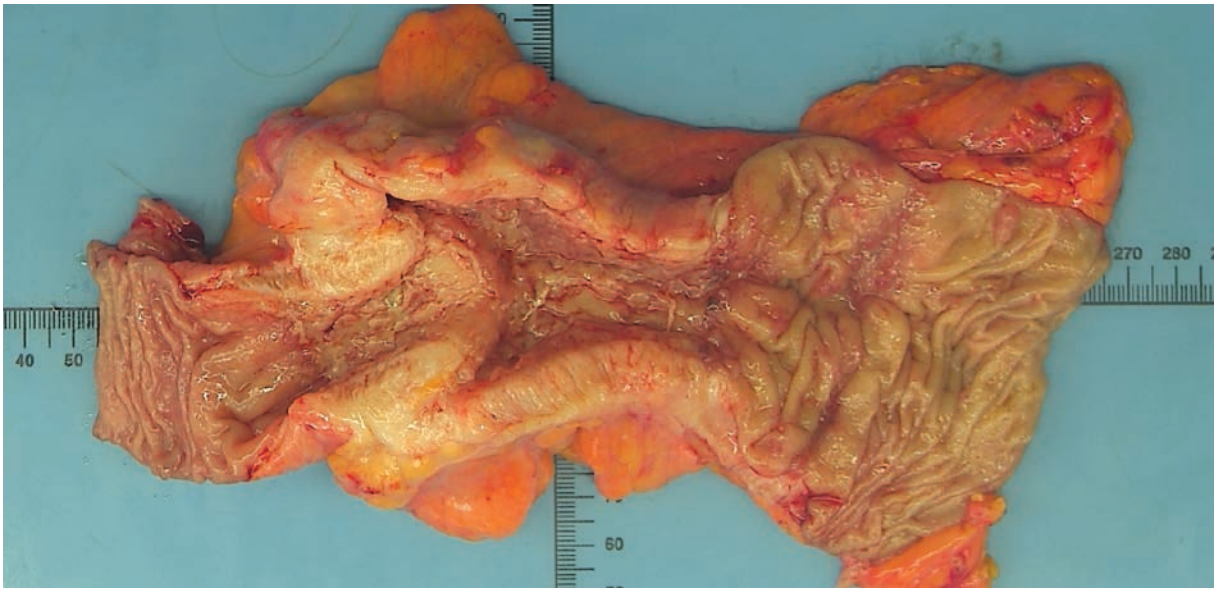

Figure 6. *Ileocecal region. Thickening of the intestinal wall and narrowing of the lumen at the ileocecal junction*

a low-bacillary (low concentration of mycobacteria) disease, their detection is difficult, which explains the low sensitivity of these tests [13]. In recent years, agar-based nutrient media with various growth additives and the use of a gas mixture have been proposed to accelerate the growth of mycobacteria. To obtain the growth of microorganisms on these media, an atmosphere with a high content of carbon dioxide (4%-7%) is created, special CO_2 incubators are used for this. Automated systems have received the greatest development: MGIT-BACTEC-960 and MB/Bact [5].

The sensitivity of this method varies from 19% to 70% [14].

The use of polymerase chain reaction (PCR) in the diagnosis of abdominal tuberculosis is associated with great difficulties. To perform PCR, deoxyribonucleic acid (DNA) molecules of the pathogen must be isolated from biopsies. For biopsy lysis, an enzyme (proteinase K) is used at a final concentration of 200–500 mg/l at a temperature of 56°C overnight. An excess of nonspecific DNA in PCR analysis often causes inhibition of the reaction, which requires repeated DNA extraction [5]. In a recent meta-analysis of nine studies, the combined sensitivity and specificity of PCR with the release of ARM was 44% and 95%, respectively [15].

Endoscopic diagnostics occupies one of the key places in the verification of diagnosis, but it is also quite complex and ambiguous. The criteria for the diagnosis of Crohn's disease during colonoscopy are regional (intermittent) mucosal lesion, a symptom of "cobblestone pavement" (a combination of deep longitudinally oriented ulcers and transversely directed ulcers with islands of edematous hyperemic mucosal layer), linear ulcers (ulcers-fissures), aphthae, and in some cases strictures and the mouth of fistulas [16]. Macroscopic manifestations of the large intestine tuberculosis are extremely diverse. Any part of the large intestine can be involved in the process, but changes are more often registered in the right sections with lesions of the ileocecal valve and ileum. As a rule, there is a loss of vascular pattern, straightening of mucosal folds, less often "millet-like" rashes on the intestinal mucosal layer are visualized. The characteristics of ulceration formed during the development of caseous necrosis in tuberculous granulomas, in most cases, depends on the timing of their occurrence. In the early stages of formation, single lesions, as a rule, are located against the background of a visually unchanged mucosal layer, have a rounded shape, smooth rounded edges, a smooth bottom covered with a coating of fibrin. The size of ulcers in most cases does not exceed 1 cm, their depth depends on the level of lesion to the intestinal wall (for the entire thickness of the mucosal layer or to the submucosal base). Due to reactive hyperplasia of lymphoid tissue in the area of ulcerative lesion formation, it always rises above the level of the surrounding mucosal layer. There is no contact bleeding. With the progression and chronization of the process, ulcers increase in size along the perimeter of the intestine, their bottom deepens (they often penetrate into the muscular layer of the intestinal wall), acquires a rough, fine-grained appearance, which is due to the formation of tuberculous granulomas. The development of granulation tissue at the edges of lesions gives them a bumpy appearance. The spread of ulcers is in the transverse direction. Large ulcers, as a rule, circularly cover the lumen of the intestine [17]. When the large intestine is affected, the inflammatory process can manifest itself by the development of strictures, hypertrophic lesions resembling polyps or tumors, segmental ulcers [18].

CT or MRI are the preferred methods of differential diagnosis of lesions of the small and large intestine [19]. In a meta-analysis by Kedia S., et al. a number of signs (crest symptom, lymph node lesion, asymmetric thickening of the intestinal wall, proliferation of adipose tissue, wall dissection, involvement of the ileocecal region) and their role in the verification of pathology were analyzed. The lymph node lesion had the highest accuracy (sensitivity — 23%; specificity — 100%) for the diagnosis of intestinal tuberculosis, and the crest sign (sensitivity — 82%, specificity — 81%) — for Crohn's disease. When analyzing the sensitivity of other signs, their diagnostic accuracy, with the exception of asymmetric thickening of the intestinal wall, remained the same [20].

A decisive role in the diagnosis of abdominal tuberculosis belongs to the detection of specific granulomas in the affected organs and tissues during histological examination, which in the classical version represent a site of cellular detritus — caseous necrosis surrounded by so-called epithelioid cells, giant Pirogov-Langhans cells and lymphocytes along the periphery [3]. Tuberculous granulomas are usually large, prone to fusion, dense, located in the submucosal layer and characterized by central caseosis, and granulomas in Crohn's disease are small (microgranulomas), discrete, rare and poorly defined, without areas of necrosis. The detection of ARM in biopsy samples with Cyll-Nielsen staining, although very specific, is infrequent [21].

If, after all, it is not possible to differentiate Crohn's disease and intestinal tuberculosis, and it is necessary to start treatment, then the use of glucocorticosteroids (GCS) in such a situation can contribute to the generalization of the tuberculosis process and be fatal. This problem can be circumvented with the help of empirical prescription of anti-tuberculosis therapy (ATT). The 2016 consensus of the Asia-Pacific Region on the management of patients with Crohn's disease mentions that in patients with the "IBD/abdominal tuberculosis" dilemma, the diagnosis of

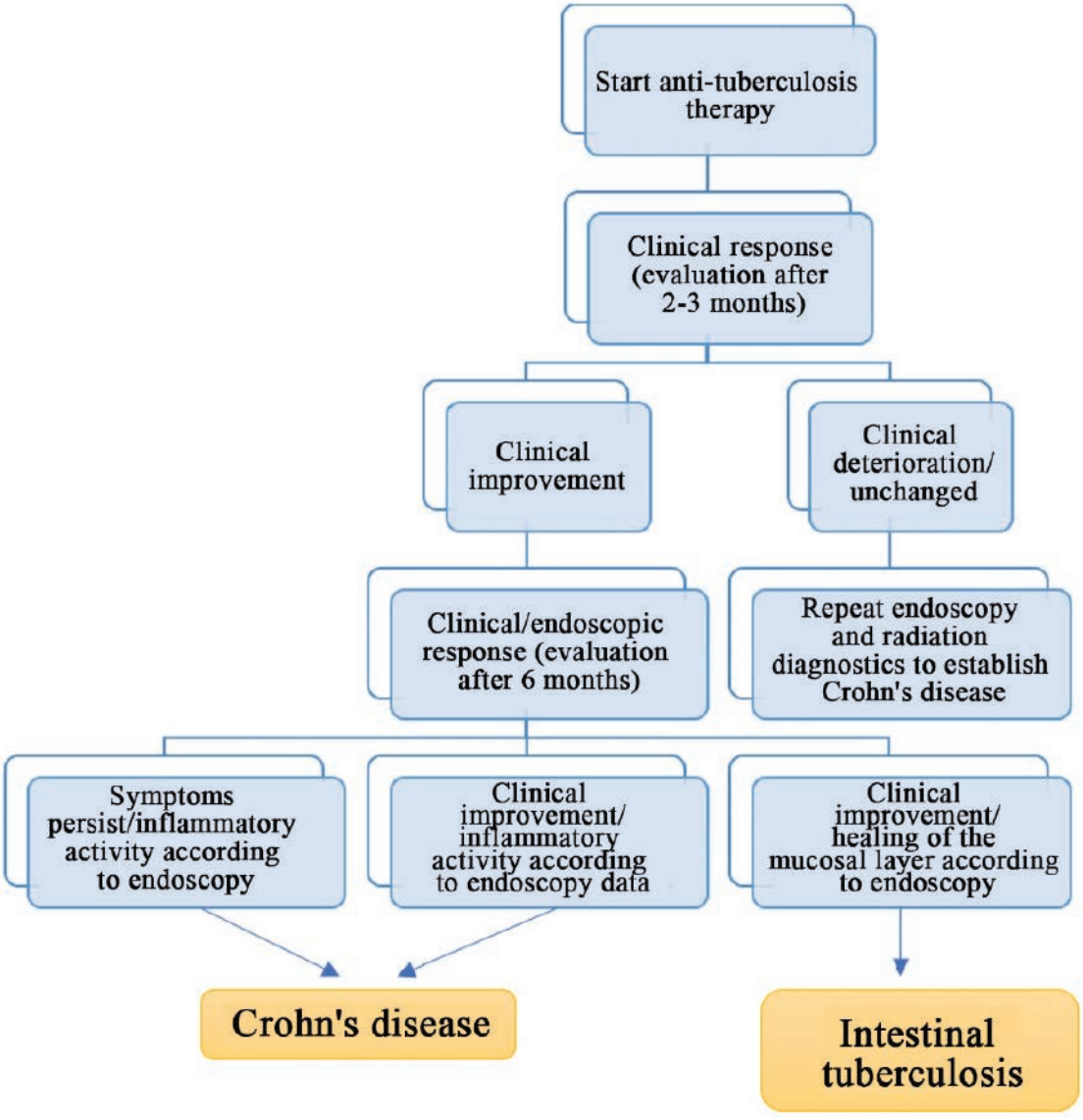

Figure 7. *Algorithm for the patients receiving empirical anti-tuberculosis therapy [13]*

Crohn's disease should be considered only if there is no response to ATT [22]. However, the time frame through which it is necessary to evaluate the effectiveness of therapy is still uncertain. In a study by Kedia, S., et al. out of 358 patients with Crohn's disease, 135 (38.0%) received ATT for at least 3 months before they were finally diagnosed with Crohn's disease. Their response to the therapy was compared with 157 patients with intestinal tuberculosis. After 3–6 months, more than 90% of patients with tuberculosis had a positive effect of treatment compared to 38% of patients with Crohn's disease. During the year, the response to the therapy was maintained with abdominal tuberculosis, and in 80% of cases, the condition of patients worsened with Crohn's disease. Moreover, repeated colonoscopy after 6 months of treatment showed mucosal layer healing in 100% of patients with intestinal tuberculosis, whereas an endoscopic response was observed in < 5% of patients with Crohn's disease. Therefore, based on these results, the authors proposed an algorithm for monitoring patients who underwent empirical ATT [12] (Fig. 7). Indications for surgical treatment of abdominal tuberculosis are defined as absolute: complications of tuberculosis of intra-abdominal lymph nodes and other abdominal organs (abscesses, peritonitis, intestinal fistulas, intestinal obstruction, perforation, bleeding), and individual: the question of surgery depends on the characteristics of clinical manifestations of the disease in a particular patient [5]. About 20–40% of patients with abdominal tuberculosis have a clinical picture of an "acute abdomen" and need surgical treatment [23]. In a prospective study by Barot M. et al., it was shown that the most common indication for surgical treatment was a lesion of the small intestine and ileocecal zone with the development of intestinal obstruction [24]. Surgeries performed for intestinal tuberculosis are mainly of three types [25]. The first type is surgeries that are performed to bypass the involved segments of the intestine, for example, enteroenterostomy or ileotransverzostomy. The second type is segmental resections, for example, limited ileocecal resection. At the same time, asthenization of patients and the prevalence of the lesion are often limiting factors. The third type is stricturoplasty. For cases with multiple strictures, it is suggested as a method that has advantages over multiple resections and enteroanastomoses, since it avoids the risk of short bowel syndrome or blind loops. Extended strictures with active inflammation or multiple strictures may require resection [26].

CONCLUSION

This clinical observation demonstrates the entire complex differential diagnostic path from the moment of the first symptoms to the verification of the diagnosis, which took the patient more than six months. The nonspecific nature of the symptoms forced the patient to consult a therapist, a general practitioner, a surgeon, an oncologist, a gastroenterologist, a phthisiologist. Various laboratory and instrumental examinations were performed. Radiation imaging methods described various pathological changes, but did not allow them to be identified by belonging to a certain nosological form. An endoscopic examination followed by a morphological description of the biopsy material provided significantly more information and helped clinicians to decide on a further search. But, as indicated in the literature, only a histological examination could finally confirm the diagnosis of intestinal tuberculosis. Thus, the awareness of specialists in relation to EPT, perseverance in the diagnostic search, the involvement of doctors of various specialties contributed to a favorable outcome.

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Перианальные свищи при болезни Крона (обзор литературы)

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РЕЗЮМЕ *Лечение прямокишечных свищей как перианальных проявлений болезни Крона (ППБК) является важной задачей, решение которой до сих пор не найдено. В первую очередь, это связано с изнурительными, снижающими качество жизни, симптомами. Неправильная тактика в лечении данного заболевания может приводить к развитию анального недержания, а в ряде случаев и к удалению прямой кишки. Целью данного обзора было изучение эффективности различных хирургических методов лечения перианальных поражений, особенностей их применения при различных видах свищей, а также оценка влияния оперативного лечения на функцию запирательного аппарата прямой кишки. Установлено, что большинство описанных методов применялось у строго отобранной ограниченной группы больных и позволяло лишь временно ликвидировать клинические проявления ППБК. Неудовлетворительные результаты лечения, особенно в отдаленном послеоперационном периоде, малое число клинических наблюдений в опубликованных научных работах, посвященных лечению перианальных проявлений болезни Крона, а также низкая достоверность результатов, диктуют необходимость проведения дальнейших исследований с включением большего числа пациентов.*

КЛЮЧЕВЫЕ СЛОВА: *болезнь Крона, свищи прямой кишки при болезни Крона, перианальные проявления болезни Крона, хирургическое лечение*

КОНФЛИКТ ИНТЕРЕСОВ: *авторы заявляют об отсутствии конфликта интересов.*

ДЛЯ ЦИТИРОВАНИЯ: Аносов И.С., Нанаева Б.А., Варданян А.В., Захаров М.А. Перианальные свищи при болезни Крона (обзор литературы). *Колопроктология*. 2023; т. 22, № 1, с. 128–137. https://doi.org/10.33878/2073-7556-2023-22-1-128-137

Perianal fistulas in Crohn's disease (review)

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ABSTRACT *Treatment of anal fistulas as perianal manifestations of Crohn's disease is an important task, the solution of which has not yet been found. First of all, this is due to debilitating symptoms that reduce the quality of life. Incorrect tactics in the treatment of this disease can lead to the development of anal incontinence, and in some cases to the removal of the rectum. The purpose of this review was to study the effectiveness of various surgical methods for the treatment of perianal fistulas, the features of their use in various types of fistulas, as well as to assess the impact of surgical treatment on the function of the anal sphincter. It was found that most of the described methods were used in a strictly selected limited group of patients and allowed only temporary elimination of the clinical manifestations of Crohn's disease. Unsatisfactory results of treatment, especially in the late postoperative period, a small number of clinical observations in published scientific papers on the treatment of perianal manifestations of Crohn's disease, as well as low reliability of the results, dictate the need for further studies involving more patients.*

KEYWORDS: *Crohn's disease, Perianal fistulas, Anorectal fistula, Surgical treatment*

CONFLICT OF INTEREST: *The authors declare no conflict of interest*

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ВВЕДЕНИЕ

Лечение прямокишечных свищей как перианальных проявлений болезни Крона (ППБК) является важной задачей, решение которой до сих пор не найдено. В первую очередь, это связано с изнурительными, снижающими качество жизни симптомами: боль, обильные слизисто-гнойные выделения, вызывающие раздражение, мокнутие и необходимость ношения прокладок. Неправильная тактика в лечении данного заболевания может приводить к развитию анального недержания, а в ряде случаев и к удалению прямой кишки.

Наиболее часто ППБК встречаются у пациентов с поражением ободочной и прямой кишки [1]. У 5–10% [2,3] больных перианальные свищи являются первым проявлением воспалительного заболевания кишечника. Однако установлено, что совокупная частота встречаемости прямокишечных свищей среди пациентов с болезнью Крона возрастает по мере увеличения продолжительности анамнеза: через 5 лет — 15%, через 10 лет — 18%, через 20 лет — 23% и через 30 лет — 24% [4,5]. Чаще всего ППБК фиксируются в возрастной категории от 16–30 лет, а второй пик отмечается в возрасте от 76 до 90 лет. У мужчин перианальные проявления встречаются несколько чаще — 15,8%, чем у женщин — 11,6% [6].

Сложные свищи при БК встречаются примерно в 80% наблюдений [7] и представляют собой наиболее значимую проблему. Это обусловлено тем, что при показателе первичного заживления в 65%, только у 37% пациентов удается избежать рецидива заболевания по прошествии 10 лет.

Классификация

В настоящее время в Российской Федерации используют традиционную классификацию свищей заднего прохода, утвержденную в национальных клинических рекомендациях [8]. Она применима и к перианальным проявлениям болезни Крона, но, в тоже время, не отражает особенностей данного заболевания, а выбор тактики лечения только на ее основании затруднителен. За рубежом наиболее распространена классификация, принятая Американской ассоциацией гастроэнтерологов в 2003 году, разделяющая свищи на простые и сложные [9]. К простым свищам относят интрасфинктерные и транссфинктерные фистулы, вовлекающие подкожную порцию наружного сфинктера. В свою очередь, к сложным свищам относят транссфинктерные, захватывающие поверхностную и глубокую порции наружного сфинктера, ректовагинальные и экстрасфинктерные свищи любой степени сложности, а также свищевые ходы, имеющие затеки любой локализации. Кроме того, свищевой ход считается сложными при таких специфических для болезни Крона проявлениях как наличие стриктуры или выраженного воспалительного процесса в анальном канале либо прямой кишке. Вышеизложенные факторы, безусловно, оказывают непосредственное влияние на выбор тактики хирургического лечения.

Диагностика

Магнитно-резонансная томография

Пациентам со сложными свищами БК выполняют магнитно-резонансную томографию (МРТ) органов малого таза с контрастным усилением в качестве основного метода инструментальной диагностики, а также с целью динамического наблюдения и послеоперационного контроля [10]. МРТ органов малого таза позволяет получить информацию о степени активности БК в прямой кишке, оценить выраженность проктита, фиброзных изменений стенки кишки [11], а также получить точные данные о топографии свищевого хода [12]. Эффективность визуализации свища и его расположения относительно мышечных структур таза, локализации и распространенности гнойных полостей и затеков достигает 76–100% [13]. Кроме того, магнитно-резонансная томография позволяет выявлять клинически «немые» абсцессы и степень перифокального инфильтративного воспаления [14]. Т2-взвешенное изображение с жироподавлением является оптимальной методикой для МР-визуализации свищей. Т1-взвешенное изображение с внутривенным контрастированием используют для дифференциальной диагностики содержимого затеков/гнойных полостей между жидкостью/гноем и грануляционной тканью. Наружные катушки, имеющие большее поле обзора, применяют для визуализации экстрасфинктерных свищей и свищей высокого уровня [16]. В литературе имеются данные об эффективном применении эндоанальных катушек, дающих преимущество в идентификации внутренних отверстий, а также в диагностике ректовагинальных фистул [16].

Эндоректальное ультразвуковое исследование (ЭУЗИ)

При отсутствии рубцово-воспалительных стриктур анального канала и нижнеампулярного отдела прямой кишки пациентам с ППБК выполняют ЭУЗИ как в В-режиме, так и с трехмерной реконструкцией изображения [15]. При наличии острого гнойно-воспалительного процесса и при выраженных болевых ощущениях целесообразно выполнение исследования под обезболиванием. В качестве дополнительного метода при невозможности введения датчика в просвет кишки, возможно применение трансперинеального УЗИ, однако его точность в диагностике глубоких абсцессов довольно низкая (47,1%) в связи с ограниченным полем зрения [16].

ЭУЗИ (с частотой 5–16 МГц) позволяет детально визуализировать свищевой ход и его расположение относительно мышечных структур в 86–95% наблюдений, идентифицировать внутренние свищевые отверстия в 62–94% случаев. При наличии наружных свищевых отверстий, введение в них перекиси водорода значительно улучшает визуализацию свищевого хода [16]. Однако значительным недостатком данного исследования является операторозависимость [17]. Внедрение УЗИ с трехмерной реконструкцией изображения позволило решить проблему зависимости от квалификации врачей УЗ-диагностики. Метод обладает высокой диагностической точностью, прост в исполнении, безболезненен и не требует подготовки пациента. 3D-УЗИ также целесообразно выполнять при динамическом наблюдении в послеоперационном периоде, что менее затратно в отличие от МРТ-исследования [18].

Следует отметить, что, по мнению многих авторов, наилучшие результаты в диагностике ППБК достигаются при выполнении обоих методов исследования — как МРТ, так и ЭУЗИ, так как они дополняют друг друга [19]. С помощью УЗИ целесообразно проводить диагностику пациентам с низкими интрасфинктерными и транссфинктерными свищами, в тоже время МРТ позволяет более точно диагностировать высокие свищи и затеки, расположенные выше пуборектальной петли [18].

В настоящее время для диагностики ППБК не выполняют фистулографию и компьютерную томографию, что обусловлено их худшей диагностической ценностью в сравнении с описанными выше методиками, а также дополнительным негативным влиянием рентген-излучения [16].

Хирургическое лечение

По данным большинства авторов, наилучших результатов лечения ППБК возможно достичь путем проведения оперативного вмешательства в сочетании с медикаментозной терапией [20,21]. Мультидисциплинарный подход в лечении перианальных проявлений болезни Крона способствует повышению частоты заживления свищей, снижению риска рецидива и увеличению времени возникновения рецидива [22–24]. Хирургическое лечение ППБК должно быть индивидуальным для каждого конкретного пациента. Необходимо учитывать состояние больного, топографию свища (расположение отверстий, траекторию хода и степень его сложности), выраженность проктита и наличие либо отсутствие рубцового стеноза [25].

Хирургическое лечение простых свищей

Иссечение (рассечение) свища в просвет кишки

Иссечение свища в просвет кишки или рассечение свища (фистулотомия) выполняют пациентам с простыми свищами [26–29]. При выполнении оперативного вмешательства необходимо также рассечение всех возможных ответвлений хода. Целесообразно выполнить обработку свищевого хода ложкой Фолькмана или электрокоагуляцией. В зависимости от размеров дефекта на перианальной коже операцию можно дополнить подшиванием краев раны ко дну. Заживление в срок до 3-х месяцев у пациентов с ППБК наблюдается в 72–100% случаев [30–33]. Противопоказанием к выполнению фистулотомии являются: индекс активности болезни Крона (CDAI) выше 150 [27] и выраженные воспалительные изменения перианальной области и промежности [26].

Иссечение свища в просвет кишки у пациентов с ППБК сопряжено с высоким риском развития анального недержания. Возникновению клинических проявлений НАС способствуют учащенный стул и рубцовые изменения структур анального канала. По некоторым данным, частота каломазания после таких вмешательств достигает 61% [33]. Таким образом, фистулотомия у данной группы пациентов должна выполняться относительно редко и с осторожностью.

Следует отметить, что существуют исследования, описывающие двухэтапное лечение простых свищей, при котором первым этапом проводят дренирующую латексную лигатуру, а иссечение свища выполняют позже, на фоне отсутствия выраженных воспалительных изменений в перианальной области [26].

Хирургическое лечение сложных свищей

Вскрытие и дренирование абсцесса

Вскрытие и дренирование абсцесса в качестве первого этапа лечения выполняют пациентам с гнойными полостями и затеками независимо от их расположения и размеров [28,29]. Полноценное вскрытие гнойника позволяет проводить иммуносупрессивную терапию по поводу БК без риска развития абсцесса в перианальной области или генерализации инфекции. При точном обнаружении внутреннего свищевого отверстия возможно проведение дренирующей латексной лигатуры в один этап со вскрытием гнойника [28].

Дренирующая латексная лигатура (Seton)

Пациентам со сложными свищами при БК в качестве первого этапа хирургического лечения выполняют проведение дренирующей латексной лигатуры (Seton) [34,35]. Показаниями к проведению двухэтапного лечения являются:

– наличие абсцессов или гнойных полостей, затеков;
– проктит средней и тяжелой степени [36].

Дренирующую латексную лигатуру обычно используют в качестве дополнения к медикаментозной терапии БК как средство обеспечения адекватного дренирования свищевого хода для предотвращения

Таблица 1. *Результаты долгосрочного применения дренирующей латексной лигатуры*
Table 1. *Results of long-term use of draining latex ligature*

Автор	Год	Количество пациентов	Сроки установки лигатуры, мес. (диапазон)	Возврат клинических проявлений (%)
William et al.	1991	55	54 (6–120)	0
Thornton et al.	2005	28	13 (2–81)	21
Takesue et al.	2002	32	62 (25–133)	3 (33)
Galis-Rozen et al.	2010	17	8 (6–9)	40

повторного образования абсцессов и ликвидации местной воспалительной реакции в окружающих тканях. Зачастую установка дренирующей лигатуры является подготовительным этапом к выполнению радикальной операции по ликвидации свища. Однако проведение seton может являться и самостоятельным методом лечения, позволяющим минимизировать клинические проявления ППБК. Преимуществами этого метода являются: низкая стоимость, возможность предотвращения формирования новых свищевых ходов и гнойных полостей, снижение потребности во временной или постоянной стоме, а также низкая частота повторных вмешательств (от 10% до 20%) [35]. Так, применение seton с его последующим удалением было описано в шести ретроспективных когортных исследованиях, включающих, в общей сложности, 329 пациентов с ППБК [31,37–41]. По этим данным краткосрочное заживление свищей отмечали в достаточно широком диапазоне 14–81%.

Конкретные сроки, необходимые для удаления дренирующей лигатуры, не определены. Согласно общему мнению, ликвидацию seton рекомендуется выполнять после завершения индукционного курса биологической терапии или после стихания явлений проктита (Табл. 1) [90].

При слишком раннем удалении лигатуры велик риск развития рецидива абсцесса, в тоже время, при её длительном нахождении (более 34 недель) происходит эпителизация хода и снижается вероятность или шанс самопроизвольного заживления свища [42,43]. В исследовании ACCENT 2 все сетоны были ликвидированы на 2-й неделе после их проведения, при этом частота рецидива острого парапроктита составила 15%. В 98% случаев удаление дренирующей лигатуры выполняют в срок от 4 до 33 недель при условии проведения эффективной медикаментозной терапии [44,45].

В тоже время, дренирующая латексная лигатура может быть установлена и на более длительный срок. Kotze P.G. и соавт. [46] сообщили, что среднее время до удаления seton у пациентов с ППБК составляет 7,3 месяца, при этом максимальная длительность достигает 36 месяцев [35]. Тем не менее, по данным ретроспективного исследования Bouguen G. и соавт., при установке лигатуры на более длительный срок (средняя продолжительность — 33 недели) частота возникновения рецидива абсцесса по-прежнему составляет 22% [44].

Пациентам с ППБК не рекомендуется использование прорезывающих лигатур. По результатам систематического обзора 20 исследований (n = 520), установлено, что средняя частота анальной инконтиненции после лечения свищей режущим сетоном составила 32% [47], при этом некоторые исследователи сообщили о развитии недержания в 57% случаев [48]. Следует отметить, что недостаточность анального сфинктера 2-й степени была зафиксирована у 22% пациентов, а 3-й — в 6% наблюдений [47].

В настоящее время пациентам со сложными свищами рекомендуется использование дренирующей латексной лигатуры (Seton) в сочетании с анти-ФНО препаратами. На основании рандомизированного исследования Wasmann K. и соавт. установлено, что заживление свища в группе сетон + анти-ФНО составляет 64% против 42% — в группе с изолированной установкой лигатуры [49]. По данным метаанализа четырех когортных исследований, включающих 132 пациента с ППБК, в которых проводилось сравнение двух групп — с установкой лишь сетона, и с установкой сетона, сопровождающейся введением биологической терапии, установлено, что сочетание лигатуры и анти-ФНО препаратов сопровождается более высоким процентом заживления [50].

Иссечение свища с низведением лоскута стенки прямой кишки

В качестве радикального лечения пациентам со сложными свищами ППБК, в том числе со свищами высокого уровня и ректовагинальными фистулами, возможно выполнение иссечения свища с низведением лоскута стенки прямой кишки [51,52]. При этом лоскут может быть как слизисто-подслизистый, так и слизисто-мышечный. Преимуществами методики являются отсутствие воздействия на структуры запирательного аппарата прямой кишки (ЗАПК) и минимизация раневых дефектов.

Следует отметить, что для выполнения данной операции необходимо соблюдение следующих условий:

– отсутствие гнойных полостей и затеков;
– отсутствие явлений проктита;

Таблица 2. *Результаты применения пластики внутреннего отверстия свища лоскутом стенки прямой кишки*
Table 2. *Results of the application of plastic surgery of the internal opening of the fistula with a flap of the rectal wall*

Автор	Год	Количество	Заживление (%)	Рецидив (Р) или недержание (НАС) (%)
Van Koperen et al.	2009	9	45	55 (Р)
Soltani et al.	2010	91	64	9,4 (НАС)
Roper et al.	2019	39	92,6	19,5 (Р)
Stellingwerf et al.	2019	64	61	7,8 (НАС)
Praag et al.	2019	21	60	19 (Р) 15,8 (НАС)

Таблица 3. *Результаты LIFT у пациентов с БК*
Table 3. *LIFT results in patients with CD*

Автор	Год	Количество	Заживление (%)	Рецидив (Р) или недержание (НАС) (%)
Gingold et al.	2014	15	60	40 (Р)
Kaminski et al.	2017	23	48	52 (Р)
Praag et al.	2019	19	89,5	21,1 (Р) 21,4 (НАС)
Stellingwerf et al.	2019	64	53	1,6 (НАС)

– отсутствие грубых рубцовых изменений стенки анального канала и прямой кишки, препятствующих мобилизации лоскута [53].

В общей популяции у пациентов с криптогландулярными свищами эффективность методики составляет, в среднем, 80% (от 24 до 100%) при частоте развития анального недержания 13% (0–35%) [54]. У пациентов с ППБК средняя частота заживления составляет 64% (33–92%) при частоте развития инконтиненции в 9.5% наблюдений (0–29%) (Табл. 2.) [53–57].

Проведение иммунологической терапии как до иссечения свища с низведением лоскута прямой кишки, так и в послеоперационном периоде улучшает результаты лечения пациентов с перианальными проявлениями болезни Крона [55]. По данным более ранних исследований, выполненных в 1990–2000 гг. до широкого распространения иммунологической терапии, частота рецидива свища при ППБК через 24 месяца после пластики лоскутом составила 50% [58]. В тоже время исследования, описывающие применение иммунотерапии в срок 531–550 дней до операции и в послеоперационном периоде, демонстрируют частоту первичного заживления, составляющую 83,9% при частоте рецидива — 37,5% через два года после хирургического лечения ($p = 0.03$) [59–62].

Следует отметить, что, по некоторым данным, наличие превентивной стомы улучшает результаты лечения ППБК с низведением лоскута стенки прямой кишки, однако статистически значимых результатов получено не было в виду малого числа пациентов в исследованиях [63].

Перевязка свищевого хода в межсфинктерном пространстве (LIFT)

Метод перевязки свищевого хода может быть применен при транссфинктерных свищах у пациентов с БК, за исключением фистул, проходящих через глубокую порцию наружного сфинктера. Рекомендуется применять процедуру перевязки свищевого хода в качестве второго этапа лечения после удаления сетона у пациентов с низкой частотой стула [64] и при отсутствии явлений выраженного проктита [65].

При лечении криптогенных свищей прямой кишки эффективность LIFT составляет от 53,9% до 84,3% при частоте развития рецидива заболевания, варьирующей от 14,8% до 29%. При этом явления послеоперационной анальной инконтиненции наблюдаются в 0,4–2,8% случаев [56].

У пациентов с ППБК при краткосрочном наблюдении в течение одного года, по данным Gingold D.S. и соавт. ($n = 15$), перевязка свищевого хода в межсфинктерном пространстве позволила добиться успеха в 67% случаев [66]. При более длительном сроке наблюдения (23 месяца) эффективность LIFT снижается до 48%, однако отмечено, что 75% рецидивов свищей при болезни Крона возникают в течение первого года после операции [67]. По данным систематического обзора Stellingwerf M. и соавт., ухудшение функции держания отмечено лишь у 1 из 64 (1,6%) пациентов, перенесших перевязку свищевого хода в межсфинктерном пространстве (Табл. 3.) [56].

Видеоассистированный метод лечения свищей (VAAFT — videoassisted anal fistula treatment)

Пациентам со сложными свищами при БК оправдано применение видеоассистированного метода как в качестве сфинктеросохраняющего радикального метода лечения, так и для более точной диагностики [68] высоких полостей и затеков у пациентов со свищами высокого уровня.

По результатам систематического обзора литературы и метаанализа Emile S.H. и соавт., включающего 11 исследований и 788 пациентов со свищами прямой кишки, средневзвешенная частота рецидивов составила 14,2% (7,5%–33%) с медианой наблюдения в 9 месяцев, а частота осложнений 4,8% при отсутствии явлений послеоперационной недостаточности анального сфинктера [69].

О лечении свищей с применением VAAFT у пациентов с болезнью Крона в настоящее время опубликованы результаты единичных нерандомизированных исследований. Так, Schwander O. описал результаты лечения 11 пациентов с болезнью Крона и свищами прямой кишки, однако применение видеоассистированного метода дополняли закрытием внутреннего отверстия лоскутом прямой кишки при наличии превентивной стомы. Таким образом, полученные в 82% случаев положительные результаты лечения нельзя объяснить только лишь применением метода VAAFT [70]. По данным Adegbola S.O. и соавт., 84% пациентов (n = 21) со свищами прямой кишки и болезнью Крона после применения VAAFT отметили снижение интенсивности болевых ощущений и гнойного отделяемого из свищевых ходов [71].Стоит отметить, что широкому внедрению метода препятствуют не только скудные данные об эффективности его применения, но и высокая стоимость оборудования.

Лазерная облитерация свищевого хода (FiLaC — Fistula Laser Closure)

Лазерная облитерация свищевого хода — малоинвазивный и сфинктеросберегающий метод лечения свищей прямой кишки. Наиболее целесообразно применять данную методику при сформированном свищевом ходе, в частности — в качестве второго этапа лечения после удаления дренирующей латексной лигатуры.

В общей популяции при использовании FiLaC в сочетании с различными вариантами закрытия внутреннего свищевого отверстия отсутствует влияние на функцию анального держания, а частота заживления свищей варьирует от 40 до 83,5% в срок наблюдения за пациентами от 15 до 20 месяцев [72–74]. По данным метаанализа Elfeki H. и соавт., включающим результаты лечения 454 пациентов методом FiLaC в 7 ретроспективных исследованиях, при медиане наблюдения 23,7 месяца средневзвешенная частота заживления свищей составила 67,3%, а частота анальной инконтиненции — 1% [75].

Результаты применения лазерных технологий у пациентов с перианальными проявлениями болезни Крона также ограничены единичными ретроспективными исследованиями [72,76–78]. Тем не менее, в августе 2022 года Cao D. и соавт. был опубликован первый систематический обзор литературы и метаанализ, посвященный эффективности и безопасности FiLaC при свищах прямой кишки при болезни Крона, включающий анализ результатов лечения 50 пациентов в 6 исследованиях. Лазерная термооблитерация свищевого хода привела к положительному результату лечения в 68% случаев и не повлияла на функцию запирательного аппарата прямой кишки ни у одного пациента [79]. Однако данный метаанализ имеет существенные ограничения в связи с малым количеством пациентов во включенных в него исследованиях и ретроспективным их характером, что говорит о необходимости проведения качественных рандомизированных исследований и анализе отдаленных результатов лечения, прежде чем этот малоинвазивный метод займет свою «нишу» в хирургическом лечении свищей прямой кишки у пациентов с болезнью Крона.

Биопластические материалы

К биопластическим материалам можно отнести фибриновый клей, который вводится непосредственно в свищевой ход, и «fistula plug» — так называемые герметезирующие тампоны, которые устанавливают в области внутреннего свищевого отверстия. Данные методики могут быть применены у пациентов со сложными свищами в качестве второго этапа лечения после удаления дренирующей лигатуры, в том числе и у пациентов с ректовагинальными свищами с целью минимизации оперативного воздействия на мышечные структуры ЗАПК. Важным условием использования биоматериалов является отсутствие активного воспаления в анальном канале и прямой кишке.

При сравнении эффективности герметизирующих тампонов в общей популяции и у пациентов с ППБК достоверных различий по частоте заживления (в 55% случаев) и количеству осложнений получено не было [80, 81]. Однако, по данным многоцентрового рандомизированного исследования, проведенного группой GETAID в 2016 году (n = 54, срок наблюдения 12 недель), эффективность применения «пробок» вторым этапом была несколько выше (31,5%), чем у пациентов, которым выполняли только удаление дренирующей лигатуры (23,1%) (p = 0,19) [82].

По данным систематического обзора Lee M.J. и соавт. (n = 219), применение фибринового клея эффективно у 40–67% пациентов в общей популяции [30].

В 2010 году Grimaud J. и соавт. опубликовали результаты многоцентрового рандомизированного исследования, посвященного применению фибринового клея у пациентов с ППБК (n = 77). Через 2 месяца после операции эффективность процедуры составила 38%, против 16% — в контрольной группе (ОШ 3,2, ДИ 1,1–9,8, p = 0,04). Следует отметить, что наибольшая частота заживления все же наблюдалась у пациентов с простыми свищами БК [83].

Таким образом, вышеуказанные ограниченные результаты применения биопластических материалов у пациентов с ППБК не позволяют рекомендовать данные методики к рутинному применению у данной категории больных (Табл. 4) [84].

Формирование стомы

Пациентам с обширными перианальными поражениями, сопровождающимися выраженными

Таблица 4. *Результаты применения биопластических материалов*
Table 4. *Results of application of bioplastic materials*

Автор	Год	Количество	Заживление (%)
Champagne et al.	2006	20	80
Schwandner et al.	2009	9	77
Ellis et al.	2010	12	66
Cintron et al.	2013	8	50
Herold et al.	2016	4	25

клиническими проявлениями, несмотря на установленные ранее дренирующие лигатуры и при неэффективности медикаментозного лечения, целесообразно формирование стомы или выполнение проктэктомии. При этом отключение пассажа предпочтительнее, так как полноценная резекция зачастую осложняется формированием полостей в ложе удаленной кишки и длительно незаживающих обширных ран промежности [85]. У пациентов со сложными свищами при БК частота формирования отключающей стомы варьирует в пределах 31–49%. По данным метаанализа Singh S. и соавт., включающего 15 исследований (n = 556), 63,8% (95% ДИ: 54,1–72,5%) пациентов отметили явное стихание клинических проявлений ППБК в короткие сроки после выведения стомы. Восстановление непрерывности кишечника было предпринято у 34,5% (95% ДИ: 27,0–42,8%) пациентов, однако в 26,5% (95% ДИ: 14,1–44,2%) случаев рецидив ППБК послужил причиной для повторного отключения кишечного пассажа. Кроме того, 41,6% (95% ДИ: 32,6–51,2%) больным на фоне продолжающегося воспалительного процесса потребовалось удаление кишки, несмотря на наличие отключающей стомы. Таким образом, лишь у 16,6% (95% ДИ: 11,8–22,9%) пациентов стому можно считать временной [86]. Широкое внедрение в клиническую практику биологической терапии позволило снизить частоту формирования постоянных стом с 60,8% до 19,2% ($p < 0,05$) [87]. Есть мнение, что формирование отключающей стомы более чем в 60% случаев не позволяет добиться заживления перианальных поражений, что в конечном итоге приводит к удалению прямой кишки [91].

Удаление прямой кишки (проктэктомия)

Удаление прямой кишки является окончательным вариантом лечения тяжелой ППБК при неэффективности других методик, а необходимость в проктэктомии возникает в 8–40% случаев [1,88]. Показаниями к выполнению травматичной операции являются: клинически выраженное анальное недержание, наличие рубцового стеноза прямой кишки и анального канала, а также сопутствующее поражение других отделов толстой кишки. Следует отметить, что в ряде случаев, несмотря на сформированную ранее стому, выраженный воспалительный процесс в отключенной кишке способствует прогрессированию ППБК, что в конечном итоге также приводит к необходимости выполнения проктэктомии [84]. Особенностью в методике выполнения проктэктомии у пациентов с тяжелой ППБК является необходимость выполнения мезоректумэктомии, так как сохраняющиеся в околопрямокишечной клетчатке воспалительные гранулемы способны поддерживать воспалительный процесс в промежности даже после удаления прямой кишки [89].

ЗАКЛЮЧЕНИЕ

Широкое внедрение в клиническую практику биологических препаратов, безусловно, улучшило результаты хирургического лечения пациентов с перианальными свищами при БК, что лишний раз доказывает необходимость мультидисциплинарного подхода с участием как хирургов, так и гастроэнтерологов. При этом показания к различным методам оперативного лечения свищей у пациентов с болезнью Крона по-прежнему не определены.

Таким образом, несмотря на значительное число различных методик хирургического лечения, до сих пор не существует единой концепции в алгоритме лечения данной категории пациентов. Большинство описанных методов применялось у строго отобранной ограниченной группы больных и позволяло лишь временно ликвидировать клинические проявления ППБК. Неудовлетворительные результаты лечения, особенно в отдаленном послеоперационном периоде, малое число клинических наблюдений в опубликованных научных работах, посвященных лечению перианальных проявлений болезни Крона, а также низкая достоверность результатов, диктуют необходимость проведения дальнейших исследований с включением большего числа пациентов.

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Colorectal cancer in ulcerative colitis (review)

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ABSTRACT *Ulcerative colitis (UC) is an inflammatory bowel disease that mainly affects young people. Colorectal cancer (CRC) is one of the UC complications. This review considers the epidemiology, risk factors, diagnosis and screening, and drug prevention of CRC in UC. Various treatment options for dysplasia and CRC associated with UC are described. Taking into account the lack of literature to standardize colorectal cancer treatment approaches (especially rectal cancer) for UC, further studies are warranted to evaluate both oncological and functional treatment outcomes.*

KEYWORDS: *colorectal cancer, ulcerative colitis, dysplasia*

CONFLICT OF INTEREST: *the authors declare no conflict of interest*

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INTRODUCTION

According to the WHO, in 2020, colorectal cancer (CRC) ranks 3rd among all registered oncological diseases after breast cancer and lung cancer, while 1,931,590 people were diagnosed with it during the year [1].

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucosal layer. The UC incidence ranges from 0.6 to 24.3 per 100,000 people; the prevalence reaches 505 per 100,000 people. The peak of morbidity is between 20 and 30 years of life, and the second peak of morbidity is described at the age of 60–70 years [2,3].

Chronic inflammation of the large intestine in ulcerative colitis can become a substrate for the development of dysplasia, carcinoma *in situ* and even invasive adenocarcinoma [4]. According to Triantafillidis J.K., et al., IBD-associated large intestine cancer accounts for less than 2% of the total CRC [5], and is the third most common after cancer associated with familial large intestine adenomatosis and Lynch syndrome [6].

To date, there are conflicting data on the rate of the CRC against the UC background. Perhaps these changes are related to the accumulation of experience and improvement of technical methods for the diagnosis of IBD [7]. Approaches to the treatment of UC-associated colorectal cancer are also ambiguous, in comparison with sporadic cancer, due to the peculiarities of its pathogenesis and the prevalence of inflammatory changes in the large intestine mucosa [8].

EPIDEMIOLOGY OF CRC AGAINST THE BACKGROUND OF UC

IBD-associated cancer has epidemiological, clinical and morphological differences from sporadic CRC.

The cancer site in UC can equally be both in the rectum and in the right and left colon; tumors are more likely to be synchronous and have a higher degree of histological differentiation. Mucinous carcinomas are more common in UC. Recently, there has been an increase in the detection rate of IBD-related cancer in the early stages (stages I-II), which reaches 60%. Delaunoit T., et al. associate this with an increased level of awareness about this disease, early start of screening and improved diagnosis [9].

Recent population studies have shown a reduction in the risk of CRC in IBD. So, Jess T., et al.

have shown that the risk ratio of the CRC in IBD is comparable to the general population — 1.07 (95% CI, 0.95–1.21). At the same time, correcting that the risk ratio of the CRC decreased from 1.34 (95% CI, 1.13–1.58) in 1979–1988 to 0.57 (95% CI, 0.41–0.80) in 1999–2008. The authors attribute this to an improvement in the results of anti-inflammatory therapy in IBD [4]. Similar results were obtained in the study by Rutter M., et al. from St. Mark's Hospital, who reported the results of the 30-year follow-up of patients with dysplasia and cancer on the UC background. The cumulative risk of CRC morbidity in this group was 2.5% after 20 years, 7.6% after 30 years and 10.8% after 40 years from the UC disease onset [10].

RISK FACTORS FOR CRC AGAINST THE UC BACKGROUND

The early age of the disease onset, the prevalence of inflammatory changes, duration and severity of the disease, family history of CRC and the presence of primary sclerosing cholangitis (PSC) were recognized as factors that increase the risk of CRC in patients with UC [11].

The most important risk factor is the duration of the disease, while the CRC occurs relatively rarely during the first 8 years after diagnosis [12].

In a large meta-analysis involving 116 studies and 54,478 patients, by Eaden J., et al., it was shown that the risk of UC-associated CRC is 0.3% per year. The cumulative CRC incidence in patients with UC was 2% after 10 years, 8% after 20 years and 18% after 30 years from the disease onset. The average duration from the diagnosis of UC to the development of CRC was 16.3 years [13].

Söderlund S., et al. revealed the dependence of the lesion extent (according to the Montreal classification) of colitis and the risk of CRC. Thus, the relative risk of developing CRC for all patients with UC was 2.7, while for proctitis — 1.7, and for total colitis — 5.6 [14]. At the same time, patients without severe inflammation of the large intestine are not at increased risk of CRC [15].

Inflammation in UC is a pathogenetic factor in the CRC, and the degree of inflammation activity is directly related to the risk of its development [16]. The presence of post-inflammatory polyps and strictures is also associated with an increased risk of a malignant process. At the same time, the large intestine strictures is an important marker of the disease severity.

It is noteworthy that almost 3.5% of large intestine strictures were diagnosed with dysplasia or CRC during biopsy. Predictors of the malignancy of strictures are their development after 20 years of illness, the location proximal to the splenic flexure and the clinical picture of bowel obstruction [10].

Patients with PSC have a higher risk of CRC. Thus, in patients with a 20-year history of UC with PSC, CRC was found in 33% of cases [17].

DIAGNOSIS AND SCREENING OF CRC IN UC

The aim of screening is to detect any dysplasia before the development of CRC, or cancer at an earlier stage, in order to improve outcomes, patient quality of life and survival [18].

Cochrane Review edited by Collins, P. et al. demonstrates that screening is effective in reducing mortality from CRC in UC by detecting cancer at an earlier stage [19]. Similar data were obtained in the study by Lutgens M., et al., which included 149 patients with CRC on the UC background. Thus, the 5-year survival rate in the screening group was 100%, while in the non-screening group it was 74%, and in the screening group colorectal cancer was detected at an earlier stage [20].

Most guidelines for UC emphasize that screening colonoscopy should be performed in patients with clinical remission, since active inflammation makes it difficult to detect dysplasia. According to the European Clinical Guidelines for the IBD treatment (ECCO), screening colonoscopies in patients with UC should be started 8–10 years after the onset of the disease for patients with left-sided or total colitis [21]. According to the Russian national clinical guidelines, screening should begin in 6–8 years [2].

The American Cancer Society (ACS) recommends screening colonoscopy in 8 years after the onset of total colitis and in 12–15 years after the onset of left-sided colitis [12].

Traditionally, screening programs recommend endoscopy in white light (WLE) with random four biopsies every 10 cm of the large intestine to detect dysplasia, which results in about 33 biopsies [2,21]. However, with a random biopsy, less than 1% of the total area of the large intestine mucosa

is examined, and the incidence of detection of dysplasia is < 2 per 1,000 biopsies [22].

The use of high-resolution endoscopic equipment leads to better visualization of the mucosal layer, which significantly increases the diagnostic value when dysplasia is detected against the UC background.

A retrospective study by Pulusu S., et al. with participation of 357 patients with IBD, has shown that high-resolution colonoscopy revealed twice as many dysplastic lesions compared to standard WLE. Moreover, it was demonstrated that dysplasia detected by random biopsy during WLE was detected in 90%-94% of cases when using high-resolution endoscopic equipment [23].

Currently, the focus is on targeted biopsies performed using chromoendoscopy (CE), or other new endoscopic methods, such as endoscopy with narrow-beam imaging (NBI) technology [22]. The sensitivity of CE in the detection of dysplasia reaches 97%, and the specificity is 93%. A prospective randomized trial by Kiesslich, R. and coauthors demonstrated the superiority of CE using methylene blue over the random biopsy technique in WLE [24].

DYSPLASIA IN UC

Most cases of CRC on the UC background develop from dysplastic lesions which can be polypoid, flat, localized or multifocal. Dysplasia is defined as a neoplastic change in the intestinal epithelium which remains confined to the basal membrane without invasion into its own plate [25].

In 1983, Riddell R., et al. developed a classification of dysplasia in IBD, which still remains relevant and includes four main categories: absence of dysplasia, indefinite dysplasia, low-grade dysplasia (LGD) and high-grade dysplasia (HGD) [26].

The pathogenesis of CRC in IBD can follow a standard path of development from the absence of dysplasia to LGD and HGD and, ultimately, lead to large intestine cancer. And also, it can develop from any dysplastic lesion (indefinite, LGD or HGD), without following the standard path. According to Navaneethan U., et al., the rate of progression of LGD to HGD or CRC over 3 years was 4.9%.

At the same time, the risk of malignant transformation is higher in flat dysplasia and dysplasia located in the distal parts of the large intestine [27]. The most important predictor for HGD and CRC from LGD is the non-polypoid (not raised above the mucosal surface). Other predictors are macroscopically invisible dysplasia, lesion size > 1 cm, and previously identified indefinite dysplasia. The greater the number of these prognostic factors, the higher the risk of LGD transformation into HGD or CRC [28].

In the presence of visible foci of dysplasia in the large intestine segments, without endoscopic signs of active inflammation, standard polypectomy should be resorted to, and further monitoring should be continued depending on the individual risk [2,12].

For visible foci of dysplasia located in polypoid lesions, endoscopic mucosal resection (EMR) is possible, but only if complete removal is achievable [29]. Currently, the standard of endoscopic resection includes taking additional biopsies from the flat mucosal layer around the site of polypectomy in order to exclude dysplasia in the surrounding tissues [30].

Follow-up of patients with fully resected dysplastic polypoid lesion depends on the lesiontype.

If there is visible dysplasia in the polypoid lesion, careful control with colonoscopy is recommended after 6–12 months. Patients with large, broad-based lesions removed by EMR or non-radical resection should repeat colonoscopy after 3–6 months, followed by annual monitoring, if initial observation revealed no signs of residual polyp growth [31]. In cases where the lesion is not subject to endoscopic resection, or there is evidence of endoscopically invisible multifocal dysplasia of low grade, or invisible dysplasia of high grade, total proctocolectomy (PCE) should be recommended [30].

Non-polypoid visible lesions should be evaluated for the safety and effectiveness of endoscopic resection [12]. In the case of endoscopic resection, a biopsy should be taken near the removal site and endoscopic tattooing should be performed in this area to facilitate future observation [32].

According to the SCENIC study, it is recommended to perform a control colonoscopy in 3–6 months after resection of non-polypoid dysplastic lesions [31]. In the case when non-polypoid formations with confirmed dysplasia cannot be removed endoscopically, the possibility of performing PCE

regardless of the dysplasia grade should be considered [12,33].

Endoscopically invisible dysplasia detected by random biopsies should be confirmed by a second independent pathologist with experience in the IBD diagnosis [2,21,34,35].

Invisible dysplasia is associated with the presence of synchronous CRC. In fact, synchronous CRC is diagnosed in 22% of patients with invisible LGD, while the CRC rate with invisible HGD ranges from 45% to 67% [10].

It is recommended to refer such patients to reference centers that treat patients with IBD and have the ability to perform high-resolution chromoendoscopy and endoscopy with repeated biopsies [31]. If dysplastic lesions are detected during chromoendoscopy, then it should be recommended to perform PCE.

In a study by Ullman, T. et al., it was demonstrated that 15.2% of patients observed with LGD developed CRC, while 23.5% of patients who underwent colectomy for LGD were also found to have HGD or CRC during histological examination [36].

This condition is an indication for performing a proctocolectomy due to the high risk of developing CRC or the presence of a synchronous lesion. According to a number of studies, when HGD was detected, a connection with synchronous CRC was revealed in 25%-67% of cases [10,36,37]. Thus, HGD is an absolute indication for PCE in most clinical guidelines [33].

To date, there is insufficient data to assess the risks and benefits of PCE with LGD in non-elevated lesions. The decision to remove the large intestine or continue follow-up should be made individually for each patient after discussion. At the same time, if the approachis chosen in favor of screening, the incidence of colonoscopy should be at least 1 time per year [2,38].

TREATMENT OF CRC IN UC

Treatment of colorectal adenocarcinoma in UC is largely based on the same principles as sporadic adenocarcinoma, with one exception — in these patients, removal of the entire colon and rectum is needed. In some cases, it is possible to restore anal defecation by J-pouch [2,39,40]. The main reason for these recommendations is the high risk of metachronous (and latent synchronous) cancer due to the UC lesion of the mucosal layer of the entire large intestine [8]. In recent reports, a number of patients have been offered more adapted treatment, including segmental resection or subtotal colectomy. In particular, the authors emphasize the importance of the specific features of the patient and the disease, such as the duration of the anamnesis, the prevalence of inflammation, clinical and endoscopic activity, the results of the biopsy and the patient's age, the state of health and his personal priorities [41,42]. In any case, the decision on the surgeryscope should be made with a consultation by coloproctologist, oncologist, gastroenterologist, and endoscopist and be discussed together with the patient.

So, the study by Khan, N. et al., included 59 patients with CRC in UC, who underwent surgery. Segmental resections were performed in 40.7%, such as low anterior rectal resection, sigmoid resection, left-sided and right-sided hemicolectomy, as well as subtotal colectomy [42]. Patients in the segmental resection group were significantly older and had less severity and prevalence of large intestine inflammation.

None of those patients developed metachronous CRC at a median follow-up of 7 years, and the results of overall survival were comparable with the results of patients from the PCE group.

In patients with a preoperative diagnosis of dysplasia or CRC, proctocolectomy should be performed according to oncological principles with high vascular ligation. Restoration of anal defecation with J-pouchis possible for most patients, whereas abdomino-perineal excision or intersphincter resection with end ileostomy should be performed in patients with low rectal cancer, in whom it is impossible to achieve adequate distal clearance, or who have anal incontinence [37].

In case of rectal cancer (RC) in ulcerative colitis, it is mandatory to conduct a multidisciplinary consultation, taking into account many available treatment options, in order to achieve optimal oncological and functional results. In addition, it was found that patients with UC have an increased risk of mortality from rectal cancer — 3.69 (95% CI, 1.66–8.22), while for colon cancer this indicator is comparable to the general population, which emphasizes need for improving the results of treatment of this particular group of patients

[44]. Treatment of RC includes radiation therapy, chemotherapy, their combination (both neoadjuvant and adjuvant), and various procedures (taking into account the radicality and functional state) [8].

In general, total mesorectumectomy (TME) is the standard treatment for early rectal cancer, while neoadjuvant chemoradiotherapy is recommended for cancers with an invasion depth greater than T2 or with lesions of regional lymph nodes [45].

In some patients, as an intermediate stage before J-pouch, colectomy with the ileo-rectal anastomosis (IRA) can be considered as a method of choice. Most often, this surgery is offered to young females who have not given birth and have no signs of inflammation or dysplasia in the rectum, in order to reduce the risk of infertility [21,43].

In cases where total proctocolectomy is performed, the only possible option to avoid permanent ileostomy and preservation of anal defecation is J-pouch [46].

Currently, the national clinical guidelines of the Russian Association of Gastroenterology and the Russian Association of Coloproctology for the diagnosis and treatment of ulcerative colitis do not recommend J-pouch in patients with rectal cancer in UC [2]. However, a number of researchers continue to look for the possibility of preserving anal defecation in this group of patients.

So, in the study by Remzi F., et al., 26 patients with RC on the UC background who underwent PCE with J-pouch are presented [47]. At the same time, the mean distance from the edge of the anal canal to the distal border of the tumor was not presented. With a follow-up period of up to 17 years, satisfactory functional results were obtained in most patients, with two deaths with the RC progression.

Thus, the authors argue that patients with RC in UC may be susceptible to TME with J-pouch if oncological principles are followed.

Merchea A., et al. described the results of treatment of 41 patients with RC on the UC background [48]. In most cases, the tumor was diagnosed at stage I or II, and was in the middle ampullary rectum. Eleven patients underwent J-pouch, while none of them underwent neoadjuvant radiation therapy. After the J-pouch, one patient developed a leakage of the ilealpouch-analanastomosis, and another, who had undergone adjuvant radiation therapy, developed radiation enteritis which required the J-pouch removal.

The overall and disease-free 5-year survival rate in this group was the same and amounted to 62%. At the same time, 89% of recurrences were in patients with stages III and IV. Thus, the authors conclude that the J-pouch in early RC on the background of UC is a justified approach.

Radiation therapy (RT) is currently the standard treatment for sporadic rectal cancer with an invasion depth greater than T2 or the presence of affected regional lymph nodes, especially in the neoadjuvant mode [45,49]. Radiation therapy for rectal cancer against the UC background has the same indications as for sporadic cancer, although its administration requires consideration of additional risk factors. There is evidence of a higher risk of severe acute toxicity in patients with IBD [50,51]. The role of RT in relation to the results of the J-pouch is not clear, since the experience is limited to a small number of clinical cases. A very high incidence of pouch anastomosis leakage during adjuvant therapy has been reported due to the effect of radiation therapy on the small intestine used in its formation [48,52,53]. In addition, pouch anastomosis leakage rate is higher, even when radiation therapy is performed in a neoadjuvant mode. But, in general, if RT is planned and the possibility of J-pouch is not excluded, neoadjuvant radiation therapy should always be preferred, as indicated in the guidelines of the European Organization for the Treatment of Crohn's Disease and Ulcerative Colitis [21,39,52,53].

Low rectal cancer is defined as rectal cancer that occurs at a distance of less than 5 cm from the edge of the anal canal during rigid proctoscopy [45]. The complexity of surgical treatment of these tumors is due to the desire to preserve the anal sphincter. For tumors located in the mesorectal margin or below, an indentation of 1 cm is considered safe enough [49]. Sporadic cancer located distal than 1 cm from the dentate line, as a rule, requires abdomino-perineal excision of the rectum (APE), although in some cases it is possible to perform intersphincter resection with ultralow anastomosis. The safe clearance along the distal edge of resection of 1 cm is based on the results of studies that have shown that distal intramural spread > 1 cm occurs only in 4%-10% of cases [54].

In addition, in a later study by Guillem J., et al. it was found that the positive distal edge of resection due to intramural growth with low sporadic RC was detected only in 1.8% of cases, and amounted to < 0.95 cm [55].

While a large number of studies for sporadic RC aimed not only at improving oncological results, but also at improving functional results, the literature data on the RC treatment against the UC background remain rather scarce do not allow to standardize the approach to its treatment. In addition, it is often difficult to specify the exact rectal lesions sites in UC during endoscopy due to their growth in a flat (not elevated) mucosa.

Hotta S., et al. analyzed the results of treatment of 11 patients with very low rectal cancer in UC [56]. In 9 cases, PCE was performed with J-pouch and pouch-anal anastomosis, and in 2 cases — APE. At the same time, the authors emphasized that in 89% of 9 cases, the cancer was in a flat (not elevated) mucosal layer surrounded by chronic inflammation, which confirms the difficulties in determining the safe distal edge of resection. As a result, neither in the PCE group with J-pouch (9 patients) nor in the APE group (2 patients) did any patient receive neoadjuvant or adjuvant radiation therapy. At the same time, the authors reported 100% overall 5-year survival in both groups. Thus, reconstructive surgery with the pouch-anal anastomosis is possible with low RC with good oncological results. However, the available literature data are insufficient for a final judgment.

The presence of ultralow RC in patients with UC causes additional concerns, because compared with colo-anal anastomosis, the J-pouch with inter-sphincter resection after PCE exposes the patient to a greater risk of unsatisfactory functional results. In patients with J-pouch after PCE, the number of daily defecations ranges from 1 to 30 (7 on average), about 5% of pouches are eventually removed due to poor functional results and unsatisfactory quality of life [57]. Therefore, with ultralow RC against the UC background, due to the high risks of unsatisfactory functional results and concerns about oncological safety, J-pouch surgery is often not offered.

In the literature, only a few successful cases of RC treatment against the UC background at a distance of less than 2 cm from the dentate line have been described, in which PCE with the J-pouch formation was performed [53,56]. And despite the success of these clinical cases, we cannot recommend this method of treatment for all patients. Neoadjuvant RT makes it possible to reduce the size and depth of tumor invasion, increasing the likelihood of reconstructive surgery [58,59]. On the other hand, it can negatively affect the function of the anal sphincter, especially in combination with low anastomosis. There is evidence that collagen deposition and nerve plexus lesion occur in the irradiated sphincter [60] and, apparently, is the main factor of poor anal function [61]. It should be emphasized that for the final decision on reconstructive surgery, along with oncological safety, it is extremely important to motivate the patient and his/her willingness to adapt and rehabilitate in the postoperative period.

PROGNOSIS FOR CRC AGAINST THE UC BACKGROUND

In a meta-analysis by Reynolds, I. et al., survival data of 243,186 patients with IBD and their risk of developing CRC in comparison with general population risks were reported. As a result, the overall 5-year survival rate of patients with IBD-associated CRC did not differ from patients with sporadic CRC — OR — 1.11 (95% CI, 0.41–2.95; $p = 0.842$). However, patients with IBD had higher risks of synchronous tumors — OR — 4.4 (95% CI, 2.32–8.36; $p < 0.001$), and the risks of rectal tumors, on the contrary, are lower — OR — 0.83 (95% CI, 0.74–0.93; $p = 0.002$) [62].

Similar data were demonstrated in the study by Thicoïpé A., et al., in which the results of treatment of two groups of patients were compared: a group with IBD-associated CRC and a group with sporadic CRC. Both groups were comparable in gender, stage and localization of the tumor.

The study showed that the cancer-specific and overall survival rates were the same in the groups of patients with CRC against the UC background and patients with sporadic CRC, 71% and 69% ($p = 0.801$), and 81% and 78% ($p = 0.845$), respectively, despite the older age in the group of sporadic CRC and a high rate of primary multiple synchronous cancer in the IBD group [63].

Summing up, it can be concluded that the prognosis for CRC associated with IBD is similar to the prognosis for sporadic CRC.

CONCLUSION

In the XXI century, the CRC incidence in 30 years after the UC diagnosis decreased from 18% to 7.6%, which is most likely due to improved results of anti-inflammatory therapy in UC. However, often, when long-term clinical remission is achieved in the treatment of UC, patients neglect to undergo screening colonoscopy, as a result of which the development of epithelial dysplasia and even CRC may be missed.

The treatment of colorectal cancer developing in patients suffering from ulcerative colitis is largely based on the same principles as in sporadic cancer, with one exception — in these patients, removal of the entire colon and rectum is indicated. In some cases, it is possible to restore anal defecation by forming a pelvic small intestine pouch.

In some patients, colectomy with the formation of ileo-rectal anastomosis can be considered as a method of choice. Patients with low localization of rectal cancer, anal sphincter incontinence should undergo colectomy with abdominal-perineal extirpation or abdominal-anal resection and ileostomy formation according to Bruck. The problem of treating rectal cancer against the UC background is quite urgent due to the lack of clear algorithms and the ambiguity of literature data. The use of radiation therapy in such patients is associated with a high risk of severe toxicity and the development of a number of severe complications in the case of the J-pouch formation.

When the patient is motivated to form J-pouch, and there are indications for CRT, the latter should be used only in the neoadjuvant mode. For the final decision on reconstructive surgery, along with oncological safety, it is extremely important that the patient is ready for a long period of adaptation and rehabilitation after surgery.

AUTHORS CONTRIBUTION

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Conservative treatment of inflammatory bowel diseases during pregnancy. Review of current safety and efficacy data

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ABSTRACT *The incidence of ulcerative colitis (UC) and Crohn's disease (CD) worldwide falls on the childbearing age. High activity of inflammatory bowel diseases (IBD) during pregnancy is a risk factor for the development of obstetric complications, and therefore it is necessary to control the course of diseases. Due to the lack of safety information, drug therapy is often unreasonably canceled during pregnancy. The publication provides up-to-date on the safety of basic and targeted therapy of UC and CD in pregnant.*

KEYWORDS: *ulcerative colitis, Crohn's disease, inflammatory bowel diseases, pregnancy.*

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LIST OF ABBREVIATIONS

IBD — inflammatory bowel diseases
5-ASA — 5-aminosalicylic acid

GEBT — genetically engineered biological therapy

In the XXI century, the prevalence of IBD is becoming global, affecting ethnic groups and regions that were previously not susceptible to these diseases. The prevalence of UC and CD is highest in industrially developed and developing countries [1]. According to experts, the peak prevalence of IBD has not yet been reached. The most vulnerable to IBD is the age group of 20–39 years, i.e. persons of childbearing, socially active age. Approximately half of them are women. Modern IBD therapy has significantly expanded the possibilities of the disease control and, in many cases, allows patients to achieve reliable remission and to lead a normal socially active life, one of the components of which is childbirth. In this regard, reproductive health issues in patients with IBD are becoming increasingly relevant. The prevalence of IBD in Western countries is 0.5% [2]. In the USA, IBD affects about 800,000 women [3]. In Russia, data on the prevalence of IBD are scattered and limited to only some individual regions.

Pregnancy in women with IBD, as in many chronic immuno-inflammatory diseases, is associated with an increased risk of obstetric complications [4–7]. These complications include spontaneous miscarriage, premature birth and low weight of the fetus relative to the gestational age. However, it should be noted that the risk of these complications is directly related to the activity of inflammation in the intestine. The outcomes of pregnancies occurring against the background of persistent remission of UC and CD, in general, do not differ from a healthy population [8].The UC and CD during pregnancy is largely determined by the inflammatory status of diseases at the time of conception. Thus, the activity of the inflammatory process in the intestine at conception in two-thirds of cases is a predictor of the persistence of inflammation or its intensification [9–11]. Prolonged persistent remission at the onset of pregnancy correlates with its preservation in 80% of cases throughout the

gestation period. Factors that additionally contribute to the recurrence of IBD during pregnancy include the cancel of supportive drug therapy, exacerbation of the disease in previous pregnancy, the presence of UC, prolonged or complicated CD, requiring the immunosuppressive therapy [3,12]. These data became the basis for guidelines on optimal pregnancy planning for the period of reliable controlled remission of UC and CD [9,10].

Conservative treatment of IBD during pregnancy is aimed not only at controlling the activity of inflammation in the bowel, but also indirectly plays an essential role in maintaining the normal pregnancy and preventing perinatal complications.

It is known from practice that only half of women previously committed to drug treatment continue therapy during pregnancy [13]. The explanation for this may be a lack of awareness about the safety of IBD conservative treatment during pregnancy. Published in 2021 by a group of German researchers, the results of a survey of 533 women with IBD confirmed the insufficient level of knowledge among women with UC and CD about pregnancy planning with their disease. Of the total number of survey participants, 36% of women expressed concern about the possible adverse effects of taking medications for the fetus, among which the most often were the fear of congenital malformations, miscarriage, as well as the possibility of offspring inheriting the mother's disease [14].

In recent years, the data on the safety of IBD drug therapy in pregnant women has been continuously updated. The present paper discusses modern pharmacotherapy of UC and BC during pregnancy and breastfeeding.

5-ASA and Sulfasalazine Drugs

Mesalazines or 5-aminosalicylic acid agents (5-ASA) overcome the placental barrier and are detected in the fetal bloodstream in minimal amounts due to their rapid metabolism and renal clearance. According to meta-analysis data, the use of this group of agents is not associated with an increase in the risks of fetal abnormalities, miscarriage and premature birth [15]. Oral drugs containing dibutylphthalate in the shell have a restriction for use. In the experiment, cases of impaired development of the genitourinary system and skeleton were demonstrated in animals, as well as in humans — disorders of thyroid function and the formation of the reproductive system [16–18].

Sulfasalazine, in addition to the mesalazine molecule, contains sulfapyridine, which penetrates the placenta and is found in umbilical cord blood. An undesirable property of sulfasalazine in pregnant women is its ability to disrupt folic acid metabolism, and although no cases of teratogenic and embryotoxic effects have been reported, it should be used in combination with folic acid at a dose of 2 mg/24-hr, or be replaced with mesalazinedrugs [9,19].

Steroids

Systemic steroids are used to induce remission of moderate and severe IBD. The drug penetrates the placental barrier, but, due to the rapid conversion of placental enzymes into less active metabolites, it appears in umbilical cord blood in low concentrations [20]. In early studies, concerns were expressed about the relationship of the use of steroids in the first trimester of pregnancy with the risk of facial malformations, namely cleft palate. In a later large population study [21], which included 51,973 pregnancies in women who received steroids in the first trimester, these data were not confirmed.

At the same time, in a number of studies, steroids in high doses over long courses was associated with an increased risk of gestational diabetes mellitus, premature birth, low body weight and adrenal suppression in a newborn [22–24]. Taking into account that steroids are prescribed with high activity of diseases, in most cases it is difficult to differentiate the true cause of complications.

Budesonide is a topical steroid, significantly, up to 80–90% metabolized during the first passage through the liver. In recommended doses (3–9 mg per 24 hours), the drug has significantly fewer systemic side effects characteristic of systemic steroids. It can be assumed that due to these metabolic features, budesonide penetrates less into the fetal blood in comparison with systemic steroids [25]. Published data on the budesonide during pregnancy in patients with IBD are limited to a small case series. Thus, in one of the published studies [26] with cohort of 6 patients with CD who took budesonide during pregnancy, there was no increase in the risk of gestational diabetes

mellitus, congenital malformations of the fetus, hypertonia or adrenal suppression. Also, according to a recently published study [27], taking budesonide during pregnancy in 5 patients with autoimmune hepatitis was not associated with the adverse side effects from the fetus and pregnancy outcomes.

Despite the fact that limited data indicate possible undesirable effects of steroids during pregnancy, it should be taken into account that the high activity of inflammation in the intestine itself represents a more significant risk of complications. In this regard, if indicated, steroids may be prescribed with caution regarding the development of gestational diabetes mellitus, preeclampsia in the mother and adrenal insufficiency in the newborn [9,28,29].

Thiopurines

Thiopurines have a low risk of adverse effects on pregnancy and fetus [30,31]. Azathioprine and its metabolites are able to be transported through the placenta into the fetal blood, while the concentrations of these substances in umbilical cord blood are significantly less than in maternal [32]. In addition, it has been shown that the activity of some enzymes involved in drug metabolism, including azathioprine, increases significantly during pregnancy. As a result, the balance of thiopurine metabolites shifts from the 6-thioguanine nucleotide towards the less toxic and pharmacologically inactive 6-methylmercaptopurine [33]. The enzyme inosinate phosphorylase, which converts azathioprine into its active metabolites, is not expressed in the neonatal liver, which can be regarded as another factor of fetal protection from the clinical effects of the drug [34].

The effect of azathioprine on anemia/cytopenia in newborns demonstrated in early studies has not been confirmed in later studies [33]. Two meta-analyses in 2013 demonstrated minimal risk of taking azathioprine during pregnancy. In the first of them, there were no differences in the incidence of congenital malformations of the fetus, the small weight of the newborn (< 2,500 gr) in comparison with pregnant women with thiopurines intake[31]. Significant differences were noted in the rate of congenital malformations in comparison with the general population, which were not significant when compared with patients with IBD. In the second meta-analysis, these risks for the fetus were not confirmed [35]. At the same time, both meta-analyses revealed an increase in the rate of premature birth (earlier than 37 weeks of pregnancy), which was associated with high activity of IBD during pregnancy.

In a prospective cohort study involving 309 pregnant patients with IBD, 35% of whom got thiopurines, there was no increase in miscarriage, adverse pregnancy outcomes and morbidity in children in the first year of life [36]. These data are confirmed in the meta-analysis published in 2021 [37]. The authors analyzed pregnancy outcomes in 1,201 patients with IBD who received thiopurines during gestation compared with 4,189 women who received other therapy for UC and CD. The rate of congenital malformations in the fetus, low birth weight and low body weight for gestational age were comparable in the two groups.

The American Gastroenterological Association, the Toronto Consensus on the Management of Pregnancy in Women with IBD and the European Organization for the Study of UC and CD (ECCO) recommend the continuation of taking thiopurines during pregnancy [29,30,38]. A similar opinion is shared by the European Anti-Rheumatic League (EULAR), which does not note sufficient basis for stopping thiopurines during pregnancy, and recommends continuing their intake at a dose not exceeding 2 mg/kg of body weight [39]. The Russian clinical guidelines of the Association of Rheumatologists also classify thiopurines as safe drugs during pregnancy [40, 41]. However, thiopurines are not recommended for the first time during pregnancy due to the risks of pancreatitis, leukopenia and delayed response to therapy [9]. Also, due to the increased risk of infections in a child in the first year of life, as shown in some studies [30, 42], combination therapy with tumor necrosis factor inhibitors α and thiopurines is not recommended. Nevertheless, the decision to cancel thiopurines should be made individually, taking into account the indications for combination therapy and the severity of the course of the disease [9].

Methotrexate and cyclosporine are not recommended during pregnancy due to the high risk of teratogenicity. Patients with IBD who are taking methotrexate and planning pregnancy are advised

to stop taking it at least 3 months before trying to get pregnant in order to minimize the risk of teratogenicity [29,38].

Rifaximin

The drug is used in the treatment of IBD, including the treatment of chronic pouchitis [43]. According to the manufacturer's instructions, in an experiment, the administration of rifaximin to animals during pregnancy at doses many times higher than therapeutic ones led to the development of teratogenic effects [44]. Rifaximin is a broad-spectrum antibiotic with a low ability to intestinal absorption, and presumably does not reach clinically significant concentrations in maternal blood or breast milk [45,46]. Due to the fact that the number of publications on the use of rifaximin in humans during pregnancy is extremely small, the issue of its administration should be decided individually with discussion by a multidisciplinary medical team.

Genetic Engineering Biological Therapy

Drugs of genetically engineered biological therapy (GEBD) are monoclonal IgG antibodies that are able to overcome the placenta, starting from the middle of the second trimester. Active transport of GEBD is carried out using a neonatal Fc-receptor located in the placenta. In the first trimester of pregnancy, the Fc-receptor is not expressed by syncytiotrophoblast cells, and from the middle of the second trimester of pregnancy, its expression increases linearly [47]. From this moment, during pregnancy and until the moment of delivery, the transplacental transport and the concentration of GEBD in the fetal blood increases in parallel. The IgG structure has infliximab, adalimumab, golimumab, vedolizumab and ustekinumab. Certolizumab pegol does not have in its molecule the Fc-fragment necessary for active transfer through the placenta, and overcomes it in minimal quantities due to passive transport [48].

Inhibitors of Tumor Necrosis Factor α

The levels of tumor necrosis factor α (anti-TNF) inhibitors in umbilical cord blood correlate with the duration of pregnancy and exceed the maternal serum concentration at the time of birth [48, 49]. Clearance of anti-TNF in children in the first months of life is slower than in adults, which is associated with immaturity of the reticulo-endothelial system. Monoclonal antibody molecules are in the bloodstream of a child up to six months old. Some cases are described when infliximab was determined in a child up to one year old [48,49].

Certolizumab pegol, due to its reduced antibody structure, practically does not overcome the placenta, and its ratio in the blood of a newborn to the maternal concentration is 0.0009. These minimal clinically insignificant concentrations are an argument in favor for pregnant women to continue taking certolizumab pegol until delivery [50].

To date, significant data have been accumulated on the safety of taking anti-TNF drugs by pregnant women. Thus, in a meta-analysis and systematic review [51] with an analysis of more than 1,500 pregnancies against the background of anti-TNF, the risks associated with pregnancy complications, miscarriages, premature birth, congenital malformations and intrauterine fetal growth retardation were not confirmed.

In the prospective American PIANO-register (Pregnancy and Neonatal Outcomes in Women with IBD) [52], which includes data on the course of pregnancy in more than 1,000 patients with IBD followed by four-year follow-up of the health of children who received intrauterine anti-TNF, there was no increase in the frequency of infections and developmental delay. In a large multicenter prospective observational study by Mahadevan U. et al., the outcomes of 1,490 pregnancies in patients with IBD were evaluated by five parameters (congenital malformations, spontaneous miscarriages, premature birth, low fetal body weight and the incidence of infections in the child) when the mother used thiopurines, biological drugs or a combination thereof during pregnancy [53]. In the same study, the health status, including the frequency of infections and psychomotor development, was monitored in 1,010 children throughout the year.

In general, in terms of the fetal malformations rate, spontaneous miscarriages, low fetal weight, infections in the first year of the child's life and premature birth, the group did not differ from the general population. At the same time, the activity of the disease in the mother directly correlated with the rate of spontaneous miscarriages, premature births and infections in the first year of the child's life. When analyzing IBD during pregnancy, it was found that patients with UC had an increase

in disease activity more often than women with CD. At the same time, the probability of an exacerbation during pregnancy was higher in patients who did not receive immunosuppressive therapy with thiopurines or anti-TNF.

There was also no relationship between the incidence of pregnancy complications and the class of GEBD.

Similarly, there was no correlation between congenital malformations and medications taken or the nosological type of the disease (UC or CD). These results indicate both the role of controlling the activity of the disease during pregnancy and the safety of the use of biological therapy and thiopurines during this period [53]. The European retrospective multicenter study TEDDY [54] compared pregnancy outcomes and health status in 388 children whose mothers received anti-TNF therapy during pregnancy with 453 children whose mothers did not receive this therapy. The incidence of infections in the two groups of children did not differ during 4 years of follow-up. At the same time, premature birth was associated with severe infections (1.6% vs. 2.8%, HR = 1.2 [95% CI 0.8–1.8]). In the comparison groups, there were no differences in the incidence of obstetric complications, including premature discharge of amniotic fluid, placenta previa, chorioamnionitis, eclampsia and intrauterine fetal growth retardation.

It is worth noting that previously there was a strong belief about the need to stop the use of anti-TNF therapy in the II-III trimester due to the fear of potential risks of neonatal immunosuppression and the impact on the subsequent formation of the fetal immune system as the transport of drugs through the placenta increases in the second half of pregnancy.

This is reflected in the consensus of the British Society of Rheumatology (BSR), ECCO, EULAR, the American College of Rheumatology and Russian clinical guidelines for the treatment of ankylosing spondylitis and rheumatoid arthritis, published in 2018 and 2020, respectively [28,39,40,41,55]. At the same time, studies of the last few years have questioned the validity of the fear of the risks of a prolonged biological therapy during pregnancy.

The results of a long-term 5-year follow-up of the health status of 1,000 children from mothers with IBD, 20% of whom received anti-TNF during pregnancy, demonstrated associations of the use of GEBD by the mother with an increase in the risk of infectious diseases, adverse reactions to vaccination, developmental delays, autoimmune and oncological diseases in children [56]. Similar data were obtained in another retrospective study [53] involving 869 women with IBD, in which the risks to the fetus and pregnancy complications were not confirmed with the continuation of anti-TNF monotherapy or in combination with thiopurines in the second and third trimesters of pregnancy. In a retrospective analysis of the National Database of the French Healthcare System, the use of anti-TNF during pregnancy in 1,457 patients did not correlate with an increase in perinatal risks and infectious morbidity in the first year of a child's life [57]. Another argument in favor of the expediency of continuing biological therapy during pregnancy turned out to be data on an increase in the incidence of exacerbations in late pregnancy after its cancellation [57]. These data are confirmed in two recently published studies by Truta B. et al., which evaluated pregnancy outcomes in patients with IBD with "early" (more than 90 days) and "late" (less than 90 days before the expected date of delivery) withdrawal of infliximab or adalimumab [58,59].

With the "early" discontinuation of anti-TNF, there was an increase in the incidence of IBD reactivation in late pregnancy or an increase in the activity of inflammation in the initial absence of remission, requiring steroids. Reactivation of the disease in the group of patients with early suspension of drug intake significantly correlated with an increase in the incidence of premature birth. It is important to note that in the group of patients with late withdrawal of GEBD, the rate of pregnancy complications, miscarriage, intrauterine fetal growth retardation, congenital malformations of the fetus did not differ from the general population. The data obtained in the studies, according to the authors, indicate the absence of positive effects on the fetus with early withdrawal of infliximab and adalimumab. In contrast, the continuation of therapy in the third trimester of pregnancy contributes to maintaining remission of IBD and minimizes the risk of their exacerbations [58].

The given data on the safety of anti-TNF were the basis for the guidelines of the American

Gastroenterological Association on the continuation of therapy with GEBD throughout pregnancy with their last administration before childbirth at a time equal to the interval of planned administration of the drug [9]. The British Society of Gastroenterologists and ECCO advise discussing with pregnant women the possible risks and benefits of continuing anti-TNF therapy, but at the same time recommend continuing this therapy throughout pregnancy to patients with active IBD or having a high risk of exacerbation of the disease [28,43].

As for **golimumab**, there are significantly fewer publications on the use during pregnancy in the available literature in comparison with studies of other anti-TNF, but they indicate a low risk of adverse outcomes for pregnancy and fetus [60, 61].

Biosimilars

Biosimilars, due to their affordability, are increasingly entering clinical practice. The first reports of pregnancy observations in women who received anti-TNF biosimilars during this period appear in the literature. In the first published retrospective study, the course of pregnancy was evaluated in 18 patients receiving biosimilars of infliximab, adalimumab and etanercept for various indications [55]. The study included 9 women suffering from rheumatological diseases (ankylosing spondylitis, rheumatoid arthritis, psoriatic arthritis), 6 with IBD and 2 patients with combined forms of autoimmune inflammatory diseases. The use of biosimilars was not associated with an increase in cases of congenital malformations of the fetus, premature birth and other perinatal complications. Anti-TNF cancel during pregnancy directly correlated with childbirth in the earlier stages of pregnancy, as well as the exacerbation of maternal diseases during pregnancy or in the postpartum period.

Another study published in abstract form [62] presents data on the use of infliximab biosimilar (CT-P13) in 20 pregnant patients with IBD. In 19 cases, pregnancy ended with the birth of full-term live, healthy children, in 1 case — premature birth with a live fetus, and in one case a spontaneous miscarriage was recorded. There were no cases of perinatal complications and severe fetal malformations in the studied group, with the exception of 1 case of cleft palate. These results correspond to the available data on the safety of the original anti-TNF and the absence of risks of congenital malformations, perinatal and obstetric complications [10,63,64]. The results obtained, despite the limited number of cases, demonstrate the first convincing evidence of the safety and necessity of the use of biosimilars by pregnant women, comparable to those shown for the original anti-TNF drugs [55,62]. Without a doubt, a continuation of the evidence base is required to finally confirm the initial optimistic data on the safety of biosimilars during pregnancy.

Vedolizumab

Vedolizumab is a humanized monoclonal antibody that specifically binds to $\alpha 4\beta 7$-integrin located on lymphocytes. The recent data obtained on the safety of vedolizumab is significantly less than is available for anti-TNF, and they are mainly limited to small cohorts.

Like other GEBD with the IgG1 structure, vedolizumab overcomes the placental barrier, but is found in umbilical cord blood concentrations lower than maternal [65,66]. In the study by Mitrova K. et al., the ratio of umbilical cord and maternal concentrations of vedolizumab at the time of delivery was 0.59 [67].

In animals, the administration of the drug in supraphysiological doses was not associated with disorders of pre- and postnatal development [68].

In 2019, the results of a retrospective case-control multicenter international study on the safety of the use of vedolizumab in pregnant CONCEIVE were published [69]. In this study [69], there was no evidence of adverse effects of vedolizumab in relation to the course and outcomes of pregnancy and the health of the child in the first year of life. The incidence of spontaneous miscarriages, premature birth, congenital malformations of the fetus, fetal weight at birth and assessment on the Apgar scale, as well as the health indicators of children in the first year of life, the incidence of oncological and infectious diseases did not significantly differ from those of women with IBD who received anti-TNF or basic IBD therapy.

Another study [70] analyzed the course and outcomes of pregnancy in 24 pregnant women taking vedolizumab, compared with 82 women treated with anti-TNF and 224 pregnant patients on basic IBD therapy. Basically, the vedolizumab group

consisted of patients who suffered from CD and had a more severe, refractory course of the disease and had a history of inefficiency of one or more biological agents. In this group, the rate of exacerbations of IBD at the time of conception was higher than in other observation groups — 30% of cases. Spontaneous miscarriages (20.8%) and premature birth (20%) were significantly more common in patients receiving vedolizumab. Such a high rate of miscarriage, according to the authors, could be associated with the initially high activity of diseases in a larger number of patients in this group, which has been proven to be interrelated with pregnancy complications in patients with IBD. In this group of patients, there were other independent risk factors for miscarriage: older age and the use of assisted reproductive technologies.

According to the authors, the use of vedolizumab in this study was not associated with an increased risk of adverse pregnancy outcomes.

In another prospective study [67] involving 39 patients, the use of vedolizumab during pregnancy was not associated with an increased risk of miscarriage, intrauterine fetal growth retardation, congenital malformations of the fetus, as well as disorders of psychomotor development, infectious, allergic diseases in a child during the first year of life.

In a systematic review and meta-analysis in 2020, an increase in the rate of premature birth and spontaneous miscarriages associated with taking vedolizumab compared with taking anti-TNF was shown [71]. According to the researchers, this may be due to a smaller number of cases of pregnancies against the background of vedolizumab, a more severe phenotype of diseases and an older age of patients.

Ustekinumab

Ustekinumab is a fully human monoclonal antibody of the IgG1 class, the target of which is the p40 subunit common to the IL-12 and IL-23 receptors.

Like other genetically engineered drugs, ustekinumab overcomes the placental barrier starting from the second half of pregnancy. At the time of delivery, its level is maximal and the ratio of fetal and maternal levels of ustekinumab in the blood is 1.67 [67]. In animals, ustekinumab did not increase the risks of fetal malformations and disorders of neonatal development in offspring [72]. Data from observational studies are few and do not demonstrate an increase in the number of cases of undesirable effects during pregnancy and an increase in infectious complications in children whose mothers took ustekinumab during pregnancy [43,53,61,73,74]. The use of the drug in the second and third trimesters of pregnancy in a number of studies also did not increase the rate of adverse pregnancy outcomes [75,76].

In 2022, the materials of the ustekinumab global safety database on all cases of use of the drug during pregnancy registered in the world were published [77]. In total, the outcomes of 420 pregnancies did not differ from the general population. There was no increase in the frequency of spontaneous miscarriages, congenital malformations of the fetus, premature birth and stillbirth. Pregnancy outcomes were also similar, regardless of the indications for the administration of ustekinumab, the duration of its use during pregnancy and the prescribed dose (45 mg and 90 mg). There is no consensus in the international recommendations regarding the possibility of continuing taking vedolizumab and ustekinumab. There is no information about ustekinumab and vedolizumab during pregnancy in the ECCO consensus of 2015. By the time of publication in 2016 of the North American Consensus in Toronto, cases of pregnancy against the background of the use of the drug were sporadic. At that time, it was proposed to suspend the administration of vedolizumab and ustekinumab with the onset of pregnancy. The guidelines of the American Gastroenterological Association were published 5 years later, in 2019, when information about the safety of these drugs during pregnancy was significantly updated [9]. This became the basis for recommendations on the safety of continuing therapy with vedolizumab and ustekinumab during gestation [9]. The Italian group of experts on the study of IBD in a review released in 2022 suggests discussing the possibility of using vedolizumab and ustekinumab during pregnancy in individual cases, if there are indications [78]. Despite the positive data available at the time of publication on the safety of vedolizumab and ustekinumab, further studies are required to finally understand their impact on

pregnancy outcomes and routine guidelines for use.

Tofacitinib

Due to its small size, Tofacitinib is able to diffuse freely through the placenta and penetrate into the fetal bloodstream. In animals in supratherapeutic doses during pregnancy, tofacitinib increased the risk of malformations in offspring [79]. The first few data from clinical and post-marketing studies did not demonstrate an increase in perinatal and maternal risks in comparison with the general population [52,80]. Nevertheless, currently, the use of tofacitinib during pregnancy, until sufficient data on its safety is obtained, is contraindicated [34]. According to the manufacturer's instructions, after taking the last dose of the drug, women of childbearing age should use reliable contraception for 4–6 weeks.

Breastfeeding

Conservative treatment in the postpartum period and during breastfeeding does not lose its significance due to the high probability of reactivation of the inflammatory process in the intestine, especially in patients with UC [81]. The causes of exacerbations of IBD after childbirth or an increase in the activity of inflammation may be hormonal influences, discontinuation of drug therapy, psychoemotional factors [82]. Women with IBD are more likely than in the general population to refuse breastfeeding due to fear of adverse effects on the child of drugs secreted into breast milk [83]. About 56% of women with IBD consider medications for the treatment of their disease contraindicated during breastfeeding [84]. At the same time, breastfeeding has undeniable benefits for both mother and child. According to systematic reviews, breastfeeding can partially offset the risk of early IBD in children from parents with IBD by up to 30% [85]. The probability of developing undesirable effects of drug therapy taken by the mother in a breastfed child is determined by the toxicity and ability of the drugs to be secreted into breast milk, reaching clinically significant levels.

Most drugs used in the treatment of IBD are detected in breast milk in concentrations that are safe for the child.

Mesalazine is minimally excreted into breast milk, reaching less than 0.1% of the maternal plasma concentration, which has no clinical significance [86]. At the same time, the levels of sulfapyridine in breast milk when the mother takes sulfasalazine are significantly higher than mesalazines [87]. Cases of fever, bloody diarrhea and vomiting in children when taking sulfasalazine by the mother are described [88]. In this regard, it is considered safer to replace sulfasalazine for nursing mothers with mesalazinedrugs. International recommendations define mesalazines as compatible and safe drugs during breastfeeding [28].

Azathioprine is found in breast milk in trace amounts of less than 10% of the maternal serum level [89]. The peak concentration of azathioprine in breast milk is reached 4 hours after taking the drug. In an observational case-control study in 15 children whose mothers took azathioprine while breastfeeding, there were no abnormalities in physical and mental development, as well as an increase in the risk of infections [90].

Methotrexate and cyclosporine are contraindicated during breastfeeding. Methotrexate is secreted into breast milk and can accumulate in the tissues of a child with the risk of immunosuppression, neutropenia and has the potential for the development of oncological processes [7]. Breastfeeding while taking cyclosporine according to the latest recommendations of the American Pediatric Association is contraindicated [7].

Steroids are detected in breast milk in low concentrations, which are maximal in the first 4 hours after their oral taking. In this regard, it is recommended to observe a 4-hour interval between taking corticosteroids and breastfeeding [91]. With intravenous prednisolone, its concentration in breast milk is only 0.025% of maternal and is not regarded as clinically significant for a child [92].

Antibacterial drugs (metronidazole and ciprofloxacin) are capable of excretion into breast milk, and therefore their use is not recommended [13,92].

Short courses of admission with the precautionary measures are considered acceptable. According to the guidelines of the American Academy of Pediatricians, breastfeeding is recognized as safe 12–24 hours after a single dose of metronidazole at a dose of 2 g and 48 hours after taking the last dose of ciprofloxacin [13,93].

Genetically engineered biological drugs are large molecules with a high molecular weight that do not penetrate well into breast milk. In studies that evaluated the content of anti-TNF in breast milk, the level of drugs was about 1% of the maternal serum concentration [94–96]. In the study by Matro R. et al., the rate of infections in the first year of life and deviations in psychomotor development in children from mothers with IBD who received and did not receive GEBD (infliximab, adalimumab, golimumab or ustekinumab) did not significantly differ [97]. Once in the gastrointestinal tract of a child, GEBD are proteolized by digestive enzymes, and only a small part of them is absorbed and then enters the systemic circulation. Theoretically, these trace concentrations do not carry clinically significant risks for the child [9].

As in the case of transplacental transfer, the absence of the Fc-fragment in the structure of the certolizumab molecule determines its lower secretion into breast milk in comparison with the other anti-TNF. In the CRADLE study, certolizumab pegol was detected in breast milk of women suffering from CD, rheumatoid arthritis, axial spondyloarthritis or psoriatic arthritis, in 0.15% of its serum concentration [98].

International European and American recommendations of recent years define the use of anti-TNF as safe and compatible with breastfeeding [9,79,99].

Domestic clinical recommendations of the Association of Rheumatologists of Russia also classify anti-TNF as safe during lactation [40,41]. The exception is golimumab due to the small number of publications about its use during breastfeeding.

Data on the safety of golimumab, vedolizumab and ustekinumab during breastfeeding are still limited.

In the work by Sun, W. et al. the average level of vedolizumab in breast milk in 11 lactating women with IBD was 0.4–2.2% of the maternal serum concentration [100]. In two other small studies, the maximum concentrations of vedolizumab in breast milk were also low and amounted to 1% or less of the serum content [101,102].

European experts in the published guidelines (joint consensus of the Austrian Society of Gastroenterologists, Hepatologists, Rheumatologists and Rehabilitologists, 2019; review of the Italian IBD study group 2021) take a more cautious position regarding the safety of vedolizumab and ustekinumab and do not recommend breastfeeding while taking them [78,99]. However, in the guidelines of the American Gastroenterological Association, the use of all GEBD is classified as compatible with breastfeeding [9].

Vaccination — Transfer

Anti-TNF drugs, vedolizumab and ustekinumab circulate for a long time in the child's body and can potentially have an immunosuppressive effect on the production of antibodies in response to vaccines.

This is directly related to the ability of the child's immune system to form an adequate post-vaccination response, as well as possible vulnerability to the introduction of live vaccines. In studies, the level of antibodies in response to inactivated vaccines and toxoids (for example, tetanus) in children whose mothers received GEBD during pregnancy did not differ from the control group [103].

The data from the register of the Dutch National Vaccination Program indicate that there are no differences in the effectiveness and safety of vaccination against viral hepatitis B in children who received intrauterine anti-TNF from the mother, compared with the control group [104]. These data substantiate the possibility of immunizing the cohort of children under discussion with inactivated vaccines according to the national standard vaccination schedule [103]. A multicenter study involving 28 gastroenterological clinics in France evaluated the response to live vaccines (Bacillus Calmette-Guérin — BCG, rotavirus, MMR-measles, mumps, rubella vaccine) in children from 143 mothers who received anti-TNF during pregnancy. The aim of the study was to evaluate the incidence of vaccinations with live vaccines of children before and after 6 months of life, against the background of breastfeeding by a mother taking GEBD, and to identify the rate of undesirable effects [105]. Half of the women in the group breastfed their children without developing any complications during vaccination. Before

the recommended period of administration, earlier than 6 months, BCG was administered in 19 (16%) cases, rotavirus vaccine — in 5 cases and MMR — in 6 cases. There was 1 post–vaccination reaction to BCG in the form of an abscess at the injection site and in 1 case, an increase in temperature was noted. Recommendations on the need to adjust the vaccination schedule came mainly from gastroenterologists (in 86% of cases) and much less often from obstetricians and pediatricians (23% and 12% of cases, respectively). This underlines the need to better inform obstetricians and pediatricians about the features of vaccination of children who were prenatally influenced by the GEBD received by the mother [105]. Thus, vaccination with live vaccines is recommended to be carried out no earlier than the first half of the life of a child born to mothers treated with GEBD, and the introduction of rotavirus vaccine should be abandoned due to the lack of clinically significant benefit after 6 months of life [43].

CONCLUSION

Drug therapy of UC and CD during pregnancy provides not only control over the activity of diseases, but also indirectly contributes to the prevention of complications of pregnancy and the antenatal period.

Most of the drugs for the treatment of IBD are compatible with pregnancy and breastfeeding.

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ЮБИЛЕЙ

Хитарьян Александр Георгиевич — 55 лет

14 января 2023 года отметил свой 55-й юбилей доктор медицинских наук, профессор Александр Георгиевич Хитарьян.

В 1991 году Александр Георгиевич окончил с отличием лечебно-профилактический факультет Ростовского государственного медицинского университета. В 1991 году поступил в клиническую ординатуру на кафедру общей хирургии РостГМУ.

В 1993 году защитил кандидатскую диссертацию на тему «Восстановление моторно-эвакуаторной функции желудочно-кишечного тракта после операций на желудке» С 1993 по 1994 гг. был ординатором хирургического отделения БСМП №1, а с 1994 по 1999 гг. — ординатором хирургического отделения лечебно-диагностического центра «Здоровье». Одним из первых в г. Ростове-на-Дону внедрил лапароскопические операции на пищеводе, желудке, печени, внепеченочных желчных протоках, почках, органах малого таза. В 2001 году под руководством Хитарьяна А.Г. создана первая в Ростове клинико-экспериментальная лаборатория эндохирургии. Это дало возможность молодым врачам-хирургам оттачивать профессиональные практические навыки на доклиническом этапе.

В 1998 году защитил диссертацию на соискание ученой степени доктора медицинских наук на тему «Грыжи пищеводного отверстия диафрагмы (этиология, патогенез, современная диагностика и лечение)».

Начиная с 1999 года — заведующий Первым хирургическим отделением Дорожной клинической больницы СКЖД. В 2002 году было присвоено звание профессора. С 2005 по 2009 гг. — профессор кафедры хирургических болезней №1 с курсом анестезиологии и реанимации ГБОУ ВПО РостГМУ. В 2015 году избирается по конкурсу заведующим кафедрой хирургических болезней №3 ФГБОУ ВПО РостГМУ, где работает по настоящее время.

По инициативе А.Г. Хитарьяна создан «Центр амбулаторной проктологии», в котором в настоящее время получают современную, высокотехнологичную помощь более 600 пациентов в год.

Является автором 50 изобретений и 350 научных работ по самым различным проблемам хирургии. Под руководством Александра Георгиевича защищено 9 кандидатских диссертаций. В 2021 г. за большой вклад в отечественное здравоохранение, многолетний плодотворный труд, а также вклад в развитие современной медицины в России, Александру Георгиевичу было присвоено почетное звание «Заслуженный врач Российской Федерации».

Приоритетными направлениями клинической и научно-исследовательской работы Александра Георгиевича является выполнение оперативных вмешательств с использованием ICG-ангиографии в хирургии желудочно-кишечного тракта. Хитарьян А.Г. — один из ведущих специалистов по изучению эффективности использования лазерных технологий в лечении параректальных свищей и геморроидальной болезни.

В 2022 году Александр Георгиевич впервые в РФ освоил и внедрил в работу клиники новейшую телеуправляемую роботическую систему Senhance.

Хитарьян А.Г. — член Ассоциации колопроктологов России, Российского общества эндоскопических хирургов, редакционного совета журнала «Колопроктология» и редакционной коллегии журнала «Амбулаторная хирургия».

Коллектив Клинической больницы «РЖД-Медицина» г. Ростов-на-Дону и редколлегия журнала «Колопроктология» сердечно поздравляют Александра Георгиевича с днем рождения и желают творческих успехов и счастья в личной жизни.

Общероссийская общественная организация «Ассоциация колопроктологов России», созданная 3 октября 1991 г. по инициативе врачей-колопроктологов РФ, является уникальной в своей сфере и одной из старейших общественных медицинских организаций. На данный момент в Ассоциации состоит более 800 колопроктологов практически из всех субъектов РФ

ОСНОВНЫЕ ЦЕЛИ И ЗАДАЧИ ОРГАНИЗАЦИИ

- совершенствование и улучшение лечебно-диагностической помощи больным с заболеваниями толстой кишки, анального канала и промежности;
- профессиональная подготовка, специализация врачей-колопроктологов, повышение их профессионального, научного и интеллектуального уровня;
- защита профессиональных и личных интересов врачей-колопроктологов в государственных, общественных и других организациях в РФ и за рубежом;
- разработка и внедрение новых организационных и лечебно-диагностических технологий и более рациональных форм организации помощи колопроктологическим больным в практику работы региональных колопроктологических центров, отделений и кабинетов;
- издание научно-практического медицинского журнала «Колопроктология», входящего в перечень рецензируемых журналов и изданий ВАК Министерства образования и науки РФ;
- международное сотрудничество с организациями и объединениями колопроктологов и врачей смежных специальностей, участие в организации и работе различных зарубежных конференций;
- организация и проведение Всероссийских Съездов колопроктологов, а также общероссийских межрегиональных и региональных конференций, симпозиумов и семинаров по актуальным проблемам колопроктологии.

ПРЕИМУЩЕСТВА ЧЛЕНСТВА В АССОЦИАЦИИ

- более низкие регистрационные взносы на участие в Общероссийских научно-практических мероприятиях;
- преимущества при зачислении на цикл повышения квалификации;
- информационная поддержка и юридически-правовая защита членов Ассоциации;
- членам Ассоциации выдается сертификат установленного Правлением образца.

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Членами Ассоциации могут быть граждане РФ и иностранные граждане, имеющие высшее медицинское образования, прошедшие специализацию по колопроктологии, работающие в области колопроктологии не менее 3-х лет, признающие Устав организации и участвующие в ее деятельности

ОБУЧЕНИЕ КОЛОПРОКТОЛОГОВ НА БАЗЕ ФГБУ «НМИЦ КОЛОПРОКТОЛОГИИ ИМЕНИ А.Н. РЫЖИХ» МИНЗДРАВА РОССИИ

Ординатура по специальности:

- Анестезиология-реаниматология
- Ультразвуковая диагностика
- Гастроэнтерология
- Колопроктология
- Эндоскопия

Профессиональная переподготовка:

- Колопроктология
- Эндоскопия

Повышение квалификации:

- Колопроктология
- Эндоскопия
- Колоноскопия. Теория и практика выполнения
- Обеспечение анестезиологического пособия колопроктологическим больным
- Лапароскопические технологии в колопроктологии
- Функциональные методы диагностики и лечения болезней толстой кишки
- УЗ-методы диагностики в колопроктологии
- Гастроэнтерология
- Дополнительная профессиональная программа повышения квалификации «Колопроктология: симуляционный курс по отработке практических навыков»

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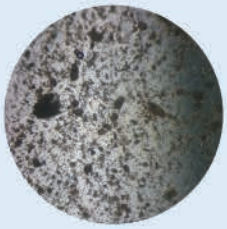

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