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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

Elena A. Belousova[2], Yuri A. Shelygin[1], Sergey I. Achkasov[1], Igor E. Khatkov[3], Igor G. Bakulin[4], Maria I. Skalinskaya[4], Oleg V. Knyazev[3], Anna V. Kagramanova[3], Tatiana V. Shkurko[1], Bella A. Nanaeva[1], Nataliya V. Nikitina[2], Maria N. Zakharova[14], Larisa V. Tarasova[15], Olga P. Alekseeva[13], Maksim V. Zlobin[13], Vladimir V. Pavlenko[11], Elena V. Mishchenko[10], Anastasiya I. Dolgushina[8], Alexander V. Lakhin[9], Alexander V. Tkachev[12], Diana I. Abdulganieva[5], Olga V. Vasilyeva[6], Irina V. Gubonina[7]

[1]Ryzhikh National Medical Research Center of Coloproctology (Salyama Adilya st., 2, Moscow, 123423, Russia)
[2]Moscow Regional Research and Clinical Institute MONIKI (Shchepkina st., 61/2, bld. 1, Moscow, 129110, Russia)
[3]Loginov Moscow Clinical Scientific Center, Moscow Healthcare Department (Entuziastov shosse, 86, Moscow, 111123, Russia)
[4]Mechnikov North-Western State Medical University of the Ministry of Health of Russia (Kirochnaya st., 41, St. Petersburg, 191015, Russia)
[5]Kazan State Medical University of the Ministry of Health of Russia (Butlerova st., 49, Rep. Tatarstan, Kazan, 420012, Russia)
[6] Regional Clinical Hospital (Sudogodskoe shosse, 41, Vladimir, 600023, Russia)
[7]Military Medical Academy named S.M. Kirov (Academician Lebedev st., 37, bld. 3, St. Petersburg, 195009, Russia)
[8]South Ural State Medical University of the Ministry of Health of Russia (Vorovsky st., 64, Chelyabinsk, 454092, Russia)
[9]Lipetsk Regional Clinical Hospital (Moskovskaya st., 6a, Lipetsk, 398055, Russia)
[10]Belgorod Regional Clinical Hospital of St. Joasaph (Nekrasova st., 8/9-2, Belgorod, 308007, Russia)
[11]Stavropol Regional Clinical Hospital (Semashko st., 1, Stavropol, 355029, Russia)
[12]Rostov State Medical University of the Ministry of Health of Russia (Nakhichevan per., 29, Rostov-on-Don, 344022, Russia)
[13]Nizhny Novgorod Regional Clinical Hospital named N.A. Semashko (Rodionova st., 190, Nizhny Novgorod, 603126, Russia)
[14]State autonomous health care institution «Kuzbas regional clinical hospital named after S.V. Belyaev» (Ave. Oktyabrsky, 22, Kemerovo, 650000, Russia)
[15]Federal State Budgetary Educational Institution of Higher Education «Chuvash State University named after I.N. Ulyanov» (Moskovsky Ave., 15, Cheboksary, 428015, Russia)

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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ADDRESS FOR CORRESPONDENCE: *Yuri A. Shelygin, Ryzhikh National Medical Research Center of Coloproctology; Salyama Adilya st., 2, Moscow, 123423 Russia; phone: +7 (499) 642-54-40; e-mail: info@gnck.ru*

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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).

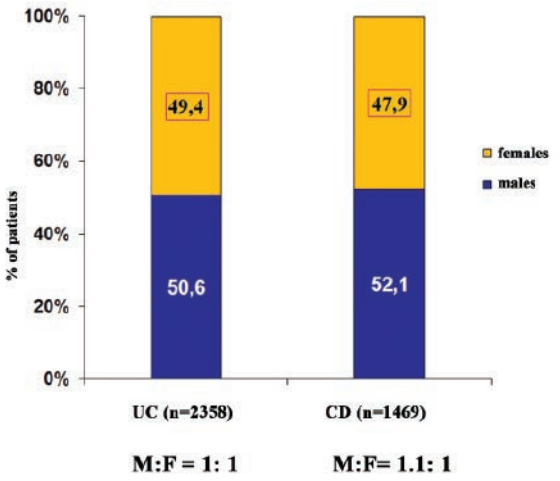


Figure 1. *The ratio of males and females with UC and CD according to the National Register*

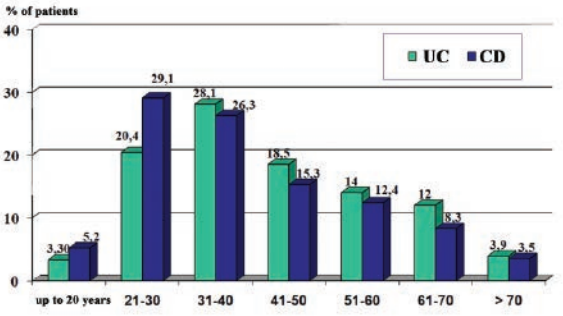


Figure 2. *Age of patients with IBD in the Russian Federation at the time of inclusion in the National Register*

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

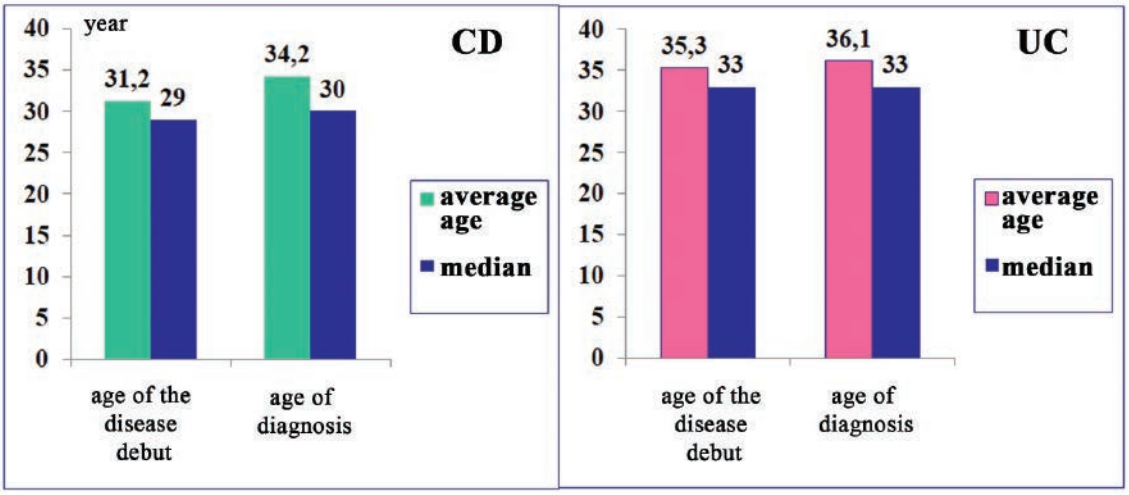
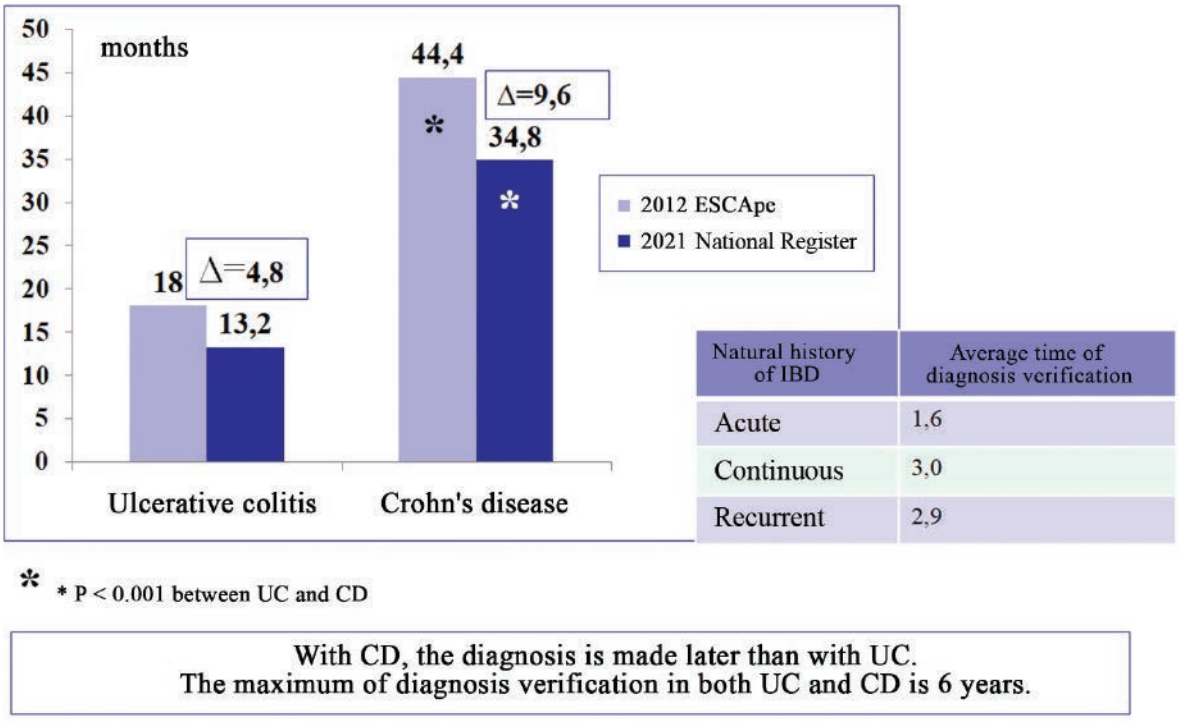


Figure 3. *Age of disease onset and age of diagnosis in IBD according to the National Registry*



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

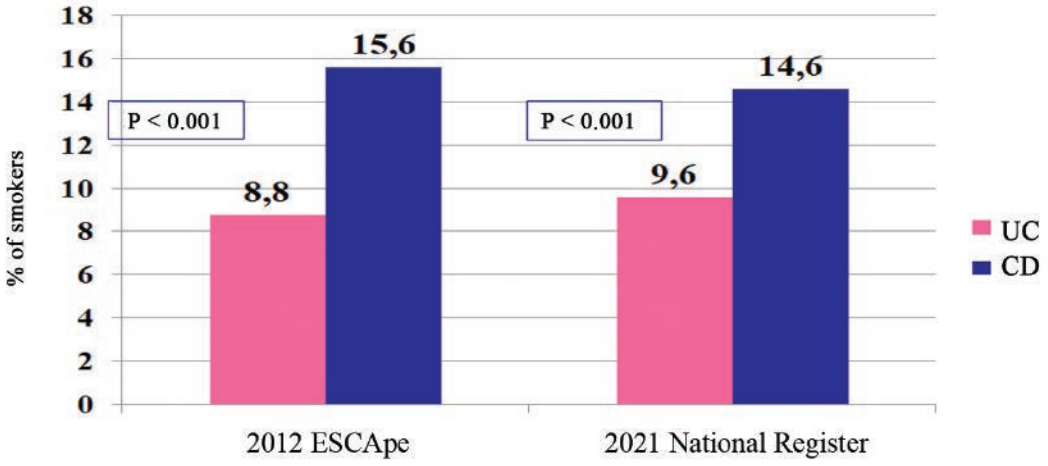


Figure 5. *Smoking status in IBD. The proportion of patients who smoke in UC and CD*

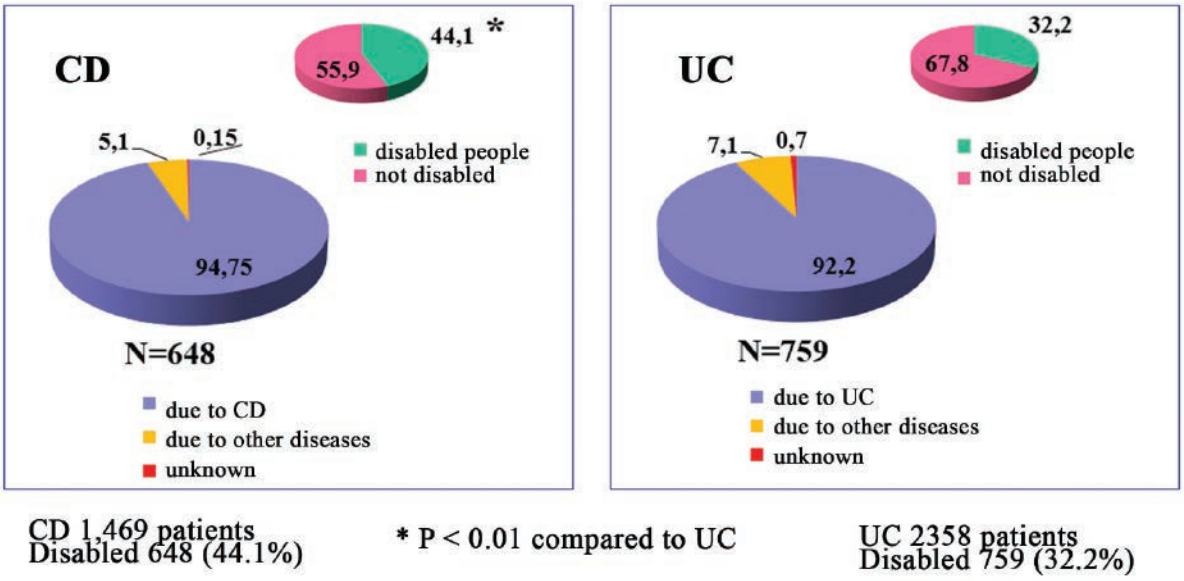


Figure 6. *Rate and cause of disability of IBD according to the National Register (%)*

(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

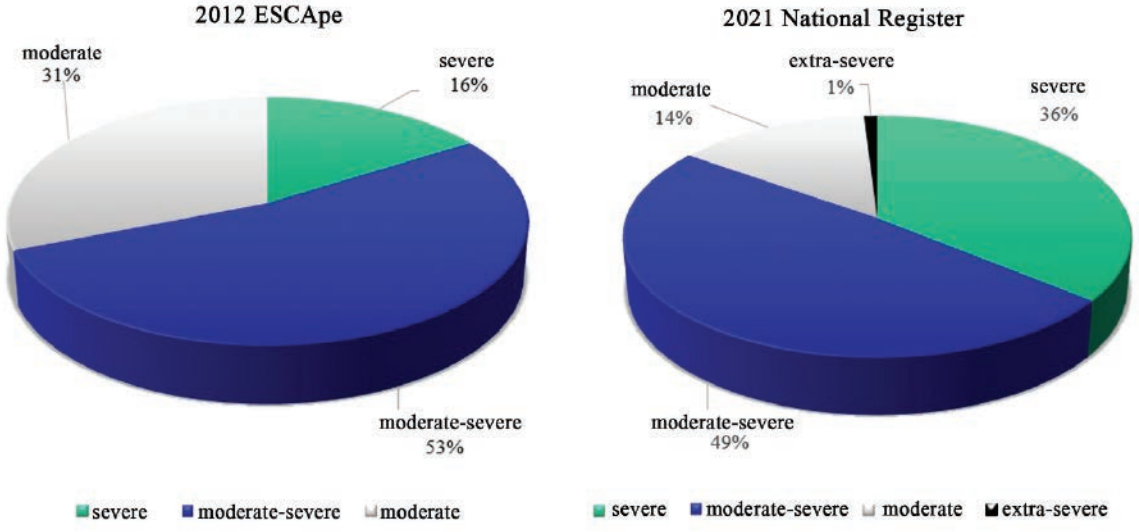


Figure 7. *The severity of the UC in Russia*

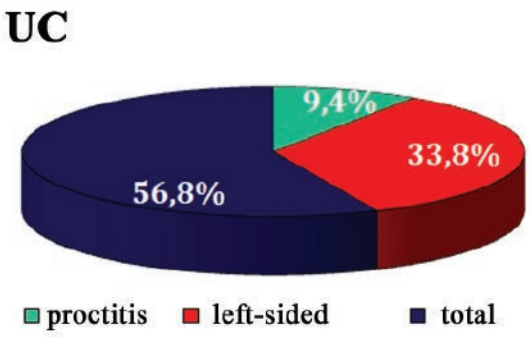


Figure 8. *The extent of UC according to the National Register*

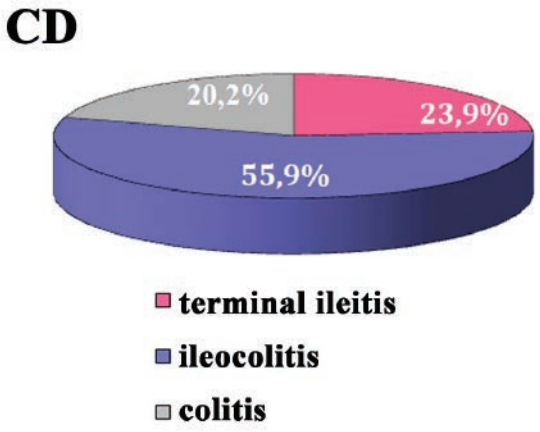


Figure 9. *Localization of Crohn's disease according to the National Register*

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.

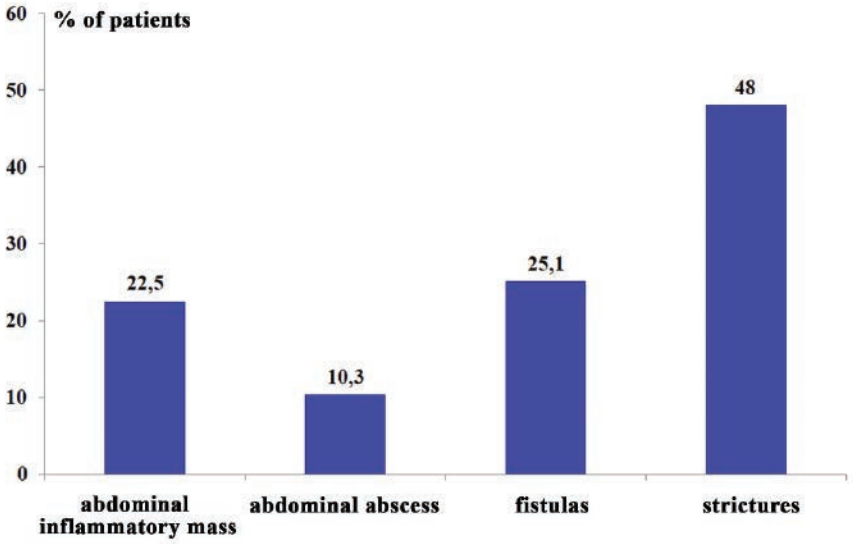


Figure 10. *The incidence and nature of complications in Crohn's disease*

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.

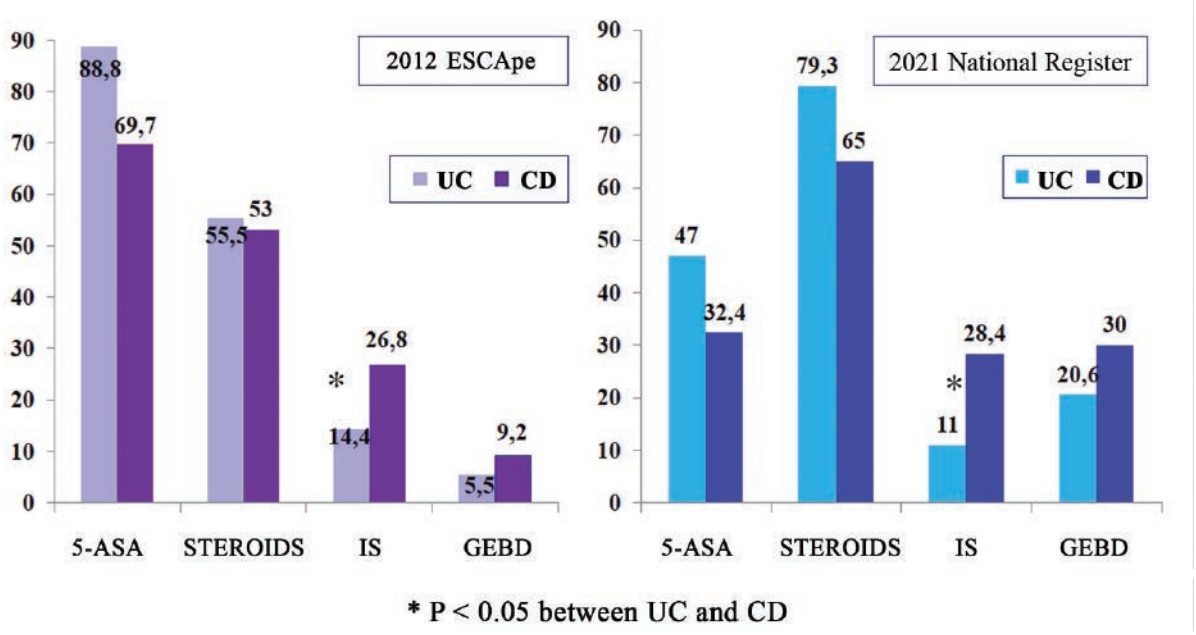


Рисунок 11. *Частота разных видов терапии ВЗК с разницей в 9 лет*
Figure 11. *The incidence of different types of IBD therapy with a difference of 9 years*

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.

AUTHORS CONTRIBUTION

Concept and design of the study: *Yuri A. Shelygin, Elena A. Belousova, Sergey I. Achkasov, Igor E. Khatkov, Igor G. Bakulin, Tatiana V. Shkurko*
Collection and processing of the material: *Igor G. Bakulin, Maria I. Skalinskaya, Anna V. Kagramanova, Oleg V. Knyazev, Bella A. Nanaeva, Nataliya V. Nikitina, Maria N. Zakharova, Larisa V. Tarasova, Olga P. Alekseeva, Maksim V. Zlobin, Vladimir V. Pavlenko, Elena V. Mishchenko, Anastasiya I. Dolgushina, Alexander V. Lakhin, Alexander V. Tkachev, Diana I. Abdulganieva, Olga V. Vasilyeva, Irina V. Gubonina, Tatiana V. Shkurko*
Statistical processing: *Tatiana V. Shkurko, Bella A. Nanaeva, Anna V. Kagramanova*
Writing of the text: *Elena A. Belousova, Yuri A. Shelygin*
Editing: *Yuri A. Shelygin, Sergey I. Achkasov, Tatiana V. Shkurko*

INFORMATION ABOUT THE AUTHORS (ORCID)

Elena A. Belousova — 0000-0003-4523-3337
Yuri A. Shelygin — 0000-0002-8480-9362
Sergey I. Achkasov — 0000-0001-9294-5447
Igor E. Khatkov — 0000-0002-4088-8118
Igor G. Bakulin — 0000-0002-6151-2021
Maria I. Skalinskaya — 0000-0003-0769-8176
Tatiana V. Shkurko — 0000-0002-7502-2437
Anna V. Kagramanova — 0000-0002-3818-6205
Oleg V. Knyazev — 0000-0001-7250-0977
Vladimir V. Pavlenko — 0000-0003-0210-3268
Alexander V. Tkachev — 0000-0002-5554-7084
Larisa V. Tarasova — 0000-0003-1469-0689
Olga P. Alekseeva — 0000-0002-1475-6584
Maksim V. Zlobin — 0000-0002-8200-3293
Anastasiya I. Dolgushina — 0000-0003-2569-1699
Alexander V. Lakhin
Diana I. Abdulganieva — 0000-0001-7069-2725
Elena V. Mishchenko
Bella A. Nanaeva — 0000-0003-1697-4670
Olga V. Vasilyeva — 0000-0001-8828-4252
Nataliya V. Nikitina
Maria N. Zakharova
Irina V. Gubonina — 0000-0002-6302-7767

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