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The course of complicated Crohn's disease during therapy with Russian biosimilars of infliximab and adalimumab

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ABSTRACT *AIM: to assess the course of complicated forms of CD against the background of therapy with Russian biosimilars of infliximab and adalimumab, as well as the survival rate of therapy in this group.*

PATIENTS AND METHODS: a retrospective evaluation of patients with complicated CD who received infliximab or adalimumab with follow up at the institution for at least three consecutive years was performed. A total of 15 patients with complicated CD received infliximab therapy and 14 received adalimumab. The main clinical and demographic parameters and the rate of intra-abdominal complications during 3 years of follow up of patients were analyzed.

RESULTS: in the infliximab group, a decrease in the rate of stenosis was noted during 3 years of follow up (from 12/15 (80%) to 3/6 (50%)), the rate of detection of other complications did not change, in addition, during the specified period, resection was performed in all patients in this subgroup. The median survival of therapy in this group was 11 (8.5; 24) months. In the adalimumab group, all 6 patients followed up showed resolution of stenosis at the beginning of the third year of therapy, while over the course of two years, the frequency of their detection remained the same as before the start of treatment. By the end of the 1st year of therapy, complete resolution of paraintestinal infiltrates was noted. During three years of observation, only 1 patient underwent resection, the median survival of therapy was 20.5 (14–24) months.

CONCLUSION: the study obviously has a number of limitations typical for a retrospective analysis of small samples. However, there is a decrease in the incidence of complications with infliximab or adalimumab therapy. There is a need for a well-designed prospective study on the dynamics of intra-abdominal complications in patients with CD against the background of GEBD.

KEYWORDS: Crohn's disease, complications, GEBD, infliximab, adalimumab, Crohn's disease

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INTRODUCTION

Crohn's disease (CD) is a chronic, recurrent disease of the gastrointestinal tract (GIT) of unknown etiology, characterized by transmural, segmental, granulomatous inflammation with local and systemic complications [1]. The prevalence of CD is about 322 people per 100,000 ones of population [2]. In 46.0–57.4% of cases, the course of the disease is followed by intra-abdominal complications (strictures, intestinal infiltrates, fistulas, abscesses) [3,4]. The natural

history of CD involves a gradual change in the phenotype of the disease from the luminal to the penetrating form. Most likely, this morphogenesis proceeds at different rates in different patients, depending on the intensity of the inflammatory process in the gastrointestinal tract [5,6,7]. Prior to the start of active use of GEBD, the patient's presence of intra-abdominal complications of CD was an absolute indication for surgery due to the low effectiveness of conservative approach. Today, this concept is undergoing radical changes: surgical treatment becomes

Table 1. Clinical and demographic indicators of patients with complicated Crohn's disease

Indicator	Infliximab for CD, N = 15
Median age of debut, years (Q1–Q3)	22 (19–28)
Median duration of the disease before the start of therapy, months (Q1–Q3)	66 (22.5–109.5)
Gender, <i>n</i> (%):	
Male	8 (53.3)
Female	7 (46.7)
Hormonal resistance, <i>n</i> (%)	2 (13.3)
History of resections, <i>n</i> (%)	4 (26.7)
Surgeries for perianal manifestations in the anamnesis, <i>n</i> (%)	7 (46.7)
Inefficiency of azathioprine, <i>n</i> (%)	5 (33.3)
Inefficiency of methotrexate, <i>n</i> (%)	1 (6.7)
GEBD in the anamnesis, <i>n</i> (%)	7 (46.7)
Inefficiency of adalimumab, <i>n</i> (%)	4 (26.7)
Inefficiency of certolizumab pegol, <i>n</i> (%)	2 (13.3)
Smoking, <i>n</i> (%)	5 (33.3)
Lesion of the upper gastrointestinal tract, <i>n</i> (%)	1 (6.7)
Perianal manifestations, <i>n</i> (%)	8 (53.3)
Concomitant non-immune diseases, <i>n</i> (%)	4 (26.7)

mandatory only in the presence of emergency, life-threatening conditions. This is due to the emergence of more efficient GEBD. Treatment regimens with various GEBD have shown good results in the framework of randomized clinical trials and data from real clinical practice [8]. Nevertheless, there is little information about the course of the complicated form of CD on the background of GEBD therapy.

AIM

The aim of the study was to evaluate the course of complicated forms of CD during therapy with Russian biosimilars infliximab and adalimumab, as well as the survival of the therapy in this group.

PATIENTS AND METHODS

Patients with a complicated form of CD who received infliximab or adalimumab and were

followed up at the institution facility for at least three consecutive years were retrospectively evaluated. The analysis included the case histories of 15 patients with a complicated form of CD (stricture and penetrating phenotypes) who were treated and monitored in the conditions of the RNMRC of Coloproctology of the Ministry of Health of Russia, who started the infliximab therapy in the period between 2017 and 2019. Given the retrospective nature of the study, it was not possible to establish strict deadlines for the examinations. In this regard, ranges of follow-up periods were established as follows: 6–12 months, 12–24 months, 24–36 months. There were 7 (46.7%) women and 8 (53.3%) men in the subgroup, the median age of onset of the disease was 22 years (19–28). In 12 (80%) patients, narrowing of the small intestine was observed (the median length of the process in the small intestine was 22.13 (10.93; 30.33) cm, in 7 (46.7%) patients — a para-intestinal infiltrate with inter-intestinal fistulas. The clinical

Table 2. *Clinical and demographic indicators of patients with complicated CD*

Indicator	Adalimumab for CD, N = 14
Median age of debut, years (Q1–Q3)	22 (17–27)
Median duration of the disease before the start of therapy, months. (Q1–Q3)	90 (47–133)
Gender, <i>n</i> (%): Male Female	8 (57.1) 6 (42.9)
Hormonal resistance, <i>n</i> (%)	1 (7.1)
History of resections, <i>n</i> (%)	6 (42.9)
Surgeries for perianal manifestations in the anamnesis, <i>n</i> (%)	3 (21.9)
Inefficiency of azathioprine, <i>n</i> (%)	8 (57.1)
GEBD in the anamnesis, <i>n</i> (%)	3 (21.4)
Inefficiency of infliximab, <i>n</i> (%)	3 (21.4)
Inefficiency of certolizumab pegol, <i>n</i> (%)	1 (7.1)
Smoking, <i>n</i> (%)	2 (14.3)
Lesion of the upper gastrointestinal tract, <i>n</i> (%)	1 (7.1)
Perianal manifestations, <i>n</i> (%)	7 (50.0)
Extra-intestinal manifestations, <i>n</i> (%)	3 (21.4)
Concomitant non-immune diseases, <i>n</i> (%)	2 (14.3)

Table 3. *Concomitant therapy in patients with CD treated with infliximab*

Drugs	Infliximab for CD, N = 15
Glucocorticosteroids, <i>n</i> (%)	12 (80)
Antibiotics, <i>n</i> (%)	9 (60)
Thiopurines, <i>n</i> (%)	10 (66.7)

and demographic indicators of patients are presented in more detail in Table 1.

The analysis of the medical documentation of 14 patients with a complicated form of CD (stricturing and penetrating phenotypes) who were treated with adalimumab in the conditions of the RNMRC of Coloproctology of the Ministry of Health of Russia from 2017 to 2019.

There were 6 (42.9%) women and 8 (57.1%) men in the subgroup, the median age of onset of the disease was 21 (16; 27) years. 8 (57.1%) patients had narrowing of the terminal ileum with a median length of 23.16 (13.69; 32.64) cm, 6 (42.9%) patients had a para-intestinal infiltrate with inter-intestinal fistulas, while 1 patient had an abscess of the infiltrate and

anileovesical fistula. The conservative management tactics of the patient was chosen due to the large length of the intestine involved in the inflammatory process and the absence of dysuria. There were no external intestinal fistulas in the subgroup.

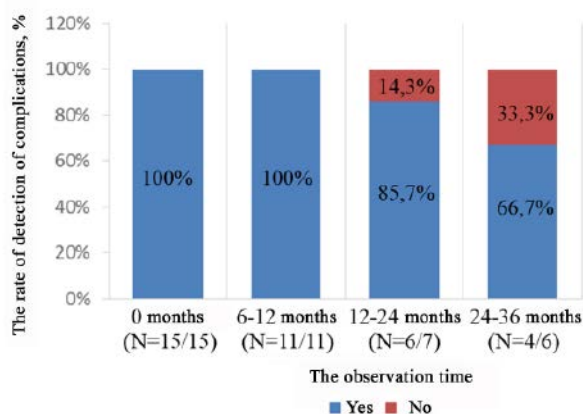
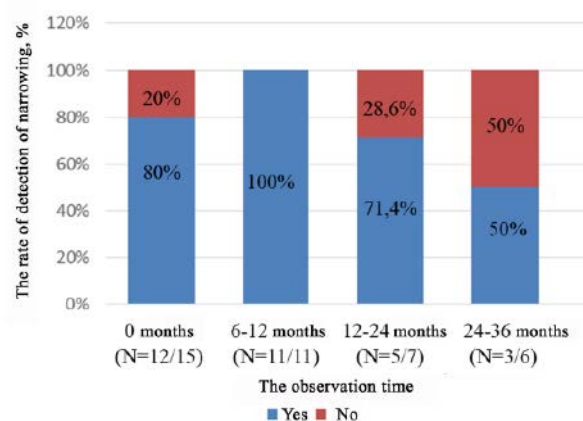
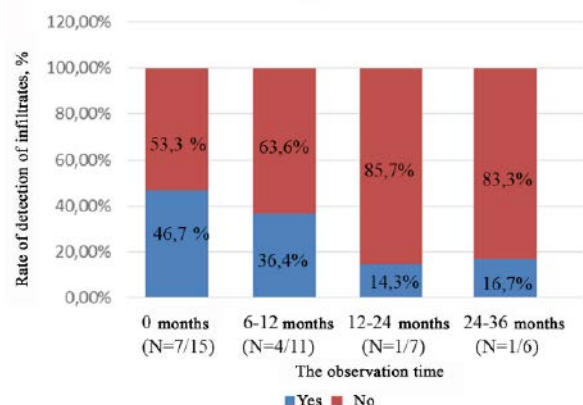
The clinical and demographic indicators of patients are presented in more detail in Table 2.

Statistical Analysis

The statistical analysis was performed using the StatTech v. 4.6.3 program (developed by Stattech LLC, Russia). Quantitative data were described using the median (Me), lower and upper quartiles (Q1-Q3); categorical data — with absolute values and percentages.

Table 4. Concomitant therapy in patients with CD treated with adalimumab

Drugs	Adalimumab for CD, N = 14
Glucocorticosteroids, n (%)	7 (50.0)
Antibiotics, n (%)	10 (71.4)
Thiopurines, n (%)	7 (50.0)

**Figure 1.** Complication rate in patients with CD receiving infliximab during 3 years of follow-up**Figure 2.** The rate of detection of narrowing in patients with CD receiving infliximab for 3 years of the follow-up**Figure 3.** The rate of detection of intestinal infiltrates during the infliximab therapy

RESULTS

The Course of the Complicated Form of CD on the Background of Infliximab Therapy

At the time of initiation of the infliximab therapy, 12 (80%) patients received glucocorticoids, out of whom, 3 (20.0%) patients received topical budesonide therapy, 6 (40.0%) patients — systemic glucocorticoids at the rate of 1 mg/kg in terms of prednisone, and 3 (20.0%) ones — 2 mg/kg. Antibacterial drugs were given to 9 (60.0%) patients, 10 (66.7%) patients received the infliximab therapy in combination with thiopurines (azathioprine at the rate of 2–2.5 mg/kg per day) (Table 3).

Combination therapy with other drugs was not performed in this group.

The rate of complications (constrictions, infiltrates) remained unchanged for the 1st year of the therapy, decreasing from 100% (15/15) to 66.7% (4/6) by the beginning of the third year of the follow-up (Fig. 1).

The rate of detection of narrowing decreased by the end of the second year of the follow-up from 80% (12/15) to 50% (3/6), the rate of intestinal infiltrates detection decreased from 46.7% (7/15) to 16.7% (1/6) (Fig. 2, 3).

In this subgroup, 60% (9/15) of patients with a median therapy survival of 11 (8.5; 24) months continued to receive the drug. The primary inefficiency of the drug was recorded in 46.7% (7/15) of cases, in 6.7% (1/15) of cases — loss of response, and in another 6.7% (1/15) cases — intolerance. Within 3 years, all patients in the subgroup underwent resection of the affected area of the intestine, except for one who had clinically and instrumentally remitted

Crohn's disease by the end of the first year of the therapy.

The Course of Complicated CD during Therapy with Adalimumab

In this subgroup, in seven (50%) patients, the adalimumab therapy was initiated in

conjunction with glucocorticoids, out of whom 3 (21.4%) patients received budesonide therapy, 3 (21.4%) patients received systemic glucocorticoids at the rate of 1 mg/kg in terms of prednisone, and 1 (7.1%) patient — 2 mg/kg. 10 (71.4%) patients received antibacterial drugs; 7 (50%) patients received adalimumab therapy in combination with thiopurines (Table 4).

Combination therapy with other drugs was not performed in this group.

The rate of complications remained unchanged for almost 2 years of the therapy, decreasing to 66.7% (4/6) by the beginning of the third year of the follow-up (Fig. 4).

At the same time, 2 (33.3%) out of 6 patients had the disappearance of narrowing on the background of the conservative treatment. However, for two years, the rate of their detection remained close to that before the start of the treatment. At the same time, it was noted that by the end of the 1st year of the therapy, a complete resolution of para-intestinal infiltrates was noted (Fig. 5, 6).

In this subgroup, 50% (7/14) of patients with a median therapy survival of 20.5 (14–24) months continued to receive the drug. Primary drug inefficiency was recorded in 35.7% (5/14) of cases, in 7.1% (1/14) of cases — loss of response, and in another 7.1% (1/14) — intolerance. Over the course of 3 years, 1 patient underwent resection of the affected area of the intestine (with abscessed para-intestinal infiltrate) and 3 patients underwent surgery for perianal manifestations of CD.

DISCUSSION

The first clinical manifestations of CD are often associated with the appearance of complications such as strictures or para-intestinal infiltrates. Such a complicated course of the disease often leads to the need for resection of the affected area of the intestine. During the natural course of the process, complications recur after a while, which requires repeated resection.

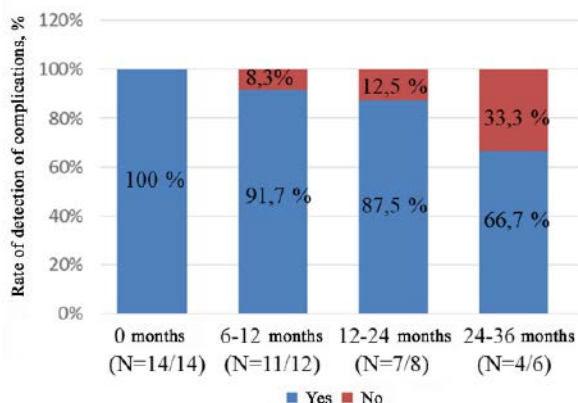


Figure 4. *Complication rate in patients with CD receiving adalimumab during 3 years of follow-up*

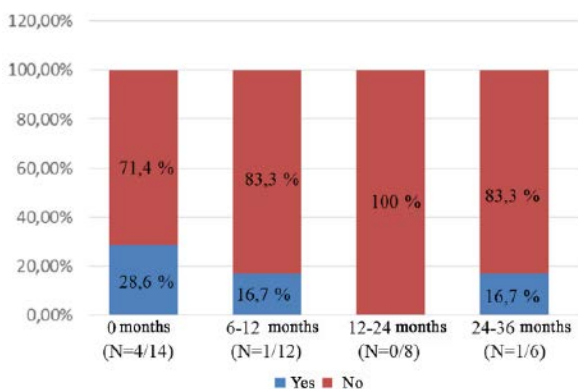


Figure 5. *The rate of detection of infiltrates in patients with CD receiving adalimumab for 3 years of the follow-up*

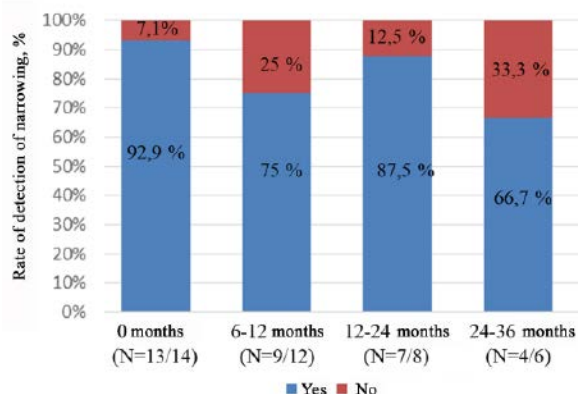


Figure 6. *The rate of detection of narrowing in patients with CD receiving infliximab for 3 years of the follow-up*

Patients with multiple intestinal resections are at risk of developing short bowel syndrome [6]. Therefore, the need to reduce the incidence of resections in patients with CD is beyond doubt. One of the possible options is conservative management of patients with a complicated form of CD using GEBD. Very few studies are devoted to the course of the complicated form of CD on the background of GEBD therapy [8]. In this regard, we analyzed the course of complicated CD against the background of GEBD therapy, and also studied the survival rate in this cohort of patients.

Our analysis has a number of limitations typical of retrospective studies and small samples. It is likely that when conducting a well-planned prospective study, the conclusions may be different. However, our study demonstrates the fundamental possibility of conservative treatment of patients with complicated CD with TNF inhibitors such as infliximab and adalimumab.

CONCLUSION

The results of adalimumab therapy are encouraging. In patients with CD complications,

complete resolution of complications was detected by the third year, with the exception of one patient who underwent resection of the affected area of the intestine due to an infiltrate abscess.

More prospective studies on the course of various forms of inflammatory bowel diseases in various GEBD are needed with an assessment of, among other things, the survival of therapy.

AUTHORS CONTRIBUTION

Concept and design of the study: *Timofei L. Alexandrov, Bella A. Vykova*

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