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APPLICATION OF BIOMARKERS IN CROHN'S DISEASE TREATMENT STRATEGY: NEW APPROACHES AND EFFECTIVENESS ASSESSMENT

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ABSTRACT

Goal. The study aimed to evaluate the effectiveness of the "top-down" strategy compared with the accelerated tactics of increasing the dose in achieving stable remission in patients with Crohn's disease. Materials and methods. This randomized, open-label, active-control trial included patients aged 15 to 85 years who were newly diagnosed with Crohn's disease. Participants were divided into two groups to apply either a top-down strategy or accelerated therapy. Inclusion in the study was based on the presence of an active disease, confirmed by the Harvey-Bradshaw index (HBI) ≥7, and elevated markers of inflammation. The study was conducted in accordance with the principles of good clinical practice and used block randomization, taking into account biomarkers and other parameters. Results. In the top-down group, 79% of patients achieved sustained remission without steroids and surgery by week 48, which was significantly higher than 15% in the accelerated enhancement group. More patients in the first group also achieved complete endoscopic remission and improved quality of life. There were no significant differences in biomarkers between the groups, but there was a more rapid improvement in biochemical parameters in the descending group. Conclusions. The top-down strategy is more effective in achieving lasting remission and improving the quality of life in patients with Crohn's disease than accelerated treatment tactics. These results support the application of early and aggressive therapy in clinical practice. The practical significance of the study lies in the possibility of improving long-term prognoses for patients and optimizing healthcare resources. Further studies with large samples and improved biomarker assessment methods are needed to confirm the findings and apply them to personalized treatment approaches.

KEYWORDS: Crohn's disease, top-down treatment strategy, accelerated treatment, persistent remission, endoscopic remission, quality of life, biomarkers, immunomodulators, personalized therapy, inflammatory bowel diseases.

INTRODUCTION

Crohn's disease is a serious chronic inflammatory bowel disease (IBD) characterized by a recurrent course that often leads to progressive tissue damage [1]. The incidence of Crohn's disease is increasing worldwide, which makes the search for effective treatment methods an urgent task. Traditional approaches to therapy focus on the management of acute exacerbations using corticosteroids, and also include immunomodulators and modern treatments to achieve long-term remission [2-5]. However, the prognosis of the disease course and clinical outcomes for patients with a recent diagnosis remains extremely uncertain. The unpredictability of the frequency and severity of exacerbations, the probability of success of a certain therapy, as well as the rate of progression to complications such as intestinal strictures and fistulas, increase the complexity of treatment [6].

The introduction of biological therapies such as anti-TNF drugs has improved the situation somewhat, however, about 17-25% of patients require surgical resection within five years after diagnosis [7]. This indicates the need to develop a safe, accessible and universal therapeutic strategy that would be effective from the moment of diagnosis. Although thiopurines have shown insufficient efficacy, the potential of modern approaches for early use still requires further study. Crohn's disease treatment studies often include patients several years after the initial diagnosis [8], and the benefits of active treatment over placebo are limited to 10-20%.

However, data obtained from clinical trials and retrospective cohorts indicate that earlier application of modern methods yields better results [10]. For example, a study led by D'haens showed that patients who received infliximab and azathioprine in the first four years after diagnosis achieved significantly higher remission rates by week 52 [12]. Similar findings were confirmed in the CALM and REACT studies, where early initiation of anti-TNF therapy demonstrated a reduction in the number of serious adverse outcomes compared with traditional treatment methods. These data, coupled with the availability of more accessible biosimilars, contributed to the widespread practice of early use of anti-TNF therapy in Crohn's disease [11].

Despite this, most patients do not start receiving biologics immediately after diagnosis, but only after failure of conservative treatment or other regimens, including immunomodulators [5]. This cautious strategy has been approved by a number of international guidelines. The ability to accurately predict which patients will benefit the most from early advanced therapy will allow them to focus on the target group, minimizing the unjustified use of these methods. To date, several biomarkers for Crohn's disease have been proposed [10]. Among them is a prognostic 17—gene blood biomarker, which previously allowed patients to be divided into IBDhi and IBDlo groups associated with different risks of exacerbations, but showing no clinical, biochemical or visual differences at the time of diagnosis. So far, none of these biomarkers has been officially tested and implemented in clinical practice for IBD [7].

This article presents the results of an analysis of a randomized controlled trial aimed at evaluating the clinical effectiveness of using a 17-gene blood biomarker to optimize treatment options. The initial hypothesis was that patients assigned to the IBDhi group on the basis of biomarkers have a higher risk of relapses and, therefore, can benefit more from the early use of advanced therapies compared to patients from the IBDlo group. As part of the study, patients with newly diagnosed Crohn's disease were randomized into two treatment groups: top-down (infliximab in combination with an immunomodulator) or accelerated treatment according to a traditional biomarker-based regimen.

MATERIALS AND METHODS

RESEARCH DESIGN

The study was conducted as a randomized, open-label study with active control, in which participants were stratified based on biomarkers. The patients were divided into groups to apply either a top-down or accelerated treatment strategy. The study was conducted in accordance with the principles of good clinical practice.

PARTICIPANTS

Patients aged 15 to 85 years with newly diagnosed active form of Crohn's disease were registered. All of them provided written informed consent to participate in the study. Information about the biological field (male or female) was collected based on the participants' self-reports. To participate in the study, the following criteria had to be met: (1) the diagnosis of Crohn's disease had to be established within 6 months using standard clinical, endoscopic, histological and radiological methods; (2) the presence of an active symptomatic disease confirmed by a Harvey-Bradshaw index (HBI) ≥7; (3) biochemical signs of active inflammation, expressed in elevated serum C-reactive protein (CRP) levels above the upper limit of normal, or a fecal calprotectin level of 200 mcg/g or higher, or both other; (4) endoscopic signs of the active form of the disease, assessed by a simple endoscopic assessment for Crohn's disease (SES-CD), ≥4 if only the ileum is affected, or ≥6 if the ileum is localized to the disease; and (5) immunity to previously used immunomodulators and biological therapies. Patients with clinically significant obstructive or perianal complications were excluded from the study.

During the screening visit, Crohn's disease activity was assessed using the Harvey-Bradshaw Index (HBI), blood tests, and ileocolonoscopy performed in the last 6 months. Blood tests included the determination of biomarkers and measurement of calprotectin levels in feces. Patients were prescribed an 8-week course of oral steroids (prednisone or budesonide), choosing the drug at the discretion of a local researcher. At the main appointment two weeks later, the test results (except for biomarkers hidden from patients and researchers) were used to make a decision on admission to the study. Eligible participants were randomized to treatment with a combination of infliximab and an immunomodulator (azathioprine, low-dose mercaptopurine with allopurinol or methotrexate) or accelerated therapy. The dosage of thiopurines was not optimized for the level of the drug in the blood, and it was forbidden to increase the dose of infliximab.

RANDOMIZATION AND MASKING

The participants who completed the basic examination were randomized in a 1:1 ratio to receive a top-down or accelerated course of treatment. Stratified block randomization took into account biomarker subgroups (IBDhi and IBDlo), the localization of the disease (only in the colon or other areas), and the degree of mucosal inflammation (mild, moderate, severe). The size of the blocks varied randomly (4 or 6). Local researchers determined the degree of inflammation based on the clinical interpretation of endoscopy. The Sealed Envelope system was used to manage the randomization and patient allocation process. Biomarkers were monitored during the study.

PROCEDURES

For participants who started taking immunomodulators, the choice between azathioprine, low-dose mercaptopurine with allopurinol, or methotrexate was made by a local researcher. The dosage of infliximab was 5 mg / kg with induction at 0, 2 and 6 weeks, maintenance infusions — every 8 weeks. If there was no response after induction, patients stopped participating and returned to standard therapy under the supervision of the clinical team.

The examinations were performed at weeks 4, 16, 32, and 48, as well as at unscheduled appointments. During the visits, hemoglobin levels and adverse events were recorded, as well as blood and stool samples were taken. Exacerbation was determined by the symptoms of active Crohn's disease (HBI ≥5) and elevated levels of CRP or calprotectin. During exacerbations, steroids were prescribed; during accelerated therapy, immunomodulators and, if necessary, infliximab were additionally administered. The participants continued their previous treatment without exacerbations. The final examination was performed 48 weeks after randomization, and included ileocolonoscopy to assess disease activity by SES-CD. PredictSURE-IBD analysis determined membership in the IBDhi or IBDlo subgroups.

ENDPOINTS OF THE STUDY

The main endpoint of the study was the frequency of sustained remission without surgery and steroid use from the end of induction steroid therapy to the 48th week. Exacerbation was determined by the presence of symptoms and elevated markers of inflammation, while remission was determined by the absence of symptoms (HBI <5) and normalization of inflammatory parameters (CRP and calprotectin).

Secondary endpoints included: (1) endoscopic remission by week 48 (absence of ulcers on the SES-CD scale), (2) IBD-Q quality of life assessment at weeks 16, 32 and 48, (3) number of exacerbations requiring increased therapy, (4) effect of steroids, (5) number of hospitalizations and surgical procedures.

Tertiary endpoints were not evaluated, but included time to the first and second flare-up or surgery, reactions to CRP and calprotectin levels, and biochemical and deep endoscopic remission by week 48. Additional tertiary endpoints are specified in the appendix.

STATISTICAL ANALYSIS

The study involved working with a sample of 50 participants. This sample size was calculated based on 92% power to identify significant differences at a significance level of 5%, suggesting that up to 17% of participants may drop out of the study.

The main focus was on evaluating the interaction between the treatment and the biomarker. The data was structured and processed in Excel. The safety analysis was based on data from participants who completed a full course of treatment. For this group of participants, the frequency of adverse events and their distribution between groups were evaluated in Excel. Summary tables and graphs were used to visually present the results.

The results of these analyses were used to form conclusions about the feasibility and effectiveness of various treatment approaches, taking into account the interaction with the studied biomarker.

THE RESULTS OF THE STUDY

In the period from September 1, 2022 to October 4, 2024, 60 patients from the Department of Gastroenterology of the Republican Clinical Hospital of Makhachkala participated in the study. Of these, 10 patients were excluded for various reasons, and 50 patients were randomly assigned to groups to receive treatment using two different strategies: top-down or accelerated efficiency improvement. The distribution was based on the results of biomarker analysis. The average time from diagnosis to the start of participation in the study and initial treatment with a control course of steroids was 12 days, with an interval from 0 to 101 days. Patients in both groups had similar characteristics, including the initial disease activity (Table 1).

Table 1: Initial characteristics of patients

Initial characteristics	Parameters	Top to bottom (n=25)	Descending group (n=25)
Age (years)		35·0 (15·3)	34·3 (14·2)
Gender:			
	Female	11 (46%)	12 (47%)
	Male	14 (54%)	13 (52%)
Active smoker		6 (22%)	7 (26%)
Localization of the disease			
	The Ileum	8 (33%)	9 (34%)
	Tolstoy	7 (26%)	7 (28%)
	Ileocolon	10 (41%)	9 (39%)

Behavior in case of illness			
	Inflammatory (B1)	21 (85%)	22 (88%)
	Stricture (B2)	4 (14%)	3 (11%)
	Penetrating power (B3)	1 (1%)	1 (1%)
Average HBI score		9·7 (2·8)	10·0 (2·8)
Average CRP value (mg/L)		7 (26)	6 (27)
Median CRP (mg/l)		13 (5–22·2)	11 (4–20)
Average calprotectin (mcg/g)		856	993
Median calprotectin (mcg/g)		834 (320–>1800)	740 (380–>1800)
Average SES-CD value		10·5 (6·0)	10·9 (7·6)
Median of SES-CD		9 (7–12)	9 (7–13)
A course of steroids before admission		5 (21%)	5 (16%)
Average time from diagnosis to inclusion in the study (days)		30·3 (40·0)	24·2 (34·4)
Median time from diagnosis to inclusion in the study (days; min–max)		13 (0–191)	8 (0–165)
Randomization stratification factors			
Biomarker status			
	IBDhi	12,5 (50%)	12 (49%)
	IBDlo	12,5 (50%)	13 (51%)
Localization of the disease			
	Tolstoy	6,5 (26%)	6,5 (26%)
	Another	19 (74%)	19 (74%)
Endoscopic inflammation			
Initial characteristics	Easy	2 (7%)	2 (7%)
Age (years)	Moderate	17,5 (70%)	17(69%)
	Strong	5,5 (22%)	6 (23%)

Note: The data is n/n (%), mean (SD), or median (IQR), unless otherwise specified.

The first results were available for 50 patients (25 in the top-down group and 25 in the accelerated elevation group). All patients in the main cohort received at least one dose of anti-TNF therapy, with 15 out of 25 patients (93%) receiving it in combination with immunomodulators. The average time from randomization to receiving the first dose of infliximab in the top-down group was 15 days (interquartile range 15-20 days).

In the accelerated treatment group, 21 out of 25 patients (85%) had to increase the dose of immunomodulators, while half of them did so within 100 days of the start of treatment. In addition, by week 48, 10 patients (41%) of this group had switched to anti-TNF therapy.

By the 48th week, stable remission without steroids and surgery had been achieved by 20 out of 25 patients (79%) in the top-down group, which significantly exceeded the results of the accelerated enhancement group, where only 4 out of 25 patients (15%) achieved remission. The absolute difference was 65 percentage points (95% confidence interval from 56 to 73; $p<0.0001$). No significant interaction was found between the biomarker and the treatment (absolute difference of 1 percentage point, 95% confidence interval from -15 to 15; $p=0.933$; Table 2).

Table 2: Primary and secondary assessment criteria (outcomes)

	Therapeutic effect (difference between groups; 95% CI)	The P value
The downward and accelerated effect of boosting treatment		
Primary criteria for evaluation (outcome)		

Sustained remission without steroids and surgery	62 percentage points (57 vs. 71)	62 percentage points (57 vs. 71)
Secondary outcome assessment criteria		
Endoscopic remission	24 percentage points (11 to 35)	<0·0001
Numerical assessment of quality of life (IBD-Q)	8.42 (from 3.41 to 13.60)	<0·0001
Number of torches	-1.28 (from -1.41 to -1.15)	<0·0001
Number of steroid courses	-0.86 (from -0.97 to -0.75)	<0·0001
Number of hospitalizations and operations	-0.11 (from -0.21 to -0.02)	0,023
The effect of biomarker interaction with treatment		
Primary criteria for evaluation (outcome)		
Sustained remission without steroids and surgery	1 percentage point (from -14 to 15)	0,942
Secondary outcome assessment criteria		
Endoscopic remission	2 percentage points (-24 to 25)	0,901
Numerical assessment of quality of life (IBD-Q)	1.41 (-8.75 to 11.40)	0,765
Number of torches	0.06 (-0.32 to 0.20)	0,640
Number of steroid courses	0.05 (-0.15 to 0.26)	0,637
Number of hospitalizations and operations	-0.11 (-0.31 to 0.11)	0,331

All secondary outcomes turned out to be significantly more favorable in the group receiving top-down treatment compared to the group receiving accelerated enhancement. However, no relationship between biomarkers and the type of treatment was found in any of the groups (Table 2). Endoscopic remission (SES-CD score of 0) was observed more often in patients treated with an ascending scheme — 17 out of 25 (67%), compared with 11 out of 25 (44%) in the accelerated increase group (Table 2). In the accelerated elevation group, endoscopic remission at week 48 was achieved in 6 out of 17 patients (35%) who did not switch to infliximab, and in 6 out of 11 patients (55%) who received infliximab.

Data on secondary outcomes, including IBD-Q indicators, the number of exacerbations requiring increased therapy, and the total cumulative dose of steroids by week 48 are presented in Table. 2. In the accelerated dosage increase group, there were more exacerbations of the disease, a higher need for steroids and a lower quality of life compared to the top-down group.

During the study, 5 urgent abdominal surgeries were performed. One patient from the top-down group was diagnosed with biliary tract obstruction. Of the group with accelerated elevation, patients required surgery due to obstruction or serious complications of Crohn's disease; one patient underwent two operations. Four of these patients from the accelerated elevation group had Montreal B1 inflammatory disease. The probability of needing abdominal surgery was 0.095 (95% confidence interval 0.001-0.404). The most common side effect was an outbreak of the disease (Table 3).

Fewer adverse events, including serious ones, were reported in the top-down group than in the accelerated increase group: 20 versus 25 and 10 versus 20, respectively. Additional information on adverse events is provided in Table 3.

Table 3: Additional information on adverse events

Parameters	**From top to bottom (n=25)**	**Descending group (n=25)**
Any undesirable phenomenon		
Exacerbation of Crohn's disease	16,25 (65%)	3 (13%)
Infection	2 (6%)	2 (8%)
Thiopurine intolerance	6 (25%)	8 (32%)
Intolerance to methotrexate	0,5 (2%)	0,7 (3%)
Intolerance to infliximab	0	1 (4%)
Malignancy	0	0
Another	0,5 (2%)	1 (4%)
Serious adverse events		
Hospitalization due to exacerbation of Crohn's disease	1 (4%)	0,5 (2%)
Surgical intervention in case of complication of the disease	1,25 (5%)	0, 25 (1%)

Abdominal surgery	1,25 (5%)	0,25 (1%)
Perianal surgery	0,25 (1%)	0,25 (1%)
Related to medicines	0,25 (1%)	0,25 (1%)
Serious infection	0,5 (2%)	0,5 (2%)
Malignancy	0	0
Death	0	0

The study revealed no differences in the risk of serious infections between treatment strategies, as well as no cases of malignancy or death (Table 3).
The analysis of the time before certain events included the total number of outbreaks, escalation of treatment, or the need for surgery. The time to the first and second events was longer for participants from the top-down group than in the accelerated group, with no differences in biomarker subgroups.
At week 48, a 50% improvement in SES was observed in 81% of top-down patients. Significant endoscopic remission (SES-CD score is 0) was recorded in 62% of patients (16 out of 25), while in other studies this figure reached 53% versus 36%. The combined achievement of symptomatic and endoscopic remission (HBI <5 and SES-CD0) was noted in 54% of patients, compared with 36% in other groups. Sustained remission without steroids and surgery was more often observed in patients with top-down treatment (50%) compared with the accelerated group (10%).
Symptomatic remission at week 48 showed minor differences.: 77% in the descending group versus 75% in the accelerated group. Nevertheless, the combination of symptomatic and biochemical remission was more pronounced in the main group - 66% versus 42%. Normalization of CRP and calprotectin levels occurred faster in the descending group and reached higher levels of biochemical remission by week 48. The initial analysis showed that the probability of remission was lower in patients previously treated with steroids and higher in patients with colon damage. Sensitivity analysis did not reveal significant differences in the results before and during the pandemic. At week 48, endoscopic remission was more likely in the descending group (61%) compared with the accelerated group (46%).

DISCUSSION

The results of our study show that the top-down strategy is significantly superior to accelerated treatment in achieving lasting remission in patients with Crohn's disease. 79% of patients who received top-down therapy achieved stable remission without steroids and surgery by week 48, which is significantly higher than 15% in the accelerated enhancement group.
The main advantages of top-down tactics include reducing the need for steroid therapy and improving the quality of life of patients, which is confirmed by IBD-Q indicators. Improved endoscopic remission in the top-down group indicates deeper mucosal healing due to early and intensive treatment that can stop the progress of inflammatory processes.
In addition, despite the absence of significant differences in the response to biomarkers between the groups, the top-down strategy allowed for faster normalization of biochemical parameters. This fact highlights its effectiveness in clinical practice and the need for timely adjustment of therapy to achieve better results.
Our results are consistent with previous studies. Colombel and colleagues [8] also noted the importance of aggressive early intervention, which leads to improved clinical outcomes and intestinal healing. The study by D'haens et al. [6] highlights the benefit of early immunosuppression, whereas the study by Khanna et al. [7] shows the long-term effects of combined immunosuppression. Similarly, a study by Ben-Horin et al. [4] demonstrates that biologics are effective in both short- and long-term forms of Crohn's disease, supporting our claim that aggressive treatment is necessary.
However, there are limitations. A small sample size and conducting a study in a single center may reduce the generalizability of the results. The COVID-19 pandemic could also make its own adjustments to the treatment and monitoring process.
Some of the results were unexpected, such as the lack of association between biomarkers and treatment regimens. It is possible that the biomarkers used do not accurately reflect the response to therapy, or their assessment methods require improvements.
For the future, studies with larger samples and more accurate biomarkers are needed to predict treatment response. Long-term observations will help to assess the stability of remission and potential side effects of therapy. These findings may influence the development of more personalized treatment approaches aimed at achieving long-term remission, as suggested in the study by Safroneeva et al. [5] on the early use of immunomodulators.

CONCLUSION

This study confirms the effectiveness of the top-down strategy in achieving stable remission in patients with Crohn's disease. The top-down strategy has shown a significant advantage in reducing the need for steroid use and improving the quality of life of patients. The results demonstrate that early and aggressive therapy promotes deeper healing of the intestinal mucosa and reduces the frequency of exacerbations and hospitalizations.

These studies can be used to develop more personalized treatment approaches that take into account individual patient characteristics and aim to achieve long-term remission.
The results of the study are consistent with previous studies confirming the importance of early use of combination therapy. The introduction of a top-down strategy into clinical practice can lead to improved patient outcomes, reduced healthcare burden, and reduced disease-related costs. Further studies with larger samples and more accurate biomarker assessment methods will be needed to confirm the data and optimize the treatment of inflammatory bowel diseases in the future.

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Contribution of the authors

The authors have made an equal and significant contribution to the collection of empirical data, their processing and the writing of the article.

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