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Efficacy of Tofacitinib as a «rescue therapy» in patients with severe ulcerative colitis

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ABSTRACT *AIM: to evaluate the effectiveness of tofacitinib (TFCB) as a second line treatment.*
PATIENTS AND METHODS: the study included 12 patients, 4 (33.34%) males and 8 (66.66%) females, age was 41 ± 5 years. All patients admitted to the hospital with a severe flare-up of ulcerative colitis, which was the inclusion criterion in this study. Clinical manifestations, laboratory parameters, and colonoscopy were done at the time of administration of tofacitinib, on days 3 and 7, and after 12 weeks.
RESULTS: a fast clinical response on 3 day of treatment, reduction in stool frequency, decrease blood in stool were noted in 10 (83.3%) patients. After 7 days from the start of TFCB therapy, all patients showed a decrease from severe activity to mild activity, as well as a decrease in inflammatory blood markers and hemoglobin levels. During the follow-up for 12 weeks, 100% of patients showed positive clinical and laboratory changes. In 10 (83.4%) patients, remission or maintenance of negligible minimal activity was noted.
CONCLUSION: the primary results obtained show that the use of TFCB in steroid-resistant patients can be effective as a second line of "rescue therapy".

KEYWORDS: *inflammatory bowel diseases, tofacitinib, ulcerative colitis*

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

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease of unknown etiology, characterized by diffuse inflammation of the bowel mucosa and extraintestinal (systemic) manifestations [1].

Epidemiological studies done for recent decades indicate a significant increase in the UC incidence, as well as high costs for the treatment of patients. According to the structure of admissions, the UC incidence raise within the period of between 2012 and 2015 was 31.7% [2]. The choice of treatment based on the flare-up severity, the extent of the lesion, the presence of extraintestinal manifestations, the disease natural history, the effectiveness and safety of previous therapy, as well as the risk of UC complications. Patients with UC need constant anti-recurrence therapy to maintain clinical and endoscopic remission [3]. Surgery is needed in 10-20% of patients [4]. The introduction of biological drugs (BD) made it possible to more effectively overcome steroid resistance and steroid dependence of UC, increase the time of relapse-free period, reduce the risk of relapse, reduce the incidence of surgery and improve the quality of life of patients [5]. However, there is a need to develop new types of drugs for the treatment of UC that would allow rapid induction of clinical remission, reduce the risk of immunogenicity and other side effects [6] and have the least number of side effects [7]. Tofacitinib (TFCB) is an oral non-selective janus-kinase inhibitor that has shown

efficacy and safety in patients with moderate to severe ulcerative colitis in the third phase of a randomized OCTAVE trial [8,9]. In 2018, a small-molecule drug was approved by the FDA and EMA for the treatment of moderate to severe UC [10]. A retrospective analysis of the OCTAVE study has revealed that TFCB has a rapid effect, significantly reducing the frequency of stool and the amount of blood within 3 days from the start of the therapy [11]. The rapid onset of the effect and the elimination of the drug from the body in a short time allow the use of TFCB as a "rescue therapy" in patients with a severe flare up of UC. Currently, the intravenous therapy with steroids is the first-line therapy for patients with a severe flare up of ulcerative colitis [12]. In the absence of a response to steroid therapy, the second line of therapy is infliximab (IFL) or cyclosporine (CSP) [13]. In a systematic review and meta-analysis of randomized clinical trials, there were no differences between IFL and CSP in the response to the therapy and the risk of colectomy after 3 and 12 months of follow-up, which demonstrates the equivalent effectiveness of these drugs [14]. In a number of patients with severe UC flare up, the consistent use of these agents is possible [15]. If conservative therapy is ineffective or in the case of a fulminant ulcerative colitis, the question of colectomy considered [12]. In 2019, Berinstein et al. described the experience of effective and safe use of TFCB in a dose of 10 mg 3 times per day in 4 patients with severe ulcerative colitis, which made it possible to avoid colectomy [16]. In all 4 cases, the ineffectiveness of steroids or IFL was previously noted [16]. In another series of cases, Kotwani et al. assessed the efficacy and safety of TFCB in 4 patients with severe ulcerative colitis with a high risk of colectomy [17]. The patients included in the study had a history of ineffectiveness of two biological drugs, including an anti-TNF-α drug (infliximab and/or adalimumab) and an anti-integrin drug (vedolizumab), as well as resistance to steroid therapy [17], before admission. According to the guidelines, the patients received steroids therapy at the first stage and in case of development of steroid resistance in a hospital setting, the therapy with TFCB started at the dose of 10 mg 2 times per day orally for 21 days [18]. For 90-day follow-up, no patient had a need for a colectomy [18]. Similar data obtained in a number of other studies based on a small number of clinical cases [22–24]. Several studies have shown that TFCB was effective in achieving remission, both in anti-TNF-α-naive patients and in patients with no response to anti-TNF-α therapy in the history. Numerous studies have shown that high doses of intravenous steroids are the first-line therapy for patients with a severe ulcerative colitis flare up, both in anti-TNF-α-naive and with no effect from anti-TNF-α therapy in the history. Bionaive patients with no effect from steroid therapy recommended to use IFL and CSP. The results of recent studies demonstrate that TFCB can be an effective second-line therapy, as well as IFL and CSP, but the use of TFCB should be discussed in a multidisciplinary team in IBD centers, taking into account an individual approach, after a thorough assessment of the risk-benefit ratio [25].

PATIENTS AND METHODS

The use of TFCP as a second-line therapy analyzed. Of the 12 patients included in the study, there were 4 (33.3%) males and 8 (66.7%) females. The age of the patients was, on average, 41 ± 5 years. The diagnosis of ulcerative colitis in patients verified by colonoscopy and pathomorphology in accordance with the Clinical Guidelines for the diagnosis and treatment of ulcerative colitis [1]. All the patients (100%) had a clinical picture of a severe ulcerative colitis at the time of admission, which was the criterion for including patients in this study. The severity of the flare up assessed by the Truelove-Witts criteria. The main demographic, clinical and laboratory characteristics of UC patients presented in Tables 1–2.

All the patients at the time of admission received intravenous therapy with systemic steroids. In the absence of a positive response on the 3rd day, as an alternative to surgery, the patients prescribed the therapy with a synthetic targeted drug TFCB. The aim of this therapy was to achieve clinical and endoscopic remission. We evaluated the rate of a clinical response on days 3 and 7, as well as the possibility of maintaining a clinical response to the therapy. All the patients underwent clinical and laboratory

Table 1. *Clinical characteristics of patients*

Indicator	Value
Gender (m/f), *n* (%)	4 (33.3)/8 (66.7)
Median age, years (M ± m)	41 ± 5
Disease time	7.67 ± 0.95
Age at the time of diagnosis, (M ± m)	25 ± 5
Smoking	
Yes	0 (0)
No	10 (83.4)
Smoked before	2 (16.6)
BMI	
< 18.5	1 (8.3)
18.5- < 25.0	10 (83.4)
⩾ 25.0	1 (8.3)
Median disease time	
< 5 years	2 (16.6)
⩾ 5 years	10 (83.4)
The extent of the lesion, *n* (%)	
Proctitis	0 (0)
Left-sided colitis	2 (16.6)
Total colitis	10 (83.4)
Intestinal complications, *n* (%)	4 (25.0)

M + m — median ± standard deviation

Table 2. *Treatment before Tofacitinib*

Drugs	Value, *n* (%)
5-ASA, *n* (%)	12 (100.0)
Immunomodulators, *n* (%)	7 (58.3)
Corticosteroids, *n* (%)	12 (100.0)
Bionaive, *n* (%)	10 (83.4)
GEBD, *n* (%) including:	
Infliximab, *n* (%)	1 (8.3)
Adalimumab, *n* (%)	1 (8.3)
Golimumab, *n* (%)	1 (8.3)
Vedolizumab, *n* (%)	1 (8.3)

monitoring to assess the condition with the possibility of continuing this therapy. The laboratory and instrumental tests performed with modern specialized licensed equipment, which undergoes regular scheduled verification. The patients also underwent an endoscopy at the time of therapy start to assess the condition of the colon mucosa and determine the "window of opportunity" for conservative therapy and then after 12 weeks to assess the endoscopic remission. The clinical assessment of the severity of the condition carried out according to the Mayo index. The statistical analysis was performed using the Microsoft ® Office Excel 2003 application software package; STASTICA 7.0., Primer of Biostatistics Version 4.03 by Stanton A. Glantz 1998. Student's t-test applied to determine the significance of differences between the mean values with the normal distribution of aggregates.

RESULTS

According to the results of the initial clinical, laboratory and endoscopic examination, a severe UC flare up detected in all 12 patients (Table 3). All the patients got TFCB in an induction dose of 10 mg 2 times a day. A rapid clinical response on the third day of treatment, characterized by a decrease in the frequency of stools and a decrease in blood in the feces, was noted in 10 (83.3%) of 12 patients. The rate of achieving a clinical response correlates with the data obtained by analyzing the questionnaires included in the OCTAVE study [11,27].

After 7 days from the start of the TFCB therapy, all the patients (100%) showed a decrease in the activity of a severe flare up to a mild one, as well as a decrease in inflammatory markers of the blood tests, normalization of hemoglobin levels (Table 4). After 7 days, in all the patients who responded to the TFCB therapy, the Mayo index in the group, on average, decreased from 10.67 ± 0.20 to 4.33 ± 0.27, $p = 0.001$ (Table 5).

In 11 (91.6%) patients, clinical remission on the Mayo scale was noted at week 8 of the therapy, in 1 (8.3%) case, a positive trend was revealed in the form of a decrease in the Mayo index from 11 scores to 5, but no stable clinical response was achieved. Of the 12 patients who received a full induction course for 8 weeks,

Table 3. *Initial clinical and laboratory characteristics of patients with UC before Tofacitinib*

N	Mayo Index (clinical and endoscopic), scores	Hemoglobin g/l	Leukocytes, x10⁹/l	Rod neutrophils, %	Thrombocytes, x10⁹/l	ESR mm/h	Total protein g/l	Albumin g/l	CRP mg/l
1	11	99.0	8.99	1.0	262.0	30.0	55.0	33.0	9.5
2	11	94.5	6.61	5.0	383.5	34.0	68.0	40.0	5.8
3	10	118.0	11.28	2.0	314.0	29.0	55.0	30.0	81.8
4	11	104.0	11.51	1.0	345.0	17.0	51.0	34.0	7.2
5	10	96.0	14.5	3.0	557.0	25.0	61.0	31.0	4.6
6	12	97.0	13.41	1.0	369.0	14.0	57.0	33.0	9.4
7	10	103.0	19.64	3.0	542.2	30.0	54.0	34.0	3.4
8	10	110.0	5.6	2.0	254.7	12.0	55.0	29.0	0.6
9	11	94.6	4.2	2.0	242.6	17.0	50.0	30.0	8.6
10	11	101.0	8.74	4.0	281.0	22.0	61.0	33.0	6.1
11	10	108.0	6.63	1.0	273.0	12.0	55.0	33.0	9.5
12	11	98.3	11.3	1.0	505.0	6.0	52.0	30.0	13.3

Table 4. *Clinical and laboratory characteristics of patients with UC after 7 days of Tofacitinib use*

N	Mayo Index (clinical and endoscopic), scores	Hemoglobin g/l	Leukocytes, x10⁹/l	Rod neutrophils, %	Thrombocytes, x10⁹/l	ESR mm/h	Total protein g/l	Albumin g/l	CRP mg/l
1	5	111.0	7.27	1.0	339.0	3.0	56.0	36.0	1.5
2	5	101.0	5.8	1.0	324.0	13.0	69.0	39.0	1.4
3	4	126.0	6.83	1.0	362.0	11.0	60.0	38.0	1.0
4	5	123.0	7.2	1.0	323.0	12.0	56.0	39.0	1.1
5	5	113.0	8.4	4.0	320.0	22.0	67.0	35.0	1.4
6	4	111.9	11.2	1.0	350.0	12.0	65.0	39.0	1.9
7	4	114.0	11.8	5.0	421.3	16.0	64.0	38.0	1.3
8	2	122.0	6.41	2.0	231.3	15.0	59.0	33.0	0.5
9	5	102.0	4.44	2.0	213.5	3.0	51.0	30.0	1.8
10	5	101.0	11.7	4.0	303.0	20.0	69.0	37.0	1.1
11	4	111.0	7.2	1.0	339.0	3.0	55.0	33.0	1.5
12	4	106.0	8.25	1.0	277.0	6.0	55.0	34.0	0.1

Table 5. *Changes in clinical and laboratory parameters after 7 days of Tofacitinib use*

N	Indicators	Before the start of the therapy	After 7 days from the start of the therapy	*p*
1	Mayo Index (clinical and endoscopic), scores (M ± m)	10.67 ± 0.2	4.33 ± 0.27	0.001
2	Hemoglobin, g/l (M ± m)	102.02 ± 2.14	111.83 ± 2.57	0.001
3	Leukocytes, $\times 10^9$/l (M ± m)	10.2 ± 1.31	8.04 ± 0.71	0.001
4	Platelets, $\times 10^9$/l (M ± m)	360.75 ± 34.53	316.97 ± 16.98	0.001
5	ESR, mm/h (M ± m)	20.67 ± 2.69	11.3 ± 1.96	0.001
6	CRP, mg/l (M ± m)	13.32 ± 6.58	1.17 ± 0.17	0.001

M + mmedian ± standard deviation

10 (83.3%) had not previously received anti-TNF-α drugs. The need for a prolonged induction course of TFCB was required in one patient (8.3%).

During the follow-up for 12 weeks, 100% of the patients showed positive clinical and laboratory dynamics. In 10 (83.4%) patients, there was a remission of the inflammatory process or the preservation of minimal activity. The Mayo index was 0.67 ± 0.23 scores.

After 12 weeks, the median hemoglobin values were 124.7 ± 3.05; leukocytes — 5.68 ± 0.59, rod-shaped neutrophils — 1.33 ± 0.15; platelets — 296.2 ± 19.96; ESR — 7.67 ± 2.15; CRP — 1.88 ± 0.35, significantly different from the initial ones.

In one (8.3%) female patient, due to the increase in intestinal symptoms during the transition to maintenance therapy of TFC 10 mg/day, the dose was optimized to an induction dose of 10 mg 2 times a day with a positive effect in the form of normalization of clinical and laboratory parameters. When deciding to return to the induction dose, we took into account the experience gained in the OCTAVE study, in which patients who did not respond to induction were transferred to the open phase of the study (OCTAVE Open), and they received TFCB in a dose of 10 mg 2 times a day for another 8 weeks. After 14 days of continued induction, the patient achieved clinical and laboratory remission. In another case, the moderate endoscopic and clinical activity of the inflammatory process remained, and therefore, taking into account the ineffectiveness of the entire basic therapy and the presence of increased risks of complications (including a long history of UC), indications for elective surgery were determined.

It should be noted that in this patient, the ineffectiveness of treatment with several biological drugs (including vedolizumab, adalimumab, golimumab) was confirmed in the history. Against the background of the use of TFCB, positive clinical and endoscopic dynamics were noted (relief of a severe ulcerative colitis flare up). However, it was not possible to achieve clinical and endoscopic remission, which regarded as a failure of the therapy. Thus, in the group of the patients (n = 12) receiving TFC, a prolonged induction course of TFCB was required only in 1 (8.3%) patient.

The majority of patients with clinical remission at the 8th and 12th weeks also showed mucosal healing. At week 8, a clinical and laboratory assessment was performed, of which 11 (91.6%) patients were produced clinical remission. At week 12, 12 patients were examined, and 10 (83.3%) of them showed the healing of the colon mucosa. It should be noted that patients who did not achieve endoscopic remission (complete healing of the mucous layer) had previously received biological therapy. It should be noted that all patients who achieved endoscopic remission after the induction course retained it by week 12.

After 26-week follow-up, 7 (58.3%) patients with ongoing therapy with TFCB in a dose of 5 mg 2 times a day maintained a clinical response, and the remission of the inflammatory process confirmed according to the laboratory and endoscopic tests. One (8.3%) patient required dose optimization of TFCB — 10 mg 2 times a day with the

achievement of a clinical response in 7 days after the start of the therapy. It should be emphasized that our initial experience with the use of TFCB has demonstrated satisfactory tolerance. In no one case, the appearance of undesirable phenomena that could cause the withdrawal of the drug noted.

DISCUSSION

Significant progress in the diagnosis and treatment of ulcerative colitis achieved, but there is still a need for new treatment opportunities that can help reduce the adverse clinical consequences of the disease, improve the quality of life of patients, reduce the economic costs associated with the disease, and ideally change the natural course of the disease. Tofacitinib, as the first drug registered for the treatment of UC in the class of Janus-kinase inhibitors, represents a promising new alternative in the treatment of severe UC flare up.

The traditional method of treating patients with a severe UC flare up is the administration of intravenous steroids in a dose equivalent to 125 mg of prednisone. In the presence of steroid resistance, the continuation of steroid monotherapy or an increase in the dose of steroids not indicated. If there is no immediate threat to the patient's life or the development of severe complications requiring urgent surgery, it is recommended to prescribe a "second-line" therapy (in English-language literature: "rescue therapy"), which includes the following treatment options: IFL or CSP. If the latter prescribed, it is necessary to monitor the indicators of kidney function and determine the concentration of the drug in the blood. However, we have clinical confirmation that in patients who previously received therapy with anti-TNF-α drugs and did not respond to intravenous therapy with steroids, in addition to the use of CSP, tofacitinib may be a good alternative [25].

However, to confirm this hypothesis, randomized controlled trials are required to determine the possibility of using tofacitinib instead of IFL or CSP as a second-line therapy in the treatment of severe ulcerative colitis.

The interim results obtained in the study show that the use of TFCB in steroid-resistant patients can be effective as a second-line "rescue therapy." Now, the study is ongoing, and the search for prognostic parameters for evaluating the effectiveness of the TFCB is also being carried out.

AUTHORS CONTRIBUTION

Concept and design of the study: *Darya V. Podolskaya, Oleg V. Knyazev, Marina V. Shapina, Bella A. Nanaeva*

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