https://doi.org/10.33878/2073-7556-2019-18-4-86-99

EXPERIENCE OF TOFACITINIB USING IN THERAPY OF ULCERATIVE COLITIS IN REAL CLINICAL PRACTICE

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AIM: to demonstrate the first Russian experience with the use of tofaciminib (TOFA) for the treatment of moderate and severe UC in real clinical practice.

PATIENTS AND METHODS: eighty-five patients with UC (aged 41.38±14.69 years, average disease duration 9.55±5.27 years, mild UC – 3.5%, moderate UC – 41.2%, severe – 52.9%, acute severe UC – 2.6%), resistant to corticosteroid therapy (36.5%) and biological agents (61.2%), were prescribed with TOFA at an induction dose of 10 mg 2 times a day, followed by a decrease in the dose to a maintenance dose (5 mg 2 times a day). Early clinical response, clinical and endoscopic remission, prevalence and dynamic of extraintestinal manifestations were assessed at 8 and 12 weeks of treatment, as well as safety and tolerability.

RESULTS: Sixty-eight (80.0%) patients completed induction treatment with TOFA for 8 weeks, other patients continue to receive TOFA. A quick response within one week was detected in 41 (50.6%) patients, on average, on the 5th day of therapy. At the end of induction, 52 (76.5%) patients achieved clinical remission, 3 (4.4%) achieved a clinical response, 13 (19.1%) patients showed no positive changes. Of the 53 patients observed over 12 weeks, 41 (77.4%) had clinical remission, 6 (11.3%) had clinical improvement, and 6 (11.3%) patients had no response to the treatment. The changes of extraintestinal manifestations were positive: 55.2% of patients at week 8 and 77.8% of patients at week 12 showed clinical improvement, mainly in relation to the joint syndrome. One episode of herpes zoster infection, one case of anemia, was identified during 12 weeks of follow-up.

CONCLUSION: TOFA in UC is effective in achieving a rapid clinical response, clinical remission and mucosal healing in patients who do not adequately respond to therapy with basic as well as biological drugs. Tofacitinib is an effective and safe therapeutic option for this challenging patient population.

[Key words: Ulcerative colitis, Inflammatory bowel disease, Tofacitinib, JAK inhibitors]

For citation: Belousova E.A., Abdulganieva D.I., Alekseeva O.P., Bakulin I.G., Vasilyeva O.V., Veselov A.V., Kagramanova A.V., Kashnikov V.N., Knyazev O.V., Koroleva M.V., Mishchenko E.V., Nikitina N.V., Nikolaeva N.N., Tkachev A.V., Chashkova E.Yu., Shapina M.V. Experience of tofacitinib using in therapy of ulcerative colitis in real clinical practice. *Koloproktologia*. 2019; v. 18, no. 4(70), pp. 86-99.

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INTRODUCTION

Inflammatory bowel diseases (IBD) such as ulcerative colitis (UC) and Crohn's disease (CD) represent one of the most serious and unsolved problems in current gastroenterology. Medical treatment of UC includes 5-aminosalicylic acid (5-ASA) drugs, systemic and/or topical glucocorticoids (GCs), immunomodulators (azathioprine, 6-mercaptopurine and cyclosporine) and biological agents including antibodies to tumor necrosis factor alfa (anti-TNF) (infliximab, golimumab and adalimumab) and antiintegrins (vedolizumab) [1]. Despite a wide drug array, the possibilities of medical treatment of moderate to severe UC remain limited. Significant number of patients do not primarily respond to therapy with biological agents and from 10% to 20% of patients lose their response during a year which leads to the need of dose optimization or switch to the other drug [2-4]. Lack or loss of response to corticosteroids are noted in approximately a half of patients in Russia in total [5]. This served as stimulus for the development of new approaches to the pharmacotherapy of IBD, including the use of low molecular weight synthetic drugs (the so-called small molecules) that inhibit JAK (Janus) kinases, which action is based on other pathophysiological mechanisms [6-9]. The first representative of a new class of Janus-kinases inhibitors was tofacitinib (TOFA) first in the world registered in Russia on May 2018 for the treatment of patients with moderate and severe active UC with insufficient response, loss of response, or intolerance to corticosteroids, azathioprine, 6-mercaptopurine, or biologics.

TOFA shows high efficiency in different types of patients with ulcerative colitis in «bio-naive» patients and patients with inadequate response to TNF within wide program of clinical trials [10-12] including prolonged phases [13]. There are also several publications regarding the use of TOFA in clinical practice [14-16].

Nevertheless, we are at the initial stage of TOFA usage in UC since the practical experience of it in Russia and in the world is small.

This article presents the first multicenter, open-label, prospective, uncontrolled, cohort study of TOFA efficiency and safety in patients with active UC.

AIM

To evaluate the efficacy and safety of TOFA therapy in real clinical practice in patients with active UC who did not respond to various options of basic and biological therapy.

PATIENTS AND METHODS

Study characteristics: multicenter, open-label, prospective cohort study.

Patient characteristics: 85 patients with active UC from 12 centers in 10 cities of the Russian Federation are enrolled into the observation group. Demographic, clinical, laboratory and endoscopic data were obtained from the Registry of patients with inflammatory bowel diseases in the Russian Federation (ROSMED. INFO – Russian online-platform targeted to quality improvement of medical care service for patients of different therapeutic profiles). Follow in characteristics were analyzed: patient features (age at baseline, age at diagnosis), disease features (disease duration, severity and extension of UC, endoscopic activity, presence of complications, presence and location of extraintestinal manifestation) (Table 1), prior treatment (therapy with 5-ASA, immunomodulators, GCs, biological agents and reasons for their discontinuation) (Table 2).

Treatment characteristic: the reasons for the TOFA administration were steroid resistance 31 (36.5%), steroid dependence 59 (69.4%), primary inefficiency or loss of response to biological agents 52 (61.2%). TOFA was prescribed according to the standard scheme: for induction course 10 mg BID for 8 weeks with further dose reduction up to maintenance dose 5 mg BID.

Criteria for treatment assessment: a) early clinical response (frequency of reduction or disappearing of clinical symptoms after the first treatment week), b) clinical response (dynamics of clinical and endoscopic symptoms, extraintestinal signs after induction course at 8 weeks), c) dynamics of clinical symptoms and endoscopic pattern at 12 treatment weeks.

The study was approved by the institutional ethics review board. None of the patients participated in other tofacitinib clinical trials (including the OCTAVE program).

Thus, majority of patients enrolled in the study had long-term UC history (more than 9 years), high clinical and endoscopic disease activity, 78.8% of patients were diagnosed with total UC, the third of patients showed extraintestinal signs.

Table 2 shows the therapy used for UC treatment before enrolling patients in the study. Majority of patients were treated with 5-ASA, immunosuppressants and GCs. Steroid dependence was noted in 69.4% of patients and resistance to corticosteroid therapy was in 36.5%. More than a half of patients – 52 (62.2%) were treated with biologics, including 23 (27.2%) – with two or three biological agents. Among the biologics more often infliximab (42.6%) was prescribed as a first line therapy, other TNF inhibitors were administered twice less frequent (22.1-

23.5%) mostly in 2 and 3 lines of biological therapy. Vedolizumab was used in 4 (5.9%) patients. Among reasons of biological therapy termination, the loss of therapeutic effect was most common during treatment with infliximab (48.1%) as the first biologic medication in majority of cases, while it was 26.7% and 37.5% in using of other TNF inhibitors – adalimumab and golimumab, respectively. Primary inefficiency as a reason of discontinuation with infliximab treatment was identified in 22.2% of patients while percentage of such patients was almost twice bigger for adalimumab and golimumab (47.6% and 43.7% respectively). These drugs were administered in 2-3 treatment line for majority of patients which is likely resulted from decrease of therapeutic response. Adverse events became a reason for biological therapy termination in 6 (11.5%) of patients. Besides, significant part of patients stopped the therapy due to administrative reasons (17.3%, n=9).

Thus, examined group is mainly presented with patients with moderate and severe ulcerative colitis, majority of patients has total colitis with high endoscopic activity, the third of patients has developed steroid resistance and a half of them had previously failed biological therapy.

It is notable that characteristics of patients in examined cohort are comparable to analogous ones in patients enrolled in clinical program OCTAVE [10].

Response to treatment was assessed as Mayo score reduction not less than 30%, remission was defined as Mayo score of 0-3 points. Endoscopic remission was assessed as Mayo endoscopic subscale value of 0 points. Lack of significant improvement of symptoms, termination of tofacitinib treatment or surgery were defined as a therapy failure.

Statistical analysis was performed using IBM SPSS Statistics 24.0 program. Analysis of qualitative parameters was performed according to frequency incidence. Quantitative variables were checked at normality of distribution. To describe the quantitative variables, descriptive statistics methods were used: mean, standard deviation.

Table 1. *Clinical characteristic of patients with UC (n=85)*

Rate	Value
Age, years (M±s)*	41.4±14.7
Age at the diagnosis (M±s)	31.9±15.4
Disease duration, (M±s)	9.6±5.3
Total Mayo score, n (%)	
0-3	8 (9.4)
4-6	24 (28.2)
7-9	42 (49.4)
10-12	11 (12.9)
Endoscopic Mayo subscale, n (%)	
0	2 (2.4)
1	7 (8.2)
2	40 (47.1)
3	36 (42.3)
Disease severity, n (%)	
Mild	3 (3.5)
Moderate	35 (41.2)
Severe	45 (52.9)
Acute severe	2 (2.4)
Disease extent, n (%)	
Left-sided colitis	18 (21.2)
Total colitis	67 (78.8)
Presence of intestinal complications, n (%)	5 (5.9)
Extraintestinal manifestations, n (%)	
Total	29 (34.1)
Musculoskeletal	17 (20.0)
Skin and mucosallesions	6 (7.1)
Gastrointestinal tract damage	6 (7.1)

* *M – meanvalue, s–standard deviation.*

Table 2. *Characteristic of therapy in patients with UC (n=85) before included in study*

Rate	Value
5-ASA, n (%)	84 (98.8%)
Immunomodulators, n (%)	71 (83.5%)
Corticosteroids, n (%)	82 (96.5%)
Steroid dependence, n (%)	59 (69.4%)
Steroid resistance, n (%)	31 (36.5%)
Biological drugs, n (%)including:	52 (61.2%)
Infliximab	35 (41.2%)
Adalimumab	17 (20.0%)
Golimumab	21 (24.7%)
Vedolizumab	5 (5.9%)
Number of previous biological drugs, n (%)	
1	29 (34.1)
2	19 (22.3)
3	4 (4.8)

RESULTS

TOFA was prescribed for all patients in induction dose of 10 mg 2 BID. Early response to therapy with tofacitinib was assessed at 1 week. Rapid clinical response at the first treatment week was identified in 41 (50.6%) of 85 patients enrolled in the study, the effect was noted at 5-th day of drug intake on average. Sixty-eight (80.0%) of 85 patients completed induction course of treatment, other 17 patients continue induction course and they are not included in this analysis.

Clinical remission was observed in 52 (76.5%) patients at the 8th week of therapy, three patients (4.4%) achieved a clinical response, and 13 (19.1%) patients showed no positive changes (Fig. 1).

Of the 68 patients who received a full induction course, 53 (62.3%) completed 3 months of therapy by the time the data were analyzed. In 41 (77.4%) patients the achieved clinical remission was preserved, in 6 (11.3%) the clinical effect was noted, in 6 (11.3%) the clinical symptoms did not improve (Fig. 1).

Majority of patients achieved clinical remission at 8 and

12 weeks also achieved mucosal healing. Endoscopy was performed for 38 patients at 8 weeks, 24 (63.2%) of them were diagnosed with remission. Thirty-six patients were examined at 12 week and 22 (61.1%) of them registered mucosal healing (Fig. 2). It is notable that all patients achieved endoscopic remission after induction course maintained it by 12 weeks.

Extraintestinal manifestations of UC before the start of therapy with TOFA were noted in 29 of 85 patients (34.1%). Majority of them (17 patients 20.0%) had musculoskeletal lesions (peripheral arthritis, axial damage), per 6 (7.1%) had skin and mucosal lesions and liver diseases (primary sclerosing cholangitis (PSC), autoimmune hepatitis (AIH). Reduction of symptoms of extraintestinal disease was identified in 16 (55.2%) of 29 patients, without any changes – in 13 (44.8%) at 8 weeks of therapy. Positive changes were observed in 77.8% patients (14 of 18) by 12 weeks, there was no improvement in 4 (22.2%) of 18 patients. No increase in symptoms of extraintestinal manifestations of any localization was observed in any patient (Fig. 3).

In general the agent was characterized by good tolerability. Adverse events were the reason of therapy termination within 12 weeks in 2 (2.9%) of 68 patients, activation of herpes infection (1 patient) and hemoglobin decrease lower than 80 g/L (1 patient).

DISCUSSION

This study of TOFA in patients with UC showed high agent efficiency in patients with steroid dependence and steroid resistance, inadequate response to basic and biological therapy. Significant number of patients noted a clinical response at the first week (at the 5 day of treatment on average) and it was characterized by reduction of main symptoms – decrease of stool frequency and rectal bleeding. Time to clinical response achievement in this analysis correlates with data obtained by analyzing questionnaires of patients

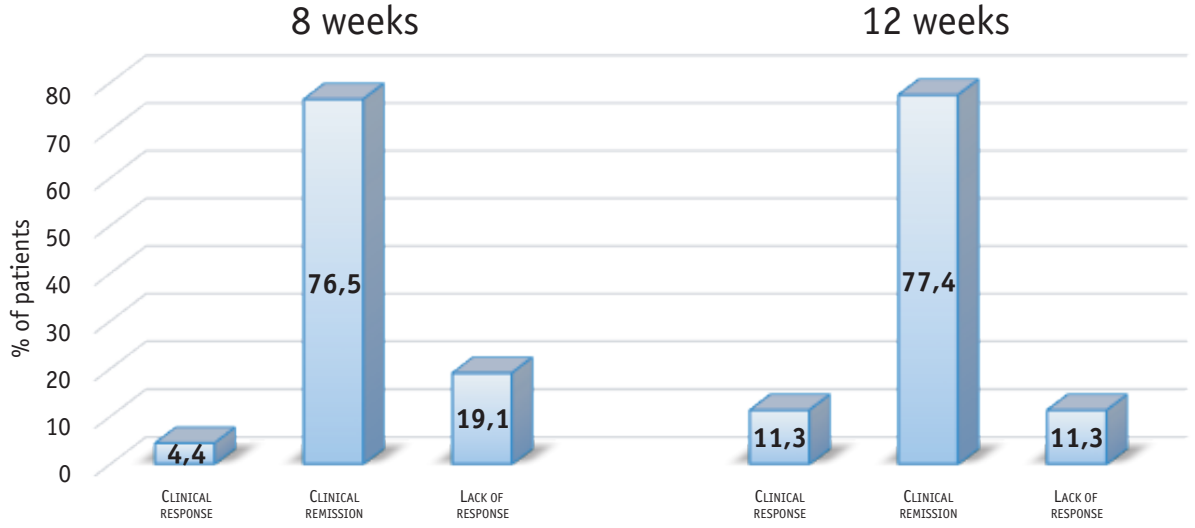

Figure 1. *Clinical results of therapy with TOFA (8 and 12 weeks)*

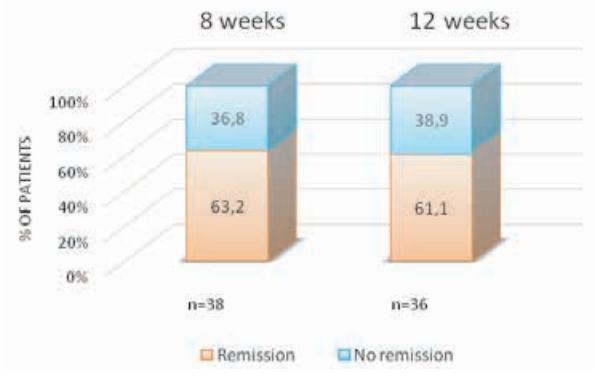

Figure 2. *Endoscopic remission within therapy with TOFA at 8 and 12 weeks*

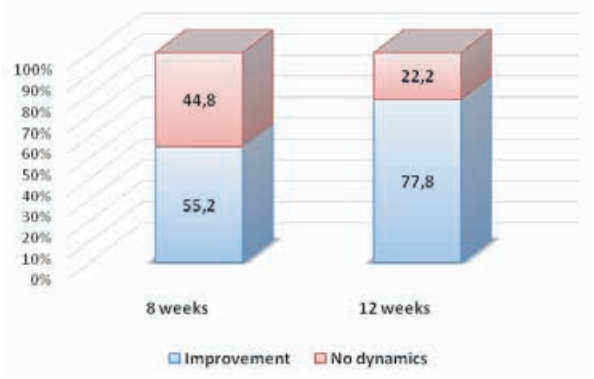

Figure 3. *Dynamics of extraintestinal manifestations at 8 and 12 weeks*

included in study OCTAVE Induction 1,2 in which rates of stool frequency and rectal bleeding at the third day of therapy were statistically significantly lower in patients received TOFA compared with patients who received placebo [17]. Response after induction course was noted in majority of patients (80.9%) and 76.5% among them achieved clinical remission. More than a half of patients (63.1%) also attained endoscopic remission during induction and maintained it by 3 months of therapy.

By 12 week of therapy total number of «responders» was increased up to 88.7%, there was 77.4% of achieved clinical remission among them. 7 of 13 patients (53.8%) who did not respond to standard induction regime achieved clinical response at 12 weeks, furthermore 3 of them achieved not only clinical response but also remission. It is consistent with data of clinical program OCTAVE where patients who did not respond to induction were transferred to the open phase of study (OCTAVE Open) and they received tofacitinib in a dose of 10 mg BID for 8 additional weeks. After 2 weeks of continuing induction 60.1%, 25.7% and 16.2% of patients achieved clinical response, remission and mucosal healing respectively [18]. 2 (15.4%) patients did not respond to therapy by 12 week and continued treatment, 2 (15.4%) patients have not complete 12 weeks of therapy yet and for 2 (15.4%) patients drug was cancelled due to adverse events (anemia, Herpes virus activation). Two patients required therapy optimization up to 10 mg BID after the lost of efficacy on maintaining dose. The data of the currently published observations in real clinical practice do not allow a comparison with this analysis, since they have a population bias and different treatment efficiancy criteria and further study in this area is required [14-16].

Positive changes of extraintestinal manifestations was noted in 56.7% patients in 8 weeks and in 72.2% in 12 weeks.

Performed systematic reviews and meta-analysis showed that frequency of side effects and serious adverse events did not differ between tofacitinib and other treatment modalities [19-21].

In this analysis, the safety profile of TOFA was acceptable, the frequency and spectrum of adverse events corresponded to data previously obtained in registration studies and clinical practice [10,14-16].

CONCLUSION

Tofacitinib as the first in class Janus-kinases inhibitor for UC therapy is a new promising alternative in UC treatment. Data of our study have demonstrated high efficiency in induction and maintenance therapy in patient with severe and moderate UC, resistant to basic and biological treatment. Treatment with TOFA was characterized by good tolerability. There were no new safety signals revealed. Further investigations are necessary to study long-term TOFA efficiency and safety in real clinical practice.

The authors declare no conflicts of interest.

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