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Effectiveness of upadacitinib and tofacitinib for one year in ulcerative colitis in real clinical practice

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ABSTRACT *AIM: to compare the one-year efficacy of upadacitinib (UPA) and tofacitinib (TOFA) for moderate to severe attacks of ulcerative colitis (UC).*

PATIENTS AND METHODS: a retrospective study included electronic medical records of patients who were initiated by UPA and TOFA for the treatment of UC between January 2022 and January 2023. In consisted of 74 patients (37 in each group). In all patients, demographic data were assessed, the severity of the attack was assessed using the partial Mayo index, laboratory data, endoscopy at the start of therapy (day 0), at the 8th, 26th and 56th week of therapy, the incidence and nature of adverse events for the period of therapy. In order to create comparable groups for endoscopic activity before the start of therapy, the method of optimal pairing was used.

RESULTS: endoscopic response was found in 10/34 (29%) patients in the TOFA group and 18/36 (50%) in the UPA group (p = 0.08) when assessing changes in the endoscopic picture between 8 and 0 weeks of therapy; 14/30 (47%) on TOFA and 13/29 (45%) on UPA (p = 0.9) between 26 and 8 weeks; 6/26 (23%) on TOFA and 13/28 (46%) on UPA (p = 0.09) between 56 and 26 weeks, respectively. In the TOFA and UPA groups, endoscopic remission by week 56 was achieved in 18/26 (69%) patients and 15/28 (54%) patients, respectively. Secondary outcomes data did not reveal a significant difference between the 2 groups regarding optimization of therapy or the need for surgery. Laboratory data, as well as the severity of UC, did not differ between groups at all time control points.

CONCLUSION: endoscopic response and remission were not statistically different between the two groups. A randomized, prospective study is needed to compare the efficacy of upadacitinib with tofacitinib.

KEYWORDS: *ulcerative colitis, tofacitinib, upadacitinib*

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

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INTRODUCTION

Ulcerative colitis (UC) is a chronic disease of the large intestine characterized by immune inflammation of its mucous layer [1]. Traditional treatment strategies, including drugs such as aminosalicylates, steroids and immunosuppressants are often ineffective [2]. The emergence of genetically engineered biological drugs (GEBD), in particular tumor necrosis factor inhibitors, has revolutionized the treatment of UC, but has not become universally effective, and therefore, there is still a need to explore new therapeutic possibilities [3]. In recent years, deeper knowledge of the pathophysiology of inflammatory bowel diseases (IBD) has led to a significant expansion of the therapeutic arsenal. Thus, JAK inhibitors are a family of small molecules that block one or more intracellular tyrosine kinases, including JAK-1, JAK-2, and JAK-3. They, in turn, play a key role in cytokine signaling and immune regulation [4]. JAK inhibition is a targeted approach to modulating immune responses involved in the pathogenesis of immune-inflammatory diseases. JAK inhibitors disrupt the signaling cascades of various pro-inflammatory cytokines involved in the pathogenesis of UC, such as interleukin (IL)-6, IL-12, IL-23, and interferon-gamma [5], which

has an anti-inflammatory effect, suggesting a new therapeutic strategy for patients with UC who have ineffective basic therapy or biologics [6].

In the Russian Federation, two JAK kinase inhibitors, upadacitinib (UPA) and tofacitinib (TOFA), have been approved for the treatment of moderate to severe UC [1]. TOFA, a non-selective inhibitor of JAK with a predominant effect on JAK-1 and -3 and, to a lesser extent, on JAK-2 and tyrosine kinase 2 (TYK-2), UPA is a selective inhibitor of JAK-1 [7]. It is worth noting that this class of drugs is notable for the rate of response to the therapy [9,10], the effect on a wide range of cytokines, and the lack of immunogenicity [8]. There are few clinical studies comparing the efficacy and safety of these agents in UC in the literature, and therefore, a comparative analysis with an assessment of clinical response, clinical remission, endoscopic response, endoscopic remission, and the safety of the therapy in patients with UC during 56 weeks of the treatment is relevant.

PATIENTS AND METHODS

A retrospective analysis of electronic medical records of patients who were initiated by UPA and TOFA for the treatment of UC in the period from January 2022 to January 2023 was carried out. Patients who developed complications requiring surgery during a short follow-up period, as well as patients who were treated with UPA and TOFA for indications unrelated to UC, were excluded from the analysis. Initially, the TOFA group consisted of 50 patients, UPA — 37.

Demographic indicators were evaluated in all patients included in the analysis, the severity of the attack was analyzed taking into account partial Mayo's index, laboratory parameters at the beginning of the therapy (day 0), on the 8th, 26th and 56th weeks of the therapy, the frequency and nature of adverse events during the therapy. The nature of previous therapy, including steroids, was evaluated with an analysis of the incidence of steroid dependence and steroid resistance. The agents were prescribed according to the standard scheme with an induction course and further maintenance therapy. For UPA, an induction course of 45 mg per day for 8 weeks, followed by a reduction in the dose to maintenance (30 or 15 mg per day, depending on the nature of the disease). For TOFA, the induction course is 20 mg per day for 8 weeks, followed by a dose reduction to a maintenance dose of 10 mg per day.

The primary endpoint was the achievement of an endoscopic response (according to Schroeder's mucosal assessment scale < 1 point) on week 8 of the therapy. It was determined using the following multi-level criteria based on available medical documentation: 1) partial assessment on Mayo's scale and 2) severity of the attack (according to Truelove-Witts criteria).

The secondary points were endoscopic response (on Schroeder's mucosal assessment scale < 1 point) and endoscopic remission (on Schroeder's mucosal assessment scale = 0) on weeks 26 and 56. In order to create comparable groups in endoscopic activity, the optimal matching method was used before the start of the therapy; no matching was performed for other initial characteristics. Thus, the analysis included 37 patients in each group with initially comparable endoscopic activity of the inflammatory process.

Statistical Analysis

Statistical data processing was performed in RStudio (R v. 4.3.2 (R CoreTeam, Vienna, Austria)) using the libraries dplyr, gtsummary, MatchIt, survival, survminer, ggplot2. All quantitative values are presented as medians, lower and upper quartiles (Me (Q1; Q3)), for some the minimum and maximum values (Min-Max) are indicated; the groups were compared using Wilcoxon's rank sum test for unrelated samples; the change in the values of the indicator within one group between 2 time-points was estimated using the Wilcoxon'stest for related selections. The qualitative results were given in the form of absolute and relative frequencies (*n* (%) or *n*/N (%)). The groups were compared using Pearson's c^2 with expected values > 10 for 2 × 2

tables and > 5 for multi-field tables; with lower values, precise two-way Fisher's test was used.

In order to assess the therapy survival, Kaplan-Meyer's curves were constructed (drug withdrawal was taken as the outcome). The differences were considered statistically significant at $p < 0.05$.

Characteristics of the Groups

An analysis of 74 patients in the TOFA and UPA groups was performed. The TOFA group included 18/37 (49%) women, 19/37 (51%) men, while the UPA group was dominated by males — 25/37 (68%) compared with women — 12/37 (32%); however, there were no statistically significant gender differences in the analyzed groups ($p = 0.2$). No significant differences were found in the groups with respect to other demographic indicators (Table 1). According to the extent of the lesion, the groups were comparable, and the majority of patients had a widespread inflammatory process. Also, 4/37 (11%) patients in both groups were diagnosed with extra-intestinal manifestations (musculoskeletal and dermal equally). Table 1 shows an analysis of the data on the presence of steroid dependence and steroid resistance in patients, and at the time of the therapy initiation, there were no statistically significant differences in the groups according to these indicators ($p = 0.6$ and $p = 0.5$, respectively) (Table 1).

It is worth noting that 17/37 (46%) patients to TOFA and 16/37 (43%) patients to UPA were bio-naive, while 1/37 (2.7%) patient in the TOFA group and 3/37 (8.1%) patients in the UPA group had a history of receiving various GEBD and had the ineffectiveness of 3 or more drugs. At the time of the therapy initiation, simultaneous steroid use was observed in the both groups, but it differed by almost half (27/37 (73%) in the TOFA group compared with 15/37 (41%) in the UPA group, $p = 0.005$) (Table 1). Thus, the analyzed group is more represented by patients with moderate UC, with a widespread inflammatory process, with the presence of steroid dependence or steroid resistance, as well as the ineffectiveness of previous therapy, including biological therapy.

Assessment of the Therapy Effectiveness in the Studied Groups on Week 8

On the 8th week after the treatment start, patients of both groups underwent an assessment of the induction course effectiveness. A comparative assessment of incomplete Mayo's index showed a significant decrease in the index value in both groups compared with the baseline data (Table 2). During a control endoscopic examination, endoscopic remission was achieved in 11/34 (32%) and 11/36 (31%) patients in both groups of TOFA and UPA, respectively ($p = 0.09$). Endoscopic response was registered in 10/34 (29%) patients to TOFA and 18/36 (50%) patients to UPA ($p = 0.08$).

When analyzing the laboratory data, the main indicators associated with the active inflammatory process were evaluated. When assessing the hemoglobin level in the TOFA group, there was a statistically significant increase in its dynamics from 113 (101; 123) g/l at the time of the therapy initiation to 121 (112;136) g/l after 8 weeks ($p = 0.027$); this trend persisted on the 26th and 56th weeks p (0–26 weeks) = 0.002 and p (0–56 weeks) < 0.001 (Fig. 1). It is worth noting that in the UPA group, when analyzing this indicator, it achieved a statistically significant improvement only by the 56th week of the therapy ($p = 0.004$).

As for the marker of inflammation with CRP control, the level of this indicator at the time of the therapy initiation exceeded normal values and amounted to 22 (8; 92) mg/l in the TOFA group and 17 (6; 25) mg/l in the UPA group ($p = 0.3$). By the time the induction course was completed, there was a decrease in CRP levels in the both groups, reaching values of 7 (2; 14) mg/l in the TOFA group and 4 (2; 6) mg/l in the UPA group ($p = 0.2$) (Fig. 2). There were no differences between the groups in other laboratory parameters.

Partial (incomplete) Mayo's index at the time of the therapy initiation exceeded normal values and amounted to 9 (0–9) points in the TOFA group and 5 (0–9) points in the UPA group. By the time the induction course was completed, both groups showed a decrease in Mayo's index, reaching values

Table 1. *Clinical and demographic data of patients*

Parameters	Tofacitinib, N = 37	Upadacitinib, N = 37	*p*-value
Gender Female Male	 18 (49%) 19 (51%)	 12 (32%) 25 (68%)	0.2
Age of debut, years	27 (23; 37) 18–62	31 (22; 45) 18–62	0.6
Steroid dependence	12 (32%)	14 (38%)	0.6
Steroid resistance	6 (16%)	4 (11%)	0.5
Biological drugs in the anamnesis	20 (54%)	21 (57%)	0.8
Infliximab in the anamnesis	13 (35%)	9 (24%)	0.3
Adalimumabin the anamnesis	7 (19%)	3 (8.1%)	0.2
Golimumab in the anamnesis	5 (14%)	2 (5.4%)	0.4
Vedolizumab in the anamnesis	2 (5.4%)	12 (32%)	**0.003**
Tofacitinib in the anamnesis	¾	5 (14%)	¾
Ustekinumab in the anamnesis	0	1 (2.7%)	1.0
The number of biological drugs in the anamnesis 0 1 2 3	 17 (46%) 13 (35%) 7 (19%) 0	 16 (43%) 13 (35%) 5 (14%) 3 (8.1%)	0.4
CMV in the anamnesis	5 (14%)	3 (8.1%)	0.7
Severity of the attack (as per Truelove-Witts's criteria) Mild Moderate Severe	 6 (16%) 23 (62%) 8 (22%)	 12 (32%) 17 (46%) 8 (22%)	0.2
Partial assessment on Mayo's scale	6 (5; 7) 3–9	5 (4; 7) 2–8	0.11
Extra-intestinal manifestations	4 (11%)	4 (11%)	1.0
Extent of the lesion Left-sided Total	 8 (22%) 29 (78%)	 5 (14%) 32 (86%)	0.4
Endoscopic activity (according to Schroeder) Minimal Moderate Pronounced	 3 (8.1%) 12 (32%) 22 (59%)	 5 (14%) 6 (16%) 26 (70%)	0.2
Hemoglobin, g/l	113 (101; 123) 51–151	116 (104; 131) 84–153	0.3
Leukocytes, 10^9/l	9.5 (6.7; 11.7) 4.4–24.0	7.7 (6.4; 11.0) 4.0–16.6	0.2
Thrombocytes, 10^9/l	376 (339; 494) 170–777	365 (310; 517) 136–753	0.4
Albumin, g/l	36 (31; 40) 21–46	37 (32; 40) 28–45	0.6
Fibrinogen, g/l	3.50 (3.08;4.20) 2.10–5.80	3.69 (3.20;4.22) 2.22–4.93	0.8
CRP, mg/l	22 (8; 92) 0–441	17 (6; 25) 1–111	0.3
ST Induction	27 (73%)	15 (41%)	**0.005**

Note: CMV — cytomegalovirus infection, CRP — c-reactive protein, ST — steroids

of 3 (0–9) points in the TOFA group and 2 (0–9) points in the UPA group (Fig. 3). The tendency to normalize the level of Mayo's index was also found on the 26th and 56th weeks of the therapy equally in the both groups.

Taking into account the continued activity of the inflammatory process, on the 8th week of the therapy, 23/34 (67%) patients in the TOFA group required continued therapy with an induction dosage of 20 mg per day. In the UPA group, 25 (69%)

Table 2. *Data on the effectiveness of therapy in the TOFA and UPA groups 8 weeks after the start of therapy*

Parameters	Tofacitinib, N = 34	Upadacitinib, N = 36	*p*-value
Severity of the attack (as per Truelove-Witts's criteria)			**0.008**
Mild	19 (56%)	30 (86%)	
Moderate	11 (32%)	5 (14%)	
Severe	4 (12%)	0	
Endoscopic activity (as per Schroeder)			0.2
Remission	11 (32%)	11 (31%)	
Minimal	10 (29%)	18 (50%)	
Moderate	9 (26%)	4 (11%)	
Pronounced	4 (12%)	3 (8.3%)	

Table 3. *Dosage of drugs in the TOFA and UPA groups 8 weeks after the start of therapy*

Parameters	Upadacitinib		Tofacitinib	
Dosage of the drug	15 mg	30 mg	10 mg	20 mg
	19 (53%)	17 (47%)	12 (35%)	22 (65%)

patients were switched to a maintenance dosage of 30 mg per day (Table 3).

Results on Week 26 of the Therapy

Among patients in the TOFA and UPA groups, endoscopic remission on week 26 was achieved in 10/30 (33%) patients and 12/29 (41%) patients, respectively, while endoscopic improvement was achieved in 14/30 (47%) ones versus 13/29 (45%) patients, respectively, $p = 0.9$. The groups did not differ in the other indicators on week 26 (Table 4).

Results on Week 56 of the Therapy

In the groups of patients receiving TOFA or UPA, 26 and 28 people remained, respectively, after excluding those who required a change in therapy or colectomy within a year after the start of the therapy (Table 5).

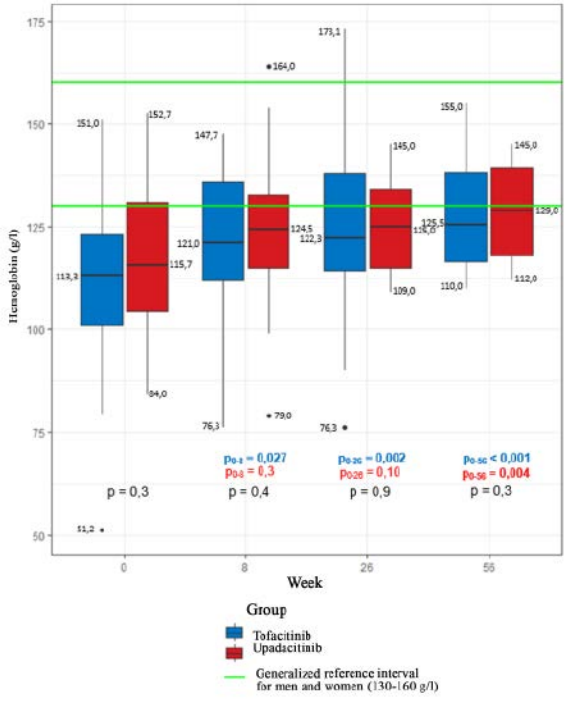

Figure 1. *Scale diagram and comparison of hemoglobin indices in the TOFA and UPA groups at 0, 8, 26, 56 weeks of therapyy*

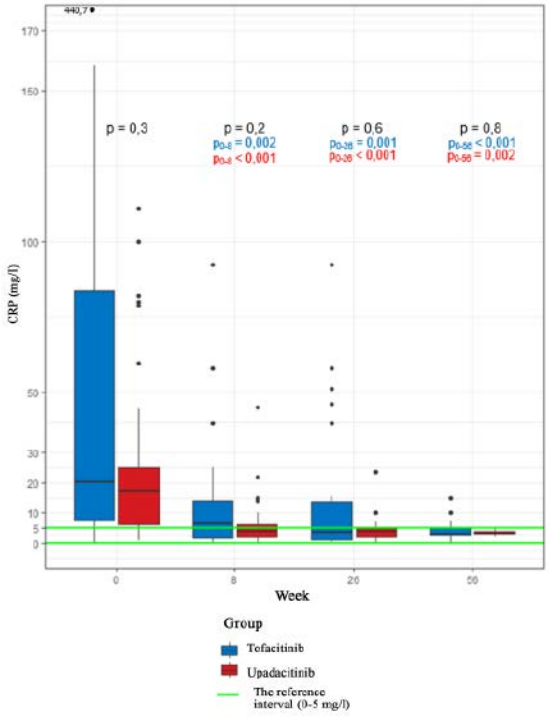

Figure 2. *A diagram of the scope and comparison of CRP indicators in the TOFA and UPA groups at 0, 8, 26, 56 weeks of therapy*

Table 4. *Data on the therapy effectiveness in the TOFA and UPA groups after 26 weeks from the start of the therapy*

Parameters	Tofacitinib, N = 30	Upadacitinib, N = 29	*p*-value
Severity of the attack (as per Truelove-Witts's criteria)			0.3
Mild	19 (63%)	24 (83%)	
Moderate	8 (27%)	4 (14%)	
Severe	3 (10%)	1 (3.4%)	
Endoscopic activity (as per Schroeder)			0.9
Remission	10 (33%)	12 (41%)	
Minimal	14 (47%)	13 (45%)	
Moderate	4 (13%)	3 (10%)	
Pronounced	2 (6.7%)	1 (3.4%)	

Table 5. *Data on the effectiveness of therapy in the TOFA and UPA groups after 56 weeks from the start of therapy*

Parameters	Tofacitinib, N = 26	Upadacitinib, N = 28	*p*-value
Severity of the attack (as per Truelove-Witts's criteria)			1.0
Mild	25 (96%)	27 (96%)	
Moderate	1 (3.8%)	1 (3.6%)	
Endoscopic activity (as per Schroeder)			0.1
Remission	18 (69%)	15 (54%)	
Minimal	6 (23%)	13 (46%)	
Moderate	1 (4%)	0	
Pronounced	1 (4%)	0	

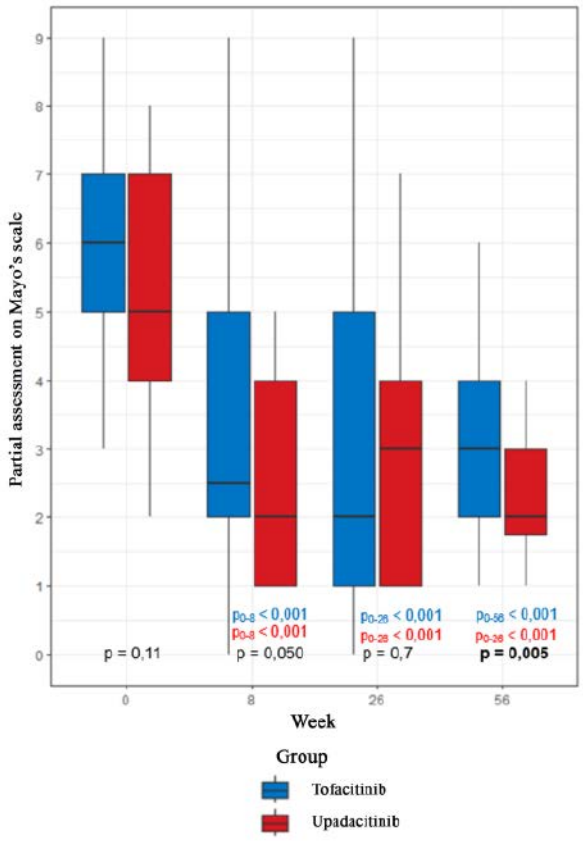

Figure 3. *Comparison of the partial index on the Mayo scale in the TOPH and UPA groups*
Note: Partial (incomplete) Mayo's index without endoscopy data: 0–1 point clinical remission (with the parameter "rectal bleeding" = 0 point); 1–2 points mild attack; 3–5 points moderate attack; ⩾ 6 points: severe attack

In the TOFA and UPA groups, endoscopic remission was achieved in 18/26 (69%) patients and 15/28 (54%) patients, respectively. Also, endoscopic improvement was noted in the TOFA group in 6/26 (23%) cases, and 13/28 (46%) cases in the UPA group, respectively, on week 56 (p = 0.09). The analysis of secondary results did not reveal significant differences between the 2 groups regarding changes in the therapy or the need for surgery (Table 5). There were no differences in the laboratory parameters between the groups on week 56 of the therapy.

It is important to note that during the analyzed period, due to the ineffectiveness of the therapy, 5/37 (14%) patients required surgical treatment, (3/37 (8%) patients were bio-naïve to TOFA) and in 2/37 (5.4%) cases to UPA (p = 0.4). When analyzing the rate of adverse events in the groups, 2 cases were identified in the UPA group: 2 cases of herpes infection. Both adverse events were recorded at an induction dose of 45 mg per day (Table 6).

The analysis of the primary therapy ineffectiveness showed statistically significant differences between the groups of TOFA 11 (30%) and UPA 4 (11%) (p = 0.081). When analyzing the overall survival of the therapy during the year (Fig. 4), there were no statistically significant differences

Table 6. *Comparison of indicators of the development of NS and colectomy in the groups of UPA, TOFA*

Parameters	Tofacitinib, N = 37	Upadacitinib, N = 37	*p*-value
Primary inefficiency	11 (30%)	4 (11%)	**0.081**
AE* (herpes infection)	0	2 (5.4)	0.5
Loss of response	2 (5.4%)	1 (3.1%)	1.0
Colectomy	5 (14%)	2 (5.4%)	0.4

Note: AE — adverse events

between TOFA and UPA (p = 0.66). In the both groups, the median survival was not reached. It is worth noting that all cases were complete (there were no censored cases). Thus, by week 56, the drug was retained in 26/37 (70%) patients in the TOFA group and 28/37 (76%) patients in the UPA group (p = 0.6).

DISCUSSION

An analysis of the data obtained showed a higher frequency of achieving an endoscopic response and remission to the UPA therapy on the 26th and 56th weeks for UC. The effectiveness in the treatment was higher in the UPA group, despite the greater number of previous biological drugs. The data suggest that UPA may be more effective in achieving both an endoscopic response and remission of UC during 1 year of the therapy compared with TOFA, although these results need to be confirmed in larger prospective randomized trials.

Similar results were obtained by other researchers. A recent study involving 81 patients treated with upadacitinib showed significantly higher chances of achieving clinical remission without steroids (OR 3.01, 95% CI 1.39–6.55) compared with TOFA; however, no differences in endoscopic response or remission were detected [12]. Boneschansker et al. compared the effectiveness of TOFA and UPA for the induction of remission in moderate and severe UC attacks. Using the data from electronic medical records, the study included 119 patients with UC treated with TOFA and 35 patients with UC treated with upadacitinib. UPA demonstrated efficacy with a higher proportion of patients who achieved clinical remission (40% vs. 18%, p = 0.006) and a lower rate of non-response (9% vs. 34%, p = 0.004) compared with TOFA [11]. However, the study considered only the induction phase of the treatment for JAK, since the follow-up was 8–10 weeks. In a study by Pannacionne et al., the effectiveness of the treatment of moderate and severe UC was studied using a network meta-analysis, which also included UPA and TOFA. The authors found that UPA was the most effective treatment for both induction and maintenance of clinical response, clinical remission, and endoscopic improvement in patients with moderate to severe UC attack, regardless of prior biological therapy. In terms of side effects, there was no significant difference between the treatment groups [13]. Another systematic review and network meta-analysis in several countries, which was conducted by Juan S. Lasa et al., showed that UPA was significantly superior to other drugs for inducing clinical remission and achieving endoscopic remission [14].

We found a lower use of intravenous steroids, as well as a lower frequency of colectomies for the UPA group compared to the TOFA group for 12 months. It is worth noting that serious adverse events, such as herpes infection in two patients, were reported against the background of the UPA therapy. Against the background of the TOFA

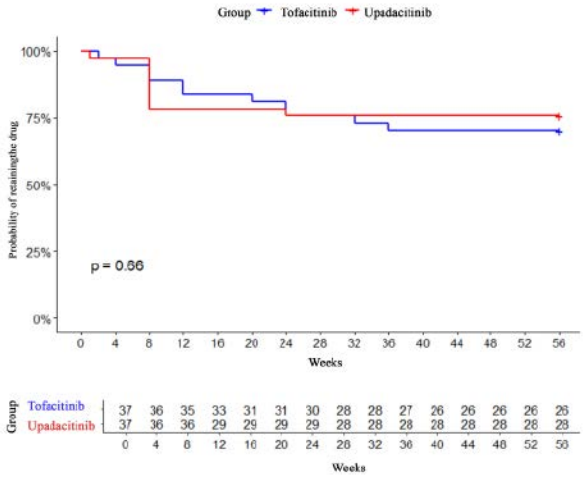

Figure 4. *Treatment survival curves during the year*

therapy, no serious AE were noted, which corresponds to the data of previously described studies in real clinical practice. [26,27] It should be noted that in this group there were fewer patients who underwent therapy in combination with steroids, which may be due to the fact that initially the UC attack in this group was less severe. Recent papers emphasize the importance of long-term safety assessments of JAK inhibitors [15]. This is especially relevant in light of new data suggesting potential differences in the safety profiles of various JAK inhibitors [16]. Information regarding the safety of JAK was mainly obtained in studies of patients with rheumatoid arthritis [17–20]. The possibility to extrapolate safety data from rheumatoid arthritis studies on UC is often questioned due to the different etiopathogenesis of the diseases. Moreover, a recent meta-analysis did not show an increased risk of venous thromboembolism (VTE), pulmonary embolism, and deep vein thrombosis in patients with immune-mediated inflammatory diseases taking JAK inhibitors [21]. At the same time, new data from observational studies emphasize the importance of individual approaches to treatment [22]. In phase III clinical trials of upadacitinib, the incidence of nasopharyngitis was 5–14%, arthralgia — 2–6%, headaches — 2–3%, and serious adverse events — 3–7%, depending on the treatment regimens. 4% of patients developed shingles, and 1% developed non-melanoma skin cancer. 1% of patients developed VTE, and none of the patients had serious adverse cardiovascular events in the U-ACHIEVE study [23].

The differences observed in the results between the groups of patients undergoing the therapy with upadacitinib or litofacitinib emphasize the importance of understanding the differences in the mechanisms of action of drugs. A possible explanation for the clinical superiority of upadacitinib over tofacitinib is that the selectivity of upadacitinib to JAK1 allows the use of higher dosages without affecting safety [24]. It should be noted that in almost all online meta-analyses conducted to date, higher doses of upadacitinib have been more effective than other drugs [12,13]. The dose-response relationship for JAK inhibitors has been described previously in other immunoinflammatory diseases [25].

CONCLUSION

Upadacitinib compared with tofacitinib showed no significant differences between groups in the treatment of moderate and severe ulcerative colitis attacks. A distinctive feature of our study was a comprehensive assessment of the clinical and endoscopic results of the therapy. Endoscopic response and remission did not differ between the two groups. Given the small number of patients in each study group, and a retrospective analysis of the data, the results should be considered preliminary rather than final. A randomized prospective trial is needed to compare the efficacy of upadacitinib with tofacitinib for the treatment of UC.

AUTHORS CONTRIBUTION

Concept and design of the study: *Tatiana A. Baranova*
Collection and processing of material: *Tatiana A. Baranova, Kristina A. Sergeeva*
Statistical processing: *Maria A. Ignatenko*
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