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Experience with upadacitinib using in treatment of ulcerative colitis in real clinical practice (pooled data)

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ABSTRACT *AIM: to evaluate the efficacy and safety of Upadacitinib (UPA) — an oral selective janus-kinase 1 (JAK1) inhibitor in real clinical practice for the treatment of ulcerative colitis.*
PATIENTS AND METHODS: in 2021–2023, as part of a multicenter, prospective, open, uncontrolled study, forty-six patients with mild-to-moderate ulcerative colitis (UC) were included (male: female ratio = 16:30, mean age 34 ± 3.1 years). Extraintestimal manifestation (EIM) initially was diagnosed in 7 patients (jonts and skin). Indications for UPA administration were: resistance to corticosteroids, ineffectiveness of basic and previously biologics treatment. The effectiveness was evaluated using the Mayo score, the Schroeder endoscopic index, as well as dynamic of hemoglobin, CRP and ESR. UPA was prescribed in accordance with the instructions for use: 45 mg for induction and 15/30 mg for maintenance therapy. The evaluation criteria were: the frequency of early primary clinical response within 1 week, the rate of clinical response/remission and endoscopic response/remission, the changes of EIM and the rate of adverse events (AE) in 8 weeks of induction and in 48 weeks of maintenance treatment.
RESULTS: all patients completed the induction course of UPA for 8 weeks. Early clinical response within 1 week with reduction of stool movements to 3 or less per day, absence of blood in stool was achieved in 25 (54.3%) patients. Clinical remission developed in 34 (73.9%) and clinical response in 3 (6.5%) of patients at the end of induction. Normal CRP and ESR levels and endoscopic remission was detected in 24 (52.2%) of patients in 8 weeks. The severity of EIM at the end of induction decreased in 4/7 (57.1%). One case of herpes zoster was registered as serious AE with drug withdrawal within the induction. The results of UPA maintenance therapy at week 48 were assessed in 16 patients. Clinical remission was maintained in 14/16 (87.5%) patients, with 11/16 (68.7%) of them receiving UPA at a maintenance dose of 30 mg per day, and 3/16 (31.3%) patients receiving 15 mg per day. In 2/16 cases (12.5%), clinical activity was maintained. Endoscopic remission developed in 10/16 (62.5%) patients, which was expressed in a decrease in the endoscopic Schroeder index decreases to ⩽ 1 points, with 8 patients receiving a maintenance dose of 30 mg per day, and 2 patients receiving 15 mg per day. In the remaining patients, 4/16 (25%) (3 — UPA 30 mg, 1 — UPA 15 mg) cases had mild inflammation, and 2/16 (12.5%) (UPA 15 mg) had moderate activity.
CONCLUSIONS: in real practice, UPA allows to achieve an early clinical response, clinical and endoscopic remission after induction with good tolerability and safety in UC patients who refractory to corticosteroids and biologics.

KEYWORDS: *ulcerative colitis, inflammatory bowel disease, upadacitinib*

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

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INTRODUCTION

Ulcerative colitis (UC) is a chronic inflammatory disease characterized by diffuse immune inflammation of the large intestine mucosa and almost mandatory (95%) involvement in the pathological process of the rectum [1,2]. Despite a significant arsenal of drugs, the treatment of patients is not always successful. Achievement of short- and long-term control of disease activity remains

a difficult task, which reduces the quality of life of patients [2,3,4]. Basic therapy (aminosalicylates, steroids, immunosuppressants), as well as therapy with genetically engineered biological drugs (GEBD), are ineffective in about 2/3 of cases for inducing and maintaining UC remission during the first year of treatment [5,6,7,8], which determines the need for new therapeutic options. The therapeutic range of drugs used for the treatment of UC, in addition to basic drugs and GEBD, has recently included a class of janus-kinase (JAK) inhibitors that block the transmission of pathological signals at the intracellular level [9]. Upadacitinib (UPA) is an oral low-molecular-weight drug that selectively inhibits JAK1, has a rapid effect, a short half-life, and a lack of immunogenicity [10], which distinguishes it from monoclonal GEBD. The drug is approved for patients with moderate to severe forms of UC and Crohn's disease, with ineffectiveness or intolerance to basic drugs and GEBD [11].

To evaluate the efficacy and safety of UPA in UC, two key registration studies U-ACHIEVE (UC1) and U-ACCOMPLISH (UC2) of an 8-week induction course at a dose of 45 mg/day and a further study U-ACHIEVE (UC3) were conducted to evaluate the maintenance therapy of UPA at doses of 30 and 15 mg per day for 52 weeks [11].

These studies demonstrated a rapid clinical response and the possibility of achieving clinical and endoscopic remission already during the induction course, as well as during maintenance therapy. However, it is important to remember that real patients differ significantly from the cohort of patients selected for randomized trials according to strict inclusion/exclusion criteria. Therefore, it is very important to evaluate the effectiveness of drugs (in this case, UPA) in real clinical practice, including to obtain more complete data on the criteria for selecting patients and specifying the profile of patients for the treatment with UPA.

AIM

To evaluate the efficacy and safety of an oral selective inhibitor of janus-kinase 1 (JAK 1) in real clinical practice in the treatment of UC.

PATIENTS AND METHODS

Characteristics of the study: multicenter, prospective, open, uncontrolled study. *Patients' characteristics:* the studied group included 46 patients with active UC who received UPA therapy from June 2021 to June 2023 in the 3 research centers: National Medical Research Center named after A.N. Ryzhykh of the Health Ministry of Russia, Moscow Regional Scientific Research Clinical Institute named after M.F. Vladimirsky, Moscow Clinical Research Center named after A.S. Loginov of Moscow Health Department.

Demographic, clinical, laboratory, and endoscopic data were evaluated. The following characteristics were analyzed: the severity, extent, and nature of the course of UC, endoscopic activity, the presence of complications, and the presence and type of extra-intestinal manifestations. The previous treatment (therapy with 5-ASA drugs, immunosuppressants, steroids, GEBD) was also analyzed. UPA was prescribed according to the standard regimen: for induction, 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 course) [1]. The following criteria were used to evaluate the effectiveness of the therapy: early clinical response (reduction or disappearance of clinical symptoms after the first week of the treatment); clinical response, clinical remission, dynamics of laboratory parameters (hemoglobin, ESR, CRP), dynamics of the endoscopic picture (response/remission), dynamics of EIM. The response to the treatment was assessed as a decrease in the number of points on Mayo's scale by at least 30%. The lack of clinical improvement, discontinuation of UPA therapy, and surgical treatment were defined as ineffective therapy.

Statistical Analysis

The statistical analysis was performed using the StatTech v. 4.0.4 software (Stattech LLC, Russia). Quantitative indicators were evaluated for compliance with the normal distribution using Shapiro-Wilk's test. Quantitative indicators with a normal distribution were described using arithmetic averages (M) and standard deviations (SD). In the absence of a normal distribution, quantitative data were described using the median (Me); lower and upper quartiles (Q1; Q3). Categorical data were described with absolute values and percentages. When comparing three or more dependent totalities, nonparametric Friedman's criterion was used with posteriori comparisons using Conover-Iman'stest with Holm's correction for quantitative quantities. Categorical features were compared by Pearson's c^2. The differences were considered statistically significant at $p < 0.05$. To visualize the changes in quantitative indicators in dynamics, an illustration was carried out using scale diagrams.

RESULTS

Forty-six patients received UPA therapy, of whom 30 (65.2%) were women, the average age of the patients was 34 ± 3.1 years. Most patients included in the study (87.0%) had a continuous course of UC, a widespread (89.1%) inflammatory process, and clinical activity (severity) of the disease according to partial Mayo index of ⩾ 6 points (54.3%), while the remaining 45.7% had Mayo's index of 5 or less points. 82.6% of patients had high Schroeder's endoscopic activity at the time of initiation of the therapy, while 17.4% had moderate and minimal activity. Also, 7 (15.2%) patients were diagnosed with EIM: 5 (10.9%) patients had spondyloarthritis with lesions of the spine and/or peripheral joints, and 2 (4.3%) patients had lesions of the skin and mucous layers (Table 1).

Table 2 shows the agents used to treat UC before patients were included in the study. Prior to the start of the study, most patients received 5-ASA drugs, immunosuppressants, and steroids. Steroid dependence was noted in 45.7% of patients, and resistance to steroid therapy in 19.6%. More than half of the patients, namely 30 (65.2%) patients, had previously received various GEBD, of whom 21 patients took two or three drugs. Vedolizumab and infliximab were used most frequently by 16 (34.8%) patients and 14 (30.4%) patients, respectively. The main reason for drug withdrawal was the loss of therapeutic effect, less often — adverse events. In addition, some patients stopped taking medications for administrative reasons.

Table 1. *Clinical characteristics of patients before inclusion in the study*

Indicators	All patients, N = 46
Gender	
Male	16 (34.8)
Female	30 (65.2)
Age, years	34 ± 3.1
Nature of the disease course	
Acute	1 (2.2)
Chronic relapsing	5 (10.9)
Chronic continuous	40 (87.0)
Extent of the lesion	
Left-sided	5 (10.9)
Total	41 (89.1)
Endoscopic activity before the start of the therapy (as per Schroeder)	
Pronounced	38 (82.6)
Moderate	4 (8.7)
Minimal	4 (8.7)
Impurity of blood in stool before starting the therapy	33 (71.7)
Mayo's Index before starting the therapy	7.3 ± 2.1
Extra-intestinal manifestations	7 (15.2)
Musculoskeletal manifestations	5 (10.9)
Skin and mucous layer lesion	2 (4.3)

Thus, the studied group is represented by patients with moderate to severe UC, with a widespread inflammatory process, high endoscopic activity, with the presence of steroid dependence / steroid resistance, as well as the ineffectiveness of previous therapy, including GEBD. All patients were prescribed UPA at an induction dosage of 45 mg/day.

Early response to the therapy was assessed after one week. As part of the assessment of the early response, clinical manifestations such as stool frequency and the presence of blood in stools were indicated. The blood in stools disappeared in 25 (54.3%) patients during the first 7 days of the

Table 2. *Characteristics of treatment before inclusion in the study*

Drugs	Number of patients, *n* (%)	Reason for drug withdrawal
5-АСК 5-ASA	45 (97.8%)	
Immunosuppressants	25 (54.3%)	Inefficiency/AE
Steroids		
Steroid dependence	21 (45.7%)	
Steroid resistance	9 (19.6%)	
GEBD		
Infliximab	14 (30.4%)	Primary non-response/loss of response
Adalimumab	10 (21.7%)	Primary non-response/loss of response
Golimumab	4 (8.7%)	Primary non-response/loss of response
Vedolizumab	16 (34.8%)	Primary non-response/loss of response
Ustekinumab	4 (8.7%)	Primary non-response/loss of response
Tofacitinib	8 (17.4%)	Primary non-response/loss of response
Bio-naive patient	16 (34.8%)	
Induction by systemic GC at the time of initiation of UPA therapy	25 (54.3%)	

Table 3. *Assessment of early clinical response: dynamics of blood in stool*

Indicators	Stages of observation			p
	Before starting the therapy	Day 3	Day 7	
Blood impurities in stool	33 (71.7)	21 (45.7)	8 (17.4)	< 0.001

therapy, and the stool frequency decreased from 6 (4; 10) to 3 (3; 4) times a day ($p < 0.001$ in both cases) (Fig. 1, Table 3).

As part of monitoring the effectiveness of the induction therapy with UPA, laboratory data were evaluated on week 8 of the treatment. An analysis of changes in hemoglobin levels in dynamics showed that its median at the time of initiation of the therapy in the patients was 106 (100; 123) g/l, which corresponds to mild anemia. During 7 days of the treatment, a positive trend was noted, and the indicator was 114 (101; 128) g/l. By the end of the induction course, there was a significant increase to 130 (123; 145) g/l and its normalization compared to the baseline level (p 0.001) (Fig. 2).

As for markers of inflammation with controlled ESR and CRP, the median of these indicators at the time of the treatment initiation exceeded normal values (38.5 (26; 51) mm/h and 21.5 (10; 70) mg/l, respectively). It is noteworthy that a statistically significant (p 0.001) decrease in these indicators was noted already on day 3 of the therapy. Thus, the ESR decreased to 19.5 (10; 37) mm/h and a further decrease was noted, reaching a value of 12

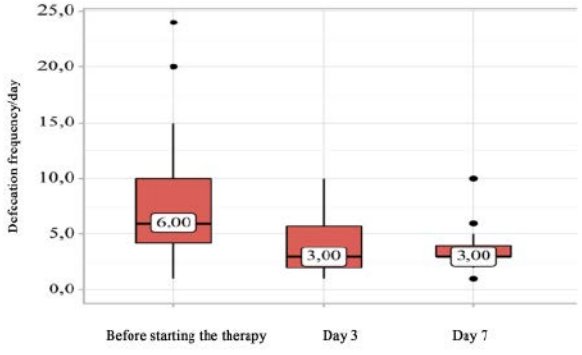

Figure 1. *Stool frequency*

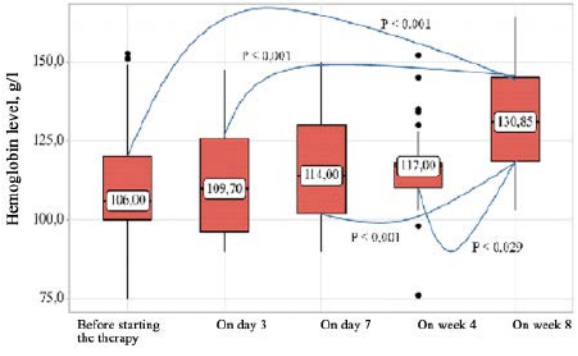

Figure 2. *Hemoglobin during the treatment*

(7; 18) mm/h by the end of the induction course (Fig. 3).

The CRP was 5 (1; 13) mg/L on day 3, 11.5 (5; 15) mg/L on day 7, and in 8 weeks after the start of the therapy, it had a normal mean value of 3.6 (1; 4) mg/l ($p < 0.001$ compared with the initial level). Evaluation of these laboratory values allows us to conclude a decrease in the activity of the inflammatory process and normalization of laboratory parameters (Fig. 4).

All 46 patients completed the induction course. Clinical remission was noted in 34 (73.9%) cases on week 8 of the therapy, 3 (6.5%) patients achieved a clinical response, and 9 (19.6%) did not show positive clinical changes. It is worth noting that by the end of the induction course, all the patients had undergone an endoscopy to assess the degree of healing of the large intestine mucosa. Most patients with clinical remission had endoscopic remission on week 8 of the therapy (24 (52.2%) patients), and 13 (28.3%) patients had minimal endoscopic activity. Primary inefficiency was found in 9 (19.6%) cases, in 4 (8.7%) cases with moderate activity, and in 5 (10.9%) cases with pronounced activity of the inflammatory process, which caused the discontinuation of the therapy (Table 4).

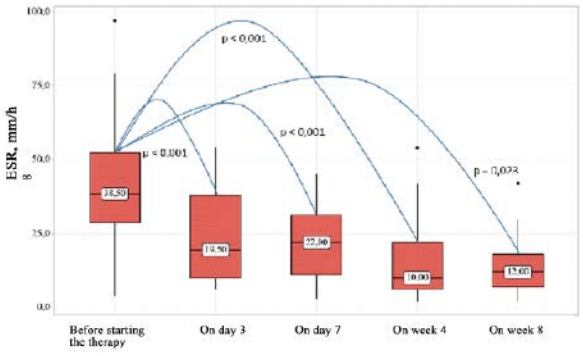

Figure 3. *ESR during the treatment*

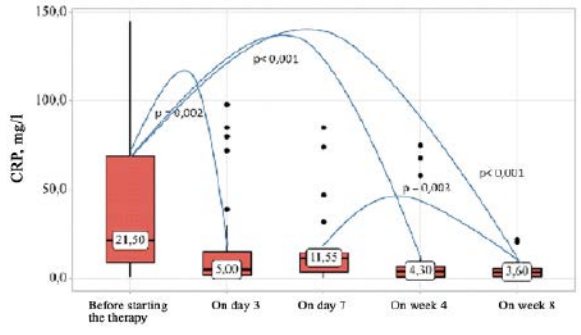

Figure 4. *Box plot illustrating the dynamics of CRP during the treatment*

Table 4. *Clinical and endoscopic evaluation of therapy effectiveness after 8 weeks*

Indicators	All patients, N = 46
Clinical activity Clinical remission Clinical response No response	34 (73.9) 3 (6.5) 9 (19.6)
Endoscopic activity (as per Schroeder) Endoscopic remission Minimal activity Moderate activity Pronounced activity	24 (52.2) 13 (28.3) 4 (8.7) 5 (10.9)

The clinical and endoscopic efficacy of the maintenance therapy was evaluated after 48 weeks in 16 patients, 11 of whom received a maintenance dose of 30 mg per day, and 5 patients received 15 mg per day. Endoscopic remission was noted in 10 (62.5%) of the 16 patients, while 8 patients received a maintenance dose of 30 mg per day and 2 patients received 15 mg per day. Of the remaining patients, in 4 (3 — UPA 30 mg, 1 — UPA 15 mg) cases, minimal inflammatory activity was noted, in 2 (UPA 15 mg) cases — moderate activity (Table 5).

On week 8 from the start of the therapy, a decrease in the severity of EIM was noted in 4 out of 7 patients. It is important to note that, in general, the patients tolerated the drug well. The reason for drug withdrawal as part of the induction course was an AE of herpes zoster infection in 1 (2.2%) patient.

DISCUSSION

This study has shown the high effectiveness of UPA in the treatment of patients with steroid dependence/steroid resistance, inefficiency or intolerance by various groups of GEBD. In most patients, a clinical response was achieved with a decrease in stool frequency to 3 or less per day

Table 5. *Clinical and endoscopic evaluation of therapy effectiveness after 48 weeks of treatment*

Indicators	All patients, (N = 16)	UPA therapy, 30 mg/day, (N = 11)	UPA therapy, 15 mg/day, (N = 5)
Clinical activity			
Clinical remission	14 (87.5)	11 (100)	3 (60.0)
No response	2 (12.5)	0	2 (40.0)
Endoscopic activity (as per Schroeder)			
Endoscopic remission	10 (62.5)	8 (72.7)	2 (40.0)
Minimal activity	4 (25.0)	3 (27.3)	1 (20.0)
Moderate activity	2 (12.5)	0	2 (40.0)

and the disappearance of blood in stools during the first week of the therapy. The speed of achieving a clinical and laboratory response in our study correlates with the literature data [12,13,14], where there was a significant improvement in the clinical manifestations of UC on therapy compared with placebo as early as day 3 of taking the drug. Monitoring of laboratory data showed a statistically significant decrease in indicators already at the early stages of the therapy and the maintenance of reliably low levels of inflammatory markers throughout the induction course, which is comparable with the data from published studies. Thus, the analysis of our data showed that the initial ESR level was 38.5 (26; 51) mm / h, and by the end of the induction course 12 (7; 18) mm / h, and CRP — 21.5 (10; 70) mg / l (more than 4 norms), after 2 months — 3.6 (1;4) mg / l. Positive changes with the achievement of clinical remission was noted in the vast majority of patients (73.9%) at the end of the induction course. It is worth noting that 9 patients showed ineffectiveness of the therapy while maintaining clinical symptoms, which required a change in treatment tactics and switching to another type of GEBD. By the end of the induction course, half of the patients had achieved endoscopic remission. When evaluating the effectiveness of the maintenance therapy for 48 weeks, endoscopic remission was noted in 10 out of 16 patients who underwent endoscopic monitoring. At the same time, a dose-dependent effect developed; in particular, the retaining of endoscopic remission was observed mainly in patients receiving a high maintenance dose of UPA 30 mg and only in 2 patients on a dosage of UPA 15 mg. This corresponds to the results obtained in the studies on identifying the effectiveness of the induction and maintenance therapy with UPA (U-ACCIEVE and U-ACCOMPLISH) [15]. Thus, the results of the U-ACHIEVE study showed a higher incidence of clinical remission on week 52 in patients receiving UPA at a dose of 30 mg than UPA at a dose of 15 mg (52% and 42%, respectively). In all patients with preserved inflammatory activity who received a dose of UPA 15 mg, further therapy was continued with an increase in the dose of the drug to 30 mg per day with further monitoring. In patients with active inflammation, according to a control examination on the therapy with 30 mg of UPA, its ineffectiveness was established and indications for a change of therapy were given.

The analysis data of EIM in our study show that the most common manifestation at the initial level was joint manifestations, a decrease in the severity of which was noted as part of the induction course against the background of UPA 45 mg. There was no worsening of the EIM symptoms during the entire follow-up period. Analyzing the results based on the frequency and nature of AE, it is worth noting that the safety profile in our study was satisfactory. In various clinical studies [15,16,17] evaluating the effectiveness of UPA, a safety profile is systematically demonstrated according to various criteria. The most frequently reported AE described in the literature include herpes zoster infections, which is confirmed by data from an online meta-analysis [18], which showed that, in general, janus-kinase and UPA inhibitors, in particular, at a dose of 45 mg per day, increase the risk of herpes zoster. So, the vaccination against herpes zoster should be recommended as a preventive measure.

CONCLUSION

UPA is a selective type 1 janus-kinase inhibitor for oral administration, currently approved for the treatment of a number of immune-mediated inflammatory diseases, including rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, UC and CD. The presented data from real clinical practice demonstrate the effectiveness of the drug for the induction and maintenance of remission in patients with moderate to severe forms of UC, with the ineffectiveness of basic therapy and GEBD therapy. The treatment is characterized by a rapid onset of clinical response and good tolerability. Further studies of actual practice are needed to assess the survival of therapy with the inclusion of a larger number of patients and a longer follow-up period.

AUTHORS CONTRUBUTION

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