

EFFECTIVENESS AND SAFETY OF UPADACITINIB – DATA FROM REAL CLINICAL PRACTICE IN BULGARIA

R. Moraliyska, S. Bogdanova, St. Dimitrov, G. Gerganov, St. Hristova, Ts. Georgiev, T. Shivacheva

Rheumatology Clinic, „Sv. Marina“ Hospital, Medical University – Varna

Abstract. Objectives: The aim of the study was to assess the therapeutic efficacy and safety of upadacitinib in rheumatoid arthritis (RA) patients with moderate to high disease activity in real-world clinical practice and to identify predictors of therapeutic success. **Materials and methods:** A retrospective single-center study was performed in RA patients treated with upadacitinib 15 mg daily. Demographic and clinical indicators were analyzed. The effectiveness and safety of the medication were evaluated over a six-month period. Disease activity was assessed with index-based scores. The primary endpoint was defined as low disease activity over a six-month treatment period with upadacitinib 15 mg/day ($\text{DAS28CRP} \leq 3.2$, $\text{CDAI} \leq 10$ and $\text{SDAI} \leq 11$). **Results:** 41 patients were included, mean age 56.56 years (± 13.4), with long-standing RA (8 years ± 5.8), mostly female (80.5%). 19.5% of them were obese ($\text{BMI} \geq 30 \text{ kg/m}^2$), 80.5% had osteoarthritis and 58.5% – hypertensive disease. Erosive arthritis was observed in 41.5% of patients and 61% had functional class III motor deficit. „Bio-naïve“ were 58.5%, the rest had previous experience with biologic therapy. Upadacitinib was used as monotherapy in 90% of patients and in combination with Methotrexate in 10%. There was a significant reduction in the painful and swollen joint counts, VAS and CRP six months after starting treatment with upadacitinib. Low disease activity was achieved by a significant proportion of patients ($\text{DAS28CRP} - 70.7\%$, $\text{CDAI} - 60.5\%$, and $\text{SDAI} - 63.2\%$). Therapeutic outcome was not determined by demographics, clinical factors, comorbidities, or prior biologic treatment. Increase in liver enzymes ($n = 3$), decrease in hemoglobin levels ($n = 2$), and urinary tract infection ($n = 2$) were the adverse events recorded over the six-month treatment period. One patient deceased due to COVID 19. **Conclusion:** A significant proportion of RA patients on treatment with upadacitinib 15 mg were able to achieve the therapeutic target in real clinical settings. No predictors of therapeutic efficacy were found. The registered side effects do not differ from the safety profile of the medication.

Key words: upadacitinib, rheumatoid arthritis, efficacy, safety, real clinical practice

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, inflammatory joint disease that most commonly presents with symmetrical and erosive polyarthritis. It has been found to affect approximately 0.24 to 1% of the population and is two to four times more common in women compared to men [1]. In the long term, RA can lead to functional disability, impaired work ability and reduced quality of life. Lower survival rates in RA patients compared to the general population are due to increased cardiovascular risk [2], as well as increased incidence of infectious and malignant diseases [3]. Adequate control of disease activity determines the long-term prognosis in these patients.

In daily practice, the main goal of RA treatment is to achieve remission or low disease activity, defined by relevant validated tools [4, 5]. Current therapeutic options are conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biologic/biosimilar disease-modifying anti-rheumatic drugs

(bDMARDs/bsDMARDs) and targeted synthetic disease-modifying anti-rheumatic drugs (tsDMARDs). Over 30-40% of patients on biologic therapy fail to achieve a satisfactory long-term clinical response [6], indicating the need for new therapeutic options. A relatively new class of oral medications, Janus kinase (JAK) inhibitors, have emerged as an effective alternative treatment for RA patients with inadequate response or intolerance to csDMARDs and/or bDMARDs. The selective JAK1 inhibitor upadacitinib, sold under the brand name Rinvoq®, is the third drug of the group approved by the European Medicines Agency for the treatment of moderate to severe active RA in adult patients.

The efficacy of upadacitinib was evaluated in a large number of RA patients in six global randomized trials: SELECT-EARLY, SELECT-NEXT, SELECT-MONOTHERAPY, SELECT-COMPARE, SELECT-BEYOND, and SELECT-CHOICE. The drug has demonstrated efficacy in various subgroups of RA patients, including treatment-naïve patients and

patients with an inadequate response to csDMARDs or bDMARDs [7, 8, 9, 10]. Favourable outcomes have been observed compared to active comparators such as methotrexate (MTX) and adalimumab [7,8,11], and when administered as monotherapy or in combination with csDMARDs [7,8,9]. Based on these trials, in the 2019 EULAR recommendations, upadacitinib is designated as a second-line treatment for RA, along with bDMARDs and other tsDMARDs.

The long-term safety of upadacitinib was studied in phase III integrated analysis SELECT and is comparable to that of biologics. Rates of serious infections, malignancies, serious cardiovascular events, and venous thromboembolism were similar among patients receiving upadacitinib, adalimumab, and MTX [12]. Compared to adalimumab, patients on upadacitinib were found to have an increased risk of Herpes Zoster virus infection and were more likely to have elevation in creatinine phosphokinase and liver enzymes [12]. In July 2021, upadacitinib was reimbursed by the Bulgarian healthcare system for the treatment of RA patients in Bulgaria.

Real-world data are crucial in assessing the post-marketing effectiveness and safety of drugs in RA patients, as it reflects diverse populations and clinical practices encountered in routine clinical practice. Furthermore, real-world data provide long-term follow-up and capture patients who may not have been included in clinical trials, offering a more inclusive perspective on the performance of upadacitinib and informing treatment decisions in real-world settings. Therefore, it is of paramount importance to evaluate the six-month efficacy and safety of upadacitinib 15 mg daily in patients with moderate to high active RA in real-world clinical practice and to identify predictors of therapeutic efficacy.

MATERIALS AND METHODS

A retrospective single-center study that examined RA patients older than 18 years was conducted. The included patients were diagnosed with rheumatoid arthritis based on the ACR 1987 classification criteria [14] and all were found to have positive RF (assayed by quantitative immunoturbidimetry, with a cutoff of normal < 12). A six-month treatment with upadacitinib, sold under the brand name Rinvoq®, was performed. All patients were treated with csDMARDs and/or bDMARDs before initiation of therapy.

Exclusion criteria for upadacitinib therapy were pregnancy, breastfeeding, presence of active infection, impaired liver function – initial increase in ALT

and AST above reference values, hematological abnormalities – hemoglobin levels below 90 g/l, leukocytes less than 4000, platelets less than 100,000, history of neoplastic disease. Hepatitis B virus surface antigen (HBsAg), Hepatitis C virus antibodies (Anti-HCV) and IFN- γ -based test (Interferon-Gamma Release Assays – IGRAs) or Mantoux test were performed to rule out active or latent infection in all patients.

The patients were examined in the diagnostic-consultative unit of the clinic of rheumatology at the University Hospital „Sv. Marina“ from May 2021 to April 2022. Outpatient procedure No. 42 was performed, which included: interview and physical examination by a rheumatologist, laboratory and imaging tests, assessment of RA activity with composite indices.

An administrative database was analyzed for demographic and clinical characteristics: age, sex, body mass index (BMI), comorbidities, radiographic stage (defined on the basis of ACR criteria in determining progression of RA), functional class of motor disability (according to Steinbrocker functional classification of RA) [13]. The efficacy and safety of upadacitinib was studied over a period of 6 months.

The therapeutic efficacy of the drug was evaluated by determining the painful joint count (PJC), swollen joint count (SJC), pain severity (VAS 100 mm), CRP value, Patient Global Assessment (PGA, VAS 10 mm), Elevator Global Assessment (EGA, VAS 10 mm). Three validated composite indices, Disease activity score 28 CRP (DAS 28 CRP), Clinical disease activity index (CDAI) and Simplified Disease Activity Index (SDAI) with generally accepted thresholds were used to present the results.

A therapeutic target was defined as low disease activity at month six of treatment, presented simultaneously with each of these three composite indices. All manifested adverse drug reactions within the 6-month treatment period were tracked and described.

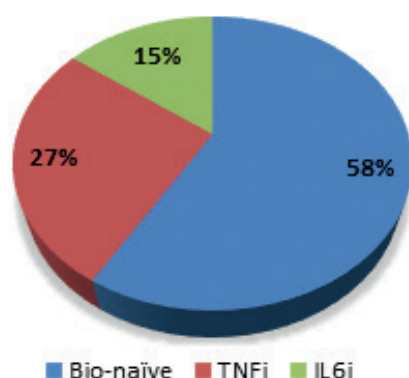
Statistical data processing was performed using SPSS v23 software for Windows. Descriptive statistics, nonparametric tests for quantitative variables, Student T-test, and binary logistic regression were used. A significance level of $p < 0.05$ was assumed.

RESULTS

The study included 41 RA patients, mean age of 56.5 years (± 13.4), with long-standing RA – 8 years (± 5.81), mostly females (80.5%). Erosive disease was present in 41.5% of patients, functional class III motor deficit was observed in 61%. The mean BMI

was 25.4 kg/m² (± 4.96), whereas 19.5% were with obesity (BMI > 30 kg/m²). The most common comorbidities, registered in the medical records of the patients, were osteoarthritis (OA) – 80.5%, arterial hypertension (AH) – 58.5%, diabetes mellitus type 2 (DM2) – 9.5%. The clinico-demographic characteristics of the patients are presented in Table 1.

According to prior therapy, the proportions of bio-naïve patients and those with prior biologic experience were similar (58.5% vs 41.5%, $p > 0.05$). Among the bio-experienced patients, significantly more were on TNF inhibitor therapy compared to IL6 inhibitor therapy (26.8% vs 14.7%, $p < 0.05$) (Figure 1).



Legend: Bio-naïve, patients with no prior experience with biologic drug; TNFi, Tumor necrosis factor inhibitor; IL6i, Interleukin 6 inhibitor.

Fig. 1. Distribution of patients according to prior therapy

The patients on monotherapy with upacitinib were significantly more in comparison with those on combination therapy with MTX (90% vs 10% $p = 0.001$).

The mean values of the indices, forming the disease activity scores, displayed significant improvement within six months of upadacitinib treatment. Pain severity and the tender joint count decreased by more than twice compared to baseline (72.5 vs 30.3 and 11.8 vs 3.1 respectively, $p < 0.001$). At the end of the six-month period, the mean swollen joint count was 1.1, which was 7 times lower in comparison with the baseline (7.8 vs 1.1, $p < 0.001$).

The mean values of DAS28 CRP, SDAI, CDAI before and after six months of upadacitinib treatment revealed a statistically significant reduction in RA activity (Table 2).

At the month six of treatment, DAS28CRP ≤ 3.2 (low activity) was reached by a significantly high proportion of patients (70.7% 95% CI 53.7-84.3%, $p = 0.0107$), while DAS28CRP ≤ 2.6 (remission) was achieved in a small proportion (39.5%, 95% CI 24.1-56.6%, $p > 0.05$). According to CDAI and SDAI, patients with low disease activity were numerically superior, but the data did not reach statistical significance (60.5% and 63.2%, respectively, $p > 0.05$).

There was no statistically significant difference between the proportions of bio-naïve and bio-experienced patients in low-activity RA after 6-month treatment with upadacitinib ($p > 0.05$; Figure 2).

Table 1. Clinico-demographic characteristics of the patients

Demographic and RA features	Value
Age mean (± SD)	56.5 (± 13.4)
Gender (female) n (%)	33 (80.5)
BMI (kg/m ²) mean (± SD)	25.43 (± 4.96)
BMI > 30 kg/m ² n (%)	8 (19.5)
RA duration (years) mean (± SD)	8.0 (± 5.81)
Erosive disease n (%)	17 (41.5)
Functional class disability ≥ III n (%)	25 (61)
Comorbidities	
Arterial hypertension n (%)	24 (58.5)
Diabetes mellitus n (%)	4 (9.8)
Osteoarthritis n (%)	33 (80.5)
Prior therapy	
No treatment with biologic agents n (%)	24 (58.5)
Treatment with biologic agents n (%)	17 (41.5)
TNFi n (%)	11 (26.8)
IL6i n (%)	6 (14.7)
Concomitant therapy	
NSAIDs n (%)	20 (48.8)
Methotrexate n (%)	10 (24.4)
Glucocorticoids n (%)	15 (36.6)

Acronyms: SD, Standard deviation; n, number; BMI, Body mass index; TNFi, Tumor necrosis factor inhibitor; IL6i, Interleukin 6 inhibitor; NSAIDs, Non-steroidal anti-inflammatory drugs.

BMI ≥ 30 kg/m², radiographic stage, functional capacity, combination therapy with MTX, and bio-naïve status were not considered as factors influencing the outcome of upadacitinib treatment, which was expressed with CDAI ≤ 10 , SDAI ≤ 11 and DAS28 CRP ≤ 3.2 (Table 3).

When examining the association of the mean values of subjective and objective parameters (VAS, CRP, TJC, SJC) at the month six of upadacitinib treatment and the comorbidities: AH, DM and OA, it was found that the mean TJC and SJC were signifi-

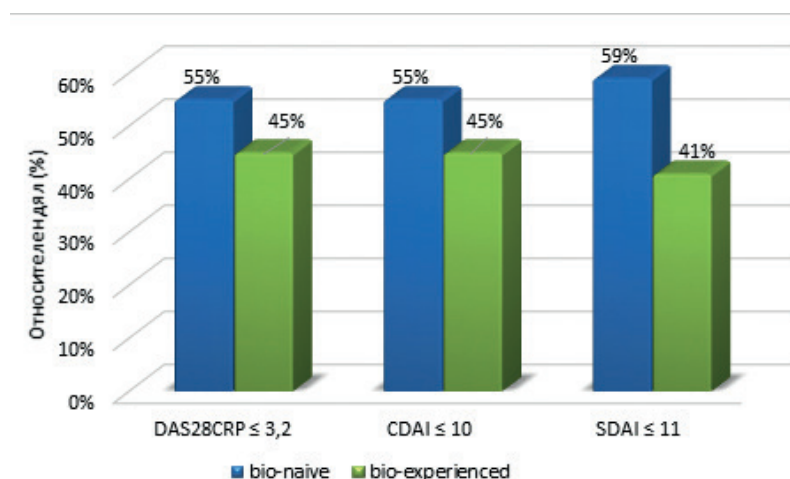
cantly higher in patients with hypertensive disease (Table 4).

Serious adverse events were identified in one patient: death due to infection with SARS-CoV-19. The most common side-effect recorded from upadacitinib treatment was an increase in liver enzymes, observed in three patients (transient and not requiring treatment withdrawal). A decrease in haemoglobin levels (unrelated to RA activity) was observed in two of the patients and two others were diagnosed with urinary tract infection.

Table 2. Mean change in RA activity indices, VAS for pain, CRP, SJC and TJC at the sixth month of treatment

Clinical indicators	Prior to treatment	After six months of treatment	P value*
VAS/mm (mean $\pm$ SD)	72.55 $\pm$ 17.9	30.34 $\pm$ 15.5	< 0.001
Tender joint count (mean $\pm$ SD)	11.8 $\pm$ 6.4	3.1 $\pm$ 2.0	< 0.001
Swollen joint count (mean $\pm$ SD)	7.8 $\pm$ 5.2	1.1 $\pm$ 1.9	< 0.001
CRP mg/L (mean $\pm$ SD)	15.79 $\pm$ 19.7	7.2 $\pm$ 11.4	< 0.001
SDAI (mean $\pm$ SD)	35.7 $\pm$ 12.1	10.8 $\pm$ 6.1	< 0.001
CDAI (mean $\pm$ SD)	34.2 $\pm$ 11.3	10.1 $\pm$ 5.6	< 0.001
DAS28 CRP (mean $\pm$ SD)	5.62 $\pm$ 0.97	2.93 $\pm$ 0.85	< 0.001

Legend: SD, Standard deviation; VAS pain, Visual Analogue Scale for pain (100 mm); TDJ, Tender joint count; SJC, Swollen joint count; CRP, C-reactive protein; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; DAS28 CRP, Disease Activity Score in 28 joints using the C-reactive protein level, *- Student T-test



Legend: Bio-naïve, patients with no prior experience with biologic drugs; Bio-experienced, patients with prior experience with biologic drugs; SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index; DAS28 CRP, Disease Activity Score in 28 joints using the C-reactive protein level.

Fig. 2. Therapeutic efficacy of upadacitinib according to disease activity scores and previous experience with biologic drugs

Table 3. Low RA activity in patients with upadacitinib treatment and connection to clinical and demographic characteristics

Variables not in the equation											
			SDAI ≤ 11			CDAI ≤ 10			DAS28 CRP ≤ 3.2		
			SCORE	DF	p-value	SCORE	DF	p-value	SCORE	DF	p-value
Step 0	Variables	BMI≥30 kg/m²	2.867	1	0.09	.134	1	.134	1.591	1	0.207
		Radiographic stage	1.028	1	0.31	.158	1	.158	.035	1	0.850
		Functional class	1.103	1	0.294	.192	1	.192	.001	1	0.970
		Bio-naïve	0.131	1	0.717	.192	1	.192	.277	1	0.599
		Combination therapy with MTX	1.775	1	0.183	.056	1	.056	.903	1	0.342
	Overall Statistics		8.936	8.936	6	.177	.068	6	3.297	5	0.654

Legend: SDAI, Simplified Disease Activity Index; CDAI, Clinical Disease Activity Index, DAS28 CRP, Disease Activity Score in 28 joints using the C-reactive protein level

Table 4. Value of subjective and objective indicators at the sixth month of treatment with upadacitinib in accordance with comorbidities

		VAS/mm (mean)	p-value	TJC Count (mean)	p-value	SJC Count (mean)	p-value	CRP mg/L (mean)	p-value
AH	no	26.20	0.188	2.13	0.005	0.20	0.009	8.5007	.542
	yes	33.04		3.74		1.65		6.1691	
DM2	no	31.37	0.166	3.09	0.842	1.17	0.332	7.1337	.936
	yes	18.33		3.33		0.00		6.5733	
OA	no	28.50	.0711	2.63	0.458	0.38	0.263	2.7925	.231
	yes	30.83		3.23		1.27		8.2353	

Legend: VAS, Visual Analog Scale; TJC, Tender joint count; SJC, swollen joint count; CRP, C-reactive protein; AH – Arterial Hypertension; DM2, Diabetes Mellitus Type 2; OA, Osteoarthritis

DISCUSSION

Good control of disease activity is a leading factor in improving quality of life, work ability and long-term prognosis in RA patients. After treatment with the first bDMARD, approximately 30-50% of the patients present with persisting moderate disease activity [15]. Based on the results of the SELECT phase III program, the selective JAK1 inhibitor upadacitinib is a promising new therapeutic option.

This retrospective study of the therapeutic efficacy and safety of upadacitinib in patients with RA in real clinical practice is the first of its kind in Bulgaria. The most notable aspects of the study are that it is based on real-life data, it was not a cross-sectional study, rather it was conducted over a six month period and it includes both clinical indicators and composite indices (DAS28 CRP, CDAI and SDAI) measuring RA disease activity. Therapeutic efficacy was considered in light of prior therapy, radiographic stage, functional class and comorbidities.

The RA patients included in the analysis had a long-standing disease (8.0 ± 5.81 years) and in most of them (80.5%) secondary osteoarthritis was present. The prevalence of arterial hypertension among the studied group corresponded to the general population-prevalence, but due to the small sample size, it did not reach statistical significance (58.5%, $p > 0.05$) [16, 17].

Over 6 months, upadacitinib 15 mg daily resulted in significant improvement in both the subjective and objective indicators of RA activity, which was reflected in an improvement in the combined indices. There was a numerical superiority of patients in low disease activity and these results were independent of previous experience with biologics. Similar results are reported in the SELECT phase III clinical pro-

gram of upadacitinib and by other authors presenting data from real-world clinical practice.

In the SELECT-MONOTHERAPY, SELECT-NEXT, and SELECT-BEYOND studies, low disease activity ($\text{DAS28-CRP} \leq 3.2$) at the week 12 of treatment was achieved by 45%, 48%, and 43% of patients, respectively [8, 9,10]. The lower percentage of patients with low disease activity can be explained by the early assessment period, the week twelve. In the SELECT-COMPARE study, at the end of the 26-week observation period, $\text{SDAI} \leq 11$ was found in 54% of patients [11].

The first data on the therapeutic efficacy of Upadacitinib 15 mg/day in real clinical settings are from Germany. At the month six of treatment, the percentage of patients achieving low disease activity defined by $\text{DAS28CRP} \leq 3.2$, $\text{CDAI} \leq 10$ and $\text{SDAI} \leq 11$ was 79.1%, 74.6%, 73.6%, respectively [18]. An analysis based on UR-NICE database showed that patients with $\text{DAS28CRP} \leq 3.2$ and $\text{CDAI} \leq 10$ at the month six of targeted therapy were 91% and 60%, respectively [19].

The results on the therapeutic efficacy of upadacitinib reported in this study are consistent with those from the clinical trials and registries. The observed statistically significant reduction in pain intensity, TJC, SJC and CRP level is reflected in the values of the combined indices (DAS28 CRP, CDAI, SDAI). In real clinical settings, a six-month treatment period with the medication resulted in achieving low RA activity in 70.7% of patients according to DAS28 CRP. The more restrictive CDAI and SDAI also showed that approximately two-thirds of patients were in low RA activity after 6 months of therapy (60.5% and 63.2%). These results were constant regardless of whether the patients were bio-naïve or bio-experienced and whether treatment was administered as monotherapy or in combination with MTX.

Identification of predictive factors for a favourable clinical response to the ongoing treatment is important for refining the selection of patients suitable for a given drug and aims to personalise and individualise the therapeutic approach. According to the analysis performed, no associations were found between the change of disease activity scores and the following: radiological stage, functional class of disability, combination therapy with MTX, or prior experience with biologic medications. The therapeutic success of upadacitinib was not determined by demographic (BMI), clinical factors (X-ray stage, functional capacity), prior treatment with biologic medications and comorbidities such as OA and DM. The mean number of swollen and tender joints at six months of treatment was significantly higher in patients with AH compared to those without. Hypertensive heart disease is associated with increased cardiovascular morbidity in RA patients [20]. Considering the correlation between the RA activity and cardiovascular risk, it is not unexpected that higher disease activity scores were observed in patients with AH [21].

The adverse events recorded in this study over six months in 41 patients on 15 mg daily upadacitinib did not differ in type and frequency from those known to date.

No case of Herpes zoster, a class-specific adverse event, was recorded for six months. The risk of activation of Herpes zoster infection is slightly increased in patients with immune-mediated rheumatic musculoskeletal diseases, such as RA. Furthermore, the risk of infection in these patients is further increased in association with immunosuppressive treatment, especially corticosteroid administration, as well as in association with age, ethnicity, diabetes, smoking, etc [22]. Upadacitinib treatment increases this risk even further. In a large clinical trial evaluating the effectiveness of upadacitinib 15 mg in RA patients with inadequate response to biologics, Herpes zoster reactivation rates were 1% at 24 weeks [10]. In light of these data, our results are understandable given the small number of patients enrolled and observed for a relatively short period.

In clinical trials of upadacitinib in RA patients, abnormalities in liver function tests are common, although usually mild. Some degree of ALT elevation has been observed in up to 11% of patients treated with upadacitinib compared with 7% treated with placebo. Values greater than 3 times the upper limit of normal were found in 2% or less of the patients. Furthermore, similar rates of ALT elevation occurred in patients treated with Methotrexate or bDMARDs [23]. In this study, elevated liver enzymes were ob-

served in two of the studied patients. The level of increase did not exceed three times the upper limit of normal and treatment was not discontinued.

No cardiovascular events or venous thromboembolism were detected. The only recorded patient's death was due to severe SARS-COV-2 virus infection.

The need to individualize the therapeutic approach in each patient and to carefully assess the risk-benefit ratio before initiating treatment was confirmed. Due to the limited number of patients included in the study, no definitive conclusion could be drawn about the safety profile of the drug.

The study also has its drawbacks: small number of patients, retrospective design, short study period.

CONCLUSION

Upadacitinib, administered as monotherapy or in combination with MTX is effective in RA patients with inadequate response to conventional and/or biologic therapy in real clinical practice. The safety profile of the medication established by this study is consistent with the generally known one. In order to confirm the efficacy and sustainability of the achieved results and the safety of upadacitinib in real clinical practice, large-scale and long-term research is needed.

Библиография / References

1. Cross M, Smith E, Hoy D, et al. The global burden of rheumatoid arthritis: estimates from the global burden of disease 2010 study. *Ann Rheum Dis*. 2014, 73(7), 1316-1322.
2. Avina-Zubieta JA, Thomas J, Sadatsafavi M, et al. Risk of incident cardiovascular events in patients with rheumatoid arthritis: a meta-analysis of observational studies. *Ann Rheum Dis* 2012,; 71(9), 1524-1529.
3. Simon TA, Thompson A, Gandhi KK, et al. Incidence of malignancy in adult patients with rheumatoid arthritis: a meta-analysis. *Arthritis Res Ther* 2015, 17(1), 212.
4. Smolen JS, Landewé R, Bijlsma J, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. *Ann Rheum Dis* 2017, 76(6), 960-977.
5. Singh JA, Saag KG, Bridges SL, et al. 2015 American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Care Res* 2016, 73(7), 924-939.
6. Kalden JR, Schulze-Koops H. Immunogenicity and loss of response to TNF inhibitors: implications for rheumatoid arthritis treatment. *Nat Rev Rheumatol* 2017, 13(12), 707-718.
7. Van Vollenhoven R, Takeuchi T, Pangan AL, et al. Efficacy and Safety of Upadacitinib Monotherapy in Methotrexate-Naïve Patients with Moderately-to-Severely Active Rheumatoid Arthritis (SELECT-EARLY): A Multicenter, Multi-Country, Randomized, Double-Blind, Active Comparator-Controlled Trial. *Arthritis Rheumatol*, 2020, 72(10), 1607-1620.
8. Smolen JS, Pangan AL, Emery P, et al. Upadacitinib as monotherapy in patients with active rheumatoid arthritis and inad-

- equate response to methotrexate (SELECT-MONOTHERAPY): a randomised, placebo-controlled, double-blind phase 3 study [published correction appears in Lancet. 2019 Jun 29;393(10191):2590]. Lancet, 2019, 393(10188), 2303-2311.
9. Burmester GR, Kremer JM, Van den Bosch F, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomized, double-blind, placebo-controlled phase 3 trial. Lancet, 2018, 391(10139), 2503-12.
 10. Genovese MC, Fleischmann R, Combe B, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomized controlled phase 3 trial. Lancet, 2018, 391(10139), 2513-2524.
 11. Fleischmann R, Pangan AL, Song IH, et al. Upadacitinib Versus Placebo or Adalimumab in Patients with Rheumatoid Arthritis and an Inadequate Response to Methotrexate: Results of a Phase III, Double-Blind, Randomized Controlled Trial. Arthritis Rheumatol., 2019, 71(11), 1788-1800.
 12. Cohen SB, Van Vollenhoven R, Winthrop K, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the SELECT Phase 3 clinical program. [published correction appears in Ann Rheum Dis. 2021 May, 80(5), e83]. Ann Rheum Dis, 2021, 80(3), 304-311.
 13. Steinbrocker O, Traeger CH, Batterman RC. Therapeutic criteria in rheumatoid arthritis. J Am Med Assoc. 1949, 140(8), 659-662.
 14. Arnett FC, Edworthy SM, Bloch DA, et al. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. Arthritis Rheum 1988 Mar;31(3), 315-24
 15. Flouri I, Markatseli TE, Voulgari PV, et al. Comparative effectiveness and survival of infliximab, adalimumab, and etanercept for rheumatoid arthritis patients in the Hellenic Registry of Biologics: low rates of remission and 5-year drug survival. Semin Arthritis Rheum. 2014, 43(4), 447-57.
 16. Gonzalez A, Maradit Kremers H, Crowson CS, et al. Do cardiovascular risk factors confer the same risk for cardiovascular outcomes in rheumatoid arthritis patients as in non-rheumatoid arthritis patients?. Ann Rheum Dis., 2008, 67(1), 64-69.
 17. Chung CP, Oeser A, Solus JF, et al. Prevalence of the metabolic syndrome is increased in rheumatoid arthritis and is associated with coronary atherosclerosis. Atherosclerosis, 2008, 196(2), 756-763.
 18. Witte T, Kiltz U, Haas F on behalf of the UPwArds Study Group, et al AB0255 Baseline characteristics of patients with rheumatoid arthritis treated with upadacitinib in german real-world practice: results from the post-marketing observational UPwArds study; Annals of the Rheumatic Diseases 2021, 80, 1153-1154.
 19. Gibofsky A, Pearson ME, Concoff A, et al, POS0686 Effectiveness of upadacitinib in the treatment of rheumatoid arthritis: analysis of 6-month real-world data from the United rheumatology normalized integrated community evidence (UR-NICETM) database. Annals of the Rheumatic Diseases 2022, 81, 621-622.
 20. Baghdadi LR, Woodman RJ, Shanahan EM, et al. The impact of traditional cardiovascular risk factors on cardiovascular outcomes in patients with rheumatoid arthritis: a systematic review and meta-analysis. PLoS One, 2015, 10(2), e0117952.
 21. Arts EE, Fransen J, den Broeder AA, et al. The effect of disease duration and disease activity on the risk of cardiovascular disease in rheumatoid arthritis patients. Ann Rheum Dis., 2015, 74(6), 998-1003.
 22. Kim H, Cho SK, Lee J, et al. Increased risk of opportunistic infection in early rheumatoid arthritis. Int J Rheum Dis, 2019, 22(7), 1239-1246.
 23. LiverTox: Clinical and Research Information on Drug-Induced Liver Injury [Internet]. Bethesda (MD): National Institute of Diabetes and Digestive and Kidney Diseases; 2012-. Upadacitinib. [Updated 2022 Aug 30]. Available from: <https://www.ncbi.nlm.nih.gov/books/NBK574351/>.

Постъпил за печат: 12.04.2023 г.

Submitted: 12.04.2023

✉ Адрес за кореспонденция:

Доц. д-р Цветослав Георгиев, дм
МУ – Варна
e-mail: tsetso@medfaculty.org

✉ Correspondence address:

Assoc. Prof. Tsvetoslav Georgiev, MD, PhD
MU – Varna
e-mail: tsetso@medfaculty.org