ORIGINAL INVESTIGATIONS

Characteristics of clinical manifestations and pharmacotherapy in patients with rheumatoid arthritis requiring switching between biologic disease-modifying antirheumatic drugs and Janus kinase inhibitors

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Biologic disease-modifying antirheumatic drugs (bDMARDs) and Janus kinase inhibitors (JAKis) do not always allow to achieve remission and low inflammatory activity in rheumatoid arthritis (RA), necessitating switching of therapy.

Objective: *to evaluate the clinical characteristics and features of pharmacotherapy in patients with RA requiring a switch from bDMARD/JAKi.*

Material and methods. *The study group consisted of 103 patients with RA (85.4% women, mean age 46.9±13.7 years) who had persistent disease activity (DAS28-CRP – 5.42±0.9) despite treatment with bDMARD/JAKi or who experienced adverse events requiring therapy switching. Patients were divided into three groups: Group 1 – patients who underwent one switch (n=50), Group 2 – 2 switches (n=39), Group 3 – ≥3 switches (n=14) of bDMARD/JAKi therapy. Clinical manifestations, disease activity and pharmacotherapy were assessed.*

Results and discussion. *The main reason for switching therapy was ineffectiveness of bDMARD/JAKi (in 81.6% of patients). There was a tendency towards higher DAS28-ESR (p=0.052) and DAS28-CRP values (p=0.057) in groups 2 and 3 compared to group 1, as well as significant differences in CDAI (p_{1-2}=0.015 and p_{1-3}=0.011) and SDAI (p_{1-2}=0.013 and p_{1-3}=0.01). In group 3, there was a tendency towards higher DAS28-CRP, CDAI and SDAI values compared to group 2: 5.82±0.92 and 5.53±0.89; 40.5 [33.0; 45.0] and 35.2 [30.3; 43.9]; 36 [32; 42] and 32.0 [28.5; 38.5], respectively. However, these differences were statistically insignificant. Patients in groups 2 and 3 had a significantly higher number of painful joints compared to patients in group 1 (p_{1-2}=0.048 and p_{1-3}=0.036) and a significantly higher patient global assessment of disease activity (p_{1-2}=0.004 and p_{1-3}=0.013). Patients in group 3 took glucocorticoids significantly longer and at higher doses than patients in group 1. Tumour necrosis factor-α inhibitors were used more frequently in groups 1 and 2 (50.0 and 41.0%, respectively), and interleukin-6 inhibitors in group 3 (50.0%).*

Conclusion. *Patients with RA who required ≥2 switches of bDMARD/JAKi had higher disease activity compared to patients who required only one switch of therapy.*

Keywords: *rheumatoid arthritis; biologic disease-modifying antirheumatic drugs; Janus kinase inhibitors; switching therapy.*

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The main guideline for the treatment of rheumatoid arthritis (RA) is a treat-to-target (T2T) strategy to achieve remission or low disease activity (LDA) in clinical practice [1–5]. To reach this goal, the current pharmacotherapy is actively used, including bDMARDs: tumor necrosis factor inhibitors (TNFi), the T-cell co-stimulation inhibitors – abatacept (ABA), the B cell depletion therapies – rituximab (RTX), interleukin 6 inhibitors (IL6i), and the targeted disease-modifying antirheumatic drugs (tsDMARDs): Janus kinase inhibitors (JAKi – tofacitinib, upadacitinib and baricitinib, filgotinib*, peficitinib*) [6–8].

However, only 40-60% of RA patients achieve remission/LDA; furthermore, a considerable proportion of patients lose their initial response or develop adverse events (AE) over time. For example, K. Lauper et al. [9] analyzed 19 registries of RA patients treated with bDMARDs and JAKi (a total of 31,846 courses). The response rates (remission and LDA by CDAI (Clinical Disease Activity Index) were registered for TNFi (n=17,522) in 16% and 54%, ABA (n=2775) in 12% and 50%, IL6i (n=3863) in 16% and 55%, and JAKi (n=7686) in 15% and 56%, respectively. The multinational prospective observational RA-BE-REAL study (n=1073) showed that patients treated with baricitinib achieved remission/LDA in 41.1% and 15.2%; with TNFi – in 36.4% and 16.2%; with another bDMARDs – in 30.4% and 7.6%, respectively [10]. Similar results were obtained using data of 4816 patients who received bDMARDs and JAKi (tofacitinib) within CORRONA (Consortium of Rheumatology Researchers of North America Rheumatoid Arthritis Registry) RA registry for 1-year follow-up [11]. Remission according to CDAI was achieved by 17.6% vs 16.3%, LDA by 39.9% vs 41.6% in the TNFi group and non-TNFi group, respectively.

Thus, up to 40–50% of patients do not achieve the T2T target in real clinical practice and have to switch to another bDMARD or JAKi [7, 12, 13]. It is important to note that the

*not registered in the Russian Federation not registered in the Russian Federation.

population was divided into those who started their first b/tsDMARD before and after 2010. The first ones switched to another TNFi (cycling strategy). The use of non–TNFi drugs has generally increased after 2010; drugs with a different mechanism of action (MOA; swapping strategy) have been used more frequently as the second-line treatment due to the growth in the number of bDMARDs and the emergence of JAKi [10–12].

There is no consensus on the issue, and both approaches show comparable efficacy [11, 14, 15]. At the same time, ABA, RTX and IL6i are prescribed as often as TNFi as the first-line therapy [9, 16–18].

The relevance of the b/tsDMARDs switching problem is highlighted by the Kyoto University Rheumatoid Arthritis Management Alliance (KURAMA) cohort including 1816 patients who initiated bDMARDs [19]. According to the 10-year follow-up data, 54.8% of these patients had to switch to another b/tsDMARD [19]. A recent data from UK registry of 22,934 RA patients demonstrated that after the failure of the first b/tsDMARD 47.2% of patients had to switch to another drug, 22.0% had two switches, 9.3% – three switches, 3.3% – four switches of drugs [15].

The development of DMARDs with different MOA available for the treatment of RA has contributed to an increase in the number of patients switching between different b/tsDMARDs. However, a significant number of patients remain resistant to multiple drugs. Patients whose disease activity cannot be controlled even with the use of two or more b/tsDMARDs with different MOA are referred to as bearing «difficult-to-treat RA» (D2T RA) [5, 20–25]. Therefore, particular attention has been paid to identifying predictors of treatment response when switching between bDMARDs/JAKi [13, 16, 19, 26].

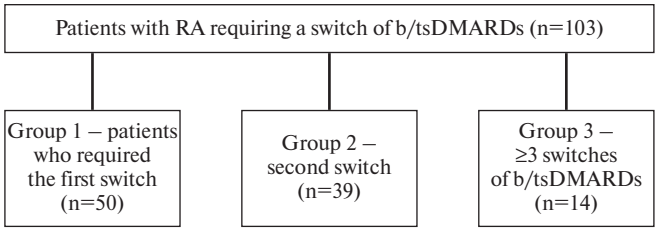

Fig. 1. *Groups of patients with RA*

The aim of this study was to evaluate the clinical characteristics and pharmacological features of RA patients who needed b/tsDMARDs switching.

Materials and methods. We studied 502 patients who met the ACR/EULAR (American College of Rheumatology / European Alliance of Associations for Rheumatology) criteria of RA and were admitted to the clinic of V.A. Nasonova Research Institute of Rheumatology from October 2022 to October 2023 due to disease exacerbation and inefficiency of current treatment.

Inclusion criteria were age ≥18 years, the use of bDMARDs/JAKi before the hospitalization, the evidence of inefficacy (persistent activity of disease) or intolerance (adverse reactions, AEs) of b/tsDMARDs, a need for a new b/tsDMARDs therapy.

Table 1. Clinical and demographical characteristics of RA patients (n=103)

Variable	Value	Variable	Value
Age, mean (SD)	46.9 (13.7)	Swollen joint count, median (IQR)	6.0 (4.0, 9.0)
Females, n (%)	88 (85.4)	Patient global assessment (VAS), median (IQR)	70.0 (60.0, 80.0)
RA duration, years, median (IQR)	11.0 (6.0, 16.5)	Physician global assessment (VAS), median (IQR)	70.0 (60.0, 70.0)
Juvenile onset, %	14.6	ESR, mm/h, median (IQR)	36.0 (14.0, 64.5)
BMI, mean (SD)	26.8 (6.37)	CRP, g/l, median (IQR)	14.6 (4.05, 33.15)
Extra-articular manifestation, %	48.5	DAS28-ESR, mean (SD)	5.87 (1.11)
Rheumatoid nodules, %	19.4	DAS28-CRP, mean (SD)	5.42 (0.90)
Vasculitis, %	2.9	SDAI, median (IQR)	32.5 (25.6, 42.0)
Sjogren's syndrome, %	29.1	CDAI, median (IQR)	32 (23.5, 37.5)
ILD, %	3.9	csDMARDs, %:	
Joints erosions, %	90.3	MTX	32.0
Steinbrocker stage, %:		LEF	30.1
II	42.7	HCQ	11.7
III	32.0	SASP	11.7
IV	25.2	GC, %	62.1
RF positive, %	78.6	Total duration of GC intake, months, median (IQR)	40.5 (11, 101)
ACPA positive, %	71.8	Maximum GC dose, mg/day, median (IQR)	10.0 (10.0, 15.0)
Tender joint count, median (IQR)	11.0 (7.0, 15.5)	NSAID, %	80.6

Note. ILD – interstitial lung disease, BMI – body mass index (here and in Table 2); csDMARDs – conventional synthetic disease-modifying antirheumatic drug; MTX – methotrexate; LEF – leflunomide; HCQ – hydroxychloroquine; SASP – sulfasalazine.

Patients with discontinuation of b/tsDMARDs due to non-medical reasons were not included in the study.

Finally, 103 RA patients were recruited. Most were middle-aged women with long disease duration (median >10 years), who had radiographic erosions, moderate or high disease activity according to DAS28, CDAI, SDAI (Simplified Disease Activity Index). About half of the patients had extra-articular manifestations, and most were taking glucocorticoids (GCs) and non-steroidal anti-inflammatory drugs (NSAIDs; Table 1).

At the time of research inclusion, all patients initiated a new b/tsDMARD. RTX was prescribed in 44.7% of cases, IL6i in 30.1%, TNFi in 14.6%, JAKi in 9.6% and ABA in 1% of cases.

Patients were divided into three groups according to the number of bDMARDs or tsDMARDs classes before the current treatment initiation (Figure 1).

The term «switching» mean changing to b/tsDMARDs with a different MOA. All patients underwent a standard clinical and instrumental examination. We collected laboratory results such as erythrocyte sedimentation rate (ESR), C-reactive protein (CRP) and clinical features such us tender joint count (TJC) and swollen joint count (SJC), patient global assessment and physician global assessment. Disease activity indicators were assessed using a visual analogue scale (VAS, 0–100 mm), DAS28-ESR (Disease Activity Score by ESR level), DAS28-CRP (Disease Activity Score by CRP level), CDAI and SDAI scores. Baseline RA therapy was also analyzed.

Statistical analysis of the data. All statistical analyses were performed with SPSS (IBM SPSS Statistics 27, IBM Corp., USA). Demographic and descriptive continuous variables with normal distribution are expressed as mean±standard deviation (SD), whereas non-normally distributed data are presented as median values with interquartile range (IQR). The normality of the data was assessed using the Shapiro–Wilk test. Categorical variables are expressed as percentages. Pearson's χ^2 or Fisher's exact test was used for comparison of categorical and Kruskal–Wallis test or one-way analysis of variance (ANOVA) for continuous variables. p values ≤0.05 were considered statistically significant.

Informed consent was provided by all patients at the time of entry into the study. Ethical approval was provided by the ethics committee of V.A. Nasonova Research Institute of Rheumatology (number of 23, 17 November 2022).

Results. The studied groups did not differ statistically significantly in the main characteristics such as gender, age, duration disease, onset under 18 years of age, body mass index (BMI), Steinbrocker stage, extra-articular manifestations, rheumatoid factor (RF) and anti-citrullinated protein antibody (ACPA) positivity (Table 2).

Table 2. Clinical and demographical characteristics of RA patients by groups

Variable	Group 1 (n=50)	Group 2 (n=39)	Group 3 (n=14)	p
Age, mean (SD)	48.0±13.6	45.8±14.2	46.0±13.6	0.719
Female/male, %	86.0/14.0	87.2/12.8	78.6/21.4	0.727
RA duration, years, median (IQR)	8 [4; 15]	13 [9.5; 17.5]	12 [6; 20]	**p_{1-2}= 0.01**
Juvenile onset, %	10.0	17.9	21.4	0.422
BMI, mean (SD)	27.9±6.00	25.4±6.29	26.4±7.48	0.093
Extra-articular manifestation, %	54.0	48.7	28.6	0.243
Rheumatoid nodules, %	22.0	17.9	14.3	0.778
Vasculitis, %	4.0	0	7.1	0.255
Sjogren's syndrome, %	28.0	33.3	21.4	0.681
ILD, %	6.0	0	7.1	0.25
Joints erosions, %	86.0	94.9	92.9	0.431
Steinbrocker stage, %:				
II	48.0	35.9	42.9	0.833
III	30.0	35.9	28.6	
IV	22.0	28.2	28.6	
RF positive, %	80.0	79.5	71.4	0.777
ACPA positive, %	72.0	71.8	71.4	0.999

Note. ILD – interstitial lung disease, BMI – body mass index. Bold – statistically significant differences.

We found differences in inflammatory activity indices, as well as in the therapy administered. For example, TJC and patient global assessment scores were significantly higher in groups 2 and 3 than in group 1. Group 3 patients took significantly longer and higher doses of GC compared to Group 1 patients. No statistically significant difference was found between Group 2 and Group 3 (Table 3).

Patients in groups 2 and 3 compared to patients in group 1 showed a marked trend toward higher DAS28-ESR (p=0.052) and DAS28-CRP (p=0.057) indices and a statistically significant difference in CDAI (p1–2=0.015 and p1–3=0.011) and SDAI (p1–2=0.013 and p1–3=0.01). The disease activity scores (DAS28, CDAI and SDAI) were higher in group 3 than in group 2, but there was no statistically significant difference (Figure 2).

Table 3. Baseline disease activity indices in RA patients (n=103)

Variable	Group 1 (n=50)	Group 2 (n=39)	Group 3 (n=14)	p
Tender joint count, median (IQR)	9.5 [6; 14]	12 [9; 15.5]	14 [11; 16]	**p_{1-2}=0.048** **p_{1-3}=0.036**
Swollen joint count, median (IQR)	5 [4; 7]	7 [4; 10]	8.5 [4; 10]	0.151
Patient global assessment (VAS), median (IQR)	60 [60; 70]	70 [65; 80]	75 [60; 80]	**p_{1-2}=0.004** **p_{1-3}=0.013**
Physician global assessment (VAS), median (IQR)	60 [50; 70]	70 [60; 70]	70 [60; 70]	0.059
ESR, mm/h, median (IQR)	36 [14; 58]	36 [16.5; 65.5]	38 [20; 70]	0.811
CRP, g/l, median (IQR)	14.6 [4.3; 33.0]	12.5 [2.3; 30.6]	27.0 [6.6; 42.8]	0.564
csDMARDs, %:				
MTX	32.0	35.8	21.4	0.609
LEF	28.0	30.8	35.7	0.851
HCQ	16.0	7.7	7.1	0.573
SASP	16.0	5.1	14.3	0.243
GC, %	54.0	69.2	71.4	0.252
Total duration of GC intake, months, median (IQR)	23 [7; 70]	65 [28; 141]	61.5 [30; 180]	**p_{1-2}=0.003** **p_{1-3}=0.024**
Maximum GC dose, mg/day, median (IQR)	10 [5; 15]	10 [8.75; 15]	15 [10; 20]	**p_{1-3}=0.012**
NSAID, %	78.0	76.9	100.0	0.141

Note. Bold – statistically significant difference.

The main reason for switching to another drug was its inefficacy (i.e. persistence of disease activity), which was observed in 81.6% of the total number of patients (n=103): in Group 1 – in 84.0%, in Group 2 – in 84.6% and in Group 3 – in 64.3% (p=0.2). The second reason for discontinuation was AEs, which were recorded in 36.2% of all enrolled patients: in group 1 – in 24.0%, in group 2 – in 17.9%, and in group 3 – in 57.1%. The rate of AEs was statistically significantly higher in group 3 vs. groups 1 and 2 (p1–3=0.027, p2–3=0.016).

We analyzed previously prescribed b/tsDMARDs, the number of patients treated with TNFi was 41 (39.8%), JAKi – 23 (22.3%), IL6i – 17 (16.5%), RTX – 11 (10.7%), ABA – 11 (10.7%). It is important to note that, 50% of patients in group 1 had previously used TNFi, while there were no such patients in group 3 (p=0.003). Group 3 was characterized by more frequent use of IL6i (in 50% of cases) than in Groups 1 and 2 (14.0% and 7.7%, respectively; p1–3=0.006, p2–3=0.002). The other patients in group 3 used ABA (14.3%) and JAKi (35.7%). Intragroup analysis showed that TNFi were more frequently prescribed in Groups 1 and 2 (50.0% and 41.0%, respectively), and IL6i – in Group 3(50.0%). We should also note a wide use of JAKi: in 18.0% of patients in Group 1, 23.1% in Group 2, and 35.7% in Group 3.

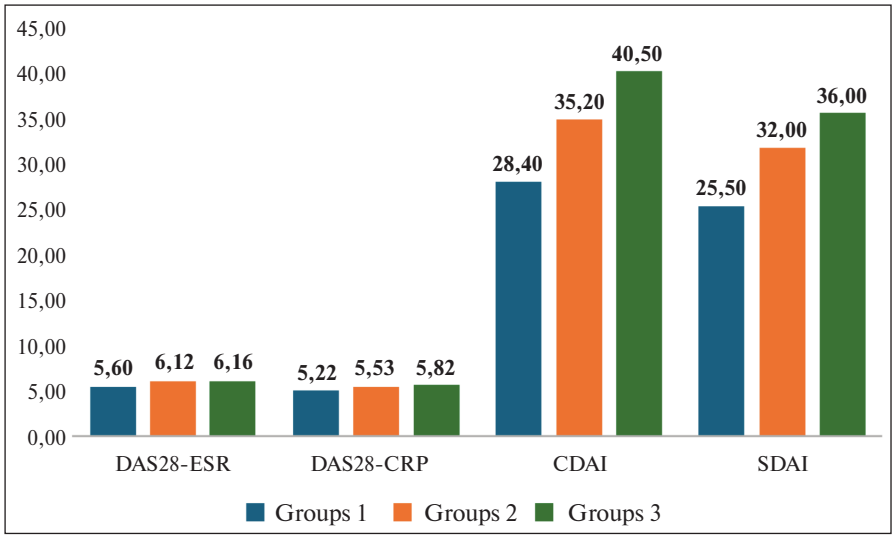

Fig. 2. *Comparison of RA activity indices in patients of three groups*

The drugs initiated during hospitalization differed significantly between the groups. Thus, the most common drugs for a new switch were RTX – 46 patients (44.7%), and IL6i – 31 patients (30.1%), less common – TNFi – 15 patients (14.6%) and JAKi – 10 patients (9.6%). Only 1 patient with a severe infectious and allergic history was prescribed ABA.

Discussion. The results of our study showed that the groups of patients with repeated switches of b/tsDMARDs were characterized by a larger TJC, higher patient global assessment score and higher DAS28, CDAI and SDAI scores, longer use of GC, higher daily dose of GC than the group of patients with ineffectiveness of the first b/tsDMARDs/ JAKi who needed only one switch.

Our data are generally consistent with the results presented by E.A. Galushko et al. [2], who compared the clinical status of 35 D2T RA patients and 291 RA patients with ineffective bDMARDs/JAKi therapy or its discontinuation for non-medical reasons. The authors showed that the disease activity was higher in the D2T group, i.e. patients who had ≥2 b/tsDMARDs switches. It is important to note that our data and the research by E.A. Galushko et al. are based on the analysis of patient groups recruited at different time (in 2021 and 2022–2023, respectively) [2]. The similarity of the results confirms the fundamental unity of the pathophysiologic patterns underlying the poor response to bDMARDs/JAKi therapy. On the other hand, all patients included in our study had medical causes for changing the drug in contrast to the study by E. A. Galushko et al.

The most interesting results we obtained by comparing patients in groups 2 and 3. Although the number of patients is relatively small in these groups, nevertheless, we identified an important tendency that the more switches had poor response (failure to achieve remission/LDA or AEs), the higher the RA activity was. We found no statistically significant differences between Group 2 and Group 3 in DAS28, CDAI and SDAI, but all scores were higher in Group 3. Similarly, longer duration of GC use and higher daily dose of GC, as well as the necessity to take NSAIDs regularly, indicated higher RA activity in patients with ≥3 b/tsDMARDs switches. These data suggest that RA patients with insufficient effect of several consecutively applied bDMARDs and JAKi had a more severe disease, which is associated with persistent autoimmune inflammation. Thus, in a recently published paper by A. Bertsias et al. [27], which compared 251 patients with D2T RA and 1013 individuals with non-D2T RA, showed an initial higher disease activity in patients with repeated therapy switches. The DAS28-ESR values were 5.59±1.23 and 5.93±1.14, respectively ($p<0.0001$) in these patients at the time of therapy initiation.

Indirect evidence of a more severe course of RA patients with multiple b/tsDMARDs switches was less significant treatment results at each subsequent drug change. Thus, the tendency to a decreased efficacy of bDMARDs and JAKi in multiple switches is illustrated by S.S. Zhao et al. [15], who evaluated the treatment outcomes of 22,934 patients with RA. After the first switch remission/LDA was achieved in 17% and 29% of patients, after the second switch – in 13% and 23%, and after the third-sixth switch – in 8–13% and 17–22%.

It is interesting to note the change in the type of therapy with multiple switches observed in this study. Among the bDMARDs, TNFi was most commonly used for the first switch (50% of patients). However, patients in group 3 were not prescribed TNFi. The main drugs used to continue treatment were IL6i and JAKi. However, this did not lead to therapeutic success. The decreased frequency of TNFi use with multiple switches was also reported by S. Zhao et al. [15], while TNFi were the leading drugs for the first and second switches, accounting for 90% and 60% of all cases, respectively. RTX was most commonly used for the third switch (39%), IL6i – for the fourth switch (33%), ABA – for the fifth switch (32%) and JAKi for the sixth switch (28%).

Conclusions. In summary, RA patients with repeated switching of b/tsDMARDs represent a serious medical problem. One of the key findings is that the greater the number of switches, the more difficult it is to achieve a good response to treatment. Unfortunately, the use of both IL6i and JAKi in the setting of inefficiency or intolerance to TNFi [17, 26] is not always successful. Further studies are needed to identify predictors of poor response to b/tsDMARDs and to determine whether it is possible to modify treatment to achieve remission or LDA.

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