

Janus kinase inhibitors in the treatment of psoriatic arthritis

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The article presents an analysis of literature data on the use of a new group of targeted synthetic disease-modifying antirheumatic drugs (DMARDs) Janus kinase (JAK) inhibitors – tofacitinib (TOFA) and upadacitinib (UPA) – in psoriatic arthritis (PsA). The results of randomized placebo-controlled clinical trials and long-term observational studies indicate the high efficacy and safety of using TOFA and UPA in the treatment of patients with PsA who are resistant to synthetic DMARDs and tumor necrosis factor- α inhibitors. The information obtained so far allows us to recommend JAK inhibitors as a new pathogenetic approach to the treatment of PsA.

Key words: psoriatic arthritis; Janus kinase inhibitors; tofacitinib; upadacitinib; targeted synthetic basic anti-inflammatory drugs.

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Psoriatic arthritis (PsA) is a chronic systemic immune-inflammatory disease with a variety of manifestations, including peripheral arthritis, enthesitis, dactylitis, spondylitis, and psoriatic lesions of the skin and nails [1, 2]. Due to the progressive damage to the musculoskeletal system and skin, PsA has a negative impact on the ability to work, quality of life (QOL) and social adaptation of patients.

In accordance with the recommendations of EULAR (The European Alliance of Associations for Rheumatology) 2019 [3] the goal of PsA therapy is to achieve remission or minimal activity of all clinical manifestations of the disease (arthritis, spondylitis, enthesitis, dactylitis and psoriasis), prevent structural damage, normalize function and maintain the best quality of life for patients.

The treatment of PsA consists of the sequential administration of non-steroidal anti-inflammatory drugs (NSAIDs), intra-articular glucocorticoids, synthetic DMARDs (sDMARDs), mainly methotrexate (MT), targeted synthetic DMARDs (tsDMARDs), and genetically engineered biological drugs (GIBDs) with different mechanisms of action: inhibitors of tumor necrosis factor α (iTNF α) and interleukins (IL) 12/23, IL17 and IL23 [1, 3–5].

The use of GIBDs, especially in combination with the Treat to Target strategy, significantly improved the clinical and radiological outcomes of PsA. The initiation of GIBDs therapy in early PsA made it possible to achieve remission at least once during 24 months of observation according to the DAS (Disease Activity Score) and DAPSA (Disease Activity in Psoriatic Arthritis) indices in 82 and 79% of patients, and minimal disease activity (MDA) – in 82%. However, remission was not achieved in approximately 20% of cases on the background of GIBDs, and in 15% there was an exacerbation of the disease according to DAS/DAPSA, which developed on average after 1 year of treatment due to the elusive effect [6]. The development of secondary inefficacy due to the accumulation of neutralizing antibodies, which is characteristic of some GIBDs, mainly TNF α , is often the reason for changing therapy. It has been noted that about a third of patients with PsA, rheumatoid arthritis (RA), and ankylosing spondylitis (AS) never achieve remission, despite the use of GIBDs, and the frequency of "drug-free" remission does not exceed 10–15% [7–9].

As a result, there remains a need for new targeted drugs that effectively affect all the main clinical manifestations of PsA.

A new promising direction in the pharmacotherapy of PsA is the creation of low-molecular chemically synthesized drugs that inhibit intracellular "signaling" molecules – Janus kinase (JAK) [10, 11]. The anti-inflammatory and immunomodulatory action of JAK (iJAK) inhibitors is based on blocking the activation of the JAK signaling pathway, which consists of four cytokine receptors: JAK1, JAK2, JAK3 and TYK2 (Tyrosine Kinase 2) and 7 transcription factors STAT (Signal Transducer and Activator of Transcription), which regulates the synthesis of more than 50 cytokines, interferons (IFN) and growth factors [10, 12]. iJAKs are characterized by a rapid development of the anti-inflammatory effect after their administration and cessation of action against the background of withdrawal, which is associated with a reversible blockade of the adenosine triphosphate-binding site of JAK. The selectivity of these drugs is manifested in the selective blocking of certain cytokine JAK receptors. All iJAKs block JAK1/JAK2 dependent cytokines, which include IL6, IFN γ , and JAK1/TYK2 signaling responsible for IL10, IFN α [13].

iJAKs are classified as oral tsDMARDs, which include tofacitinib (TOFA), upadacitinib (UPA), and baricitinib (BARI). Two JAK inhibitors, TOFA and UPA, are registered in the Russian Federation for the treatment of active PsA.

TOFA is the most studied representative of this class of drugs, the efficacy of which has been shown in immunoinflammatory rheumatic diseases. It was the first of the iJAKs to be approved for the treatment of RA [14] and PsA [15–17], and later for AS [18–21].

TOFA predominantly inhibits signaling through JAK1 and JAK3 and to a lesser extent through JAK2. After oral administration, TOFA is rapidly (within 24 hours) excreted from the bloodstream, about 70% of the drug is metabolized by the liver, 30% is excreted in the urine. It is assumed that TOFA is metabolized mainly by hepatic enzymes – cytochrome CYP3A4 and less actively by CYP2C19 [22].

In accordance with international and Russian guidelines, TOFA is used to treat active PsA in patients with insufficient effi-

cacy of sDMARDs and the phosphodiesterase 4 inhibitor apremilast, and also as an alternative to GIBDs (recommendations for the treatment of PsA by the American College of Rheumatology, ACR) [3, 4, 23].

The efficacy of TOFA in PsA has been studied in two randomized placebo controlled phase III clinical trials (RPCT) under the general name OPAL Broaden [24] and OPAL Beyond [25]. The results obtained indicated the efficacy of TOFA in PsA patients resistant to sDMARDs (OPAL Broaden) and IFN α (OPAL Beyond) in relation to all major clinical manifestations of the disease (psoriasis, arthritis, dactylitis, enthesitis, and spondylitis) with a significant improvement in the QoL of patients [26]. It was found that, in terms of its effect on the main clinical manifestations of PsA, TOFA is comparable to TNF α adalimumab (ADA) [24] and, like TNF α , IL12/23 and IL17 inhibitors, it has the ability to significantly slow down the progression of structural changes [25, 27]. When evaluating the dynamics of the total Sharp score (van der Heijde-modified Total Sharp Score, mTSS), modified for PsA, after 12 months, 91–98% of patients treated with TOFA, as well as ADA, showed no joint destruction [28].

The OPAL Broaden 12-month RPCT included 422 bionactive patients with active PsA and inadequate response to sDMARDs. Participants were randomized into four groups: TOFA 5 mg 2 times a day; TOFA 10 mg 2 times a day; ADA 40 mg subcutaneously once every 2 weeks and placebo (PL) with blind switching to TOFA at a dose of 5 or 10 mg 2 times a day after 3 months [24]. All patients had polyarticular lesions, more than half of them had enthesitis and dactylitis, the severity of psoriasis was moderate. In all groups, according to radiography of the hands and feet, in 90% of cases, erosions of the joints and functional disorders of the musculoskeletal system were found. All patients were on stable therapy with sDMARDs, mainly MT at an average dose of 15.5 mg/week.

Already after 3 months of using TOFA at doses of 10 and 20 mg per day, 50% and 61% of patients, respectively, achieved a response according to the ACR20 criteria, which was almost 2 times more than with PL (33%), and comparable to those in the ADA group (52%). By 3 and 12 months of therapy, a positive trend was also noted in the dynamics of the severity of enthesitis and dactylitis. The improvement in the HAQ-DI index (Health Assessment Questionnaire Disability Index) in the TOFA 5 and 10 mg 2 times a day groups was more pronounced (-0.35 and -0.40, respectively) than in the PL group (-0.18).

After 12 months, the response to ACR50 and ACR70 in the TOFA 5, 10 mg and ADA groups was comparable: 45; 48 and 41% and 23; 31 and 39% respectively. After 3 months, in the TOFA groups 5 and 10 mg, MDA was noted in 26% of patients, and in the ADA group – in 25%, after 12 months of observation – in 34; 40 and 41% of patients, respectively. When analyzing all additional performance indicators, it was found that TOFA is superior to PL in terms of the main response criteria.

The efficacy of TOFA in PsA was confirmed in the 6-month RPCT OPAL Beyond [25], which included patients (n=395) with an insufficient response to at least one IFN α . They were randomized into three groups: TOFA 5 mg 2 times a day (n=132); TOFA 10 mg 2 times a day (n=132) and PL (n=131) for 3 months, which was then replaced with the drug. All patients received sDMARDs, mainly MTX.

In general, the results of the study indicated that TOFA at doses of 5 and 10 mg 2 times a day for 3 months of therapy is more effective than PL in reducing PsA activity in patients with inefficacy of TNF α . At the same time, significant differences were noted

in the frequency of achieving ACR20 (50 and 47% in the TOFA groups versus 24% in the PL group) and ACR50 (30 and 28% versus 15% in the PL group, respectively), but not ACR70 (16.8% in TOFA 5 mg versus 7.6% in the PL group). A high response to PASI75 (Psoriasis Activity and Severity Index) after 3 months of treatment was registered only in the TOFA 10 mg group, in 43% of patients.

In both studies, along with a decrease in the number of affected joints, manifestations of enthesitis and dactylitis, fatigue on the FACIT (Functional Assessment of Chronic Illness Therapy) scale significantly decreased, and the mental and physical components of the SF-36 questionnaire improved. The improvement in these parameters was maintained until the end of the follow-up: up to 6 and 12 months in OPAL Beyond and OPAL Broaden, respectively. At the same time, in OPAL Broaden, according to similar indicators, TOFA was characterized by efficiency comparable to that of ADA.

Additional analysis of the dynamics of PsA-specific composite activity indices, such as PASDAS (PsA Disease Activity Score), DAPSA and CPDAI (Composite Psoriatic Disease Activity Index), showed a significant improvement by the 3rd month of taking TOFA 5 and 10 mg 2 times a day with an increase in the effect by the 6th month of therapy compared with PL.

A pooled analysis of the RPCT data from OPAL Broaden and OPAL Beyond demonstrated that after 3 months, the efficacy of TOFA 5 mg twice daily for ACR20, ACR50, and ACR70 was significantly higher ($p \leq 0.05$) compared to PL (50.0; 29.0 and 16.8% versus 28.0, 12.3 and 7.6%, respectively). There was a significant improvement in HAQ-DI compared to baseline (-0.38 vs -0.16; $p < 0.001$), PASI75 (32% vs 14.3%), enthesitis (-1.2 vs -0.5) and dactylitis (-4.6 vs -2.5). In the TOFA group, enthesitis (36.7% versus 21.5%) and dactylitis (43.3% versus 30.6%) disappeared in the vast majority of patients [29].

In the RPCT OPAL Broaden and OPAL Beyond, the effect of TOFA on axial manifestations of PsA was not specifically studied, however, according to the summary analysis, in the presence of spondylitis, a significant improvement in the BASDAI index (Bath AS Disease Activity Index) was found by 3 months of therapy with TOFA 10 and 5 mg each. compared to PL: LSM (Least Squares Mean) = -2.15 vs. -1.01 and 37.2% vs. 15.8%, respectively. The improvement was maintained in both groups and up to 6 months of treatment [29].

In addition to reducing the inflammatory activity of spondylitis according to the BASDAI index, according to MRI data, a significant effect of TOFA on the dynamics of osteitis in the sacroiliac joints was noted, which allows us to recommend this drug to patients with axial PsA who have active sacroiliitis and high activity of spondylitis [30].

The safety and tolerability of TOFA was investigated in detail in the OPAL Balance open-label, long-term extension study [31–33], which included patients seen in the OPAL Broaden and OPAL Beyond RPCT. Overall, treatment of PsA with TOFA at a dose of 5 mg twice daily in combination with sDMARDs was characterized by satisfactory safety and tolerability profiles. The most common infections of the upper and lower respiratory tract, urinary tract, nausea, abdominal pain, anemia, leukopenia and increased levels of hepatic transaminases. The study identified 6 cases of severe infections (0.9%), 10 cases of herpes virus infection (1.5%), and 1 case (0.15%) of activation of latent tuberculosis [29]. The frequency of adverse drug reactions (ADRs) increased with the use of TOFA at a dose of 10 mg 2 times a day.

The goal of OPAL Balance, in addition to recording possible delayed adverse drug reactions and effect escape, was to confirm the long-term effect of the drug – for 36 months [32, 33]. The study included 686 patients who received TOFA at a dose of 5 or 10 mg 2 times a day. Preliminary results indicate that TOFA remains highly effective for 24–36 months of treatment in relation to all manifestations of PsA. In patients who completed a 24-month course of combined therapy with TOFA and MT (n=180), MT discontinuation did not lead to a decrease in its efficacy compared with patients who continued combined treatment for the next 12 months [33].

As a result, it was shown that the effectiveness of the drug was maintained for 3 years, and the safety profile was similar to that after 3 and 6 months after the start of therapy in previous OPAL studies.

RPCTs usually do not include patients with clinically significant comorbidities. In real practice, in contrast to RPCTs, treatment is prescribed to persons with concomitant pathology, which aggravates the course of the underlying disease and the general condition of patients. In a study conducted at the Federal State Budgetary Scientific Institution “Scientific Research Institute of Rheumatology named after V.A. Nasonova [34], included patients with various comorbidities, including latent tuberculosis, hepatitis A, and a history of iron deficiency anemia, with the exception of serious infections and decompensated conditions. Based on the data obtained, in the short term, TOFA did not reveal a negative effect on the function of the liver, the cardiovascular system, or the course of a number of comorbidities, but there was an increased risk of developing infectious diseases (acute respiratory viral infections, folliculitis). When TOFA was prescribed to patients with active PsA with an insufficient response to previous therapy with sDMARDs and/or GIBAs, good tolerability and high clinical efficacy of the drug were observed. The results of the use of TOFA in real practice significantly supplement the already available data on its efficacy and safety and make it possible to include this drug in the general paradigm of PsA therapy [34, 35].

UPA is selective for iJAK, which predominantly blocks the JAK1 signaling pathways responsible, in particular, for IL6, IL2, and IFN γ . Studies of UPA activity in cell cultures in order to predict the pharmacodynamic response in vivo revealed its selectivity for JAK1, which is 50–70 times higher than that for JAK2 and more than 100 times for JAK3. When administered to rats with experimental arthritis, UPA suppressed inflammation, synovial hypertrophy, cartilage destruction, and bone erosions. Nevertheless, the selectivity of iJAK is relative, does not always correspond to the expected clinical efficacy and the development of ADR, depends on the dose of drugs, their ability to penetrate into cells, and JAK genetic polymorphism [13, 36, 37].

Initially, the efficacy and safety of UPA were studied in a series of RPCTs in RA: a significant decrease in arthritis activity and an improvement in the quality of life of patients were demonstrated [38–40].

Subsequently, the ability of UPA at a dose of 15 and 30 mg/day to reduce the activity of arthritis, dactylitis, enthesitis, psoriasis and to restrain the progression of structural changes in the joints in PsA was shown in international RPCTs SELECT-PsA-1 and SELECT-PsA-2. For comparison, the first study used iTNFi ADA. UPA became the second iJAK approved for use in PsA.

The SELECT-PSA-1 RCT evaluated the efficacy and safety of UPA compared with ADA and PL in 1704 patients with active PsA who were resistant to MT or other sDMARDs [41, 42]. Pa-

tients were randomized into four groups: UPA 15 mg/day (n=429); UPA 30 mg/day (n=423); ADA (n=429) and PL (n=423). The primary end point at 12 weeks was the ACR20 score. Response by ACR20 was achieved in 70.6 and 78.5% of patients receiving UPA 15 and 30 mg/day, respectively, in 65% of cases against the background of ADA and only in 36.2% against the background of PL. The effectiveness of both doses of UPA in response to ACR20 by 12 weeks was not lower than that of ADA, and UPA 30 mg/day was even superior in efficacy to ADA. After 24 weeks, the analysis of secondary endpoints (ACR50/70) showed a higher efficacy of UPA (15 and 30 mg/day) compared to PL and UPA 30 mg/day compared to ADA, as well as the dynamics of HAQ-DI and pain only for UPA 30 mg/day. It has been shown that UPA treatment not only contributes to a decrease in PsA activity, but also inhibits radiological progression. After 24 weeks, while taking the drug, a more pronounced slowdown in the progression of joint destruction (mTSS) was found than in the PL group ($p<0.001$). At week 24, in the UPA 15 mg/day group, resolution of enthesitis (Leeds Enthesitis Index, LEI=0) was observed in 54% of patients compared with 47% and 32% in the ADA and PL groups, respectively ($p\leq 0.001$ for UPA 15 mg/day, days compared with PL), and dactylitis (Leeds Dactylitis Index, LDI=0) in 77% of patients compared with 74 and 40% in the ADA and PL groups, respectively (nominal $p\leq 0.001$ for UPA 15 mg compared with PL). After 16 weeks, among patients with an initial area of skin lesions of psoriasis $\geq 3\%$ of the PASI75 response, 63% of patients used UPA 15 mg/day, while in the ADA and PL groups, 53 and 21%, respectively. At the same time, the missing data were assessed as the absence of a clinical response (non-responder imputation).

The frequency of ADRs in the groups of UPA 15 mg/day, ADA and PL did not differ, but moderately increased in patients who received UPA 30 mg/day. By week 24, the number of ADRs when taking UPA 15 mg/day was 66.9%, UPA 30 mg/day – 72.3%, ADA – 64.8% and PL – 59.6%. Serious ADRs were identified in 1.2; 2.6; 0.7 and 0.9% of cases, respectively. Liver disease was observed in 9.1 and 12.3% of patients treated with UPA 15 and 30 mg/day, respectively. In all groups, 2% of patients had an increase in the level of hepatic transaminases, which exceeded the upper limit of the norm by 3 times [42].

In the SELECT-PSA-1 RPCT at week 56, the UPA 15 mg/day group showed further improvement in most clinically relevant PsA manifestations, including musculoskeletal and skin symptoms, functional activity, QoL, and other patient-reported outcomes, as well as slowing of radiographic progression [43]. In addition, the proportion of patients who achieved MDA also continued to increase. Notably, at extended follow-up, UPA 15 mg/day showed results comparable to ADA, and significantly better for some endpoints based on nominal p values. The safety of treatment for 56 weeks was consistent with the data obtained up to the 24th week of observation and the safety profile of UPA in RA. The incidence of malignancy, major cardiovascular events, venous thrombosis and embolism in the UPA 15 mg/day group was comparable to that of ADA. No new safety data were found.

The SELECT-PSA-2 RPCT evaluated the efficacy of UPA in PsA patients with inadequate response to BAs or intolerance to them [44, 45]. Of the 642 patients included in the study, resistance to 1 GIBD was noted in 61%, to 2 GIBDs in 18%, to 3 or more GIBDs in 13%. Study participants were randomized into four groups (2:2:1:1): UPA 15 mg/day (n=211); UPA 30 mg/day (n=218) and PL (n=212) who switched to UPA 15 or 30 mg/day at week 24. After 12 weeks, against the background of UPA, a sig-

nificant decrease in the activity of peripheral arthritis was achieved compared with PL: the ACR20 response in the compared groups was 56.9; 63.8 and 24.1%, respectively ($p < 0.0001$ in both cases). After 24 weeks, in the analysis of secondary endpoints, UPA was superior to PL in response to ACR50/70, dynamics of HAQ-DI, SF-36, FACIT-F and SAPS (Self-Assessment of Psoriasis Symptoms). By the 24th week, MDA was more often detected in the PAN groups – in 25.1 and 28.9% of cases, respectively, compared with the PL group – 2.8% ($p < 0.001$ in both cases). The incidence of ALR by the 24th week of therapy was the same when taking PL and UPA 15 mg/day, however, in patients receiving UPA 30 mg/day, there was a moderate increase in it. Serious infections occurred in the same percentage of cases (0.5%) in the PL and UPA 15 mg/day groups and more than 5 times more often (2.8%) during treatment with UPA 30 mg/day [45].

In the SELECT-PsA-1 and SELECT-PsA-2 RPCT, the effect of UPA on axial manifestations of PsA was assessed [46]. The presence of psoriatic spondylitis in PsA patients was determined by the duration of inflammatory back pain, imaging data, and age at the onset of axial symptoms. The effectiveness of UPA 15 and 30 mg/day or PL was analyzed after 12 and 24 weeks according to the dynamics BASDAI and ASDAS (Ankylosing Spondylitis Disease Activity Score) and achieve a BASDAI50 response. Approximately 31% of patients from SELECT-PsA-1 (534/1704) and 34% from SELECT-PsA-2 (219/640) had axial manifestations. In patients treated with UPA, there was a significantly more pronounced improvement in the activity indices BASDAI, ASDAS-CRP (Ankylosing Spondylitis Disease Activity Score according to the level of CRP) and the dynamics of pain intensity compared with the PL group. By 12 and 24 weeks, significantly more patients in the UPA groups achieved a BASDAI50 response compared to PL (31.2; 43.7; 12.2% and 49.3; 47.1; 18.5%, respectively). After 12 weeks low activity according to ASDAS-CRP reached 47.9 and 62.1% of patients taking UPA 15 and 30 mg/day, inactive disease – 20.9 and 33.5%, respectively. At week 24, in the PAN groups, the number of patients with low activity of psoriatic spondylitis according to ASDAS-CRP increased to 57.7 and 65.0%, while those with inactive disease increased to 37.2 and 43.2%, respectively, which was significantly higher vs. PL. When analyzing the data, 1 new case of uveitis was identified,

respectively, during treatment with PL and UPA 30 mg/day. No cases of inflammatory bowel disease have been reported during UPA therapy.

Thus, UPA proved to be effective not only in peripheral arthritis, dactylitis, enthesitis, and psoriasis, but also in axial manifestations of PsA, which is confirmed by the results of the study obtained in AS. Thus, the phase II/III SELECT-AXIS1 RPCT demonstrated the efficacy of UPA in patients with active AS who did not receive GIBDs and who had an inadequate response (intolerance) to at least 2 NSAIDs [47].

Based on data from the SELECT-PsA-1 and SELECT-PsA-2 RPCT, the efficacy of UPA in mono- or combination therapy with sDMARDs was analyzed [48]. Of the 1916 patients included in the analysis, 574 (30%) received UPA as monotherapy and 1342 (70%) in combination with sDMARDs, in most cases (84%) with MT. The analysis took into account the following endpoints: ACR20/50/70 response, change at week 12 from baseline in pain, and HAQ-DI; a doctor's overall assessment of psoriasis and an improvement of at least 2 points from baseline; PASI 75/90/100 response at week 16; the proportion of patients who achieved resolution of enthesitis, dactylitis, and MDA at week 24. ADRs were analyzed and summarized up to the 24th week. The results of the analysis showed comparable efficacy and safety of UPA both in monotherapy and in combination with sDMARDs.

The safety profile of UPA in PsA is consistent with previously published results in RA. The most common ADRs reported with UPA were upper respiratory tract infections (colds, sinusitis), nausea, cough, fever, rarely severe infections, malignancy, thrombosis, gastrointestinal perforations, laboratory abnormalities, embryofetal toxicity, and very rarely cardiovascular events.

Thus, the data obtained so far allow us to recommend iJAK as a new pathogenetically substantiated approach to the treatment of PsA. The results of RPCTs and long-term observational studies indicate the high efficacy and safety of TOFA and UPA in patients resistant to sDMARD and TNF α therapy. However, the true place of these drugs in the treatment of PsA can only be determined in the process of their use in real clinical practice in comparison with other JAKs and GIBDs in international and national registries. The use of TOFA and UPA will undoubtedly expand the possibilities of PsA therapy.

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Conflict of Interest Statement

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