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# BARICITINIB IN THE BASIC THERAPY OF RESISTANT RHEUMATOID ARTHRITIS

Muhammadieva S. M.
Nabidzhonova D. D.
Abdusolieva Z. T.
Tashkent Medical Academy

**Abstract**

The review presents the latest data on the use of the selective Janus kinase inhibitor (jak) baricitinib (BARI) in patients with rheumatoid arthritis (RA). The results of the use of BARI in RA indicate that it is comparable in effectiveness to genetically engineered biological drugs (GIBP) and tofacitinib, while showing the possibility of achieving the goal of therapy to reduce the dose of BARI to 2 mg / day without loss of effect in most patients and relief of exacerbation that occurred against the background of a reduced dose.

According to data from registries in many countries and open observational studies, BARI has good tolerance for long-term use, including in older patients with ⩾1 risk factor for cardiovascular diseases. There was also a high survival rate of BARI therapy, exceeding, according to some registries, that of tumor necrosis factor α inhibitors. Against the background of taking BARI, rapid (within 1-3 months) a statistically significant reduction in pain, regardless of the degree of suppression of disease activity, correlated with an improvement in the functional status and general condition of patients. The possibility of suppressing the progression of structural damage in RA patients has also been shown, which makes it possible to choose an individual management strategy for such patients.

**Keywords**: Rheumatoid arthritis, Janus kinase inhibitors, baricitinib, efficacy, tolerability.

## INTRODUCTION

Rheumatoid arthritis (RA) currently remains one of the most significant medical and social problems. The number of cases is high in different populations, including among the able-bodied population. This disease is characterized by the severity of the articular process, leading to permanent disability, as well as multiple systemic manifestations. The key element of the pathological process is the synovial membrane of the joint, the inflammation and proliferation of which with the formation of pannus are considered as the most important mechanisms of destruction of articular cartilage and underlying bone. Uncontrolled proliferation of synoviocytes suggests a certain analogy between RA and the cancer process and is one of the reasons for the use of cytotoxic immunosuppressants such as methotrexate as a basic therapy for RA. Nevertheless, despite the rather aggressive therapy using combined immunosuppressive therapy, achieving a significant effect is possible only in some patients. Thus, according to foreign experts, brief episodes of remission over the course of 2 years have been reported in only 45% of patients, while long-term remission is achievable in no more than 14% of patients receiving adequate RA



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therapy [1]. According to modern international and national recommendations, the “Treat to target” strategy provides for achieving remission, if possible, or low disease activity with the mandatory use of synthetic basic anti–inflammatory drugs (HDL) and, if necessary, biological agents. The “gold standard” for starting RA therapy is methotrexate. If monotherapy with methotrexate or its combination with other basic drugs is ineffective, the use of genetically engineered biological drugs (GIBPS) with anti-cytokine effects (TNF-alpha inhibitors, IL-6 inhibitors, etc.) or modulators of the activity of immunocompetent cells (B-lymphocytes, T-lymphocytes) is indicated [2]. It should be emphasized that in the initial treatment of RA, preference is given to synthetic HDL not only because of the lower cost, but also due to their other features, such as low antigenic potential, since they are not protein molecules. Despite a fairly large range of drugs used for the treatment of RA, serious difficulties arise in daily clinical practice when implementing the "T2T" strategy, which is largely due to poor tolerance of recommended doses of standard HDL, contraindications to their use, as well as the development of serious side effects. The most common reasons limiting the long-term use of GIBP are secondary inefficiency, including those related to the immunogenicity of drugs, and serious adverse events. Biological preparations, especially those with the structure of monoclonal antibodies (MCA), are capable of inducing the production of specific anti-drug antibodies, which not only reduce the effectiveness of GIBP, but also lead to the development of secondary immunopathological phenomena, including the development of anaphylactoid reactions [3]. The discovery of the key mechanisms of RA immunopathogenesis provides the basis for new approaches to the pharmacotherapy of this disease [4]. Currently, the role of intracellular signaling systems, in particular the JAK-STAT system, in the activation of immunocompetent cells in response to various extracellular agents has been proven. As is known, the JAK-STAT system provides information transfer from receptors to the cell nucleus and thereby affects DNA transcription. JAK-STAT is a signaling complex consisting of Janus kinases (they got their name due to the presence in one molecule of two kinase domains facing in different directions – like the images of the ancient Roman god Janus) and a signaling protein – a transducer and activator of transcription of STAT (Signal Transducter and Activator of Transcription). The JAK family belongs to the tyrosine kinase group and consists of 4 proteins: JAK1, JAK2, JAK3, and TYK2, which have enzymatic activity and are associated with cytokine receptors. The main function of JAK is to transmit signals from various mediators, in particular from interferon and cytokines (IL6), and to provide a response to these signals from the corresponding target cells. During the interaction of cytokines and the cytokine receptor, janus kinases phosphorylate STAT signaling molecules with the participation of adenosine triphosphate (ATP). The phosphorylation process leads to the activation of STAT proteins, which penetrate into the cell nucleus and induce transcription of those genes whose expression is regulated by this cytokine. Thus, the OFL-STAN system transmits a stimulating signal through transmembrane receptors directly to the promoters of target genes in the cell nucleus, thereby ensuring the functional activation of the effector cell.

In general, the function of JAK is to transmit signals from interferons and cytokines, in particular IL6, and to provide a response to these signals of functional activation of target cells - proliferation, differentiation, migration, apoptosis, etc. The JAK-STAT signaling system plays an important role in many pathological processes, including polycythemia (when a mutation of JAK2 and other



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hematological diseases is observed), as well as in autoimmune pathology, in particular in graft-versus-host reactions, bronchial asthma and RA.

In recent years, a new drug from the class of JAK kinase inhibitors has been proposed for the treatment of RA - tofacitinib (TOFA), a low–molecular-weight oral reversible competitor to the ATP-binding site of JAK, which has a chemical structure similar to ATP. TOFA reversibly inhibits JAK1 and JAK3 and is characterized by functional specificity towards JAK2. This ensures the interruption of the signaling pathway involving the JAK-STAT system: the signal supplied by the cytokine is not transmitted to the cell nucleus, and the biological effects of the cytokine are not carried out [4]. The foreign literature of recent years has presented convincing data on the high efficacy and good tolerability of TOFA, obtained during clinical trials of this drug in patients with RA [1, 8, 9].

Baricitinib (BARI) is an oral selective inhibitor of Janus kinases JAK1/JAK2 with lower affinity for JAK3 and tyrosine kinase. Currently, JAK, targeted synthetic basic anti-inflammatory drugs (NSAIDs), have firmly entered the arsenal of pharmacological agents for the treatment of rheumatoid arthritis (RA).

BARI is approved as monotherapy or in combination with methotrexate (MT) for the treatment of adult patients with moderate to severe active RA. It inhibits the development of X-ray changes, provides improvements in clinical and laboratory parameters, as well as indicators that are evaluated by the patients themselves. In a number of randomized controlled trials (RCTs), it was proved that in groups of patients with insufficient response to classical synthetic basic anti-inflammatory drugs (NSAIDs), including MT, and to tumor necrosis factor α (iTNFa) inhibitors, BARI was statistically significantly more effective than placebo and adalimumab [2-5], and had an equivalent or higher efficacy compared to other targeted drugs, including genetically engineered biologics (GIBP) and tofacitinib (TOFA). In accordance with the latest recommendations of the EULAR (European Alliance of Associations for Rheumatology) 2022, BARI and other iACS are used in the second line of RA therapy, as well as GIBP [6].

Currently, data have emerged on the long-term use of BARI in real clinical practice, in particular on its effectiveness and safety during long-term treatment in comparison with GIBP of various mechanisms of action. These data form the basis of this report. The generalized results of the extended phases (LTE) of the BARI study (up to 9.5 years) are presented in the RA BEYOND study [7-10]. It included patients initially randomized to the RA-BEGIN [4], RA-BEAM [3], or RA-BUILD [2] trials. In RA-BUILD, patients who completed the course before week 24 were included in LTE and received BARI at a dose of 4 or 2 mg/day; in RA-BEAM, patients who completed week 52 were also included in LTE and received BARI at a dose of 4 mg/day. The performance indicators were evaluated as the proportion of patients who were followed for 7 years (364 weeks) and achieved low disease activity (SDI): SDAI (Simplified Disease Activity Index) <11, DAS28 CRP (Disease Activity Score 28, including CRP level) <3.2, CDAI (Clinical Disease Activity Index) <10, as well as remissions: SDAI <3.3, DAS28-CRP< 2.6, CDAI <2.8, and HAQ-DI (Health Assessment Questionnaire Disability Index) <0.5. The data from the RA-BEYOND study demonstrated the continued effectiveness of therapy and maintenance of physical functions for 7 years against the background of the use of BARI in patients with insufficient effect of NSAIDs. Long-term treatment is usually associated with the need to interrupt therapy for



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organizational reasons, due to the need for surgical intervention or due to adverse events (AES). The question arises: will interruptions in treatment lead to a marked exacerbation of the disease? The analysis of the phase III BARI study (RA-BEAM, RA-BUILD, and RA-BEACON) [2-4] showed that 8.5–18.1% of patients interrupted treatment within 24 weeks, most often due to HYPERTENSION (79.2–91.9%), while the break in treatment lasted less than 2 weeks and, as a result, It was usually observed in the first 2 months of BARI treatment in patients who did not receive MT; The first interruption of treatment was observed after an average of 4-5 months [9,11]. During short–term breaks in taking BARI, RA symptoms worsened in many patients: in more than 59% of patients, the duration of morning stiffness increased and in 86-90%, its severity increased, fatigue and pain in the joints increased. At the same time, the deterioration was insignificant – the increase in the duration of morning stiffness did not exceed 30 minutes, and other parameters – 2 points. After resuming BARI's treatment, the patients' condition improved. AES were usually short-term and did not affect the long-term effectiveness of therapy. Although AES were the most common reason for discontinuation of BAR treatment, they rarely recurred after resuming the drug [11].

ACR (American College of Rheuma tology) [12] and EULAR [6] recommends considering the possibility of reducing the dose of basic anti-inflammatory drugs (NSAIDs) in patients who have achieved stable remission. The results of the long-term RA-BEYOND study showed that patients with stable RA or remission of RA who received BARI at a dose of 4 mg/day for ≥15 months or reduced the dose to 2 mg/day maintained the achieved dose (in 80% of patients at a dose of 4 mg/day and in 67% – 2 mg/day) and remission (in 40% of patients – 4 mg/day and in 33% – 2 mg/day) [13]. Reducing the dose to 2 mg/day led to an undetected but statistically significant increase in disease activity after 12, 24 and 48 weeks, and earlier and more frequent relapses were also observed compared with using a dose of 4 mg/day (in 23% of patients taking a dose of 4 mg/day, and in 37% – 2 mg/day; p=0.001). At the same time, patients who received BARI at a dose of 2 mg/day were less likely to have infections, including non-serious ones, than those who continued to take the drug at a dose of 4 mg/day [13]. Overall, the RA-BEYOND study showed that BARI at a dose of 2 mg/day provided acceptable efficacy, and only 1 out of 5 patients returned to a dose of 4 mg/day, which provided the same disease control as before the dose reduction [13]. This may be of particular interest in the treatment of patients at risk of complications.

The general assessment of the patient's disease activity (GAAP) was used in a number of open observational studies. In the RA-BE-REAL study, 6 months after the start of treatment (n=1074), there was a decrease in GAAP by an average of 2.3 points compared with the baseline level with the use of BARI (n=509; monotherapy in 51% of patients). The average change did not significantly differ from that in patients receiving other NSAIDs/GIBP [12]. At the same time, the BARI value was applied to French patients (n=55; monotherapy – in 45%), regardless of whether or not GIBP and MT had been previously treated, GAAP decreased from about 70 to 30 mm on the visual analog scale during 3 months of treatment, which was accompanied by a decrease in pain and an improvement in other clinical parameters (the number of painful and swollen joints, morning stiffness) [15]. In the Japanese cohort (n=32), BARI treatment led to an early decrease in GAAP, and a statistically significant decrease compared to the baseline level after the first month of treatment was recorded in patients who did not use GIBP (from 49.9±18.6 to 21.2±17.6 mm),



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as well as those who had previously used them (from 66.6±25.2 up to 25.4±24.3 mm; p<0.001), but with continued treatment, a more pronounced decrease in GAAP after 3 and 6 months was observed in patients who had not previously received GIBP [14]. In another study in Japanese patients (n=59; in 47.5% – monotherapy) with an inadequate response to NSAIDs or their intolerance to GAAP and the severity of pain during BARI treatment also significantly decreased within 4 weeks, and the achieved improvement persisted throughout the follow-up [18]. In general, studies have shown that pain reduction and GAAP were recorded with the use of BARI both in the first line and after previous treatment with NSAID/GIBP.

Clinical observations in real practice have demonstrated that the appointment of BARI led to a significant improvement in the functional ability of patients in the early stages of therapy – after 3-6 months. [13, 15, 16, 17], and in the cohort of Japanese patients – after the 1st month of treatment [16], and sometimes this improvement was more more pronounced than when using iTNFa [15, 18]. The data of Japanese authors [49] are interesting, who assessed the functional status of patients (n=67) in whom BARI was discontinued when the CDAI dose was reached (n=23), compared with patients who continued taking this drug (n=28). The authors did not note a statistically significant difference in HAQ-DI, although its median increased by 0.17 after discontinuation of treatment (i.e., function may worsen in some patients). The reappointment of BARI made it possible to return to the low disease activity and improve its functional status.

An important place in evaluating the effectiveness of RA pharmacotherapy is occupied by the ability of the drug to suppress the progression of structural damage. It is known that early controlled therapy in accordance with the “Treat-to-Target” strategy [16] leads to a slowdown in the progression of erosive arthritis in the joints of the hands and feet. The development of joint destruction is associated with a greater severity of synovial inflammation, which is more active in patients positive for rheumatoid factor (RF) and/or antibodies to cyclic citrullinated peptide (ACCP) [19]. However, an analysis of targeted drug therapy (HDL and GIBP) in 10 countries in the RABO DA M study (n=511) showed that stricter adherence to the principles of T2T did not lead to a lower progression of radiological changes. The ability of BARI to suppress destruction in RA has been proven in RCT [9]. A thorough analysis of the dynamics of structural damage depending on the degree of suppression of RA activity [20] revealed that BARI, both in monotherapy and in combination with MT, even while maintaining moderate or high RA activity, contributed to the suppression of structural progression, which was more pronounced when administered in combination with MT. These data are of great practical importance, since inhibiting structural progression, regardless of the activity of the disease, can provide medium- and long-term prevention of disability in patients who cannot achieve remission/ low disease activity or who need more time to achieve such a goal. This has another significance for the clinician: compliance with the principles of T2T requires a quick drug change if the goal of treatment (remission or low disease activity) is not achieved. However, when the patient's condition consistently improves while taking BARI, although not to the desired extent [6], the decision to change treatment may be postponed for some time, since there is no need to fear the progression of joint damage and, consequently, irreversible loss of function. Thus, many years of experience in the use of BARI in active RA in real clinical practice has shown its high effectiveness both in the case of previous ineffectiveness of NSAIDs, NSAIDs and GIBP, and as a first-line



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targeted therapy drug with greater efficacy in patients who had not previously received NSAIDs or GIBP. The high safety of the BAR was noted with prolonged use, including with regard to cardiovascular and oncological complications, in the absence of new NSAIDs. Rapid pain reduction has been demonstrated, and data on suppressing the progression of structural damage are also important, even during the period when remission or low disease activity has not been achieved.

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