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A REVIEW OF BARICITINIB: EFFICACY AND SAFETY IN RHEUMATIC DISEASES

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Abstract

Baricitinib is an oral Janus kinase (JAK) inhibitor and a member of the targeted synthetic disease-modifying anti-rheumatic drugs. Baricitinib competitively binds to adenosine triphosphate and inhibits the synthesis of cytokines that play prominent roles in arthritis rheumatoid arthritis pathogenesis by selectively inhibiting JAK1 and JAK2 at an effective dose. Its bioavailability is approximately 80%, and 64% is excreted via the kidney. To evaluate the efficacy and safety of baricitinib, 19 clinical pharmacological studies and 3 phase II, 4 phase III, and one extension study were conducted in patients with rheumatoid RA. The effectiveness of baricitinib has been shown in these studies. Clinical research and real-world data suggest that barictinib is a safe drug; however, it has been reported to have some well-known side effects such as neutropenia, anemia, elevation of transaminase levels, hyperlipidemia, and increased risk of infections. In these studies, major cardiovascular events were found to be similar in frequency to placebo, and the incidence of malignancy was found to be similar to that of age-related cancer in the general population. However, as is the case with other JAK inhibitors, it is recommended to be used with caution in patients with risk factors for deep vein thrombosis, such as advanced age, obesity, and inactivity.

Keywords: Janus kinase, baricitinib, rheumatoid arthritis, disease-modifying anti-rheumatic drug

INTRODUCTION

As the roles of cytokines and the pathophysiological pathways of autoimmune diseases have become clearer, new therapeutic agents have been introduced. Among these agents, Janus kinase (JAK) inhibitors have been approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis (RA) and have been added to the treatment guidelines as second-line therapy.

JAK is a member of the intracellular tyrosine kinase (TYK) family and plays an important role in the signaling pathways of proinflammatory cytokines involved in the pathogenesis of inflammatory and autoimmune diseases. Participating in the signal transduction of Type I and Type II cytokine receptors, this intracellular molecule has 4 different isoforms, JAK1, JAK2, JAK3, and TYK2. These isoforms usually exist as dimers and are responsible for the phosphorylation of other intracellular proteins. Different cytokines use different dimers, and autophosphorylation of JAKs occurs when cytokines bind to receptors on the cell surface. Activated JAKs induce gene transcription and cytokine synthesis by phosphorylating intracellular proteins signal transducers and activators of transcription (STAT) (1,2).

JAK inhibitors are classified by European League Against Rheumatism as targeted synthetic disease-modifying anti-

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rheumatic drug (DMARDs). Of these agents, tofacitinib, baricitinib and upadacitinib are FDA-approved for the treatment of RA. Each JAK inhibitor binds to these receptors with varying selectivity. Tofacitinib inhibits JAK1/3, baricitinib inhibits JAK1/2 and upadacitinib inhibits JAK1 selectively (Figure 1) (1-3).

Methotrexate (MTX) is the gold standard treatment in RA and is recommended as first-line therapy (4,5). Patients who do not respond to this treatment are considered MTX-resistant, and it is recommended to switch to second-line therapy in these patients. Treatment guidelines include biological (b) DMARDs and targeted synthetic DMARDs as second-line therapy. Generally, combination therapy is administered in RA, but MTX treatment is discontinued in one-third of patients due to drug intolerance. In such cases, bDMARDs and JAK inhibitors, which can also be used as monotherapy, stand out as alternative treatment options (4,6).

The first JAK inhibitor, tofacitinib, was approved by the FDA in 2009. In 2017, baricitinib was approved in Europe alongside tofacitinib. Baricitinib competitively binds to the adenosine triphosphate (ATP)-binding site of JAK and blocks phosphate transfer from ATP to JAK, thereby inhibiting JAK activation and JAK/STAT phosphorylation and consequently inhibiting cytokine synthesis. The activation of the JAK1 and JAK2 signaling pathway leads to the synthesis of interleukin (IL)-6, IL-23, granulocyte colony-stimulating factor, granulocyte-macrophage colony-stimulating factor, interferon, and erythropoietin, which play prominent roles in RA pathogenesis. Baricitinib inhibits the synthesis of all these cytokines by selectively inhibiting JAK1 and JAK2 at an effective dose (2).

Oral baricitinib (4 mg) is rapidly absorbed after administration and reaches peak plasma concentration in 1.5 hours. Because its half-life is around 14 hours, it is recommended to be used once daily. Bioavailability is approximately 80%. While 64% is excreted via the kidney without being metabolized, 15% is excreted through the feces. Because of its high renal excretion, a dose reduction is recommended if creatinine clearance is 30-60 mL/min, whereas it is not recommended as a therapeutic option if creatinine clearance is below 30 mL/min. Its absorption is not affected by meals or using it with drugs that affect gastric pH, such as omeprazole. However, it acts as a substrate for many

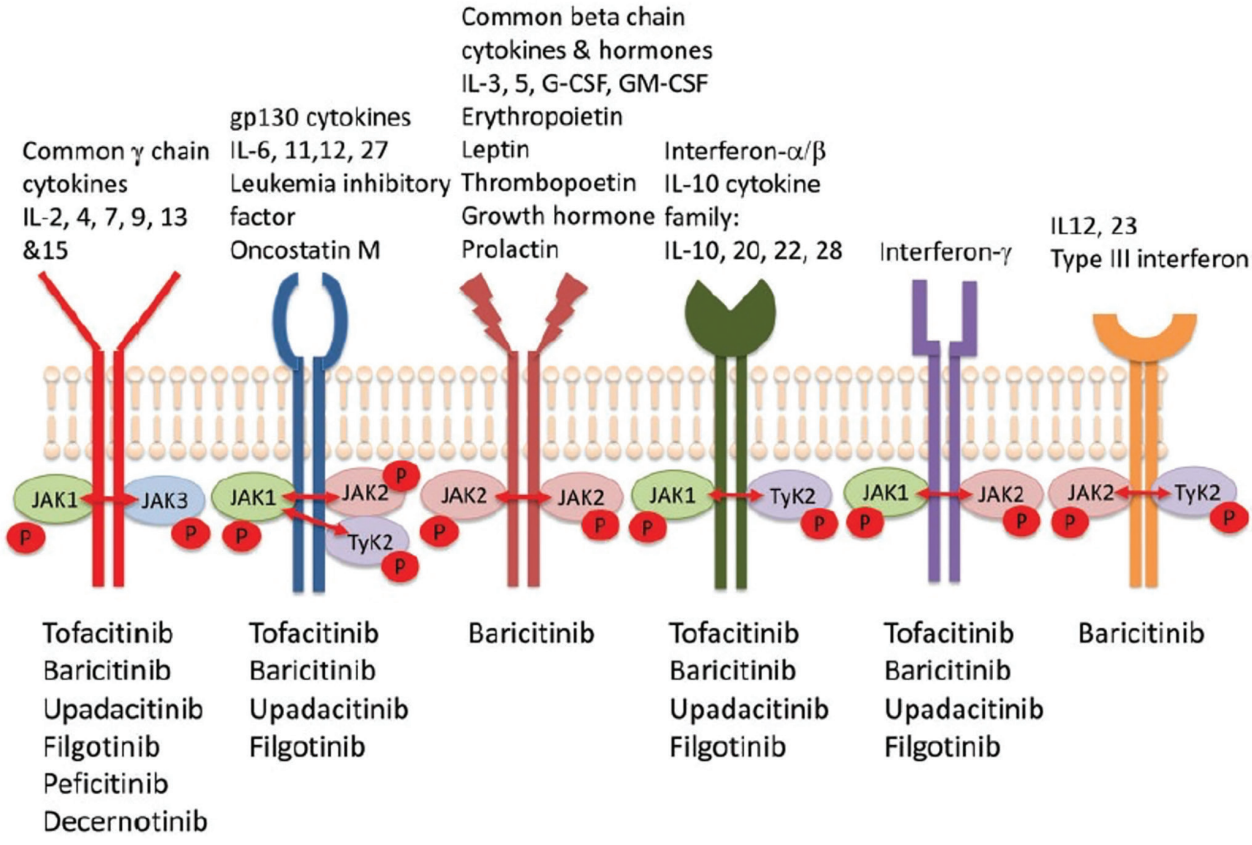

Figure 1. Relationship between JAK inhibitors and cytokines (2)
JAK: Janus kinase, IL: Interleukin, G-CSF: Granulocyte colony-stimulating factor, GM-CSF: Granulocyte-macrophage colony-stimulating factor

renal transporter proteins and may theoretically affect the plasma concentration of drugs such as probenecid, ibuprofen, diclofenac, and leflunomide. In addition, it is recommended to limit the baricitinib dose so that it does not exceed 2 mg daily in patients using probenecid (2).

Efficacy Data

To evaluate the efficacy and safety of baricitinib, 19 clinical pharmacological studies and 3 phase II, 4 phase III, and one extension study were performed. One of the phase III studies, RA-BEGIN, compared 4 mg/day baricitinib with MTX in bDMARD-naive patients with early RA. In this study, it was shown that both baricitinib monotherapy and combination therapy with MTX were superior to MTX monotherapy in terms of efficacy at week 12, and the efficacy was sustained until week 52. In the RA-BEAM study, baricitinib (4 mg) was compared with adalimumab (40 mg) in MTX-resistant RA patients, and American College of Rheumatology (ACR) response at week 12 (70% vs 61%; p=0.014) and the change in disease

activity score 28-C-reactive protein (DAS28-CRP) (-2.24 vs -1.95; p<0.001) were greater in the baricitinib group. This study also emphasized that there was greater improvement in several quality-of-life indices in baricitinib recipients compared with those on placebo and adalimumab, and that this efficacy was sustained for 52 weeks (2,7-9).

In a meta-analysis of MTX-resistant patients, Fakhouri et al. (5) found that the baricitinib-MTX combination was superior to the combination of MTX with other bDMARDs (adalimumab, abatacept, rituximab, infliximab, tocilizumab) in terms of ACR20 and ACR70 responses at week 24, but there was no difference between the two groups in terms of ACR50 responses. No significant superiority was found against the tofacitinib-MTX combination (5).

In a phase III study investigating the efficacy of baricitinib in patients with RA who were resistant to bDMARDs (RA-BEACON), responses to placebo and baricitinib were compared. The authors noted an ACR20 response of 55% for baricitinib and 27% for placebo at week 12 (p<0.001). It was also reported that changes in DAS28-CRP and health assessment questionnaire-disability index scores favored baricitinib (10).

In the RA-BEGIN study, ACR20 responses at week 24 were 77% with baricitinib monotherapy and 62% with MTX monotherapy (p≤0.01). In the same study, structural damage at week 52 was also evaluated, and the odds ratio was 0.62 [95% confidence interval (CI): 0.35, 1.09] in baricitinib monotherapy and 0.39 (95% CI: 0.22-0.70) in combination therapy compared with MTX. It was emphasized that there was a lower likelihood of progression regarding structural damage in patients without a permanent clinical response to the baricitinib-MTX combination and that progression was associated with high hs-CRP, high clinical disease activity index score, female sex, smoking history, and lower body mass index (8,11). Radiological response was evaluated in the RA-BEAM and RA-BUILD studies, and baricitinib was found to significantly prevent the progression of structural joint damage (2,8).

Real-world data from an Italian study of 446 RA patients (34% bDMARD-naive and 66% bDMARD-resistant) treated with baricitinib 4 mg showed a remission rate of 64% and low disease activity rate of 17% at 12 months, with a superior clinical response in the bDMARD-naive group. In this study, it was also emphasized that oral glucocorticoid treatment could be discontinued in 50% of patients in the first year. It was also reported that 24% of patients discontinued treatment because of ineffectiveness and 13% because of side effects, and that the risk of discontinuation because of ineffectiveness was lower in patients with rheumatoid factor and cyclic citrullinated peptide positivity or bDMARD-naive patients (12). With real-world data from Japan (n=4731), it was observed that 24.8% of patients stopped taking the drug before week 24, and the reason for discontinuation in most of the cases (10.1%) was reported to be ineffectiveness (13). In a 9.3-year study comparing baricitinib treatment as monotherapy or in combination with MTX, there was no difference in drug continuation at week 96 between monotherapy (62%) and MTX combination (56%). In this study, it was reported that 30.1% of patients discontinued treatment due to ineffectiveness and 8.6% discontinued treatment due to side effects (14). In a study including 19 different country databases, JAK inhibitors users (41% baricitinib, 59% tofacitinib) were less likely to discontinue because of ineffectiveness and more likely to discontinue because of side effects compared with tumor necrosis factor inhibitors users (15).

Safety Data

Clinical research and real-world data suggest that baricitinib is a safe drug; however, it has been reported to have many effects on laboratory parameters besides its established side effects. Hemograms showed a decrease in neutrophil count in the first month and a return to baseline values after treatment discontinuation. Neutropenia (<1000/mm^3) is rare (<1% of patients) and has not been associated with serious infection. It was reported that lymphocyte count increased in the first month and returned to baseline levels at follow-up. A relationship between lymphopenia and the risk of infection was noted, but this did not appear to increase the likelihood of serious infections. Although

a decrease in platelet count was expected considering the effect of the JAK-2 pathway on thrombopoietin, an increase in platelet count was observed. The platelet count reached baseline levels at week 2 of treatment and remained stable. No significant relationship was found between the thrombocytosis experienced during this period and the potential development of pulmonary embolism (PE)/deep vein thrombosis (DVT). Although a decrease in hemoglobin level is observed at the beginning of treatment because of its effects on erythropoietin, this effect is transient and levels have been reported to return to baseline levels within a short period. Drug discontinuation due to anemia is rare, and the frequency of cases where hemoglobin levels fall below 8 mg/dL is less than 1% (2,7). Nonetheless, it is recommended to discontinue treatment if the absolute neutrophil count is below 1000/mm^3, if the absolute lymphocyte count is below 500/mm^3, and if the hemoglobin level is below 8 mg/dL during baricitinib treatment, and to resume treatment only when laboratory values return to normal (2).

Various changes in the lipid profile have also been reported with baricitinib. Although there was an average increase of 9.5 mg/dL in low density lipoprotein (LDL) cholesterol, 7.3 mg/dL in high density lipoprotein (HDL) cholesterol and 8.5 mg/dL in triglyceride levels, the LDL/HDL ratio did not change and these values reached a plateau at week 12 and remained stable thereafter. Creatinine levels increased by an average of 3.8 µmol/L at week 2 after the initiation of treatment and it was noted that a slight decrease in glomerular filtration rate may develop without loss of renal function. In addition, elevated alanine aminotransferase and aspartate aminotransferase levels were detected in 1.9% and 1.3% of baricitinib monotherapy recipients, respectively, and these elevations in liver function tests were transient in most cases (2,7). However, hepatic dysfunction with a rate of 2.77% during the 24-week follow-up was also reported in a Japanese cohort (13).

During the 24-week follow-up in the RA-BEACON study, side effects were reported in 64% of the placebo group, 71% of the baricitinib 2 mg group, and 77% of the baricitinib 4 mg group. The rate of serious side effects was 7% in the placebo group, 4% in the baricitinib 2 mg group, and 10% in the baricitinib 4 mg group, and the serious infection rates were 3%, 2%, and 3%, respectively. Although herpes zoster (HZ) infections were observed in all groups, they were most common in the baricitinib 4 mg group (4%). None of the groups demonstrated disseminated HZ involvement or organ involvement (10). When the safety data of 9 studies on baricitinib were analyzed, the frequency of serious infections was found to be similar to placebo in a 5.5-year follow-up of 3492 patients, with the most commonly observed serious infections being pneumonia (0.5/100 patient-years), HZ infection (0.4/100 patient-years), urinary tract infection (0.3/100 patient-years), and cellulitis (0.1/100 patient-years). Tuberculosis was reported in only 10 cases, and it was emphasized that these subjects were living in countries with high tuberculosis incidence (2,8,16). In a systematic review of tuberculosis cases associated with JAK inhibitors, the incidence of tuberculosis was reported to be 0.28% (79/28099) with tofacitinib and 0.23% (10/4310) with baricitinib (17).

Looking at the frequency of adverse events in real-world data, adverse events were found to have occurred in 26.87% of patients, whereas serious adverse events occurred in 4.29% of patients during a 24-week follow-up in the Japanese cohort (n=4731). In this cohort, where 54% of the patients were 65 years and older, the frequency of serious infection and HZ were 1.90% and 3.09%, respectively (13). In a database study from Italy, it was observed that within 1 year, 13% of patients discontinued treatment because of side effects, and it was emphasized that the frequency of discontinuation because of side effects was higher, especially in elderly patients and in the bDMARD-resistant patient group [hazard ratio (HR): 1.03, 95% CI: 1.01-1.06; p=0.008 and HR: 1.93, 95% CI: 1.01-3.67; p=0.045, respectively] (12).

When the safety data of 9 studies on baricitinib were evaluated, the frequency of serious adverse events, including death, was 9/100 and the mortality rate was 0.33/100 patient-years in a 5.5-year follow-up of 3492 patients (2). Long-term data from these 9 studies revealed an exposure-adjusted incidence rate (EAIR) of 0.56 for death. Of the 85 deaths, 22.4% were related to cardiovascular events, 22.4% to infection, 22.4% to malignancy, and 15% to respiratory problems, irrespective of the dosage (16). In the Japanese cohort of 4731 patients, mortality was reported to be 0.38% (13).

Major cardiovascular events (MACE) were similar in frequency to placebo, and there was no data that baricitinib aggravated heart failure (2). The data of all studies over a period of 9.3 years showed incidence rates of 0.5 for MACE, 0.35 for DVT, and 0.49 for DVT/PE, and these rates remained stable over time. When patients with PE and DVT were analyzed, it was found that these patients had risk factors such as DVT history, family history, hypertension, chronic obstructive pulmonary disease, pulmonary fibrosis, and varicose veins (2,16). In a Japanese cohort of 4731 patients, MACE and venous thromboembolism were similarly reported to be detected in 0.15% of patients (13).

There were 3 malignancy cases in the RA-BEAM study, whereas there was one malignancy in each of the RA-BUILD and RA-BEGIN studies. The incidence of malignancy in extension studies was similar to that in placebo (baricitinib 0.5/100 patient-years,

placebo 0.5/100 patient-years) (2,8). The long-term data from 9 studies on baricitinib showed that pulmonary and mediastinal malignancies (n=26/EAIR: 0.17), malignancies of the breast (n=23/EAIR: 0.15), and gastrointestinal malignancies (n=19/EAIR: 0.13) were the most common malignancies. These rates were found to be similar to age-related cancer incidence in the general population (16). The malignancy rate was 0.36% within the 24-week follow-up period in the Japanese cohort (13).

In the entire baricitinib case series, diverticulosis was detected at rates similar to those in the general population, and the incidence of gastrointestinal perforation was reported to be 0.06%. It was emphasized that patients with gastrointestinal perforation had non-steroidal anti-inflammatory drugs and steroid use, and that perforation was less common than that reported with tofacitinib and bDMARDs (2,16).

The effects of baricitinib on the reproductive system have not been clearly identified, but animal studies have shown that it has teratogenic effects and a negative impact on female fertility. Severe metrorrhagia in one patient and erectile dysfunction in another patient were reported in clinical trials. As data are insufficient, baricitinib is accepted to be contraindicated during pregnancy (8).

Further Indications

JAK inhibitors are already used for treating RA and are one of the most promising therapeutic agents for many other diseases. Considering the cytokines involved in the pathogenesis of spondyloarthropathy (SpA), JAK inhibition is considered a viable therapeutic objective in PsA and AS. The following studies showing its efficacy and safety in PsA and AS, tofacitinib received FDA approval for both indications. Although there are no studies on baricitinib in SpA, a study in patients with moderate to severe psoriasis reported significant improvements in psoriasis area and severity index 50 and PASI75 scores (18-22). Moreover, there are ongoing studies on baricitinib in systemic lupus erythematosus, giant cell arteritis, alopecia areata, and chronic graft-versus-host disease (8).

CONCLUSION

In conclusion, baricitinib is a targeted drug with proven efficacy and safety in RA with its ease of use as a once-daily oral agent, and it is a good option in RA treatment with similar efficacy to bDMARDs. However, its side effects should be taken into consideration, as is the case with other JAK inhibitors, and it should be used with caution in patients with risk factors for DVT such as older age, obesity, immobility, or a history of DVT.

Footnote

Authorship Contributions

Design: A.Y., S.Ş., Literature Search: A.Y., S.Ş., Writing: A.Y., S.Ş.

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