Baricitinib As A Novel Therapeutic Option for Rheumatoid Arthritis-Mechanism and Efficacy: A Review

ABSTRACT:

Rheumatoid arthritis (RA) is characterized by systemic synovitis, which destroys joints. With the discovery of biological disease-modifying anti-rheumatic medicines (bDMARDs) and the combination of traditional DMARDs, clinical remission is now seen as a reasonable and achievable aim for many patients. However, bDMARDs must be administered via intravenous or subcutaneous injection, and some patients may not react or lose their main response. Under these conditions, targeted synthetic DMARDs (tsDMARDs), which are low-molecular-weight molecules that may be taken orally, have emerged. Five phase 3 studies of Baricitinib, a JAK1 and JAK2 inhibitor, demonstrated good clinical effectiveness in patients with active RA who were naïve to sDMARDs or had an unsatisfactory response to sDMARDs, MTX, or bDMARDs. In patients with rheumatoid arthritis who had not previously been treated with biologic disease-modifying antirheumatic medications (DMARDs), Baricitinib, an oral inhibitor of Janus kinase 1 and 2, decreased disease activity.

Keywords:

Rheumatoid arthritis, Baericitinib, bDMARDs, tsDMARDs, JAK1 inhibitor, JAK2 inhibitors, MTX

INTRODUCTION:

Rheumatoid arthritis (RA) is a systemic autoimmune illness linked to a persistent inflammatory process that can harm extra-articular organs such as the kidney, lung, heart, digestive tract, eyes, skin, and nervous system in addition to joints . To categorise arthritis into non-inflammatory (osteoarthritis) and inflammatory (pseudogout, basic calcium phosphate disease, gout) types, as well as bacterial and viral infections (Staphylococcus aureus, Neisseria gonorrhoea, complications of Lyme disease, parvovirus, enterovirus), and autoimmune processes, a great deal of research and description has been done on arthritis.

Systemic synovitis-induced joint degradation is a characteristic feature of rheumatoid arthritis (RA) [1]. When chondrocytes and fibroblasts are stimulated, cartilage and bone are broken down, leading to the production of osteoclasts and metalloproteinases and joint injury [2,16]. These processes are facilitated by the overproduction of pro-inflammatory cytokines by immune cells in the synovium, such as macrophage colony stimulating factor, interleukins-6 and-17, and tumour necrosis factor-α. [2,17]. This medication has been authorised by the FDA for use in adult patients with moderately to severely active rheumatoid arthritis when other DMARDs, such as tumour necrosis factor antagonist therapies, have not proven to be helpful [3]. Baricitinib is an oral selective inhibitor of JAK1 and JAK2, specifically formulated to treat patients with active rheumatoid arthritis [4].

Baricitinib, a JAK1 and JAK2 inhibitor, has been subjected to five phase 3 trials that have demonstrated excellent clinical efficacy in patients with active RA who have not responded

well to sDMARDs, MTX, or bDMARDs. Adalimumab, MTX, and placebo were used as comparators in studies where there was a positive response for clinical and functional criteria. Additionally, it is stated that safety was bearable within the short trial duration [1,9,10]

JAK inhibitors provide an alternative to traditional RA treatments by targeting cytokine signaling pathways linked to the pathophysiology of RA. In clinical studies including individuals with RA 1–5, the oral, selective JAK1 and JAK2 inhibitor baricitinib has demonstrated clinical effectiveness and tolerable tolerability. Adults with moderately-to-severely active RA are eligible to receive baricitinib therapy in over 50 countries, including the US, Japan, and several European nations [5].

The main therapy goal for individuals with established RA is to achieve minimal disease activity. [28,29] .Many DMARD treatments have been tried by a sizable portion of patients with established RA, but they have not been successful in reaching a low disease activity state. According to clinical research, response rates to all presently prescribed medications decline as cDMARD and bDMARD experience increases [30]. Studies involving patients who have not responded to prior bDMARDs are especially significant since this cohort is growing and has the biggest unmet demand in the RA field. The RA-BEACON trial did not previously evaluate the degree to which patient variables, such as age, illness duration, serological status, or history of using certain bDMARDs, impact the response to baricitinib [31]. These crucial queries are covered in the present analysis [6]

This article aims to compile and summarize the available information about the impact of baricitinib on the development of structural joint damage as well as the underlying mechanisms of these effects. Results measured by magnetic resonance imaging (MRI) or radiographic progression of joint erosion and joint space narrowing in clinical studies and post hoc analyses of patients with RA who are naive to disease-modifying antirheumatic drugs (DMARDs) or who do not respond well to conventional synthetic DMARDs (csDMARDs) are presented. These results were obtained with approved doses of baricitinib (2 mg or 4 mg once daily, except in the USA, Canada, and China, where the approved dose is 2 mg once daily). Furthermore, preclinical baricitinib study results are discussed [2].

DISCUSSION:

When traditional DMARDs are insufficient for treating rheumatoid arthritis, baricitinib, a disease-modifying anti-rheumatic medication, may be used. Adult patients with moderately to severely active rheumatoid arthritis who have not reacted well to previous DMARDs, including tumor necrosis factor antagonist treatments, may use this medicine, according to approval from the U.S. Food and Drug Administration (FDA). Moreover, baricitinib is FDA-approved for the treatment of COVID-19, making it a viable option for hospitalized patients when combined with other medications. This includes pediatric instances that require extracorporeal membrane oxygenation, invasive mechanical ventilation, or supplemental oxygen. Reviewing all the important information on baricitinib therapy in the clinical setting, including mechanisms, side effects, and contraindications, is the aim of this exercise. This exercise is specifically designed to fulfill the requirements of an interdisciplinary medical team that treats patients with rheumatiod arthritis, alopecia areata, and COVID -19 [3] concluded by et al Aman Ahmad.

Mechanism of action

An oral, selective, and reversible JAK inhibitor is called baricitinib. The tyrosine-protein kinase family of intracellular enzymes, JAK, regulates signals from growth factor receptors and cytokines that are important for immune cell activity [3,18] concluded by et al Anam Ahmad, Amanda Mogul, PharmD, BCACP.

Four JAK proteins—TYK2, JAK1, JAK2, and JAK 3—form distinct pairings in different cell receptors to produce homodimers or heterodimers. These JAK dimers stimulate intracellular activity, including the transcription of inflammatory mediator genes, by phosphorylating the STAT proteins. This ultimately sets off an autoimmune reaction [3,19] concluded by et al Anam Ahmad, Musumeci, Francesca.

There is an increased affinity of baricitinib for JAK1 and JAK2. The medication works by blocking these JAK proteins, which stop STATs from becoming phosphorylated and activated. Furthermore, baricitinib modifies the signaling pathway of certain growth factors, interleukins, and interferons. Additionally, baricitinib causes cell death and reduces the growth of JAK1/JAK2 expression in mutant cells. Within one week of starting therapy, baricitinib dramatically lowered blood C-reactive protein levels in rheumatoid arthritis patients.

Alopecia areata is thought to be caused by a confluence of immunological dysregulation and hereditary factors. Important cytokines that depend on JAKs for intracellular signaling, like interleukin-15 and interferon-γ, are implicated in the illness process. Baricitinib has proven to be beneficial in helping people with severe alopecia areata regrow their hair [3,20] concluded by et al Anam Ahmad. Brett King, M.D., Ph.D.

Pharmacokinetics

Absorption: Baricitinib has a 97% bioavailability and is quickly absorbed from the gastrointestinal tract. Baricitinib takes an average of 1.5 hours to reach peak plasma concentration, although it can take anywhere from 0.5 to 3 hours. It has not been demonstrated that administering food alters the peak plasma concentration.

Distribution: Approximately 50% of baricitinib can bind to plasma proteins. Baricitinib's apparent volume of distribution is 76 L, which suggests that the medication is widely distributed throughout the body's tissues.

Metabolism: The hepatic metabolism of approximately 10% of the medication occurs through oxidation by the CYP3A4 enzyme and organic anion transporter-3 (OAT3). The strong OAT3 inhibitor probenecid causes a two-fold rise in blood levels of baricitinib. Consequently, patients taking probenecid at the same time should cut their baricitinib dosage in half [3] concluded by et al Anam Ahmad.

Elimination: In clinical pharmacology trials, the gastrointestinal tract eliminates 20% of the medication, and the kidneys clear about 75% of it. In patients with rheumatoid arthritis, baricitinib has an approximately 12-hour elimination half-life and a renal clearance of about 12 L/h [3,21] concluded by et al Anam Ahmad. Jack G. Shi PhD.

Administration

Available Dosage Forms and Strengths

Oral administration of baricitinib is possible in two dosage forms: 2 mg and 4 mg. For rheumatoid arthritis, a dose of 2 mg taken once daily by mouth is advised. Clinical trials evaluated the effects of 2 mg oral baricitinib in conjunction with 10–14 days of antiviral medication in the setting of COVID-19 infection [22] concluded by et al Feng Huang

Adult dosage

For rheumatoid arthritis, 2 mg of baricitinib taken orally once daily, with or without food, is the suggested dosage. The medication can be taken either alone or in conjunction with methotrexate or non-biologic DMARDs.

COVID-19: The National Institutes of Health advises against using baricitinib as a secondary immunomodulatory medication and in favor of dexamethasone in COVID-19 patients who are exhibiting rapidly increasing oxygen requirements and systemic inflammation. Adults should take 4 mg of baricitinib once a day for a period of 14 days, or until they are released from the hospital [23] concluded by et al S Honda, M Harigai.

Adverse effects

Baricitinib is generally regarded as a safe and well-tolerated drug. However, its immunosuppressive qualities raise the risk of serious infections. The most common adverse events recorded in alopecia areata patients throughout clinical trials were upper respiratory tract infections, acne vulgaris, headaches, urinary tract infections, and folliculitis.[24,25] concluded by et al Egídio Freitas, T Bieber, N Katoh. Herpes zoster infections are also on the rise. Baricitinib has been linked to bone marrow suppression and hematological abnormalities such as anemia, neutropenia, and lymphopenia and should be monitored regularly in the lab. Another side effect commonly seen after 12 weeks of baricitinib treatment is an increase in mean cholesterol, low-density lipoprotein (LDL), and high-density lipoprotein (HDL) levels without an increase in the LDL to HDL ratio. Furthermore, some individuals may have a rise in creatine phosphokinase levels [26,27] concluded by et al D Van Der Heijde, 27 PC Taylor.

Baricitinib for the Treatment of Rheumatoid Arthritis

Since the mid-1990s, the treatment approach to rheumatoid arthritis has undergone significant modifications in the area of rheumatology. With the increased use of traditional synthetic DMARDs, the advent of biologic treatments, and, most recently, the development of novel small compounds that target the JAK pathway, treatment paradigms have changed. A strong and specific JAK1 and JAK2 inhibitor is baricitinib. It has been proposed that various medicines may exhibit differential clinical effects based on their profiles of JAK inhibition [7,32] concluded by et al Mark C. Genovese, M.D., Joel Kremer, M.D., Omid Zamani, M.D., JJ O'Shea, J Israel, H Hakobyan.

Adults with mild to severe active RA are advised to take baricitinib once a day. It is usually administered as a second-choice medication after patients have tried using TNF inhibitors but

did not experience meaningful relief or could not handle the medication owing to adverse effects because of several potentially dangerous side effects.Both brands warn of potential significant adverse effects. Both caution against administering the medicine if there is a known severe illness, such as tuberculosis (TB), and recommend TB screening prior to therapy. Other adverse effects may include kidney, cardiovascular, and eye health [8,33] concluded by et al Ivan Urits1, Jacob Israel2.

Since the mid-1990s, the treatment approach for rheumatoid arthritis has changed dramatically. Treatment paradigms have shifted with the increased use of traditional synthetic DMARDs, the advent of biologic medicines, and, most recently, novel small compounds targeting the JAK pathway. Baricitinib is a very effective and specific inhibitor of JAK1 and JAK2. It has been proposed that medicines with varied JAK inhibition profiles may have unique clinical outcomes.

The purpose of this evaluation was to evaluate the safety and effectiveness of baricitinib in patients with active rheumatoid arthritis who were using conventional synthetic DMARDs but had not responded adequately to earlier biologic DMARD therapy. In this patient cohort, once-daily oral baricitinib resulted in substantial clinical improvements at 12 weeks when compared to placebo. The therapeutic advantages were greater with the 4 mg dosage than with the 2 mg dose. Adverse events, such as non-serious infections, were more common in the baricitinib group than in the placebo group. Baricitinib was associated with lower neutrophil counts, higher creatinine levels, and higher low-density lipoprotein cholesterol levels. These adjustments were primarily modest and did not result in their removal from the research [7] concluded by et al Mark C. Genovese, M.D., Joel Kremer, M.D., Omid Zamani, M.D.

Efficacy of baricitinib in phase II Studies

In the JADA research (phase 2), 301 patients with active RA receiving steady-state MTX and MTX-IR were included. At week 12, 76% of patients in the combined baricitinib 4 and 8 mg group had an ACR20 [11] concluded by et al David T. Felson MD, MPH, response, compared to 41% in the placebo group [12] concluded by et al David T. Felson MD, MPH, .The placebo and 4 mg groups showed significant differences in secondary endpoints, including minimal disease activity and remission. The JADN research (phase 2) included 145 Japanese patients with active RA and MTX-IR receiving steady background MTX. At week 12, the combined baricitinib 4 mg and 8 mg group had a significantly greater ACR20 response rate (77%) than the placebo group (31%), according to a primary efficacy study [13] concluded by et al Yoshiya Tanaka. At week 12, the 2, 4, and 8 mg groups improved similarly across efficacy measures. However, the 4 and 8 mg groups showed earlier onset than the 1 and 2 mg groups as early as week 2 [1] concluded by et al Satoshi Kubo.

Efficacy of Baricitinib in phase III studies

Six phase 3 trials on baricitinib for RA are underway or completed to establish its efficacy, evaluate adverse effects, and compare it to other DMARDs or placebos. In these

investigations, patients in both the baricitinib and control groups received corticosteroids at baseline. Baricitinib should be compared to MTX with corticosteroids, as early RA patients typically get both medications. However, no trials have compared baricitinib to MTX with corticosteroids [1] concluded by et al Satoshi Kubo.

The RA-BEACON trial (JADW) comprised 527 individuals with active RA and TNF-IR. At week 12, 55% of patients who received the 4 mg dosage of baricitinib had an ACR20 response, compared to 27% who received the placebo [14] concluded by et al Charles Ludivico, M.D. Compared to the placebo, there were substantial improvements in the SDAI ≤3.3 ratio. Downloaded by [Weill Cornell Medical College] at 06:35 on July 20, 2016. Week 24 for the baricitinib 4 mg group. All subgroup analyses showed a favorable treatment impact, regardless of prior bDMARD usage (number or kind) [15] concluded by et al Dario Ummarino.

Safety and tolerability of Baricitinib

In the RA-BEACON study[14], concluded by etal Charles Ludivico, M.D. 527 adult patients with moderately to severely active RA who had not responded to or were intolerant to at least one biologic TNF-α inhibitor and were taking background csDMARD therapy experienced more treatment-emergent adverse events (TEAEs) than those taking placebo. Patients receiving the 2 mg and 4 mg doses of baricitinib experienced more adverse events (71%) and 77%, respectively, compared to those receiving the placebo (64%), including infections (44% and 40%, vs. 31%). Mild upper respiratory tract infections were found to significantly lead to imbalances. The baricitinib group saw briefer, transitory disruptions of the study medicine. SAE rates were 4%, 10%, and 7% for the three groups, respectively. The proportion of patients experiencing an SAE was consistent across treatment groups. There were only two non-melanoma skin tumors in the baricitinib 4 mg group, with no reports of solid organ, hematologic, or other malignancies. The trial found two treatment-emergent serious adverse cardiovascular events (MACE): one myocardial infarction (baricitinib 4 mg) and one basilar artery thrombosis (baricitinib 4 mg), which also resulted in one death. No patients had a gastrointestinal perforation.Serum creatinine and LDL cholesterol levels increased, and neutrophil counts somewhat decreased when baricitinib was administered. In the baricitinib groups, very few patients experienced a treatment-emergent laboratory abnormality that led to a permanent discontinuation of the study medicine [1] concluded by et al Satoshi Kubo

CONCLUSION:

In the review, we have described the potential of the JAK inhibitor baricitinib. Baricitinib has demonstrated a greater selectivity for JAK1 and JAK2 than for the other tyrosine kinases, JAK3 and Tyk2, in basic research investigations, suggesting that it may be useful as a molecular target medication. The use of baricitinib in RA is supported by strong evidence, particularly when combined with the existing DMARD treatment.

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