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JANUS KINASE INHIBITORS IN THE TREATMENT OF RHEUMATOID ARTHRITIS - A LITERATURE REVIEW

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterised by persistent joint inflammation, leading to their destruction and deformities. The disease may also manifest with extraarticular symptoms. The pathogenesis of RA is multifactorial, involving genetic, environmental, and immunological factors. Treatment includes disease-modifying antirheumatic drugs, glucocorticosteroids, nonsteroidal anti-inflammatory drugs, biologic TNF-α inhibitors, and janus kinase (JAK) inhibitors. The objective of this study is to present the characteristics of JAK inhibitors, their mechanisms of action, efficacy, and safety. A literature review was conducted using PubMed, Cochrane, Medline, and Google Scholar databases. Data on clinical efficacy, safety profile, and tolerability of tofacitinib, baricitinib, upadacitinib, and filgotinib were collected and analysed. JAK inhibitors block the JAK-STAT pathway, inhibiting pro-inflammatory cytokine signalling. Treatment with tofacitinib, baricitinib, upadacitinib, and filgotinib led to rapid symptom improvement, reduced joint damage, and enhanced quality of life. JAK inhibitors have shown efficacy in patients with methotrexateresistant RA. Adverse effects include infections, gastrointestinal disturbances, and hypercholesterolemia. These drugs can be used as monotherapy or in combination with standard treatment. JAK inhibitors provide an effective and safe alternative for patients with moderate to severe RA who have an inadequate response to other therapies. Treatment with these drugs results in rapid clinical improvement, limits progression of joint damage, and improves patients' quality of life, representing a modern treat-to-target therapeutic strategy.

KEYWORDS

Rheumatoid Arthritis, Rheumatology, Arthritis, Janus Kinase

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Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease characterized by persistent inflammation of the synovial membrane, developing symmetrically, primarily in the small joints of the hands and feet [1,2]. Joint discomfort involves pain, swelling, and heat. Furthermore, range of motion is limited. Over time, inflammation leads to joint and tendon destruction and even joint deformation [3]. Changes in the anatomy and physiology of joints cause hyperplasia of the synovial membrane and activation of endothelial cells, which then leads to cartilage destruction and bone erosion [4]. RA does not only affect the joints. The most common extra-articular symptoms include malaise, fatigue, vasculitis, pericarditis, pleurisy, rheumatoid nodules, and inflammation of the eye structures [5]. The pathogenesis of the disease is multifactorial. Predisposing factors for RA include, among others, low education, smoking, low economic status, epigenetic factors, and traumatic experiences [1]. Furthermore, there are reports suggesting that in individuals with a genetic predisposition, environmental factors such as infections may trigger an excessive immune response against autoantigens located in the joints, contributing to the development of the disease [6]. The 2015 American College of Rheumatology (ACR) guidelines and the European Alliance of Associations for Rheumatology (EULAR) guidelines recommend initiating treatment for patients with RA as soon as possible due to the severe course of the disease [7]. Drugs used in the treatment of RA include immunosuppressants, anti-inflammatory drugs, analgesics, and biologics [1]. Disease-modifying antirheumatic drugs (DMARDs) include methotrexate, sulfasalazine, leflunomide, chloroquine, and hydroxychloroquine. Glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs) are particularly used to treat disease flares. It should be noted that glucocorticoids require cautious use due to their well-documented adverse effects. Biological drugs used in the treatment of RA include, primarily, tumor necrosis factor alpha (TNF-α) inhibitors, as well as golimumab, adalimumab, certolizumab, infliximab, and etanercept. Biological drugs with a different mechanism of action include tocilizumab, rituximab, and abatacept [8]. A new class of oral drugs in the treatment of RA are Janus-activated kinase (JAK) inhibitors. These include tofacitinib, baricitinib, upadacitinib, and filgotinib [1]. According to the ACR guidelines, JAK inhibitors are recommended as part of a treat-to-target approach. This recommendation involves optimizing methotrexate dosing and subsequently adding other disease-modifying antirheumatic drugs [9]. Indirect comparisons using systematic reviews and meta-analyses suggest that although there are differences in the tolerability and efficacy profiles of JAK inhibitors, all four JAK inhibitors - tofacitinib, baricitinib, upadacitinib, and filgotinib - are effective alternatives for the treatment of RA in patients with inadequate response to disease-modifying antirheumatic drugs [10]. The aim of this review is to provide a comprehensive overview of JAK inhibitors approved for use in the treatment of RA.

Methods

A literature review was conducted using the PubMed Cochrane and Medline databases, as well as Google Scholar. Data regarding the clinical efficacy, safety profile, and tolerability of JAK inhibitors - tofacitinib, baricitinib, upadacitinib, and filgotinib - were searched. Articles from 2017 to 2025 were focused on the literature. Older publications were also included where relevant. The review included Phase II and III clinical trials, including the ORAL, RA-BEGIN, RA-BEAM, SELECT, and FINCH studies. Information on use in pediatric patients and guidelines for treatment during pregnancy and breastfeeding were also included. Exclusion criteria included case reports, non-peer-reviewed sources, and those not relevant to the subject matter of the paper.

Mechanism of action of JAK inhibitors

Janus kinase inhibitors are enzymes belonging to the tyrosine kinase family, strongly associated with the intracellular domains of type I and II receptors. Type I receptors bind interleukins and hormones, while type II receptors bind interferons and cytokines related to interleukin-10 [11]. The pharmacological target of JAKs is to modify cytokine signaling. These drugs bind to the signal transducers and activators of transcription (STAT) family of proteins. These proteins generate rapid expression of target genes in response to cytokines [12]. JAK inhibitors block a specific ATP-binding pocket, which disrupts the intracellular JAK-STAT signaling cascade. This ultimately leads to the transition of immune cells to a proinflammatory phenotype. Four different types of JAKs-JAK1, JAK2, JAK3, and TYK2 - and seven different STATs - STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6-can combine in various combinations to activate numerous signaling pathways, including those dependent on interferons, interleukins, and hematopoietic hormones [13,14]. Interaction between cytokines and their respective receptors induces dimerization of these receptors and subsequent JAK activation. Cytokine receptors utilize the binding of JAK enzymes to autophosphorylate

tyrosine residues present in the cytoplasmic domains of cytokine receptors. This phosphorylation leads to the activation of STAT proteins, followed by the dimerization of ScTAT monomers and the translocation of STAT dimers into the cell nucleus. After translocation into the nucleus, STAT dimers act as transcription factors, regulating the expression of target genes [15].

Tofacitinib

The first JAK inhibitor developed for the treatment of autoimmune diseases was tofacitinib [16]. Tofacitinib is a first-generation, non-selective JAK inhibitor. It works by inhibiting JAK1, JAK2, JAK3, and, to a lesser extent, TYK2 kinases. It is currently used for three indications. In addition to rheumatoid arthritis, it is also used for psoriatic arthritis and ulcerative colitis [17]. The Food and Drug Administration (FDA) approved this drug in 2012, and the European Medicines Agency (EMA) approved it in 2017. This drug is approved for use as monotherapy or in combination with DMARDs, including methotrexate. It is effective in patients with RA who have not achieved a satisfactory response to methotrexate treatment. The dosing regimen is 5 milligrams twice daily [16]. Following oral administration, the drug is rapidly absorbed, with steady-state achieved within 24-48 hours of the first dose. STAT inhibition wears off within approximately 24 hours of discontinuing treatment, but in patients who have been taking the drug for at least 28 days, this effect may persist for up to 2 weeks after discontinuation [18]. The drug's efficacy in the treatment of RA was confirmed in six randomized phase III trials within the ORAL study and in long-term studies. Long-term efficacy was assessed in the ORAL Sequel study in 4,481 patients. Using the drug as monotherapy or in combination with classic disease-modifying antirheumatic drugs, clinical and radiological improvement was demonstrated compared to placebo and efficacy comparable to adalimumab. The effects were noticeable after the first month of treatment and were maintained during long-term follow-up for up to 96 months. Long-term use of the drug was associated with sustained remission in patients and limited progression of structural damage [1,19-22]. Randomized clinical trials in adult patients with RA demonstrated efficacy in both early and advanced disease. Its efficacy has also been confirmed in clinical practice. Tofacitinib prevents progression of joint damage and leads to rapid improvement in patient-reported symptoms [16]. Adverse effects include infections and gastrointestinal disorders. In one study, herpes zoster virus (ZV) occurred in 13 of 373 (3.5%) patients in the group receiving the drug at a dose of 5 milligrams and in 18 of 397 (4.5%) patients in the group receiving tofacitinib at a dose of 10 milligrams [23]. In addition, nasopharyngitis, lower respiratory tract infection, reactivation of herpes zoster virus (HZV), urinary tract infection, nausea, increased serum creatinine, dyslipidemia, increased liver enzymes, anemia, and headache were frequently observed in more than 1 in 10 patients studied [24].

Baricitinib

Another first-generation JAK inhibitor, obtained by modifying the structure of tofacitinib, is baricitinib. It prevents the activation of JAK 1 and JAK 2 molecules, which consequently inhibits the expression of interleukin 6 [1]. This interleukin is one of the main factors causing the inflammatory response associated with rheumatoid arthritis, contributing to joint damage and other complications [25]. In adult patients, this drug is administered orally at a dose of 2 milligrams once daily. It can be used in combination with methotrexate and other disease-modifying antirheumatic drugs in patients who partially respond to these drugs. Baricitinib can be used as monotherapy in patients who discontinue treatment due to drug intolerance or failure to achieve the therapeutic target. Individuals over 75 years of age, with renal impairment, and with recurrent infections should use a dose of 1 milligram once daily. The drug is contraindicated in patients with severe hepatic impairment and in those with creatinine clearance less than 30 mL/min/1.73 m2 [1]. Clinical trials assessed ACR improvement criteria, which include a percentage reduction in the number of tender and swollen joints compared to pretreatment, by 20, 50, or 70%, and a percentage improvement in at least 3 of 5 criteria. These criteria include the patient's global assessment of disease activity, the physician's global assessment of disease activity, subjective assessment of pain intensity, disability level, and erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP) level [26]. The clinical efficacy of baricitinib used as monotherapy or in combination in patients with RA was assessed in four randomized, double-blind, placebo-controlled phase III clinical trials. The RA-BEGIN and RA-BEAM studies were long-term, 52-week, active-controlled trials. The RA-BUILD and RA-BEACON trials were 24-week, randomized, placebo-controlled trials. All studies met their primary endpoint, which consisted of the percentage of patients meeting the ACR20 improvement criteria at week 12 or 24. Improvement was defined as a patient achieving at least a 20% improvement in clinical and laboratory parameters. Key secondary endpoints were achieved in the baricitinib group compared with the placebo group. These included the ACR 50 and 70 response rates, as well as the CRP-based Disease Activity Score 28 (DAS 28-CRP), the Simplified Disease Activity Index (SDAI), and the Health Assessment Questionnaire Disability Index (HAQ-DI). The DAS28-CRP is an index that assesses RA activity based on the number of tender and

swollen joints, CRP levels, and the patient's subjective assessment of health status. It allows for objective classification of disease activity and monitoring of treatment response, including assessment of remission. The SDAI combines the number of tender and swollen joints, CRP, and patient and physician assessments to determine disease activity. The HAQ-DI measures the patient's daily function and the impact of the disease on their ability to perform basic activities [27–30]. Studies show that in patients with rheumatoid arthritis who had an inadequate response to methotrexate, baricitinib was associated with better clinical improvement compared to placebo. This drug also demonstrated better results than adalimumab. In patients with rheumatoid arthritis, baricitinib treatment significantly reduced CRP levels within 1 week of treatment initiation [29]. Baricitinib is rapidly absorbed from the gastrointestinal tract and has a high bioavailability of approximately 97%. Peak concentrations are achieved within approximately 30 minutes to 3 hours. The half-life is approximately 12 hours, necessitating daily administration [31]. Among the adverse events, the most frequently reported were infections and hypercholesterolemia. The most common infections were varicella-zoster virus (VZV) infections. Hypercholesterolemia was a dose-dependent adverse effect. When using the drug, the risk of HZV reactivation and inflammation of the stomach, intestines, lungs, and urinary tract was increased [32].

Upadacitinib

Upadacitinib is a selective JAK1 inhibitor. It has been approved by the FDA and EMA at a dose of 15 milligrams once daily for adult patients with moderately to severely active rheumatoid arthritis who do not respond adequately to or are intolerant to methotrexate [32,33]. The efficacy of upadacitinib was evaluated in two Phase II trials, including BALANCE 1 and BALANCE 2.The trial included patients who had failed methotrexate and biologics. The results showed rapid, dose-dependent improvement in symptoms, with a similar tolerability profile to other JAK inhibitors [34]. The drug was also studied in multiple Phase III RCTs, including the SELECT-NEXT, SELECTMONOTHERAPY, SELECT-COMPARE, and SELECT-EARLY trials. The studies included patients with an inadequate response to at least one disease-modifying antirheumatic drug. One group of patients received the drug at a dose of 15 milligrams or 30 milligrams, while the other group received a placebo. The results showed significant improvements in ACR20 responses within 7 days, and ACR50 and ACR70 responses from day 14 of therapy. DAS28-CRP scores and the Clinical Disease Activity Index (CDAI) improved after treatment. Approximately half of the patients rated their disease activity as low by week 12. Quality of life and physical function also significantly improved, and morning stiffness and fatigue decreased [35,36]. This drug is also used for psoriatic arthritis, ankylosing spondylitis, atopic dermatitis, Crohn's disease, and ulcerative colitis [9]. Upadacitinib is not recommended for use with other JAK inhibitors, azathioprine, and cyclosporine, but it can be combined with methotrexate [37]. Following oral administration of the extended-release formulation of upadacitinib, absorption occurs within 2 to 4 hours [9]. The most commonly reported adverse reactions include upper respiratory tract infections such as acute sinusitis, laryngitis, nasopharyngitis, pharyngitis, and tonsillitis, rhinitis, and nausea. Fever, cough, and elevated liver enzymes have been reported less frequently [36].

Filgotinib

The drug is approved for the treatment of moderately to severely active rheumatoid arthritis in adult patients who have failed to respond to or are intolerant to one or more disease-modifying antirheumatic drugs (DMARDs). It is administered orally at a dose of 100 or 200 milligrams per day. Concomitant use of filgotinib with other JAK inhibitors, biologic disease-modifying antirheumatic drugs (DMARDs), cyclosporine, azathioprine, or tacrolimus is not recommended [10]. The efficacy and safety of filgotinib in patients with rheumatoid arthritis who failed to respond to methotrexate were evaluated in two Phase IIa studies. Both studies demonstrated a satisfactory efficacy profile [38]. In one study, a single-center, four-week proof-of-concept study conducted in 2017, patients were randomly assigned to receive filgotinib at a dose of 200 milligrams daily or placebo. A statistically significant number of patients achieved an ACR20 response compared to placebo. Patients treated with filgotinib also experienced a reduction in serum CRP and DAS28-CRP scores. The study demonstrated a satisfactory efficacy profile, with no safety concerns reported [38]. The DARWIN 1 and DARWIN 2 Phase IIb studies evaluated a wide range of doses and different dosing regimens. The results showed that the drug at a dose of 100 milligrams or 200 milligrams once daily was well tolerated and effective. It can be administered as monotherapy or in combination in patients with active RA [39,40]. Results from the 24-week phase III FINCH2 study confirmed the efficacy of the drug at doses of 100 and 200 milligrams once daily in patients with refractory RA [41]. Filgotinib is as effective as adalimumab in achieving low disease activity in patients with an inadequate response to methotrexate. The most commonly reported adverse events include nausea, urinary tract infections, dizziness, and upper respiratory tract infections [10].

JAK Inhibitors in children

The pathogenesis of RA and juvenile idiopathic arthritis (JIA) is similar, and more than 50% of patients with JIA may develop RA in the future. Currently, there are no published data regarding the use of baricitinib in children with JIA [42]. The FDA has approved the use of baricitinib only for the treatment of respiratory disease caused by SARS-CoV-2 infection in hospitalized pediatric patients aged 2 to 17 years who require oxygen therapy, continuous extracorporeal membrane oxygenation (ECMO), or mechanical ventilation [31]. Three Phase III clinical trials assessed the safety and efficacy of this drug in patients aged 2 to 18 years [42]. The evidence for the use of other JAK inhibitors in pediatric patients is also very limited. Phase II and III clinical trials are currently underway for tofacitinib in children [43]. Studies on the use of upadacitinib in children are ongoing, but they are focused on alopecia areata. Currently, therapeutic options for this drug in pediatric patients with rheumatological diseases are very limited [44]. Regarding filgotinib, the safety and efficacy of use in patients under 18 years of age have not been established [10].

JAK inhibitors during pregnancy and breastfeeding

Due to the potential teratogenic effects and effects on fetal birth weight, baricitinib should be discontinued at least one month before a planned pregnancy, while women of childbearing age are advised to use effective contraception. Currently, there are no data on whether this drug passes into human milk, so it is recommended to discontinue it during breastfeeding [31]. Based on studies on the use of tofacitinib during pregnancy, it can be assumed that unintentional exposure to the drug does not appear to be associated with an increased risk to the fetus compared to the risk in the general population [45]. Due to the teratogenic risk of upadacitinib, this drug should also not be used during pregnancy. Contraception is recommended during treatment and for at least 4 weeks after its completion. Women are also advised to refrain from breastfeeding during therapy, as animal studies have shown that this drug is excreted in breast milk. Breastfeeding should be avoided for 6 days after the last dose of upadacitinib [46]. Breastfeeding should also be avoided during treatment with filgotinib, and contraception is recommended during treatment and for more than one week after its discontinuation [10].

Summary

JAK kinase inhibitors are a modern class of drugs used in the treatment of rheumatoid arthritis, particularly in patients who fail to achieve the desired therapeutic effect or experience adverse reactions with disease-modifying antirheumatic drugs. These drugs act by blocking the JAKSTAT kinase, ultimately inhibiting the signaling of proinflammatory cytokines. This leads to a reduction in disease activity, limited joint destruction, and improved quality of life for patients. Tofacitinib has been approved by the FDA and EMA for use as monotherapy or in combination therapy. Phase III clinical trials conducted as part of the ORAL program have confirmed its clinical efficacy, with effects observed after just one month of treatment. Long-term follow-up has demonstrated maintenance of remission for up to 96 months. The drug is rapidly absorbed and reaches steady-state concentrations within 24-48 hours. The most common adverse events include respiratory and urinary tract infections, HZV reactivation, dyslipidemia, nausea, and elevated liver enzymes. Baricitinib's effectiveness has been demonstrated in Phase III trials: RA-BEGIN, RA-BEAM, RABUILD, and RA-BEACON. The drug acts rapidly, lowering CRP levels in as little as one week. The most frequently reported adverse events are infections and hypercholesterolemia. This drug is contraindicated in patients with severe renal or hepatic impairment. Upadacitinib is approved for the treatment of adult patients with moderate to severe RA. Phase II and III clinical trials, including SELECT-NEXT, SELECTMONOTHERAPY, and SELECT-COMPARE, demonstrated rapid therapeutic effects, observed after just seven days, with increases in the second week of treatment. The drug improves quality of life and reduces morning stiffness. Its most common side effects include upper respiratory tract infections and elevated liver enzymes. Filgotinib is used in adult patients with moderate to severe RA. Efficacy was confirmed in the DARWIN 1 and 2 and FINCH2 studies, which demonstrated significant clinical improvement and good treatment tolerability. Adverse effects include nausea, urinary tract infections, dizziness, and upper respiratory tract infections. The use of JAK inhibitors in children is limited due to insufficient data on safety and efficacy. Studies are ongoing on tofacitinib and baricitinib for selected pediatric indications. JAK inhibitors are contraindicated during pregnancy and breastfeeding due to the risk of teratogenicity and the potential risk of excretion in breast milk.

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