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JAK INHIBITORS IN THE TREATMENT OF RHEUMATOID ARTHRITIS: EFFICACY, SAFETY AND CURRENT PERSPECTIVES

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Abstract: Objective: To analyze the role of JAK inhibitors in the treatment of rheumatoid arthritis, assessing their efficacy, safety and impact on patients' quality of life. **Methodology:** Bibliographic review conducted according to the PVO strategy. Articles were searched in the PubMed-MEDLINE database using descriptors related to rheumatoid arthritis and JAK inhibitors. After applying inclusion and exclusion criteria, 28 articles were selected for analysis. **Discussion:** RA is a chronic immune-mediated inflammatory disease which, in addition to joint involvement, can cause extra-articular manifestations such as pericarditis, vasculitis and pleural effusion, impacting on the patient's quality of life. With an incidence of approximately 1% of the population, RA is more prevalent in women and its frequency increases with age. The development of JAK inhibitors, such as tofacitinib, baricitinib, upadacitinib and filgotinib, represented a breakthrough in treatment, reducing inflammatory activity and preserving joint function. However, the safety profile of these molecules varies according to their selectivity for JAK isoforms. While more selective drugs, such as upadacitinib and filgotinib, reduce the impact on hematopoietic pathways, others, such as tofacitinib and baricitinib, inhibit multiple isoforms, increasing the risk of opportunistic infections, cardiovascular events and potentially increasing the risk of malignancy. **Final considerations:** JAK inhibitors are an effective therapeutic alternative for RA, comparable to biological DMARDs and with convenient oral administration. However, long-term safety requires close monitoring. Future research is essential to refine patient selection and optimize therapeutic strategies, ensuring a balance between clinical benefits and potential risks.

Keywords: Rheumatoid arthritis; JAK inhibitors; Chronic inflammation; Extra-articular manifestations; Therapeutic safety.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic, immune-mediated inflammatory disease with an etiology that is not yet fully understood. It predominantly affects females, with a peak incidence around the age of 50 (Oliveira *et al.*, 2019). Clinically, it is characterized by pain, swelling, heat and redness in the joints, mainly affecting the hands and wrists. In addition, it can compromise segments of the spine, such as the cervical, thoracic and lumbar discs, and trigger extra-articular manifestations, including pleural effusion, pericarditis and vasculitis, increasing morbidity and negatively impacting patients' quality of life (Yoshida *et al.*, 2023). Early identification of the disease and appropriate treatment are essential, as uncontrolled progression can lead to irreversible damage.

Over the last few decades, the treatment of RA has undergone significant advances, especially with the development of biological anti-rheumatic drugs that modify the course of the disease (MMCDbio) and, more recently, Janus kinase (JAK) inhibitors. Initially approved for cases refractory to conventional treatment with synthetic DMARDs (DMARDs), JAK inhibitors have established themselves as a promising alternative for controlling inflammation and preventing disease progression. The first representative of this class, tofacitinib, was approved in Japan in 2013, followed by baricitinib (2017), peficitinib (2019), upadacitinib (2020) and filgotinib (2020), all of which have demonstrated efficacy comparable to those of biosimilar DMARDs, despite differences in the mechanism of action and route of administration (Morinobu, 2020; Kaneko, 2020).

Despite their therapeutic benefits, the safety profile of JAK inhibitors requires close monitoring. These drugs are associated with an increased risk of opportunistic infections, liver and kidney dysfunction, as well as hematological effects such as lymphopenia. Recent studies also point to a possible increase in the incidence of malignancies and major adverse cardiovascular events (MACEs) in patients treated with JAK inhibitors, making continuous surveillance essential to optimize the management of these risks (Fleischmann *et al.*, 2024; Yoshida *et al.*, 2023).

Among the JAK inhibitors available, peficitinib stands out, a pan-JAK inhibitor approved in Japan and South Korea, which simultaneously blocks all members of the JAK family, differentiating it from other drugs in this class. Clinical trials have shown its efficacy in reducing inflammatory activity and preserving joint function , with a safety profile similar to that of other JAK inhibitors, including an increased risk of herpes zoster and elevated liver enzymes (Kaneko, 2020).

The substantial impact of RA on patients' quality of life, recent advances that broaden the therapeutic options available, and challenges such as the risk-benefit ratio of JAK inhibitors, access barriers due to the high cost and the need for specific protocols for their safe use are still issues that require further study and research.

This study aims to analyze the efficacy and safety of JAK inhibitors in the treatment of moderate to severe rheumatoid arthritis by analyzing the main drugs in this class, including tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib, with an emphasis on their mechanisms of action, pharmacological characteristics and clinical impact.

METHODOLOGY

A literature review developed according to the criteria of the PVO strategy, an acronym that stands for: population or research problem, variables and outcome. This strategy was used to develop the research question What is the efficacy and safety of JAK inhibitors, including tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib, in the

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treatment of patients with moderate to severe rheumatoid arthritis? The searches were carried out using the PubMed - MEDLINE (Medical Literature Analysis and Retrieval System Online) databases. The search terms were used in combination with the Boolean terms "**AND" and "OR",** (mention which operators were used), using the following search strategy: ("Arthritis, Rheumatoid") AND (("Janus Kinase Inhibitors") OR (tofacitinib) OR (baricitinib) OR (upadacitinib) OR (filgotinib) OR (peficitinib)). From this search, **877** articles were found, which were then submitted to the selection criteria. The inclusion criteria were: : articles in the English language; published between 2020 and 2025 and which addressed the themes proposed for this research, studies of the type (narrative review, systematic review, meta-analysis, observational studies, experimental studies. The exclusion criteria were: duplicate articles, articles available in abstract form, articles that did not directly address the proposal studied and articles that did not meet the other inclusion criteria. After applying the search strategy to the database, a total of **36** articles were found. After applying the inclusion and exclusion criteria, **21** articles were selected from the PubMed database to make up this study's collection.

DISCUSSION

Rheumatoid arthritis is a chronic, systemic autoimmune disease characterized by an adverse prognosis that mainly affects the synovium and joints, leading to their degeneration (Chen *et al.*, 2023). Van Vollenhoven *et al.* (2024) state that RA is an inflammatory condition affecting the whole organism that can lead to loss of functionality, persistent pain and a higher risk of mortality, significantly compromising patients' quality of life. In addition, the disease can also manifest itself beyond the joints, causing inflammation in organs such as the eyes, skin, heart and lungs (Kim; Keam; Susan, 2021)The worldwide prevalence of RA is approximately 1%, and it is more common in women (Ivorra; Llevate; Montoro, 2022). Its occurrence rate varies between 3.1 and 10.7 per 1000 individuals in Europe, the United States and Japan, and between 60% and 69% of patients have the disease at a stage of moderate to severe activity (Chan *et al.,* 2021). In addition, the prevalence of rheumatoid arthritis increases with age, being more frequently diagnosed in women in the sixth decade of life (Martinez-Molina *et al.,* 2024).

Although it can occur in any age group, elderly patients are at greater risk of disease complications and treatment-related adverse events. Research shows that discontinuation of JAK-STAT pathway inhibitors is more associated with adverse effects than lack of efficacy, with an increased risk in older patients (HR: 1.98; p = 0.030), as evidenced by discontinuation rates: 14.4% in young people versus 26.3% in the elderly (p = 0.019) (Martinez--Molina *et al.*,2024). These findings highlight the need for personalized therapeutic strategies to improve adherence to treatment in different age groups.

The Janus kinase and transcription activator (JAK-STAT) pathway is fundamental in the regulation of the immune system and is involved in the intracellular signaling of various cytokines associated with RA (Traves *et al.*, 2021). The process of activating this pathway begins with the binding of a cytokine to its receptor on the cell membrane, promoting the phosphorylation of Janus kinase proteins (JAKs). These, in turn, activate transcription transducers and activators (STATs), which dimerize and migrate to the nucleus, modulating the transcription of inflammatory genes and contributing to the perpetuation of the autoimmune response. In humans, there are four members of the JAK family: JAK1, JAK2, JAK3 and TYK2, the first three of which are associated with cytokine receptor signaling,

while TYK2 interacts indirectly in this process (Clarke *et al*., 2021). In order to mitigate the inflammatory process caused by the cytokines present in RA, it is important to evaluate the role of the JAK-STAT pathway, whose isoforms are known to be related to the control of inflammation, hematopoiesis and immunity. The study by Traves *et al.* (2021) evaluated the selectivity and pharmacodynamic effects of the Janus kinase inhibitors (JAKinibs) filgotinib, baricitinib, tofacitinib and upadacitinib in in vitro and ex vivo models, using blood samples from healthy individuals and patients with rheumatoid arthritis. There were significant differences in the inhibition of the different forms of the JAK enzyme, especially filgotinib, which showed greater selectivity for JAK1, with less inhibition of JAK2 and JAK3-dependent pathways, compared to the other inhibitors. Although the methodology of this study did not take into account the full physiological complexity of humans and was limited to blood samples, it indicates a possible greater safety profile of the JAK1 pathway inhibitor drug, which is related to a lower risk of adverse events related to the bone marrow and immunosuppression, as seen in other studies evaluating the isolated efficacy of JAKinibs. However, extrapolating the possible mechanistic data obtained to the human context should be done with caution, and large-scale studies are needed to obtain better evidence to confirm the results.

The SELECT-EARLY study evaluated upadacitinib (15 mg or 30 mg) in patients with moderate to severe RA, without previous use of methotrexate (MTX), with follow-up of up to five years. Upadacitinib (15 mg) demonstrated sustained efficacy in improving physical function, reducing pain and decreasing morning stiffness. However, limitations include selection bias in patients who responded well to treatment, lack of population heterogeneity and a higher incidence of adverse events with the 30 mg dose. Despite these limitations, the study reinforces the potential of innovative therapies in cases of intolerance to standard treatment, with a positive impact on patients' quality of life (Van Vollenhoven *et al*., 2024).

The chronic inflammation observed in RA is associated with high levels of pro-inflammatory cytokines, such as Tumor Necrosis Factor α, Interleukin 6, Interleukin 1β (TNF-α, IL-6 and IL-1β), which play a central role in the activation of inflammatory genes and the progression of joint damage. These cytokines promote chromatin remodeling, the persistent activation of fibroblast-like synoviocytes (FLS) and the induction of osteoclastogenesis, resulting in bone and joint destruction. TNF--α, in particular, stimulates the activation of inflammasomes, such as NLRP3, leading to the release of IL-1β and caspase-1, which are fundamental in the process of pyroptosis - a form of inflammatory cell death that aggravates the progression of the disease (Chen *et al*., 2023). Although studies in animal models are useful for understanding these pathophysiological mechanisms, extrapolation to the human context should be done with caution. Thus, understanding the pathophysiology of RA and the involvement of the JAK-STAT pathway in the pathogenesis of the disease provides a basis for the use of target therapies, such as JAK inhibitors. Continued research into these mechanisms and the clinical validation of new drugs are essential to optimize the treatment of RA, providing greater control of inflammatory activity and a better quality of life for patients.

MECHANISM OF ACTION OF JAK INHIBITORS

Persistent inflammation in RA is directly related to the activation of several intracellular pathways, including the JAK-STAT signal transducer pathway. This pathway involves four main members: JAK1, JAK2, JAK3 and TYK2 (Russell *et al.*, 2023) and is essential for the transduction of inflammatory cytokine signals that perpetuate the disease. Unlike traditional biological treatments, which act by blocking individual cytokines, JAK inhibitors have the advantage of modulating multiple inflammatory pathways simultaneously, making them a relevant alternative in the management of the disease (Kim; Keam; Susan, 2021).

The evolution of treatments includes targeted synthetic disease-modifying antirheumatic drugs (tsDMARDs), such as JAK inhibitors (JAKi), in addition to conventional synthetic DMARDs (csDMARDs), such as methotrexate (MTX), and biological DMARDs (bDMARDs) (Liu *et al.*, 2022). However, conventional approaches have limitations, such as progressive loss of efficacy due to immunogenicity. To get around these issues, JAK inhibitors have been divided into first generation, such as tofacitinib and baricitinib, and second generation, such as upadacitinib and filgotinib.

While first-generation inhibitors have demonstrated efficacy, their lack of selectivity has raised concerns about adverse effects such as cytopenias. For this reason, second-generation inhibitors have been developed to offer an improved safety profile, with greater selectivity for specific targets of the JAK-STAT pathway (Kim; Keam; Susan, 2021).

First-generation inhibitors, such as tofacitinib, act predominantly on JAK1 and JAK3 (Ivorra; Lllevate; Montoro, 2022). The inhibition of these kinases interferes with the inflammatory response by reducing the signaling of type I and II interferons and interleukins essential for the activation of immune cells, such as IL-2, IL-4, IL-6, IL-7, IL-9, IL-15 and IL-21 (Ivorra; Lllevate; Montoro, 2022). Clinical studies show that tofacitinib improves the DAS28 score, reduces joint tenderness and swelling, and reduces inflammatory markers such as C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR). However, there is controversy about its adverse effects, favoring the search for more selective inhibitors (Ivorra; Lllevate; Montoro, 2022).

Among the second generation inhibitors, filgotinib stands out as one of the most promising, being the second of this class approved for RA in the European Union. It is characterized as a competitive and reversible ATP inhibitor, acting preferentially on JAK1, with less effect on JAK2 and JAK3. This profile reduces interference with hematopoietic and immunological pathways, making it a potentially safer therapeutic option (Kim; Keam; Susan, 2021). The FINCH 2 study, a phase III clinical trial, evaluated the efficacy of filgotinib in patients with moderate to severe RA who had an inadequate response to bDMARDs. After 24 weeks of treatment, more than 30% of patients achieved disease remission, with DAS28-CRP < 2.6 (Mysler; Lizarraga, 2021), consolidating filgotinib as an effective treatment for cases of active RA.

Another second-generation inhibitor, upadacitinib, has increased selectivity for JAK1, being 74 times more selective for this kinase than for JAK2 (Mysler; Lizarraga, 2021). Clinical trials have indicated that this drug reduces the progression of joint structural damage, especially when administered as monotherapy compared to methotrexate (MTX), in patients with moderate to severe RA who had never been treated with MTX (Mysler; Lizarraga, 2021). However, Cox progression analyses pointed to an association between the use of upadacitinib and a higher incidence of Herpes Zoster and elevated Creatine Phosphokinase (CPK) levels, when compared to placebo, MTX

and adalimumab. Thus, understanding the selectivity and possible risks of JAK inhibitors is essential for optimizing RA treatment and avoiding significant adverse events.

PHARMACOLOGICAL PROFILES

JAKis have emerged as a promising alternative in the treatment of RA, modulating the JAK-STAT pathway to control inflammation. Currently, the main drugs available include tofacitinib, baricitinib, upadacitinib, filgotinib and peficitinib, each with distinct pharmacological profiles and different degrees of selectivity for the isoforms of the JAK family. Tofacitinib, the first JAK inhibitor approved for RA, acts predominantly on JAK1 and JAK3, while baricitinib acts on JAK1 and JAK2. In turn, upadacitinib and filgotinib act selectively on JAK1, an approach that may confer a more favorable safety profile by reducing interference with other physiological pathways. On the other hand, peficitinib, being a pan-JAK inhibitor, interferes with all isoforms of the JAK family, which may provide broader inflammatory suppression, but at the cost of an increased risk of adverse events associated with immunosuppression (Joyo *et al*., 2022; Conaghan *et al*., 2021; Russell *et al*., 2023).

The selectivity of JAK inhibitors has a direct impact on both the therapeutic response and the safety profile of the drugs. Baricitinib, for example, has been shown to reduce synovial inflammation by modulating the activation of the STAT1 protein, an essential factor in the cytokine-mediated inflammatory response. This mechanism directly affects synovial fibroblasts, which play a crucial role in the progression of RA. Furthermore, by targeting JAK1 and JAK2, baricitinib can offer effective inflammatory control without compromising essential immune functions. Upadacitinib, on the other hand, showed clinical superiority over adalimumab, achieving higher remission rates and promoting improved joint function in the first few months of treatment. This efficacy is related to its high selectivity for JAK1, reducing the inhibition of other isoforms involved in hematopoietic and immunological processes (Joyo *et al*., 2022; Conaghan *et al*., 2021).

Despite the proven efficacy of JAK inhibitors, their safety profile calls for caution. Studies indicate an increased incidence of serious infections, reactivation of herpes zoster and cardiovascular events among users of these drugs. In addition, there are concerns about the risk of malignancies, especially when compared to tumor necrosis factor inhibitors (TNFi). Although the incidence of cancer among JAKi users was not significantly different from that observed in patients treated with placebo or methotrexate, a recent meta-analysis revealed an increased risk compared to TNFi. These findings highlight the importance of continuous patient monitoring and individualized assessment of the risk-benefit ratio for each clinical case (Russell *et al*., 2023).

The differentiation between selective and pan-JAK inhibitors also influences their clinical applications. Highly selective drugs, such as upadacitinib and filgotinib, were developed with the aim of minimizing adverse effects by acting predominantly on JAK1, considered the main mediator of inflammation in RA. In contrast, peficitinib, by acting on all JAK isoforms, may provide more robust inflammatory suppression, but with a greater risk of immunosuppression. In addition, new molecules are being developed to optimize selectivity and reduce adverse events, which may broaden therapeutic options in the future. Thus, the choice of the most appropriate JAK inhibitor must be individualized, taking into account the particularities of each drug, the severity of the disease and the patient's clinical history, ensuring an appropriate balance between efficacy and safety (Joyo *et al*., 2022; Conaghan *et al*., 2021; Russell *et al*., 2023).

The increasing use of JAK inhibitors, such as tofacitinib and baricitinib, has prompted investigations into their impact on the risk of malignancies and cardiovascular events in patients with RA. According to Yoshida *et al.* (2023), a cohort study evaluated 427 patients to analyze the incidence of major adverse cardiovascular events (MACEs) and malignancies associated with the use of JAKi compared to IL-6 inhibitors. The following doses were administered:

- Baricitinib: 2 or 4 mg/day,
- Tofacitinib: 5 mg, once or twice a day,
- Upadacitinib: 15 mg/day,
- Filgotinib: 100 or 200 mg/day.

The study included patients with RA, including those with associated kidney or liver failure. The results indicated that the rates of MACEs and malignancies were similar among users of baricitinib and tofacitinib, but higher than those observed in patients treated with TNFi. In addition, the incidence of cardiovascular events was equivalent between patients treated with JAK inhibitors and those receiving IL-6 inhibitors. However, the data suggest a higher risk of developing MACEs and cancer in patients who used JAKi compared to those treated with IL-6i.

Another study, by Khosrow-Khavar *et al.* (2022), analyzed the risks of malignancies associated with the use of tofacitinib. Two groups of RA patients were evaluated: one made up of adults aged 18 and over and the other of patients over 50 with at least one cardiovascular risk factor. Both groups were treated with tofacitinib. The results showed no significant difference in the risk of adverse events compared to TNFi in the younger group. However, among patients over the age of 50 and with previous cardiovascular risk, an increased risk of malignancy was observed (pooled weighted HR: 1.17; 95% CI: 0.85-1.62). These findings highlight the need for new long-term studies with larger samples to accurately assess the safety of different JAK inhibitors. This in-depth study is essential in order to improve the clinical condition of patients and minimize the risks associated with treatment.

RESULTS OF PHASE II AND III CLINICAL TRIALS AND OTHER SYNTHETIC AND BIOLOGICAL THERAPIES

Advances in scientific research have enabled the introduction of new therapeutic approaches for the treatment of rheumatoid arthritis (RA), either as an alternative to conventional therapies or as adjuvants to these strategies. This evolution is based on rigorous clinical trials that assess the efficacy and safety of new drugs, seeking to optimize inflammation control and reduce adverse events. Within this context, synthetic disease-modifying antirheumatic drugs (tsDMARDs), such as Janus kinase inhibitors (JAKi), stand out for their ability to modulate essential inflammatory pathways, preventing structural damage and improving clinical outcomes in patients with RA. The main representatives of this class include baricitinib, tofacitinib, decernotinib, filgotinib and upadacitinib, each with specific efficacy and safety profiles (KieŁbowski *et al.*, 2024).

The efficacy of JAK inhibitors has been widely documented in phase II and III randomized clinical trials. According to Qu *et al.* (2024), a meta-analysis covering 33 randomized clinical trials, with a total of 15,961 participants, demonstrated that JAK inhibitors are superior to placebo in the treatment of RA. Among these drugs, decernotinib showed greater clinical efficacy, but its safety profile was considered unsatisfactory, limiting its applicability. On the other hand, tofacitinib, administered in low doses, showed a balanced relationship between efficacy and safety and is recommended for the treatment of RA (Qu *et al.*, 2024).

According to Taylor *et al.* (2022), baricitinib demonstrated satisfactory clinical efficacy and an acceptable safety profile, with no significant impact on the mortality of treated patients. The drug maintained a similar incidence of adverse events when compared to other therapeutic classes used in RA, including infections, venous thromboembolism and diverticulitis. These findings reinforce the need for continuous evaluation of the risk-benefit profile of this drug.

Upadacitinib has stood out due to its performance in both monotherapy and combination therapies, and has been extensively evaluated in phase III clinical trials. The SELECT-MONOTHERAPY study, a randomized, double-blind clinical trial, demonstrated that this drug promotes significant clinical remission, preventing structural damage and improving joint function. These effects were especially notable in patients with previous exposure to methotrexate (MTX), suggesting a potential benefit in combination therapies (Van Vollenhoven *et al.*, 2024).

Filgotinib, which has been extensively studied in phase II and III clinical trials, has shown good tolerability and an acceptable safety profile. However, there remains a need for monitoring of adverse events, which may vary according to dose and individual patient characteristics. Although studies indicate a lower incidence of serious adverse events, the long-term safety of filgotinib still needs to be better elucidated, especially in subgroups of patients with a greater predisposition to complications (Burmester *et al.*, 2024).

When analyzing the safety profiles of each JAK inhibitor, it can be seen that the most common adverse events include infections, reactivation of herpes zoster and hematological alterations. Baricitinib, for example, showed a reduction in the risk of emerging infections, with no significant increase in the incidence of herpes zoster compared to the other drugs in the class. In addition, there was no increase in the mortality of treated patients, which reinforces its safety profile comparable to other immunomodulatory therapies. However, the possible effects of this class on the risk of malignancies still remain uncertain, making further studies necessary to confirm these findings (Taylor *et al.*, 2022).

In the population taking filgotinib for a long time, the main adverse events reported were nasopharyngitis, upper respiratory tract infections and urinary tract infections. This drug did not show a significant association with cardiovascular adverse events or thromboembolism, suggesting a possible more favorable safety profile compared to other JAKi. In addition, the data indicated that filgotinib reduced the incidence of herpes zoster, making it a viable alternative for patients with greater susceptibility to this type of complication (Burmester *et al.*, 2024).

Another relevant aspect of the clinical trials was the concomitant use of methotrexate (MTX). During the studies, 79% of the population analyzed used MTX in combination with JAK inhibitors, allowing inferences to be made about the impact of this association. The results indicated that there was no increase in the risk of malignancy in patients treated with JAKi + MTX, when compared to those treated with MTX alone. In addition, JAK inhibitors did not show an increased risk of malignancy when compared to synthetic or biological DMARDs. However, as this is a recent area of research, long-term studies are needed to assess the safety of these drugs in different populations and clinical conditions (Taylor *et al.*, 2022).

Thus, clinical evidence points to JAK inhibitors as an effective therapeutic alternative for RA, with clear benefits in reducing inflammation, improving function and preventing disease progression. However, long-term safety remains a crucial factor in therapeutic deci-

sion-making, and it is essential to continue research to assess potential risks and optimize the use of these drugs. In addition, future studies should focus on directly comparing the different JAK inhibitors, as well as elucidating their mechanisms of action and possible adverse effects, ensuring greater safety in clinical practice (Qu *et al*., 2024).

FINAL CONSIDERATIONS

Janus kinase (JAK) inhibitors, regardless of whether they act on JAK1, JAK2, JAK3 or TYK2, play an essential role in the simultaneous modulation of multiple inflammatory pathways. This characteristic makes them strategic therapeutic agents in the management of rheumatoid arthritis (RA), reducing cytokine-mediated inflammation and significantly impacting patients' quality of life. Both first-generation inhibitors, such as tofacitinib and baricitinib, and second-generation inhibitors, such as upadacitinib and filgotinib, have shown efficacy in reducing disease activity. However, the main distinction between these classes lies in their safety profile, since the second-generation inhibitors were developed with the aim of improving selectivity and minimizing potential adverse effects. Therefore, the choice of the most appropriate JAK inhibitor must be individualized, taking into account the severity of the disease, the patient's clinical history and the pharmacokinetic and pharmacodynamic particularities of each drug. This personalized decision-making process makes it possible to balance efficacy and safety, enabling an optimized therapeutic approach that is more in line with the individual needs of patients with rheumatoid arthritis.

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