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THERAPEUTIC APPROACHES FOR ATOPIC DERMATITIS WITH JAK INHIBITORS

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Abstract: Objective: To evaluate the efficacy and safety of JAK inhibitors in the treatment of atopic dermatitis, analyzing their clinical effects, impact on quality of life and associated risks. **Methodology:** Literature review in the PubMed - MEDLINE database according to the following search strategy: ("Atopic Dermatitis") AND (("Janus Kinase Inhibitors") OR (JAK)) from 2020 to 2025. **Discussion:** Atopic dermatitis consists of eczematous lesions, pruritus and barrier dysfunction, generating multiple physical and emotional compromises for patients who suffer from it. Among the current therapeutic alternatives, JAK inhibitors have emerged as an effective treatment, available in topical and oral presentations, although further studies are needed to differentiate between the two. Promising in relation to methotrexate and corticosteroids, JAK inhibitors regulate the transmission of inflammatory signals, whose action triggers the expression of mediators amplifying inflammation, inhibiting the transduction of signals from the cell surface to the nucleus, where gene transcription is regulated. Despite the different pharmacological profiles of this class, Abrocitinib is the most studied for moderate to severe atopic dermatitis. Among the side effects described are laboratory alterations, risk of inducing malignancy, induction and/or worsening of acne and herpes zoster, among others, while methotrexate and corticosteroids have dependence and epithelial atrophy as their main side effects. **Final considerations:** Although widely studied in many areas of activity, the use of JAK inhibitors shows promise in relation to the treatment of moderate to severe AD, however further studies are needed, especially in relation to long-term treatment safety, tolerability and side effects.
Keywords: Atopic Dermatitis, JAK inhibitors, Dermatology.

INTRODUCTION

Atopic dermatitis (AD) is a chronic and recurrent inflammatory skin condition characterized by intense itching and dryness. It usually begins in childhood and can persist into adulthood in approximately half of all cases. In the United States, it is estimated that between 11% and 15% of children and 7% to 10% of adults are affected by this condition (Agboola *et al.*, 2022). The severity of symptoms varies, but intense itching often compromises sleep, causing daytime fatigue, psychological stress and a negative impact on school and work performance. In addition, the appearance of chronic AD can contribute to social stigmatization and isolation (Tsai *et al.*, 2021).

Therapeutic approaches include hydration with emollients, topical corticosteroids to control outbreaks and, in more persistent cases, calcineurin inhibitors or crisaborole. For patients with an inadequate response to topical therapies, options such as phototherapy and systemic immunomodulators, including cyclosporine and azathioprine, can be used (Agboola *et al.*, 2022).

Although topical treatments are the first--line approach, systemic therapy is indicated for patients who do not achieve a satisfactory response to this therapy (Tsai *et al.*, 2021). Among the emerging alternatives are monoclonal antibodies and Janus kinase (JAK) inhibitors. The latter include oral, topical and systemic options, blocking the action of cytokines involved in the pathogenesis of AD. Currently, several JAK inhibitors are being studied to determine their long-term efficacy and safety (Singh *et al.*, 2020).

Pre-clinical studies show that inhibition of the JAK/STAT pathway has promising therapeutic potential. Evidence suggests that JAK inhibitors have moderate efficacy in the treatment of AD, while safety issues are considered tolerable. However, there is a need for prospective studies with prolonged follow-up, especially to assess adverse events and cost-effectiveness in the clinical use of these drugs (Tsai *et al.*, 2021).

These drugs have great therapeutic potential, as they selectively block inflammatory pathways, reducing itching, inflammation and skin lesions. However, there are limitations in the data from clinical trials, which, although promising, still require long-term evaluation. In addition, genetic and environmental factors and individual metabolic variations can influence the response to treatment, highlighting the importance of therapeutic personalization (Dhar *et al.*, 2024). In view of this, this study aims to evaluate the efficacy and safety of JAK inhibitors in the treatment of atopic dermatitis, analyzing their clinical effects, impact on quality of life and associated risks.

METHODOLOGY

A literature review developed according to the criteria of the PVO strategy, which 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 in the treatment of patients with moderate to severe atopic dermatitis?". 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", using the following search strategy: ("Atopic Dermatitis") AND (("Janus Kinase Inhibitors") OR (JAK)). From this search, 687 articles were found, which were then submitted to the selection criteria. The inclusion criteria were: articles in English; published between 2020 and 2025 and which addressed the themes proposed for this research, studies of the type (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 inclusion and exclusion criteria, 21 articles were selected from the PubMed database to make up the collection of this study.

DISCUSSION

Atopic dermatitis (AD) is a chronic inflammatory skin disease that significantly affects patients' quality of life and is characterized by intense itching and skin barrier dysfunction (Lee *et al.*, 2023). Its pathophysiology involves the Th2 immune response and the JAK-STAT signaling pathway, which is fundamental in the transduction of inflammatory signals (Nogueira; Torres, 2021). Janus kinase inhibitors (JAKi) have emerged as an innovative therapeutic approach for moderate to severe AD, selectively blocking JAK isoforms and reducing inflammation (Wan *et al.*, 2022). In addition, IL- 4/IL-13 inhibitors have been shown to be effective in managing the disease (GARGIULO et al., 2024). Despite these advances, more studies are needed to assess the long-term safety and efficacy of these therapies (Lugovic-Mihic *et al.*, 2023).

JAKi are a class of advanced systemic therapy used in the treatment of moderate to severe atopic dermatitis, acting by blocking one or more isoforms of JAK, interrupting the transduction of signals from the cell surface to the nucleus and selectively reducing inflammation (Kirchhof *et al.*, 2024). As the degree of inhibition of the JAK-STAT pathway varies between the available drugs, the choice of the ideal inhibitor must be personalized for each patient. In addition, other targeted therapies, such as IL-4/IL-13 inhibitors and selective IL-13 inhibitors, have been incorporated into the therapeutic arsenal, both in topical and systemic formulations. IL-4 and IL-13 are central mediators in the pathogenesis of AD, associated with chronic inflammation, skin barrier dysfunction and intense pruritus, reinforcing the importance of blocking these pathways in the therapeutic approach (Shih; Li; Yong, 2023).

JAK inhibitors have different pharmacological profiles, which directly influences their efficacy and safety in the treatment of AD. The main drugs available include tofacitinib and ruxolitinib, which are non-selective JAK 1, 2 and 3 inhibitors, while baricitinib and upadacitinib are selective JAK 1 and 2 inhibitors, allowing for more specific treatment and a lower risk of off-target adverse effects. Abrocitinib, a selective JAK 1 inhibitor, is effective but associated with adverse events such as acne and herpes zoster, while upadacitinib 30 mg shows greater efficacy in clinical response, despite the increased risk of adverse reactions. In addition to inhibiting JAK 1 and JAK 2, baricitinib has shown good results when associated with topical corticosteroids. Comparative studies suggest that, among the available inhibitors, tofacitinib has a superior safety profile to ruxolitinib, with a lower incidence of adverse events (Nogueira and Torres, 2021; He *et al.*, 2024; Nezamololama *et al.*, 2020; Alves *et al.*, 2023).

The safety of JAKi has been widely evaluated in randomized clinical trials, in which the occurrence of adverse events (AEs) and treatment-emergent adverse events (TEAEs) are monitored as clinical endpoints (Wan *et al.*, 2022; Li *et al.*, 2022). In addition to clinical effects, laboratory changes such as increased CPK, triglyceride and cholesterol levels have been observed, although heterogeneity between studies limits direct comparisons between drugs (Zhao *et al.*, 2021 and Alves *et al.*, 2023). The management of atopic dermatitis with JAKi has shown promise compared to conventional therapies. The use of corticosteroids and methotrexate, although widely used, is restricted by the significant adverse effects associated with their prolonged use, such as skin atrophy, secondary infections and

rebound effects after stopping treatment (He *et al*., 2024, Zhao *et al*., 2021 and Gargiulo *et al*., 2024). JAK inhibitors have therefore emerged as a viable and potentially safer alternative (Kirchhof *et al*., 2024; Shih; Li; Yong, 2023).

Despite initial concerns about the risk of infections, malignancy and venous thrombosis in rheumatoid arthritis patients treated with JAKi, studies focused on atopic dermatitis did not observe these complications in the majority of cases. An evidence-based consensus indicated that the use of these drugs does not increase the risk of venous thrombosis in women who use contraceptives, although one study did point to an increased risk of malignancy (Gargiulo *et al*., 2024; Haag *et al.*, 2025). Factors such as advanced age, obesity, smoking, a history of thromboembolism and cardiovascular disease have been identified as risk factors for adverse events, but their incidence appears to be rare, making the administration of JAKi a viable therapeutic option (He *et al*., 2024, Nezamololama *et al*., 2020, Li *et al*., 2022, Gargiulo *et al*., 2024, Shih; Li; Yong, 2023, Lytvyn *et al*., 2022 and Le *et al*., 2021).

Despite the favorable safety profile, the topical formulation of JAKi still has few studies, which limits its clinical use. Clinical trials indicate that topical use reduces systemic adverse effects, restricting them to localized irritation, but the scarcity of data does not yet make it possible to establish a recommendation based on robust evidence to replace systemic use with topical JAKi (Sedeh *et al*., 2022; Li *et al.*, 2022). In addition, choosing the optimal JAKi for each patient still faces challenges due to the variability of the available evidence. Abrocitinib is the most studied inhibitor for AD, while there is less data on other drugs (He *et al*., 2024; Wan *et al*., 2022). A meta-analysis of phase II and III clinical trials concluded that tofacitinib generated fewer adverse events than ruxolitinib, but no statistically significant comparisons could be made between the other drugs (Alves *et al*., 2023). In general, selective JAK 1 inhibitors tend to cause fewer adverse effects than those that block JAK 2, JAK 3 and TYK2 (Nogueira; Torres, 2021, Zhao *et al*., 2021 and Lytvyn *et al.*, 2022).

Finally, although JAKi are considered a safe and effective class for the treatment of moderate to severe atopic dermatitis, more studies are still needed to assess the long-term risks and make direct comparisons between the different drugs and their formulations. More robust evidence will make it possible to define the role of JAKi in the management of AD more precisely, ensuring greater safety, efficacy and personalization of treatment for patients (Lee *et al.*, 2023; Szalus;Trzeciak; Nowicki, 2020; Lugovic-Mihic *et al*., 2023).

FINAL CONSIDERATIONS

JAK inhibitors have emerged as a promising alternative in the treatment of moderate to severe atopic dermatitis, offering significant therapeutic efficacy with a higher safety profile than conventional therapies such as corticosteroids and immunosuppressants. These drugs act to regulate the transmission of inflammatory signals, inhibiting the transduction of signals from the cell surface to the nucleus, which reduces inflammation, itching and skin lesions. However, there are still limitations in terms of long-term safety, variability in tolerance between patients and side effects depending on the dosage and presentation of the drug. In addition, the scarcity of data on topical formulations restricts the generalization of the findings to all forms of administration. Therefore, additional studies are needed to assess the incidence of rare adverse events, compare different inhibitors and individualize treatment based on patient characteristics, enabling more precise and safer management of atopic dermatitis.

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