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Upadacitinib - New Janus Kinase Inhibitor - Literature review

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Abstract:
Atopic dermatitis (AD) is a chronic, recurrent dermatosis that affects an increasing percentage of the population. It usually affects children and resolves spontaneously; however, symptoms can persist into adulthood and even appear de novo later in life. The skin lesions that appear in this disease significantly reduce patients' quality of life. Visual skin symptoms are exacerbated during stress, and pruritus leads to sleep problems. The effect of an inadequately controlled disease can even be a reduction in social activities and a reluctance to leave the house. The basis of treatment is skin care using emollients and avoiding triggers and aggravating factors. In the next stage, the doctor may prescribe topical or systemic treatment for the patient, depending on the severity of the disease. Such measures may not be enough, so more and more new drugs are being registered for the treatment of atopic dermatitis. One of them is upadacitinib, which appears to be extremely effective compared to other medications used to treat moderate to severe ad. It is a selective JAK inhibitor that reduces the inflammatory response by inhibiting migration, proliferation and cytokine secretion by granulocytes. It brings rapid and sustained effects in reducing skin lesions and reducing one of the most bothersome symptoms, pruritus.It may serve as a good alternative to the existing methods for treating moderate to severe atopic dermatitis The purpose of our study is to describe this new drug, its mechanism of action and discuss its possible benefits versus side effects.

Keywords: upadacitinib, atopic dermatitis, Janus kinase inhibitor, pruritus

Introduction

Atopic dermatitis is an inflammatory, chronic, recurrent dermatosis, usually with onset in early childhood (~20%). [1,2] By the age of five, it develops in 90% of patients. The

incidence has increased significantly over the past decades in both developed and developing countries. [3] Although it is a disease specific to childhood, it can also occur in adults. Usually observed course from childhood, but we can also note de novo cases after the age of 18. [4] The clinical picture is dominated by erythematous, papular, exudative lesions and dry skin of varying severity in typical age-specific locations. An indistinguishable symptom is persistent pruritus. Once the years pass, the described symptoms lead to thickening of the skin and lichenification. [5] The disease significantly reduces the quality of life, interferes with daily functioning, leads to sleep problems and even insomnia. It economically affects the entire family, but is also a social problem, burdening the indirect costs necessary to combat AD. [6,7,8,9] Due to insufficient results with basic treatments, the frequency and severity of exacerbations, researchers are looking for more and more new drugs to optimally and effectively control the disease. To this end, modern JAK1 kinase inhibitors and monoclonal antibodies have begun to be used. In this study, we will focus on their performance, efficacy, risks and side effects.

Upadacitinib is one of the oral, systemic, selective, reversible JAK inhibitors. It exhibits greater inhibitory potency against JAK1 than JAK2, JAK3 or tyrosine kinase 2.[10] The JANUS group of kinase molecules mediates signals from receptors on the cell surface to the cell nucleus, leading to the transcription of genes involved in inflammatory responses. JAK1 is essential to produce granulocyte colony-stimulating factor, which stimulates the production of granulocytes and stem cells and interferons. [11] Thus, activation of JAK molecules causes migration, proliferation and maturation of immune cells. Thus, the use of inhibitors will inhibit the interaction between cytokines and effector cells limiting the inflammatory response. [12] Thus, we can attribute to them immunomodulatory and anti-proliferative effects. [13]
JANUS kinase inhibitors are a relatively new group of drugs, showing high efficacy in the treatment of immune- mediated diseases. Above that, they have a stable safety profile, which has been proven in studies on rheumatoid arthritis and psoriatic arthritis. [14,15]

Currently available studies show promising results, illustrating the effect of significant skin clearing and pruritus relief in patients with moderate to severe atopic dermatitis, with statistically significant superiority of upadacitinib over dupilumab. The study comparing the two drugs showed that within week 1 of treatment, only 8.8% of dupilumab- treated patients achieved improvement in pruritus, while up to 31.4% of upadacitinib-treated patients did.
The superiority of the second drug was also illustrated in terms of the percentage of patients who achieved EASI75 by week 2. Investigators taking upadacitinib achieved a score as high as 43.7%, compared to 17.4% taking dupilumab. [16] More than that, the efficacy of upadacitinib

has been documented in patients who previously had an inadequate response to therapy with dupilumab. [17] These results are extremely optimistic in terms of improved treatment and subjective quality of life for AD patients.

Methodology

An electronic search was conducted in the PubMed database. Recommendations were extracted from the identified articles and collected as topics. We must emphasize that, because this drug has been approved in August 2021 for the treatment of atopic dermatitis, there are still some gaps in the public's knowledge of its use in daily practice.

Discussion

Long-term response rates in terms of skin clearing and itch relief appear to be sustained, with a safety profile comparable to that presented in short-term studies. Moreover, the 3-year treatment in Japan was well tolerated by the subjects. [17]

One of the most commonly reported side effects after upadacitinib use is acne. In the study conducted by Pedro Mendes-Bastos et al. patients were divided into three groups taking 15 mg of upadacitinib, 30 mg of upadacitinib and placebo, respectively. Among all reported cases of acne, only one was severe. The others were classified as mild to moderate. Two patients dropped out of continued treatment due to moderate severity of acne lesions. Acne did not require intervention in 40.5% and 46.6% of patients receiving upadacitinib 15 and 30 mg, respectively. In most patients, lesions were treated with topical benzoyl peroxide, retinoids and antibiotics. Interestingly, it was shown that acne as a side effect occurred more frequently in young women, of non-white race. [18] Other adverse events following the use of the drug we discussed include cough, headache, urinary tract infection, URI, nasopharyngitis and transient elevation of CPK levels. As this is an immunomodulatory drug, we must also mention infections among the side effects, which most often included herpes zoster, herpes zoster, herpangina and isolated cases of pneumonia or tuberculosis. Considering the incidence of specific infections, hemiplegia and herpetic eczema predominate with upadacitinib, and conjunctivitis with dupilumab. Alarmingly, several patients were diagnosed with skin cancer, other than melanoma, after 3 months of therapy. [19] A meta-analysis of randomized phase II/III/IV clinical trials (RCTs) and long-term extension trials (LTEs) showed that the incidence of all malignancies, including non-melanoma skin cancers (NMSCs), was not significantly different

between JANUS kinase inhibitors, placebo and methotrexate. In contrast, however, JAKs were associated with an increased incidence of malignancy compared to TNFi. [20]

Despite this, it is worth noting that in many studies, the authors highlight the safety and relatively, rare occurrence of the adverse events described above. Which, as Chisa Nakashima et al. point out, will make the new JANUS kinase inhibitors additional therapeutic options for the treatment of moderate to severe atopic dermatitis. [25] Study discontinuation rates due to adverse effects of upadacitinib are low, although higher in the higher-dose (30mg) treatment group. [19] Safety reports are reassuring. [26]

To tailor appropriate treatment in patients, researchers in one study focused on a comparative assessment of baseline clinical and laboratory parameters between responders and non-responders to upadacitinib at specific doses. In their conclusions, they emphasized that older patients with lower baseline EASI were more likely to achieve a response with 15 mg of upadacitinib. In contrast, considering the 30 mg dose of the drug we described, predictive factors for response are lower initial IgE levels and LDH. [21]

Other important questions began to arise as the drug became more widespread. Should we keep it for life? Can it be switched back on after secondary hypothyroidism? Will it be effective in combination with biologic drugs? Unfortunately, so far there are not many reports on this subject. Single cases have been described in the literature, including a woman treated with 30 mg of upadacitinib for 2.5 years achieving spectacular progression (0 on the EASI, BAS and WI-NRS scale). After this period, the decision was made to discontinue the drug, and unfortunately, after only 3 three months, the symptoms of atopic dermatitis recurred. An attempt was made to restart the drug and after 4 weeks, a complete improvement was achieved with good tolerance after 8 months of treatment. In the same study, doctors described two cases of men who lost the effectiveness of the drug despite initial satisfactory results. As a result, therapy was changed, and biologic drugs were introduced. After 6 months, the results of the treatment were not satisfactory so in one of them upadacitinib 30 mg was reintroduced, and in the other the biologic drug was maintained and upadacitinib 30 mg was added. After 5 months of follow-up, no exacerbations or side effects occurred in either case. Patients with a severe course of azs are presented, in whom discontinuation and re-inclusion of the described drug resulted in good disease control. The authors emphasize that the results of their single observation must be confirmed in later studies. However, we can surmise potential in upadacitinib as a useful drug for the treatment of chronic and recurrent AD. [22]

Mention should also be made of possible drug combinations to achieve satisfactory results. In a Japanese study of subjects aged 12-17 years who received upadacitinib 15 mg plus

twice-daily topical corticosteroids to treat moderate to severe atopic dermatitis, significant improvements were achieved. Achievement rates at weeks 4 or 12 were 64.1% or 62.5%, respectively, for EASI 75, 93.5% or 73.1% for ADCT <7 points, and 80.6% or 60% for PP-NRS ≥4 points of improvement, indicating a peak at week 4 and a slight decrease at week 12. [23] A case of a man with severe azs, after multiple therapeutic failures with topical and systemic treatments, is also described. It was decided to include upadacitinib 30 mg with moderate improvement after 6 months. To intensify therapy, tralokinumab was added in combination. Significant improvement in skin lesions and reduction in pruritus was noticeable after just 3 weeks of such treatment. Currently, the patient remains on a combination of these two agents and a combination of topical treatments with no adverse events reported with an EASI and BAS <1%. [24] Combinations of biologics, JANUS kinase inhibitors and topical therapy may have satisfactory results, which requires additional studies to refine the criteria and treatment regimens.

Summary

Finally, given the severity of symptoms and the inability to achieve satisfactory treatment results with traditional methods, upadacitinib may prove to be an invaluable alternative in the treatment of atopic dermatitis. As an immunomodulatory drug, it reduces the body's immune response, thereby reducing skin lesions and the finishing sensation of itching. As a result, we can achieve an improvement in patients' quality of life. By combining upadacitinib with other drugs, remission can be achieved quickly and fully, and the reintroduction of the drug allows good control of the disease. Although the drug was relatively recently registered by the European Medicines Agency, it is achieving positive results in clinical trials and may represent a significant advance in the treatment of moderate to severe atopic dermatitis.

Disclosures

Author's contribution:

Conceptualization Methodology: JG, KK, AS Software: not applicable; Check: JP, AF, AG, AM, Formal analysis: MG, EK, PK, AF, Investigation: AS, AG, JP, Resources: not applicable; Data curation: Writing - rough preparation: EK, PK, AM, KK, JG, MG, Writing - review and

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