Baricitinib for the treatment of Atopic Dermatitis

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ABSTRACT

Introduction: Atopic dermatitis is a common, chronic and recurrent inflammatory skin disease, with a prevalence of 15 to 20% in developed countries. It often appears in childhood but can last into adulthood. It negatively impacts patients, their families and society in general. Treatments are meant to reduce symptoms and prevent worsening of the disease, in association with a favorable safety profile. There is an unmet need in this area, with patients requiring new pharmacologic agents that are safe and effective. New developments on the pathophysiology of atopic dermatitis and its relationship with the JAK/STAT pathways has led to the development of agents that block this intracellular signaling pathway, the JAK inhibitors. Baricitinib shows high selectivity for JAK1 and JAK2, making it appealing for the treatment of this condition.

Objectives: The purpose of this review is to make an assessment of the safety and clinical effectiveness of baricitinib for the treatment of atopic dermatitis.

Methods: A search on the pathophysiology and the role of JAK/STAT pathway in atopic dermatitis was made, along with a review of the data on clinical evidence of the efficacy and safety of baricitinib. The research for this review was performed using PubMed and GoogleScholar. The publication of the articles used covers the period from 1995 to 2021. The articles were selected by the relevance of the abstract and established objectives. Bibliographic references present in the selected articles were also included.

Discussion: Atopic dermatitis is a condition with intricate environmental and genetic susceptibility elements. There are many factors involved in its pathogenesis, including a Th2-skewed immune response. The JAK/STAT pathway is used for signal transduction by various cytokines and growth factors, being involved in many processes that are critical in the pathogenesis of this disease, such as Th2 cell response augmentation. Phase II and phase III trials have been carried out to assess the efficacy and safety of baricitinib, a selective oral JAK1/2 inhibitor. The results are encouraging concerning its efficacy, in addition to a favorable safety profile.

Conclusion: JAK inhibitors act in a broad way, inhibiting multiple steps that are associated with the pathogenesis of atopic dermatitis, which can potentially translate into greater therapeutic advantages. Baricitinib, being a selective JAK1 and JAK2 inhibitor, may have an advantage from a therapeutic standpoint over the other oral JAK inhibitors being studied for this condition due to the additional inhibition of JAK2. This drug represents one more treatment option for atopic dermatitis patients who have no history of serious renal impairment or severe hepatic impairment and who favor oral therapy over injections. Nevertheless, more studies will be necessary to assess the long-term safety of this drug in atopic dermatitis, including the clinical setting.
Keywords: Atopic Dermatitis; Atopic Eczema; Baricitinib; Pathophysiology; JAK Inhibitors; JAK/STAT.
RESUMO

Introdução: A dermatite atópica é uma doença de pele inflamatória comum, crónica e recorrente, com uma prevalência de 15 a 20% nos países desenvolvidos. Aparece frequentemente na infância, podendo prolongar-se até à idade adulta. Tem um impacto negativo nos doentes, suas famílias e na sociedade em geral. Os tratamentos visam reduzir os sintomas e prevenir o agravamento da doença, em associação com um perfil de segurança favorável. Há necessidade de novos agentes farmacológicos seguros e eficazes. Novos avanços relativos à fisiopatologia da dermatite atópica e sua relação com a via JAK/STAT levaram ao desenvolvimento de agentes que bloqueiam esta via de sinalização intracelular, os inibidores da JAK. O baricitinib apresenta uma elevada selectividade para JAK1 e JAK2, tornando-o atractivo para o tratamento desta patologia.

Objectivos: A presente revisão bibliográfica tem como objectivo realizar uma avaliação da segurança e eficácia clínica do baricitinib para o tratamento da dermatite atópica.


Desenvolvimento: A dermatite atópica é uma patologia com intrincados elementos de susceptibilidade ambiental e genética. Há um grande número de fatores envolvidos na sua patogénese, incluindo uma disfunção imune do tipo 2. A via JAK/STAT é utilizada para a transdução de sinal por várias citocinas e factores de crescimento, estando envolvida em diversos processos críticos na patogénese desta doença, tais como no aumento da resposta de células Th2. Os resultados são encorajadores relativamente à sua eficácia, para além de revelar um perfil de segurança favorável.

Conclusão: Os inibidores da JAK actuam de uma forma ampla, inibindo múltiplas etapas que estão associadas à patogénese da dermatite atópica, o que pode ser traduzir-se em maiores vantagens terapêuticas. O baricitinib, sendo um inibidor seletivo da JAK1 e JAK2, pode ter uma vantagem do ponto de vista terapêutico sobre os outros inibidores de JAK orais, devido à inibição adicional de JAK2. Este medicamento representa mais uma opção de tratamento para pacientes com dermatite atópica sem história de insuficiência renal ou hepática grave e que preferem a terapia oral. Contudo, serão necessários mais estudos para avaliar a segurança a longo prazo deste fármaco na dermatite atópica, incluindo o contexto clínico.
Palavras-chave: Dermatite Atópica; Eczema Atópico; Baricitinib; Patofisiologia; Inibidores da JAK; JAK/STAT.
LIST OF ABBREVIATIONS

AD – Atopic dermatitis
CCL18 – Chemokine (C-C motif) ligand 18
CPK – Creatine Phosphokinase
EASI – Eczema Area and Severity Index
EMA – European Medicines Agency
GM-CSF – Granulocyte macrophage colony stimulating factor
IFN-γ – Interferon gamma
IL – Interleukin
JAK – Janus kinase
MCP-1 – Monocyte chemoattractant protein-1
NRS – Numerical Rating Scale
OAT3 – Organic anion transporter 3
STAT – Signal transducer and activator of transcription
Th – T helper
TSLP – Thymic stromal lymphopoietin
TYK2 – Tyrosine kinase 2
SCORAD – Scoring Atopic Dermatitis
vIGA – Validated Investigator Global Assessment Scale
INTRODUCTION

Atopic dermatitis (AD), or atopic eczema, is a common, chronic and recurrent inflammatory skin disease, with a prevalence of 15 to 20% in developed countries. It often appears in childhood but can last into adulthood. Approximately 60% of patients develop AD before 1 year of age, 90% up to 5 years, and in 10% of people it appears in adulthood. \(^1,2\)

Regarding its clinical features, this condition is characterized by recurrent eczematous lesions, that can be red or brownish, associated with xerotic, scaly or cracked skin and intense itching, displaying heterogeneity in its clinical presentation. \(^3,4\) In infants and young children, eczematous lesions tend to appear on the face, scalp and extensor areas. Older children and adults tend to have lesions in the flexor areas. \(^5\) On the other hand, in adults, particularly those whose onset or recurrence appears in adulthood, lesions tend to appear preferentially on the head/neck and hands. \(^6,7\)

There is an association between AD and other atopic diseases, such as asthma, hay fever, food allergies and eosinophilic esophagitis. Chronic pruritus, inflammation and psychosocial stress can lead to increased anxiety, depression or suicidality, and people with AD also appear to have an increased cardiovascular risk and an increased risk of infections. \(^8\)

AD negatively impacts the overall quality of life of patients and affects the occupational, academic and social areas, resulting in an enormous financial burden for patients, their families and society in general, through direct medical costs, as well as in a decrease in productivity. \(^9\)

 Treatments in AD are meant to reduce symptoms and prevent worsening of the disease, while maintaining a favorable safety profile. While mild forms can be treated with the use of topical anti-inflammatories and skin hydration, patients with moderate to severe AD may need systemic therapy. \(^10-12\)

As first line therapy, topical corticosteroids are commonly used. There is little risk with its adequate intermittent use but local side effects, such as skin atrophy, striae, purpura, dyspigmentation, telangiectasias and facial acneiform changes may be caused by unsuitable use. Despite being very uncommon, systemic side-effects such as growth retardation or hypothalamic–pituitary–adrenal suppression can occur. \(^13-15\)

For sensitive skin areas, like facial or flexural skin, topical calcineurin inhibitors (tacrolimus and pimecrolimus) are approved for short-term and chronic intermittent use in children aged 2 and older and adults. Nevertheless, their reduced clinical efficacy, symptoms like burning and pruritus in the first days of use and their cost holds back their use. \(^16-18\)

Phototherapy can be considered if topical therapy fails, but its limited efficacy and safety concerns, along with being impractical to most patients, limits its use. \(^19,20\)
Systemic treatment is recommended if topical or phototherapy fails or becomes unfeasible. Systemic corticotherapy can only be used in short courses and, in terms of efficacy and safety profile, systemic immunosuppressants such as cyclosporine, azathioprine, methotrexate and mycophenolate-mofetil have several contraindications and safety issues and are not suitable for long-term use. (21, 22)

The development of dupilumab, an IL-4 receptor α-antagonist that inhibits IL-4 and IL-13 signaling through blockade of the shared IL-4α subunit, changed the paradigm of AD treatments by allowing the long-term management of moderate-to severe AD patients. (23-25) Long-term safety and efficacy of this drug have been shown in clinical trials. (26) However, in addition to its cost, some people may prefer a non-injectable route of administration.

New developments on the pathophysiology of AD and its relationship with the Janus kinase (JAK) and signal transducer and activator of transcription (STAT) pathways has led to the development of agents that block this intracellular signaling pathway, the JAK inhibitors, opening a new realm of opportunities for the treatment of this condition.

Multiple steps in AD pathogenesis are regulated by the JAK-STAT pathway, making the current class of small-molecule agents called JAK inhibitors appealing for AD treatment. (27)

First generation JAK inhibitors inhibit multiple JAK, showing no selectivity. Second generation JAK inhibitors, on the other hand, have increased selectivity for one or more JAK isoforms. Baricitinib shows high selectivity for JAK1 and JAK2. (28-30)

Indeed, there is an unmet need in AD, with patients in need of new pharmacologic agents that are safe and effective, making the subject of this study important to pursue. From this perspective, this review proves pertinent due to the context and currentness of the analysis.

The purpose of this review is to make an assessment of the safety and clinical effectiveness of Baricitinib for the treatment of atopic dermatitis.
METHODS

A search on the pathophysiology and the role of JAK/STAT pathway in AD was made, along with a review of the data on clinical evidence of the efficacy and safety of baricitinib. The research for this review was performed using PubMed and GoogleScholar, using the following keywords: “atopic dermatitis” or “atopic eczema”, “baricitinib”, “pathophisiology”, “JAK inhibitors”, “JAK/STAT”.

The publication of the articles used covers the period from 1995 to 2021. The articles were selected by the relevance of the abstract and established objectives. When pertinent to the dissertation, the bibliographic references present in the selected articles were also included. Only articles in English were considered.
DISCUSSION

Pathogenesis of Atopic Dermatitis and the role of the Janus Kinase (JAK) and Signal Transducer and Activator of Transcription (STAT) Pathway

AD is a condition with intricate environmental and genetic susceptibility elements. Regarding its pathogenesis, there are a large number of factors involved, including defects in the response of the innate immune system, abnormalities at the skin barrier level, Th2-skewed adaptive immune response, as well as changes in the microbial flora residing in the skin. To explain the cause of AD, two theories have been presented: the “inside-out” and the “outside-in” hypotheses. The “inside-out” hypothesis argues that skin inflammation is initiated by immune dysregulation, stating that allergic triggering is what leads to a weakened skin barrier which, in turn, further contributes to the introduction and presentation of allergens, thus suggesting that inflammation is responsible for the dysfunctional skin barrier, leading to an increased penetration of allergens and microorganisms. The “outside-in” hypothesis states that the barrier dysfunction is at the origin of the skin inflammation, meaning that the dysfunctional skin barrier precedes the AD, being fundamental for the immune dysregulation to happen. For example, the filaggrin mutation (FLG) can make the skin more vulnerable to immune dysregulation, leading to AD. While it is still under discussion which theory is the correct one, it is likely that they are not mutually exclusive, but that both contribute to the explanation of the pathogenesis of this disease.

People suffering from AD have a genetically impaired skin barrier function, leading to an increase in transepidermal water loss, with a greater severity of the condition associated with higher levels of water loss. Imbalances between stratum corneum protease (such as kallikrein) and antiprotease activity (such as LEKTI), abnormalities in tight junctions, microbial colonization of the skin and pro-inflammatory cytokines are all factors that can lead to skin barrier disruption. The skin epidermis acts as a barrier that blocks the entry of microorganisms, allergens and irritants into the body, also preventing transepidermal water loss. In addition, there are structural proteins (such as filaggrin or regulatory enzymes) that, through interactions with keratinocytes on the skin surface, maintain its permeability. Mutations or deficiencies of filaggrin appear to be a key factor to an abnormal skin barrier. Indeed, there is an association between early-onset AD and asthma in the context of AD with filaggrin mutations. A process through which filaggrin defects can promote inflammation is by the secretion of epithelial cell-derived cytokines, such as IL-25, IL-33 and TSLP, that are up-regulated in patients with AD. Nevertheless, only 30% of European individuals with AD have filaggrin mutations which, despite being associated with the development
of AD, raises the question of whether there are other genetic variants that may also account for AD pathogenesis. (45)

The first line of defense against infections is the innate immune system which, in the case of the skin of individuals with AD, is altered, as is the case with the regulatory T cells. Indeed, it has been found that there are reduced antimicrobial peptides on the skin of these patients, which may elucidate their vulnerability to infections. In fact, there is frequent colonization of *Staphylococcus aureus* in both lesional and healthy skin of these patients, that further exacerbates their condition. (46-48)

AD is found to present a biphasic inflammation, concerning its immune response. In the initial acute phase, a Th2-biased immune response dominates, with eosinophils, TSLP, IL-4, IL-5, IL-13, IL-31 and CCL18, associated with Th22 responses, like IL-22 and S100A proteins. These seem to downregulate terminal differentiation genes and tight junction products which causes skin barrier dysfunction. (49-57) IL-4 and IL-13 are known to play a significant part in the pathogenesis of this condition and AD has been proven to be genetically related to IL-4 and IL-13 polymorphisms. (58-61)

In addition, in the presence of IL-4 and IL-13, keratinocytes show an appreciably decrease in filaggrin gene expression. (62) IL-4 and IL-13 also downregulate loricrin and involucrin in the skin of patients with AD. (53) On the other hand, there seems to be a Th1 / Th0 dominance, with IL-12, IL-5, IFN-γ and GM-CSF, in the chronic phase. (49, 63)

The Janus kinase / signal transducer and activator of transcription (JAK / STAT) pathway is used for signal transduction in AD by various cytokines and growth factors, being involved in Th2 cell response augmentation, suppression of regulatory T cells, as well as activation of eosinophils. (64) In mammals, the Janus kinases (JAK) are a family of four tyrosine kinases including JAK 1, JAK 2, JAK 3 and TYK2. (65) They belong to a group of intercellular pathways that transmit extracellular information to the cell, so as to alter the cell or entire tissues behavior through the activity of protein kinases. (66)

By binding to specific transmembrane receptors, the cytokines lead to the activation of JAK, which is in the cytoplasm. Then, JAK phosphorylates its molecular targets and gives rise to a cascade of molecular reactions in the other components of the system including STAT activity. This leads to STAT dimerization, which can translocate to the nucleus, altering gene expression or regulating other intracellular proteins. In humans, the STAT family is comprised by STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B and STAT6. (67, 68)
The JAK/STAT pathway is activated via cytokine receptors by a variety of combinations of different JAKs and STATs, demonstrating the pathway’s versatility \(^{(69)}\) and there is increased signaling by all four JAKs in AD, in contrast to what happens in other inflammatory diseases. \(^{(70)}\)

JAK1 and JAK3 are required for Th2 differentiation. \(^{(64)}\) Th2 cells produce IL-31, which is implicated in AD and is critical in the transmission of itch sensation to the central nervous system. Additionally, it prevents eosinophil apoptosis and is implicated in disruption of skin barrier, stimulating the secretion of pro-inflammatory cytokines and chemokines through JAK-STAT. \(^{(64, 71)}\)

Several pathways, including JAK1/JAK2, are activated when IL-31 binds to its receptor (IL-31R). \(^{(72)}\)

IL-5 induces B-cell proliferation and differentiation and activates eosinophils. IL-5 acts in eosinophils, regulating genes associated with cell proliferation, survival and effector functions, through the JAK2-STAT1/STAT5 and MAP kinases pathways. \(^{(64)}\) Also, TSLP binds to a heterodimeric receptor consisting of the TSLP receptor and the IL-7 receptor to activate JAK1 and JAK2, resulting in STAT5 activation. \(^{(73)}\) In addition, IL-4 and IL-13 bind to the IL-4 receptor or the IL-13 receptor, activating JAK1 and JAK3, which in turn activates STAT6. \(^{(73)}\) The JAK-STAT pathway is, therefore, used by several cytokines that are critical in the pathogenesis of AD, such as IL-4, IL-5, IL-13, that undertake pathophysiologic roles, such as triggering Th2, activating eosinophils, maturing B-cells, up-regulating epidermal chemokines and down-regulating anti-microbial peptides. \(^{(73)}\)

**Baricitinib:**

**Chemistry, Pharmacodynamics and Pharmacokinetics**

The chemical formula of Baricitinib is C\(_{16}\)H\(_{17}\)N\(_{7}\)O\(_{2}\)S and its molecular weight is 371.42 g/mol. The chemical name is 2-(1-(Ethylsulfonyl)-3-(4-((2-((7-(2-(trimethylsilyl)ethoxy)methyl)-7H-pyrrolo[2,3-d]pyrimidin-4-yl)-1H-pyrazol-1-yl)azetidin-3-yl)acetonitrile. Baricitinib selectively and reversibly inhibits JAK1 and JAK2, with half-maximum inhibitory concentrations (IC\(_{50}\)) of 5.9 and 5.7nmol/L, respectively. The other two isoforms, TYK2 and JAK3, are still inhibited by baricitinib, although with a lower potency, with IC\(_{50}\) levels of 53 and 560 nmol/L. By inhibiting JAK1 and JAK2, baricitinib inhibits IL-6 induced STAT3 phosphorylation and subsequent production of MCP-1, as well as IL-23 induced STAT3 phosphorylation and the ensuing production of IL-17 and IL-22. \(^{(74-77)}\)

Regarding the pharmacokinetic profile of baricitinib, it was observed that it was dose proportional in the therapeutic dose range, in healthy volunteers, after being orally administrated, being linear over time. The plasma concentration of baricitinib reaches its peak within 1.5 hours (within a range of 0.5 to 3h) after oral administration and steady-state plasma concentrations were
reached 48 hours after the first dose. Its absolute bioavailability is about 79% and there is no significant clinical effect with administration with meals. The mean volume of distribution to tissues is 76L after intravenous infusion and about 50% of baricitinib binds to plasma proteins.\(^{(75, 76)}\)

This substance excretion is mainly done through renal elimination (around 75%) by glomerular filtration and active secretion via OAT3, and gastrointestinal elimination (about 20%), in a predominantly unchanged form. When there is co-administration of drugs that inhibit OAT3 (such as probenecid or ibuprofen) there is a significant increase in plasmatic baricitinib levels and a substantial decrease in renal elimination. Baricitinib exposure was observed to be increased with renal impairment, so the dose should be reduced in patients with creatinine clearance of 30-60 mL/min and it should not be administered in patients with creatinine clearance < 30 ml/min. As for patients with mild or moderate hepatic impairment, there was no clinically relevant effect on the pharmacokinetics of baricitinib.\(^{(75, 76)}\)

**Efficacy**

The efficacy and safety of baricitinib in patients with moderate-to-severe AD were assessed in a phase II, randomized, double-blind, placebo-controlled trial (NCT02576938) (Table 1). Patients stopped taking all systemic therapy for AD as well as other drugs not allowed for inclusion in the trial four weeks before randomization and continued to do so in the study, with the exception of a topical corticosteroid (0.1% triamcinolone). This trial involved 124 patients aged 18 or older, who were randomized into 3 arms: once daily placebo (49 patients), 2 mg of baricitinib once daily (37 patients), or 4 mg of baricitinib once daily (38 patients), in a 4 : 3 : 3 ratio, for 16 weeks. For this study, the primary endpoint was the proportion of patients with a 50% or greater reduction in the Eczema Area and Severity Index (EASI-50) score at week 16. The percentage of participants in the baricitinib 4 mg arm who achieved EASI50 at week 16 was 61 %, while this was achieved in 57 % in the baricitinib 2 mg arm, and 37 % in the placebo arm. The difference between the baricitinib 4mg arm compared to the placebo proved to be statistically significant \(p=0.027\), while the difference between the baricitinib 2 mg arm and the placebo arm was not significant \(p=0.065\). It should be noted that the subjects in the baricitinib arms used approximately 30% less topical corticosteroids, per month, than the placebo group. Improvements in terms of sleep and pruritus were also reported with baricitinib.\(^{(78)}\)

Eight phase III trials have been conducted to explore the efficacy and safety of baricitinib as monotherapy or in combination with topical corticosteroids. BREEZE AD-1 (NCT03334396), BREEZE AD-2 (NCT03334422), BREEZE AD-3 (NCT03334435), BREEZE AD-4 (NCT03428100), BREEZE AD-5...
BREEZE AD-1 (Table 1) and BREEZE AD-2 (Table I) were two similar multicentre, randomized, double-blind, placebo-controlled studies that evaluated the efficacy and safety of baricitinib as monotherapy. BREEZE AD-1 study had 624 participants and BREEZE AD-2 had 615 participants. The subjects were randomized in a 2:1:1:1 ratio, receiving placebo, 1 mg, 2 mg or 4 mg of baricitinib, once daily. The primary endpoint was the proportion of patients with ≥ 2-point improvement and a score of 0 or 1 on the Validated Investigator Global Assessment Scale (vIGA), at 16 weeks. (79)

In both studies, a significantly higher proportion of patients in the 4 mg and 2 mg baricitinib arms met the primary endpoint, in comparison to placebo, at week 16. In BREEZE AD-1, the percentage of subjects achieving vIGA-AD (0, 1) was 16.8% in the baricitinib 4 mg arm (P≤0.001 vs placebo), 11.4% in the baricitinib 2 mg arm and 11.8% in the baricitinib 1 mg (baricitinib 1 mg and 2 mg, P ≤ 0.05) and 4.8% for placebo. In BREEZE AD-2, the percentage of subjects achieving the primary endpoint was 13.8% for baricitinib 4mg, 10.6% for baricitinib 2 mg, 8.8% for baricitinib 1mg and 4.5% for placebo (baricitinib 2 mg, P ≤ 0.05; baricitinib 4 mg, P ≤ 0.001 vs. placebo). Overall, in the two studies, at week 16, EASI75, EASI90 and SCORAD75 were observed in a significantly higher proportion of patients in the 2 mg and, particularly, in the 4 mg arms. In addition, there were improvements in terms of sleep, pruritus, skin pain and quality of life measures, as early as week 1, for the baricitinib groups of 4 and 2 mg. (79)

The BREEZE-AD-7 trial (Table 1) was similar to the last two aforementioned studies, in terms of inclusion criteria and endpoints. The use of topical corticosteroids with low to moderate potency was allowed and the subjects were randomized in a 1:1:1 ratio, receiving placebo, 2mg or 4mg of baricitinib, once daily. At week 16, 31% of subjects in the baricitinib 4 mg group attained vIGA 0 or 1 vs 15% in the placebo group (P=0.004). In the baricitinib 2 mg, 24% attained vIGA 0 or 1 (P=0.08). When compared to placebo, a higher proportion of subjects in the baricitinib 4mg group (48%, p = 0.01) and the baricitinib 2mg group (43%, p = 0.001) reached EASI75 by week 16. There was a marked improvement of ≥4-Point in Itch NRS score from baseline by week 4 in the baricitinib groups, particularly in the 4mg group (52%, P<0.001), with a reduction from then on, presenting the value of 44% in the same group, by week 16. (80)

Results from the BREEZE-AD-5 trial (Table 1), a study where 440 participants were
randomized in a 1:1:1 ratio, receiving once daily placebo, 1 mg or 2 mg of baricitinib, as monotherapy, were released. The primary endpoint was the proportion of patients achieving at least 75% (EASI75), at week 16 and a key secondary point was the proportion of patients achieving a vIGA score of 0 or 1 with ≥ 2-point improvement. The proportion of patients achieving EASI75, at week 16, was 30% for baricitinib 2 mg (P ≤ .001), 13% for baricitinib 1 mg and 8% in placebo. EASI75 is associated with clinically significant changes in signs, symptoms, and overall quality of life in AD and, with baricitinib 2 mg, the proportion of patients achieving EASI75 diverged from placebo-treated patients at week 2. The proportion of patients achieving vIGA of 0 or 1 was 24% for the baricitinib 2 mg arm (P ≤ .001), 13% for the baricitinib 1 mg and 5% for placebo. As for the proportion achieving ≥4-point improvement on the Itch NRS was 25% for baricitinib 2 mg (P ≤ .001), 16% for 1 mg and 6% in the placebo group. (81)

BREEZE-AD-4 (Table 1) is a trial to evaluate the efficacy and safety of baricitinib in combination with topical corticosteroids in participants with moderate-to-severe atopic dermatitis who have experienced failure to cyclosporine or are intolerant to, or have contraindication to cyclosporine. This study was similar to BREEZE-AD-5 in terms of endpoints and the results were announced in a press release by Eli Lilly and Company and Incyte. In this trial, the 463 patients were randomized in a 1:1:1:1 ratio, receiving once daily placebo, 1 mg, 2 mg or 4 mg of baricitinib. The proportion of patients achieving EASI75, at week 16, was 32% for baricitinib 4 mg (P ≤ .05), 28% for baricitinib 2 mg, 23% for baricitinib 1 mg and 17% in the placebo arm. Regarding the proportion of patients who achieved vIGA of 0 or 1, it was 22% on baricitinib 4 mg, 15% on 2 mg, 13% on 1 mg and 10% on placebo. The proportion achieving ≥4-point improvement in Itch NRS, at week 16, was 38% of patients in the baricitinib 4 mg group, 23% in the 2 mg, 23% in the 1 mg and 8% in the placebo. (82)

Recently, the BREEZE-AD-3 (Table 2) study released findings addressing the long-term (68 week) efficacy of baricitinib. The goal of this study was the assessment of the long-term efficacy of this drug in adults with moderate to severe AD who were treatment responders or partial responders (vIGA-AD of 0 or 1, or 2) in the BREEZE-AD-1 and BREEZE-AD-2 trials. These patients stayed on their previously assigned treatment for 52 weeks, which accounts for a total of 68 weeks of continuous therapy. The findings revealed that the proportion of responders and partial responders treated with 4 mg baricitinib that achieved or maintained vIGA-AD of 0 or 1 remained consistent throughout the study, with 45.7% at week 16 (baseline) and 47.1% at week 68. As for the EASI75 score, it diminished slightly from 70% at baseline to 55.7% at week 68. When it comes to the responders and partial responders who were treated with 2 mg baricitinib, the proportion of
these who achieved or maintained vIGA-AD of 0 or 1 was 46.3% at week 16 and 59.3% at week 68, displaying consistency and a modest increase. EASI75 showed a similar pattern, with 74.1% at baseline and 81.5% at week 68. Hence, the first study that assesses the long-term efficacy of baricitinib in patients with moderate to severe AD points to a maintained long-term efficacy in these patients. (83)

**Safety**

In the phase II trial (NCT02576938) (Table 1), the percentage of participants that discontinued the trial due to adverse events was 10% in the placebo group, 3% in the baricitinib 2 mg group and 13% in the baricitinib 4 mg group. The adverse events that caused the discontinuation in the active arms were abnormal lymphocyte count, neutropenia, headache and eczema. (78)

In the active arms, the most common adverse events were headache, nasopharyngitis and an increase in the creatine phosphokinase blood levels, with the baricitinib 4 mg group experiencing more dose-dependent overall adverse events. (78)

In the BREEZE-AD-1 and BREEZE-AD-2 phase III trials (Table 1), the adverse events and serious adverse events were comparable in the placebo and baricitinib arms. Treatment-emergent adverse events occurred in 54%, 54%, 58% and 58% of subjects and in 56%, 53%, 58% and 54% of subjects receiving placebo, baricitinib 1 mg, 2 mg, and 4 mg in BREEZE-AD-1 and BREEZE-AD-2, respectively. (79)

The overall adverse effects were consistent with the previous study, with the most common on treatment adverse effects being nasopharyngitis, headache, increased serum CPK levels and upper respiratory tract infections. Only in the BREEZE-AD-1 study were herpes simplex infections observed more often in the baricitinib 4 mg arm, and there were no reports of herpes zoster infections in any active arms in any of the studies. There were no reports of deaths, cardiovascular events, thrombosis, gastrointestinal perforation or malignancies in either trial. (79)

As for the BREEZE-AD-7 trial (Table 1), adverse effects from treatment affected 38%, 56% and 58% of patients who received placebo, 2mg and 4 mg, while serious adverse effects occurred in 4%, 2% and 4% of the participants who received placebo, 2mg and 4 mg baricitinib, respectively. Nasopharyngitis, upper airway infections, and folliculitis were the most common adverse effects. A pulmonary embolism occurred in the higher-dose baricitinib arm and an opportunistic toxoplasmosis eye infection occurred in the placebo group. The rate of oral herpes and herpes
simplex virus infections in the control group was 2.8%, 4.6% in the baricitinib 2 mg group, and 6.3% in the 4-mg group. No deaths, non-malignant tumors or major adverse cardiovascular events were reported. \(^{(80)}\)

In the BREEZE-AD-5 study (Table 1), adverse events were reported in 49% of the patients in the placebo arm, in 54% of the baricitinib 1 mg group and 51% in the 2 mg, with 2%, 1%, and 1% experiencing serious adverse events, respectively. Upper respiratory tract infection, nasopharyngitis and diarrhea were the most common adverse events. There was a case of neutropenia reported with baricitinib 1 mg and 2 cases of lymphopenia - one with placebo and one with baricitinib 2 mg. There were no cases of malignancy, gastrointestinal perforation, deep vein thrombosis, pulmonary embolism, major adverse cardiovascular events, or deaths. \(^{(81)}\)

The safety profile on the BREEZE-AD-4 trial (Table 1) was in line with the previous studies on baricitinib, according to the news release from Eli Lilly and Company and Incyte. Nasopharyngitis, headache and influenza were the most common treatment-emergent adverse events and no venous thromboembolic events or deaths were reported. \(^{(82)}\)

A study with the results of a pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized trials was published with favorable results (Table 3). This study included data from 6 double-blinded RCT, namely the phase II trial NCT02576938, the BREEZE-AD-1, BREEZE-AD-2, BREEZE-AD-4, BREEZE-AD-5, BREEZE-AD-7 phase III trials, one double-blinded, randomized, long-term extension study, the BREEZE-AD-3 and one open-label long-term extension study, the BREEZE-AD-6. The results revealed a low frequency of serious adverse events that was comparable to those seen in placebo-treated patients. Nasopharyngitis, headache, CPK elevations and diarrhea were the most common treatment-emergent adverse events with this treatment. In the first 16 weeks, there was an increase in herpes simplex infections relative to placebo, however there was no evidence of an increased incidence of herpes infection with its continued use. There was also no increase in skin infections needing antibiotic care, serious adverse cardiovascular events or conjunctival disorders with baricitinib. \(^{(84)}\)
CONCLUSION

AD is a highly prevalent disease that has a detrimental impact on affected patients’ quality of life and the need for more treatment options remains relevant, especially in moderate-to-severe AD.

The pathophysiology of AD is complex, but it is known to be partly due to increased Th2 immunity mediated by JAK-STAT signaling downstream of many cytokines. (34) Novel developments on the pathophysiology of AD and its association with JAK-STAT pathways have prompted the development of agents that act at this level. In this regard, 2 groups of drugs can be distinguished: monoclonal antibodies and JAK inhibitors. In respect to monoclonal antibodies, dupilumab, which inhibits IL-4 and IL-13 signaling, and tralokinumab and lebrikizumab, which specifically neutralizes the IL-13 cytokine may be highlighted. Indeed, while monoclonal antibodies inhibit few cytokines, such as IL-4 and/or IL-13, which might be insufficient, JAK inhibitors act in a broader way, inhibiting multiple steps that are associated with the pathogenesis of AD, which can potentially translate into greater therapeutic advantages.

JAK inhibitors block various cytokine, growth factor, and/or hormone receptor signaling pathways, depending on their relative specificity. Baricitinib, being a selective JAK1 and JAK2 inhibitor, may have an advantage over the other oral JAK inhibitors being studied for AD, since these inhibit only JAK1. A hyper Th2 milieu, which is known to exist in AD, promotes the release of cytokines, such as IL-5, which can, through JAK2-STAT5 pathway, activate eosinophils and attract them to the skin, which worsens AD. (64) Therefore, the additional inhibition of JAK2 can prove to be an advantage of baricitinib, from a therapeutic standpoint. On the other hand, the inhibition of JAK2 interferes with erythropoiesis, myelopoiesis, and platelet activation, which could be a drawback. However, the clinical trials’ findings in AD subjects do not seem to point to safety issues of this matter.

There are currently no comparative efficacy studies between baricitinib and other drugs. For this reason, it is not feasible to make an indirect comparison between these therapies, due to differences in the trial designs, used methodologies and populations.

Baricitinib was shown to be effective in the phase II and phase III randomized controlled trials carried out in patients with moderate-to-severe AD. It has also shown to have a favorable safety profile with respect to AD patients. Increased risk of severe adverse effects, such as serious infections, malignancy, and thrombosis were not seen in the AD subjects, although they occurred in trials regarding the use of baricitinib in rheumatoid arthritis.

EMA approved baricitinib as monotherapy or in conjunction with methotrexate, in 2017, for the treatment of moderate-to-severe active rheumatoid arthritis in adults who have not
responded to or are intolerant of one or more disease-modifying anti-rheumatic drugs. In the end of 2020, EMA extended its indication of baricitinib to include the treatment of moderate-to-severe atopic dermatitis in adult patients who are candidates for systemic therapy.

Therefore, baricitinib has shown to be effective and that it has a favorable safety profile in the AD population, representing one more treatment option for AD patients who have no history of serious renal impairment or severe hepatic impairment and who favor oral therapy over injections.

Nevertheless, more studies will be necessary to assess the long-term safety of this drug in AD, particularly in the clinical context.

It is also worth mentioning that the results of the BREEZE-AD-PEDS study will be of high significance due to the prevalence of atopic dermatitis in children, who constitute a population that also requires more therapeutic alternatives.
APPENDICES

APPENDIX 1

Table I - Studies on efficacy and safety of baricitinib in AD

<table>
<thead>
<tr>
<th>Study</th>
<th>Design</th>
<th>Outcomes</th>
<th>Efficacy</th>
<th>Safety</th>
</tr>
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</table>
| NCT02576938 | (Phase II, randomized double-blind, placebo-controlled study) | -124 patients aged 18 or older  
- moderate-to-severe AD  
- TCS for 4 weeks before randomization  
- 3 arms (4:3:3, 16 weeks):  
  - placebo (49 patients)  
  - 2mg baricitinib (37 patients)  
  - 4mg baricitinib (38 patients)  
  - Primary outcome: Proportion of patients achieving ≥50% reduction in EASI-50 compared to placebo  
  - Secondary outcomes: Changes from baseline in EASI, SCORAD75, IGA score of 0 or 1 with ≥2 point improvement from baseline, NRS, DLQI, POEM | - Primary endpoint: Placebo arm: 37%.  
2mg arm: 57%, (P=0.065, compared to placebo).  
4mg arm: 61%, (P=0.027, compared to placebo).  
2mg, 4mg arms: 30% less TCS per month and improvements in terms of sleep and pruritus.  
- Secondary endpoints: Significant improvement in difference for the baricitinib arms compared to placebo | - Treatment emergent adverse events: Placebo arm: 49%  
2mg arm: 46%  
4mg arm: 71%  
- The most common adverse events: Headache, nasopharyngitis and an increase in the CPK blood levels |
| BREEZE-AD1 | (NCT03334396) | (Phase III, multicentre, randomized, double-blind, placebo-controlled study) | -624 participants aged 18 or older  
- moderate-to-severe AD  
- efficacy and safety of baricitinib as monotherapy.  
- 4 arms (2:1:1:1, 16 weeks):  
  - Placebo (249 patients)  
  - 1mg baricitinib (127 patients)  
  - 2mg baricitinib (123 patients)  
  - 4mg baricitinib (125 patients)  
  - Primary outcome: Proportion of patients with ≥ 2-point improvement and a score of 0 or 1 on the vIGA scale, at 16 weeks.  
  - Secondary outcomes: vIGA-AD score of 4, SCORAD75, Body surface area affected, Itch NRS, Skin Pain NRS, ADSS item 2, POEM, DLQI | - Primary endpoint: Placebo arm: 4.8%  
1mg arm: 11.8%, (P=0.05, compared to placebo)  
2mg arm: 11.4%, (P=0.05, compared to placebo)  
4mg arm: 16.8%, (P≤0.001, compared to placebo)  
- Secondary endpoints: EASI75, EASI90 and SCORAD95 were observed in a significantly higher proportion of patients in the 2mg and, particularly, in the 4mg arms.  
Improvements in terms of sleep, pruritus, skin pain and quality of life measures, as early as week 1, for the baricitinib groups of 4 and 2 mg. | - Treatment emergent adverse events: Placebo arm: 54%  
1mg arm: 54%  
2mg arm: 58%  
4mg arm: 58%  
- The most common adverse events: nasopharyngitis and headache.  
No cardiovascular events, venous thromboembolism, gastrointestinal perforation, significant haematological change, or death.  
Herpes simplex infections observed more often in the baricitinib 4mg arm.  
No reports of herpes zoster infections in any active arms |
### BREEZE-AD-2 (NCT03334422)
(PHASE III, MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY)

- **Participants:** 615 participants aged 18 or older
- **Efficacy and Safety:** Efficacy and safety of baricitinib as monotherapy
- **Design:** 4 arms (2:1:1:1, 16 weeks):
  - Placebo (244 patients)
  - 1mg baricitinib (125 patients)
  - 2mg baricitinib (123 patients)
  - 4mg baricitinib (123 patients)

**Primary Outcome:** Proportion of patients with ≥2-point improvement and a score of 0 or 1 on the VIGA scale, at 16 weeks

**Secondary Outcomes:**
- vIGA score of 4, SCORAD75, Body surface area affected, Itch NRS, Skin Pain NRS, ADSS item 2, POEM, DLQI

**Primary Endpoint:**
- Placebo arm: 4.5%
- 1mg arm: 8.8%, (P=0.085, compared to placebo)
- 2mg arm: 10.6%, (P=0.05, compared to placebo)
- 4mg arm: 13.8%, (P≤0.001, compared to placebo)

**Secondary Endpoints:**
- EASI75, EASI90 and SCORAD75 were observed in a significantly higher proportion of patients in the 2mg and, particularly, in the 4mg arms.
- Improvements in terms of sleep, pruritus, skin pain and quality of life measures as early as week 1, for the baricitinib groups of 4 and 2mg.

**Treatment-emergent adverse events:**
- Placebo arm: 56%
- 1mg arm: 53%
- 2mg arm: 58%
- 4mg arm: 54%

**The most common adverse events:**
- Nasopharyngitis and headache.
- No cardiovascular events, venous thromboembolism, gastrointestinal perforation, significant haematological changes, or death.
- No reports of herpes zoster infections in any active arms.

### BREEZE-AD-7 (NCT03733301)
(PHASE III, MULTICENTRE, RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY)

- **Participants:** 329 participants aged 18 or older
- **Study Design:** 3 arms (1:1:1, 16 weeks):
  - Placebo (109 patients)
  - 2mg baricitinib (109 patients)
  - 4mg baricitinib (111 patients)

**Primary Outcome:** Proportion of patients with ≥2-point improvement and a score of 0 or 1 on the VIGA scale, at 16 weeks.

**Secondary Outcomes:**
- EASI75, Percent change from baseline in total EASI score, ≥4-point improvement on Itch NRS score, Change from baseline, EASI90, SCORAD75

**Primary Endpoint:**
- Placebo arm: 15%
- 2mg arm: 24%, (P=0.008, compared to placebo)
- 4mg arm: 31%, (P=0.004, compared to placebo)

**Secondary Endpoints:**
- EASI75
  - 4mg group (48%, p=0.01 vs placebo)
  - 2mg group (43%, p=0.001 vs placebo)
- EASI90
  - 4mg group (24%)
  - 2mg group (17%)
  - Placebo group (14%)
- SCORAD75
  - 4mg group (18%)
  - 2mg group (11%)
  - Placebo group (7%)

**24-point improvement in Itch NRS score from baseline by week 4**
- 4mg group (52%, P<0.001)
- 2mg group (11%)

**Treatment-emergent adverse events:**
- Placebo arm: 38%
- 2mg arm: 56%
- 4mg arm: 58%

**Serious adverse events:**
- Placebo arm: 4% (toxoplasmosis eye infection)
- 2mg arm: 2%
- 4mg arm: 4% (pulmonary embolism)

**Rate of oral herpes and herpes simplex virus infections**
- Placebo arm: 2.8%
- 2mg arm: 4.6%
- 4mg arm: 6.3%

**The most common adverse events:**
- Nasopharyngitis, upper airway infection and folliculitis.

No deaths, non-malignant tumors or major adverse cardiovascular events.
| **BREEZE-AD-5** | 440 participants aged 18 or older | -Primary outcome: Proportion of patients achieving at least 75% reduction (EASI75) at week 16 | -Primary endpoint: Placebo arm- 8% 1mg arm- 13% 2mg arm- 30%, (P≤0.001, compared to placebo) |
| (NCT03435081) | adults with moderate-to-severe AD who responded inadequately or were intolerant to topical therapy. | -Secondary outcomes: Proportion of patients achieving a vIGA score of 0 or 1 with ≥2-point improvement, SCORAD75, Itch NRS, Skin Pain NRS, ADSS item 2, POEM, DLQI | -Secondary endpoints: vIGA score of 0 or 1 Placebo arm- 5% 1mg arm- 5% 2mg arm- 24%, (P≤0.001, compared to placebo) |
| **BREEZE-AD-4** | 463 participants aged 18 or older | -Primary outcome: Proportion of patients achieving at least 75% reduction (EASI75) at week 16 | -Primary endpoint: Placebo arm- 17% 1mg arm- 23% 2mg arm- 28% 4mg arm- 32% (P≤0.05, compared to placebo) |
| (NCT03428100) | adults with moderate-to-severe AD who have experienced failure to cyclosporine or are intolerant to or have contraindication to cyclosporine | -Secondary outcomes: Proportion of patients achieving a vIGA score of 0 or 1 with ≥2-point improvement, SCORAD75, Itch NRS, Skin Pain NRS, ADSS item 2, POEM, DLQI | -Secondary endpoints: vIGA score of 0 or 1 Placebo arm- 10% 1mg arm- 13% 2mg arm- 15% 4mg arm- 22% (P≤0.05, compared to placebo) |
| **BREEZE-AD-4** | -efficacy and safety of baricitinib in combination with TCS | 4 arms (1:1:1:1, 16 weeks): | 4x-point improvement on the Itch NRS Placebo arm- 8% 1mg arm- 23% (P≤0.05, compared to placebo) 2mg arm- 23% (P≤0.01, compared to placebo). 4mg arm-38%, (P≤0.001, compared to placebo). |
| (Phase III, multicentre, randomized, double-blind, placebo-controlled study) | Placebo (93 patients) | The most common adverse events: No cases of malignancy, gastrointestinal perforation, deep vein thrombosis, pulmonary embolism, major adverse cardiovascular events or deaths | The most common adverse events: nasopharyngitis, headache and influenza |
| **BREEZE-AD-4** | Placebo (147 patients) | -Treatment emergent adverse events: Placebo arm- 49% 1mg arm- 54% 2mg arm- 51% | No venous thromboembolism events or deaths were observed |
| (NCT03428100) | 1mg baricitinib (147 patients) | -Serious adverse events: Placebo arm- 2% 1mg arm- 1% 2mg arm- 1% | -The most common adverse events: upper respiratory tract infection, nasopharyngitis and diarrhea |
APPENDIX 2

Table II – Long-term double-blind extension study of 2 randomized clinical trials

EASI, Eczema Area and Severity Index; NRS, Numeric Rating Scale; SCORAD, vIGA-AD, Validated Investigator’s Global Assessment of atopic dermatitis.

<table>
<thead>
<tr>
<th>Design</th>
<th>Outcomes</th>
<th>Efficacy</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BREEZE-AD-3</strong> (NCT03334435)</td>
<td><strong>Primary outcome:</strong> The proportion of patients achieving a vIGA-AD score of 0, 1 at week 16, 36 and 52</td>
<td>vIGA-AD of 0 or 1</td>
</tr>
<tr>
<td>(Phase III, Ongoing, long-term, multicentre, double-blind, randomized, placebo-controlled study)</td>
<td><strong>Secondary outcomes:</strong> Proportion of patients achieving 75% or more improvement from baseline in EASI75 score</td>
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<tr>
<td>-221 participants aged 18 or older</td>
<td>4-point improvement or more from baseline in Itch NRS</td>
<td>4mg baricitinib: 52.5% at week 16 45.9% at week 32 2mg baricitinib: 44.2% at week 16 39.5% at week 32</td>
</tr>
<tr>
<td>-adults with moderate-to-severe AD who were treatment responders or partial responders (vIGA-AD of 0 or 1, or 2) in the BREEZE-AD-1 and BREEZE-AD-2 trials</td>
<td></td>
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<tr>
<td>-The long-term (68 week) efficacy of baricitinib</td>
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<tr>
<td>-4 arms:</td>
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<tr>
<td>• Placebo (52 patients)</td>
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<tr>
<td>• 1mg baricitinib (45 patients)</td>
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<tr>
<td>• 2mg baricitinib (54 patients)</td>
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<tr>
<td>• 4mg baricitinib (70 patients)</td>
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APPENDIX 3

Table III - Pooled safety analysis of baricitinib in atopic dermatitis from 8 randomized clinical studies

<table>
<thead>
<tr>
<th>Trials included</th>
<th>Patients</th>
<th>Safety outcomes</th>
<th>Events</th>
<th>Conclusion</th>
</tr>
</thead>
</table>
| Pooled safety analysis of baricitinib in adult patients with atopic dermatitis from 8 randomized clinical trials | -NCT02576938
- BREEZE-AD-1
- BREEZE-AD-2
- BREEZE-AD-4
- BREEZE-AD-5
- BREEZE-AD-7
- BREEZE-AD-3
- BREEZE-AD-6 | -2531 patients
- Baricitinib for 2247 patient years (median duration 310 days) | -Treatment emergent adverse events
- Adverse events of special interest
- Abnormal laboratory changes | - Eczema herpeticum: n=11, IR=0.5
- Cellulitis: n=6, IR=0.1
- Pneumonia: n=3, IR=0.1
- Opportunistic infections: n=4, IR=0.2
- Herpes simplex: 4mg arm - 6.1%
  2mg arm – 3.6%
  Placebo arm – 2.7%
- Major adverse cardiovascular events: Venous thrombosis events – n=2 (4mg group) | - Most common treatment emergent adverse events:
  - Nasopharyngitis
  - Headache
  - CPK elevations
  - Diarrhea
- No evidence of an increased incidence of herpes infection, skin infection needing antibiotic care or conjunctival disorders
- Low frequency of serious adverse events (comparable to those seen in placebo-treated patients)
REFERENCES


