REVIEW

# Efficacy and safety of baricitinib in patients with alopecia areata: evidence to date

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## Abstract

Alopecia areata (AA) is a chronic, tissue-specific autoimmune disorder, characterized by non-scaring hair loss, with a global prevalence of approximately 2%. Typically, it affects a young population, with initial onset frequently occurring before the age of 30 years. Even though the exact pathogenesis of AA remains unclear, the predominant hypothesis is the breakdown of immune privilege of the hair follicle, resulting in increased self-antigen and major histocompatibility complex expression in the follicular epithelium. The relapsing nature of the disease negatively impacts patients' quality of life and makes them more susceptible to developing psychiatric comorbidities. Although many treatment modalities have been proposed, there are no currently available treatments able to induce and sustain disease remission. Traditional treatment modalities, despite being widely used, present limited results and a high risk of adverse effects. Hence, there exists an unfulfilled requirement for treatments that are both more efficient and safer. The latest understanding of the pathophysiology of AA and its connection to the JAK–STAT pathway has prompted the advancement of JAK inhibitors. These small-molecule agents function by obstructing the JAK–STAT intracellular signalling pathway. Baricitinib an orally administered, selective JAK1 and JAK2 inhibitor is a promising alternative to the available treatments, and is already approved for the treatment of AA.

**Keywords:** alopecia areata, baricitinib, JAK–STAT, JAK inhibitors, pathophysiology, treatment.

# Introduction

Alopecia areata (AA) is an autoimmune disease that causes non-scarring hair loss on the scalp or any hair-bearing surface. Typically, this condition has different clinical hair loss patterns.[1] The most common pattern is one or multiple well-defined patches of bald lesions (patchy AA) that may proceed to comprise all scalp hairs (alopecia totalis) or all scalp and body hairs (alopecia universalis).[2] Patients with AA often exhibit concomitant autoimmune disorders such as systemic lupus erythematosus, vitiligo, autoimmune haemolytic anaemia and thyroid diseases.[3] Nail lesions, including trachyonychia and nail pitting, can be present as can eye pathology consisting of focal retinal hypopigmentation, opacities of the lens and cataracts.[3,4]

The diagnosis is mostly clinical and is based on visual inspection and dermoscopy; however, histopathology can be utilized when the clinical presentation is unclear.[1] AA has a dynamic course with intermittent flares and remissions. Relapse rates range from 85% to nearly 100% for those who have had the diagnosis for >20 years, indicating progression over time.[5]

Given the unpredictable and relapsing course of the disease, patients have a reduced quality of life and are often affected by psychiatric comorbidities, mostly anxiety and depression.[6,7] One in every 1000 people is affected by AA, the majority of whom are younger than 30 years. Global prevalence is approximately 2%, impacting people of both sexes as well as all ages and ethnicities.[8,9]

AA currently has no preventive or curative treatment.[10] However, as the molecular mechanisms underlying the pathophysiology of AA are clarified, novel treatment strategies are becoming more available such as Janus

kinase (JAK) inhibitors, biologics, several small-molecule agents and platelet-rich plasma injections.[11]

Amongst these agents, JAK inhibitors have collected the most evidence, being the most supported by clinical trials and literature so far.[12] Several cytokines involved in the pathogenesis of AA, including γc cytokines and IFNγ, depend on JAK signalling, making this class of small-molecule agents very attractive.[13]

Recently, an important milestone on the treatment of AA was achieved. Baricitinib, an oral, selective, reversible JAK inhibitor was approved for the treatment of AA, making it the first and only existing on-label drug for adults with AA.[14,15]

In this review, we summarize the efficacy, safety and mechanism of action of baricitinib for the treatment of AA and explore the pathophysiological pathways leading to this disorder.

# Methods

This review included original and review articles published from 2006 to 2023. Only articles written in English were included. The selection of articles was based on the relevance of their abstracts, defined objectives and subsequent comprehensive analysis of their full texts. Additionally, relevant bibliographic references from the chosen articles were included when applicable.

# Review

## AA pathophysiology

The hair follicle is a site of immune privilege, meaning that the expression of molecules associated with effective immunity is downregulated.[16] Even though the pathophysiology of AA is not fully understood, it is known that loss of immune privilege in anagen hair plays a significant role.[17] This collapse promotes an effector T cell response against hair follicle cells and a premature shift from anagen to the non-proliferative catagen and telogen stages.[16,18] Interestingly, epithelial stem cells in the hair follicle are generally not affected, preserving the follicle's capacity to develop new hair in the future, whether through natural remission or effective treatment.[19]

AA is a multifactorial disease, with genetic and environmental factors contributing to its pathogenesis.[1] Genome-wide association studies have identified polymorphisms in genes related to the immune system, structural proteins and antioxidant enzymes, which increase susceptibility to this disorder.[20] These studies focused on the HLA class II loci, UL16-binding proteins 3/6

loci, CTLA4, IL-2/IL-21 locus, IL-2RA locus and Eos locus.[21] These genes are essentially involved in T cell activation and/or survival and facilitate the autoreactive cells to bypass peripheral tolerance mechanisms.[22]

Immune privilege in healthy hair follicles is accomplished by downregulation of major histocompatibility complex (MHC) in anagen hair bulbs, which prevents auto-autoantigen recognition by CD8$^+$ T cells. In addition, there is local secretion of immunosuppressive agents, such as transforming growth factor-β1 (TGFβ1), IL-10, α-melanocyte-stimulating hormone (αMSH), indoleamine-2,3-dioxygenase (IDO) and vasoactive intestinal peptide (VIP).[23] Keeping this evasive status may be especially crucial during the anagen stage, where substantial tissue-specific peptides and antigens are being produced.[24] Melanocyte and keratinocyte epitopes are thought to be the hair follicle autoantigens involved in AA. Although lack of MHCs helps to maintain immune privilege, it can, paradoxically, increase natural killer (NK) cell attack.[25] To avoid this, there is downregulation of NK cell receptor ligands along with the production of immunosuppressive factors such as macrophage migration inhibitory factor (MIF).[26,27]

AA hair follicles present an upregulation of NKG2D-activating ligands (e.g. MICA and ULBP), increased expression of MHC class I and MHC class II, enhanced levels of pro-inflammatory cytokines (e.g. IL-15, IL-2 and CXCLs), as well as a vast inflammatory cell infiltrate (e.g. CD8$^+$ T cells, CD4$^+$ T cells, dendritic cells, NK T cells, mast cells and eosinophils).[28] CD8$^+$ T cells found near the hair follicle normally express an activating receptor related to the NK cell lineage, the NKG2D receptor.[26] This sub-set of CD8$^+$NKG2D$^+$ T cells was found to be sufficient for the development of AA.[29] When activated, they produce IFNγ via the JAK1 and JAK3 pathways, which stimulates the secretion of IL-15, via JAK1 and JAK2 signalling, by follicular epithelial cells. This cytokine then binds to CD8$^+$NKG2D$^+$ T cells, causing them to produce even more IFNγ, generating a positive feedback loop.[30] Through the JAK–STAT pathway IL-15 stimulates CD8$^+$ T cell production of perforin and cytotoxic granzymes.[22] IFNγ is the main inducer of immune privilege collapse as it leads to an increase in pro-inflammatory factors (e.g. MHC I/II, MICA, ULBP, CXCLs) and a decrease in immunosuppressive mediators (e.g. TGFβ1, IL-10, αMSH, VIP). These changes in the hair follicle microenvironment result in a wider exposure of anagen autoantigens to effector CD8$^+$ cells. These effector T cells induce hair follicle dystrophy and premature catagen phase, ultimately causing AA.[17] Although CD4$^+$ T cells might not directly cause hair loss, when activated, they are able to release inflammatory cytokines that induce hair follicle cells to secret more cytokines, with the consequent recruitment of more T cells and NK cells.[22] Moreover, it is recognized that CD4$^+$ T cells produce IL-2,

which may stimulate CD8^{+} T cell activity, and a sub-type of these cells, T helper 1 ($T_H1$) cells, IFNγ when activated release, which contributes to the inflammatory environment of AA.[24] Another factor contributing to AA pathogenesis is the decreased number of T regulatory cells, which makes the hair follicle more vulnerable to auto-immune attack.[31]

## Janus kinase inhibitors

The JAK–STAT signalling pathway is one of the key communication hubs for cellular activity, being involved in haematopoiesis, inflammation and immune function.[32,33] Various interleukins, interferons and growth factors use this pathway to transmit signals from the cell membrane to the nucleus.[34] There are four members of the JAK family: JAK1, JAK2, JAK3 and TYK2, each composed of seven homology domains.[33] It is well established that γc cytokines, such as IL-2, IL-7, IL-15 and IFNγ, rely on the JAK–STAT signalling pathway to enhance proliferation and activation of autoreactive T cells in AA.[35,36]

One of the new treatment options under investigation are JAK inhibitors. These immunomodulatory drugs are currently approved for the management of autoimmune conditions, including rheumatoid arthritis, atopic dermatitis, psoriatic arthritis, ulcerative colitis and myeloproliferative disorders.[37] JAK inhibitors work by targeting the kinase portion of JAKs. This prevents the phosphorylation of the JAK protein, which in turn interrupts the downstream regulatory signalling cascade involving STAT activation.[38] Inhibition of the JAK–STAT pathway induces a reduction in the accumulation of autoreactive CD8^{+} T cells by blocking the downstream signalling of IFNγ and γc cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 and IL-23).[29] Other effects include inhibition of CD4^{+} T helper cell differentiation and the subsequent $T_H1$, $T_H2$ and $T_H17$ type responses, as well as stimulation of hair follicle stem cells.[38,39] JAK inhibitors were first found to be efficient in AA in 2014.[29] Since then, there has been a growing interest in this class as well as several clinical trials that demonstrate their efficacy, with remarkable hair regrowth even in patients with a prolonged, therapy-resistant disorder.[40] Nevertheless, recurrence of hair loss following treatment discontinuation has been described in approximately half of patients treated with JAK inhibitors.[41] Thus, in patients that tolerate and are good responders to JAK inhibitors, it is recommended to maintain continuous treatment.[42] First-generation JAK inhibitors, such as tofacitinib, ruxolitinib, baricitinib and oclacitinib, are non-selective and inhibit two or more JAKs, which might optimize their therapeutic efficacy.[40] Within this category, tofacitinib, ruxolitinib and baricitinib have been widely investigated for AA treatment.[34] There is also a second generation of JAK inhibitors, such as ritlecitinib, brepocitinib, delgocitinib and deuruxolitinib (CTP-543), that are more selective by inhibiting a single JAK isoform, which have been showing efficacy in AA treatment in emerging studies.[43–45] This mechanism may allow enhanced treatment precision whilst minimizing adverse effects.[43] The vast range of possible adverse effects found across this pharmacological class reflects their non-specific anti-inflammatory and immunosuppressive actions.[46] The main safety issues with their use include the risk of varicella zoster emergence, pneumonia, tuberculosis, thromboembolism and malignancy.[46] Minor adverse effects commonly reported comprise acne, headache, urinary and respiratory tract infections, cytopenia, and elevated creatinine and LDL levels.[47] Most of these safety data and side-effect profiles come from clinical trials of tofacitinib and baricitinib conducted on patients with rheumatoid arthritis.[48] Therefore, these adverse effects should be carefully regarded until more extensive safety trials tailored to AA are concluded.[24]

## Baricitinib

Baricitinib has a molecular weight of 371.42 g/mol and the following molecular structure: $C_{16}H_{17}N_7O_2S$.[49,50] By inhibiting JAK1 and JAK2, baricitinib prevents a wide spectrum of cytokines from signalling, hence its potent anti-inflammatory effects.[51] In AA specifically, baricitinib blocks downstream signalling of IFNγ and γc cytokines (IL-2, IL-4, IL-7, IL-9, IL-15, IL-21 and IL-23) as well as IL-6-induced STAT3 phosphorylation, crucial for T cell differentiation and inflammation[51–53] (Table 1).

### Clinical efficacy

Two case reports, one from 2015 and the other from 2019, provided the first clinical evidence of baricitinib's efficacy in two adult patients with AA.[54,55]

The efficacy and safety of baricitinib were assessed in patients with severe AA (Severity of Alopecia Areata Tool (SALT) score ≥50%: with 0% corresponding to no scalp hair loss and 100% corresponding to total scalp hair loss) in a phase II, randomized, double-blind, placebo-controlled trial, BRAVE-AA1 (NCT03570749). A total of 110 patients were randomized 1:1:1:1 into four experimental groups: placebo (28 patients), 1 mg (28 patients), 2 mg (27 patients) or 4 mg (27 patients) of baricitinib once a day.[56]

Eligible patients were adults between the ages of 18 and 60 for men and between 18 and 70 for women. Additionally, patients experiencing a current episode of AA that lasted longer than 6 months were included. Patients with episodes lasting longer than 8 years were considered eligible only if they had experienced hair regrowth episodes during the preceding 8 years. The exclusion criteria encompassed patients who had previously shown an unsatisfactory response to oral JAK inhibitors. Patients

using topical, systemic or intralesion corticosteroids within 1 and 2 weeks, respectively, before randomization, were also excluded. Finasteride (or other 5α-reductase inhibitors), oral or topical minoxidil, and bimatoprost ophthalmic solution for eyelashes, if at a stable dose at trial entrance, were the only simultaneous AA treatments allowed. Across the treatment groups, the mean SALT scores varied between 83.4 and 90.0. The average age of the participants was 41 years, with women comprising 74.5% of the total. Overall, there were no notable disparities in baseline characteristics amongst the groups, though the 2 mg and 4 mg groups had a higher proportion of women.[56]

The primary objective of the initial interim analysis was to identify the two baricitinib doses that would proceed to phase III of the study. The selection of doses was based on the proportion of patients achieving a ≥30% improvement from baseline in SALT score (referred to as SALT30) at week 12. Additionally, for patients with available data at week 16, the proportion of patients achieving a ≥50% improvement from baseline in SALT score (referred to as SALT50) at week 16 was considered.

After 12 weeks of treatment, the 2 mg and 4 mg groups demonstrated the highest percentages of patients

achieving SALT30 scores (29.6% and 33.3%, respectively) compared with 17.9% in the 1 mg group and 10.7% in the placebo group. Amongst the 87 patients who reached week 16 or were discontinued, 31.8% in the 2 mg group and 38.1% in the 4 mg group achieved SALT50, in contrast to 18.2% in the 1 mg group and 4.5% in the placebo group. Based on these findings, the 2 mg and 4 mg groups were selected to proceed to phase III. Patients initially receiving a 1 mg dose were transitioned to a 4 mg dose for the remainder of the trial.[56]

For the subsequent interim analysis at week 36, the primary endpoint was the frequency of patients with a SALT score of ≤20. Secondary endpoints included the percentage change from baseline in SALT score; absolute SALT score of ≤10; percentage of patients achieving a patient-reported outcome (PRO) for Scalp Hair Assessment score of 0 or 1 (0 to 20% of scalp missing hair) at week 36 with ≥2 point improvement from baseline; and percentage of patients achieving a PRO and a Clinician-Reported Outcome (ClinRO) Measure for Eyebrow/Eyelash Hair Loss of 0 or 1 (full eyebrow/eyelash coverage or minimal gaps) at week 36 with a ≥2 point improvement from baseline.[56]

In the groups receiving doses of 2 mg and 4 mg, the percentage of patients who achieved a SALT score of

**Table 1.   Studies on efficacy and safety of baricitinib in AA.**

| Study | Design | Outcomes | Efficacy | Safety |
|---|---|---|---|---|
| BRAVE-AA2 (NCT03899259)[56] | Phase III, randomized, double-blind, placebo-controlled trial<br><br>546 patients adult patients with severe AA<br><br>3 arms (3:2:2, 36 weeks) | Primary outcome: SALT score of ≤20, at week 36% of patients<br><br>Secondary outcomes: Scalp Hair PRO score of 0 or 1 with ≥2 point improvement from baseline at week 36% of patients<br><br>ClinRO for EB and EL of 0 or 1 with a ≥2 point improvement from baseline at week 36% of patients | Primary endpoint: Placebo arm: 3.3% 2 mg arm: 19.4 % 4 mg arm: 35.9%<br><br>Secondary endpoints: *Scalp Hair PRO* Placebo arm: 5.1% 2 mg arm: 18.5% 4 mg arm: 37.8%<br><br>*ClinRO for EB* Placebo arm: 5.5% 2 mg arm: 13.2% 4 mg arm: 38.9%<br><br>*ClinRO for EL* Placebo arm: 6.9% 2 mg arm: 12.3% 4 mg arm: 36.8% | Treatment-emergent adverse events: Placebo arm: 63.0% 2 mg arm: 68.4% 4 mg arm: 66.1%<br><br>Most common adverse events: acne, upper respiratory tract infections, headache, urinary tract infection, and elevated CPK levels |

(*Continued*)

**Table 1.   (Continued)**

| BRAVE–AA1 (NCT03570749)[56,57] | Phase III, randomized, double-blind placebo-controlled trial<br><br>654 patients adult patients with severe AA<br><br>3 arms (3:2:2, 36 weeks) | Primary outcome: SALT score of ≤ 20, at week 36% of patients<br><br>Secondary outcomes: Scalp Hair PRO score of 0 or 1 with ≥2 point improvement from baseline at week 36% of patients<br><br>ClinRO for EB and EL of 0 or 1 with a ≥2 point improvement from baseline at week 36% of patients | Primary endpoint: Placebo arm: 6.2% 2 mg arm: 22.8% 4 mg arm: 38.8%<br>Secondary endpoints: *Scalp Hair PRO* Placebo arm: 5.9% 2 mg arm: 17.1% 4 mg arm: 35.8%<br><br>*ClinRO for EB* Placebo arm: 4.4% 2 mg arm: 22.0% 4 mg arm: 35.2%<br><br>*ClinRO for EL* Placebo arm: 4.4% 2 mg arm: 14.8 % 4 mg arm: 36.2% | Treatment-emergent adverse events: Placebo arm: 51.3% 2 mg arm: 50.8% 4 mg arm: 59.6%<br><br>Most common adverse events: acne, upper respiratory tract infections, headache, urinary tract infection, and elevated CPK levels |
| | Phase II, randomized, double-blind, placebo-controlled trial<br><br>110 patients adult patients with severe AA<br><br>4 arms (1:1:1:1, 36 weeks) | Primary outcome: SALT score of ≤20, at week 36% of patients<br><br>Secondary outcomes:<br><br>Percentage change from baseline in SALT score<br><br>Absolute SALT score ≤10, at week 36% of patients<br><br>Scalp Hair PRO score of 0 or 1 with ≥2 point improvement from baseline, at week 36% of patients | Primary endpoint: Placebo arm: 3.6% 2 mg arm: 33% 4 mg arm: 51.9%<br><br>Secondary endpoints: *Percentage change from baseline in SALT score*: Placebo arm: −11.7±7.8 2 mg arm: −48.2±7.9 4 mg arm: −58.1±7.8<br><br>*Absolute SALT score ≤10*: Placebo arm: 0% 2 mg arm: 25.9% 4 mg arm: 40.7%<br><br>*Scalp Hair PRO* Placebo arm: 3.6% 2 mg arm: 33.3% 4 mg arm: 37.0% | Treatment-emergent adverse events: Placebo arm: 60.7% 2 mg arm: 70.4% 4 mg arm: 77.8%<br><br>Most common adverse events: Upper respiratory tract infection, acne and nausea |

AA, Alopecia areata; ClinRO, clinician-reported outcome; CPK, Creatine Phosphokinase; EB, eyebrow; EL, eyelash; PRO, Patient-reported outcome; SALT, Severity of Alopecia Tool.

≤20 at week 36 was 33% ($p$=0.016) and 51.9% ($p$=0.001), respectively, compared with 3.6% in the placebo group. For secondary outcomes, the change in SALT score from the baseline was −58.1±7.8 in the 4 mg group, −48.2±7.9 in the 2 mg group and −11.7±7.8 in the placebo group. Compared to placebo, a greater proportion of participants in the 4 mg group (40.7%, $p$=0.008) and the 2 mg group (25.9%) reached a SALT score of ≤10 by week 36. The percentage of patients achieving a score of 0 or 1 on the ClinRO Measure for Eyebrow/Eyelash Hair Loss was 39.1%/60.0% for the 4 mg group, 28.6%/40.0% for the 2 mg group and 4.3%/5.9% for the placebo group. Furthermore, the percentage of participants in the 4 mg, 2 mg and placebo groups who achieved a score of 0 or 1 on the PRO Measure for Scalp Hair Assessment was 37.0% ($p$=0.007), 33.3% and 3.6%, respectively. As for the proportion of participants achieving a score of 0 or 1 on the PRO Measure for Eyebrow/Eyelash, it was 45.8%/57.9% in the 4 mg group,

40.0%/27.8% in the 2 mg group and 0%/0% in the placebo group. Ultimately, this trial demonstrated that longer treatment durations with higher doses of baricitinib were well tolerated and effective in promoting hair regrowth.[56]

As a result of the previous trial's successful results, two double-blind, randomized, placebo-controlled, phase III trials, named BRAVE-AA1 (NCT03570749) and BRAVE-AA2 (NCT03899259), were conducted to evaluate the efficacy of 2 mg and 4 mg of oral baricitinib in the treatment of severe AA (SALT score ≥50%). BRAVE-AA1 included 654 patients whilst BRAVE-AA2 included 546 patients. In each trial, patients were randomized in a 3:2:2 ratio, receiving placebo, 2 mg or 4 mg of baricitinib once daily. The percentage of patients with a SALT score of ≤20 at week 36 was the primary outcome. The key secondary outcomes mirrored those observed in the phase II segment of the BRAVE-AA1 trial. These outcomes encompassed the percentage of patients achieving a PRO for Scalp Hair Assessment score of 0 or 1 at week 36, demonstrating a minimum improvement of two points compared with baseline. Additionally, it included the percentage of patients attaining a ClinRO Measure for Eyebrow/Eyelash Hair Loss score of 0 or 1 at week 36, also with a minimum improvement of two points from baseline. Furthermore, the analysis involved evaluation of the percentage change from baseline in SALT score as well as the absolute SALT score being ≤10. The inclusion and exclusion criteria as well as the permitted concomitant AA treatments were the same as in the prior phase II trial. The average age of patients in all treatment groups was 37.5 years, with 61% of them being women. In both studies, the median SALT score was 96, whilst the mean duration of AA from onset was 12.2 years. The average duration of the current episode of alopecia was 3.9 years.[57]

In the BRAVE-AA1 study, the primary outcome was achieved by different proportions of patients across the treatment groups. Specifically, the 4 mg group had a success rate of 38.8%, the 2 mg group had a rate of 22.8% and the placebo group had a rate of 6.2%. The difference between the baricitinib 4 mg arm and the placebo group was 32.6% (95% CI 25.6–39.5), whilst the difference between the baricitinib 2 mg arm and the placebo group was 16.6% (95% CI 9.5–23.8). Both differences were statistically significant (p<0.001 for each dose compared with placebo). Regarding the key secondary outcomes, the proportions of patients achieving a PRO Measure for Scalp Hair Assessment score of 0 or 1 were 35.8% (p<0.001) in the 4 mg group, 17.1% in the 2 mg group and 5.9% in the placebo group. For the ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of 0 or 1, the rates were 35.2% (p<0.001) in the baricitinib 4 mg group, 22.0% in the 2 mg group and 4.4% in the placebo group. Similarly, the percentages of patients achieving ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of

0 or 1 were 36.2% (p<0.001) in the 4 mg group, 14.8% in the 2 mg group and 4.4% in the placebo group. The SALT score changed by -47.1±2.7% from baseline in the 4-mg arm, -32.7±3.1% in the 2-mg arm and -9.0±3.1% in the placebo arm. Moreover, a greater percentage of patients in the 4 mg group (27.9%) and the 2 mg group (13.0%) had SALT score of ≤10 by week 36 compared with the placebo group (4.1%).[48] In BRAVE-AA2, the 4 mg group had 35.9% of patients reaching the primary outcome, the 2 mg group had 19.4% and placebo had 3.3%. The difference between the 4 mg/2 mg group and placebo was 32.6 % (95% CI 25.6–39.6) and 16.1 % (95% CI 9.1–23.2), respectively, both proved to be statistically significant (p<0.001 for each dose versus placebo). Regarding important secondary outcomes, the percentage of patients in the 4 mg, 2 mg and placebo groups reaching a PRO Measure for Scalp Hair Evaluation score of 0 or 1 was 37.8% (p<0.001), 18.5% and 5.1%, respectively. ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of 0 or 1 were observed in different proportions amongst treatment groups. Specifically, 38.9% (p<0.001) of patients in the baricitinib 4 mg arm achieved this outcome, whilst 13.2% in the baricitinib 2 mg arm and 5.5% in the placebo arm achieved the same. Similarly, the percentage of patients attaining ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of 0 or 1 in the 4 mg group was 36.8% (p<0.001), 12.3% in the 2 mg group and 6.9% in the placebo group. Furthermore, the percentage change in SALT score from baseline differed across the treatment arms. Specifically, the change was -48.7±2.6 in the 4 mg arm (p<0.001), -29.9±2.8 in the 2 mg arm and -4.3±2.8 in the placebo arm. By week 36, the proportion of patients achieving an absolute SALT score of ≤10 was 25.6% in the baricitinib 4 mg group, 12.0% in the 2 mg group and 1.0% in the placebo group. In both trials, a higher percentage of patients in the 4 mg baricitinib group were able to reach a SALT score of ≤20 at week 36 compared with placebo, starting at week 8 in BRAVE-AA1 and week 12 in BRAVE-AA2. The baricitinib 4 mg arm also exhibited a consistent response in most of the secondary endpoints. Overall, baricitinib was shown to be superior to placebo in terms of hair regrowth in patients with severe AA.[57]

Recent publications have provided data on the extended durations of the BRAVE-AA1 and BRAVE-AA2 studies. These reports highlight the findings after 52 weeks of observation. The results demonstrate a notable increase in the proportion of patients achieving favourable SALT scores, specifically SALT scores of ≤20 and ≤10. This improvement was most evident amongst individuals receiving a dosage of 4 mg of baricitinib. In BRAVE-AA1, 21.2% and 24.4% of patients achieved a SALT score of ≤20 under baricitinib 2 mg and 40.9% and 36.8% under baricitinib 4 mg. Similarly, in BRAVE-AA2, the percentages were 40.9% and 36.8% under baricitinib 4 mg. For SALT scores of ≤10, 14.1% and 16.7% of patients achieved this

outcome with baricitinib 2 mg in BRAVE-AA1, and 29.9% and 27.8% with baricitinib 4 mg. In BRAVE-AA2, the percentages were 29.9% and 27.8% under baricitinib 4 mg. The trials also demonstrated an increase in the rates of eyebrow and eyelash response over the 52-week period. At week 52, 27.9% and 16.3% of patients with initial ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of 2 or 3 for eyebrow hair loss experienced an improvement of ≥2 points and achieved a ClinRO Measure for Eyebrow/ Eyelash Hair Loss score of 0 or 1 with baricitinib 2 mg. For baricitinib 4 mg, the percentages were 39.4% and 49.7% in BRAVE-AA1 and BRAVE-AA2, respectively. Likewise, at week 52, 21.6% and 30.3% of patients with initial ClinRO Measure for Eyebrow/Eyelash Hair Loss scores of 2 or 3 for eyelash hair loss showed an improvement of ≥2 points and achieved a ClinRO Measure for Eyebrow/ Eyelash Hair Loss score of 0 or 1 with baricitinib 2 mg. For baricitinib 4 mg, the percentages were 40.7% and 50.7% in BRAVE-AA1 and BRAVE-AA2, respectively.[58]

## Safety

The safety outcomes were categorized into different aspects, including treatment-emergent adverse events (AE), AEs of special interest and abnormal laboratory changes. In the phase II segment of the BRAVE-AA1 trial, which involved an observational period of up to 52 weeks, a significant proportion of patients experienced treatment-emergent AEs. Specifically, in the baricitinib 4 mg group, 77.8% (incidence rate (IR) 244.5) of patients encountered such events, whilst in the baricitinib 2 mg group, the percentage was 70.4% (IR 224.2). In comparison, 60.7% (IR 179.6) of patients in the placebo group experienced treatment-emergent AEs. It is noteworthy that no deaths or serious AEs, including major adverse cardiovascular events, thromboembolic events, malignancies or serious infections, were observed in any of the groups.[56]

Amongst the individuals receiving baricitinib treatment, the most commonly reported AEs were upper respiratory tract infection, acne and nausea. It is important to note that, though certain laboratory abnormalities were observed, they were not associated with any AEs. Specifically, in the baricitinib 4 mg group, there was one occurrence of thrombocytopenia, whilst in the placebo group, one case of neutropenia was reported. Furthermore, elevated levels of creatine phosphokinase were observed in one patient from the placebo arm and three patients from the 2 mg baricitinib arm.[56]

In the BRAVE-AA1 and BRAVE-AA2 phase III trials, treatment-emergent AEs were documented in 59.6%, 50.8% and 51.3% of patients, and in 66.1%, 68.4% and 63.0% of patients receiving 4 mg baricitinib, 2 mg baricitinib, and placebo in BRAVE-AA1 and BRAVE-AA2, respectively. The discontinuation rates due to AEs were consistently low across the study groups. In the BRAVE-AA1 trial, serious AEs affected 2.1% of patients receiving 4 mg baricitinib, 2.2% of patients receiving 2 mg baricitinib and 1.6% of patients in the placebo group. Similarly, in the BRAVE-AA2 trial, serious AEs occurred in 3.4% of patients who received 2 mg baricitinib 2.6% of patients who received 4 mg baricitinib and 1.9% of patients in the placebo group. Notably, in the BRAVE-AA1 trial, one patient with cardiovascular risk factors who was receiving 2 mg baricitinib experienced a myocardial infarction. In BRAVE-AA2, one patient in 4 mg group developed B cell lymphoma, whilst one patient in the placebo group developed prostate cancer. There were no reports of venous thromboembolic events, opportunistic infections or gastrointestinal perforations in either trial.[57]

The overall occurrence of AEs was consistent with the findings from the previous study. In both trials, the most frequently observed AEs were upper respiratory tract infections, acne, urinary tract infection, headache and elevated levels of creatine kinase. Only a modest proportion of patients experienced herpes zoster infection, which was more frequent in those receiving baricitinib compared with those receiving placebo in BRAVE-AA2. In both trials, increased LDL cholesterol levels were observed in 25% of patients in the baricitinib groups, whilst increased HDL cholesterol levels were reported in 40% of patients receiving baricitinib.[57]

The recently published data covering a period of 52 weeks provided insights into the most commonly observed treatment-emergent AEs. These included upper respiratory tract infection, headache, urinary tract infection, nasopharyngitis, COVID-19 infection, acne and elevated levels of creatine phosphokinase. The occurrence of AEs leading to discontinuation was infrequent and comparable across all groups. During the extension phase of the BRAVE-AA1 trial, isolated incidents of herpes zoster, COVID-19 infection and appendicitis were reported in patients receiving baricitinib 4 mg. However, it is important to note that all affected individuals recovered, and none were required to discontinue the study. In the BRAVE-AA2 extension period, one patient receiving baricitinib 4 mg discontinued the study due to a COVID-19 infection. In the BRAVE-AA1 trial, cases of squamous cell carcinoma and ductal carcinoma in situ were reported after 16 months and 10 months, respectively, in a patient receiving baricitinib 2 mg and 4 mg. Notably, there were no instances of opportunistic infections, tuberculosis, venous thromboembolism, gastrointestinal perforations or deaths reported in any of the studies during the extension period. The majority of laboratory changes were similar amongst the groups receiving baricitinib in both studies, and these findings were consistent with the data observed at the 36-week mark.[58]

## Other JAK inhibitors on investigation for AA

Ritlecitinib, brepocitinib, delgocitinib and deuruxolitinib (CTP-543) are second-generation JAK inhibitors that have been showing efficacy in AA in emerging studies.[43–45,59] Notably, in randomized control trials, ritlecitinib, a selective inhibitor of JAK3 and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) family kinases and deuruxolitinib, a selective inhibitor of JAK1 and JAK2, showed treatment success in up to 30.6% (38/124) and 41.7% (15/36) of patients , defined as ≥80% scalp coverage, respectively, after 24 weeks of treatment with each agent.[43,45] In a double-blind RCT with brepocitinib, a selective inhibitor of TYK2 and JAK1, 53.2% (25/47) of patients achieved a 50% improvement in the SALT score.[45]

# Conclusion

AA is a common autoimmune disorder that has a significant negative impact on patient quality of life, mental health and productivity, representing much more than an aesthetic concern. Considering the overall burden on quality of life and the lack of efficient treatment options, there is an urgent need for treatment alternatives.

Over the past decade, broad-acting immunosuppressants have gradually been replaced by agents targeting the various pathways implicated in AA pathogenesis, which minimizes side-effects as well as off-target downstream effects. The JAK–STAT pathway plays a crucial role in AA maintenance because the cytokines responsible for the activation and proliferation of autoreactive T cells rely on it. JAK inhibitors are competitive inhibitors of JAK enzymes at their ATP binding sites; they work by inhibiting IFNγ and γc cytokines, which decreases the accumulation of autoreactive $CD8^+$ T cells, and by inhibiting $CD4^+$ T helper cell differentiation.

Currently, the available data points to oral JAK inhibitors as a promising new class of drugs that can promote significant hair regrowth whilst having mild to moderate side-effects.

Baricitinib, a selective and reversible inhibitor of JAK1 and JAK2, was shown to be effective in phase II and III randomized controlled trials conducted in adult patients with severe AA. It also appeared to be well tolerated, with most events being classified as mild or moderate. There were no reports of venous thromboembolic events, opportunistic infections or gastrointestinal perforations. To evaluate the long-term efficacy and safety of baricitinib, extension phases of the two phase III trials are currently ongoing.

The demonstrated efficacy from large-scale clinical trials led to the approval of baricitinib by the EMA and FDA for the treatment of AA in 2022. Nevertheless, longer trials will be necessary to assess the long-term safety of this drug in the treatment of AA.

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