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REVIEW ARTICLE

Baricitinib for the Treatment of Alopecia Areata

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Abstract

Alopecia areata (AA) is a relapsing, chronic, immune-mediated disease characterized by nonscarring, inflammatory hair loss that can affect any hair-bearing site. AA clinical presentation is heterogeneous. Its pathogenesis involves immune and genetic factors and several pro-inflammatory cytokines involved in AA pathogenesis, including interleukin-15 and interferon-γ, as well as Th2 cytokines, such as IL-4/IL-13, that signal through Janus kinase (JAK) pathway. AA treatment aims to stop its progression and reverse hair loss, and JAK inhibition has been shown to stop hair loss and reverse alopecia and has exhibited promising results in treating AA in clinical trials. Baricitinib, an oral, reversible, selective JAK1/JAK2 inhibitor, was shown to be superior to placebo on hair growth after 36 weeks of treatment in adults with severe AA in a phase 2 trial and recently in two phase 3 trials (BRAVE-AA1 and BRAVE-AA2). In both studies, the most common adverse events were upper respiratory tract infections, urinary tract infection, acne, headache, and elevated creatine kinase levels. On the basis of these trial results, baricitinib was recently approved by the European Medicines Agency (EMA) and US Food and Drug Administration (FDA) for the treatment of adults with severe AA. Nevertheless, longer trials are needed to determine the long-term efficacy and safety of baricitinib in AA. Current trials are ongoing and are planned to remain randomized and blinded for up to 200 weeks.

Key Points

Several pro-inflammatory cytokines involved in alopeica areata (AA) pathogenesis, including interleukin-15, interferon-γ, and type 2 cytokines, signal through the Janus kinase (JAK) pathway.

Baricitinib was shown to be superior to placebo for hair growth after 36 weeks of treatment in adults with severe AA in a phase 2 trial and recently in two phase 3 trials (BRAVE-AA1 and BRAVE-AA2).

On the basis of BRAVE-AA1 and BRAVE-AA2 results, baricitinib was recently approved by the EMA and US FDA for the treatment of adults with severe AA.

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1 Introduction

Alopecia areata (AA) is a relapsing, chronic, immune-mediated disease characterized by nonscarring, inflammatory hair loss that can affect any hair-bearing site [1]. AA clinical presentation is significantly heterogeneous. Classically, AA presents as a single or multiple asymptomatic, well-demarcated, circular, and smooth patches of hair loss [1]. Patchy scalp alopecia can progress to alopecia totalis (total scalp hair loss) or alopecia universalis (total body hair loss) [1]. AA affects patients of all genders, ethnicities, and age groups, with an incidence and prevalence in the general population of 0.7–4% and approximately 0.2%, respectively [2, 3]. AA is unusual in children younger than 3 years of age, but common in young people, as up to 66% of patients with AA are younger than 30 years, and only 20% are older than 40 years [4]. AA is associated with an increased overall risk of other concomitant autoimmune diseases (16%), including atopic conditions such as atopic dermatitis (the highest association), vitiligo, autoimmune thyroid disease, and systemic lupus erythematosus [5–9]. In addition, AA has an enormous psychological impact on patients, being associated with high rates of anxiety and depression [3, 10]. Suicides have also been reported in adolescents recently diagnosed with AA who had no previous psychological disorders [3, 10].

AA treatment aims to stop its progression and reverse hair loss. Although spontaneous resolution may occur in mild episodes lasting less than 12 months, extensive AA is unlikely to regress without treatment [11]. Current treatment options are limited. Glucocorticoids (topical, intralesional, and systemic), contact immunotherapy, and other immunosuppressive agents (methotrexate, azathioprine, cyclosporine) have variable efficacy in severe AA cases and are not approved by the European Medicines Agency (EMA) and Food and Drug Administration (FDA) [12].

AA pathogenesis involves immune and genetic factors [13, 14]. AA has a polygenic inheritance [15]. Several pro-inflammatory cytokines involved in AA pathogenesis, including type 1 [such as interleukin (IL)-15 and interferon-γ (IFN-γ)] and type 2 cytokines (e.g., IL-13) signal through Janus kinase (JAK) pathway [16]. JAK inhibition has shown to stop hair loss and to reverse alopecia once installed, exhibiting promise in treating AA in clinical trials [14, 17]. In patients with significant scalp and/or body hair loss, AA has been associated with systemic inflammation, suggesting the need for systemic treatment [18].

Baricitinib, an oral, reversible, selective JAK1/JAK2 inhibitor, was shown to be superior to placebo on hair growth after 36 weeks of treatment in adults with severe AA, in a phase 2 trial and recently in two phase 3 trials (BRAVE-AA1 and BRAVE-AA2) [17]. On the basis of these trial results, baricitinib was recently approved by the EMA and FDA for the treatment of adults with severe AA [19, 20].

This article intends to review the current literature on baricitinib in AA management.

A review of the published literature was conducted (up until March 2023) using the PubMed database, published abstracts and virtual presentations from scientific meetings, data from industry press releases, and results published on ClinicalTrials.gov. Manuscripts with trial results, case series, clinical trial data from ClinicalTrials.gov, and articles highlighting expert perspectives on the topic of the article were selected.

2 The Role of the JAK-STAT Pathway in AA Pathogenesis

The hair follicle has a relative immunological privilege, and AA is associated with abnormalities in this hair follicle immune privilege, with anagen hair follicles, especially the pigment-producing hair follicle, being targeted by inflammatory cells [21, 22]. Cytotoxic $CD8^+$ $NKG2D^+$ T cells have been shown to play a critical role in AA development [14]. The IL-15 upregulation in hair follicles contributes to the loss of its immunological privilege, by triggering the recruitment and activation of $CD8^+$ $NKG2D^+$ T cells, provoking IFN-γ production [14]. The infiltration of this subset of T cells into the hair follicle epithelial layers triggers an upregulation of several γ-chain cytokines and IFN-γ response promoting the $CD8^+$ $NKG2D^+$ T-cell activation and survival [14]. Antibodies against IL-2, IFN-γ, or IL-15Rβ prevented the AA development, reducing the cutaneous accumulation of $CD8^+$ $NKG2D^+$ T cells [14]. A genome-wide association study recognized connections between several genes that control regulatory T-cell activation and proliferation, IL-2/IL-21, cytotoxic T lymphocyte-associated antigen 4 (CTLA4), the antigen region human leukocyte (HLA), and IL-2 receptor A (IL-2RA) and AA [13]. The importance of environmental factors in provoking the disease remains unknown [23]. No correlation between AA and stress hormone levels has been found in controlled clinical studies with humans [24].

The JAK family is composed of four intracellular enzymes (cytoplasmic tyrosine kinases): JAK1, JAK2, JAK3, and TYK2. They interact with type 1 and 2 cytokine receptors and mediate intracellular signal transduction, affecting the cells' proliferation, migration, differentiation, and apoptosis [25]. JAKs play an essential role in hematopoiesis, immune responses, and host defense [26]. Cell signaling via IL-15, IFN-γ, and several other cytokines involved in AA (IL-2, IL-7, IL-13, and IL-21) occurs through the JAK signal transducer and activator of the transcriptional (STAT) signaling pathway [7–9, 14, 18]. In AA, IFN-γ has been shown to promote IL-15 production in hair follicles through JAK1/2 signaling. IL-15 also stimulated IFN-γ production by T cells via JAK1/3 signaling, amplifying the inflammatory response around hair follicles. Thus, JAK inhibitors appear to be a potential therapeutic option for AA treatment [27, 28].

3 Baricitinib

Baricitinib selectively inhibits JAK1 and 2 [29]. Baricitinib exhibited 100-fold selectivity for JAK1 and JAK2 over JAK3. The lower affinity for JAK3 could potentially decrease the immunosuppressive effects expected as a consequence JAK3 inhibition [30]. Baricitinib has an oral bioavailability of approximately 80%. Metabolism is mainly carried out via CYP3A4 [31].The half-life is approximately 12 h. Approximately 75% of the drug is eliminated via urine and 20% via feces. Of the drug eliminated, 69% is unchanged in urine and 15% in feces [29].

Baricitinib is currently approved for the treatment of moderate to severe rheumatoid arthritis (2017/2018, EMA [32] and FDA [33], respectively), moderate to severe atopic dermatitis (2020, EMA [34]), and more recently coronavirus disease 2019 (COVID-19) in hospitalized adults requiring supplemental oxygen, non-invasive or

invasive mechanical ventilation, or extracorporeal membrane oxygenation (2022, FDA [35]). In May and June 2022, baricitinib was approved for severe alopecia areata by the EMA [20] and FDA [19], respectively.

3.1 Phase 2 Trials

3.1.1 Clinical Efficacy

BRAVE-AA1 (NCT03570749), a phase 2/3 adaptive, placebo (PBO)-controlled, double-blind trial, evaluated the efficacy and safety of oral baricitinib in patients with AA who had ≥ 50% scalp hair loss. A total of 110 patients were randomized 1:1:1:1 to receive baricitinib 1 mg (28 patients), 2 mg (27 patients), or 4 mg (27 patients) once daily (OD) or placebo (28 patients). The trial had two interim analysis after all patients completed 12/16 weeks and 36 weeks of treatment or early discontinuation. The first interim analysis (12/16 weeks) aimed to identify two doses of baricitinib to advance to a second phase 3 trial (BRAVE-AA2) and study's phase 3 part, and the second analysis to assess the drug's efficacy and safety [36]. More detailed information can be found in Table 1.

The trial included patients with severe AA [Severity of Alopecia Tool (SALT) score of 50–94% of scalp hair loss] or very severe AA (SALT score 95–100%), aged ≥ 18 to ≤ 70 years and ≥ 18 to ≤ 60 years for women and men, respectively, and with a current episode of AA lasting > 6 months to < 8 years, with no spontaneous improvement (≤ 10 point reduction in SALT score) in the past 6 months or lasting > 8 years, but with regrowth episodes in the previous 8 years. Different age limits were set due to differences in the severity and prevalence of androgenetic alopecia (AGA) between the sexes [36].

Patients with "diffuse" AA or other types of alopecia, patients who received topical corticosteroids or topical JAK inhibitors 1 and 4 weeks, respectively, before the start of the study, or intralesional, systemic corticosteroids, or oral JAK inhibitors 8 weeks before randomization, were excluded. During the trial, no other treatments for AA were allowed [36].

In the first interim analysis, the proportion of patients who achieved a ≥ 30% baseline improvement in SALT score (SALT30) at week 12 or ≥ 50% baseline improvement in SALT score (SALT50) at week 16 was used in the decision on the two doses. The primary endpoint in the second interim analysis was the proportion of patients who achieved a SALT score ≤ 20 at week 36 [36].

At week 12, 33.3%, 29.6%, 17.9%, and 10.7% of patients achieved a SALT30 when treated with baricitinib 4 mg, 2 mg, 1 mg, and placebo, respectively. Of patients who completed 16 weeks or discontinued earlier (87 patients), SALT50 response was achieved by 31.8%, 38.1%, 18.2%, and 4.5% patients treated with baricitinib 2 mg ($P = 0.057$ versus PBO), 4 mg ($P = 0.036$ versus PBO), 1 mg, and placebo, respectively. On the basis of the results presented, the 2 mg and 4 mg doses were selected for phase 3 studies. Patients on baricitinib 1 mg were transferred to the baricitinib 4 mg group but were not included in subsequent analyses [36].

At week 36, a significantly higher proportion of patients achieved a SALT ≤ 20 in the baricitinib 4 mg and 2 mg group compared with PBO (51.9%, 33.3% versus 3.6%, $P = 0.016$ and $P = 0.001$, respectively). Patients treated with baricitinib 4 mg and 2 mg had a significantly greater percent change from baseline in SALT score (least square mean ± standard error) than PBO (− 58.1 ± 7.8, $P < 0.001$; − 48.2 ± 7.9, $P < 0.001$; and − 11.7 ± 7.8; respectively). The SALT 10 score was achieved significantly higher in patients in the baricitinib 4 mg (40.7%, $P = 0.008$) and baricitinib 2 mg (25.9%, $P = 0.046$) group compared with the PBO (0%). SALT50, SALT75, SALT90, and SALT100 responses were significantly higher in patients treated with baricitinib 4 mg compared with PBO. The more detailed results can be found in Table 1 [36].

3.1.2 Safety

The most frequently observed adverse events (AEs) in patients taking baricitinib were nausea, acne, and upper respiratory tract infection. Treatment-emergent adverse events occurred in 77.8%, 70.4%, and 60.7% of patients on baricitinib 4 mg, 2 mg, and PBO, respectively. In none of the treated groups was there a serious adverse event or death. No thromboembolic events, malignancies, serious infections, or major adverse cardiovascular events were observed [36].

3.2 Phase 3 Trials

3.2.1 Clinical Efficacy

BRAVE-AA1 (NCT03570749) and BRAVE-AA2 (NCT03899259) are parallel-group, randomized, double-blind, 36-week, placebo-controlled trials that included 654 and 546 patients, respectively [17]. BRAVE-AA1 was an adaptive phase 2–3 trial as indicated earlier, but the results of the phase 3 part are included here (Table 1). The trials have the same eligibility criteria (already mentioned above) and primary and secondary endpoints. The primary outcome was a SALT score of 20 or less at week 36. Patients were

Table 1 Baricitinib results in the treatment of AA

Study	Phase	Study design	Eligibility and exclusion criteria	Endpoints	Results	Main adverse effects
A Study of Baricitinib (LY3009104) in Participants With Severe or Very Severe Alopecia Areata (BRAVE-AA1) [NCT03570749] [36]	2/3	Randomized, PC, DB Study's phase 2 portion 110 patients 12/16 weeks Via oral Randomized 1:1:1:1 Baricitinib 1 mg once daily (OD) (28 patients) Baricitinib 2 mg OD (27 patients) Baricitinib 4 mg OD (27 patients) Placebo OD (28 patients) Study's phase 3 portion 654 patients 36 weeks Via oral Randomized 3:2:2 Baricitinib 2 mg OD Baricitinib 4 mg OD Placebo OD Long extension period 52 weeks	Eligibility criteria Patients with severe AA (Severity of Alopecia Tool [SALT] score of 50-94% of scalp hair loss) or very severe AA (SALT score 95-100%) AND ≥18 to ≤70 years and ≥18 to ≤60 years for women and men, respectively AND A current episode of AA lasting > 6 months to < 8 years, with no spontaneous improvement (≤10 point reduction in SALT score) in the past 6 months or lasting > 8 years, but with regrowth episodes in the previous 8 years Exclusion criteria "Diffuse" AA or other types of alopecia Patients who received topical corticosteroids or topical JAk inhibitors one and four weeks, respectively, before the start of the study Patients who received intralesional, systemic corticosteroids, or oral JAK inhibitors eight weeks before randomization Who had previously shown an inadequate response to oral JAK inhibitors.	Study's phase 2 portion At the first interim analysis Dose decision was based: At week 12 The proportion of patients achieving ≥30% improvement from baseline in SALT score (SALT30) At week 16 The proportion of patients achieving ≥50% improvement from baseline in SALT score (SALT50) At the second interim analysis Primary: % patients to achieve SALT score ≤20 at week 36 Study's phase 3 portion Same Primary and Secondary endpoints as At the second interim analysis except: At week 16 % patients to achieve a SALT score of 20 or less; At Week 36 % patients to achieve a SALT score of 20 or less; % patients to achieve a SALT score of 10 or less; At Week 52 % patients to achieve a SALT score of 20 or less	Study's phase 2 portion At week 12 SALT30 response achieved by 29.6%, 33.3%, 17.9% and 10.7% patients treated with baricitinib 2mg, 4mg, 1mg and placebo, respectively. At week 16 SALT50 response achieved by 31.8%, 38.1%, 18.2% and 4.5% patients treated with baricitinib 2mg ($P = 0.057$ vs PBO), 4mg ($P = 0.036$ vs PBO), 1mg and placebo, respectively Primary endpoint: At week 36 % patients achieving SALT score ≤20 was significantly higher with baricitinib 2-mg (33.3%, $P = 0.016$) and 4-mg (51.9%, $P = 0.001$) versus PBO (3.6%) Study's phase 3 portion Primary endpoint: At week 36 % patients achieving SALT score ≤20 was significantly higher with baricitinib 2-mg (22.8%, $P = < 0.001$) and 4-mg (38.8%, $P < 0.001$) versus PBO (6.2%) At week 52 SALT score ≤20 was achieved in 21.2% and 40.9% of patients under baricitinib 2mg and baricitinib 4mg, respectively	Study's phase 2 portion The most frequently observed AEs in patients taking baricitinib were nausea (7.4%), acne (7.4% and 11.1%, Baricitinib 2mg and 4mg, respectively), and upper respiratory tract infection acne (11.1% and 22.2%, Baricitinib 2 mg and 4 mg, respectively) Study's phase 3 portion Adverse events (AE) occurred in 59.6%, 50.8%, and 51.3% of patients treated with baricitinib 4 mg, 2 mg, and placebo, respectively Serious adverse events occurred in 2.1%, 2.2% and 1.6% of patients on baricitinib 4mg, 2mg and placebo, respectively Acne and the incidence of urinary tract infections were more common in the baricitinib-treated groups

Table 1 (continued)

Study	Phase	Study design	Eligibility and exclusion criteria	Endpoints	Results	Main adverse effects
A Study of Baricitinib (LY3009104) in Adults With Severe or Very Severe Alopecia Areata (BRAVE-AA2) [NCT03899259] [17]	3	Randomized, PC, DB 546 patients 36 weeks Via oral Randomized 3:2:2 Baricitinib 2 mg OD Baricitinib 4 mg OD Placebo OD Long extension period 52 weeks		Same Primary and Secondary endpoints as Study's phase 3 portion of NCT03570749	Primary endpoint: At week 36 % patients achieving SALT score ≤ 20 was significantly higher with baricitinib 2-mg (19.4%, $P = < 0.001$) and 4 mg (35.9%, $P < 0.001$) versus PBO (3.3%) At week 52 SALT score ≤ 20 was achieved in 24.4% and 36.8% of patients under baricitinib 2 mg and baricitinib 4 mg, respectively	AEs occurred in 68.4%, 66.1%, and 63.0% of patients treated with baricitinib 4 mg, 2 mg, and placebo, respectively Serious adverse events occurred in 3.4%, 2.6%, and 1.9% of patients on baricitinib 4 mg, 2 mg and placebo, respectively, respectively Acne and the incidence of urinary tract infections were more common in the baricitinib-treated groups

AA alopecia areata, *AE* Adverse events, *ClinRO* Clinician-Reported Outcome, *DB* double-blind, *OD* once daily, *PBO* placebo, *PC* placebo (PBO)-controlled, *PRO* Patient-Reported Outcome Severity of Alopecia Tool [SALT], *SALT30* ≥ 30% improvement from baseline in SALT score, *SALT50* ≥ 50% improvement from baseline in SALT score, *SALT75* ≥ 75% improvement from baseline in SALT score

randomized in a 3:2:2 ratio to receive oral baricitinib 4 mg, 2 mg, or placebo OD for 36 weeks [17].

At week 36, the percentage of patients achieving a SALT20 score was 38.8%, 35.9% in the baricitinib 4 mg group, 22.8%, 19.4% in the baricitinib 2 mg group, and 6.2%, 3.3% in the PBO group, in BRAVE-AA1 and BRAVE-AA2, respectively [17]. In BRAVE-AA1 and BRAVE-AA2, the difference between the baricitinib 4 mg group and the PBO group was 32.6 percentage points in both studies [95% confidence interval (CI) 25.6–39.5 and 25.6–39.6, respectively], and the difference between baricitinib 2 mg and placebo was 16.6 and 16.1 percentage points, respectively (95% CI 9.5–23.8 and 9.1–23.2, respectively) ($P < 0.001$ for each dose versus placebo in both studies) [17]. The results of the baricitinib 4 mg treated group were significantly superior compared with placebo in all the outcomes within the graphical test scheme, in BRAVE-AA1 [37]. In BRAVE-AA2, the baricitinib 4 mg group also differed significantly compared with the placebo, except for SALT10 at week 24 and the two subsequent secondary endpoints. In BRAVE-AA1, the graphical test procedure failed at SALT20 at week 16 in patients on baricitinib 2 mg and a ClinRO Measure for Eyelash Hair Loss score of 0 or 1 with a decrease of at least 2 points from baseline at week 36 did not pass the graphical test scheme. Meanwhile, in BRAVE-AA2, the baricitinib 2 mg group failed the graphical test procedure on the ClinRO measure for eyebrow hair loss at week 36. Additionally, the results of the eight subsequent outcomes did not differ significantly compared with the PBO [17].

Data from the long-term extension periods of BRAVE-AA1 and BRAVE-AA2, after 52 weeks, have recently been published. At 52 weeks, an increase in the proportion of patients achieving a SALT score ≤ 20 and a SALT score ≤ 10 was shown, most pronounced in patients on baricitinib 4 mg. SALT score ≤ 20 was achieved in 21.2% and 24.4% of patients under baricitinib 2 mg and 40.9% and 36.8% under baricitinib 4 mg in BRAVE-AA1 and BRAVE-AA2, respectively. SALT ≤ 10 was achieved in 14.1% and 16.7% of patients under baricitinib 2 mg and 29.9% and 27.8% under baricitinib 4 mg in BRAVE-AA1 and BRAVE-AA2, respectively [38]. Over the 52-week period, the trials also showed that eyebrow and eyelash response rates increased. At week 52, 27.9% and 16.3% of patients with baseline ClinRO Measure for Eyebrow Hair Loss scores of 2 or 3 had an improvement ≥ 2 points and a ClinRO Measure for Eyebrow Hair Loss score of 0 or 1 on baricitinib 2 mg and 39.4 % and 49.7% of patients on baricitinib 4 mg, in BRAVE-AA1 and BRAVE-AA2, respectively. At week 52, 21.6% and 30.3% of patients with baseline ClinRO Measure for Eyelash Hair Loss scores of 2 or 3 had an improvement ≥ 2 points and a ClinRO Measure for Eyebrow Hair Loss score of 0 or 1 on baricitinib 2 mg and 40.7% and 50.7% of

patients on baricitinib 4 mg, in BRAVE-AA1 and BRAVE-AA2, respectively [38].

3.2.2 Safety

In BRAVE-AA1, AEs occurred in 59.6%, 50.8%, and 51.3% of patients treated with baricitinib 4 mg, 2 mg, and placebo, respectively. In BRAVE-AA2, AEs occurred in 68.4%, 66.1%, and 63.0% of patients treated with baricitinib 4 mg, 2 mg, and PBO, respectively. The proportions of patients who discontinued the study regimen due to AEs were low and were similar between study groups [17]. Serious AEs occurred in 2.1%, 2.2%, and 1.6% of patients on baricitinib 4 mg, 2 mg, and PBO, respectively, in BRAVE-AA1, and 3.4%, 2.6%, and 1.9%, respectively, in BRAVE-AA2. In both studies, acne and the incidence of urinary tract infections were more common in the baricitinib-treated groups. At least one infection was seen in 31.4% of patients on baricitinib 4 mg, 25.1% on baricitinib 2 mg, and 28.0% on PBO in BRAVE-AA1, and 29.6%, 37.4%, and 29.2% under baricitinib 4 mg, 2 mg, and PBO, respectively, in BRAVE-AA2 (Table 1). Herpes zoster infections occurred in 0.7%, 0.5%, and 0.5% of patients on baricitinib 4 mg, 2 mg, and PBO, respectively, in BRAVE-AA1, and 1.3%, 1.9%, and 0.6%, respectively. respectively, in BRAVE-AA2. All herpes zoster infections were localized [17]. There were no opportunistic infections, venous thromboembolic events, or gastrointestinal perforations in any of the studies. In BRAVE-AA1, a patient with cardiovascular risk factors suffered a myocardial infarction on baricitinib 2 mg. In BRAVE-AA2, one case of prostate cancer was reported in a patient on a PBO and one case of B-cell lymphoma in a patient on baricitinib 4 mg [17]. In BRAVE-AA1, one patient with a history of gastrointestinal bleeding experienced grade 4 anemia (defined as a hemoglobin level < 6.5 g/dl) when treated with baricitinib 4 mg and had to discontinue the study. In both studies, elevated levels of low-density lipoprotein (LDL) and high-density lipoprotein (HDL) cholesterol were observed in approximately 25% and 40% of baricitinib-treated patients, respectively [17]. The recently published 52-week data showed that the most frequent treatment-emergent AEs included headache, upper respiratory tract infection, nasopharyngitis, urinary tract infection, COVID-19 infection, acne, and creatine phosphokinase elevation. The frequency of discontinuations due to AEs was low and similar between groups. During the BRAVE-AA1 extension phase, there was one case of herpes zoster, COVID-19, and appendicitis on baricitinib 4 mg, all patients recovered, and none discontinued. During the BRAVE-AA2 extension period, a COVID-19 infection in one patient on baricitinib 4 mg led to study discontinuation. In BRAVE-AA1, squamous cell carcinoma and ductal carcinoma in situ were reported after 16 months and 10 months in a patient on baricitinib 2 mg and 4 mg, respectively. No opportunistic infections, tuberculosis, venous thromboembolism (VTE), gastrointestinal perforations, or deaths were reported in any of the studies during the extension period. Most laboratory changes were similar between the baricitinib groups in both studies and similar to those reported in the 36-week data [38].

4 Discussion

AA is a chronic autoimmune disease with a huge impact on patients' quality of life, especially in a severe form [1]. Recent advances in the AA pathogenesis have shown that JAK-STAT pathway plays a role in intracellular signaling of cytokines involved in the development of AA [14]. Therefore, JAK inhibitors are being investigated as therapies for this disorder [39–42]. Tofacitinib, a pan-JAK inhibitor, has been widely used off-label in the management of AA. Case series and open-label studies have demonstrated that tofacitinib is effective in the treatment of adults and adolescents with AA [43–45]. However, as tofacitinib is a pan-JAK inhibitor, it may be associated with adverse events [46]. Furthermore, a recent study comparing tofacitinib with tumor necrosis factor inhibitor showed that tofacitinib was associated with a higher risk of adverse cardiovascular events and cancers [47]. Baricitinib, a JAK1–JAK2 inhibitor, was recently approved for AA, after being studied for the treatment of adults with severe AA through two studies that included 1200 patients (BRAVE-AA1 and BRAVE-AA2) [17]. Several other JAK inhibitors are under investigation in ongoing clinical trials, namely CTP-543, deuruxolitinib, an oral inhibitor of JAK1 and JAK2, in phase 3 trial (NCT04518995) [48]; ritlecitinib, an inhibitor of JAK3 and tyrosine kinase expressed in hepatocellular carcinoma, in phase 2b/3 and 3 trials (NCT03732807 and NCT04006457) [49, 50]; and brepocitinib, an inhibitor of JAK1 and TYK2, in a phase 2 trial (NCT05076006) [51].

Baricitinib was superior to placebo at 36 weeks in potentiating hair growth, with a greater proportion of patients achieving significant hair regrowth resulting in 80% or more scalp coverage with baricitinib 2 mg and 4 mg compared with PBO. Similar results were reported with the Scalp Hair Assessment PRO instrument. At week 36, most patients that achieved the primary endpoint reached SALT90. In contrast to patients treated with baricitinib 4 mg, where the secondary endpoints supported the primary endpoint, the results for most key secondary outcomes with 2 mg baricitinib did not support the results for the primary outcome. Among patients with substantial eyebrow and eyelash hair loss at baseline, improvements in the area's coverage were seen for patients taking baricitinib 4 mg OD at 36 weeks. The BRAVE-AA1 hierarchical analysis was changed on the basis

of the BRAVE-AA2 results, which may have limited conclusions regarding secondary outcomes in BRAVE-AA1. In both studies, the most common AEs were upper respiratory tract infections, urinary tract infection, acne, headache, and elevated creatine kinase levels. Herpes zoster occurred in a low percentage of patients, but in BRAVE-AA2 it was slightly more common in patients treated with baricitinib compared with PBO [17]. Approximately 40% of patients on baricitinib had an increase in HDL levels, and about a quarter of patients treated with baricitinib had an increase in LDL cholesterol. The most recent data showed that the proportion of patients achieving hair, brow, and eyelash growth increased over 52 weeks of treatment, and the safety findings were consistent with the known safety profile of baricitinib. Although hair growth with baricitinib is superior to placebo, it is important to note that the proportion of patients achieving SALT 75, SALT 90, and SALT 100 responses is relatively low (< 50%).With the objective of verifying the adverse effects for longer periods, the extension phases of the trials are ongoing [52].

In both studies, several groups of patients were excluded, mainly patients with an episode lasting 8 years or longer without any hair growth and patients with a previous inadequate response to oral JAK inhibitors. It is not known whether the excluded patients would have benefited from baricitinib treatment. Several studies performed with tofacitinib in AA have shown that patients with a current episode of AT or AU of longer than 10 years in duration were less likely to respond to treatment. It may be possible that a long duration of current episode of AA decreases the probability of therapeutic response, highlighting the importance of early treatment of severe AA with JAK inhibitors [44, 53, 54].

Furthermore, despite efforts to limit the influence of AGA on trial results, it is possible that this influence may have partially affected the assessment of disease severity and response to treatment. Given the AA impact on patients' quality of life, another limitation of the two studies is the omission of quality-of-life measures results. It could be argued that such measures, rather than hair regrowth, should be the primary endpoints [52]. In fact, a small trial with weekly dupilumab in AD showed significant changes in quality-of-life assessments with drug that correlated with clinical hair regrowth evaluations [7]. Further, the durability of hair growth after treatment cessation or reduction (from 4 to 2 mg) with baricitinib was not documented. The effects of withdrawing tofacitinib and ruxolitinib (JAK1/2 inhibitor) have been evaluated in uncontrolled studies, occurring within 8 weeks after stopping treatment [44, 45, 55]. Recently, a single-blind extension of a phase 2a randomized clinical trial with brepocitinib and ritlecitinib evaluated the maintenance, withdrawal, and retreatment of these drugs in the AA treatment. It was shown that only 18% and 39% of patients treated with ritlecitinib and brepocitinib, respectively, did not require retreatment after withdrawal. The median time after the discontinuation to re-treatment was 16.1 and 24.1 weeks with ritlecitinib and brepocitinib, respectively. The study showed that treatment effectiveness appears to have decreased after retreatment compared with the initial response. Therefore, additional studies are needed to demonstrate the withdrawal effect of baricitinib treatment in these patients [56].

On the basis of the results from the phase 3 trials, baricitinib was recently approved by the FDA and EMA as a first-in-disease systemic treatment for adults with severe AA. The recommended starting dose is baricitinib 2 mg/day, with an increase to 4 mg/day if treatment response is inadequate. For patients with nearly complete or complete scalp hair loss, with or without substantial eyelash or eyebrow hair loss, consider treating with 4 mg/day. As there are no studies combining therapies with baricitinib, the concomitant use of baricitinib with other biological immunomodulators, JAK inhibitors, cyclosporine, or other potent immunosuppressants is not recommended [19, 20].

During its November 2022 meeting, the Pharmacovigilance Risk Assessment Committee of the European Medicines Agency recommended measures to minimize risk of serious side effects with Janus kinase inhibitors for chronic inflammatory disorders [57]. These side effects include cardiovascular conditions, blood clots, cancer, and serious infections. These recommendations follow a review of available data, including the final results from a clinical trial of the tofacitinib and preliminary findings from an observational study involving baricitinib. The PRAC recommends that these medicines be used in the following patients only if no suitable treatment alternatives are available: those aged 65 years or above, those at increased risk of major cardiovascular problems (such as heart attack or stroke), those who smoke or have done so for a long time in the past, and those at increased risk of cancer. The PRAC also recommends using JAK inhibitors with caution in patients with risk factors for blood clots in the lungs and in deep veins (venous thromboembolism, VTE) other than those listed above. Further, the doses should be reduced in some patient groups who may be at risk of VTE, cancer, or major cardiovascular problems. These recommendations will provide important guidance to physicians in evaluating appropriate treatment choices for patients with AA. Nevertheless, it is important to highlight that these recommendations emerged from the data mainly in patients with rheumatoid arthritis, and until now baricitinib has been shown to have a favorable safety profile in patients with AA. Moreover, compared with the current available therapeutic options to treat AA (in particular systemic immunosuppressants), baricitinib appears to have a more favorable benefit/risk ratio [58, 59].

This approval marks a milestone in the treatment of patients with extensive AA, who face significant daily

challenges, including social stigma, limited public knowledge about the disease, and a lack of treatment options.

Recently, hair regrowth with JAK inhibitors raised interest in the treatment of AA and shed additional light on its evolving pathogenesis and effect on patients [60]. As seen in other chronic inflammatory skin diseases, this approval is expected to be the launch pad for the emergence of new targeted therapies for this long-neglected condition.

5 Conclusion

In the phase 3 studies with severe AA, oral baricitinib OD was superior to placebo in terms of hair growth. Longer trials are needed to determine the efficacy and safety of baricitinib in AA. Current trials are ongoing and are planned to remain randomized and blinded for up to 200 weeks.

Declarations

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Conflict of interest Egídio Freitas has no conflicts of interest to declare. Emma Guttman-Yassky declares the following conflicts of interest: AbbVie, Almirall, Amgen, AnaptysBio, Asana Biosciences, Boehringer-Ingelheim, Cara Therapeutics, Celgene, Concert, DBV, Dermira, Dermavant, DS Biopharma, Eli Lilly, EMD Serono, Escalier, Galderma, Glenmark, Innovaderm, Janssen Pharmaceuticals, Kiniksa, Kyowa Kirin, LEO Pharma, Mitsubishi Tanabe, Novan, Pfizer, Ralexar, RAPT Therapeutics, Regeneron, Sanofi, Sienna Biopharma, UCB, and Union Therapeutics. Tiago Torres declares the following conflicts of interest: AbbVie, Amgen, Almirall, Arena Pharmaceuticals, Boehringer Ingelheim, Bristol Myers Squibb, Celgene, Janssen, Biocad, LEO Pharma, Eli Lilly, MSD, Novartis, Pfizer, Samsung-Bioepis, Sanofi-Genzyme and Sandoz.

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Author contributions Egídio Freitas, Emma Guttman-Yassky, and Tiago Torres had the idea for the article, performed the literature search and data analysis, and drafted and critically revised the work. All authors read and approved the final manuscript.

References

1. Pratt CH, King LE, Messenger AG, Christiano AM, Sundberg JP. Alopecia areata. Nat Rev Dis Prim. 2017;3(1):17011. https://doi.org/10.1038/nrdp.2017.11.
2. John KK-G, Brockschmidt FF, Redler S, et al. Genetic variants in CTLA4 are strongly associated with alopecia areata. J Invest Dermatol. 2011;131(5):1169–72. https://doi.org/10.1038/jid.2010.427.
3. Aldhouse NVJ, Kitchen H, Knight S, et al. "'You lose your hair, what's the big deal?' I was so embarrassed, I was so self-conscious, I was so depressed:" a qualitative interview study to understand the psychosocial burden of alopecia areata. J Patient-Report Outcomes. 2020;4(1):76. https://doi.org/10.1186/s41687-020-00240-7.
4. Miteva M, Villasante A. Epidemiology and burden of alopecia areata: a systematic review. Clin Cosmet Investig Dermatol. 2015. https://doi.org/10.2147/CCID.S53985.
5. Drucker AM, Thompson JM, Li W-Q, et al. Incident alopecia areata and vitiligo in adult women with atopic dermatitis: Nurses' Health Study 2. Allergy. 2017;72(5):831–4. https://doi.org/10.1111/all.13128.
6. Rodriguez TA, Fernandes KE, Dresser KL, Duvic M. Concordance rate of alopecia areata in identical twins supports both genetic and environmental factors. J Am Acad Dermatol. 2010;62(3):525–7. https://doi.org/10.1016/j.jaad.2009.02.006.
7. Renert-Yuval Y, da Rosa JC, Garcet S, et al. Analysis of alopecia areata surveys suggests a threshold for improved patient-reported outcomes. Br J Dermatol. 2022;187(4):539–47. https://doi.org/10.1111/bjd.21696.
8. Renert-Yuval Y, Guttman-Yassky E. The changing landscape of alopecia areata: the therapeutic paradigm. Adv Ther. 2017;34(7):1594–609. https://doi.org/10.1007/s12325-017-0542-7.
9. Song T, Guttman-Yassky E. Alopecia areata: a complex cytokine driven disease. J Investig Dermatol Symp Proc. 2020;20(1):S55–7. https://doi.org/10.1016/j.jisp.2020.04.007.
10. Liu LY, King BA, Craiglow BG. Alopecia areata is associated with impaired health-related quality of life: a survey of affected adults and children and their families. J Am Acad Dermatol. 2018;79(3):556-558.e1. https://doi.org/10.1016/j.jaad.2018.01.048.
11. Cranwell WC, Lai VW, Photiou L, et al. Treatment of alopecia areata: an Australian expert consensus statement. Australas J Dermatol. 2019;60(2):163–70. https://doi.org/10.1111/ajd.12941.
12. Strazzulla LC, Wang EHC, Avila L, et al. Alopecia areata. J Am Acad Dermatol. 2018;78(1):15–24. https://doi.org/10.1016/j.jaad.2017.04.1142.
13. Petukhova L, Duvic M, Hordinsky M, et al. Genome-wide association study in alopecia areata implicates both innate and adaptive immunity. Nature. 2010;466(7302):113–7. https://doi.org/10.1038/nature09114.
14. Xing L, Dai Z, Jabbari A, et al. Alopecia areata is driven by cytotoxic T lymphocytes and is reversed by JAK inhibition. Nat Med. 2014;20(9):1043–9. https://doi.org/10.1038/nm.3645.
15. Yang S, Yang J, Liu JB, et al. The genetic epidemiology of alopecia areata in China. Br J Dermatol. 2004;151(1):16–23. https://doi.org/10.1111/j.1365-2133.2004.05915.x.
16. Oliveira AB, Alpalhão M, Filipe P, Maia-Silva J. The role of Janus kinase inhibitors in the treatment of alopecia areata: a systematic review. Dermatol Ther. 2019. https://doi.org/10.1111/dth.13053.
17. King B, Ohyama M, Kwon O, et al. Two phase 3 trials of baricitinib for alopecia areata. N Engl J Med. 2022;386(18):1687–99. https://doi.org/10.1056/NEJMoa2110343.
18. Glickman JW, Dubin C, Renert-Yuval Y, et al. Cross-sectional study of blood biomarkers of patients with moderate to severe alopecia areata reveals systemic immune and cardiovascular biomarker dysregulation. J Am Acad Dermatol. 2021;84(2):370–80. https://doi.org/10.1016/j.jaad.2020.04.138.

19. Alopecia Areata Gets FDA-Approved Drug. 2022. https://www.dermatologytimes.com/view/alopecia-areata-gets-fda-approved-drug. Accessed 17 Aug 2022.
20. Baricitinib Recommended for Approval of Severe Alopecia Areata in Europe. 2022. https://www.medscape.com/viewarticle/974368. Accessed 17 Aug 2022.
21. Meyer KC, Klatte JE, Dinh HV, et al. Evidence that the bulge region is a site of relative immune privilege in human hair follicles. Br J Dermatol. 2008. https://doi.org/10.1111/j.1365-2133.2008.08818.x.
22. Kang H, Wu W-Y, Lo BKK, et al. Hair follicles from alopecia areata patients exhibit alterations in immune privilege-associated gene expression in advance of hair loss. J Invest Dermatol. 2010;130(11):2677–80. https://doi.org/10.1038/jid.2010.180.
23. McDonagh AJG, Tazi-Ahnini R. Epidemiology and genetics of alopecia areata. Clin Exp Dermatol. 2002;27(5):405–9. https://doi.org/10.1046/j.1365-2230.2002.01077.x.
24. Zhang X, Yu M, Yu W, Weinberg J, Shapiro J, McElwee KJ. Development of alopecia areata is associated with higher central and peripheral hypothalamic–pituitary–adrenal tone in the skin graft induced C3H/HeJ mouse model. J Invest Dermatol. 2009;129(6):1527–38. https://doi.org/10.1038/jid.2008.371.
25. Angelini J, Talotta R, Roncato R, et al. JAK-inhibitors for the treatment of rheumatoid arthritis: a focus on the present and an outlook on the future. Biomolecules. 2020;10(7):1002. https://doi.org/10.3390/biom10071002.
26. O'Shea JJ, Holland SM, Staudt LM. JAKs and STATs in immunity, immunodeficiency, and cancer. N Engl J Med. 2013;368(2):161–70. https://doi.org/10.1056/NEJMra1202117.
27. Ortolan LS, Kim SR, Crotts S, et al. IL-12/IL-23 neutralization is ineffective for alopecia areata in mice and humans. J Allergy Clin Immunol. 2019;144(6):1731-1734.e1. https://doi.org/10.1016/j.jaci.2019.08.014.
28. Schwartz DM, Kanno Y, Villarino A, Ward M, Gadina M, O'Shea JJ. JAK inhibition as a therapeutic strategy for immune and inflammatory diseases. Nat Rev Drug Discov. 2017;16(12):843–62. https://doi.org/10.1038/nrd.2017.201.
29. Mogul A, Corsi K, McAuliffe L. Baricitinib: the second FDA-approved JAK inhibitor for the treatment of rheumatoid arthritis. Ann Pharmacother. 2019;53(9):947–53. https://doi.org/10.1177/1060028019839650.
30. Fridman JS, Scherle PA, Collins R, et al. Selective inhibition of JAK1 and JAK2 is efficacious in rodent models of arthritis: preclinical characterization of INCB028050. J Immunol. 2010;184(9):5298–307. https://doi.org/10.4049/jimmunol.0902819.
31. Shi JG, Chen X, Lee F, et al. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. J Clin Pharmacol. 2014;54(12):1354–61. https://doi.org/10.1002/jcph.354.
32. European Commission Approves Once-Daily Olumiant Tablets for Treatment of Adults with Moderate-to-Severe Active Rheumatoid Arthritis. 2017. https://investor.lilly.com/news-releases/news-release-details/euro. Accessed 17 Aug 2022.
33. FDA Approves OLUMIANT® (baricitinib) 2-mg Tablets for the Treatment of Adults with Moderately-to-Severely Active Rheumatoid Arthritis. 2018. https://investor.lilly.com/news-releases/news-release-details/fda-approves-olumiantr-baricitinib-2-mg-tablets-treatment-adults. Accessed 17 Aug 2022.
34. CHMP Recommends Approval of Lilly's Baricitinib for the Treatment of Adults with Moderate to Severe Atopic Dermatitis. 2020. https://investor.lilly.com/news-releases/news-release-details/chmp-recommends-ap. Accessed 17 Aug 2022.
35. FDA Approves Baricitinib for Certain Hospitalized Adults With COVID-19. 2022. https://www.contagionlive.com/view/fda-issues-approval-for-baricitinib-for-hospitalized-adults-with-covid-19. Accessed 17 Aug 2022.
36. King B, Ko J, Forman S, et al. Efficacy and safety of the oral Janus kinase inhibitor baricitinib in the treatment of adults with alopecia areata: phase 2 results from a randomized controlled study. J Am Acad Dermatol. 2021;85(4):847–53. https://doi.org/10.1016/j.jaad.2021.05.050.
37. Bretz F, Posch M, Glimm E, Klinglmueller F, Maurer W, Rohmeyer K. Graphical approaches for multiple comparison procedures using weighted Bonferroni, Simes, or parametric tests. Biometrical J. 2011;53(6):894–913. https://doi.org/10.1002/bimj.201000239.
38. Kwon O, Senna MM, Sinclair R, et al. Efficacy and safety of baricitinib in patients with severe alopecia areata over 52 weeks of continuous therapy in two phase III trials (BRAVE-AA1 and BRAVE-AA2). Am J Clin Dermatol. 2023. https://doi.org/10.1007/s40257-023-00764-w.
39. Phan K, Sebaratnam DF. JAK inhibitors for alopecia areata: a systematic review and meta-analysis. J Eur Acad Dermatol Venereol. 2019;33(5):850–6. https://doi.org/10.1111/jdv.15489.
40. King B, Mesinkovska N, Mirmirani P, et al. Phase 2 randomized, dose-ranging trial of CTP-543, a selective Janus Kinase inhibitor, in moderate-to-severe alopecia areata. J Am Acad Dermatol. 2022;87(2):306–13. https://doi.org/10.1016/j.jaad.2022.03.045.
41. King B, Guttman-Yassky E, Peeva E, et al. A phase 2a randomized, placebo-controlled study to evaluate the efficacy and safety of the oral Janus kinase inhibitors ritlecitinib and brepocitinib in alopecia areata: 24-week results. J Am Acad Dermatol. 2021;85(2):379–87. https://doi.org/10.1016/j.jaad.2021.03.050.
42. Wang EHC, Sallee BN, Tejeda CI, Christiano AM. JAK inhibitors for treatment of alopecia areata. J Invest Dermatol. 2018;138(9):1911–6. https://doi.org/10.1016/j.jid.2018.05.027.
43. Craiglow BG, Liu LY, King BA. Tofacitinib for the treatment of alopecia areata and variants in adolescents. J Am Acad Dermatol. 2017;76(1):29–32. https://doi.org/10.1016/j.jaad.2016.09.006.
44. Kennedy Crispin M, Ko JM, Craiglow BG, et al. Safety and efficacy of the JAK inhibitor tofacitinib citrate in patients with alopecia areata. JCI Insight. 2016. https://doi.org/10.1172/jci.insight.89776.
45. Jabbari A, Sansaricq F, Cerise J, et al. An open-label pilot study to evaluate the efficacy of tofacitinib in moderate to severe patch-type alopecia areata, totalis, and universalis. J Invest Dermatol. 2018;138(7):1539–45. https://doi.org/10.1016/j.jid.2018.01.032.
46. Qian J, Xue X, Shannon J. Characteristics of adverse event reporting of Xeljanz/Xeljanz XR, Olumiant, and Rinvoq to the US Food and Drug Administration. J Manag Care Spec Pharm. 2022;28(9):1046–52. https://doi.org/10.18553/jmcp.2022.28.9.1046.
47. Ytterberg SR, Bhatt DL, Mikuls TR, et al. Cardiovascular and cancer risk with tofacitinib in rheumatoid arthritis. N Engl J Med. 2022;386(4):316–26. https://doi.org/10.1056/NEJMoa2109927.
48. ClinicalTrials. gov. A phase 3 study to evaluate the efficacy and safety of CTP-543 in adult patients with moderate to severe alopecia areata (THRIVE-AA1) (THRIVE-AA1. https://clinicaltrials.gov/ct2/show/NCT04518995). Accessed 27 Aug 2022.
49. ClinicalTrials. gov. PF-06651600 for the Treatment of Alopecia Areata (ALLEGRO-2b/3). https://clinicaltrials.gov/ct2/show/NCT03732807. Accessed 27 Aug 2022.
50. ClinicalTrials. gov. Long-Term PF-06651600 for the Treatment of Alopecia Areata (ALLEGRO-LT). https://clinicaltrials.gov/ct2/show/NCT04006457. Accessed 27 Aug 2022.
51. ClinicalTrials. gov. Dual JAK1/TYK2 Inhibitor for Cicatricial Alopecia. https://clinicaltrials.gov/ct2/show/results/NCT05076006. Accessed 27 Aug 2022.

52. Messenger A, Harries M. Baricitinib in alopecia areata. N Engl J Med. 2022;386(18):1751–2. https://doi.org/10.1056/NEJMe2203440.
53. Liu LY, King BA. Tofacitinib for the treatment of severe alopecia areata in adults and adolescents. J Investig Dermatol Symp Proc. 2018;19(1):S18–20. https://doi.org/10.1016/j.jisp.2017.10.003.
54. Liu LY, Craiglow BG, Dai F, King BA. Tofacitinib for the treatment of severe alopecia areata and variants: a study of 90 patients. J Am Acad Dermatol. 2017;76(1):22–8. https://doi.org/10.1016/j.jaad.2016.09.007.
55. Mackay-Wiggan J, Jabbari A, Nguyen N, et al. Oral ruxolitinib induces hair regrowth in patients with moderate-to-severe alopecia areata. JCI Insight. 2016. https://doi.org/10.1172/jci.insight.89790.
56. Peeva E, Guttman-Yassky E, Banerjee A, et al. Maintenance, withdrawal, and re-treatment with ritlecitinib and brepocitinib in patients with alopecia areata in a single-blind extension of a phase 2a randomized clinical trial. J Am Acad Dermatol. 2022;87(2):390–3. https://doi.org/10.1016/j.jaad.2021.12.008.
57. Meeting highlights from the Pharmacovigilance Risk Assessment Committee (PRAC) 24. 2022. https://www.ema.europa.eu/en/news/meeting-highlights-pharmacovigilance-risk-assessment-committee-prac-24-27-october-2022. Accessed 9 Mar 2023.
58. Gupta AK, Wang T, Polla Ravi S, Bamimore MA, Piguet V, Tosti A. Systematic review of newer agents for the management of alopecia areata in adults: Janus kinase inhibitors, biologics and phosphodiesterase-4 inhibitors. J Eur Acad Dermatol Venereol. 2023;37(4):666–79. https://doi.org/10.1111/jdv.18810.
59. King B, Mostaghimi A, Shimomura Y, et al. Integrated safety analysis of baricitinib in adults with severe alopecia areata from two randomized clinical trials. Br J Dermatol. 2023;188(2):218–27. https://doi.org/10.1093/bjd/ljac059.
60. Guttman-Yassky E, Pavel AB, Diaz A, et al. Ritlecitinib and brepocitinib demonstrate significant improvement in scalp alopecia areata biomarkers. J Allergy Clin Immunol. 2022;149(4):1318–28. https://doi.org/10.1016/j.jaci.2021.10.036.