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The Efficacy and Safety of Baricitinib in the Treatment of Alopecia Areata

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Abstract

Introduction: Alopecia Areata (AA) is an autoimmune disorder that causes inflammatory circular, coin-shaped patches of hair loss on the scalp and other body parts. Baricitinib, a Janus Kinase (JAK) inhibitor, is a new medication approved for the treatment of AA. This review paper evaluates the effectiveness and safety of baricitinib in treating hair loss in patients with alopecia areata compared to no intervention.

Methods: The efficacy and safety of baricitinib in treating AA patients were evaluated by utilizing five (5) clinical articles, including randomized controlled trials, systematic reviews, and meta-analyses, sourced from PubMed.

Results: Baricitinib JAK inhibitor was shown to be safe and effective in treating AA when administrated orally at doses of 2 mg and 4 mg for continuous treatment. Some side effects were reported, including but not limited to headache, upper respiratory infection, and hyperlipidemia. At 52 weeks of therapy in the BRAVE-AA1 and BRAVE-AA2 studies, SALT scores of ≤ 20% scalp hair loss were achieved in patients with ≥ 50% scalp hair loss at baseline. Discontinuation of baricitinib treatment is associated with a high recurrence rate of 82.7%, indicating that it may require lifelong treatment.

Discussion: Baricitinib is determined to be an effective, safe, and superior treatment for patients with AA compared to no intervention. More research is needed to establish the maximum tolerated and therapeutic doses of baricitinib for treating AA, particularly by observing its long-term use and potential side effects.

The efficacy and safety of baricitinib in the treatment of alopecia areata

INTRODUCTION

Alopecia Areata (AA) is an autoimmune disorder causing inflammatory, non-scarring hair loss on the scalp and other body parts.[1] AA affects about 2% of the worldwide population, with no ethnic or gender prevalence.[2] It can occur in any age group but is more likely to peak in the third and fourth decades of life.[2] Patients with AA commonly present with circular, coin-shaped patches of hair loss accompanied by mild itching or tightness; however, hair loss can progress to the loss of all scalp hair, known as alopecia totalis (AT), or all body hair, known as alopecia universalis (AU).[3,4] Hair regrowth is commonly seen in early-stage patients with mild AA.[5] Patients with chronic AA and severe hair loss, defined as ≥ 50% scalp hair loss, are unlikely to remit without treatment and are more likely to experience a waxing and waning course of clinical remission and sudden relapse.[1,2,5] Patients with chronic AA who have frequent relapse episodes are at higher risk of developing psychosocial disorders and experiencing a reduced quality of life.[4,5] Severe hair loss can be embarrassing, impacting patients' social interactions and increasing anxiety and depression.[6] According to the Dermatology Life Quality Index (DLQI) survey, nearly 80% of AA patients report impaired quality of life.[6] As a result, pharmacological and psychosocial interventions are needed to manage patients with AA.

Various treatment options for AA aim to disrupt the immune attack on hair follicles. Available treatments include topical, intralesional, or systemic corticosteroids, minoxidil, contact immunotherapy, and conventional immunosuppressants such as cyclosporine and methotrexate.[2,3] These traditionally used treatments are often administered off-label, with limited efficacy, and do not maintain prolonged remission with hair regrowth; they are also associated with side effects.[2,3] For instance, corticosteroid therapy, the most commonly used clinical therapy

for AA, is likely to cause side effects such as endocrine disorders, acne, and weight gain.[4] Similarly, topical minoxidil, an adjunctive therapy for AA, can lead to extensive hypertrichosis, and its overuse may result in systemic absorption, causing palpitations and hypotension.[7] Therefore, a more effective and safer treatment is needed for treating patients with moderate to severe AA.

Clinical studies have shown that Janus Kinase (JAK) inhibitors and signal transducer and activator of transcription (STAT) proteins are effective in interrupting the inflammatory pathway, inducing immune suppression, and reversing AA.[1,4] JAK inhibitors work by blocking one or more intracellular tyrosine kinases in the JAK-STAT signaling pathway, which includes JAK 1, JAK 2, JAK 3, and tyrosine kinase 2 (TYK2).[4] Baricitinib is a JAK inhibitor that the Food and Drug Administration (FDA) and European Medicines Agency (EMA) first approved as a systemic drug for the treatment of AA in 2022.[3,8] The aim of this review is to evaluate the effectiveness and safety of baricitinib in treating hair loss in patients with alopecia areata compared to no intervention.

METHODS

A search via PubMed using the keywords "Alopecia areata" AND "Baricitinib" AND "Treatment" yielded 111 results. These results were reviewed and consolidated into eight (8) full-text articles by applying filters to include randomized controlled trials (RCT), systematic reviews, and meta-analyses from 2021-2024. Five (5) studies were reviewed and selected for a clinical review of the efficacy and safety of baricitinib in treating patients with alopecia areata. Four (4) of the reviewed and selected articles adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA) guidelines. Three (3) articles were excluded

from the clinical review because they either did not fully evaluate the topic, focused on phase 2 clinical results, lacked supportive evidence, or discussed other treatment options.

RESULTS

Kwon et al: In the clinical trial conducted by Kwon et al[1], adult patients with severe alopecia areata (AA) and a Severity of Alopecia Tool (SALT) score of ≥ 50% scalp hair loss, experiencing an active AA episode lasting more than 6 months to less than 8 years without improvements, were randomized in the BRAVE-AA1 and BRAVE-AA2 studies.[1] These ongoing, independent, randomized, double-blinded, parallel, placebo-controlled studies aim to evaluate the efficacy and safety of baricitinib in treating AA.[1] Patients were randomized in a 2:2:3 ratio to receive oral placebo, baricitinib 2 mg, or baricitinib 4 mg for 36 weeks.[1] At week 36, patients who responded to placebo with a SALT score of ≤ 20 continued on placebo through week 52; while placebo non-responders with a SALT score > 20 were switched to baricitinib for up to 68 weeks of additional treatment.[1] As referenced in *Table 1*, efficacy results at 52 weeks showed that patients with ≥ 50% scalp hair loss at baseline achieved SALT scores of ≤ 20% with baricitinib 2 mg and 4 mg (40.9% and 21.2% in BRAVE-AA1 and 36.8% and 24.4% in BRAVE-AA2).[1] Safety was assessed in 280 and 183 patients in BRAVE-AA1 and 233 and 155 patients in BRAVE-AA2, respectively, with treatment-emergent adverse events mostly mild or moderate in severity.[1] Reported adverse events included upper respiratory tract infection, headache, nasopharyngitis, acne, urinary tract infection, creatine phosphokinase elevation, and COVID-19 infection.[1] However, the frequency of discontinuation due to adverse events was low, and the safety findings are consistent with the established safety profile of baricitinib.[1]

Sechi et al: The systematic review conducted by Sechi et al[2] focused on the adverse events associated with JAK inhibitors (JAK-I), including baricitinib, in treating patients with

AA. A total of 5 randomized controlled trials (RCTs) and 23 case series were included in this review, assessing six JAK-I: baricitinib, brepocitinib, deuruxolitinib, ritlecitinib, ruxolitinib, and tofacitinib, involving a total of 1719 patients.[2] The results indicated that adverse events were mostly mild, with withdrawal rates due to adverse events being low and inferior to those of the placebo group (1.6% vs 2.2%).[2] As shown in *Table 1*, the most commonly encountered side effects among 909 patients taking baricitinib (2 mg or 4 mg once daily) included increased high-density lipoprotein cholesterol (21.8%), low-density lipoprotein cholesterol (18.2%), upper respiratory infection (7.3%), headache (6.1%), and acne (5.6%).[2] The study concluded that the use of JAK-I, including baricitinib, necessitates benefit-risk assessment and regular safety monitoring for each patient undergoing treatment.[2]

Papierzewska et al: The safety of JAK-I was also examined in the systematic review completed by Papierzewska et al.[8] This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines and investigated the frequency and odd ratios (OR) for the most common adverse events compared to placebo across 36 studies.[8] The most common side effects associated with baricitinib included hypercholesterolemia (18.2% vs 10.5%, OR = 1.9), headache (6.1% vs 5.1%, OR = 1.2), and upper respiratory infections (7.3% vs 7.0%, OR = 1.0).[8]

Wei et al: Wei et al[4] conducted a network meta-analysis following PRISMA guidelines, which included 5 RCTs, 2 retrospective studies, and 2 prospective studies, comparing the efficacy and safety of JAK-I in the treatment of AA among 1,689 patients.[4] As referenced in *Table 1*, Oral baricitinib (MD = 12.21, 95% CI (3.41, 43.79)), tofacitinib (MD = 10.16, 95% CI (1.02, 101.54)), and ruxolitinib (MD = 9.79, 95% CI, (1.29, 74.27)) demonstrated high response rates compared to placebo.[4] They were also found to be safe, with reduced treatment-emergent

adverse event rates compared to conventional steroid treatment (MD = 0.08, 95% CI (0.02, 0.42)), (MD = 0.14, 95% CI (0.04, 0.55)), and (MD = 0.35, 95% CI, (0.14, 0.88)), respectively.[4] The most commonly reported adverse events for JAK-I included acneiform eruptions, hyperlipidemia, upper respiratory infections, and headaches.[4] However, similar adverse events were noted in the placebo group, indicating no significant difference.[4]

Barati Sedeh et al: Lastly, a systematic review and meta-analysis by Barati Sedeh et al[9] adhered to PRISMA guidelines and compared the efficacy and safety of JAK inhibitors in treating AA using the SALT score.[9] This review included 37 studies (22 from North America, 11 from Asia, 3 from Australia, and 1 from Europe) investigating the proportion of patients treated with JAK-I achieving 30%, 50%, 75%, 90%, and 100% improvement in SALT scores.[9] For instance, in $SALT_{50}$ baricitinib 4 mg once daily was found to be superior to brepocitinib and ritlecitinib (baricitinib: RD 63%, 95% CI 44–82; brepocitinib: RD 47, 95% CI 32–62; ritlecitinib: RD 33%, 95% CI 19–47).[9] Similarly, as presented in *Table 1*, baricitinib also demonstrated superiority in $SALT_{75}$, $SALT_{90}$, and $SALT_{100}$ (RD 45%, 95% CI 25–65; RD 41%, 95% CI 22–60; RD 26%, 95% CI 1–43, respectively).[9] Baricitinib 4 mg once daily exhibited the highest efficacy in patients with ≥ 50% scalp hair loss compared to other JAK-I, leading to the conclusion that baricitinib is a promising treatment option for AA.[9]

Final Results: The selection criteria for the five (5) clinical studies primarily involved patients with severe AA, specifically focusing on scalp hair loss to evaluate the effectiveness of JAK inhibitors. Studies included randomly selected patients, with a minimum requirement of five participants. Exclusions were made for patients with hair loss in other body parts, inadequate previous responses to JAK inhibitors, or episodes lasting ≥ 8 years. For detailed selection criteria of each individual study, refer to *Table 2*.

DISCUSSION AND CONCLUSION

Alopecia areata is a chronic autoimmune disorder characterized by non-scarring, inflammatory hair loss. The pathogenesis of AA highlights the importance of the JAK-STAT pathway in the intracellular signaling of cytokines involved in its development. Overall, the results from the conducted studies support the use of baricitinib, a JAK1-JAK2 inhibitor, in treating AA, demonstrating it to be effective, safe, and superior compared to no intervention and other therapies, including other JAK inhibitors.[1,9]

In the study by Kwon et al[1], a significant proportion of patients achieved complete or near-complete hair regrowth, with the response rate for scalp hair regrowth in patients with severe AA increasing over the 52 weeks of baricitinib treatment, ultimately achieving a SALT score of ≤ 20.[1] In both the BRAVE-AA1 and BRAVE-AA2 studies, a greater proportion of patients reached efficacy endpoints with baricitinib 4 mg compared to 2 mg.[1] Consequently, further dose-related studies are needed to determine the maximum tolerated and therapeutic doses of baricitinib for treating AA. Baricitinib is considered a well-tolerated medication, associated with mild to moderate adverse events; however, regular monitoring of liver function and hematologic parameters is recommended to help mitigate risks and ensure patient safety.[1]

Kwon et al[1] study has some limitations, including its funding by Eli Lilly and Company (Lilly), which manufactures baricitinib, potentially increasing the likelihood of bias in the results. Additionally, the study did not compare outcomes with a placebo and has limited data on the long-term effects of baricitinib treating patients with severe AA.[1] Therefore, longer-term observations of baricitinib use are necessary to evaluate the full extent and stability of the clinical response and the safety of the drug.[1]

Among multiple clinical studies, including the one conducted by Sechi et al[2] and Barati Sedeh et al[9], a high response rate was observed in patients receiving baricitinib at higher doses. Findings indicate that higher doses correlate with better outcomes, while factors such as age, sex, duration of alopecia, extent of hair loss, duration of treatment, and concurrent treatment also affect response rates and treatment results.[2,9] These insights are valuable for clinicians in identifying patients who are likely to benefit from baricitinib.

Although Sechi et al[2] reported that oral JAK inhibitors are well tolerated and that drug interruption due to adverse events is less frequent compared to placebo, the limited study duration makes it difficult to accurately evaluate side effects over a longer period of treatment with JAK-I.[2] While the study reassures that baricitinib is generally safe and associated with mild adverse events, it also emphasizes the need for further evaluation to rule out severe side effects in long-term treatment.

In the analysis by Wei et al[4], oral JAK inhibitors are deemed the most effective treatment for patients who do not respond to conventional steroid therapy, as no significant response rates were observed between steroid therapy and placebo.[4] Steroid-insensitive immune cell lines, such as innate lymphocytes (ILCs), are thought to contribute to the inflammation seen in AA, making steroid therapy less effective.[3] The clinical trials reviewed in the Wei et al[4] study, funded by the National Natural Science Foundation of China and Hangzhou Medical Key Discipline Construction Project, demonstrated that patients receiving baricitinib experienced significant hair regrowth and a marked reduction in the severity of AA.[4] Although the incidence of adverse events with baricitinib was significantly lower compared to conventional steroid therapy, there are concerns about serious infections and thrombosis in patients with underlying risk factors.[4]

Consequently, clinicians are advised to regularly assess liver function and complete blood counts, as well as educate patients about potential side effects.[4]

Baricitinib is considered the most effective treatment for AA, with a 50% improvement in SALT scores observed in 63% of patients in the study completed by Papierzewska et al.[8] However, a significant limitation of JAK-I is the high recurrence rate of 82.7% noted upon treatment discontinuation.[8] Thus baricitinib is necessary for lifelong treatment to maintain efficacy.

All studies included in this review confirm that JAK inhibitors, particularly baricitinib due to its strong binding interactions with JAK1 and JAK2 inhibitors, are a promising treatment option for patients with AA. This underscores why baricitinib was the first FDA-approved treatment for AA, as it demonstrated a rapid onset of action, effectively reduces the autoimmune response, and promotes hair follicle recovery within a few weeks of initiation.[8] However, more high-quality trials and comparisons are needed to determine the most effective protocols for treating AA with JAK inhibitors, including baricitinib.

References

1. 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;24(3):443-451. Doi:10.1007/s40257-023-00764-w
2. Sechi A, Song J, Dell'Antonia M, et al. Adverse events in patients treated with JAK-inhibitors for alopecia areata: a systematic review. *J Eur Acad Dermatol Venereol.* 2023; 37: 1535–1546. https://doi-org.ezproxy.gardner-webb.edu/10.1111/jdv.19090
3. Yan D, Fan H, Chen M, et al. The efficacy and safety of JAK inhibitors for alopecia areata: a systematic review and meta-analysis of prospective studies. *Front Pharmacol.* 2022;13:950450. Doi:10.3389/fphar.2022.950450
4. Wei D, Chen Y, Shen Y, Xie B, Song X. Efficacy and safety of different JAK inhibitors in the treatment of alopecia areata: a network meta-analysis. *Front Immunol.* 2023;14:1152513. Doi:10.3389/fimmu.2023.1152513
5. Egeberg A, Linsell L, Johansson E, Durand F, Yu G, Vañó-Galván S. Treatments for moderate-to-severe alopecia areata: a systematic narrative review. *Dermatol Ther (Heidelb).* 2023;13(12):2951-2991. Doi:10.1007/s13555-023-01044-5
6. Toussi A, Barton VR, Le ST, Agbai ON, Kiuru M. Psychosocial and psychiatric comorbidities and health-related quality of life in alopecia areata: a systematic review. *J Am Acad Dermatol.* 2021;85(1):162-175. Doi:10.1016/j.jaad.2020.06.047
7. Barton VR, Toussi A, Awasthi S, Kiuru M. Treatment of pediatric alopecia areata: a systematic review. *J Am Acad Dermatol.* 2022;86(6):1318-1334. Doi:10.1016/j.jaad.2021.04.077

8. Papierzewska M, Waśkiel-Burnat A, Rudnicka L. Safety of janus kinase inhibitors in patients with alopecia areata: a systematic review. *Clin Drug Investig.* 2023;43(5):325-334. Doi:10.1007/s40261-023-01260-z
9. Barati Sedeh F, Michaelsdóttir TE, Henning MAS, Jemec GBE, Ibler KS. Comparative efficacy and safety of janus kinase inhibitors used in alopecia areata: a systematic review and meta-analysis. *Acta Derm Venereol*. 2023;103:adv00855. Doi:10.2340/actadv.v103.4536

Table 1- Summary of efficacy and safety outcome

Source	Efficacy	Safety/Adverse events
Kwon et al[1]	BRAVE-AA1: - Baricitinib 4 mg: 40.9% - Baricitinib 2 mg: 21.2% BRAVE-AA2: - Baricitinib 4 mg: 36.8% - Baricitinib 2 mg: 24.4%	- Upper respiratory tract infection - Headache - Nasopharyngitis - Acne - Urinary tract infection - Increased blood creatinine phosphokinase (CPK) - COVID-19 infection
Sechi et al[2]	N/A	- High-density lipoprotein cholesterol (21.8%) - Low-density lipoprotein cholesterol (18.2%) - Upper respiratory infection (7.3%) - Headache (6.1%) - Acne (5.6%).
Papierzewska et al[8]	N/A	- Hypercholesterolemia (18.2%) - URI (7.3%) - Headache (6.1%) - Acne (5.6%) - Nasopharyngitis (5.5%) - UTI (3.5%) - CPK elevations (3.2%) - H. simplex (1.9%) - H. zoster (1.2%) - Hypertriglyceridemia (0.6%) - Nausea (0.4%) - Neutropenia (0.1%) - New malignancy (0.1%) - Myocardial infarction (0.1%)
Wei et al[4]	- Baricitinib: MD = 12.21, 95% CI (3.41, 43.79) - Tofacitinib: MD = 10.16, 95% CI (1.02, 101.54) - Ruxolitinib: MD = 9.79, 95% CI, (1.29, 74.27)	- Acneiform eruption - Hyperlipidemia - Upper respiratory infection - Headache

Source	Efficacy	Safety/Adverse events
Barati Sedeh et al[9]	$SALT_{50}$ - Baricitinib: RD 63%, 95% CI 44–82 - Brepocitinib: RD 47, 95% CI 32–62 - Ritlecitinib: RD 33%, 95% CI 19–47) $SALT_{75}$ - Baricitinib: RD 45%, 95% CI 25–65 - Brepocitinib: RD 38%, 95% CI 24–53 - Ritlecitinib: RD 25%, 95% CI 12–38 $SALT_{90}$ - Baricitinib: RD 41%, 95% CI 22–60 - Brepocitinib: RD 32%, 95% CI 18–46 - Ritlecitinib: RD 23%, 95% CI 10–36 $SALT_{100}$ - Baricitinib: RD 26%, 95% CI 1–43 - Brepocitinib: RD 13%, 95% CI 0.3–23	N/A

CI = Confidence Interval
MD = Standard Mean Difference.
RD = Risk Difference

Table 2: Clinical studies selection criteria

Source	Inclusion criteria	Exclusion Criteria
Kwon et al[1]	- Adults with Severity of Alopecia Tool (SALT) score ≥ 50 and a current AA episode lasting > 6 months to < 8 years without spontaneous improvement over the 6 months before screening.	- Patient with current episodes lasting ≥ 8 years without any hair regrowth. - Patients with previously inadequate response to JAK inhibitors.
Sechi et al[2]	- Studies reporting information on AEs. - Randomized controlled trials (RCTs) - Observational studies: cohort, case-control, cross-sectional studies, and case series with five or more patients.	- Review articles and case series with fewer than five patients. - Commentaries, conference abstracts, and studies involving non-human subjects. - Studies with insufficient information on safety in the treated groups.
Papierzewska et al[8]	- Studies with used terms: “alopecia areata”, “alopecia totalis”, “alopecia universalis” combined with “JAK inhibitors”, “tofacitinib”, “ruxolitinib”, “ritlecitinib”, brepocitinib”, “baricitinib”, “CTP-543”.	- Studies with incomplete data: unknown number of adverse effects, case reports, in vitro studies, animal studies, reviews, book chapters, and articles in a language other than English. - Adjuvant therapies - Alopecia of beard or eyebrows. - Previous treatment with JAK inhibitors. - No division between adults and children.

Source	Inclusion criteria	Exclusion Criteria
Wei et al[4]	- Randomized controlled trials (RCT), prospective trials, and retrospective studies on JAK inhibitors for treating patients with AA. - Studies included both control and experimental groups. - Participants are definitively diagnosed with AA/AT/AU. - Intervention measures. - The control group was treated with a placebo or conventional steroid therapy. - Experimental groups treated with oral or topical JAK inhibitors. - At least two trials to confirm the efficacy of the same AA treatment regimen. - The included trials provided efficacy (scalp hair regrowth rate) and safety (adverse events) outcomes.	- Studies including patients with only eyelash and eyebrow involvement, but no scalp involvement. - Inability to extract data or missing data. - Case reports or case series (fewer than six cases); abstracts; conference presentations; editorials; reviews; or expert opinions.
Barati Sedeh et al[9]	- Human subjects - Severity of AA measured by the Severity of Alopecia Tool (SALT) score before and/or after treatment; and/or change in SALT score measured in final as a percentage change in SALT score.	- Studies that did not measure the severity of AA by using the SALT score.