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Review Article

Review of efficacy of baricitinib in the treatment of alopecia areata

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ABSTRACT

Alopecia areata (AA) is a long-term autoimmune condition characterized by patchy, non-scarring hair loss. It involves an autoimmune inflammatory process that gives immunity privilege to some hair follicles, while subsequent inflammatory attacks target previously normal hair follicles. One of the most important discoveries in the pathogenesis of this disease is the Janus kinase (JAK)-signal transducer and activator of the transcription (STAT) pathway. Now that a greater understanding of the immunological processes contributing to the pathogenesis has been gained, current trials' focus was on managing the immunological reaction involved in this disease. Baricitinib is a new first-generation JAK inhibitor that has been studied in multiple trials. This study's objectives were to review existing research and summarize information on the use of Baricitinib to treat AA. The Medline database was searched for relevant published research papers using variations of the following keywords: "AA," "Baricitinib," and "JAK inhibitors." The search covered studies published from 2010–2022. Our findings showed that baricitinib's use for severe AA in multiple studies generally led to improvement of patients' conditions with minimal side effects.

Keywords: AA, Baricitinib, JAK inhibitors

INTRODUCTION

Alopecia areata (AA), also known as alopecia vulgaris, is a long-term autoimmune disease that causes patchy, non-scarring hair loss, usually on the scalp. The disease has multiple variants; the most common is patchy (localized) alopecia, which is characterized by round hairless patches on normal-appearing skin. Other types include AA totalis (alopecia totalis), which presents as loss of all hair on the scalp, and AA universalis (alopecia universalis) which presents as loss of all hair on the scalp and body. AA also has more uncommon variants, including ophiasis (loss of occipital scalp hair); sisaipho (loss of hair in the occipital, temporal, and parietal regions); sudden graying (loss of all pigmented hair); diffuse AA (AA incognita or loss of hair over a large scalp area); and perinevoid alopecia (loss of hair around pigmented nevi).[1-3] AA most commonly occurs in individuals <40 years of age (up to 80% of patients) in which around 50% of cases develop before 20 years of age.[4] Its incidence is similar in males and females, with an increased occurrence in individuals with a family history of AA or other autoimmune conditions.[2,3]

The disease is an autoimmune inflammatory process that gives immunity privilege to some hair follicles, while subsequent inflammatory attacks target previously normal hair follicles.[5] Natural killer (NK) cells and excessive natural killer group 2, member D (NKG2D) receptor-mediated signaling have a role in the disease pathogenesis, as do interferon-gamma (IFN-γ) and interleukin-15 (IL-15) signaling pathways. Both signaling pathways act through JAK, and overexpression of JAK has been noted in skin biopsies of AA patients.[1-3]

Management of AA depends on the disease severity. For patients with patchy or limited AA (<50% scalp involvement), watchful waiting or topical treatment is recommended.[6] Topical treatment includes tretinoin 0.05% cream, corticosteroids, anthralin, and minoxidil.[7]

In severe cases, wigs or hairpieces and topical immunotherapy may be offered.[8] For unresponsive patients with persistent symptoms and/or >50% scalp involvement, systemic therapy with corticosteroids, another immunosuppressive drug (such as methotrexate or cyclosporine), or a JAK inhibitor (such as tofacitinib, ruxolitinib, or baricitinib) should be considered.[2] The effectiveness of treatment can be assessed using the Severity of Alopecia Tool (SALT) score, which is determined by visually assessing the extent of terminal hair loss when the scalp is viewed from four perspectives (score of 0-50 for each half of the scalp).[1,9]

METHODOLOGY

This article reviews the current research on the use of baricitinib for treating AA and provides an overview of the relevant literature. Relevant published research articles were searched for on MEDLINE and the Cochrane library using combinations of the following key terms: "AA," "AA," and "baricitinib." The utility of baricitinib as a therapy for AA was examined in eligible studies. The search included studies published from 2017-2022.

JAK INHIBITORS AND AA

Our general understanding of the etiology of inflammatory and immunological illnesses has advanced in recent years. The JAK-signal transducer and activator of transcription (STAT) pathway, which is an essential component of the downstream signaling of inflammatory cytokines and several growth factors, is one potential therapeutic target that has been discovered. The JAKs are a group of cytoplasmic tyrosine kinases that are activated by the bindings of specific growth factors, cytokines and chemokines to multiple cellular receptors.[10] Activation of JAKs induces phosphorylation of STAT transcription factors, which causes them to enter the nucleus and regulate the gene expression of specific genes. The following 4 types of JAKs have been identified: JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK inhibitors have been developed as effective therapeutic immunosuppressive agents due to recognition of the vital role of JAKs in the immunologic processes of inflammatory disorders.[1,11-14]

Laboratory researchers are currently investigating the autoimmune mechanisms associated with the pathophysiology of AA. Cytotoxic CD8 + T cells and NKG2D are required for the pathogenesis of AA, as evidenced by transcriptional profile analyses and comparative genomic studies in human tissue and mouse models. This type of T cell appears to produce IFN- γ, which promotes the synthesis of IL-15 in mouse hair follicles via JAK1/2 signaling.[15,16] The T-cell mediated generation of IFN- γ is also stimulated by IL-15 through JAK1/3 signaling; this enhances the inflammatory response in hair follicles. The rationale for and significance of developing and testing JAK receptor inhibitors will be evident once these pathways are confirmed to be regulated by JAK receptors.[17,18]

BARICITINIB AND AA

Baricitinib is a first-generation JAK inhibitor that primarily inhibits JAK1, JAK 2 and, JAK 3 to a lower extent.[19] It is a very strong inhibitor of JAK signaling and activity, and is activated by the inflammatory cytokines IL-6 and IL-23.[20] Atopic dermatitis, psoriasis, myelofibrosis, and rheumatoid arthritis are some of the inflammatory dermatoses for which baricitinib treatment is now being investigated in several clinical trials.[10,19,21]

The first reported case of baricitinib use to treat AA was in 2015 on a young boy diagnosed with AA and chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome. He received baricitinib at a dose of 11 mg per day (7 mg in the morning and 4 mg in the evening) for 9 months. After the 9 months, the symptoms of CANDLE syndrome were fully resolved, and he showed normal hair growth.[19] The second reported case of baricitinib use was in 2019 in a female geriatric patient with AA. She received baricitinib 4 mg daily for a period of 8 months. After 8 months, she showed almost total (97%) hair regrowth.[10,22]

In 2019, Phan and Sebaratnam published the first systematic review and meta-analysis of research on JAK inhibitor therapies, including baricitinib, for AA and its variants. There were 72.4% responders in 30 studies with a total of 289 cases; of these, 45.7% showed a good response, 21.4% showed a moderate response, and the remaining patients showed no response to baricitinib. They discovered that use of any oral JAK inhibitors was associated with a four times greater chance of response than use of topical JAK inhibitors. Age, sex, duration of AA, prior systemic medication failures, and type of JAK inhibitor agent did not appear to impact treatment outcomes. Their review also showed that the treatment had a low rate of complications. The most common side effects were infections of the upper respiratory tract and urinary tract.[18]

BARICITINIB (OLUMIANT) FDA APPROVAL

The FDA has approved baricitinib (Olumiant) for the treatment of severe AA in adults.[23] Two comparable randomized studies, BRAVE-AA1 and BRAVE-AA2, which examined the efficacy of this drug, have been conducted. The BRAVE-AA1 (phase 3) trial included 654 adults with severe AA; these were males ≤ 60 years of age and females ≤ 70 years of age (mean age: 37 years). Patients were randomized to receive 1 of 3 treatments for 36 weeks: a once-daily dose of oral baricitinib 4 mg, a once-daily dose of oral baricitinib 2 mg, or a placebo. All patients had a SALT score >50 and a disease duration of >6 months but less than 8 years, and spontaneous improvement had not occurred in the previous 6 months in any of the patients.

The average duration of AA episodes in BRAVE-AA1 was 3.6 years and that in BRAVE-AA2 was 4.3 years. 53.2% of all patients had very severe disease, defined by a SALT score of 95-100, while 90.6% received at least one treatment for AA before the trial. The 36-week treatment course was completed by 91% of patients in BRAVE-AA1 and by 90% in BRAVE-AA2.[24]

In the BRAVE-AA1 trial, the proportion of patients with a SALT score of ≤ 20 was 6.2% with the placebo, 22.8% with baricitinib 2 mg (p<0.001 vs. placebo, NNT 6) while it was 38.8% with the 4 mg dose of baricitinib (p<0.001 vs. placebo, NNT 3). In BRAVE-AA2, percentage of patients who had a SALT score of ≤20 was 35.9% with baricitinib 4 mg (p=0.001 vs. placebo, NNT 3), 19.4% with baricitinib 2 mg (p=0.001 vs. placebo, NNT 7), and 3.3% with placebo.

By week 36 of the BRAVE-AA1 trial, the proportion of patients who had initially had a scalp hair assessment patient-reported outcome (PRO) score of 0-1 that had improved by 2 points or more from the baseline was 35.8% for the baricitinib 4 mg group (p<0.001 vs. placebo, NNT 4), 17.1% for the baricitinib 2 mg group (p=0.001 vs. placebo, NNT 9), and 5.9% for the placebo group. At week 36 of the BRAVE-AA2 trial, the proportion of patients who had initially had a scalp hair assessment PRO score of 0-1 that had improved by 2 points or more from the baseline was 37.8% of the baricitinib 4 mg group (p<0.001 vs. placebo, NNT 3), 18.5% of the baricitinib 2 mg (p=0.002 vs. placebo, NNT 8), and 5.1% of the placebo group.[25,26] Efficacy outcomes of baricitinib are mentioned in Table 1.

Table 1: Efficacy outcomes of baricitinib.

Outcome	BRAVE-AA1			BRAVE-AA2		
	Baricitinib 2 mg	Baricitinib 4 mg	Placebo	Baricitinib 2 mg	Baricitinib 4 mg	Placebo
SALT score ≤ 20 at 36 weeks	22.8%	38.8%	6.2%	19.4%	35.9%	3.3%
P value	<0.001	P < 0.001		<0.001	<0.001	
Difference from placebo	16.6	32.6		16.1	32.6	
Scalp hair assessment PRO score	17.1%	35.8%	5.9%	18.5.%	37.8%	5.1%
P value	< 0.001	0.001		<0.001	0.001	
Difference from placebo	11.2	30.0		13.4	32.7	

Eyebrow (EB) and eyelash (EL) hair of AA patients with baricitinib were examined in the BRAVE-AA1 and BRAVE-AA2 trials. The analysis targeted patients with a SALT score of >20 at 36 weeks from both trials. The clinician-reported outcome for eyebrow hair (ClinRo EB) and clinician-reported outcome for eyelash hair (ClinRo EL) measures were employed to assess patients who received baricitinib 2 mg, baricitinib 4 mg, or the placebo to assess the results. A ClinRo score of (0) suggested no hair loss, while a ClinRo score of suggested minimal hair loss.[1] In patients receiving 4 mg of baricitinib, the incidence ClinRo EB (0, 1) was 19.8%, and 22.6% for ClinRo EL (0, 1), compared to 3.5-3.9% in placebo group (p≤001). Patients receiving 2 mg of baricitinib showed a ClinRo EB (0, 1) incidence of 10.4% (versus placebo, 3.5%; p≤0.01), while the incidence of ClinRo EL (0, 1) was 9.4% (versus placebo 3.9%; p=0.51). The main finding was that baricitinib treatment resulted in significantly better clinical outcomes in individuals with SALT scores > 20 at week 36. In comparison to the placebo groups in both studies, baricitinib 4 mg significantly improved both EB and EL hair loss scores.[27-29]

Another analysis of the BRAVE-AA1 and BRAVE-AA2 trails was performed to establish the effectiveness and safety of baricitinib for treating patients with an atopic background.[30-32] The safety profiles of the drug and the level of hair regrowth in individuals with AA were found to be unaffected by atopic background.[33-35]

Regarding adverse effects reported in the trials, most were mild or moderate. Acne and elevated creatine kinase and lipid concentrations matched with baricitinib than placebo.[36] No cases of venous thromboembolic, opportunistic, or gastrointestinal perforations were reported in either trial.[24,37,38] The major limitations were that patients who had previously taken oral JAK inhibitors for AA for more than 8 weeks without resultant hair regrowth were excluded; in addition, androgenic alopecia was not completely excluded.[39] Overall, longer-term clinical trials are necessary for evaluation of the safety and efficacy of baricitinib for AA.[24,40]

CONCLUSION

In conclusion, baricitinib is a new first-generation JAK inhibitor that has been studied in multiple trials. The first reported case of baricitinib treatment for AA was in 2015 for a patient with CANDLE syndrome who showed improvement with hair regrowth. The two clinical trials of baricitinib, BRAVE-AA1 and BRAVE-AA2, are most important trials studying baricitinib in the treatment of AA to date. Baricitinib (Olumiant) has received FDA approval for treating severe AA in adults after showing good efficacy after 36 weeks of treatment in the BRAVE-AA1 and BRAVE-AA2 trials. Regarding safety profile,

most side effects were mild or moderate. Further comprehensive research and long-term treatment trials should be conducted to explore the efficacy and safety of this medication.

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