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Mini Review

Utilization of JAK Inhibitors for the Treatment of Alopecia Areata

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ABSTRACT

Alopecia Areata (AA) is an autoimmune disease. Hair loss that occurs with AA is associated with T-cell infiltration around the hair follicles and is mediated by specific cytokines. Interferon-γ and γc cytokines signal through pathways involving the receptor activation of Janus kinase (JAK) and signal transducers and activators of transcription (STAT). Therefore, the JAK-STAT pathway has been targeted for the treatment of AA. In June 2022, the JAK inhibitor baricitinib was approved by the Food and Drug Administration. As a result, baricitinib is becoming a beacon of hope for patients with severe AA.

Keywords: JAK inhibitors; Alopecia areata; Alopecia totalis; Alopecia universalis

INTRODUCTION

Alopecia Areata (AA) is an autoimmune disease characterized by hair loss. The degrees of hair loss include patches of hair loss on the scalp or complete scalp hair loss (alopecia totalis), complete scalp hair loss and hair loss on other body parts (alopecia universalis), and hair loss along the hairline (ophiasis). Intractable AA can negatively affect patients' mental health and complicate their social life. Although there is no reliable and effective treatment for AA, reports of the effects of treatments comprising Janus kinase (JAK) inhibitors have accumulated.

LITERATURE REVIEW

The onset of AA is hypothesized to occur after the collapse of the Immune Privilege (IP) of the hair follicle [1]. IP is a phenomenon whereby tissues are protected from attack by the immunity of the host because major histocompatibility complex protein expression is suppressed from the bulge lesion of the hair bulb of the hair follicle epithelium during the anagen stage [2]. With AA, immune cell infiltration around the hair follicle is observed because of the collapse of IP, and because the immune cells are predominantly CD4+ and CD8+ T cells. In a murine model, the infiltration of CD8+ NKG2D+ T cells sufficiently induced AA [3]. In the JAK-signal transducer and activator of transcription (JAK-STAT) pathway, cytokines (interferon [IFN], interleukin, and other cytokines) bind to cell surface receptors and activate JAK. After JAK activation, STAT activation occurs. Then, STAT dimerizes and becomes a transcription factor for translocation into the nucleus to directly regulate gene expression. Activated CD8+ T cells produce pro-inflammatory cytokines, such as IFN-γ, which create a pro-inflammatory state in the microenvironment of hair follicles. Additionally, CD8+ T-cell cytotoxic activity is enhanced and activated. CD4+ T cells produce γc cytokine interleukin-2, which enhances CD8+ T-cell function. Furthermore, Th1 cells, which are a subset of CD4+ T cells, produce IFN-γ when activated [4]. Various cytokines and their signaling pathways appear to be involved in the development of AA after IP collapse, which is mediated by immune T cells.

The JAK-STAT pathway is involved in the onset and progression of AA; therefore, it has been targeted for the treatment of AA. During the past 10 years, there have been several reports of the effects of JAK inhibitors on AA. The four known JAKs are JAK1, JAK2, JAK3, and tyrosine kinase 2. Furthermore, the first generation of JAK inhibitors include tofacitinib (JAK1/3>2 inhibitor), ruxolitinib (JAK1/2 inhibitor), baricitinib (JAK1/2), and oclacitinib [5]. Of these, tofacitinib, ruxolitinib, and baricitinib have been examined as treatments for AA.

Tofacitinib

Tofacitinib has been approved by the Food and Drug Administration (FDA) for the treatment of rheumatoid arthritis. In 2014, the first report of the clinical efficacy of tofacitinib for the treatment of AA described a patient with alopecia universalis

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and concomitant psoriasis; after 8 months of therapy, full regrowth of hair was observed [6]. A review of the medical records indicated that 7 of 13 patients (53.8%) achieved a regrowth rate of 50%, and that 2 patients demonstrated lipid and liver abnormalities that improved with dose reduction [7]. A multicenter (two centers), open-label, single-arm study of 66 subjects indicated that 32% of patients experienced an improvement of ≥ 50% in their severity alopecia tool (SALT) scores, and that AA and ophiasis subtypes were more responsive than alopecia totalis and alopecia universalis to tofacitinib [8]. An open-label pilot study involving patients with moderate-to-severe AA found that 8 of 12 patients experienced ≥ 50% hair regrowth with tofacitinib treatment [9].

Ruxolitinib

Ruxolitinib has been approved by the FDA for the treatment of myelofibrosis. The first study of ruxolitinib for AA was conducted in 2014. Three patients with moderate-to-severe AA treated with oral ruxolitinib exhibited nearly complete hair regrowth within 3 to 5 months. Furthermore, a comparison of biopsy samples obtained at baseline and after 12 weeks of treatment demonstrated reduced perifollicular T-cell infiltration and reduced follicular expression of human leukocyte antigen class I and class II [3].

In 2016, an open-label clinical trial was conducted among 12 patients with moderate-to-severe AA and found that 75%patients demonstrated a remarkable response to treatment, with hair regrowth of 92% at the end of treatment [10]. In an *in vitro* model, ruxolitinib was administered to human dermal papilla cells pretreated with IFN-γ to evaluate cell viability and changes in JAK-STAT pathway expression. It was found that ruxolitinib suppressed the phosphorylation of JAK1, JAK2, JAK3, STAT1, and STAT3. Therefore, the authors concluded that ruxolitinib modulated and reversed IFN-induced inflammatory changes by blocking the JAK-STAT pathway in human dermal papilla cells in an AA-like environment.

Baricitinib

The efficacy of baricitinib for the treatment of AA was first suggested in 2015. Marked improvement in comorbid AA was observed during clinical trials investigating the efficacy of baricitinib for CANDLE syndrome. Therefore, preclinical studies were conducted using C3H/HeJ AA mice. These preclinical studies revealed that *in vivo* studies involving a C3H/HeJ AA mouse model demonstrated a strong correlation between resolution of the IFN signature and clinical improvement during baricitinib treatment [11,12].

Baricitinib was approved for the treatment of AA by the FDA on June 13, 2022. This is the first time that a JAK inhibitor has been approved by the FDA for AA. Clinical trials involving baricitinib as a treatment for AA in adults have been conducted recently. One such clinical trial, BRAVE-AAI, was a phase 2/3, adaptive, double-blind, placebo-controlled study that evaluated the efficacy and safety of baricitinib for patients with ≥ 50% scalp hair loss. During phase 2, 100 patients with severe AA were randomized in a 1:1:1:1 ratio to receive placebo or baricitinib (1 mg, 2 mg, or 4 mg) once daily. Consecutive interim analyses were performed after all patients completed 12 weeks and 36 weeks of treatment. The primary endpoint was the proportion of patients who achieved a SALT score ≤ 20 at week 36. After 12 weeks, SALT scores were assessed. The 2 mg and 4 mg groups presented higher frequencies of achieving a 30% improvement in SALT scores. Therefore, these two treatment groups were selected for continued usage. Patients initially assigned to the 1-mg dose were transitioned to the 4-mg dose for the remainder of the trial. An analysis after 36 weeks of treatment was performed to identify the frequency of patients with SALT scores <20. The 2 mg and 4 mg groups had significantly higher frequencies of SALT score improvement (33% and 51.9%, respectively) than the placebo group (3.6%). Therefore, the results of the phase 2 portion of the BRAVE-AA1 trial of baricitinib for patients with AA and ≥ 50% scalp hair loss support the use of the JAK inhibitor baricitinib as an effective treatment option for patients with severe AA.

Baricitinib is well-tolerated, and no new findings regarding its safety have been reported [13].

Two large-scale, randomized, placebo-controlled, phase 3 trials, BRAVE-AA1 and BRAVE-AA2, were conducted after the completion of phase 2 of the BRAVE-AA1 trial. For BRAVE-AA1, a total of 654 patients were enrolled. For BRAVE-AA2, 546 patients were enrolled. Patients were randomly assigned to receive once-daily baricitinib (4 mg or 2 mg) or placebo. After 36 weeks of treatment, the primary outcome was a SALT score ≤ 20. In the 4 mg groups of the BRAVE-AA1 and BRAVE-AA2 trials, 35.9% and 38.8%, respectively, achieved this outcome. In the 2 mg groups of the BRAVE-AA1 and BRAVE-AA2 trials, 19.4% and 22.8%, respectively, achieved this outcome. In the placebo groups of the BRAVE-AA1 and BRAVE-AA2 trials, 3.3% and 6.2%, respectively, achieved this outcome. Based on these results, the FDA approved once-daily baricitinib for adults with severe AA [14].

DISCUSSION

Many clinicians know that treating AA can be difficult, even with small patches of hair loss, and that the treatment of alopecia universalis, alopecia totalis, and ophiasis subtypes is even more challenging. The approval of baricitinib by the FDA as treatment for AA is good news for patients with AA. Although only partially discussed in this review, many reports have suggested the efficacy of baricitinib, tofacitinib, and ruxolitinib as treatments for AA. JAK inhibitors have great potential to reverse immune-related AA; however, there are concerns about side effects that may be related to immunity. The commonly documented minor adverse events experienced by patients with AA using JAK inhibitors include acne, headache, nausea, urinary tract infections, respiratory tract infections, anemia, thrombocytopenia, neutropenia, and increased creatinine levels. Patients using JAK inhibitors commonly exhibit increased low-density lipoprotein levels, which are known risk factors for cardiovascular disease. The most frequently reported serious adverse effects for patients with AA using JAK inhibitors include varicella zoster emergence, pneumonia, tuberculosis, sepsis, and non-melanoma skin cancers. A safe use manual prepared by the

Japan Society of Dermatology based on the results of the BRAVE-AA2 trial (phase 3 study) described an adverse event (varicella zoster emergence, pneumonia, tuberculosis, sepsis, and non-melanoma skin cancers) rate of ≥2% and side effects such as nausea, oropharynx, arthritis, gastroenteritis, rhinorrhea, back pain, and oral herpes. Not all patients experience side effects; however, any side effects that do occur should be observed carefully. To reduce the rate of adverse events, various examinations are necessary before the oral administration of JAK inhibitors [15].

CONCLUSION

When baricitinib was approved by the FDA, the director of the Center for Drug Evaluation and Research said the following: "Access to safe and effective treatment options is crucial for a significant number of Americans with severe alopecia. Today's approval will help fulfill a significant unmet need for patients with severe alopecia areata."

I look forward to increased treatment options with the potential approval of additional JAK inhibitors for more diseases in the future.

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