Dear Editor,

In 2022, the U.S. Food and Drug Administration (FDA) approved the use of Olumiant (Baricitinib), the first once-daily oral pill for severe alopecia areata (AA) in adults [1]. AA has a worldwide lifetime incidence nearing 2% with a median age of diagnosis of 33 years [2]. Alopecia areata is an autoimmune condition that causes hair loss, it is clinically identifiable with demarcated patches of hair loss without atrophy [3]. The main target of AA is the hair follicles which result in hair loss that ranges from the scalp to the body region. AA presents with isolated patches of hair loss that are uniquely characterized by “exclamation point hairs” found near each patch [2]. AA most commonly impacts the scalp region, but some patients suffer from hair loss in other body regions [3]. Therefore, diagnosis is usually clinical due to identifiable patterns of hair loss, but the use of trichoscopy can be utilized as a tool to confirm diagnosis as it can determine the presence of colored dots and damaged hair [2]. Importantly, the inflammation caused by AA does not afflict the stem cells of the hair follicle; consequently, the hair follicle can regenerate and heal, allowing patients to regrow their hair over time with specific treatment. The growth of hair is separated into phases that include anagen, catagen, and telogen [4]. Patients with AA suffer from hair loss and have intense feelings of embarrassment and confusion, which perpetuate into mental illnesses such as social anxiety disorder [5]. Although AA may resolve on its own over time, the emotional distress that comes from this condition may lead to clinical depression and anxiety [6].

The disease mechanism revolves around the interleukin-15 and interferon-γ cytokines which are upregulated in active AA. First, hair follicles contain an upregulation in interleukin-15 which in turn leads to the proliferation of CD8+ T cells, T helper cells, that are expressed by an activated natural killer gene 2D. From there, the CD8+ T cells produce the interferon-γ which is known to induce and regulate immune responses in the human body. The cell signaling of interleukin-15 and interferon-γ occurs through JAK enzymes [3]. The JAK family of enzymes is responsible for the signal transduction of cytokines and it consists of tyrosine kinase 2, JAK1, JAK2, and JAK3. The activation of JAK depends on the attachment of a cytokine to its respective receptor found on the cell membrane. Next, JAK is responsible for phosphorylating the cytokine receptor, thereby, allowing signaling proteins such as the STAT proteins to dock. These STAT proteins will then form dimers and move into the nucleus to contribute towards gene transcription [7]. For years, therapeutic development has focused on targeting the containing inflammation and healing hair follicles, but now studies have arisen to focus on JAK enzymes to determine inhibitory processes to reverse the effect of AA [3].

Currently, the most common medical therapy for AA is topical corticosteroids; which are used due to their ability to prevent the expansion of inflammation in local areas. In addition, these topical treatments could increase the rate of recovery for damaged hair follicles. Clinical research found that only 57% of patients who were prescribed corticosteroids had a complete reversal of AA, and patients suffered from adverse cutaneous atrophy at the site of corticosteroid application. Lastly, the relapse rates of AA reached up to 75% in patients, even with continued therapy. Other than the usage of topical corticosteroids, the other secondary treatments included ultraviolet A radiation, immunotherapy, and minoxidil [2]. Due to these variable rates of success, pharmaceutical companies focused their efforts on the therapeutic development of JAK inhibitors as potential methods of treatment for AA.

JAK inhibitors have been used successfully in the treatment of numerous conditions such as rheumatoid arthritis (RA), psoriatic arthritis, and atopic dermatitis. Baricitinib,
commercially known as Olumiant, is a JAK inhibitor that was recently approved for the treatment of AA; it was previously approved for the treatment of RA in doses of 2 or 4 milligrams per day [3]. To determine the efficacy of Baricitinib in the treatment of AA, two multi-country drug trials were conducted: BRAVE-AA1 and BRAVE-AA2. With over 1300 subjects and up to three years of consistent treatment, it was found that Baricitinib was an optimal JAK inhibitor in terms of the safety profile [8].

These findings were encouraging as previous usage of Baricitinib as a treatment in RA resulted in two key adverse reactions: viral infection risk and thromboembolic events. Clinical trials for patients with RA determined that Baricitinib specifically increased the risk of herpes zoster reactivation by 1.5 to 2 fold. Additional trials found that 39 patients administered with Baricitinib suffered from venous thromboembolic events, while 29 patients suffered from arterial thrombotic events. While these adverse effects were associated with patients diagnosed with RA, physicians need to be informed regarding the potential hazards that Baricitinib may lead to as a treatment of AA. Physicians must take into account their patient’s medical history, especially any cardiovascular illness or herpes zoster infection when deciding to prescribe Baricitinib [9]. A meta-analysis revealed the incidence rate of herpes zoster virus reactivation was 3.2 out of 100 in person-years, and the same analysis found that the 4-milligram dose of Baricitinib had a higher rate of reactivation compared to the 2-milligram dosage. Although the resulting infection was mild with no evidence of dissemination, these results do show the possibility of increased viral infection risk with the usage of Baricitinib [10]. These types of effects combined with the potential risk of thromboembolism and varicella zoster are key to guiding physicians on what dosage is necessary for an AA case without risk for complications. Patients who have coagulative disorders or are immunocompromised may not be ideal candidates for Baricitinib; a physician’s knowledge of their patient’s health and medication history is critical to maintaining safe, and effective usage of Baricitinib for the treatment of severe alopecia [7].

Fortunately, the BRAVE-AA1 and BRAVE-AA2 trials demonstrated that major risks associated with Baricitinib that were present for the treatment of RA such as cardiovascular events, thromboembolic events, or severe viral illness were low in the treatment of AA patients [8]. The most common general adverse side effect associated with Baricitinib usage in these two trials was the presence of upper respiratory infection. Additionally, acne, elevated levels of creatinine kinase, and varying levels of low-density lipoprotein cholesterol were also found in patients [8].

Most importantly, Baricitinib was determined to be the most optimal therapy due to its high efficacy results from the BRAVE-AA1 and BRAVE-AA2 trials. Results stated that patients with severe AA who were treated with baricitinib had an excellent response over 36 weeks with hair growth. This was gathered by utilizing a SALT score; a score of 20 or less was defined as a positive treatment outcome for AA. The results of the BRAVE-AA1 and BRAVE-AA2 trials are shown below and categorized by dosage; it is important to note that all data is based upon the number of subjects who scored 20 or below on the SALT [5].

<table>
<thead>
<tr>
<th>Dosage or Placebo</th>
<th>BRAVE-AA1 (%)</th>
<th>BRAVE-AA2 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4-mg Baricitinib</td>
<td>38.8%</td>
<td>35.9%</td>
</tr>
<tr>
<td>2-mg Baricitinib</td>
<td>22.8%</td>
<td>19.4%</td>
</tr>
<tr>
<td>Placebo</td>
<td>6.2%</td>
<td>3.3%</td>
</tr>
</tbody>
</table>

In the BRAVE-AA1 trial, the 4-milligram dose led to severe adverse effects in 2.1% of subjects, while the 2-milligram dose led to effects in 2.2% of the subject population. Conversely, the BRAVE-AA2 trial had severe reactions in 3.4% of the subject pool taking 4 milligrams, while only 2.6% of the subject population taking 2 milligrams suffered severe effects [5].

Importantly, the percentage of subjects suffering from Herpes Zoster infection was present, but under 2% in both doses of both trials. Fortunately, these patients had localized infections along the skin dermatome, and there was no dissemination. Furthermore, there were no venous thromboembolic events present in either trial, but there was the presence of a myocardial infarction in a patient who had cardiovascular risk [5]. In recent years, exploration regarding treatment options for AA has expanded to include new trials such as THRIVE-AA1.

A different trial for the treatment of AA, THRIVE-AA1, was conducted from 2020 to 2023. This trial studied the efficacy and safety of CTP-543 for the treatment of moderate to severe AA in adults. Specifically, the trial enrolled 706 individuals who were separated into the following groups: placebo, CTP-543 8 milligrams, and CTP-543 12 milligrams. The data support the use of CTP-543 for the treatment of AA, and the adverse reactions caused by CTP-543 were minimal. Most importantly, both doses of the drug did not cause any death during the trials. Almost all adverse reactions seen in the individuals were less than 0.5%, showing the safety profile of the drug. The only adverse reaction was seen in the 8 mg dosage as 1.14% of individuals in the group suffered from gastrointestinal disorders [12].

Due to the success seen in JAK inhibitors for the treatment of AA, numerous studies have focused on other JAK inhibitors such as tofacitinib. There have been trials showing that tofacitinib is another potential treatment option for AA. Specifically, the study included 12 patients with moderate to severe forms of AA, and the efficiency of the treatment was assessed by tracking the rate of hair growth. The study’s main goal was the percentage of patients with at least 50% scalp hair regrowth from baseline. The study saw a positive impact as 66.7% of the participants had at least a 50% regrowth of scalp hair after six to eighteen months of treatment. The study also showed that tofacitinib was generally well tolerated [13].

1 Table 1’s is based upon reference #5
Essentially, the importance of a physician's knowledge of patient history is imperative when prescribing Baricitinib as certain risk factors make it more plausible for patients to suffer from adverse reactions. Special attention to AA patients with cardiovascular conditions should be particularly studied in future trials to examine Baricitinib’s adverse side effects. Nevertheless, it is important to note that the usage of Baricitinib for the treatment of AA had an optimal safety profile with proven efficacy which led to its approval by the FDA. Further studies on this drug must be conducted over a longer period with different variables to determine relapse rate and safety to better estimate the safety profile of Baricitinib; these types of studies will give physicians the confidence to prescribe this drug to treat patients suffering from AA.

LIST OF ABBREVIATIONS

AA = Alopecia areata
FDA = Food and Drug Administration
JAK = Janus Kinase
RA = Rheumatoid arthritis

CONFLICT OF INTEREST

Dr. Craig G. Burkhart is the Editor-in-Chief of the journal The Open Dermatology Journal.

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Declared none.

REFERENCES

[8]Safety of baricitinib in adults with severe alopecia areata. Br J Dermatol 2023; 188(2) [https://doi.org/10.1093/bjd/bjac152] [PMID: 36763892].

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