Role of janus kinase inhibitors in the treatment of alopecia areata

Korn Triyangkulsri
Poonkiat Suchonwanit

Division of Dermatology, Department of Medicine, Faculty of Medicine, Ramathibodi Hospital, Mahidol University, Bangkok, Thailand

Abstract: Alopecia areata (AA) is a common hair loss disorder worldwide with characteristic exclamation mark hairs. Although AA is self-limited, it can last for several months or even years in some patients. Currently, there is no US Food and Drug Administration-approved treatment for AA. Many off-label treatments are available but with limited efficacy. Through a better understanding of molecular biology, many targeted therapies have emerged as new alternatives for various autoimmune diseases. Various janus kinase (JAK) and signal transducer and activator of transcription (STAT) proteins form signaling pathways, which transmit extracellular cytokine signals to the nucleus and induce DNA transcriptions. By inhibiting JAK, T-cell-mediated inflammatory responses are suppressed. Increasing evidence suggests that JAK inhibitors (JAKis) are effective in the treatment of many autoimmune diseases, including AA. Among these, several studies on tofacitinib, ruxolitinib, and baricitinib in AA had been published, demonstrating promising outcomes of these agents. Unlike oral formulations, efficacy of topical forms of tofacitinib and ruxolitinib reported in these studies is still unsatisfactory and requires improvement. This review aims to summarize evidence of the efficacy and safety of JAKis in the treatment of AA.

Keywords: baricitinib, JAK, JAK inhibitors, JAK-STAT pathway, ruxolitinib, tofacitinib

Introduction

Alopecia areata (AA) is an autoimmune disease characterized by a nonscarring patch or patches of hair loss with characteristic exclamation mark hairs. AA is a relatively common disease with a worldwide prevalence of 0.1%–0.2%. It is found to be associated with atopic dermatitis, vitiligo, systemic lupus erythematosus, and autoimmune thyroid diseases. Other than autoimmune factors, AA is thought to be driven by genetic predisposition. There have been several studies suggesting genetic background with familial incidence of 7%–18% depending on the type of AA. Evidence, of its prevalence in the population of about 2%, concordance in twins, a Gaussian distribution of severity, a 10-fold increased risk of first-degree relatives of affected individuals, and the aggregation of affected individuals in families with no clear Mendelian pattern of inheritance, suggests that AA fits a complex or multifactorial genetic pattern. Furthermore, AA is found to be associated with several human leukocyte antigens, such as DQ3, DR4, DR11, and DQ7. Currently, there is no United State Food and Drug Administration (FDA)-approved treatment for AA. Many off-label treatments are available but with limited efficacy. Thus, there is still room for new alternatives for the treatment of AA. Increasing evidence suggests that JAK inhibitors (JAKis) are effective in the treatment of AA. This review aims to summarize evidence on the efficacy and safety of JAKis, in the hope of improving the understanding and treatment of severe AA.
of AA, and to suggest future directions in which JAKis may be promising candidates for the treatment of other hair loss disorders.

Pathogenesis of AA

Hair follicles are immune-privileged sites with complex and intricate structures to maintain their immunity against the body immune system. The key features of an immune-privileged site are low major histocompatibility complex (MHC) class I and II expression and well-suppressed natural killer (NK) cells. Disruption of the system, namely upregulation of MHC class I or UL16-binding protein 3 (ULBP3) molecules or defect in NK cell inhibition or containment, results in loss of immune privilege and ultimately causes AA. ULBP3 was identified as an important factor in AA pathogenesis by various genome-wide association studies. Its overexpression leads to the attack of cytotoxic cluster of differentiation 8-positive (CD8+) NK group 2D-positive (NKG2D+) T cells to the hair follicles. Hair follicles that lose their immune privilege during anagen phase become the target of CD8+ T cells and NKG2D+ cells. This hypothesis is supported by the findings of CD8+ T cells and NKG2D+ cells around the peribulbar area of the affected hair follicles. Concurrently, marked interferon (IFN)-γ response and upregulation of several γ-chain (γc) cytokines, including interleukin (IL)-2, IL-7, IL-15, and IL-21, and IFN-γ elements, promote activation and survival of IFN-γ-producing CD8+ NKG2D+ T cells and contribute to immune privilege collapse of hair follicles. These events ultimately lead to hair follicle dystrophy and accelerate hair follicles into catagen phase.

JAK-STAT signaling pathway and its role in AA

JAK-STAT signaling pathway consists mainly of three components: receptor, janus kinase (JAK), and signal transducer and activator of transcription (STAT) (Figure 1). The receptor, on the cell surface, binds to specific ligands, such as IFNs, ILs, and various other cytokines and hormones. JAK is a member of tyrosine kinase family, which consists of JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). JAK, after receiving signal by the ligands, phosphorylates its own tyrosine component to activate its kinase function which in turn phosphorylates STAT component. Activated STATs translocate to promote transcription of DNA in the nucleus.

Figure 1 Illustration of JAK-STAT signaling pathway.
Notes: Specific ligands bind to their corresponding receptors and activate JAK component. JAK phosphorylates its own tyrosine component to activate its kinase function which in turn phosphorylates STAT component. Activated STATs translocate to promote transcription of DNA in the nucleus.
Abbreviations: JAK, janus kinase; STAT, signal transducer and activator of transcription.
function, which in turn phosphorylates STAT component. Phosphorylation of the STAT component dimerizes and activates STATs. The activated STATs then will, in turn, translocate to the DNA in the nucleus and promote transcription of a specific region of the DNA, leading to gene expression (Figure 1). This fundamental process of gene expression mediates cellular processes through activation of cytokines. Function of the JAK-STAT signaling pathway was first discovered as a pathway for IFN signaling.\textsuperscript{17–19} Subsequently, a large number of cytokines, particularly γc cytokines, have been found to activate the JAK-STAT pathway, leading to a myriad of gene expression.\textsuperscript{20} JAK-STAT pathway is vital in maintaining innate and adaptive immunity. Any defect in JAK component results in certain hematologic or immune-related diseases, such as myeloproliferative neoplasms or severe combined immunodeficiency.\textsuperscript{21,22}

Given a crucial role that JAK-STAT pathway plays in mediating the CD8\textsuperscript{+} NKG2D\textsuperscript{+} T cell reaction, which is a component of AA pathogenesis, JAKis seem to be an appealing option for the treatment of AA. Moreover, inhibition of this pathway results in promotion of hair growth cycle, which increases effectiveness of hair loss treatment.\textsuperscript{10} Figure 2 demonstrates the interaction between JAK-STAT pathway, in pathogenesis of AA, and JAKis. Further information regarding the relationship between JAK-STAT pathway and hair growth cycle, as well as JAKis and AA, is discussed in the next sections.

**JAK and hair growth cycle**

In terms of hair growth, key genes in the JAK-STAT pathway including Stat5A/B, Stat3, Jak1, Jak3, and Socs2/3 were highly expressed in catagen and telogen phases but suppressed in early anagen phase.\textsuperscript{23} IL-6 and oncostatin M (OSM), which signal via JAK-STAT pathway, have been shown to play a role in hair growth regulation. Overexpression of IL-6 in keratinocytes in mice results in hair growth regulation and proliferation of keratinocytes. This also causes follicular epithelial cells to promote the production of IL-15 through JAK1 and JAK2. IL-15 in turn binds to its receptor on CD8\textsuperscript{+} T cells and induces JAK1- and JAK3-mediated IFN-γ production and ultimately completes the feedback loop. Tofacitinib mainly inhibits JAK1 and JAK3, while ruxolitinib predominantly inhibits JAK1 and JAK2. Lastly, baricitinib selectively inhibits JAK1 and JAK2. These inhibitions interfere with the feedback loop and alleviate AA.

**Abbreviations:** IFN, interferon; IL, interleukin; JAK, janus kinase; MHC, major histocompatibility complex; NK, natural killer; STAT, signal transducer and activator of transcription; TAP-2, transporter associated with antigen processing-2; TCR, T-cell receptor.
retardation. IL-6 is also found to be more prominent in balding dermal papilla compared with nonbalding dermal papilla. The same study also showed that injection of recombinant IL-6 into anagen skin can induce premature onset catagen phase. Finally, IL-6 and OSM were found to inhibit hair shaft elongation in the human organ culture model. Anagen extension and hair regrowth were found in mice receiving tofacitinib, a JAKi. The study also proved that, after inhibiting JAK-STAT pathway, vascular endothelial growth factor is upregulated, resulting in angiogenesis. This suggests the role of JAK in hair growth.27 Harel et al showed that inhibiting JAK-STAT pathway promotes hair growth by stimulating the activation and/or proliferation of hair follicle stem cells and other unknown mechanisms.23 It was also shown that suppression of JAK signaling activates an antiproliferative effect during telogen phase and accelerates reentry into anagen phase in mice. However, no study was able to establish the same effect on human hair follicles.

**JAKis and AA**

Over the past few years, various JAKis have been reported to have promising efficacy in various autoimmune disorders, such as rheumatoid arthritis,29 and psoriasis,30 and myeloproliferative disorders, such as myelofibrosis or polycythemia vera.31 In the same manner, AA was also found to be responsive to JAKi treatment. Several studies had helped bring light to the mechanism of JAKis in stimulating hair growth in AA. Overexpression of JAK3 and, to a lesser extent, JAK1 and JAK2 was observed in skin biopsy specimens of patients with AA.31 In terms of hair growth in AA, a two-step mechanism needs to be fulfilled.32 First, T-cell-mediated immune response on the hair follicle must be terminated. Xing et al demonstrated that the involvement of γc cytokine and receptor family members in AA and JAKis blocked the downstream signal of such cytokines.33 JAKis also disrupt the production of inflammatory T helper (Th) 17 cells and Th1 and Th2 differentiation (Figure 2).33 Second, anagen phase must be reinstated. Restoration of anagen phase of the hair follicle by JAK inhibition has been discussed previously in this article (see JAK and hair growth cycle). Currently, there are three medications that have been reported in various trials for the treatment of AA. Each of which is reviewed in this article.

**Tofacitinib**

Tofacitinib (CP-690,550, formerly tasocitinib) is the first of the JAKi family. Its chemical formula is \( \text{C}_{161} \text{H}_{202} \text{N}_{40} \text{O} \) (Figure 3).34 It selectively inhibits JAK1- and JAK3-dependent STAT activation over JAK2, with minimal effects on TYK2 pathway.35 Tofacitinib blocks STAT phosphorylation induced by IFN-γ, IL-2, IL-4, IL-7, IL-15, and IL-21, which clearly affects the signaling pathway downstream of JAK1- and JAK3-dependent γc receptors in both mice and humans. IL-12 signaling, which depends on JAK2 and TYK2, is blocked for STAT1 activation but only mildly suppressed for STAT4.36 Additionally, anti-inflammatory effects of tofacitinib have also been described in some studies.27,33,36

Efficacy of tofacitinib in AA was first reported by Craiglow and King in 2014. A 25-year-old male patient with psoriasis and, coincidentally, alopecia universalis (AU) was treated with oral tofacitinib, showing improvement in both psoriasis and AU. Full regrowth of hair at all body sites was observed after 8 months of therapy with 15 mg per day of oral tofacitinib. Since then, several clinical studies on adolescent and adult patients have been published (Table 1).37–58 These cases were mostly diagnosed with AU and some with AA. Most of the cases were also unresponsive to their previous treatments, including various regimens of corticosteroid, cyclosporine, and/or methotrexate. In a 38-year-old male with AU and nail dystrophy associated with AA, total hair regrowth and normalization of nails were observed after 10 months of treatment with oral tofacitinib 5 mg twice daily. A case report of a 40-year-old woman with moderate-to-severe AA demonstrated almost complete regrowth of hair after 4 months of treatment with oral tofacitinib 5 mg twice daily. The same study also found that initial elevation of CXCL10 (an IFN-induced chemokine), IFN, and cytotoxic T lymphocyte signatures was decreased after 4 weeks of treatment. However, cessation of tofacitinib resulted in near-complete hair loss.41

Several retrospective studies have also been published. In the largest study conducted by Liu et al,39 efficacy of oral tofacitinib 5 mg or more twice daily as monotherapy or as combination therapy with prednisone was evaluated in 90 patients with AA and its variants. Patients aged
Table 1 Characteristics of clinical studies of tofacitinib in the treatment of AA

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study design</th>
<th>Patients</th>
<th>Indication</th>
<th>JAK inhibitor (dose)</th>
<th>Outcome</th>
<th>Side effects</th>
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<tbody>
<tr>
<td>Craiglow and King</td>
<td>2014</td>
<td>Case report</td>
<td>1</td>
<td>Alopecia universalis and plaque-type psoriasis and plaque-type psoriasis</td>
<td>Oral tofacitinib (15 mg daily)</td>
<td>Patient experienced regrowth in 8 months</td>
<td>Grade I and II infections (17): eg, URI (11), UTI (2), zoster (1)</td>
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<td></td>
<td>Alopecia areata and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>64% of patients responded to treatment</td>
<td>Headache (5), abdominal pain (5), acne (5), diarrhea (4), fatigue (4), hot flashes (3), pruritus (2), folliculitis (2), numbness (2), cough (1), nausea (1), amenorrhea (1), dry eyes (1), weight gain (1), AST/ALT elevation (1)</td>
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<td>Kennedy Crispin et al</td>
<td>2016</td>
<td>Open-label, single-arm trial</td>
<td>66</td>
<td>Alopecia areata and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>32% of patients had SALT reduced &gt;=50% in 3 months</td>
<td>All patients experienced hair loss in 8.5 weeks after cessation</td>
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<td>Liu et al</td>
<td>2017</td>
<td>Retrospective study</td>
<td>90</td>
<td>Alopecia areata and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5, &gt;5 mg BID with and without prednisone)</td>
<td>20% (13) of patients were complete responders (&gt;90% reduction in SALT, median 15 months)</td>
<td>Grade I and II infections (35): eg, URI (26), UTI (3), zoster (2)</td>
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<td>Gupta et al</td>
<td>2016</td>
<td>Case series</td>
<td>2</td>
<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>38.4% (25) of patients were intermediate responders (51%-90% reduction in SALT, median 14 months)</td>
<td>AST/ALT elevation (1), transient, Leukopenia (1), transient</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>18.5% (12) of patients were moderate responders (6%-50% reduction in SALT, median 11 months)</td>
<td>Increased TG (6), Increased LDL (15)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>23.1% (15) of patients were nonresponders (&lt;5% reduction in SALT, median 7 months)</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Hair growth was observed in 1 and 3 months</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Both patients had full regrowth in 8 months</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>All patients experienced remission of nail change within 5–6 months</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Two patients experienced hair growth</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Patient had terminal hair growth after 3 months but returned to baseline in 1 month</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Patient had total hair regrowth and normalization of nails in 10 months</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Patient had almost complete regrowth in 4 months</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Patient had near-complete hair loss after cessation</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>CXCL10, IFN-γ in tissue and ALADIN score decreased at 4 weeks</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis and plaque-type psoriasis associated with alopecia areata</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>Patient had full regrowth in 6 months</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis, plaque-type psoriasis and psoriatic arthritis</td>
<td>Oral tofacitinib (10, 15 mg daily)</td>
<td>Psoriatic arthritis also resolved</td>
<td>Viral infection and fatigue (1)</td>
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<td>Alopecia universalis, plaque-type psoriasis and psoriatic arthritis</td>
<td>Oral tofacitinib (10, 15 mg daily)</td>
<td>Patient developed new psoriatic plaque refractory to tofacitinib</td>
<td>Viral infection and fatigue (1)</td>
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Table 1 (Continued)

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<tr>
<th>Authors</th>
<th>Year</th>
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<th>Indication</th>
<th>JAK inhibitor (dose)</th>
<th>Outcome</th>
<th>Side effects</th>
</tr>
</thead>
</table>
| Liu et al        | 2018   | Open-label, pilot, single-arm trial | 10       | Alopecia areata             | Topical 2% tofacitinib (BID)                  | • One patient had excellent regrowth  
  • Two patients had partial regrowth  
  • Seven patients showed no regrowth | • Scalp irritation (4) (40%)  
  • Folliculitis (1) (10%)  
  • Minimal elevation of total cholesterol (4) (40%)                                                                                     |
| Craiglow et al   | 2017   | Retrospective study  | 13       | Alopecia areata and variants | Oral tofacitinib (10, 15 mg daily)          | • Nine patients experienced significant hair regrowth  
  • Median % SALT changed was 93% (mean 61%), mean duration was 6.5 months  
  • Seven patients achieved regrowth ≥50%, mean duration 4.2 months  
  • Two patients experienced hair loss back to baseline after 2 weeks of discontinuation | • Headache (3)  
  • URI (4)  
  • Transient elevation of liver transaminase (4)  
  • Morbilliform eruption and peripheral edema leads to medication withdrawal (1)  
  • Lipid and liver abnormalities, resolved with dose reduction (2)                                                                 |
| ibrahim et al    | 2017   | Retrospective study  | 13       | Alopecia areata and variants | Oral tofacitinib (10, 15, 20 mg daily)       | • Seven patients achieved regrowth  
  • Two patients experienced hair loss back to baseline after 2 weeks of discontinuation  
  • Morbilliform eruption and peripheral edema leads to medication withdrawal (1)  
  • Lipid and liver abnormalities, resolved with dose reduction (2)                                                                 |
| Park et al       | 2017   | Retrospective study  | 32       | Alopecia areata and variants | Oral tofacitinib (various doses)             | • Six patients had 5%–50% regrowth, median duration was 7 months  
  • Nine patients had 50%–90% regrowth, median duration was 10 months  
  • Nine patients had >90% regrowth, median duration was 10 months  
  • Eight patients showed no response  
  • One patient had 20% regrowth of eyebrows  
  • One patient had 95% regrowth  
  • One patient had 80% regrowth after 1 year  
  • One patient had no response (only data from tofacitinib-treated patients) | • Transient elevation of liver transaminase (1)  
  • Transient leukopenia (1) (only data from tofacitinib-treated patients)                                                                 |
| Bayart et al     | 2017   | Case series          | 6        | Alopecia areata and variants | • Four patients: Topical 2% tofacitinib (BID)  
  • Two patients: Topical 1%, 2% ruxolitinib (BID) | • One patient had progressive hair growth after 9 months  
  • One patient had some regrowth after 6 weeks  
  • One patient had hair regrowth after 7 months  
  • One patient had full regrowth after 6 months  
  • Patient had full regrowth in 32 weeks  
  • Patient had near-complete regrowth in 10 months | • Transient elevation of liver transaminase (1)  
  • Transient leukopenia (1) (only data from tofacitinib-treated patients)                                                                 |
| Castelo-Soccio   | 2017   | Case series          | 8        | Alopecia universalis        | Oral tofacitinib (5 mg BID)                  | • All patients experienced ≥50% regrowth in scalp hair by 5 months  
  • All patients experienced significant improvement in SALT  
  • Two patients experienced improvement in nail pitting  
  • One patient had progressive hair growth after 9 months  
  • One patient had some regrowth after 6 weeks  
  • One patient had hair regrowth after 7 months  
  • One patient had full regrowth after 6 months  
  • Patient had full regrowth in 32 weeks  
  • Patient had near-complete regrowth in 10 months | • Transient elevation of liver transaminase (1)  
  • Transient leukopenia (1) (only data from tofacitinib-treated patients)                                                                 |
| Scheinberg et al | 2017   | Case series          | 4        | Alopecia universalis        | Oral tofacitinib (5, 10 mg daily)            | • One patient had progressive hair growth after 9 months  
  • Two patients experienced improvement in nail pitting  
  • One patient had some regrowth after 6 weeks  
  • One patient had hair regrowth after 7 months  
  • One patient had full regrowth after 6 months  
  • Patient had full regrowth in 32 weeks  
  • Patient had near-complete regrowth in 10 months | • Transient elevation of liver transaminase (1)  
  • Transient leukopenia (1) (only data from tofacitinib-treated patients)                                                                 |
| Kim and Kim      | 2017   | Case report          | 1        | Alopecia universalis        | Oral tofacitinib (5 mg BID)                  | • One patient had progressive hair growth after 9 months  
  • Two patients experienced improvement in nail pitting  
  • One patient had some regrowth after 6 weeks  
  • One patient had hair regrowth after 7 months  
  • One patient had full regrowth after 6 months  
  • Patient had full regrowth in 32 weeks  
  • Patient had near-complete regrowth in 10 months | • Transient elevation of liver transaminase (1)  
  • Transient leukopenia (1) (only data from tofacitinib-treated patients)                                                                 |
| Strazzulla et al | 2017   | Case report          | 1        | Alopecia universalis        | Oral tofacitinib (unspecified dose)          | • One patient had progressive hair growth after 9 months  
  • Two patients experienced improvement in nail pitting  
  • One patient had some regrowth after 6 weeks  
  • One patient had hair regrowth after 7 months  
  • One patient had full regrowth after 6 months  
  • Patient had full regrowth in 32 weeks  
  • Patient had near-complete regrowth in 10 months | • Transient elevation of liver transaminase (1)  
  • Transient leukopenia (1) (only data from tofacitinib-treated patients)                                                                 |
<table>
<thead>
<tr>
<th>Reference</th>
<th>Year</th>
<th>Study Design</th>
<th>Population</th>
<th>Treatment</th>
<th>Outcomes</th>
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</thead>
<tbody>
<tr>
<td>Jabbari et al²</td>
<td>2018</td>
<td>Open-label, single-arm trial</td>
<td>Alopecia areata and variants</td>
<td>Oral tofacitinib (10, 15 mg daily)</td>
<td>- Patient had full regrowth in 6 months</td>
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<td>- Patient had no hair regrowth despite almost total clearance of psoriasis</td>
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<td>- Eight patients showed ≥50% regrowth from baseline</td>
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<td>- Three patients showed &lt;50% regrowth from baseline</td>
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<td>- One patient showed no regrowth</td>
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<td>- Reduction in ALADIN score in responders</td>
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<td>- No significant change in ALADIN score in nonresponder</td>
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<td>- One patient had 85% reduction in SALT score</td>
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<td>- One patient had 90% reduction in SALT score</td>
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<tr>
<td>Erduran et al³</td>
<td>2017</td>
<td>Case report</td>
<td>Alopecia universalis</td>
<td>Oral tofacitinib (10, 15 mg daily)</td>
<td>- Patient had full regrowth in 6 months</td>
</tr>
<tr>
<td>Salman et al⁴</td>
<td>2017</td>
<td>Case report</td>
<td>Alopecia universalis and plaque-type psoriasis</td>
<td>Oral tofacitinib (5 mg BID)</td>
<td>- Grade 1 and II infection (12): eg, URI (1), conjunctivitis (1)</td>
</tr>
<tr>
<td>Patel et al⁸</td>
<td>2018</td>
<td>Case series</td>
<td>Alopecia universalis</td>
<td>Oral tofacitinib (10, 15, 20 mg daily)</td>
<td>- Loose stool (3), constipation (1), bloating (1), mild acne (3), weight gain (2), hypertensive urgency (1), dizziness (1), headache (1), neuropathic pain (1), urinary retention (1), vaginal spotting (1)</td>
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<td>- Blood on urinalysis (4), asymptomatic bacteriuria (2), transaminis (1)</td>
</tr>
</tbody>
</table>

**Abbreviations:** AA, alopecia areata; ALADIN, Alopecia Areata Disease Activity Index; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BID, bis in die (twice daily); CXCL10, C-X-C motif chemokine ligand 10; iFN-γ, interferon γ; JAK, janus kinase; LDL, low-density lipoprotein; SALT, Severity of Alopecia Tool; TG, triglyceride; URI, upper respiratory tract infection; UTI, urinary tract infection.
Ibrahim et al reported a patient having morbilliform eruption and peripheral edema leading to cessation of oral tofacitinib. Information on long-term safety of tofacitinib was indirectly extrapolated from clinical trials in rheumatoid arthritis. Tuberculosis was observed in 10 mg dosage groups (incidence rate 0.5 events/100 patient-years) but not in 5 mg dosage groups (95% CI 0.1–0.9). Rate of opportunistic infection other than tuberculosis was low and limited to herpes zoster without visceral involvement or death. Lung cancer and breast cancer were the most common malignancies that occurred during tofacitinib treatment. The overall rate of occurrence of malignancies, excluding nonmelanoma skin cancer, was 0.939 events/100 patient-years (95% CI 0.737–1.198). However, all this information of adverse events must be taken into account that the studied population could be affected by rheumatoid arthritis and its treatment.

**Ruxolitinib**

Ruxolitinib (INC424 or INCB018424), a JAKi with chemical structure of C_{17}H_{18}N_{6} (Figure 4), is FDA-approved for the treatment of myelofibrosis. It selectively inhibits JAK1 and JAK2 and, to some extent, TYK2. Other than the effects of JAK-STAT pathway inhibition, ruxolitinib has been shown to have anti-inflammatory effects, which are thought to be due to interruption of the IL-17 signaling axis. Concurrently, ruxolitinib has been demonstrated to reduce cytokine-induced phosphorylation of STAT3 and levels of circulating inflammatory cytokines such as tumor necrosis factor-α and IL-6 in mice. Eyelash growth was observed in a patient with hypereosinophilic syndrome after having taken ruxolitinib, but the responsible mechanism was not elucidated.

A number of case reports and one open-label, single-arm trial of ruxolitinib have been published (Table 2). Concerning oral ruxolitinib, Xing et al, apart from establishing the effects of JAKis in alopecic skin through in vivo study, had reported three cases of AA treated with 20 mg of oral ruxolitinib twice daily. All three patients experienced near-complete regrowth within 3–5 months. Pieri et al later reported a near-complete hair growth after 15 mg of oral ruxolitinib twice daily was administered to a patient with AU and essential thrombocytopenia.

In an open-label, single-arm trial for oral ruxolitinib, 12 patients with moderate-to-severe AA were given 20 mg of oral ruxolitinib twice daily for 3–6 months. The proportion of patients with 50% or greater hair regrowth from baseline was the primary endpoint. Nine patients (75%) had significant hair growth (mean improvement of 92%). Despite promising outcomes in a mouse model reported by Craiglow et al, unfavorable efficacy of the topical form of ruxolitinib had been demonstrated in two case reports. Craiglow et al reported a case of AU treated with 0.6% ruxolitinib cream. The patient had near-complete regrowth of eyebrows, but only 10% growth of scalp hair after 12 weeks. Bayart et al revealed two cases of AU treated with 1% and 2% ruxolitinib in liposomal base. No response was observed in the patient treated with 2% ruxolitinib, whereas the other receiving 1% ruxolitinib experienced regrowth of only upper eyelashes but not the eyebrows. Similarly, Deeb and Beach reported no improvement in the patient with AA who underwent the treatment with 0.6% ruxolitinib cream.

As for the safety issue of ruxolitinib, all clinical studies on AA patients have reported only mild symptoms and grade I or II infection (Table 2). Data from studies on ruxolitinib in myelofibrosis patients show hematologic adverse events mainly dose-related anemia, thrombocytopenia, and neutropenia. These conditions can be explained by the fact that ruxolitinib inhibits JAK2-STAT signaling in normal hematopoiesis. Common nonhematologic adverse events included nonsevere bruising, dizziness, and headache. Ruxolitinib proved to be noncarcinogenic in the 6-month Tg.rasH2 transgenic mouse model and in a 2-year carcinogenicity study in the rat. Furthermore, there has yet to be any report on ruxolitinib-related malignancy in the literature.

**Baricitinib**

Baricitinib (LY3009104 or INCB028050) is a potent selective JAK1 and JAK2 inhibitor with a recognizable degree of JAK3 and various kinase inhibition. Its chemical structure.
Table 2 Characteristics of clinical studies of ruxolitinib and baricitinib in the treatment of AA

<table>
<thead>
<tr>
<th>Authors</th>
<th>Year</th>
<th>Study design</th>
<th>Patients</th>
<th>Indication</th>
<th>JAK inhibitor (dose)</th>
<th>Outcome</th>
<th>Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 Xing et al</td>
<td>2014</td>
<td>Case series</td>
<td>3</td>
<td>Alopecia areata</td>
<td>Oral ruxolitinib (20 mg BiD)</td>
<td>All patients experienced near-complete regrowth within 3–5 months</td>
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<tr>
<td>2 Pieri et al</td>
<td>2015</td>
<td>Case report</td>
<td>1</td>
<td>Alopecia universalis and essential thrombocytéma</td>
<td>Oral ruxolitinib (15 mg BiD)</td>
<td>Patient had near-complete regrowth within 10 months</td>
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<tr>
<td>3 Craiglow et al</td>
<td>2016</td>
<td>Case report</td>
<td>1</td>
<td>Alopecia universalis</td>
<td>Topical 0.6% ruxolitinib (BiD)</td>
<td>Patient had near-complete regrowth of eyebrows and 10% regrowth of scalp hair in 12 weeks</td>
<td>Leukopenia (1)</td>
</tr>
<tr>
<td>4 Mackay-Wiggan et al</td>
<td>2016</td>
<td>Open-label, single-arm trial</td>
<td>12</td>
<td>Alopecia areata</td>
<td>Oral ruxolitinib (20 mg BiD)</td>
<td>Nine patients had regrowth ( \geq 50% ) ( \geq 50% )</td>
<td>Bacterial skin infection (3)</td>
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<td></td>
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<td>Nine responders experienced reduction of hair loss from baseline by 92%</td>
<td>UTI (1)</td>
</tr>
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<td>5 Bayart et al</td>
<td>2017</td>
<td>Case series</td>
<td>6</td>
<td>Alopecia areata and variants</td>
<td></td>
<td>One patient showed no response</td>
<td>Mild pneumonia (1)</td>
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<td>One patient experienced 75% regrowth of only upper eyelashes; no regrowth of eyebrows (only data from ruxolitinib-treated patients)</td>
<td>Postoperative conjunctival hemorrhage (1)</td>
</tr>
<tr>
<td>6 Vandiver et al</td>
<td>2017</td>
<td>Case series</td>
<td>2</td>
<td>Alopecia areata</td>
<td>Oral ruxolitinib (10–30 mg daily)</td>
<td>One patient had complete regrowth in 8 months</td>
<td>Mild GI symptoms (1)</td>
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<td>One patient had near-complete regrowth in 6 months</td>
<td>Lower hemoglobin: resolved with dose reduction (1)</td>
</tr>
<tr>
<td>7 Deeb and Beach</td>
<td>2017</td>
<td>Case report</td>
<td>1</td>
<td>Alopecia areata</td>
<td>Topical 0.6% ruxolitinib (BiD)</td>
<td>Patient showed no improvement</td>
<td>–</td>
</tr>
<tr>
<td>8 Ramot and Zlotogorski</td>
<td>2018</td>
<td>Case report</td>
<td>1</td>
<td>Alopecia universalis</td>
<td>Oral ruxolitinib (20 mg BiD)</td>
<td>Patient had full regrowth of beard and 50% regrowth of scalp hair</td>
<td>–</td>
</tr>
<tr>
<td>9 Jabbari et al</td>
<td>2015</td>
<td>Case report</td>
<td>1</td>
<td>Alopecia areata and CANDLE syndrome</td>
<td>Oral baricitinib (7 mg morning and 4 mg evening)</td>
<td>Patient had full regrowth in 9 months</td>
<td>–</td>
</tr>
</tbody>
</table>

Abbreviations: AA, alopecia areata; BiD, bis in die (twice daily); CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature; GI, gastrointestinal; JAK, janus kinase; URI, upper respiratory tract infection; UTI, urinary tract infection.

is C\textsubscript{16}H\textsubscript{17}N\textsubscript{7}O\textsubscript{2}S (Figure 5). In cell-based assays relevant to autoimmune diseases, baricitinib has been shown to inhibit JAK signaling and function initiated by IL-6 and IL-23. Anti-inflammatory effects have also been observed in a mouse model with reduced CD8 infiltration and reduced MHC class I and class II expression when compared with vehicle control-treated mice. There has only been one case report concerning the efficacy of baricitinib in AA (Table 2). In 2015, Jabbari et al reported a patient with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome (CANDLE syndrome) and AA who was treated with oral baricitinib 7 mg in the morning and 4 mg in the evening. Complete regrowth of scalp hair was observed after 9 months of treatment.
With regard to safety, Jabbari et al did not report any adverse events following baricitinib use in AA. A study on baricitinib in healthy volunteers showed no serious adverse events. Reported adverse events were neutropenia and reduced reticulocyte count. Baricitinib was considered to be noncarcinogenic based on the study of carcinogenicity assessment of baricitinib in mice.

**Future directions**

Despite exceptional results in mice, researchers are still unable to reproduce similar efficacy of the topical preparation of tofacitinib and ruxolitinib in humans. Bayart et al demonstrated that a patient, who initially did not respond to the treatment, attained 95% hair growth after switching from tofacitinib in VersaBase cream formulation to liposomal base formulation. This suggests that there is still room for improvement for topical JAKis especially in terms of pharmacokinetics and pharmacodynamics. In fact, researchers have already begun investigating into nanotechnology in the hope of better drug delivery, which might greatly enhance topical JAKi efficacy.

Second-generation JAKis, equipped with a better selectivity of JAK receptor, are currently being studied in RA. Filgotinib (GLPG0634/GS-6034) and ABT-494, selective inhibitors of JAK1, and decernotinib (VX-509), a selective inhibitor of JAK3, have shown promising efficacy in Phase II studies of rheumatoid arthritis. WYE-151650, a selective inhibitor of JAK3, has been shown to have exceptional efficacy in collagen-induced arthritis in mice. These second-generation JAKis might be applicable in AA with similar efficacy and less toxicity and side effects. Future studies are needed to shed more light on the safety and efficacy of these new members of the JAKi family.

As previously mentioned, JAKis have many unexplained roles in hair growth cycle regulation in addition to their anti-inflammatory effects. Several studies regarding their mechanism on hair growth cycle are ongoing. The implementation of JAKis in hair loss disorders, including scarring and nonscarring alopecia, other than AA may also be possible and should be investigated. In the near future, JAKis may become one of the effective treatment options for various hair loss disorders.

**Conclusion**

In recent years, safety and efficacy of various JAKis have been demonstrated in previous trials of RA, myelofibrosis, and various autoimmune and hematologic diseases. Currently, there is yet to be an FDA-approved JAKi for dermatologic indication. However, based on greater knowledge in the pathogenesis of AA and molecular biochemistry, JAKis are emerging as a promising treatment for AA. In this group, tofacitinib, ruxolitinib, and baricitinib have been studied in AA and its variants with varying outcomes. These studies demonstrated exceptional efficacy of oral tofacitinib and ruxolitinib in severe AA or refractory AA but unfavorable efficacy for topical preparation. Many case reports also showed promising results of oral tofacitinib and ruxolitinib in recalcitrant cases. Furthermore, side effects of tofacitinib and ruxolitinib demonstrated in AA cases were mostly transient and nonsevere. These data suggest that JAKis could be a great addition to the dermatologist’s armament for tackling AA and a possible alternative in cases unresponsive to standard treatments. However, current evidence is based on case reports and uncontrolled trials. Well-controlled prospective studies are needed to determine long-term efficacy, safety, and cost-effectiveness, as well as to elucidate undisclosed mechanisms responsible for hair growth. As for baricitinib, available data are too sparse to conclude its efficacy and safety in AA. Further studies are needed for better understanding of baricitinib. Although JAKis are effective in various diseases, they, so far, have not been shown to provide long-term efficacy after stopping treatment in these diseases. Thus, JAKis might be more suitable for diseases with short duration or that are self-limited. Finally, from current evidence, JAKis are considered breakthrough treatment for AA.
Disclosure
The authors report no conflicts of interest in this work.

References


