Alopecia Universalis Treated With Tofacitinib: The Role of JAK/STAT Inhibitors in Hair Regrowth

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PRACTICE POINTS

- Janus kinase inhibitors target one of the cellular pathogeneses of alopecia areata.
- Janus kinase inhibitors may be an option for patients who have exhausted other treatment modalities for alopecia.

Alopecia universalis is alopecia areata (AA) with total-body involvement of hair loss. The disease progression is due to autoimmune T cells. We present a case of a patient with alopecia universalis who was successfully treated with tofacitinib.

Case Report

A 29-year-old otherwise-healthy woman presented to our clinic for treatment of alopecia universalis of 11 years’ duration that flared intermittently despite various treatments. Her medical history was unremarkable; however, she had a brother with alopecia universalis. She had no family history of any other autoimmune disorders. At the current presentation, the patient was known to have alopecia universalis with scant evidence of exclamation-point hairs on dermoscopy. Her treatment plan at this point consisted of intralesional triamcinolone to the active areas at 10 mg/mL every 4 weeks, plus clobetasol foam 0.05% at bedtime, minoxidil foam 5% at bedtime, and UVB brush therapy yet was successfully treated with tofacitinib.

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brush 3 times a week for 6 months before progressing to universalis type because of hair loss in the eyebrows and eyelashes. This treatment plan continued for 1 year with minimal improvement of the alopecia (Figure 1).

The patient was dissatisfied and wanted to discontinue therapy. Because these treatment options were exhausted with minimal benefit, the patient was then considered for treatment with tofacitinib. Baseline studies were performed, including purified protein derivative, complete blood cell count with differential, comprehensive metabolic panel, lipid profile, and liver function tests, all of which were within reference range. Insurance initially denied coverage of this therapy; a prior authorization was subsequently submitted and denied. A letter of medical necessity was then proposed, and approval for tofacitinib was finally granted.

The patient was started on tofacitinib 5 mg twice daily and was monitored every 2 months with a complete blood cell count, comprehensive metabolic panel, lipid panels, and liver function tests. She had a platelet count of 112,000/μL (reference range, 150,000–450,000/μL) at baseline, and continued monitoring revealed a platelet count of 83,000 after 7 months of treatment. This platelet abnormality was evaluated by a hematologist and found to be within reference range; subsequent monitoring did not reveal any abnormalities.

Initial hair growth on the scalp was diffuse with thin, white to light brown hairs in areas of hair loss at months 1 and 2, with progressive hair growth over months 3 to 7. Eyebrow hair growth was noted beginning at month 6. One year later, only hair regrowth occurred without any adverse events (Figure 2). After 5 years of treatment, the patient had a full head of thick hair (Figure 3). The tofacitinib dosage was 5 mg twice daily at initiation, and after 1 year increased to 10 mg twice daily. Her medical insurance subsequently changed and the regimen was adjusted to an 11-mg tablet and 5-mg tablet daily. She remained on this regimen with success.

**FIGURE 1.** A and B, A 29-year-old woman with alopecia universalis that did not respond to 1 year of treatment with intralesional triamcinolone, clobetasol foam, minoxidil foam 5%, and a UVB brush.

**FIGURE 2.** A and B, The patient’s alopecia universalis responded to tofacitinib 5 mg twice daily with hair regrowth after 1 year.
Comment

Use of JAK Inhibitors—Reports and studies have shed light on the use and efficacy of JAK inhibitors in AA (Table). Tofacitinib is a selective JAK1/3 inhibitor that predominantly inhibits JAK3 but also inhibits JAK1, albeit to a lesser degree, which interferes with the JAK/STAT (signal transducer and activator of transcription) cascade responsible for the production, differentiation, and function of various B cells, T cells, and natural killer cells. Although it was developed for the management of allograft rejection, tofacitinib has made headway in rheumatology for treatment of patients with moderate to severe rheumatoid arthritis who are unable to take or are not responding to methotrexate. Since 2014, tofacitinib has been introduced to the therapeutic realm for AA but is not yet approved by the US Food and Drug Administration.

In 2014, Craiglow and King reported use of tofacitinib with dosages beginning at 10 mg/d and increasing to 15 mg/d in a patient with alopecia universalis and psoriasis. Total hair regrowth was noted after 8 months of therapy. Xing et al described 3 patients treated with ruxolitinib, a JAK1/2 inhibitor approved for the treatment of myelofibrosis, at an oral dose of 20 mg twice daily with near-complete hair regrowth after 5 months of treatment. Biopsies from lesions at baseline and after 3 months of therapy revealed a reduction in perifollicular T cells and in HLA class I and II expression in follicles. A patient in Italy with essential thrombocythemia and concurrent alopecia universalis was enrolled in a clinical trial with ruxolitinib, and treated with 15 mg twice daily. After 10 months of treatment, the patient had progressive hair regrowth that was sustained for more than 50 months of therapy. Baricitinib, a JAK1/2 inhibitor, was used in a 17-year-old adolescent boy to assess efficacy of the drug in chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature syndrome. The patient also had longstanding patch-type AA that was resistant to treatment and progressed to an ophiasis pattern even though he was on immunosuppressive therapies. He was on 12 mg of prednisone daily at the start of therapy with baricitinib 7 mg daily initially. The baricitinib regimen was titrated up to 7 mg in the morning and 4 mg in the evening, with tapering of prednisone to 3 mg daily after 6 months of initiation. Within 3 months of therapy, hair regrowth occurred, with only a resultant patch on the occipital scalp that further resolved after 6 more months of therapy, resulting in total persistent hair growth. A 40-year-old woman with moderate to severe alopecia universalis was treated with tofacitinib 5 mg twice daily, revealing near-complete hair regrowth after 4 months of treatment; regrowth of eyebrows and eyelashes also was seen. However, discontinuation of treatment resulted in hair loss. Microarray analyses of biopsy specimens of lesioned sites at baseline revealed elevated IFN-γ and cytotoxic T cell-level signatures that subsequently decreased—albeit not to normal control levels—after 4 weeks of treatment. Being that IFN-γ receptors mediate their effects through JAK1/2, JAK1/3, tofacitinib, ruxolitinib, and baricitinib seem to be in sync with the immunopathogenesis of AA and thus may be the therapy of choice in the near future.

A recent retrospective study assessing response to tofacitinib in adults with AA (>40% hair loss), alopecia totalis, alopecia universalis, and stable or progressive diseases for at least 6 months determined a clinical response in 50 of 65 (77%) patients, with 13 patients exhibiting a complete response. Patients in this study were started on tofacitinib 5 mg twice daily with the addition of adjuvant pulsed prednisone (300 mg once monthly for 3 doses) with or without doubled dosing of tofacitinib if they had a halt in hair regrowth. This study demonstrated some benefit when pulsed prednisone was combined with the daily tofacitinib therapy. However, the study emphasized the importance of maintenance therapy, as 8 patients...
experienced hair loss with discontinuation after previously having hair regrowth; 5 (63%) of these patients experienced regrowth with augmentation of dosing or addition of adjuvant therapy.10

Another group of investigators assessed the efficacy of tofacitinib 5 mg in 13 adolescents aged 12 to 17 years, most with alopecia universalis (46% [6/13]); 10 of 13 (77%) patients responded to treatment with a mean duration of 6.5 months. The patients who had alopecia totalis and alopecia universalis for more than 10 years were poor responders to tofacitinib, and in fact, 1 of 13 (33%) patients in the study who did not respond to therapy had disease for 12 years.11 Therefore, starting tofacitinib either long-term or intermittently should be considered in children diagnosed early with severe AA, alopecia totalis, or alopecia universalis to prevent irreversible hair loss or progressive disease12,13; however, further data are required to assess efficacy and long-term benefits of this type of regimen.

Safety Profile—Widespread use of a medication is determined not only by its efficacy profile but also its safety profile. With any medication that exhibits immunosuppressive effects, adverse events must be considered and thoroughly discussed with patients and their primary care physicians. A prospective, open-label, single-arm trial examined the efficacy and safety of tofacitinib 5 mg twice daily in the treatment of AA and its more severe forms over 3 months.12 Of the 66 patients who completed the trial, 64% (42/66) exhibited a positive response to tofacitinib. Relapse was noted in 8.5 weeks after discontinuation of tofacitinib, reiterating the potential need for a maintenance regimen. In this study, 25.8% (17/66) of patients experienced infections as adverse events including (in decreasing order) upper respiratory tract infections, urinary tract infections, herpes zoster, conjunctivitis, bronchitis, mononucleosis, and paronychia. No reports of new or recurrent malignancy were noted.

### JAK Inhibitors Used to Treat Alopecia Areata and Its Variants

<table>
<thead>
<tr>
<th>Reference (year)</th>
<th>No. of patients</th>
<th>Treatment duration</th>
<th>JAK inhibitor dosage</th>
<th>Hair regrowth</th>
<th>Notes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Craiglow and King5 (2014)</td>
<td>1</td>
<td>8 mo</td>
<td>Tofacitinib 10 mg QD, increased to 15 mg QD</td>
<td>Total hair regrowth</td>
<td></td>
</tr>
<tr>
<td>Xing et al6 (2014)</td>
<td>3</td>
<td>5 mo</td>
<td>Ruxolitinib 20 mg BID</td>
<td>Near-complete hair regrowth</td>
<td></td>
</tr>
<tr>
<td>Pieri et al7 (2015)</td>
<td>1</td>
<td>10 mo</td>
<td>Ruxolitinib 15 mg BID</td>
<td>Progressive hair regrowth</td>
<td>Results sustained for 50 mo on therapy</td>
</tr>
<tr>
<td>Jabbari et al8 (2015)</td>
<td>1</td>
<td>6 mo</td>
<td>Baricitinib 7 mg QD, increased to 7 mg QAM and 4 mg QPM</td>
<td>Total hair regrowth</td>
<td>Patient was on 12 mg of prednisone QD at the start of therapy and tapered off to 3 mg QD at 6 mo</td>
</tr>
<tr>
<td>Jabbari et al9 (2016)</td>
<td>1</td>
<td>4 mo</td>
<td>Tofacitinib 5 mg BID</td>
<td>Near-complete hair regrowth</td>
<td>DC of treatment resulted in hair loss</td>
</tr>
<tr>
<td>Liu et al10 (2017)</td>
<td>65</td>
<td>12 mo median duration</td>
<td>Tofacitinib 5 mg BID or 10 mg BID</td>
<td>Hair regrowth in 77% of all patients (50/66) and complete hair regrowth in 20% (13/65) of patients</td>
<td>Patients who received 5 mg BID also got adjuvant pulsed prednisone 300 mg once monthly for 3 doses; DC of treatment in 8 patients resulted in hair loss, but subsequent augmentation of dosing caused hair regrowth in 5 of 8 (63%) patients</td>
</tr>
<tr>
<td>Craiglow et al11 (2017)</td>
<td>13</td>
<td>6.5 mo on average</td>
<td>Tofacitinib 5 mg BID</td>
<td>10 patients had hair regrowth</td>
<td>Patients were teenagers aged 12–17 y; the poor responders were patients with AT and AU for &gt;10 y</td>
</tr>
<tr>
<td>Current report</td>
<td>1</td>
<td>5 y</td>
<td>Tofacitinib 5 mg BID, increased to 16 mg QD</td>
<td>Total hair regrowth</td>
<td></td>
</tr>
</tbody>
</table>

**Abbreviations:** AT, alopecia totalis; AU, alopecia universalis; BID, twice daily; DC, discontinuation; JAK, Janus kinase; QAM, every morning; QD, daily; QPM, every evening.
REFERENCES

Other more constitutional adverse events were noted including headaches, abdominal pain, acne, diarrhea, fatigue, nausea, pruritus, hot flashes, cough, folliculitis, weight gain, dry eyes, and amenorrhea. One patient with a pre-existing liver condition experienced transaminitis that resolved with weight loss. There also were noted increases in low- and high-density lipoprotein levels.12 Our patient with baseline thrombocytopenia had mild drops in platelet count that subsequently stabilized and did not result in any bleeding abnormalities.

Duration of Therapy—Tofacitinib has demonstrated some preliminary success in the management of AA, but the appropriate duration of treatment requires further investigation. Our patient has been on tofacitinib for more than 5 years. She started at a total dosage of 10 mg/d, which increased to 16 mg/d. Initial dosing with maintenance regimens needs to be established for further widespread use to maximize benefit and minimize harm.

At what point do we decide to continue or stop treatment in patients who do not respond as expected or plateau? This is another critical question; our patient had periods of slowed growth and plateauing, but knowing the risks and benefits, she continued the medication and eventually experienced improved regrowth again.

Conclusion
Throughout the literature and in our patient, tofacitinib has demonstrated efficacy in treating AA. When other conventional therapies have failed, use of tofacitinib should be considered.