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Balance of tofacitinib efficacy and disease flare in the treatment of alopecia universalis: A case report and review of the literature

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Key words: alopecia universalis; Janus kinase inhibition; tofacitinib.

INTRODUCTION

Alopecia areata (AA) is one of the most prevalent autoimmune diseases with 1.7% lifetime risk.[1] AA is a nonscarring hair loss, typified by alopecic patches that can encompass the entire scalp in alopecia totalis (AT) or body in alopecia universalis (AU). The cause of AA is multifactorial, including an immune-mediated destruction of hair follicles[2] in conjunction with genetic predisposition.[3] There are currently no US Food and Drug Administration–approved treatments for alopecia areata, and treatment regimens are empiric, although topical, intralesional, and systemic steroids are commonly offered.[4] Improvement of AA with Janus kinase (JAK) inhibitors was first reported in 2014 by Craiglow and King[5] in a patient with AU and psoriasis treated with tofacitinib, a selective JAK 1/3 inhibitor, with full hair regrowth by 8 months. Additional cases have reported similar findings; however, less emphasis has been placed on characterizing nonresponders and transient efficacy. Here we report a case notable for transient efficacy of tofacitinib in a patient with AU.

Abbreviations used:

AA: alopecia areata
AT: alopecia totalis
AU: alopecia universalis
JAK: Janus kinase
IFN: interferon

CASE REPORT

A 17-year-old boy with 10-year history of AA and progression to AU 3 years prior, was referred for interest in tofacitinib treatment. Previous treatments included topical and intralesional steroids, topical minoxidil, prednisone, and methotrexate without significant improvement. Family history included a mother with AU. On examination, the patient had tattooed black macules on the scalp without hair (Fig 1) and sparse eyebrows, eyelashes, and body hair.

The patient was started on tofacitinib, 5 mg twice daily. At 2 months, vellus hair regrowth was noted, with fine regrowth of eyelashes and eyebrows, as well as improved mood and self-confidence, and by 4 months, he had significant regrowth (Fig 2). The patient had an episode of herpes zoster during the fifth month, and tofacitinib was discontinued for 3 days. At 6 months, scalp regrowth continued to its maximal point (Fig 2). At 8 months, a new alopecic patch appeared on the left parietal scalp in an area of previous regrowth, which the patient found distressing (Fig 3). He was initiated on escitalopram oxalate, 10 mg, as well as clobetasol 0.05% and minoxidil 5% solutions daily. At 8.5 months, continual expansion of alopecia prompted an increase in tofacitinib to 15 mg/d and excimer laser therapy twice weekly. At 9.5 months, there was continued expansion of alopecic patches (Fig 4). At 10 months, the patient

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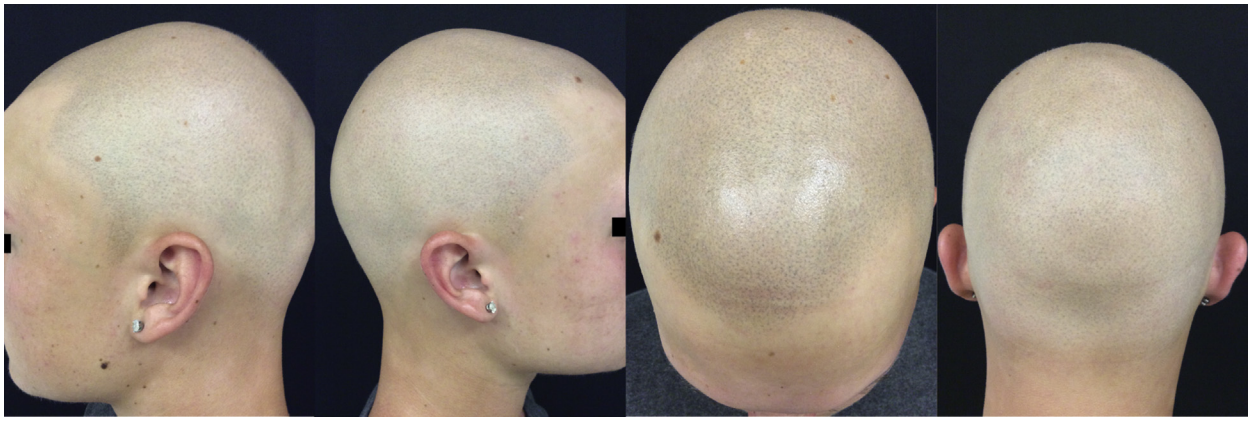

Fig 1. Representative scalp photographs at baseline with scalp tattoos that mimic individual hairs but no visible hair growth.

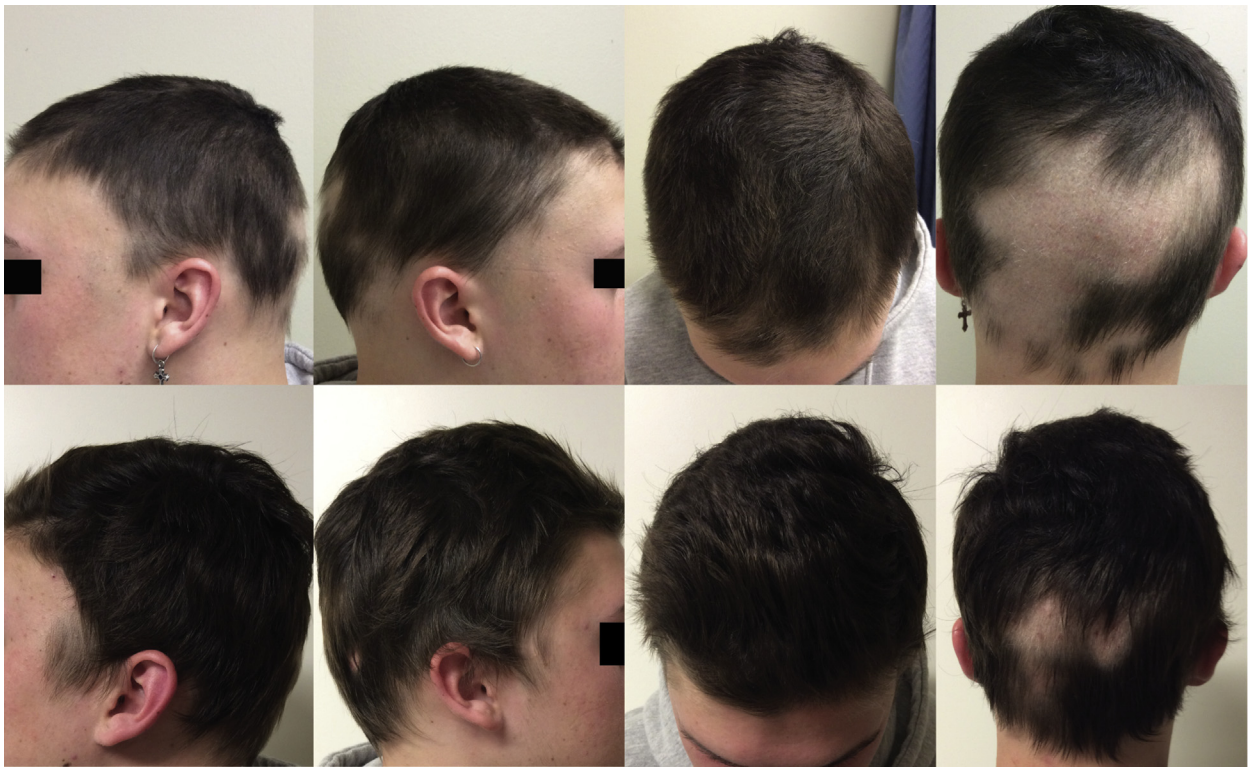

Fig 2. Representative scalp photographs after 4 and 6 months of treatment with tofacitinib, 10 mg/d. At 4 months (first row), prominent pigmented hair growth and persistent alopecia patches visible on the occipital scalp. At 6 months (second row), continued pigmented hair growth visible including over the occipital scalp.

reported that he had self-discontinued tofacitinib because of worsening alopecia, disappointment, and belief that the medication was not working. He subsequently had expansion of alopecia of the bilateral parietal, frontal, and occipital scalp.

DISCUSSION

AA is characterized by hair follicle damage by autoreactive $CD8^+$ T cells. Upregulation of JAK-STAT–dependent cytokines, interferon (IFN)-γ, and interleukin (IL)-15 drive proliferation of autoreactive T cells, necessary for AA induction.[2] Tofacitinib blocks IL-15–induced upregulation of IFN-γ expression, reducing cytotoxic T cells and dermal IFN response, preventing AA development. JAK-STAT inhibition in midtelogen activates anagen reentry and hair follicle progenitor cells.[6] JAK inhibitors have been reported in the literature as

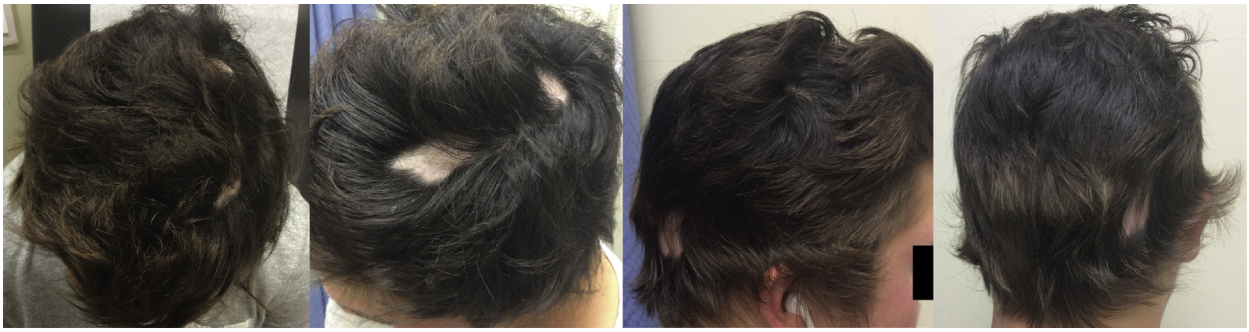

Fig 3. Representative scalp photographs at 8 months of treatment. At 8 months, new patches of alopecia were noted on the left parietal scalp in an area of previous regrowth.

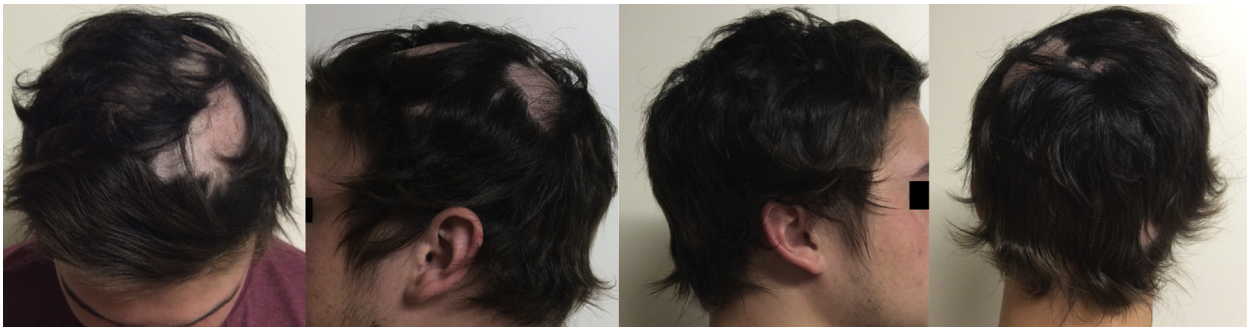

Fig 4. Representative scalp photographs at 9.5 months of treatment. At 9.5 months, there was expansion of alopecic patches on parietal and frontal scalp despite treatment with increased tofacitinib dose, 15 mg/d.

efficacious for alopecia.[7] However, there has been less emphasis on nonresponders and transient efficacy.

Nonresponders have been noted in a few studies. Based on the systematic literature review by Shreberk-Hassidim et al, Dhayalan and King reported no hair growth in an AU patient treated with tofacitinib, 10 mg/d for 2 months, then 15 mg/d for 4 months.[7] Crispin et al evaluated tofacitinib, 10 mg/d for 3 months, in 66 patients, reporting 24 nonresponders ($\leq$5% Severity of Alopecia Tool score improvement), which gene analysis accurately distinguished from significant and slow responders.[7] Relapse in significant responders occurred at median of 8.5 weeks after discontinuation. Mackay-Wiggan et al studied ruxolitinib, 40 mg/d for 3 to 6 months in 12 patients, reporting 3 patients with less than 50% regrowth.[7] Gene expression profiling of baseline and 12-week biopsies found cytotoxic T-lymphocyte and IFN signature scores distinguishing eventual nonresponders from responders. These finds suggest alternative inflammatory etiologies of hair loss in nonresponders.

There are few reports on transient efficacy of tofacitinib. A retrospective study of 90 patients treated with tofacitinib, 10 mg/d by Liu et al reported relapse in 5 responders with subsequent hair regrowth using increased tofacitinib, 20 mg/d, or adjuvant prednisone, 300 mg/mo, for 3 months.[7] A retrospective study of 13 adolescents treated with tofacitinib, 10 mg/d for an average of 6.5 months reported 3 patients experiencing minimal growth.[7] One responder with complete regrowth by 5 months developed alopecic patches, but had regrowth after dose increase to 15 mg/d. Another case reported a 51-year-old man with AU treated with tofacitinib, 10 mg/d, and methotrexate, 15 mg/wk for retinal vasculitis, who achieved growth of short terminal pigmented hair at 3 months,[8] which subsequently disappeared after 1 month leading to complete alopecia. Waning efficacy demonstrates that AA suppression by tofacitinib is an active process that if weaker than the disease process, may not allow for stable regrowth.

Our case highlights the scenario of transient tofacitinib efficacy, with rapid and near-complete regrowth by 6 months of treatment followed by disease flare and loss of regrown hair at 8 months. We speculate that as in previous cases, increased dose or adjuvant therapy might be necessary during periods of disease flare for continued remission. As

such, our patient's tofacitinib dose was increased to 15 mg/d, and excimer therapy was initiated, although worsening hair loss at 6 weeks after dose increase led to the patient self-discontinuing tofacitinib.

Alopecia is a dermatologic disorder associated with poor quality of life and high rates of depression and anxiety.[9,10] AA frequently has onset during adolescence, which can be a vulnerable and self-conscious time, leading to social withdrawal. Response to treatment can improve self-esteem and mood. Hair loss may precipitate stress, as experienced by our patient, which consequently worsens anxiety and depression.

Although tofacitinib is a promising therapeutic option for AA, its efficacy varies with disease severity, and patients should be informed early on of possible decreased treatment response and need for dosage increase. Analysis of gene expression at baseline may help identify slow responders and nonresponders to avoid disappointment associated with delayed results or nonresponse. Studies on gene expression profiles are needed to identify patients who might require stronger dose or adjuvant therapy. In addition, providers should be sensitive to the waxing and waning alopecia disease progression associated with treatment and the effects on patients' anxiety and quality of life.

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