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Brittany G Craiglow, Brett A King

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Killing Two Birds with One Stone: Oral Tofacitinib Reverses Alopecia Universalis in a Patient with Plaque Psoriasis

Brittany G. Craiglow, MD and Brett A. King, MD, PhD

Department of Dermatology, Yale University School of Medicine, New Haven, CT

Address correspondence to Brett King, MD, PhD, Department of Dermatology, Yale University School of Medicine, PO Box 208059, New Haven, CT 06520, or email brett.king@yale.edu

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To the Editor:

The patient is a 25-year-old male who presented for evaluation and management of plaque psoriasis, which had begun five years earlier. Treatment with topical corticosteroids had not been particularly helpful, and due to increasing body surface area

involvement of psoriasis, systemic therapy with adalimumab had been initiated one year before. While clearing of psoriasis was experienced early in the course of adalimumab, the improvement faded. In addition to psoriasis, the patient reported a history of alopecia areata (AA) beginning around age two years, which progressed to alopecia universalis (AU) by age 18 years. Treatment of the alopecia with topical corticosteroids had not been effective, and he had received no other therapy for it. He had no family history of either psoriasis or alopecia areata, and his past medical history was otherwise unremarkable.

On examination, the patient demonstrated numerous well-marginated pink-red scaly plaques on the scalp, torso, and elbows. He had no eyebrows, eyelashes (Figure 1a), or facial hair and no hair on his arms, legs, torso, or in the axillae or groin. Notably, the only prominent hair growth on the scalp was within areas of psoriasis (Figure 2a), reminiscent of hair growth that occurs in areas of irritant contact dermatitis generated by topical anthralin (Schmoeckel *et al.*, 1979).

As treatment options for the patient were considered, we sought a therapeutic agent that could potentially target both psoriasis and AU simultaneously. We identified tofacitinib as a promising agent and began treatment.

Tofacitinib citrate (Xeljanz®), formerly CP-690550 and tasocitinib, is a novel small molecule selective Janus kinase 1/3 (JAK 1/3) inhibitor that was FDA-approved in late 2012 for the treatment of moderate to severe rheumatoid arthritis (RA). JAK inhibition

has myriad effects on T-lymphocytes, and therefore it is not surprising that this medication may be useful in the treatment of many inflammatory diseases (Pesu *et al.*, 2005). Indeed, both oral and topical formulations of tofacitinib have been demonstrated to be safe and effective for the treatment of plaque psoriasis (Boy *et al.*, 2009; Mamolo *et al.*, 2013; Papp *et al.*, 2012; Ports *et al.*, 2013; Strober *et al.*, 2013), with additional clinical trials for psoriasis and other inflammatory disorders now underway (clinicaltrials.gov). In the case of psoriasis, increased interleukin-15 (IL-15) expression is observed in lesional skin and may lead to epidermal hyperproliferation via keratinocyte apoptotic resistance (Ruckert *et al.*, 2000). Tofacitinib, which abrogates IL-15 signaling (Johnston *et al.*, 1995), might therefore be effective in psoriasis by normalizing keratinocyte apoptosis (Ruckert *et al.*, 2000).

In a murine model of AA, a Type I cytotoxic pathway has been demonstrated to be responsible for the disease state, with NKG2D-expressing CD8+ cytolytic T-lymphocytes identified as both necessary and sufficient for induction of disease. Upregulation of IL-15 in the outer root sheath of the hair follicle activates cytolytic T-lymphocytes, which in turn produce IFNγ, leading to activation of the hair follicle and upregulation of IL-15, NKG2D ligands, and MHC molecules, all of which target the hair follicle for attack (Jabbari *et al.*, 2013). The same group has demonstrated that systemic treatment with the JAK inhibitors tofacitinib and ruxolitinib (a JAK 1/2 inhibitor) prevents the onset of AA in grafted AA mice (Jabbari *et al.*, 2012, Dai *et al.*, 2012) and that topical treatment reverses AA in these mice (Jabbari *et al.*, 2013). JAK 1/3 signaling mediates IL-15 activation of T-lymphocytes (Ghoreschi *et al.*, 2011), explaining the success of these

therapies.

After two months of tofacitinib 5 mg twice daily (the approved RA dose), there was some improvement in psoriasis with partial hair regrowth on the scalp (Figure 2b) and face. Given that higher doses of tofacitinib (up to 15 mg twice daily) have been shown to be more effective in psoriasis (Papp *et al.*, 2012), the dose was increased to 10 mg in the morning and 5 mg at night. After three more months of therapy, there was complete regrowth of the scalp hair (Figure 2c) along with significant regrowth of eyebrows, eyelashes, and facial hair along with axillary and pubic hair. After 8 months of therapy, there was full regrowth of hair at all body sites (Figures 1b and 2d), except for the arms and legs, locations where the patient reports never having more than sparse hair growth prior to the onset of AU. Improvement of the psoriasis has lagged behind reversal of the alopecia, which is likely dose-related (Papp *et al.*, 2012). While we considered increasing the dose of tofacitinib, the patient is so pleased with the regrowth of his hair (and is not particularly bothered by the remaining psoriasis) that he has chosen to continue at the present dose. The patient has tolerated tofacitinib without subjective complaints. Laboratory monitoring has revealed no abnormalities in serum creatinine, electrolytes, glucose, complete blood count, hepatic function, or lipids.

To our knowledge, this is the first report of effective pathogenesis-based therapy for a patient with alopecia universalis. While the results in this patient are provocative, a clinical trial would more fully and systematically address the safety and efficacy of tofacitinib and other JAK inhibitors in the treatment of AA and its variants. Aptly, an

open label pilot study evaluating the efficacy of ruxolitinib in moderate to severe AA is currently underway (Mackay-Wiggan, 2014). Given the potential for serious adverse effects from oral JAK inhibitors, it would be particularly useful to explore the use of topical formulations for these disorders.

The era of biological therapy has greatly enhanced the ability to make nuanced therapeutic decisions. With every new agent, more thoughtful treatment algorithms become possible, permitting better treatment of complex patients with multiple comorbidities. As in the case presented herein, seemingly disparate diseases with different pathomechanisms may be affected positively by a single agent. This case highlights the interplay between advances in basic science and therapeutics and provides a compelling example of the ways in which an increasingly complex understanding of medicine and ingenuity in treatment benefit patients.

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Figure legends:

Figure 1. Eyebrows and eyelashes at baseline (a) and after 8 months of therapy (b).

Figure 2. Representative photographs of patient's scalp at intervals of therapy.

2a. Scalp of patient at baseline. The only prominent hair growth is seen within psoriatic plaques.

2b. Scalp after 2 months of therapy. Prominent hair growth is now visible outside of areas affected by psoriasis. Psoriasis is beginning to recede in areas.

2c. Scalp after 5 months of therapy. There is near complete regrowth of scalp hair. Psoriasis continues to be present but is significantly improved compared to baseline.

2d. Scalp after 8 months of therapy. There is complete regrowth of scalp hair.