Transient efficacy of Tofacitinib in Alopecia Areata Universalis

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Transient Efficacy of Tofacitinib in Alopecia Areata Universalis

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Key Words
Alopecia areata universalis · Tofacitinib · Janus kinase inhibitors

Abstract
Alopecia areata is a common autoimmune disorder that targets hair follicles. Swarms of lymphocytes surround the basis of the follicles, inducing loss of pigmented terminal hair and subsequently inhibit further hair growth. Depending on the extent of involvement, alopecia areata can be associated with a dramatic reduction of quality of life. Currently, no targeted treatment option is available, and topical immune therapies or immunosuppressive drugs are typically used with mixed success. Recently, several cases of alopecia areata responding to Janus kinase inhibitors were published. Here, we report on a businessman with alopecia areata universalis who was treated with tofacitinib. We observed initial signs of hair regrowth in the same timeframe as previously reported, but efficacy quickly waned again, leading to renewed effluvium. Thus, even though tofacitinib and ruxolitinib are a promising new treatment option, we have yet to learn more about their potential role in each particular patient’s individual treatment strategy.

Introduction
Alopecia areata (AA), a nonscarring type of hair loss, is the most prevalent autoimmune disease, with a lifetime prevalence of 1.7\% [1, 2]. Men and women are equally affected, and onset of the disease can occur at any age; however, most cases start before the age of 30 [3]. Fifty percent of children and adolescents with AA suffer from depression [4]. Autoimmune diseases such as vitiligo, thyroid disease and atopic diseases have been associated with AA [5]. The genetic architecture has also been described [6]. A high concordance rate among
monzygotic twins was reported [7, 8], and a positive family history is linked to AA [9–11]. Additionally, human leukocyte antigen (HLA)-DQB1, HLA-DRB1, HLA-A, HLA-B, HLA-C and also the genes NOTCH4, MICA, PTPN22 and AIRE were found to be associated with AA [2, 12]. The first genome-wide association study found 8 loci (table 1) with genome-wide significance containing multiple genes involved in the adaptive T cell-driven immune response [2]. The current view is that both genetic and immune factors contribute to the development of AA (fig. 1). In addition, much less well-defined environmental and psychologic elements are sure to have some influence as well.

A Cochrane review analyzing 17 randomized controlled trials concluded that there is currently no effective evidence-based treatment for AA. Even though topical minoxidil, cyclosporine, corticosteroids (as well as systemic corticosteroids) and photodynamic therapy are used, there is no firm evidence of superiority compared to placebo [13]. However, in daily clinical use, all these drugs are used with apparent success. Recently, Suarez-Farinas et al. [14] performed microarray and RT-PCR of 27 lesional and 17 nonlesional samples of patients with AA. It was shown that TH1, TH2, and IL-23 cytokine were increased, while TH17/TH22 skewing was lacking [14]. Additionally, also ustekinumab, a monoclonal IL-12/23 inhibitor, is of interest as a potential treatment of AA. There have been case reports that ustekinumab causes AA [15–17], but in contrast, successful treatments with significant increase of hair growth were reported [18, 19].

The possibility of reversal of AA by Janus kinase (JAK) inhibitors was successfully shown in the murine model [20]. Additionally, Craiglow and King [21] published a case of a 25-year-old patient with psoriasis vulgaris and alopecia universalis, a type of AA in which complete loss of hair of the entire body is observed. After treatment with tofacitinib, a JAK1/3 inhibitor approved for the treatment of rheumatoid arthritis, complete regrowth of hair was observed [21]. Also, one case from Germany responded well to tofacitinib (U. Mrowietz, personal communication). In another case report, 3 patients suffering from AA were successfully treated with ruxolitinib, a JAK1/2 inhibitor approved for myelofibrosis [20].

Case

A 51-year-old businessman with alopecia universalis presented to our clinic. His past medical history revealed a bilateral chronic retinal vasculitis and uveitis, for which he had been treated in the past with various drugs such as methotrexate, azathioprine, oral prednisolone and infliximab. Two years before, while receiving infliximab and azathioprine, sudden loss of hair had occurred on the temples, and drug-induced AA was suspected. Even though the drug treatment was stopped, the AA worsened. Four months later, the retinal vasculitis showed progression of disease as well, so infliximab and azathioprine were started again. A dermatologic consultation was sought. Subsequently, treatment with topical and oral steroids, followed by topical diphenylcyclopropenone as well as oral methotrexate (up to 30 mg per week) was initiated. However, no regrowth of hair was observed after 6 months.

Upon his first consultation in our clinic, a skin biopsy was performed on the scalp. A biopsy confirmed sparse lymphocytic infiltrates along nonsclerotic fibrous tracts extending along the site of previous follicles. The diagnosis of a nonfibrosing AA was confirmed. Compassionate use of tofacitinib 5 mg twice daily was initiated. Methotrexate was continued at 15 mg per week. The scalp remained unchanged for 2 months (fig. 2a), but after 3 months of treatment, growth of short terminal pigmented hair was detected (fig. 2b). These, however, disappeared again within a single month, resulting in renewed complete alopecia (fig. 2c).
Discussion

The efficacy of tofacitinib has been suggested by murine experiments and by one case presentation \([20, 21]\). Tofacitinib citrate (Xeljanz®) abrogates IL-15 signaling \([22]\) and thus mediates IL-15 activation of lymphocytes \([14]\). Even though the initial clinical results were promising, the efficacy of tofacitinib waned again in our patient. This was even more striking when considering that the patient had additional immunosuppression by methotrexate for his retinal vasculitis. Notably, methotrexate monotherapy has been shown to be a safe treatment option for AA as well \([15]\). Another potential reason for treatment failure could have been the presence of antibodies specific for hair follicles \([23, 24]\); however, we were unable to measure and rule them out.

The clinical observation in this patient could be interpreted as follows: suppression of AA by tofacitinib is an active process that, if too weak, may not tip the balance towards stable hair regrowth but instead allow a reversion to a completely alopecic state. Although here we report only on a single case with all its limitations, it will be interesting to analyze the outcome of randomized clinical trials, especially in patients not showing efficacy to tofacitinib. Also, our observation may prompt the question whether combinations of immunosuppressive drugs potentiate or inhibit each other in AA.

Statement of Ethics

The authors state that the patient gave informed consent to have his photographs published.

Disclosure Statement

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Table 1. Loci with genome-wide association signals in AA

| Chromosome | Immune genes associated with genome-wide signals |
|------------|-------------------------------------------------|
| 2q33.2     | CTLA4 gene encodes for CD152, an immune checkpoint that downregulates T cell responses |
| 4q27       | IL2/IL21 locus both promote CD8+ T cell function |
| 6p21.32    | HLA super locus which encodes for the histocompatibility leukocyte antigens. Especially, HLA class II loci have shown a strong association with AA |
| 6q25.1     | Cytomegalovirus UL16-binding protein gene cluster (ULBP3) encodes for NKG2D ligand 3 and retinoic acid early transcript 1L protein, expressed especially on natural killer cells, but also on human CD8+ cytotoxic T cells and in some cases on CD4+ T cells |
| 9q31.1     | STX17 (Syntaxin-17) is a member of the soluble N-ethylmaleimide-sensitive factor-attachment protein receptors (SNARE) superfamily, which is known for vesicular trafficking and membrane fusion |
| 10p15.1    | IL2RA, also referred to as CD25, is associated with several autoimmune diseases and acts as a regulatory T cell marker |
| 11q13      | PRDX5 (Mitochondrial peroxiredoxin-5) is an oxidative stress-associated protein expressed in hair follicles and induces the elimination of DNA-damaging reactive oxygen species |
| 12q13      | Eos locus encodes for zinc finger proteins that can silence CD4+ regulatory T cells through mediation of the Foxp3-dependent gene [2, 20, 22] |
Fig. 1. Genes and immunologic factors contributing to the pathogenesis of AA.

Immune-related genes:
- HLA-superlocus
- IL2, IL2RA
- CTLA4, PTPN22
- Eos, ULBP3, MICA
- others

Hair/Skin-related genes:
- STX17
- PDX5
- NOTCH4
- others

Immune dynamics:
- T cell priming
- HLA class I expression
- ICAM

Cytokines:
- IL-1α/β, IL-2
- IFN-γ, TNF-α
- IL-4, IL-10, BAFF
- MIF

Fig. 2. a Unchanged state of alopecia areata universalis even after 2 months of therapy. b shows the regrowth of short terminal pigmented hair after 3 months, while c depicts the unfortunate relapse after 6 months of tofacitinib therapy.