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Commentary

Translational Positioning of Janus Kinase (JAK) Inhibitors in Alopecia Areata

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Alopecia areata (AA) is an autoimmune disease due to T cell attack of the hair follicles and breakdown of their immune privilege resulting in transient non-scarring hair loss which may last from weeks to decades and which presents an enormous psychological burden. As so far no FDA approved successful treatments for AA are available, new hope and light arose on the horizon with the recently published genome wide association studies in AA patients revealing new molecular pathways disrupted in AA including autophagy/apoptosis, transforming growth factor beta/Tregs and JAK (Janus family of non-receptor protein tyrosine kinase) signaling (Petukhova et al., 2010; Betz et al., 2015). Thus, today it is assumed that CD8 + NKG2D + T effector memory cells mediate alopecia areata in part through Janus kinase (JAK) signaling and that alopecia areata might be treated with JAK inhibitors. This assumption has been supported by clinical use of JAK inhibitors within a clinical study setting (Xing et al., 2014) or observed as a "side effect", when JAK inhibitor treatment of another underlying disease resulted in regrowth of longstanding patchy or universal alopecia areata (Craiglow and King, 2014; Pieri et al, 2015). Xing et al., 2014 demonstrated that the interferon-γ (IFNγ)-signaling pathway is upregulated in AA-lesional skin, and that the use of JAK inhibitors was able to reverse symptoms of the disorder in mice and in three humans with AA. While different groups (Craiglow and King, 2014; Pieri et al, 2015; Higgins et al, 2015) reported successful use of ruxolitinib, a JAK1/2 inhibitor licensed for treating myelofibrosis, others reported successful use of the JAK 1/3 inhibitor tofacitinib in AA while using it for treating psoriasis (Craiglow and King, 2014).

In this issue of *EBioMedicine*, Jabbari et al. followed up on hair growth observed in a patient under baricitinib therapy, also a JAK1/2 inhibitor and studied JAK inhibitor action in the C3H/HeJ graft-recipient mouse model of AA (Jabbari et al., 2015). Under JAK inhibitor treatment, CD8 + cell infiltrates and MHC class I and II expressions were markedly reduced in C3H/HeJ mice grafted with alopecic skin, both in a preventive and a therapeutic setting. In addition, gene expression profiling using the Alopecia Areata Disease Activity Index (ALADIN) biomarker for response to treatment confirmed the assumed normalization of the IFN-gamma gene expression signature. The approach of Jabbari et al. represents an excellent model for translational work, where a specific clinical observation made in a special patient is complemented with mechanistic work, which nicely allows to link macroscopic appearance, immunohistochemistry and gene expression profiles with the current idea of how JAK inhibitors could be beneficial in AA (Jabbari et al., 2015).

However, all euphoria should not let forget that JAK inhibitors inhibit multiple pathogenic pathways simultaneously. A broad spectrum of side effects already limits their use in the different licensed indications. Similarly, clinical studies on response rates in larger groups of patients will have to take into account the heterogeneity among AA patients. Maintenance of hair growth and relapse rates after cessation of therapy will have to be monitored carefully. Also, we have to be very aware of the fact that despite its tremendous psychosocial burden, AA is a benign lifelong genetic predisposition, with one third of AA patients being affected before 30 years of age. Safety aspects will have to be carefully considered especially in this young population. With this regard, the small molecule JAK inhibitors do not only offer advantages for effective oral delivery, but are also highly interesting candidate molecules for topical treatment. While overall penetration rates in skin especially via the transfollicular route should not be a problem, a focus of research should be put on ways to increase follicular penetration and reduce systemic absorption. Incorporation in particle-based formulations or even the design of functionalized nanocarriers capable of targeting inflammatory infiltrates along the hair follicle could be one option for future developments in AA management strategies. Such targeted delivery may help increase local drug concentration and efficacy with reduced systemic side-effects.

This translational exemplary research may pave the way to further target-oriented strategies based on insights in the disease pathogenesis rather than empiric observation, even in such complex autoimmune mediated diseases as alopecia areata.

Conflict of Interest

The authors declare no conflicts of interest.

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