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LETTER TO THE EDITOR

Leflunomide: an unlikely trigger and mechanistically a beneficial drug for alopecia areata

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We read with great interest a recent article by Koller et al. [1] and we would like to highlight some points which sufficiently show that it is unlikely that initiation of leflunomide caused alopecia areata (AA) in the given case. Moreover, this drug has a potential use in alopecia areata and we feel that research into its use may be quelled by such cases that presume correlation with causation. Firstly, drug-induced alopecia areata is very rare. Most cases of drug-induced hairloss reported in literature have been associated with the use of chemotherapeutic drugs and are either anagen effluvium or telogen effluvium or non-specific drug-induced alopecia. [2, 3] Perhaps the only drugs with substantial evidence causing AA are immune checkpoint inhibitors that induce activation of CD4 and CD8 cells targeting tumor cells, which can cross react with cutaneous antigens such as melanogenesis-associated autoantigens, resulting in an inflammatory processes and immune-mediated adverse events such as AA and vitiligo. [4] Also, cases of AA occurring during anti-tumor necrosis factor (TNF) treatment have been reported in literature but the imputability of TNF blockers in the causation of AA is debatable at best as per a national multicenter prospective study [5]. Moreover the report lacks any clinical image or histopathological finding supporting the diagnosis of AA. Thirdly, the case correlates the onset of AA after nearly 9 months of starting leflunomide making it highly unlikely as the causative agent and also the resolution of AA may be explained by the increased dose of methotrexate (which is known to work in AA) rather than the presumed discontinuation of leflunomide. [6] Lastly, the rheumatology clinic at our hospital has approximately 400 patients in a year who are on leflunomide for varying durations of time and we have not seen a single referred case for alopecia areata which largely negates the tenuous link between the drug and AA in our experience.

We feel that AA is more likely an autoimmune manifestation incidentally associated in a predisposed patient with chronic immune-mediated inflammatory disease (rheumatoid arthritis in this case) rather than a leflunomide-induced autoimmune adverse effect. Also, our published work on the successful use of leflunomide in a case of treatment refractory and extensive AA suggests that it is a novel targeted therapy for AA. [7] Although the pathogenesis of AA is still being explored, the JAK-STAT pathway has been shown to play a central role by determining the interaction of the hair follicle and the CD8+ T cells downstream the complex interplay of cytokines (such as IFN-γ and IL-15) involved in the pathogenesis of AA, and leflunomide modulates this pathway [8, 9]. Moreover, leflunomide increases the level of TGF-β, which can help in restoration of immune privilege (IP) and it inhibits immune cell migration (by acting on CXCL-1 and CD44). [10] The drug also stimulates regulatory cells and progressively removes autoimmune lymphocytes and causes a shift from Th1 to Th2 cells. [11, 12] Also, animal studies in Dundee experimental bald rats have also shown that leflunomide can promote limited hair growth. [13] Thus, leflunomide inhibits the key steps involved in the pathogenesis of AA and these may explain the favorable response seen in our singular case who had failed all therapeutic agents. While we have been using this drug in select recalcitrant cases of AA with consistently heartening results, we do feel the drug may be a potentially novel drug to treat AA. Thus, unless rigorously proven, the tenuous role of causation of AA due to leflunomide should be re examined.

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Compliance with ethical standards

Disclosures None.

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