



Response: Leflunomide: potential treatment and cause of alopecia areata

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We appreciate the thoughtful points outlined by Sardana et al. in response to our original case report and literature review which implicated alopecia areata (AA) as a possible uncommon side effect of leflunomide. While we agree that drug-induced AA is infrequent, we would argue that rarity does not preclude possibility. We used the well-validated Naranjo scale to determine the probability that AA is a possible side effect of leflunomide in our case [1]. It by no means proves a causative or mechanistic relationship but supports a “probable” association (Table 1).

As we reported in our initial article, three other cases of AA associated with leflunomide use have been published, further supporting this “probable” association and should be further explored and described [2]. Sardana et al. attest that of the 400 patients at their center on leflunomide, none have experienced AA; however, no stronger conclusions can be drawn from this anecdotal data of relatively small sample size for a potential rare side effect.

Additionally, Sardana et al. make the case that immunomodulating drugs like leflunomide are unlikely to cause AA as AA itself is an autoimmune-mediated phenomenon for which leflunomide has been used as treatment. We agree this seems mechanistically perplexing, but given the natural complexity of the immune system in which so many

factors and pathways come into play, seemingly illogical events are not inconceivable. For example, TNF inhibitors are used to treat psoriasis, yet can paradoxically cause psoriaform reactions [3]. Furthermore, as mentioned by Sardana et al., TNF inhibitors have previously been linked to AA by various published case reports [4–7] and a prospective multicenter study, in which the authors conclude that “AA is likely another autoimmune-induced adverse effect of TNF blockade, but fortuitous association cannot be excluded in some cases” [8]. There is a growing body of literature around paradoxical inflammatory reactions, and our report appears to be one of many [9–11].

We have now included supporting images for our case report, which were not printed in the initial publication (Fig. 1). While we have no histopathology to support a diagnosis of AA, the distribution of hair loss is typical. Informed consent was obtained for the publication of these images.

The research and mechanisms Sardana et al. cite on the use of leflunomide to treat recalcitrant AA are intriguing. We did not intend to discount the use of leflunomide as possible treatment for existing AA. Rather, our goal was to report AA as a possible paradoxical inflammatory reaction of leflunomide. If identified, the offending drug can be stopped, as our case and others reported suggest reversibility with discontinuation.

See related article <https://doi.org/10.1007/s10067-019-04669-0>

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Table 1 Adverse drug reaction probability scale

	Points assigned			Our case
	Yes	No	Do not know	
1. Are there previous conclusive reports on this reaction?	+1	0	0	1
2. Did adverse event appear after the suspected drug was given?	+2	-1	0	2
3. Did the adverse reaction improve when the drug was discontinued or a specific antagonist was given?	+1	0	0	1
4. Did the adverse reaction appear when the drug was readministered?	+2	-1	0	0
5. Are there alternative causes that could have on their own caused the reaction?	-1	2	0	2
6. Did the reaction reappear when a placebo was given?	-1	+1	0	0
7. Was the drug detected in any body fluid in toxic concentrations?	+1	0	0	0
8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased?	+1	0	0	0
9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure?	+1	0	0	0
10. Was the adverse event confirmed by any objective evidence?	+1	0	0	1



Two months following leflunomide discontinuation, where hair growth had commenced



Eight months after leflunomide discontinuation, with hair regrowth almost complete

Fig. 1 Hair regrowth following leflunomide-induced alopecia areata

Compliance with ethical standards

Disclosures None.

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