



Reversible alopecia areata: a little known side effect of leflunomide

Greg Koller¹ · Ina Cusnir¹ · Jill Hall² · Carrie Ye²

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Abstract

Leflunomide is a disease-modifying anti-rheumatic drug (DMARD) used in the management of rheumatoid arthritis (RA) and psoriatic arthritis. Commonly reported adverse effects include diarrhea, nausea, hepatotoxicity, hypertension, and transient global hair loss; however, additional side effects may be associated with the medication not reported in the monograph. We describe a rare case of reversible alopecia areata (AA) associated with the use of leflunomide and provide a literature review of three published similar cases. We use the Naranjo adverse drug reaction score to show the AA in our case is a “probable” side effect of leflunomide. Currently, AA is not listed as an adverse effect in the leflunomide product monograph. However, it would appear that based on our case and the three other reported cases, the likelihood of AA being an adverse effect of leflunomide is at least possible to probable.

Keywords Adverse effect · Alopecia areata (AA) · Leflunomide · Side effect

Leflunomide is a disease-modifying anti-rheumatic drug used in the management of rheumatoid arthritis (RA) and psoriatic arthritis. Commonly reported adverse effects include diarrhea, nausea, hepatotoxicity, hypertension, and transient global hair loss [1]. Previous studies have described high discontinuation rates, possibly due to associated adverse effects, with 67% of responders stopping the drug within 1 year of initiation [2]. We describe a rare case of reversible alopecia areata (AA) associated with leflunomide use. Informed consent was obtained from the patient for publication of this case.

A 39-year-old female with seronegative RA, first diagnosed in 1999, with no other comorbidities, was prescribed leflunomide 20 mg daily in May 2016 for worsening disease activity. Prior to this, she had been on stable doses of methotrexate and hydroxychloroquine since 1999. In January 2017, patchy alopecia was discovered on the left side of the patient’s scalp. The alopecia continued to worsen until a bean-shaped bald patch had developed measuring approximately 10 cm in

diameter. Given the bean shape, this may have been two confluent AA patches. In March 2017, the leflunomide was discontinued and the patient’s methotrexate was increased. At follow-up in May 2017, hair regrowth had commenced. By December 2017, hair regrowth was complete.

This AA event scored 7 out of 13 on the Naranjo adverse drug reaction probability scale, making the likelihood of the AA being an adverse event from the leflunomide “probable” [3]. Three other cases of leflunomide-associated AA have been previously reported in the literature [4–6].

The first reported potential case was by Gottenberg et al. in 2002. They describe a 46-year-old woman with a 2-year history of refractory RA, despite concomitant methotrexate and infliximab therapy, who had leflunomide added to her regimen. The patient reported patchy focal hair loss but still continued the drug, completing a total of 3 months before stopping due to suboptimal response. Hair regrowth was noted 3 months after discontinuation. Based on the Naranjo adverse drug reaction probability scale, the likelihood the AA was from the leflunomide is “probable” [3].

In 2015, Molina et al. reported another potential case in a 35-year-old female with RA. She was treated with leflunomide but had inadequate disease control after 1 year, so etanercept was added. One year after starting etanercept, the patient reported patchy focal hair loss. Subsequent dermatology consultation confirmed a diagnosis of AA. Leflunomide was discontinued (etanercept continued) and

✉ Carrie Ye
cye@ualberta.ca

¹ Department of Medicine, University of Alberta, 8-130 Clinical Sciences Building, 11350 83rd Avenue NW, Edmonton, AB T6G 2G3, Canada

² Department of Medicine, Division of Rheumatology, University of Alberta, Edmonton, AB, Canada

hair regrowth commenced after 4 months. The likelihood the AA was from the leflunomide is “possible” [3]. Although concurrent administration of etanercept confounds this case, that hair growth commenced while etanercept continued supports leflunomide as the culprit.

Finally, in 2015, Açıkgöz et al. described a 38-year-old male patient with psoriatic arthritis, who had leflunomide added due to a disease flare after 10 years on methotrexate. Three months after starting leflunomide, the patient reported patchy focal hair loss that the authors felt was consistent with AA. The medication was discontinued and 1 month later hair regrowth occurred. The likelihood the AA was from the leflunomide is “probable” [3].

It would appear that based on our case and the three others in the literature, the likelihood of AA being an adverse effect of leflunomide is at least “possible” and more likely “probable.” Interestingly, previous studies have suggested leflunomide may actually be useful in the management of AA, perhaps via its T cell modulating effects; nevertheless, the data presented here demonstrate leflunomide may also precipitate AA [7]. It is important to be aware of this possible rare side effect because based on these reports, if leflunomide is identified as the culprit early and discontinued, the AA can be reversible.

Compliance with ethical standards Informed consent was obtained from the patient for publication of this case.

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Inc L (QC): AP (2015) Arava, leflunomide tablets. Aventis Pharma Inc 1–70
2. Schultz M, Keeling SO, Katz SJ, Maksymowych WP, Eurich DT, Hall JJ (2017) Clinical effectiveness and safety of leflunomide in inflammatory arthritis: a report from the RAPPORT database with supporting patient survey. *Clin Rheumatol* 36:1471–1478. <https://doi.org/10.1007/s10067-017-3687-5>
3. Naranjo CA, Busto U, Sellers EM, Sandor P, Ruiz I, Roberts EA, Janecek E, Domecq C, Greenblatt DJ (1981) A method for estimating the probability of adverse drug reactions. *Clin Pharmacol Ther* 30:239–245
4. Gottenberg J-E, Venancie P-Y, Mariette X (2002) Alopecia areata in a patient with rheumatoid arthritis treated with leflunomide. *J Rheumatol* 29:1806–1807
5. Molina Molina MI, Pinochet Paiva CM, Quezada Morales JI (2015) Alopecia areata secondary to the use of leflunomide in patients with rheumatoid arthritis: a case report and literature review. *Medwave* 15:e6350–e6350. <https://doi.org/10.5867/medwave.2015.11.6350>
6. Askeri Tıp Akademisi G, ve Zührevi Hastalıklar Anabilim Dalı D, Gürol Açıkgöz T, et al Lenflunomide bağlı bir alopesi areata olgusu. <https://doi.org/10.4274/turkderm.29795>
7. Sardana K, Gupta A, Gautam RK (2018) Recalcitrant alopecia areata responsive to leflunomide and anthralin-potentially undiscovered JAK/STAT inhibitors? *Pediatr Dermatol* 35:856–858. <https://doi.org/10.1111/pde.13688>

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