Role of both Azathioprine and methotrexate in Management of Alopecia Areata: Review Article

Abdalla Hasan Kandil, Hassan Senoussi Houssin Osman*, Mohamed Ibrahim El Ghareeb
Department of Dermatology, Venereology and Andrology, Faculty of Medicine, Zagazig University, Zagazig, Egypt.
*Corresponding author: Hassan Senoussi Houssin Osman, Mobile: (+20) 0 109 642 2406, E-Mail: Majdooly@gmail.com

ABSTRACT
Background: Alopecia areata (AA) is a type of alopecia that does not leave scars and can affect any portion of the body or scalp. It accounts for 25% of all cases of alopecia, making it one of the most prevalent causes of hair loss treated by dermatologists. Psychosocial stigmatization makes it hard for AA patients to advocate for better medical care and treatment. To treat AA, azathioprine can be used as an effective alternative therapy, and it can be introduced early on in the treatment timeline. In the treatment of inflammatory and immune-mediated skin problems, methotrexate is a common conventional immunosuppressant. The objective of this review is to assess the possible role of both Azathioprine and methotrexate in Management of AA.

Development: Azathioprine and methotrexate were all looked for in PubMed, Google scholar, and Science direct. References from relevant literature were also evaluated by the authors, but only the most recent or complete study from March 2010 to May 2021 was included. Due to the lack of sources for translation, documents in languages other than English have been ruled out. Papers that did not fall under the purview of major scientific investigations, such as unpublished manuscripts, oral presentations, conference abstracts, and dissertations, were omitted.

Conclusion: Methotrexate as well as azathioprine can be considered an effective monotherapy or adjunctive for treating alopecia areata.

Keywords: Azathioprine, Methotrexate, Alopecia Areata, Review, Psychosocial stigmatization.

INTRODUCTION
Inflammation of the hair follicle and, in rare cases, the nail plate, is the root cause of alopecia areata, a chronic inflammatory illness. There is no fixed age of onset and no established gender or racial predominance. Though alopecia areata most commonly causes bald spots on the scalp, it can affect any place of the body where hair grows. It causes mild redness but otherwise has no visible effects on the skin (1).

Transient, non-scarring hair loss that can last anywhere from weeks to decades is just one symptom of alopecia areata, an autoimmune illness caused by T cell attack of hair follicles and dissolution of their immune privilege. There are currently no effective treatments for AA that have been authorised by the FDA (1).

Psychosocial stigmatisation makes it hard to advocate for adequate medical care and treatment for AA patients. Available therapies for AA include corticosteroids (both topically and intralesionally), minoxidil solution (topically), anthralin (topically), and contact sensitizers. The severity of the alopecia, the patient's age and overall health, the patient's motivation to undergo treatment, and the patient's physiological stress are all factors to consider when deciding whether or not to administer systemic treatment for AA. Systemic therapy may be investigated as a therapeutic option for people with rapidly advancing disease, severe hair loss, or resistant cases. Drugs with immunosuppressive properties, such as cyclosporine, systemic corticosteroids, methotrexate, or sulfasalazine, are used in systemic treatment of AA (2).

Although there have been many attempts to treat AA, currently there is no cure. As it is difficult to objectively measure the therapeutic response, the long-term efficacy of existing treatments is modest, and therapeutic response varies greatly. Therapeutic measures, such as the Severity of Alopecia Tool, have been attempted in recent clinical research (3).

It is difficult to gauge the success of these therapies due to the high percentage of spontaneous remission seen in AA patients, and there is no assurance that hair regrowth will continue after treatment has ended (4).

Treatments for alopecia areata have evolved over time and can be broadly classified as either (first line, second line, as well as third line therapies) (4).

Purine antagonist azathioprine has traditionally been thought of being an s-phase cell cycle-targeting medication. Although azathioprine has been used extensively in clinical settings for the better part of 50 years, a clear knowledge of its mechanism of action is still lacking. Because azathioprine's 6-thioguanine active metabolites inhibit the activity of endogenous purines, this is the widely accepted mechanism by which the drug exerts its cytotoxic and immunosuppressive effects. Different laboratory experiments have confirmed that azathioprine is more selective for T lymphocytes than for B lymphocytes, and that it inhibits T-cell activity and critical components of T-cell activation (interleukin-2) (5).

Many autoimmune disorders and immune-mediated dermatologic ailments, such as pemphigus vulgaris, dermatomyositis, and psoriasis, have shown improvement on azathioprine since its introduction in the early 1960s (5).

There are many ways in which azathioprine impacts the immune system beyond its effects on DNA replication. Studies have demonstrated that azathioprine can cause a dose-dependent, reversible
decrease in monocytes in circulation and tissue, but had no effect on neutrophils (6).

The thiopurine methyltransferase (TPMT) enzyme is a great example of applied pharmacogenomics and has been the subject of extensive research. When a patient with TPMT deficiency is given azathioprine, a toxic build up of thioguanine nucleotides occurs, and this manifests clinically as enhanced haematological toxicity (6).

When it comes to azathioprine side effects, nausea and diarrhoea are by far the most frequently reported. It is generally understood that azathioprine can suppress bone marrow. Initial weeks of treatment are crucial for preventing hematologic toxicities, which can be detected through complete blood count monitoring in the lab (7).

It has been observed that azathioprine interacts with a number of other medications. Allopurinol, the most often used XO inhibitor, has the most notable interaction. Concomitant usage may lead to significant azathioprine toxicity and hematopoietic problems due to the drug’s partial catabolism by XO. There is a lot of literature discussing the potential dangers of this crucial interaction (7).

The side-effect profile of azathioprine in children appears to be comparable to that in adults (8).

Patients with a chronic AA disease have a negligible chance of experiencing spontaneous hair regrowth. In cases with AA, sulfasalazine and azathioprine may be equivalent, although prospective studies are necessary to support this assumption.

Both medications have immunomodulatory and anti-inflammatory effects. Because of the high morbidity rate associated with systemic steroid use, azathioprine may be a viable alternative therapy for decreasing steroid use in patients on oral corticosteroids. Adjuvant treatment for patients with severe and resistant AA may include steroid and azathioprine combination therapy (9).

METHOTREXATE

Methotrexate (MTX) is a competitive inhibitor of dihydrofolate reductase and thus an antimetabolite. Nucleic acid replication, ribosomal replication, thymidylate synthesis, and protein synthesis are all stymied. MTX suppresses B-cell activity in addition to suppressing T-cell activation and intracellular adhesion molecule production (10).

When it comes to inflammatory and immune-mediated skin problems, MTX is a standard immunosuppressant medication that has seen extensive use. Application of MTX could be a suitable technique to manage the inflammatory process in AA, as it has recently been shown to suppress the JAK/STAT pathway, which is thought to play a large part in the pathogenesis of AA. Response rates to MTX therapy in juvenile and adult instances of AA have been found to be variable in a few prior articles (11).

Long-term usage of low- to moderate-dose methotrexate MTX has been shown to be effective, safe, and well-tolerated by patients with a wide variety of autoimmune diseases (11).

Adverse effects of methotrexate therapy in adult trials of AA and other autoimmune illnesses include nausea, vomiting, increased liver enzymes, and stomatitis (12).

Due to its severity and unpredictability, myelosuppression is one of the most terrifying side effects of MTX. 3- 24 percent of patients experience mild to moderate leukopenia (the most prevalent symptom), thrombocytopenia, and megaloblastic anaemia (12).

Folate is essential for cellular replication, growth, and blood cell development. As a result, many MTX-treated patients have gastrointestinal (GI), liver (hepatic), and blood cell (hematologic) damage due to a deficiency of folate. Both folic acid and folinic acid supplements have been demonstrated to reduce the severity of these adverse effects when taken in conjunction with MTX therapy (13).

Dose reduction or withdraw of the treatment is necessary if severe side effects happen as hepatotoxicity, pulmonary damage and myelosuppression (14).

Oral and intramuscular are the most common MTX administration routes with a usual dose range from 7.5mg to 25mg every week (15).

Children tolerate MTX well. GI intolerance (nausea, vomiting, diarrhea, anorexia, stomatitis) is the most common side effect and responds well to dose reduction. Leucopenia and transient elevation of liver enzymes are also common (16).

In severe cases of AA, methotrexate may be utilized as a supplementary therapy because it is well tolerated and comes at a low cost (16).

For patients with localized AA, intralesional MTX has been shown to be a viable and safe treatment choice. The reaction of an AA lesion to treatment can be monitored by dermoscopy (16).

Withdrawals from therapy due to adverse events were much higher for the MTX/AZA combination than for oral MTX or a number of other therapies. Due to the rather high median doses of the two medications employed in the article (AZA 50 mg/day and MTX 20 mg/week), careful laboratory monitoring was required (17).

CONCLUSION

Methotrexate as well as azathioprine can be considered an effective monotherapy or adjunctive for treating AA.

Financial support and sponsorship: Nil.
Conflict of interest: Nil.
REFERENCES