

# Systemic treatment for alopecia areata

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**ABSTRACT:** Of the world population, 1.7% is suffering from alopecia areata at some point in their lives. The exact etiology of this disease is still unknown, and the course of the disease is unpredictable. Effective treatments, especially for severe multifocal alopecia areata, alopecia areata totalis, and alopecia areata universalis, are lacking. The present article will discuss side effects and relapse rates of different systemic agents for treatment of severe and rapid progressive alopecia areata.

**KEYWORDS:** alopecia areata, hair loss, prednisone

## Introduction

Alopecia areata (AA) is an organ-specific autoimmune condition characterized by T cell-mediated attack on the hair follicle (1). The inciting antigenic stimulus is unknown. A dense peribulbar lymphocytic infiltrate and reproducible immunologic abnormalities are hallmark features of the condition. The cellular infiltrate primarily consists of activated T lymphocytes and antigen-presenting Langerhans cells. T lymphocytes play a critical role in the pathogenesis of disease (2,3) (FIG. 1).

AA may clinically present with one or several round or oval patches of hair loss on the scalp or any other hair-bearing area of the body (FIG. 2). AA may also present as a band-like alopecia on the occipital scalp (FIG. 3) or a diffuse alopecia, and can progress to a loss of all terminal hair on the scalp (AA totalis (AT)) or loss of all scalp and body hair (AA universalis (AU)) (FIG. 4).

AA occurs worldwide in the general population with a lifetime risk of 1.7% (4). The course of the disease is unpredictable; approximately 5% of cases will progress to AT and 1% to AU (5).

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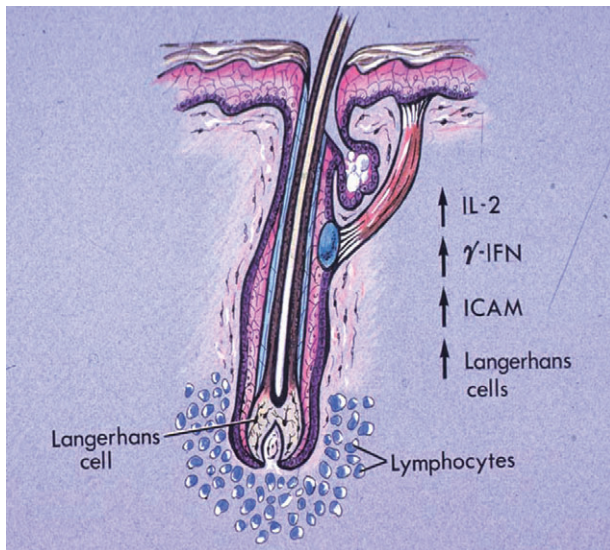
Presently available treatments for AA include topical and intralesional corticosteroids, topical minoxidil solution, topical anthralin, and contact sensitizers. In patients with rapid progressive disease or extensive hair loss (>30% scalp hair involvement) and for therapy-refractory cases, systemic treatments may be considered as therapeutic option. Systemic therapies for AA include immunosuppressant drugs like cyclosporine, systemic corticosteroids, methotrexate, or sulfasalazine. None of the topical, intralesional, or systemic therapies for AA are curative, and none are Food and Drug Administration-approved. The decision of whether to treat AA systemically depends on the extent of alopecia, patient age and general health, and on the patient's motivation for treatment and physiological strain.

The present article will discuss the benefits and limitations of different systemic agents for the treatment of AA.

## Systemic therapies

### Corticosteroids

Systemic corticosteroids have been used for many years in patients with rapid progressive and extensive AA. Different regimens have been tried, including single-dose administration (6), alternating



**FIG. 1.** Pathogenesis of alopecia areata. Langerhans cells present epitopes to peribulbar lymphocytes, followed by a cascade of immunological events with an increase of interleukin-2 (IL-2), gamma interferon ( $\gamma$ -IFN), and intercellular adhesion molecules (ICAM) (courtesy of Jerry Shapiro, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada).



**FIG. 2.** Sixty-two-year-old female patient with patchy alopecia areata in the frontal hairline in combination with loss of eyebrows and eyelashes (courtesy of Jerry Shapiro, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada).

doses of prednisone as long-term treatment (7–10) or short-term treatment with high doses of intravenous methylprednisolone (6,11); other authors suggest tapered doses over weeks (5); and some clinics use an interval therapy with tapered doses over 1 week every month for 3–6 months.

The only placebo-controlled randomized study on oral prednisone published was performed by



**FIG. 3.** Fifty-four-year-old female patient with ophiasic alopecia areata (courtesy of Jerry Shapiro, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada).



**FIG. 4.** Twenty-eight-year-old male patient with alopecia areata universalis (courtesy of Jerry Shapiro, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada).

Kar et al. (8). Forty-three patients were enrolled in the study. Twenty-three patients received 200 mg prednisone weekly over 3 months followed by a 3-month observation period. Sixty percent of the treated patients showed regrowth, whereas 30% experienced moderate to significant hair regrowth (31–60%) compared with no regrowth in the placebo arm.

Ait Ourhroui et al. recently published a prospective open-label study on 34 patients with progressive AA affecting more than 40% of the scalp. Once monthly, over 3–6 months, 300 mg oral prednisone was administered. An incomplete or cosmetically

acceptable response was noted in 28 patients (82%) (7).

Sharma et al. had used pulsed oral prednisolone 300 mg once monthly for a minimum of 4 months in patients with extensive AA and AT/AU. Cosmetically acceptable regrowth was found in 58% of patients (10).

In 1976, Winter et al. used alternate-day prednisone. The treatment was not found to be substantially effective and showed no obvious beneficial change in the natural course of AA after a 15-month follow-up period (9).

In 1999, Price recommended a treatment regimen with oral prednisone for patients with extensive and rapidly spreading AA, starting with 40 mg daily for 1 week, tapered down by 5 mg every week for 3 weeks, followed by 15 mg for 3 days, 10 mg for 3 days, and 5 mg for 3 days in combination with topical minoxidil daily and intralesional corticosteroids every 4–6 weeks (12).

A similar treatment concept was suggested by Olsen et al. in 1992; 40 mg of prednisone tapered over 6 weeks was given to patients with mild to extensive AA. The treatment was combined with either topical minoxidil or vehicle. The topical treatment was continued for an additional 14 weeks. Forty-seven percent of patients responded to the prednisone treatment with more than 25% of regrowth. Topical minoxidil was found to be helpful to prevent relapse after discontinuation of the corticosteroid treatment (13).

In 1978, Unger and Schlemmer (14) suggested low-dose oral prednisone in combination with intralesional and topical corticosteroids.

Friedli et al. used pulse therapy with intravenous methylprednisolone, 250 mg, twice daily on three consecutive days. Twelve of twenty patients with multifocal, patchy AA showed 50–100% regrowth. The regimen appeared ineffective in patients with AT, AU, or ophiasic AA (11).

In 1975, Burton and Shuster used intravenous prednisolone at 2000 mg as a single dose in 22 patients with AT, and 500 mg oral prednisolone in 13 patients with AT with an overall unsatisfactory response rate (6).

Kurosawa et al. compared different treatment modalities. They used dexamethason 0.5 mg/day for 6 months or intramuscular triamcinolone acetonide 40 mg once a month for 6 months, followed by 40 mg once every 1.5 months for 1 year or pulse therapy with oral prednisolone at 80 mg for three consecutive days once every 3 months. Response rates were found to be best with intramuscular triamcinolone acetonide in patients with multifocal AA, and relapse rates in patients with

AT/AU were found to be the lowest in the patient who received pulse therapy with oral prednisolone (15).

In general, success rates are found to be much better in multifocal AA compared with ophiasic AA, AT, and AU (6,7,11).

Downsides of systemic corticosteroids are their side-effect profile and the fact that they do not alter the long-term prognosis.

Side effects of systemic steroids include hyperglycemia, osteoporosis, cataracts, immunosuppression, obesity, dysmenorrhea, acne, weight gain, mood changes/emotional lability, and Cushing's syndrome (8,15,16).

Pulse therapy, especially those with long corticosteroid free intervals and high-dose ultra-short-term treatments seem to have less of a side-effect profile than daily or alternate day oral regimens with a reasonable treatment outcome (11,15).

Oral corticosteroids are contraindicated in children because of their side-effect profile.

## Cyclosporine

Cyclosporine is an immunosuppressant drug widely used in postallogeic organ transplant patients and in the treatment of autoimmune diseases. It was initially isolated from the Norwegian fungus *Tolypocladium inflatum*. Cyclosporine inhibits helper T cell activation and suppresses interferon gamma production.

Oral cyclosporine has shown to have some benefit in the treatment of AA (17–19). However, the occurrence of AA has been reported in organ transplant patients who were taking cyclosporine (20–23).

Gupta et al. treated six patients at 6 mg/kg/day for 12 weeks. Cosmetically acceptable terminal hair regrowth on the scalp occurred in three of six patients. Significant hair loss, however, occurred in all patients within 3 months of discontinuation of cyclosporine treatment (19). Shapiro et al. combined oral cyclosporine at 4 mg/kg/day with low-dose prednisone at 5 mg/day. Reasonable regrowth was seen in 25% of patients, but high recurrence rates were noted after discontinuation of the treatment (17) (FIG. 5A–C).

Kim et al. achieved success rates of up to 76.7% with a combination therapy of oral cyclosporine and oral methylprednisolone. Forty-six patients were treated with cyclosporine at 200 mg twice daily and methylprednisolone (24 mg twice daily for men, 20 mg twice daily for women, and 12 mg twice daily for children) (24).



**FIG. 5.** (A) Twenty-eight-year-old male patient with alopecia areata universalis for 2 years prior to treatment with cyclosporine. (B) 3 months of systemic cyclosporine at 4 mg/kg/day in combination with prednisone 5 mg/day. (C) Five months of therapy (courtesy of Jerry Shapiro, Department of Dermatology and Skin Science, University of British Columbia, Vancouver, BC, Canada).

Shaheedi-Dadras et al. treated patients with AT and AU with monthly intravenous methylprednisolone at 500 mg for 3 days and oral cyclosporine (2.5 mg/kg/day) for 5–8 months. Hair regrowth of >70% was seen in 33% of patients (25).

Drawbacks of systemic cyclosporine are the side-effect profile, which includes nephrotoxicity, immune suppression, hypertension and hypertrichosis of body hair, high relapse rates after discontinuation, and therefore the need for long-term treatment.

Topical cyclosporine at concentrations of 10% has not yet shown to be effective in patients with AA (26–28). However, Verma et al. used the Dundee bald rat as animal model and were able to show hair regrowth and reduced inflammation after application of topical cyclosporine in a lipid vehicle (29).

### Sulfasalazine

Sulfasalazine is a sulfa-drug, a derivative of mesalazine (5-aminosalicylic acid or 5-ASA), used primarily as an anti-inflammatory agent in the treatment of inflammatory bowel disease, rheumatoid arthritis, and juvenile spondyloarthropathies. It has both immunomodulatory and immunosuppressive actions, including inhibition of T cell proliferation, natural killer cell activity, and antibody production. Sulfasalazine also inhibits the T cell cytokines interleukin (IL)-2 and interferon gamma, and the monocyte/macrophage cytokines IL-1, tumor necrosis factor alpha (TNF- $\alpha$ ), and IL-6 (30).

Only a few open studies and case series can be found in literature. Ellis et al. reported a response rate of 23% in patients with severe AA. Aghaei

treated 22 patients with sulfasalazine starting with 500 mg twice daily for 4 weeks, followed by 1000 mg twice daily for 4 weeks, and 1500 mg twice daily for 4 months. Complete hair regrowth was noted in 27.3%. However, relapse occurs in 45.5% of patients. Adverse effects included gastrointestinal distress, rash, headache, and laboratory abnormalities in 31.8% (31). Rashidi and Mahd treated 39 patients with 1500 mg sulfasalazine twice daily for 6 months. 25.6% of the patients responded with full regrowth. 30.7% showed mild to moderate regrowth (32).

### Methotrexate

Methotrexate inhibits the metabolism of folic acid. It is used in the treatment of cancer and autoimmune diseases.

Only two studies can be found in the literature on treatment of AT and AU with methotrexate. Chartaux and Joly showed success rates of 63–64% with a combination of methotrexate at 15 mg weekly and prednisone at 10 mg or 20 mg daily (33,34), and hair regrowth in 57% of patients with AT and AU with methotrexate alone. The onset of hair regrowth was noted after a median delay of 3 months. Adverse events consisting of transient elevated transaminases, persistent nausea, and lymphocytopenia occurred in 21% of patients (33).

### Azathioprine

Azathioprine is a purine antagonist. Although azathioprine has been used for over 50 years, its mechanism of action is not fully understood. The generally accepted mechanism of azathioprine's

cytotoxic and immunosuppressive activities is the disruption of nucleic acids. Azathioprine seems to impair T cell function and IL-2; it seems to be more selective for T lymphocytes than for B-lymphocytes (35). Azathioprine has successfully been used in the treatment of different autoimmune diseases and immune-mediated dermatologic conditions such as pemphigus vulgaris, dermatomyositis (36).

Farshi et al. recently published an open-label study on the use of azathioprine monotherapy in moderate to severe AA. Twenty patients were treated at a dose of 2 mg/kg for 6 months. Scalp assessment was performed using severity of alopecia tool score. The mean regrowth rate was found to be 52.3%. The treatment was overall well tolerated. Side effects included elevated liver enzymes, mild leucopenia, nausea, vomiting, and gastrointestinal discomfort (37).

### Biologics

AA is considered a T cell-mediated disease. Modern immunosuppressant drugs, mainly developed for the treatment of psoriasis, like infliximab, etanercept, and adalimumab, bind to TNF- $\alpha$ , preventing it from activating TNF receptors or like efalizumab, which binds to the cluster of differentiation 11a (CD11a) subunit of lymphocyte function-associated antigen 1, have been tried for the treatment of AA. Unfortunately, all studies failed to show effectiveness. Some studies show the occurrences or worsening of AA under the treatment with these biologics (38–48). Further studies are necessary to determine whether these or other biologics are of any use for the systemic treatment of AA.

### Conclusion

AA is considered to be organ specific and is therefore a medically friendly condition. However, extensive hair loss, rapid onset with massive shedding, or the loss of all scalp hair (AT) or all scalp and body hair (AU) cause dramatic distress for the patient and often lead to depression and withdrawal from social activities. Patients with AA suffer from severe psychological strain and are seeking effective therapies. Systemic corticosteroids, cyclosporine, sulfasalazine, and methotrexate can be considered for adult healthy patients with severe AA. Systemic treatments should be combined with topical minoxidil and/or corticosteroids and intralesional corticosteroids. Pulse therapies with high doses of corticosteroids with long intervals seem to have the best ratio for risks

and benefits. Patients have to be informed that none of the systemic treatment options are Food and Drug Administration-approved, and that disease recurrence is likely after discontinuation of the treatment. The patient must be regularly monitored for side effects. More placebo-controlled studies are necessary to find better and safer regimens for the treatment of severe AA.

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