# Successful Treatment of Long-Standing Alopecia Totalis Using Combined Methotrexate and Prednisone

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Alopecia areata is a relatively common nonscarring alopecia that may progress to complete loss of scalp hair (alopecia totalis) or scalp and body hair (alopecia universalis) in a subset of patients. This extreme loss of hair results in cosmetic disfigurement and is notoriously difficult to treat. We report the ongoing successful treatment of a patient with long-standing alopecia totalis using combined methotrexate and prednisone. Our case report adds to the published evidence of the efficacy of this regimen in treating patients with refractory alopecia totalis or alopecia universalis. We conclude that combined methotrexate and prednisone is a promising treatment for long-standing alopecia totalis in patients for whom the potential benefits outweigh the risks.

Alopecia areata is a relatively common inflammatory disorder causing patches of nonscarring alopecia.[1] Although the pathogenesis is not fully understood, considerable evidence suggests that autoimmune attack of the hair follicles causes alopecia areata.[2,3] Most patients with alopecia areata have a mild disease consisting of several alopecia patches that regrow hair within a year. However, a subset of up to 10% of patients with alopecia areata have a prolonged disease course progressing to complete loss of scalp hair (alopecia totalis) or scalp and body hair (alopecia universalis).[2] This extreme hair loss results in cosmetic disfigurement that may contribute to psychosocial abnormalities such as anxiety, depression, lack of self-confidence, and poor overall mental health.[4,5] Unfortunately, these patients are difficult to treat; no therapy provides consistently successful results.[1,6] Recently, Joly[7] reported successful total hair regrowth in approximately 64% (14 of 22) of patients with alopecia totalis or alopecia universalis after treatment with methotrexate alone or combined methotrexate and prednisone. We report our experience treating a patient with long-standing alopecia totalis using a combined regimen of methotrexate and prednisone per Joly's protocol.

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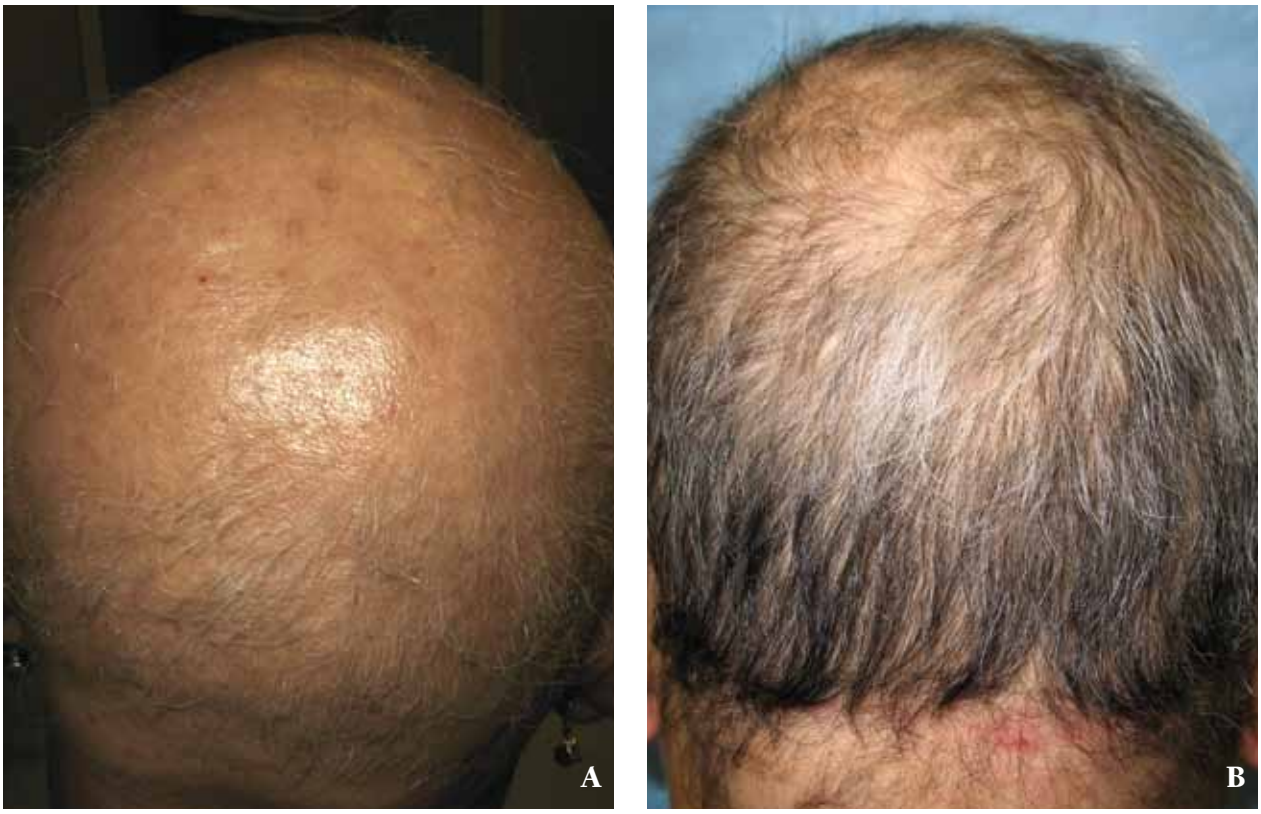
## CASE REPORT

In August 2006, an otherwise healthy 40-year-old woman presented to our clinic with an 11-year history of complete loss of scalp hair. She stated that her hair loss had been intermittent until 11 years earlier, with her first hair-loss episode occurring in early childhood. We noted on physical examination that she had complete loss of scalp hair, with only scattered white terminal hairs present. She also had patchy hair loss in her eyebrows and eyelashes and on her arms, as well as complete loss of genital and



Posterior view of the scalp of a 40-year-old female with alopecia totalis before (A) and at week 20 (B) of combined methotrexate and prednisone treatment. Before treatment, less than 5% of her scalp had terminal hair growth; most of the hair is gray and concentrated in the ophiasis area. At week 20 of treatment, diffuse growth of mostly pigmented terminal hair is evident.

axillary hair. She denied medical treatment before presentation and wore a wig to hide her scalp alopecia.

We diagnosed the patient with alopecia totalis, with evidence of progression toward alopecia universalis, and started the patient on fluocinonide ointment to her scalp twice daily. Laboratory studies, including complete blood cell count (CBC) with differential and tests for thyroid function, random serum glucose, and antinuclear antibodies, to pinpoint any associated diseases were within normal limits. Serum ferritin level was decreased at 12 ng/mL (normal range, 13–150 ng/mL), so we started the patient on 325 mg ferrous sulfate twice daily. Over the following 11 months, we achieved regrowth of the patient's eyebrows using several injections of 2.5 mg/cc intralesional triamcinolone acetonide. However, less than 5% of her scalp hair regrew with numerous treatments, including fluocinonide ointment, 5 mg/cc intralesional triamcinolone acetonide, and 5 mg oral dexamethasone on 2 consecutive days every week (Figure, A). Her ferritin level normalized to 16 ng/mL by February 2007.

Given the lack of treatment response and the patient's desire to regrow her scalp hair, we discussed with her the option of combined treatment, per Joly's protocol, with methotrexate and prednisone.[7] After we discussed the possible adverse effects, the patient decided to pursue this treatment option. A complete metabolic panel revealed normal liver and renal functions; serologic studies were negative for chronic hepatitis B or C infection. Baseline blood pressure was normal; baseline dual-energy x-ray absorptiometry scan showed no evidence of osteoporosis or osteopenia. She had undergone a bilateral tubal ligation in 1998.

In June 2007, we started the patient on 15 mg methotrexate once weekly and 20 mg prednisone once daily. Despite normalization of her ferritin level, we continued ferrous sulfate supplementation with 325 mg 3 times daily. Also, we started prophylactic treatment with 150 mg ranitidine hydrochloride twice daily, 1.5 g calcium with 800 IU cholecalciferol (vitamin D) once daily, 70 mg alendronate sodium once weekly, and 1 mg folic acid once daily.

During the first 2 months of treatment, a CBC with differential, complete metabolic panel, and blood pressure was checked every 2 weeks. All results, including random glucose levels, were within normal limits. The patient's ferritin level in August 2007 was 44 ng/mL. After 2 months of treatment, there was evidence of new, pigmented terminal-hair growth on her scalp, mostly

concentrated in the ophiasis region and vertex. Continuing treatment, we instructed the patient to apply clobetasol propionate ointment to her scalp under occlusion at bedtime, our decision having been based on previous success with this treatment.[6] Given Joly's treatment success with higher doses of methotrexate, as well as the patient's continuously normal CBC and liver- and renal-function tests, we increased her methotrexate dose at week 16 from 15 mg weekly to 20 mg weekly. We maintained prednisone at 20 mg once daily. At 20 weeks, the patient continued to show significant new terminal-hair growth on her scalp (Figure, B), with approximately 70% of her scalp displaying growth of predominantly pigmented terminal hair. All laboratory values continued to be within normal limits; ferritin level in November 2007 was 58 ng/mL. The patient was extremely happy, noting that she had not had this much natural hair on her scalp in over a decade.

Our plan is to slowly taper off prednisone starting at week 20 by decreasing the patient's daily dose by 5 mg every month. Unless she develops adverse effects, we will continue her on 20 mg methotrexate once weekly for 18 months from the start of terminal-hair growth in August 2007, after which we will taper off all oral treatment.

## COMMENT

Alopecia totalis and alopecia universalis are conditions that result in significant cosmetic disfigurement and are notoriously difficult to treat. The psychosocial effects of such disfigurement may be severe and are often underestimated. Thus, successful treatment may significantly impact a patient's quality of life. We have reported the ongoing successful use of combined methotrexate and prednisone to promote regrowth of scalp hair in a patient with long-standing alopecia. Our case report adds to Joly's observations of numerous patients with alopecia totalis or alopecia universalis treated with methotrexate with or without prednisone, providing further evidence that this regimen may be successful in patients for whom other topical and systemic treatments have failed.

Our treatment regimen differs slightly from Joly's in that we have added an application of a high-potency topical corticosteroid under occlusion to the scalp of our patient. Despite the previous failure of this as the sole treatment of the patient's alopecia, there is evidence that it induces hair growth in patients with alopecia totalis or alopecia universalis.[6] Although Joly reported success without this additional intervention, we believe that any localized increase in corticosteroid delivery to our patient's scalp optimizes our chance of successfully treating her with only minimal risk of additional adverse effects. Furthermore, given that the patient's ferritin level was initially low, we added supplemental ferrous sulfate to her treatment regimen. This supplementation has been recommended in patients with hair loss whose ferritin levels are less than 70 ng/mL, although rigorous effects of this treatment on hair loss and growth have yet to be assessed.[8,9]

Both methotrexate and corticosteroids have been used as sole agents to successfully treat alopecia areata, alopecia totalis, and alopecia universalis.[6,7,10,11] Treatment success, although limited in these reports, provides evidence that either of these agents may effectively eradicate the aberrant perifollicular inflammation that characterizes these alopecias. However, we believe that combination therapy with methotrexate and corticosteroids is a better treatment approach than either agent alone. Because each agent has a different mechanism of action, the combined use of methotrexate and prednisone results in an additive, even synergistic effect on the autoimmune response against hair follicles.[12,13] This effect may explain the increased rate of full recovery using combination therapy (69% [11 of 16 patients]) compared with methotrexate alone (50% [3 of 6 patients]) in Joly's study.[7] In addition, combination therapy allows clinicians to use each agent at a lower dose than if used alone. This allowance is important because it decreases both the incidence and the severity of adverse effects. Thus, combination immunosuppressive regimens offer a higher level of safety and efficacy compared with single-agent regimens.

The goal of combination therapy with methotrexate and prednisone in our patient was to rapidly control the immune response, then taper off the prednisone and maintain control with a relatively low dose of the corticosteroid-sparing agent methotrexate. We added a topical corticosteroid to the regimen with the goal of maximizing the local concentration of corticosteroids, but we cannot be sure that the addition contributed to the patient's hair regrowth. This treatment approach minimizes the risk of severe systemic adverse effects, such as osteoporosis, peptic ulcers, osteonecrosis, diabetes, muscle atrophy, and atherosclerosis, that are known to occur with long-term corticosteroid use.[12] It also should prevent side effects, which may worsen disease if using high-dose courses of either agent alone, such as disease rebound with corticosteroids and alopecia with methotrexate.[12,14] Furthermore, the limited use of relatively low doses of prednisone in our combination regimen should decrease the incidence of other well-known adverse effects, such as cutaneous striae, weight gain, telangiectasias, hirsutism, and acneform eruptions, that may be of particular concern to patients seeking treatment for cosmetic issues.[12] Avoiding these common adverse effects may not only prevent the need to address additional cosmetic problems but may enhance patient compliance with the treatment regimen.

Although combined treatment with methotrexate and prednisone may be effective in treating alopecia totalis

## Screening Recommendations Before Initiating Treatment With Methotrexate and Prednisone

- Blood pressure
- Fasting serum glucose level
- Baseline dual-energy x-ray absorptiometry scan
- CBC with differential
- Liver-function tests
- Blood urea nitrogen/serum creatinine tests and renal-function tests, with estimate of creatinine clearance
- Hepatitis panel
- Pregnancy test (if appropriate)
- Medication review to screen for potential interactions
- Amount of weekly alcohol consumption
- Baseline ophthalmologic examination*

Abbreviation: CBC, complete blood cell count.
*Because of the association between corticosteroids and posterior subcapsular cataracts, this examination should be performed on patients at risk for cataracts.

and alopecia universalis, it is important to always consider that hair regrowth is primarily a cosmetic issue, with no implications for future medical problems. A risk-benefit ratio of treatment with this regimen, including the psychosocial effects of hair loss, should therefore be addressed with every patient before and during treatment, since even mild systemic abnormalities are arguably unacceptable when addressing cosmetic issues. Pretreatment screening is imperative for comorbid conditions that may precipitate the adverse effects of combined methotrexate and prednisone, as is regular monitoring for adverse effects per published recommendations once treatment is started (Table).[12,13] In addition, prophylaxis treatment with calcium, cholecalciferol, a bisphosphonate (for appropriate patients), and either a histamine-2 receptor blocker or a proton pump inhibitor should be started when prednisone treatment is started. We have chosen to add 1 mg folic acid once daily, as this addition has been shown to reduce the adverse gastrointestinal effects of methotrexate.[15]

Combined methotrexate and prednisone has long been used to treat numerous immune-mediated disorders. Our case report adds to Joly's[7] observations that this regimen may effectively treat yet another likely immune-mediated disorder, alopecia totalis. Although our observations support Joly's, it is important to note that randomized, controlled studies using this regimen have not yet been performed. In addition, the long-term success of this regimen in maintaining hair regrowth is not yet known. Despite these setbacks, however, we conclude that combined methotrexate and prednisone is a promising treatment for long-standing alopecia totalis in patients for whom the potential benefits outweigh the risks.

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