The use of methotrexate alone or in combination with low doses of oral corticosteroids in the treatment of alopecia totalis or universalis

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Treatment of severe alopecia areata (AA) remains difficult. To assess the tolerance and efficacy of methotrexate (MTX) in the treatment of severe long-term AA, we retrospectively evaluated 22 patients with AA totalis or universalis with a mean duration of 11.0 ± 8.8 years who were treated with MTX either alone (n = 6) or associated with low doses of oral prednisone (n = 16). MTX was given at an initial weekly dosage of 15 mg (n = 3), 20 mg (n = 9), or 25 mg (n = 10). Oral prednisone was given at an initial dosage of 10 mg/d in one patient and 20 mg/d in 15 patients. In all, 14 patients (64%) achieved a total recovery including 3 of 6 patients treated by MTX alone and 11 of 16 who had received the combined treatment. Of the 14 patients who had total hair regrowth, 6 stopped MTX. In all, 3 patients maintained hair regrowth and 3 relapsed. Retreatment of these 3 patients by MTX resulted again in hair regrowth. No severe side effect was observed. Although limited by its uncontrolled character, this study shows that MTX and low doses of oral corticosteroids may be an effective and well-tolerated treatment for severe types of AA. (J Am Acad Dermatol 2006;55:632-6.)

Treatment of long-term alopecia areata (AA) totalis or universalis remains difficult with less than 20% of patients obtaining complete hair regrowth.[1-5] Conventional treatments including topical corticosteroids (CS), tacrolimus, topical immunotherapy, psoralen, UVA, or intravenous (IV) pulse CS are usually ineffective in these severe types of AA.[6-16]

Methotrexate (MTX) is known to be effective in the treatment of severe and chronic autoimmune disorders including psoriasis, chronic eczema, and bullous pemphigoid.[17-19] In this study. I report my experience using MTX alone or in combination with low doses of oral CS to treat patients with severe forms of AA who previously failed to respond to conventional topical and/or systemic treatments.

Abbreviations used:

AA:	alopecia areata
CS:	corticosteroids
IV:	intravenous
MTX:	methotrexate

METHODS

Patients

In all, 22 patients (7 men and 15 women; mean age 37.6 ± 13.4 years) with AA totalis or AA universalis evolving for more than 1 year without hair regrowth despite previous conventional treatments were treated by MTX. Mean duration of disease was 11.1 ± 8.8 years. None of the 22 patients had previously responded to the following treatments including: clobetasol propionate cream 0.05% (n = 22), psoralen-UVA therapy (n = 22), tacrolimus (n = 3), oral prednisone (20-40 mg/d) (n = 9), and high-dose IV pulse CS (n = 4).

Treatment regimen

MTX was given once weekly at an initial dose of 15 mg (n = 3), 20 mg (n = 9), or 25 mg (n = 10) (Table I). In all, 15 patients took MTX orally and 7 by subcutaneous injections. Three patients who did not respond to an initial dose of 25 mg had their MTX dose increased up to 30 mg once weekly. MTX was stopped in patients who did not achieve a beginning of terminal hair regrowth after 9 months of treatment. In patients with regrowth of terminal hair, MTX was continued at the same dose until 18 months after the beginning of hair regrowth. MTX doses were then gradually tapered and then later stopped.

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Table I. Baseline characteristics and follow-up data of the 22 patients with severe alopecia areata treated with methotrexate

Patient No./ sex/ age, y	Duration of disease before treatment, y	Patient weight, kg	Initial treatment methotrexate, mg/wk	Initial treatment prednisone, mg/d	Hair regrowth	Delay to the begining of diffuse regrowth	Follow-up duration, mo	Relapse during decrease of doses or after stopping treatment	Treatment at the end of study methotrexate, mg/wk	Treatment at the end of study prednisone, mg/d	Status at the end of the study
1/F/19	6	69	15	0	Incomplete	-	-	-	-	-	Failure
2/M/40	10	82	15	0	No	-	-	-	-	-	Failure
3/F/46	12	69	20	0	Incomplete	-	-	-	-	-	Failure
4/F/38	8	71	20	0	Complete	7	21	Yes; focal	0	0	Focal AA
5/F/25	13	55.5	25	0	Complete	7	16	No; relapse	25	0	Complete regrowth
6/F/23	2	55	25	0	Complete	5	11	Yes; focal	30	0	Complete regrowth
7/F/39	4	72	15	10	Incomplete	-	-	-	-	-	Failure
8/F/25	5	63	20	20	Complete	4	9	No; relapse	20	0	Complete regrowth
9/M/40	13	81	20	20	Complete	4	38	Yes; focal	0	0	Focal AA
10/F/69	33	61.5	20	20	Complete	4	14	Yes; focal	20	3	Complete regrowth
11/F/24	6	63	20	20	Complete	3	72	Yes; focal	0	0	Complete regrowth
12/F/40	1	57	20	20	Complete	3	23	Yes; multifocal	25*	5	Complete regrowth
13/F/41	9	79	20	20	No	-	-	-	-	-	Failure
14/F/50	1	64	20	20	Complete	2	6	No; relapse	20	5	Complete regrowth
15/M/31	4	74	25	20	Complete	3	6	No; relapse	25	7.5	Complete regrowth
16/F/39	30	58	25	20	Complete	3	9	No; relapse	25	5	Complete regrowth
17/M/24	20	85	25	20	Incomplete	-	-	-	-	-	Failure
18/F/41	17	70	25	20	Complete	2	28	Yes; multifocal	20*	0	Complete regrowth
19/F/42	12	66	25	20	Incomplete	-	-	-	-	-	Failure
20/M/70	22	80	25	20	Incomplete	-	-	-	-	-	Failure
21/M/37	3	72	25	20	Complete	2	24	Yes; diffuse	25*	5	Complete regrowth
22/M/25	12	84	25	20	Complete	3	6	No; relapse	25	5	Complete regrowth

AA, Alopecia areata; *F*, female; *M*, male.
*Retreatment by methotrexate.

In all, 16 patients were treated by MTX and low doses of oral CS, and 6 others by MTX without oral CS. The reasons indicated by patients who wished to be treated by MTX without CS were: failure of a previous oral or IV CS treatment; apprehension of CS adverse effects; or both. Oral prednisone was given at an initial dose of 10 mg in one patient and 20 mg/d in 15 others (Table I). Oral CS was given at the initial dose until the beginning of terminal hair regrowth. CS doses were then gradually tapered and then stopped if possible, after 6 to 12 months of treatment.

Follow-up and assessment of efficacy

Patients were monitored on a monthly basis during the first 3 months of treatment, and were then followed up every 2 months. Complete blood cell count and serum aspartate aminotransferase were obtained at monthly intervals during treatment.

Evaluation of therapy was performed clinically and by using photographs. To avoid any bias in the assessment of treatment efficacy, only a total regrowth of terminal hair during treatment was considered as treatment efficacy. Patients with patchy or

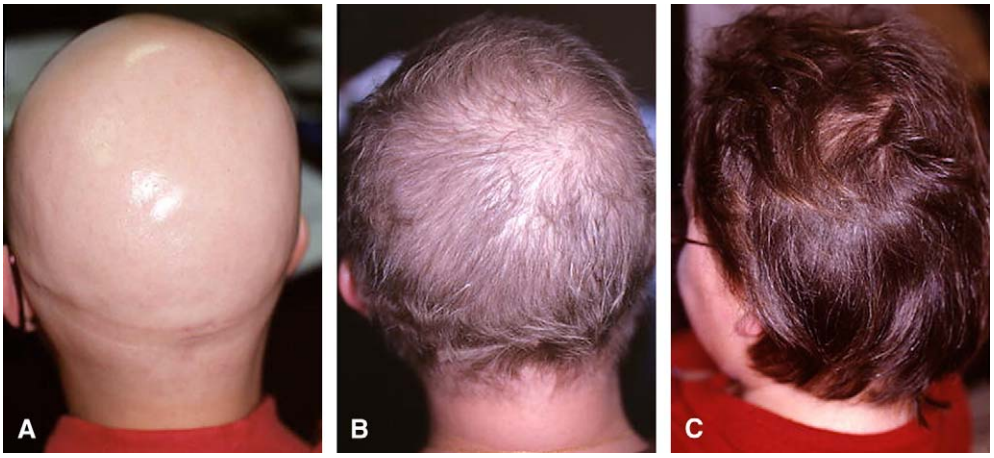

Fig 1. Patient (42-year-old woman) with alopecia totalis before treatment (**A**), and on days 160 (**B**) and 360 (**C**) of treatment.

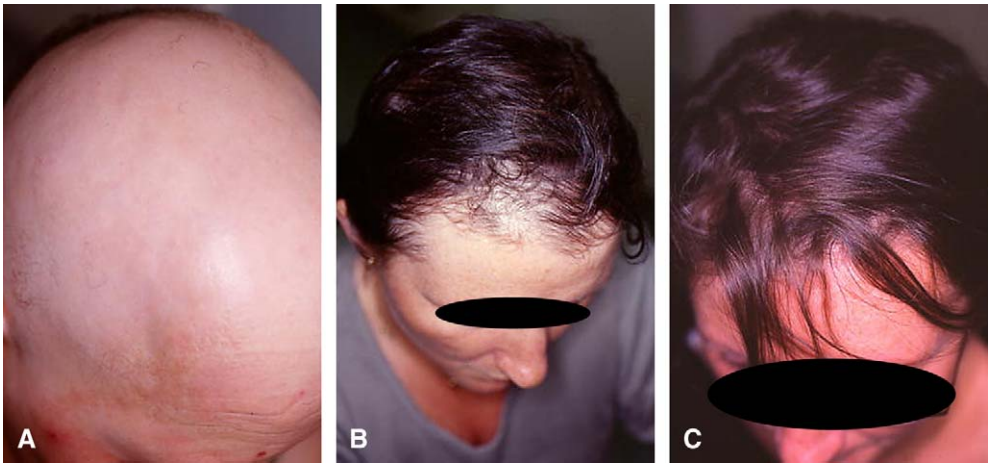

Fig 2. Patient (40-year-old woman) before treatment (**A**), and on days 240 (**B**) and 540 (**C**) of treatment.

incomplete hair regrowth were considered to have treatment failure.

Comparison between responder and nonresponder patients were carried out using a Mann-Whitney test.

RESULTS

Treatment efficacy

The main characteristics at baseline of patients are summarized in Table I.

Of the 22 patients treated by MTX, 14 (64%) had total hair regrowth, and 8 (36%) were considered to have treatment failures: 6 of them had patchy or incomplete hair regrowth and no response was observed in the two other patients. A complete hair regrowth was observed in 11 of the 16 patients (68%) treated with the combined treatment, and in 3 of the 6 (50%) treated by MTX alone (Table I). Regrowth of terminal hair began after a mean duration of 3.0 and 6.3 months, respectively (Fig 1-4).

Mean body weight of women who experienced total hair regrowth was significantly lower than that of nonresponder patients: 61.8 ± 5.6 versus 71.0 ± 4.9 kg (P = .02) (Table II).

Follow-up and treatment side effects

Median follow-up of patients after treatment was 15.0 months (6-72 months) (Table I). Oral CS had been stopped in all but 7 patients who still received prednisone (3-7.5 mg/d) at the end of the study. MTX was stopped after 18 months of treatment in 6 of the 14 patients who achieved total hair regrowth. Three patients had no relapse after a mean duration of 22.6 months after MTX withdrawal. The 3 other patients relapsed after a mean time of 3.6 months after MTX discontinuation (Table I). Interestingly, retreatment

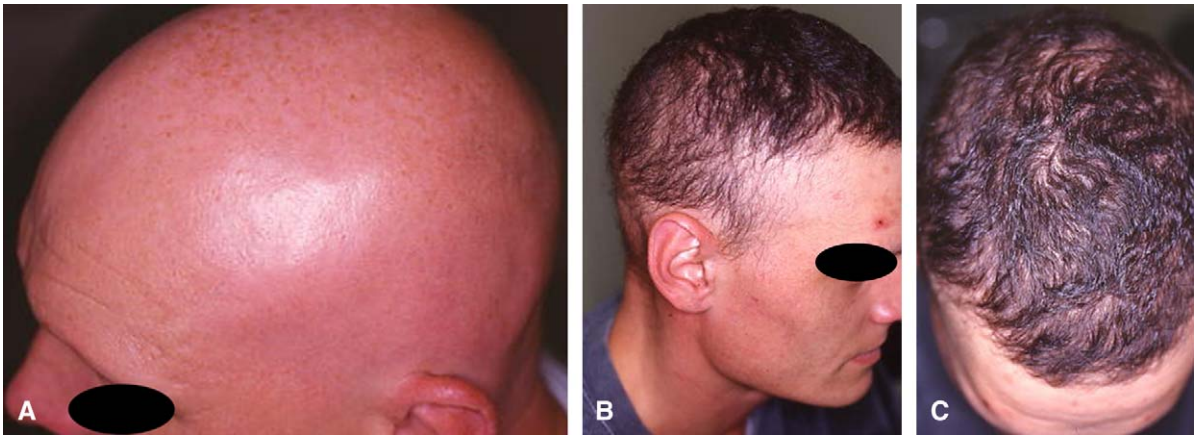

Fig 3. Patient (27-year-old man) before treatment (**A**), and on day 360 (**B** and **C**) of treatment.

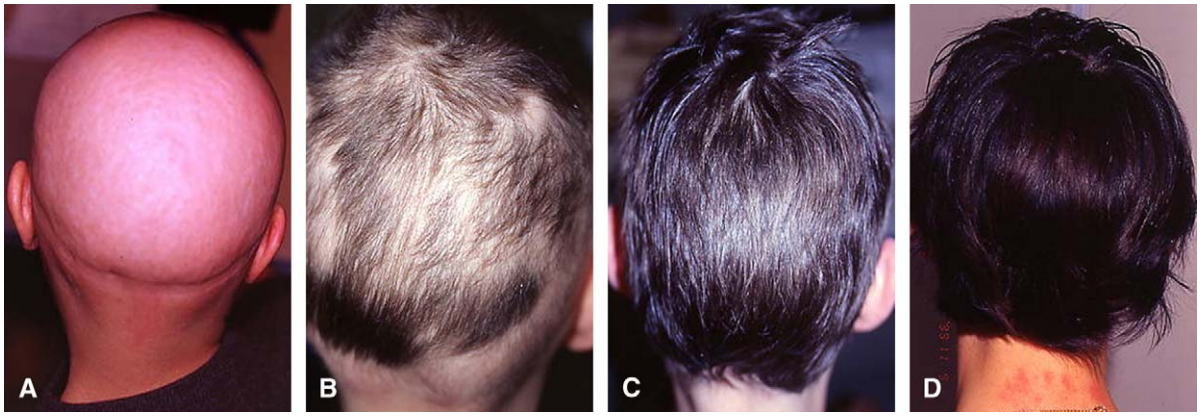

Fig 4. Patient (25-year-old-woman) before treatment (**A**), and on days 90 (**B**), 360 (**C**), and 540 (**D**) of treatment.

of these patients by MTX resulted again in a diffuse hair regrowth.

Two patients experienced transient elevated transaminase values, and one had persistent nausea after 6 months of treatment. MTX was stopped in this latter patient who was considered to have a treatment failure.

DISCUSSION

Despite its noncontrolled character, this study suggests that a treatment regimen of MTX in combination with low doses of CS may be effective in severe types of AA. MTX alone may also be considered in some patients, although the number of patients treated without CS in this study was limited. A spontaneous recovery of AA appears unlikely in these selected patients with extremely unfavorable prognoses. Indeed, all patients from this series had long-term (11.0 years) AA totalis or universalis that did not respond to numerous previous conventional therapies including topical, oral, or IV CS, and psoralen-UVA. Whereas spontaneous hair regrowth is frequently observed in recent multifocal AA, it is exceptional in long-term AA totalis or universalis.[13,20,21]

Table II. Comparison of age and weight of patients, and duration of disease between responders and nonresponders

Characteristics		Responders	Poor/ nonresponders	*P* values
No. of patients		14	8	
Mean ± SD age, y		36.2 ± 12.6	40.1 ± 15.3	.35
Mean ± SD duration, y		10.6 ± 10.2	11.9 ± 6.3	.41
Mean ± SD weight, kg	Male	77.7 ± 5.7	82.3 ± 2.5	.29
	Female	61.8 ± 5.6	71.0 ± 4.9	.02

Only total hair regrowth was considered as treatment efficacy. Despite the severity of this evaluation criteria, the 64% rate of total hair regrowth observed

using this treatment regimen is higher than that observed with all other previously tested treatments.[6,7-16] As a comparison, we did not observe any complete hair regrowth among the 30 patients with long-term AA totalis or universalis treated in our department before the study period with different treatment regimens including high-dose pulse CS therapy, psoralen-UVA, superpotent topical CS, or tacrolimus. Interestingly, none of the 3 patients treated with 15 mg/wk of MTX had a complete regrowth, as compared with 14 of 19 (74%) of those treated with 20 to 25 mg/wk.

Relapses during decrease of MTX doses or after stopping treatment were commonly observed (8/14 cases) in patients who experienced an initial complete hair regrowth. However, it should be underlined that most of these patients had focal relapses that were easily treated using topical or intralesional CS, whereas retreatment with MTX resulted again in diffuse hair regrowth in the 3 patients with more severe relapse (Table I).

An important point is the benefits/risks ratio of this treatment regimen. It should first be underlined that the impairment of the quality of life of patients with AA totalis or universalis is probably close to that observed in other chronic autoimmune dermatoses such as severe psoriasis or eczema, which are commonly treated by MTX.[22-24] Despite the fact that the treatment regimen tested in this study was well tolerated with no serious adverse events, the potential side effects of long-term MTX treatment have to be taken account. However, this is a common problem in most chronic inflammatory dermatoses such as psoriasis or chronic eczema.[17,18]

In conclusion, our study shows that MTX alone or in combination with low doses of oral CS may be a safe and successful treatment in AA totalis or universalis. The long-term efficacy of this treatment warrants further investigations.

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