HIGH-DOSE STEROID PULSE THERAPY FOR THE TREATMENT OF SEVERE ALOPECIA AREATA

Ya-Ming Tsai, WenChieh Chen, Ming-Long Hsu, and Tzu-Kai Lin

Abstract: Growing evidence shows alopecia areata (AA) to be a T cell-mediated organ-specific autoimmune disease. This study aimed to evaluate the efficacy of high-dose steroid pulse therapy in Taiwanese patients with severe widespread AA exceeding 40% of the scalp. A total of 17 Taiwanese patients with severe AA lasting less than 2 years were treated once monthly at the outpatient clinic for six sessions. Children younger than 12 years of age received oral prednisolone (5 mg/kg) in three divided doses, while for adults, 500 mg methylprednisolone was infused intravenously over 2 hours. Patients with multifocal AA exhibited the most favorable response, with more than 75% hair regrowth (9/11). Relapse occurred in two patients at 4 and 8 months after the last treatment, respectively. One patient with ophiatic AA showed a transient response, but subsequently lost hair even upon continuation of therapy. Two patients of four with alopecia totalis had full hair regrowth but one lost hair again 6 months later. In the only patient with alopecia universalis, less than 10% hair regrowth occurred. No major side effects were observed. In summary, 11 of 17 patients (64.7%) had more than 75% hair regrowth after steroid pulse therapy. Our results indicated that steroid pulse therapy, given at 5–10 mg/kg once monthly for an average of 6 months, is effective and well tolerated in Taiwanese patients with severe multifocal AA lasting less than 2 years.

(J Formos Med Assoc 2002;**101**:223–6*)*

Key words:
alopecia areata
corticosteroids
pulse therapy

Alopecia areata (AA) is a common disease of hair follicles that produces sudden, nonscarring, often patchy hair loss, and affects 1% of the population [1]. It may progress relentlessly to total hair loss in alopecia totalis (AT; 10% of AA) or alopecia universalis (AU; 3% of AA) [1]. AA involving more than 40% of the scalp area can severely affect a patient's quality of life and its management is often a challenge to dermatologists. Daily oral corticosteroids may be effective, but the side effects of prolonged therapy limit their use. High-dose steroid pulse therapy has been reported to be an effective and well-tolerated treatment option, especially for rapidly progressing extensive multifocal AA, but not for ophiatic AA, AT, and AU [2, 3]. This study aimed to evaluate the efficacy of high-dose steroid pulse therapy in Taiwanese patients with severe widespread AA.

Materials and Methods

Severe AA was defined as a balding area exceeding 40% of the scalp. Patients with severe AA lasting less than 2 years (first occurrence or relapse) were recruited for this open-label study. Patients were excluded if they had peptic ulcer, diabetes mellitus, psychosis, severe hypertension, cardiac arrhythmia, cardiac failure, acute or chronic infection, avascular necrosis of the hip, or seizure history. All patients were treated at the outpatient clinic once monthly for six sessions. For children younger than 12 years of age, oral prednisolone (5 mg/kg) was given in three divided doses during one day each month, while for adults, 500 mg methylprednisolone

Department of Dermatology, College of Medicine, National Cheng Kung University, Tainan.
Received: 24 July 2001. Revised: 20 August 2001. Accepted: 6 November 2001.
Reprint requests and correspondence to: Dr. WenChieh Chen, Department of Dermatology, College of Medicine, National Cheng Kung University, 138 Sheng-Li Road, Tainan, Taiwan.

was infused intravenously over 2 hours each month. Before commencement of therapy, laboratory examinations were performed including complete blood count, fasting glucose, bilirubin, aspartate aminotransferase, alanine aminotransferase, blood urea nitrogen, creatinine, antinuclear antibodies, antiparietal antibody, antithyroglobulin antibody, antimicrosome antibody, thyroxine, and thyroid-stimulating hormone. Patients were photographed regularly before, during, and after treatment according to a standardized procedure [4]. The extent of hair growth was evaluated by two dermatologists who were blinded to the treatment, and the results were averaged. Satisfactory response was defined as more than 75% hair regrowth.

Results

Seventeen patients (eight men, nine women) with an age range of 8 to 53 years (mean, 25.0 yr), including 11 with multifocal AA, one with ophiatic AA, four with AT, and one with AU, were included in this study and followed up for 3 to 20 months after cessation of the last treatment. Results of laboratory examinations were all within normal ranges. The most common complaints were epigastralgia, dizziness, and generalized warm sensation. No major side effect was observed. All patients with multifocal AA exhibited partial hair regrowth within 4 months, and nine (81.8%) had more than 75% hair regrowth at the completion of one to six sessions of treatment (Figs. 1 and 2). However, relapse occurred in two patients at 4 and 8 months after the last treatment, respectively. The patient with ophiatic AA showed transient hair regrowth after one treatment session, but subsequently lost hair despite continuation of therapy. Among the four patients with AT, one 23-year-old female patient lost her hair for the first time one month after she delivered her second baby, and had 90% hair regrowth after five sessions of pulse therapy. A 31-year-old man with AT had full regrowth after eight sessions of steroid pulse therapy, but had relapse 6 months later. He received another identical course of steroid pulse therapy and his hair regrew again to 90% and remained for 14 months. In the AU patient, less than 10% hair regrowth over the scalp was observed, without cosmetic significance.

Hair regrowth of more than 75% occurred in 11 of 17 patients (64.7%) after steroid pulse therapy. At a mean of 10.7 months follow-up, these patients had an average disease-free interval of 9.8 months. Three patients had relapse 4, 6, and 8 months after the last treatment, respectively. The Table summarizes the clinical characteristics, treatment response, and remission time after completion of therapy.

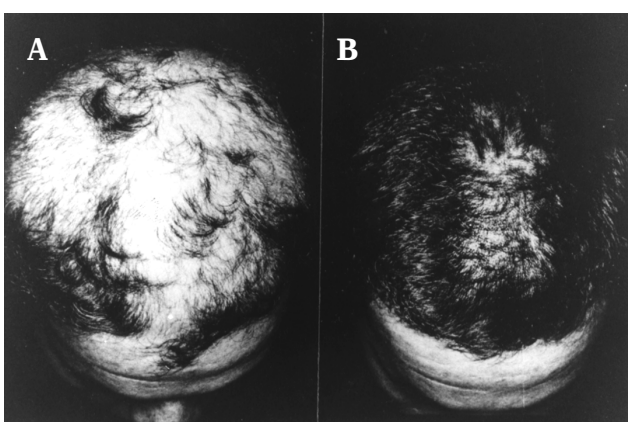

Fig. 1. *A) Scalp photograph of a 30-year-old woman with multifocal alopecia areata for 3 months; B) 10 months after beginning treatment with intravenous 250 mg methylprednisolone once monthly.*

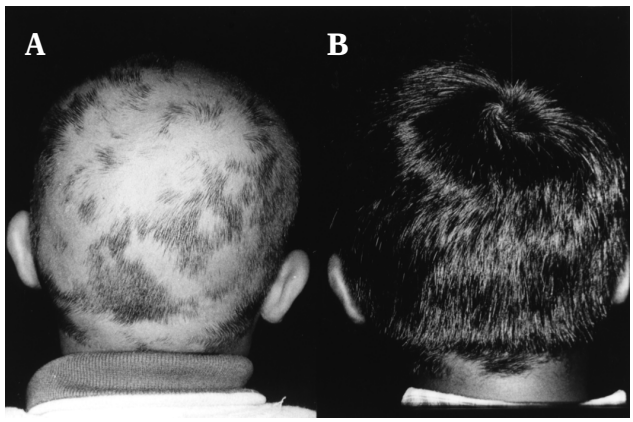

Fig. 2. *A) Scalp photograph of an 8-year-old boy with multifocal alopecia areata for 6 months; B) 7 months after beginning treatment with oral 5 mg/kg prednisolone monthly.*

Discussion

The etiology of AA is not yet fully defined. Many reports have suggested that AA is a T cell-mediated, tissue-restricted, organ-specific autoimmune disease [5–7]. High-dose steroid pulse therapy has long been used for management of transplantation rejection and autoimmune diseases [8, 9]. In dermatology, the largest experience with this regimen has been reported in patients with pemphigus [10]. Several clinical studies have shown encouraging therapeutic results for rapidly progressing extensive AA with 5 to 10 mg/kg prednisolone pulsed at 4-week intervals, or methylprednisolone 5 mg/kg given twice a day for 3 sequential days [2, 3]. The mechanism responsible for the effectiveness of this regimen is not yet completely understood. The immunosuppressive action of glucocorticoid has been proposed to be due to the following: blockage of mature T-cell proliferation through the inhibition of interleukin 2 (IL-2) production; induction of apoptosis in human peripheral blood T lymphocytes; inhibition of the production of pro-inflammatory cytokines such as tumor necrosis factor α, IL-8 and IL-1 β; and inhibition of the expression of adhesion molecules on endothelial cells, such as vascular cell adhesion molecule-1 [10–12].

Table. Profile of alopecia areata (AA) patients treated with high-dose steroid pulse therapy

AA Pattern	Age at onset (yr)	Sex	Disease duration before treatment (mo)	Treatment (sessions)	Initial response (sessions)*	Hair regrowth (75%)	Remission time after treatment (mo)
Mu	48	M	0.5	iv x4	2	≥	20
Mu	20	M	2	iv x2	1	≥	16
Mu	29	F	2	iv x1	1	≥	16
Mu	30	F	3	iv x6	4	≥	16
Mu	45	F	2	iv x5	2	≥	7
Mu	19	F	4	iv x3	1	≥	4
Mu	53	F	6	iv x3	2	≥	8
Mu	28	M	2	iv x6	2	≥	4†
Mu	8	M	6	po x6	2	≥	8†
Mu	15	F	0.5	iv x6	1	<	0
Mu	15	F	4	iv x6	1	<	0
O	13	F	6	po x6	1	<	0
AT	23	F	5	iv x5	2	≥	3
AT	22	M	24	iv x5	N	<	0
AT	16	M	12	iv x6	2	<	0
AT	31	M	2	iv x8	4	≥	6†
AU	8	M	24	po x5	N	<	0

Mu = multifocal AA; M = male; iv = 500 mg methylprednisolone intravenously monthly; F = female; po = prednisolone (5 mg/kg) monthly; O = ophiatic AA; AT = alopecia totalis; N = no response; AU = alopecia universalis. *Initial response = number of sessions needed to stop further hair loss; †relapse.

In our study, satisfactory hair regrowth (> 75%) was obtained in 11 (64.7%) patients with severe AA. This is similar to the reported response rate, which has ranged from 42.2% to 71% [2, 3]. In agreement with previous reports, no serious side effects occurred in our study. Hair regrowth was observed on average after 2 months in our study, which is compatible with the finding of 2.4 months in Sharma's series [2].

Steroid pulse therapy seems to be much less effective for ophiatic AA, AT/AU, and protracted disease lasting more than 2 years [2, 3]. Friedli et al treated 45 patients with steroid pulse therapy and satisfactory results were observed in 70% of cases of multifocal AA, but only in 10% of patients with ophiatic AA, and in 26.7% of patients with AT/AU [3]. Sharma found cosmetically acceptable hair growth in 13 of 19 (68.4%) AA patients, none of four AU patients, and the one AT patient [2]. Among our 11 patients who had more than 75% hair regrowth, relapse occurred in three (27.3%) patients at a mean time of 6 months after completion of the 6-month regimen. The treatment was repeated for one more course in one patient with AT and a comparable result was achieved.

The natural course of AA during pregnancy has been poorly delineated. Asanuma et al reported the case of a woman with AU for 7 years who had spontaneous hair regrowth up to 2.5 cm in length until the third trimester of pregnancy, but lost all of her hair again 5 months after delivery [13]. Recently, there has been further evidence to support the theory that maternal T helper cell type 1/2 cytokine balance shifts towards T helper cell type 2 dominance during pregnancy [14, 15]. This theory suggests that diseases of cell-mediated disorders such as AA may likewise have a temporary remission in gestation. However, in one of our patients, AT occurred for the first time 1 month postpartum.

Other systemic treatments for severe AA include zinc sulfate, diaminodiphenylsulfone (dapson), 8-methoxypsoralen plus ultraviolet A irradiation (PUVA), and cyclosporine [16–19]. The effect of zinc sulfate is still controversial. Ead's study of 42 patients found no improvement in the extent or activity of the disease in the zinc sulfate-treated group compared with the placebo group [16]. van Baar et al treated 27 patients with dapson for 10 months and found a response rate of 57.1% in multifocal AA and 10% in AT/AU [17]. Healy and Rogers found systemic PUVA therapy achieved hair regrowth in 53% of severe AA patients [18]. Gupta et al treated six patients (two patchy AA, three AU, one AT) with oral cyclosporine 6 mg/kg/day for 12 weeks and found cosmetically acceptable hair regrowth occurred in 50% of patients, but significant hair loss appeared in all patients within 3 months after discontinuation of the agent [19]. Compared to the efficacy rates of the other therapeutic options discussed above, our data indicated steroid pulse therapy had a slightly higher efficacy rate (64.7%) and acted within a shorter period of time.

In summary, the results of this study indicate that steroid pulse therapy is effective and well tolerated in Taiwanese patients with rapidly progressive extensive multifocal AA lasting less than 2 years. The response rate with cosmetically significant hair regrowth was more than 60% in this series. Of major concern is the long-term safety of this treatment modality. It also remains to be determined whether this therapy alters the disease course and prognosis.

References

1. Gollnick H, Orfanos CE: Alopecia areata: pathogenesis and clinical pictures. In: Orfanos CE, Happle R, eds. *Hair and Hair Diseases.* Berlin: Springer-Verlag, 1989:529–69.
2. Sharma VK: Pulsed administration of corticosteroids in the treatment of alopecia areata. *Int J Dermatol* 1996;35:133–6.
3. Friedli A, Labarthe MP, Engelhardt E, et al: Pulse methylprednisolone therapy for severe alopecia: an open prospective study of 45 patients. *J Am Acad Dermatol* 1998;39:597–602.
4. Canfield D: Photographic documentation of hair growth in androgenetic alopecia. *Dermatol Clin* 1996;14:713–21.
5. Perret C, Wiesner-Menzel L, Happle R: Immunohistochemical analysis of T-cell subsets in the peribulbar and intrabulbar infiltrates of alopecia areata. *Acta Derm Venereol* 1984;64:26–30.
6. Kalish RS, Johnson KL, Hordinsky MK: Alopecia areata. Autoreactive T cells are variably enriched in scalp lesions relative to peripheral blood. *Arch Dermatol* 1992;128:1072–7.
7. Gilhar A, Ullmann Y, Berkutzki T, et al: Autoimmune hair loss (alopecia areata) transferred by T lymphocytes to human scalp explants on SCID mice. *J Clin Invest* 1998;101:62–7.
8. Bell PR, Briggis JD, Calman KG, et al: Reversal of acute clinical and experimental organ rejection using large doses of intravenous prednisolone. *Lancet* 1971;i:876–80.
9. Cathcart ES, Idelson BA, Scheinberg MA, et al: Beneficial effects of methylprednisolone "pulse" therapy in diffuse proliferative lupus nephritis. *Lancet* 1975;i:163–6.
10. Roujeau J-C: Pulse glucocorticoid therapy. The "Big Shot" revisited. *Arch Dermatol* 1996;132:1499–502.
11. Migita K, Eguchi K, Kawabe Y, et al: Apoptosis induction in human peripheral blood T lymphocytes by high-dose steroid therapy. *Transplantation* 1997;4:583–7.
12. Kadioglu A, Sheldon P: Steroid pulse therapy for rheumatoid arthritis: effect on lymphocyte subsets and mononuclear cell adhesion. *Br J Rheumatol* 1998;37:282–6.
13. Asanuma N, Sakurai A, Aizawa T, et al: Alopecia universalis with remission during pregnancy and prednisolone therapy. *Am J Med Sci* 1997;313:67–9.
14. Iwatani Y, Watanabe M: The maternal immune system in health and disease. *Curr Opin Obstet Gynecol* 1998;10:453–8.
15. Raghupathy R: Pregnancy: success and failure within the Th1/Th2/Th3 paradigm. *Semin Immunol* 2001;13:219–27.
16. Ead RD: Oral zinc sulphate in alopecia areata—a double blind trial. *Br J Dermatol* 1981;104:483–4.
17. van Baar HM, van der Vleuten CJ, van de Kerkhof PC: Dapson versus topical immunotherapy in alopecia areata. *Br J Dermatol* 1995;133:270–4.
18. Healy E, Rogers S: PUVA treatment for alopecia areata—does it work? A retrospective review of 102 cases. *Br J Dermatol* 1993; 129:42–4.
19. Gupta AK, Ellis CN, Cooper KD, et al: Oral cyclosporin for the treatment of alopecia areata. A clinical and immunohistochemical analysis. *J Am Acad Dermatol* 1990;22:242–50.