

Treatment of Severe Alopecia Areata: Combination Therapy Using Systemic Cyclosporine A with Low Dose Corticosteroids

Deborah Lee, M.D., Doo-Jin Oh, M.D., Jung-Wook Kim, M.D.¹, Sung-Wook Park, M.D.¹,
Min-Kyung Oh, Ph.D.², Ho-Suk Sung, M.D., Seon-Wook Hwang, M.D.

Department of Dermatology, Inje University School of Medicine,

¹Gwoonsesang Dermatology Clinic, ²Clinical Trial Center, Busan Paik Hospital, Busan, Korea

Background: Combination therapy using cyclosporine A (CsA) together with low-dose corticosteroids has adequate efficacy with little toxicity for the treatment of severe alopecia areata (AA).

Objective: We wanted to evaluate the clinical efficacy of combination therapy using CsA with low-dose corticosteroid for the treatment of severe AA and we also wanted to determine the safe therapeutic concentration of CsA in the peripheral blood.

Methods: We treated 34 cases of severe AA with combination therapy for 24 weeks and we evaluated the efficacy at 12 and 24 weeks. We monitored the peripheral blood concentration of CsA to determine the therapeutic range of CsA that has the fewest side effects.

Results: Of the patients, 77.4% (n=24) and 22.6% (n=10) were classified in the responder and poor-responder groups, respectively. The mean trough concentration of CsA was 95.1 and 101.2 ng/ml in the responder and poor-responder groups, respectively. For the patients with side effects associated with CsA, the mean CsA concentration was 195.8 ng/ml.

Conclusion: We found that combination therapy with systemic CsA and low-dose corticosteroids effectively treats severe AA and this therapy results in a safe, therapeutic concentration of CsA in the peripheral blood.

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Key Words: Alopecia areata, Cyclosporine A, Low-dose corticosteroids

INTRODUCTION

Treating patients with alopecia areata (AA) remains difficult, and many treatment modalities have been used, including intralesional, topical and systemic corticosteroids, ultraviolet light and contact sensitizers¹⁻⁸. Of these, systemic corticosteroids are

effective for the treatment of severe AA³⁻⁵, but to maintain hair regrowth, an increase in the dosage is inevitable. A high dose of systemic corticosteroids poses a major concern because of the side effects of systemic steroid use, such as diabetic mellitus, hypertension, acne, psychological changes, osteoporosis and the suppression of the adrenocorticotrophic axis.

Cyclosporine A (CsA) is a cyclic, lipophilic undecapeptide that selectively and reversibly inhibits the T cell-mediated immune response by suppressing the phosphatase activity of calcineurin. Calcineurin regulates the nuclear factor of activated T cells (NFAT) and it also induces T cell activation by regulating the interleukin-2 (IL-2) gene expression and increasing the production of IL-2, which stimulates the secretion of interferon- γ (IFN- γ)^{9,10}.

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Reprint request to: Seon-Wook Hwang, M.D., Department of Dermatology, Busan Paik Hospital, College of Medicine, Inje University, 633-165, Gaeguem-dong, Busanjin-gu, Busan 614-735, Korea. Tel: 82-51-890-6135, Fax: 82-51-897-6391, E-mail: deany77@paran.com

The immunologic cascade leading to AA is believed to involve these events because IL-2 and IFN- γ are involved in the pathogenesis of AA. Therefore, CsA is thought to be effective for treating AA because it eliminates immune cells from the hair follicles.

Corticosteroids are nonselective immunosuppressive agents that inhibit the late-phase antigen-independent inflammatory reaction. In addition, they decrease the availability of nuclear factor kappa B and IL-2 gene transcription¹¹. Since CsA acts as an early immune modulator at the induction phase, combination therapy with CsA and corticosteroids may have synergistic effects on immunosuppression¹¹. Although several studies have used systemic CsA in combination with corticosteroids for the treatment of severe AA¹²⁻¹⁴, the results have been variable. Many studies that used CsA as a treatment modality recommended monitoring the peripheral blood concentration of CsA to evaluate the efficacy of treatment and avoid CsA-related toxicity¹⁵⁻¹⁷.

In this study, we evaluated the efficacy of a combination therapy using CsA with low-dose corticosteroids for treating patients with severe AA and we estimated the therapeutic range of the trough concentration of CsA for this treatment.

MATERIALS AND METHODS

Patients

Thirty-four patients (16 men and 18 women) with severe or refractory AA were enrolled in this study. Their mean age was 28.1 years (range: 6~54 years) and the duration of the disease ranged from 6 months to 16 years.

The extent of AA was evaluated in accordance with the National Alopecia Areata Foundation guidelines¹⁸: S0: no hair loss, S1: <25% hair loss, S2: 26~50% hair loss, S3: 51~75% hair loss, S4: 76~99% hair loss, alopecia totalis (AT): total scalp hair loss and alopecia universalis (AU): total scalp and body hair loss. Of the 34 patients, eight had AU and seven had alopecia totalis/universalis (AT/AU), which is defined as alopecia totalis with various degrees of body hair loss, 16 patients had patchy AA involving more than 50% of the scalp (S3: 8, S4: 7), one had involvement of less than 50% of the scalp (S2: 2) and two had ophiasis. None of the patients had previously responded to

conventional treatments at least 6 months follow-up.

Treatment regimens

CsA was started at a dose of 2.5 to 5 mg/kg/day and methyl prednisone was started at a dose of 20 to 24 mg/day. The dose of methyl prednisone was subsequently tapered to 4 mg/day for 3 weeks, and then the methyl prednisone was maintained at a dose of 2 to 4 mg/day, according to the treatment response.

Evaluation of efficacy

All the patients were monitored on a monthly basis during the 24 weeks. Each patient was photographed at baseline and at 1, 3 and 6 months of treatment.

The responders were defined as the patients who recovered more than 50% of hair regrowth, while poor responders had less than 50% of regrowth. The responders were subclassified into cosmetically acceptable responders, and these were defined as patients with 75 to 100% hair regrowth, and satisfactory responders had 50 to 74% hair regrowth.

Monitoring of the trough CsA concentration and the laboratory data

To estimate the therapeutic concentration of CsA, blood samples were collected immediately before the oral administration of CsA and then they were analyzed. The initial trough concentration of CsA was measured 2 weeks after initiating the treatment, and the maintenance trough concentration was measured 1, 3 and 6 months after beginning the treatment. Blood pressure, complete blood counts, serum transaminase, blood urea nitrogen, creatinine, direct bilirubin and urinalysis were checked at 1, 3, and 6 months to evaluate the side effects associated with CsA and corticosteroid combination therapy.

Statistical analysis

Statistical analysis was performed using SAS version 9.1.3 (SAS Institute, Cary, NC, USA). The chi-square test was used to compare the trough concentrations of CsA between the responders and poor responders and between the groups with and without side effects.

RESULTS

Response

Of all the patients, 77.4% (n=24) were classified into the responder group (Table 1). Of these 24 patients, 66.6% (n=16) were cosmetically acceptable responders, and 33.3% (n=8) were satisfactory responders (Fig. 1). The initial response time ranged from 4 to 9.5 weeks with a mean of 5.4 weeks. The mean dose of methyl prednisone during the maintenance phase was 2.9 mg/day and the dose ranged from 2 to 6 mg/day. The type with the best response was ophiasis, followed in order by patchy AA affecting more than 50% of the scalp, AU and

AT/AU. The least responsive type of AA was patchy AA affecting less than 50% of the scalp.

Of the patients, 22.6% (n=10) were classified into the poor-responder group (Table 2).

Trough CsA concentrations in the responders and poor responders

The trough CsA concentrations were determined for all the patients. For the responders, the mean CsA dose for maintenance was 3.0 mg/kg/day (2.5 ~3.9 mg/kg/day) and the mean trough concentration for an initial response was 88.4 ng/ml (range: 33.4 ~141.4 ng/ml). The mean trough concentration of CsA for maintenance was 94.2 ng/ml

Table 1. Demographic data of 24 patients of the clinical responders

	Sex/Age	Extent of AA*	Duration	Initial response (weeks)	Side effect	MTC [†] (ng/ml)	Mean CsA [†] (mg/kg)	MPDS [§] (mg/day)
1	M/35	AU	1 year	5		52.1	3.21	4
2	M/10	AU	5 years	4	Hypertrichosis	34.8	2.42	2
3	M/6	AU	1.5 years	8		34.6	2.77	2
4	F/27	AU	2.5 years	4	Hematuria, hyperbilirubinemia	143.3	4.46	4
5	M/22	AU	7 years	9.5	Hyperbilirubinemia	162.1	4.29	4
6	F/16	AT/AU	7 years	14		58.9	3.18	2
7	F/23	AT/AU	3 years	3.5	Hypertrichosis	126.9	3.37	4
8	M/40	AT/AU	1 year	6		146.8	3.08	2
9	M/16	AT/AU	4 years	6		141.4	3.23	4
10	M/29	S4	1.5 years	4		79.2	3.51	2
11	F/20	S4	16 years	2.5		87.0	3.15	2
12	F/23	S4	6 years	3	Hyperlipidemia	111.6	2.08	2
13	M/22	S4	4 years	6.5		51.5	3.33	6
14	M/15	S4	8 months	5		121.1	2.82	2
15	M/25	S4	2 years	3.5		70.1	2.36	4
16	F/20	S4	16 years	7	Hypercholesterolemia	69.4	2.17	2
17	F/54	S3	2 years	4		108.0	3.24	4
18	M/35	S3	3 years	5	Weakness	109.9	2.41	6
19	F/25	S3	5 years	4		108.9	3.70	2
20	F/16	S3	6 months	6		117.1	3.85	4
21	F/25	S3	1 year	7		22.1	2.13	2
22	F/45	S2	6 months	4		48.2	2.40	2
23	M/17	Ophiasis	4 months	2.5		100.3	2.86	4
24	F/41	Ophiasis	10 years	3	Hypertension	156.2	2.21	2

*Extent of AA: in accordance with the National Alopecia Areata Foundation guidelines: S0: no hair loss, S1: <25% hair loss, S2: 26~50%, S3: 51~75%, S4: 76~99%, Alopecia totalis (AT): total scalp hair loss, Alopecia universalis (AU): total scalp and body hair loss, Alopecia totalis/universalis (AT/AU): alopecia totalis with variable degrees of loss of body hair, [†]MTC: the mean trough concentration of cyclosporine A, [†]CsA: cyclosporin A, [§]MPDS: methylprednisone



Fig. 1. (A) A 10-year-old boy with alopecia universalis before and after 24 weeks of treatment. (B) A 23-year-old women with alopecia universalis before and after 24 weeks of treatment. (C) A 35-year-old man with alopecia universalis before and after 24 weeks of treatment. (D) A 16-year-old women with alopecia areata affecting more than 75% of hair loss before and after 24 weeks of treatment.

Table 2. Demographic data of 10 patients of the clinical poor responders

	Sex/Age	Extent of AA*	Duration	Side effect	MTC [†] (ng/ml)	Mean CsA [‡] (mg/kg)	MPDS [§] (mg/day)
1	M/10	AU	6 years	Hypertension	52.1	6.00	3
2	M/24	AU	9 months		177.6	3.57	4
3	F/48	AU	3 years		116.0	3.18	3
4	F/30	AT/AU	1.5 years		178.4	3.00	4
5	F/27	AT/AU	7 years		39.2	3.06	4
6	M/30	AT/AU	6.5 years		68.4	2.78	5
7	M/39	S3	6 months		43.8	3.44	6
8	F/40	S3	2 years	Hyperlipidemia	95.9	4.39	4
9	F/52	S3	1 year		122.2	3.85	4
10	F/52	S2	6 months	Hyperlipidemia	118.7	3.57	4

*Extent of AA: in accordance with the guidelines of National Alopecia Areata Foundation guidelines: S0: no hair loss, S1: <25% hair loss, S2: 26~50%, S3:51~75%, S4: 76~99%, Alopecia totalis (AT): total scalp hair loss, Alopecia universalis (AU): total scalp and body hair loss, Alopecia totalis/universalis (AT/AU): alopecia totalis with variable degrees of loss of body hair, [†]MTC: the mean trough concentration of cyclosporine A, [‡]CsA: cyclosporin A, [§]MPDS: methylprednisone

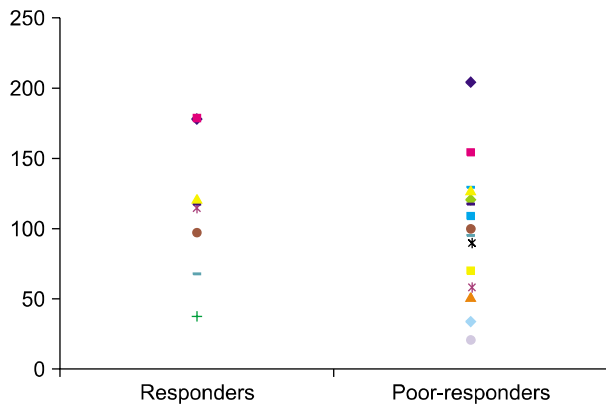


Fig. 2. Trough concentration of cyclosporine A in the responders and poor-responders. The mean trough concentration of cyclosporine A in the responders was 94.2 ng/ml (range: 22.1~162.1 ng/ml) and 101.2 ng/ml (range: 39.2~178.4 ng/ml) in the poor-responders. The responders displayed a lower mean trough concentration than did the poor-responders ($p < 0.05$).

(range: 22.1~156.2 ng/ml). For the poor responders, the mean CsA dose for maintenance was 3.7 mg/kg/day (range: 2.2~6.0 mg/kg/day) and the mean trough concentration was 101.2 ng/ml (range: 39.2~178.4 ng/ml). The mean dose of CsA for these two groups showed no statistical differences ($p > 0.05$). For the responders, most patients maintained their hair regrowth with trough CsA concentrations between 50 and 150 ng/ml (Fig. 2). The responders had a lower mean trough concentration than did the poor responders ($p < 0.05$).

In addition, the mean trough concentration was not related to either the duration of AA ($p = 0.33$) or the extent of AA ($p = 0.60$) for both groups.

Trough CsA concentration in the patients with and without side effects

In this study, 12 patients showed side effects associated with CsA (Fig. 3), including 4 with hyperlipidemia, 2 with hypertension, 2 with hypertrichosis, 2 with hyperbilirubinemia, 1 with weakness in the lower legs and 1 with hematuria (Table 1, 2). The mean dose of CsA that was used for these two groups showed no statistical differences ($p = 0.23$). For the group with side effects, the mean CsA concentration measured 195.8 ng/ml (range: 34.8~381.2 ng/ml). The mean concentration of CsA for the patients without side effects was 91.2

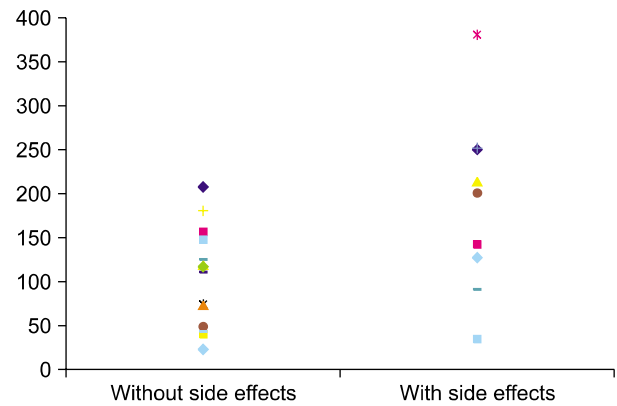


Fig. 3. Trough concentration of cyclosporine A in the patients with and without side effects. In the group with side effects, the mean concentration of cyclosporine A was 195.8 ng/ml (34.8~381.2 ng/ml). The mean concentration of cyclosporine A in the patients without side effects was 91.2 ng/ml (22.1~204.8 ng/ml). The difference of the trough concentration of cyclosporine A between these two groups was significant ($p < 0.05$).

ng/ml (range: 22.1~204.8 ng/ml). The difference in the trough CsA concentrations between these two groups was statistically significant ($p < 0.05$).

DISCUSSION

The effects of CsA for the treatment of AA have been assessed in various *in vitro* studies. Oliver et al⁹ demonstrated that oral CsA restored hair growth in the Dundee Experimental Bald Rat Model of AA by reducing the mononuclear cell infiltrate around the hair follicles and renewing hair growth. Gafer-Gvili et al¹⁰ reported that CsA-induced hair growth in mice was associated with the inhibition of the calcineurin-dependent activation of NFAT in the follicular keratinocytes. They found that CsA delays the duration of the terminal differentiation of hair follicular keratinocytes and it retards catagen induction. They further demonstrated that CsA induced hair regrowth through delaying the regression of hair follicles by inhibiting the apoptosis of follicular keratinocytes¹⁹.

However, the use of systemic CsA is also limited because its side effect profile is similar to that of systemic corticosteroids. CsA has a narrow therapeutic window and many side effects, including nephrotoxicity, neurotoxicity and hyperglycemia. Because

of these problems, therapeutic drug monitoring (TDM) is commonly used to optimize the efficacy and safety of CsA and TDM can provide a more optimal dosing strategy.

Combination therapy using systemic CsA and low-dose corticosteroid to treat AA has been previously reported on¹²⁻¹⁴, and TDM has helped to reduce the toxicity of these drugs, such as by preventing life-threatening infections via administering concentration-oriented therapy rather than dose-oriented therapy^{20,21}. However, the results of previous studies have shown variable success rates^{13,14,22} and the therapeutic range of the trough CsA concentration varied from study to study^{12,18}. Teshima et al¹² treated six AU patients using oral CsA at 2.5 mg/kg/day and prednisolone was started at a dose of 5 mg/day for 7 months. The CsA concentration was maintained at 30 to 50 ng/ml. An initial response appeared within 1 month and all the patients showed hair regrowth after 7 months of treatment. Ferrando et al¹⁸ treated 15 patients with severe AA by using CsA monotherapy; they administered CsA at a dose of 5 mg/kg/day for 6 to 12 months and they maintained the CsA concentration at 100 to 350 ng/ml. One patient discontinued treatment due to hypertension. Seven of the 14 patients had more than 70% hair regrowth, two had complete hair regrowth and five showed no response. CsA induced severe side effects such as gingival hypertrophy and hyperlipidemia. The authors recommended using CsA for 4 months duration for treating refractory AA.

In our study, 77.4% of the patients had hair regrowth exceeding 50%. They maintained the hair regrowth with trough concentrations between 50 and 150 ng/ml and they had lower mean trough concentrations than did the poor responders. Despite administering a higher dose of CsA to the poor responders, they had poorer hair regrowth rates.

In this study, 12 patients showed side effects associated with CsA. However, the side effects were either temporary or well managed. The hyperlipidemia and hypertension were controlled using hydroxymethylglutaryl-coenzyme A reductase inhibitors or antihypertensive agents, and the hyperbilirubinemia and hematuria cleared after tapering the dose of CsA. The weakness in the lower legs disappeared spontaneously within a few weeks. The mean CsA concentration was 195.8 ng/ml in the

patients with side effects and 91.2 ng/ml in those patients without side effects. Interestingly, except one patient, most of the patients without side effects maintained trough concentration under 200 ng/ml, and two-third of the patients with side effects showed side effects when the trough concentration was over 200 ng/ml. In the light of these results, we recommend that it is helpful for minimizing side effects to maintain the CsA trough concentration under 200 ng/ml. A further study with a larger number of AA patients is required to establish a more effective, safe treatment strategy with using oral CsA and low dose corticosteroids combination therapy.

Recent studies have reported on the immunologic aspects associated with the severity and prognosis of AA^{21,23}, and so further studies are needed to identify the genetic and immunologic factors that may play a role for the inter-individual variations in the pharmacokinetics of CsA or the prognosis of AA.

This study demonstrated that systemic CsA and low-dose corticosteroid combination therapy for patients suffering with severe AA led to a high response rate with steroid-sparing effects, and there were no severe side effects. The therapeutic range of the trough CsA concentration for maintenance was 50~150 ng/ml.

Further concentration-oriented studies with more patients are required to establish the optimal dose regimen of oral CsA and low dose corticosteroids combination therapy for treating patients with AA.

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