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ORIGINAL ARTICLE

# Early Intervention with High-Dose Steroid Pulse Therapy Prolongs Disease-Free Interval of Severe Alopecia Areata: A Retrospective Study

Chao-Chun Yang[1,2], Chun-Te Lee[1], Chao-Kai Hsu[1,2], Yi-Pei Lee[1], Tak-Wah Wong[1], Sheau-Chiou Chao[1], Julia Yu-Yun Lee[1], Hamm-Ming Sheu[1], WenChieh Chen[3]

[1]*Department of Dermatology,* [2]*Institute of Clinical Medicine, National Cheng Kung University, College of Medicine, Tainan, Taiwan,* [3]*Department of Dermatology and Allergy, Technische Universität München, Munich, Germany*

**Background:** Spontaneous recovery of severe alopecia areata is rare and the condition is difficult to treat. **Objective:** The aim of this study is to investigate and compare the effects and safety of steroid pulse therapy between oral and intravenous administrations between 1999 and 2010 at the Department of Dermatology, National Cheng Kung University Hospital. **Methods:** Data were retrospectively retrieved. A satisfactory response was defined as more than 75% hair regrowth in the balding area. **Results:** A total of 85 patients with more than 50% hair loss were identified and treated, with an overall satisfactory response rate of 51.8%. The mean follow-up time was 37.6 months, with a relapse rate of 22.7%. Patients with alopecia areata (hereafter, AA) of recent onset within one year showed higher response rates ($p<0.001$) and lower relapse rates compared to patients with AA persisting for more than 1 year. Further, even in patients with alopecia totalis, alopecia universalis or ophiasis type, early treatment resulted in a satisfactory response rate of 47% among the treated patients. In general, oral therapy was as effective and well-tolerated as intravenous therapy. **Conclusion:** The response rate is determined by disease severity and time of intervention, not by the administration form of steroid pulse therapy. Oral steroid pulse therapy can be considered as the first-line treatment for patients with severe AA of recent onset within one year.

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**-Keywords-**

Alopecia areata, Corticosteroids, Pulse drug therapy, Treatment

## INTRODUCTION

Alopecia areata (AA) usually runs an unpredictable course and the extent of hair loss is a critical prognostic factor[1,2]. Spontaneous remission can be expected in AA of short duration and in a limited extent[3], whereas long-term prognosis is poor for patients with severe AA[2]. Treatment of severe AA is so far frustrating. Systemic pulse administration of high-dose glucocorticoids has been reported to be an effective and well-tolerated treatment option[4,5]. However, the regimen and efficacy of steroid pulse therapy varies among studies. Hence, this study aims to evaluate the efficacy and safety of steroid pulse therapy in treating severe AA as well as compare the effects of oral with intravenous regimens.

## MATERIALS AND METHODS

Patients with severe AA treated with steroid pulse therapy between 1999 and 2010 at the Department of Dermatology, National Cheng Kung University Hospital (Tainan, Taiwan) were retrospectively recruited; their medical records were also evaluated. Severe AA was defined as more than 50% scalp hair loss[6], including alopecia totalis (AT)

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**Corresponding author:** WenChieh Chen, Department of Dermatology and Allergy, Technische Universität München, Biedersteiner Str. 29, Munich 80802, Germany. Tel: 49-89-4140-3185, Fax: 49-89-4140-3502, E-mail: wenchieh.chen@lrz.tum.de

with 100% scalp hair loss, alopecia universalis (AU; AT plus loss of body hair) and AA ophiasis (AO), due to its recalcitrance to treatment.

Steroid pulse therapy was administered systemically either with oral prednisolone or intravenous methylprednisolone at a dose of 2.5 to 10.0 mg/kg per day. Patients who had been lost to follow-up or received other treatment modalities within the 6 months after initiating pulse therapy were excluded. The extent of hair loss before and after treatment was assessed and scored by two independent dermatologists using a photographic review based on the Alopecia Areata Investigational Assessment Guidelines[6]. A satisfactory response was defined as hair regrowth covering more than 75% of the bald area at the time of the last follow-up. Relapse was defined as an increase in hair loss of more than 10% compared to the previous state in patients showing a satisfactory response. In order to identify the optimal protocol of pulse therapy, patients were subdivided into subgroups according to different factors for analysis, including the dose, route, frequency and total numbers of steroid pulse therapy. The efficacy between subgroups was compared in order to determine the conditions for a better response. Chi-square test and Fisher exact test were utilized for a comparison of the response rate between subgroups. Student t-test was used for comparing the demographic data between subgroups. This study was approved by Institutional Review Board of National Cheng Kung University Hospital (ER-100-184).

## RESULTS

Eighty-five patients consisting of 39 males and 46 females with a mean age of 28.4 years (range 4 to 60 years) were included in the study. Male patients had a higher disease severity ($p<0.01$) compared to females. The median duration of AA prior to initiating steroid pulse therapy was 4 months (range, 0.25 to 240 months). Associated findings of the study include the following: nail change in 9 patients (10.6%), thyroid diseases in 4 (4.7%), atopic dermatitis in 7 (8.2%) and vitiligo in 3 (3.5%). Moreover,

**Table 1.** Satisfactory response rates with hair regrowth >75% in different subgroups of AA patients

| Variable | Patient number with satisfactory response | *p*-value* |
|---|---|---|
| Overall patients (n=85) | 44 (51.8) | |
| Sex | | >0.05 |
| Female (n=46) | 27 (58.7) | |
| Male (n=39) | 17 (43.6) | |
| Age (yr) | | >0.05 |
| <12 (n=13) | 8 (61.5) | |
| 13~50 (n=68) | 38 (55.9) | |
| >50 (n=4) | 2 (50.0) | |
| Extent of hair loss (%) | | <0.05† |
| 50~74 (n=36) | 22 (61.1) | |
| 75~99 (n=25) | 13 (52.0) | |
| 100 (n=24) | 9 (37.5) | |
| Duration of AA (yr) | | <0.001‡ |
| <1 (n=62) | 40 (64.5) | |
| 1~2 (n=9) | 2 (22.2) | |
| >2 (n=14) | 2 (14.3) | |

Values are presented as number (%). AA: alopecia areata. *Comparison between subgroups. †Comparison between patients with 50% to 74% hair loss vs. 100% hair loss. ‡Comparison between patients with duration of AA for more than 1 year versus less than 1 year.

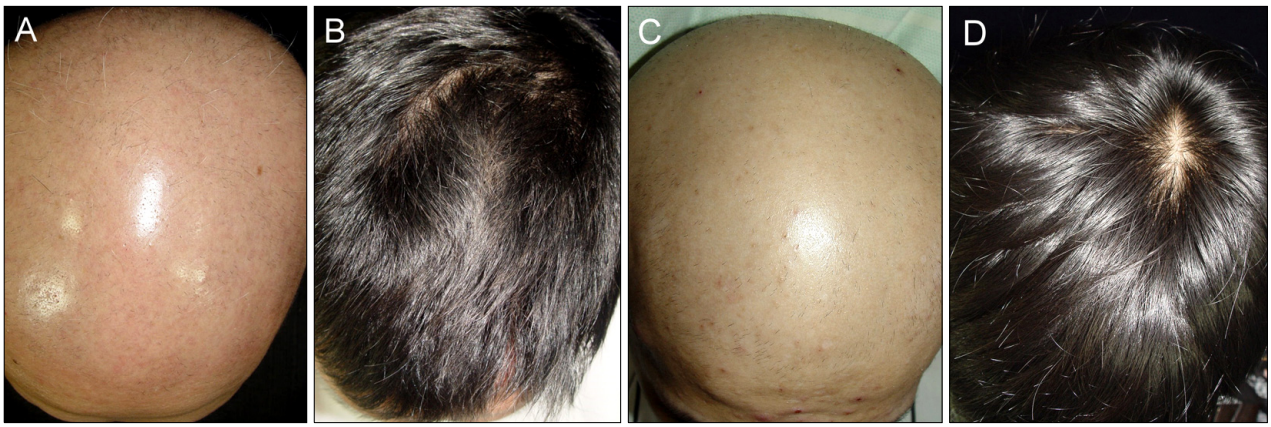


**Fig. 1.** Photography demonstrating the effect of oral steroid pulse therapy. (A) Severe alopecia areata in a 33-year-old male patient with only a small amount of hair on the occipital scalp (not shown) for 3 months. (B) Satisfactory regrowth of scalp hair was noted 6 months after initiating oral prednisolone pulse therapy at a dose of 5 mg/kg per day every 2 weeks for a total of 5 sessions. (C) Another 21-year-old male patient with alopecia totalis for 2 months. (D) Complete hair regrowth was noted 12 months after one session of oral prednisolone pulse therapy at a dose of 5 mg/kg per day for a total of 3 days.

gender difference did not exist. The mean follow-up duration after treatment initiation was 37.6 months (range, 6 to 142 months).

The overall satisfactory response rate to steroid pulse therapy was 51.8%, with complete hair regrowth observed in 32.9% of the patients (Fig. 1). In twenty patients (23.5%), either there was no response or the response rate became worse. The therapy was significantly more effective in patients with a hair loss of 50% to 74% as compared to those with AT/AU/AO ($p<0.05$), and when patients were treated within one year after disease onset ($p<0.001$) (Table 1). The satisfactory response rate declined from 64.5% to 22.2% and to 14.3% in patients with AA for less than 1 year, 1 to 2 years and more than 2 years, respectively. Relapse was noted in 10 out of 44 patients (22.7%) in whom a satisfactory response was achieved. Further, the relapse rate was lower in patients receiving an early intervention within 1 year (8/40; 20%) than in those with a later treatment (4/8; 50%). The mean time to the first relapse after completion of pulse therapy (disease-free interval) was 13.3 months (range, 4 to 36 months).

Among patients with AT/AU/AO, 20% (n=6) showed a hair regrowth of 50% to 75%, and 36% (n=9) achieved >75% regrowth. Early intervention within 1 year could yield a satisfactory response rate of 47.1% (8/17), a result that is significantly better than 14.3% (1/7) when receiving a late treatment.

Overall, the dose, frequency and total numbers of treatment are not significant determinants for a better treatment response (Table 2). Pulse therapy via the oral route was as effective as that via the intravenous route. A single course of intravenous methylprednisolone at a dose of 10 mg/kg per day for 3 consecutive days yielded a satisfactory response rate of 50.0%, which was similar to the results of other regimens. The total number of treatment sessions varying from 1 to 15 did not influence the therapeutic outcome ($p>0.05$). The side effects were usually mild and transient, and did not differ between oral vs. intravenous regimens, including facial flushing, transient hyperglycemia, increased appetite, insomnia, mild edema and palpitation. However, long-term side effects were not observed in these patients.

**Table 2.** Comparison of the response rate in different treatment protocols

| Variable | Patient number with satisfactory response | *p*-value* |
|---|---|---|
| Dosage of pulse therapy (mg/kg) | | >0.05 |
| ≤5 (n=44) | 25 (56.8) | |
| >5 and ≤10 (n=41) | 19 (46.3) | |
| Route of administration | | >0.05 |
| Oral (n=27) | 14 (51.9) | |
| Intravenous (n=58) | 30 (51.7) | |
| Total session numbers (session) | | >0.05 |
| ≥6 (n=25) | 10 (40.0) | |
| <6 (n=60) | 34 (56.7) | |
| Interval between treatments (wk) | | >0.05 |
| ≤3 (n=27) | 14 (51.9) | |
| >3 (n=44) | 22 (50.0) | |
| One single dose (n=14) | 7 (50.0) | |

Values are presented as number (%). *Comparison between subgroups.

## DISCUSSION

In the present study of 85 patients with severe AA observed over an average of a 37.6-year span; the following results were observed: 1) overall satisfactory response rate to steroid pulse therapy was 51.8%, 2) complete hair regrowth rate was 32.9%, 3) severity and duration of AA were significantly associated with the treatment response, 4) earlier treatment (within the first year of disease course) resulted in a better response rate and a lower relapse rate even in patients with complete hair loss, and 5) dose, route, frequency and total numbers of treatment were not associated with the treatment response.

Due to the retrospective nature of this study, the treatment

**Table 3.** Summary of response rates and relapse rates in the six largest series published to date using steroid pulse therapy to treat alopecia areata

| Author (year) | Case (n) | Severity (% scalp involvement) | Route of administration | Response rate, % (% recovery of hair loss area) | Relapse rate (%) | Average follow-up duration (mo) |
|---|---|---|---|---|---|---|
| Sharma[7] (1996) | 32 | >40 | Oral | 58.3 (>80) | 14.0 | 18 |
| Seiter et al.[8] (2001) | 30 | >30 | Intravenous | 40.0 (>50) | 38.0 | Up to 18 |
| Kar et al.[9] (2005) | 36 | >40 | Oral | 40.0 (>30) | 25.0 | 6 |
| Nakajima et al.[10] (2007) | 139 | Not defined | Intravenous | 47.5 (>75) | 16.7 | 15.3 |
| Im et al.[11] (2011) | 70 | >50 | Intravenous | 41.4 (>90) | 27.6 | At least 12 |
| Current study | 85 | >50 | 27 oral, 58 intravenous | 51.8 (>75) | 22.7 | 37.6 |

protocol, including the dose, interval, frequency, number and the route of administration, was not standardized in these patients. To date, six large series have been published, demonstrating the efficacy of steroid pulse therapy in the treatment of moderate to severe AA (Table 3)[7-11]. However, none of them, including ours, were carried out in a prospective double-blind placebo-controlled way, primarily due to the following practical problems. Unlike using a contact sensitizer, such as diphenylcyclopropenone, a systemic treatment cannot be applied only on one half of the scalp in the same patient. Compared to other severe inflammatory dermatoses, such as psoriasis or atopic dermatitis, the therapeutic effect cannot be assessed in a short period of time (average, 2.9 months in our study). Further, it is clinically impossible to recruit patients for placebo treatments because most of them fear a delay in treatment, further hair loss and ultimately, no hair regrowth.

A spontaneous recovery of severe AA is, in our experience, unlikely, although there are a lack of solid data. There are many regimens and novel therapies reported for the management of severe AA; however, so far the data are insufficient to show that they can substantially alter the course or prognosis of the disease. In a long-term study, severe AA tends to run a persistent or progressive course regardless of treatment modalities[2]. Among 63 patients with more than 50% hair loss at the first visit, 50 patients (79.4%) still had more than 50% hair loss after 7 years[2]. In our study, 44 out of 85 AA patients (51.8%) with an initial hair loss over 50% showed more than 75% hair regrowth in an average follow-up period of 37.6 months (Table 3). According to this result, we can speculate that an early steroid pulse therapy to induce leukocyte apoptosis and down-regulate the autoimmune response may at least achieve a longer disease-free interval[12].

In general, patients with a longer disease duration (more than one year) had a significantly lower satisfactory response rate as compared to patients treated earlier ($p<$ 0.001). This difference may be explained by the histopathological changes of a scanty peribulbar inflammatory infiltrate in long-lasting AA[13].

In the current study, oral administration is as effective as intravenous application, which may have many clinical benefits in consideration of convenience and cost-effectiveness, particularly in pediatric cases.

In conclusion, steroid pulse therapy, when given early, offers a high satisfactory response rate for the treatment of severe AA, including AT and AU. Oral application is as effective as intravenous therapy and is well-tolerated in both adults and children. Further, larger controlled studies are required in order to see if an early application of steroid pulse therapy can change the course and prognosis of severe AA as well as to identify the best responsive patient groups for an optimal therapeutic strategy.

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