کارگاه های آموزشی مرکز اطلاعات علمی چهار دانشگاهی

• مباحث پیشرفته یادگیری عمیق: شبکه های نویج کرافتی
(Graph Attention Networks)

• کارگاه آنلاین آموزش استفاده از وب آسیس

• فیلم های آموزشی

• عضویت در خبرنامه

• بلاگ

• مرکز اطلاعات علمی

• سرویس ترجمه

• سرویس های ویژه

• شورای سایه
The Effect of Methylprednisolone Pulse-Therapy Plus Oral Cyclosporine in the Treatment of Alopecia Totalis and Universalis

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The exact etiology of alopecia areata is still unknown, and no completely effective treatment has been established. The use of oral steroids for treating this disorder is controversial and may have potential side effects. Relapses are also common upon withdrawal of the medication. The objective of this study was to evaluate the therapeutic and side effects of pulse-therapy with methylprednisolone combined with oral cyclosporine in severe alopecia areata, defined as alopecia totalis and universalis. Six patients with alopecia totalis and 12 patients with alopecia universalis were referred to our center. The patients were treated with monthly intravenous methylprednisolone in doses of 500 mg for three days and oral cyclosporine (2.5 mg/kg/day) for five to eight months. Responses were categorized as: "adequate" (i.e., hair regrowth on ≥70% of the affected area) and "inadequate" (i.e., hair regrowth on <70% of the affected area).

Adequate response was observed in six (33%) patients: three with alopecia totalis and 3 with alopecia universalis. Responses were better in patients with alopecia totalis, age >20 years, negative history of atopy, negative family history of alopecia areata, presence of nail pitting, and pruritus in the affected area. No cases of relapses and no severe side effects were observed.

Patients with severe and resistant alopecia areata, if properly selected, may benefit from intravenous methylprednisolone pulse-therapy plus oral cyclosporine.

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**Keywords:** Alopecia areata • cyclosporine • pulse-therapy

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**Introduction**

Alopecia areata is a common dermatologic disorder that accounts for 2% of referrals to dermatology clinics. Natural course of this disease is variable. Sometimes, it can progress to total scalp and whole body hair loss—conditions known as alopecia totalis and universalis, respectively.1 The exact etiology of alopecia areata is still unknown, but most evidences show the role of autoimmune processes.1-3 As the disease may carry significant psychologic and social stigmata for patients, treatment is warranted to improve the quality of life for these patients.2,3 Multiple therapeutic methods have been used, but in severe cases there are only a few beneficial effects and there may be significant associated side effects. The mainstay of therapy is directed towards eliminating the underlying inflammation by means of immunosuppressive agents. As patients with severe disease often need long-term treatment, our choices should be both effective and safe in long-term use.2

Systemic steroids have been used in many cases effectively; yet in some studies, there are controversies on the recommended doses and the efficacy of these drugs. In addition, the presence of side effects with long-term systemic steroid therapy may suggest a dose reduction or even discontinuation of the treatment, which in turn may cause relapses.1 To avoid these complications, pulse-therapy with intravenous steroids had been introduced. Burton and Shuster first introduced this method, but because of inadequate responses, they did not recommend this treatment modality.4 Sharma, in turn, demonstrated a 58% adequate response rate in his patients.5 In 1993, Perriard-
Wolfensberger et al demonstrated that in severe cases of alopecia areata, disease activity was arrested with the use of steroid pulse-therapy. In 1998, Friedli et al showed favorable responses in multifocal disease. To improve the rate of responses, cyclosporine has been used in combination with systemic steroids, but there has been limited studies.

The objective of this study was to evaluate the effectiveness of monthly pulses of methylprednisolone plus oral cyclosporine in the treatment of severe alopecia totalis and universalis.

**Patients and Methods**

Six patients with alopecia totalis and 12 with alopecia universalis who were referred to our clinic entered the study. In all patients, a thorough physical examination and laboratory tests including a complete blood count, serum electrolytes, blood urea nitrogen and creatinine levels, liver function tests, thyroid function tests, fasting serum glucose, antinuclear antibody screening, urinalysis, and a chest X-ray were done. Patients with signs or symptoms of acid-peptic disease, hypertension, diabetes mellitus, severe anemia, or significant laboratory abnormality were excluded from the study. In addition to demographic indices, the presence of other dermatologic and endocrine autoimmune diseases (e.g., vitiligo, atopy, and autoimmune thyroid disorder), major stress factors (e.g., death of a first degree relative and history of military and war services during the past six months), and a family history of alopecia areata were studied.

Furthermore, the presence of pitting in nails as well as pruritus in the affected area was evaluated. The patients were then admitted to the hospital for three consecutive days in a month, and treated with intravenous pulses of methylprednisolone, 500 mg/day plus oral cyclosporine, 2.5 mg/kg/day. The length of treatment was five to eight months. At each course of treatment, any hair regrowth was recorded. At the end of the treatment cycles, the therapeutic response was evaluated as: “adequate” or “inadequate.” The definition consisted of hair regrowth on ≥70% of the affected area and hair regrowth on <70% of the affected area, respectively.

**Results**

Eighteen patients were studied (12 cases of alopecia universalis and six with alopecia totalis). The mean±SD age of the participants was 20.6±4.8 (range: 14 – 29) years. Nine patients were males and nine were females. The mean±SD duration of disease was 6.3±5 (range: 0.5 – 16) years. Eight patients were in the initial presentation of their disease. Physical and laboratory evaluations revealed mild hypertension in three patients, and thalassemia minor in two, with no contraindication for pulse-therapy; otherwise laboratory tests were normal.

The response rates in all patients and in respect to their involvement as alopecia totalis and alopecia universalis are shown in Table 1. The responses in both sexes with three patients with adequate response in each groups, were similar. In patients younger than 20 years (n=10), three had adequate responses. In those older than 20 (n=8), three patients demonstrated adequate responses. Out of the 11 patients who had a disease duration of less than six years, an adequate response was observed in five. Only one with disease duration of less than six years demonstrated an adequate response.

In patients with a positive history of atopy (n=7), two showed adequate responses. Of those without a history of atopy (n=11), four had adequate responses. Responses were adequate in two out of seven cases with family history of alopecia areata, and in four out of 11 patients without family history of alopecia areata. In patients with nail pitting (n=12), five had adequate responses while from six patients without nail pitting, only one had an adequate response.

In patients with a known stress factor at the beginning of their disease (n=7), three had adequate responses; out of those without any stress elements (n=11), three had adequate responses. Six patients had pruritus in the affected area of whom, three

<table>
<thead>
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<th>Type</th>
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<tr>
<td>Adequate</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Inadequate</td>
<td>3</td>
<td>9</td>
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<tr>
<td>Total</td>
<td>6</td>
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**Table 1.** Frequency of the patients with alopecia totalis and alopecia universalis and their therapeutic responses.
had adequate responses. Three out of 12 cases without pruritus responded adequately.

In the follow-up period of eight to 20 months, no significant relapses were seen in patients who achieved an adequate response. The side effects of this therapeutic modality were mild increase of blood pressure in one patient, reversible hyperlipidemia in two, and mild acne in another one. No changes in creatinine or BUN were recorded.

Figure 1 shows a patient with adequate response before and after the treatment.

**Discussion**

We observed 33% adequate response (25% in patients with alopecia universalis) following one course of pulse-therapy. Friedli et al reported these figures as 26% and 11%, respectively, after intravenous steroid therapy. It seems these factors may be associated with better response:

1) Alopecia totalis vs. alopecia universalis;
2) Age >20 years at the onset of disease;
3) Duration of disease of less than six years;
4) No history of atopy; and
5) No family history of alopecia areata.

These findings confirm the well-known poor prognostic factors of alopecia areata such as childhood onset, longer duration of disease, history of atopy, and family history of alopecia areata.2

Furthermore, based on our findings, we suspect that presence of nail pitting, positive history of stressful factors at the onset of disease, and pruritus in the affected areas may also affect the outcome.

Although the presence of nail dystrophy generally denotes a poor prognosis,2 there is no published data correlating the effects of nail pitting on the therapeutic responses of patients with alopecia areata. Since pitting usually coincides with the active phases of hair loss,2 and when the disease process is still in its active phases better responses can be anticipated, we hypothesized that nail pitting may be seen together with a better response.

The same correlation, noted above, can be assumed for the presence of pruritus, since pruritus is more commonly present in the early active stages of the disease and may even precede the hair loss.2 There are many reports with regards to the role of stress in alopecia areata.1 However, there is no information on its effects on therapeutic responses, and further studies are needed to analyze its role.

In the follow-up periods of nine to 18 months, there were no significant relapses in our patients. While Friedli et al had reported a 46% relapse rate seven months following one course of intravenous steroid therapy. They then proceeded with a second course therapy in patients who had significant relapses; then they observed a good therapeutic response.7 This finding supports the hypothesis that sequential pulse-therapy may be superior to single episode therapy. In our study and that of Friedli et al, no serious side effects were observed.

We believe that intravenous methylprednisolone pulse-therapy plus low doses of oral cyclosporine may be an effective therapeutic method for some patients with minimal side effects and very low rates of relapse.

**References**

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مباحث ویژه و سرویس ترجمه

محاسبه پیشرفته با روش های عمیق شبکه‌های توجه گرافی (Graph Attention Networks)