Treatment of Severe Alopecia Areata Using Methotrexate as an Adjunctive Drug in Combination with Intravenous and Oral Corticosteroid

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Abstract

Background: Alopecia areata is one of the most common human autoimmune disorders and its severe types are refractory to all conventional therapies. Corticosteroids have been used in severe alopecia areata since 1950s but there is concern over complications caused by high doses of corticosteroids. Methotrexate has been used as an adjunctive therapy in some autoimmune disorders and has been proposed to be effective in the treatment of severe alopecia areata both as a monotherapy and in combination with corticosteroids.

Methods: In this study, 120 patients of intractable alopecia areata totalis and universalis with a mean duration of 3.27 ± 1.60 years were studied. We treated them with methotrexate in combination with intravenous and low dose of prednisolone for one year. Methotrexate 10 mg per week was administered in combination with three monthly methylprednisolone and oral prednisolone 15 mg per day for one year. Response to the treatment was evaluated clinically and by serial photographs.

Results: Sixty four patients (57.7%) gained total hair regrowth after treatment with no significant difference between alopecia totalis and universalis. Almost half of the patients (44.75%) remained disease free until the end of the one-year follow-up. Relapse occurred in 34 patients (56.25%); of them 20% were focal relapses. Nine patients out of 120 patients (7.5%) experienced severe adverse effects of the therapy.

Conclusion: Our study suggested that methotrexate could be used as a safe and well tolerated adjunctive therapy for severe alopecia areata although careful monitoring of adverse effect is necessary. Furthermore, controlled prospective clinical trials are warranted to answer many of the questions regarding methotrexate therapy for severe alopecia areata. *(Iran J Dermatol 2010; 13: 91-95)*

Keywords: alopecia areata, methotrexate, corticosteroid

Introduction

Alopecia Areata (AA) is a tissue confined autoimmune disease of the hair follicle resulting in non-scaring hair loss. It is among the most frequent human autoimmune diseases with a prevalence of 0.1 % to 0.2 % of the general population. About 14–25% of the patients progress to total loss of scalp hair (Alopecia Totalis, AT) or loss of the entire scalp and body hair (Alopecia Universalis, AU), from which full recovery is unusual ranging from less than 10% to less than 20% [1-3].

Treatment of severe AA with conventional therapies such as topical corticosteroids (CS), topical immunotherapy, PUVA or intravenous (IV) pulse CS is usually disappointing; even newly introduced biological drugs such as anti-tumor necrosis factor drugs (infliximab and etanercept) and anti-CD11a (efalizumab) have been ineffective [4-12].

Methotrexate (MTX) is an effective drug in the treatment of some cases of severe and chronic eczema, refractory late-onset atopic dermatitis, psoriasis and bullous pemphigoid and is an effective and well tolerated therapy in severe AA, either as a single therapy or in combination with CS. In addition, MTX can be used as CS sparing

agent in many autoimmune disorders such as bullous pemphigoid and pemphigus vulgaris [13-16].

Systemic corticosteroids have been used in the treatment of AA since the 1950s but there is concern over the side effects of long-term treatment with high doses of CS. However, over the past years, a variety of therapy regimens with high doses of CS has been introduced including different CS pulse regimens, alternating daily dose and monthly dose of CS in order to reduce systemic side effects of CS [17-22].

In an attempt to reduce systemic side effects of CS and avoid recurrence of hair loss after treatment, we used MTX as an adjunctive and CS dose sparing agent to treat 120 patients of severe AA (AT and AU). All patients received oral MTX in combination with IV pulse and low dose CS for one year.

Patients and Methods

One hundred and twenty patients who suffered from alopecia totalis /universalis for at least 1 year were studied between October 2005 and November 2008. All patients had responded poorly to previous conventional therapies such as topical clobetasol, psoralen, phototherapy, oral CS and tacrolimus.

Patients were hematologically evaluated for complete blood count, renal and hepatic function tests and lipid profile at the beginning of the study and then monthly during treatment. Electrocardigram (ECG) was also checked for each patient before the treatment and cardiovascular monitoring was performed during corticosteroid pulse therapies. Skin tuberculin test along with chest X-ray performed for all patients to exclude suspected tuberculosis patients from the study. Contraceptive counselling was provided for all female patients of childbearing age. Patients with tuberculosis, immunodeficiency, inflammatory bowel disorders, rheumatologic disease, previous gastrointestinal bleeding and body dysmorphic disorders were excluded from the study. Furthermore, male patients who were planning to have a child were not included in the study.

All patients were treated with three cycles of intravenous methylprednisolone 500 mg daily for 3 days, administered at one-month intervals. Methotrexate 10 mg was administered once weekly in combination with oral prednisolone 15 mg daily for one year. Oral prednisolone started after the first IV pulse, administered for 9 months and then gradually tapered during the last three months of therapy and finally discontinued at the end of the year. This protocol was approved by the Ethics Committee of Shahid Beheshti Skin Research Center (Shohada Hospital, Tehran, Iran).

All patients were visited every three months during the seconed year. Besides, patients who had mild to moderate upper GI disturbance received H2-blockers or proton–pump inhibitors parallel to the therapy. Furthermore, prophylactic calcium and vitamin D and folic acid supplementation was provided for all the patients.

Therapy was discontinued in patients who did not achieve terminal hair regrowth after 6 months of treatment. Patients were clinically evaluated for hair regrowth every three months by two physicians separately. Furthermore, all patients were analyzed using photographs, first from complete baldness and then every three months during the treatment.

A complete response to treatment was defined as total regrowth of terminal hair of the scalp; therefore, patchy or local hair regrowth of the scalp or other parts of the body were considered as an incomplete response (failure of response).

Statistical analysis was performed using SPSS-16. T-test was used to compare the two groups and Chi-square test was used to assess the relationship between discrete variables. P-value less than 0.05 was considered as significant.

Results

One hundred and eleven patients out of 120 participants completed the study. Two patients with acute GI disturbance, one patient with nausea and malaise, two patients with excess weight gain, two patients with elevation of liver enzymes more than five times and two patients with peptic ulcer were excluded from the study. One of the patients who was excluded from the study was a 27-year-old woman who became pregnant within 2 months of therapy. The summary of the statistics of the patients are reported in table 1. Seventy one patients (64%) had alopecia universalis and 40 patients (36%) had alopecia totalis. Nineteen patients (47.5%) out of 40 patients with alopecia totalis and 40 patients (56.3%) out of 71 patients with alopecia universalis were female. Chi-square showed no significant relationship between type of disease (AT and AU) and gender ($p=0.37$).

The difference of treatment efficacy was not statistically significant between two types of disease (AT and AU; $p=0.22$). The mean age and mean duration of disease did not differ significantly between female and male patients (t test, $p=0.68$ and $p=0.91$, respectively). A significant difference

Table 1. *Demographic characteristics of the patients*

Sex, no. (%)	
Female	52 (46.8%)
Male	59 (53.2%)
Age, years	24.84 ± 6.61 (range: 14-44)
Female	25.08 ± 6.70 (range: 16-44)
Male	24.56 ± 6.55 (range: 14-44)
Disease duration, year	3.27 ± 1.60 (range: 1-9)
Female	3.25 ± 1.61 (range: 1-9)
Male	3.29 ± 1.60 (range: 1-8)
Weight, kg	62.68 ± 10.74 (range: 44-90)
Female	57.44 ± 7.65 (range: 44-77)
Male	68.63 ± 10.67 (range: 45-90)

was observed between the mean weight of male and female patients (t test, $p<0.0001$).

Sixty four patients (57.7%) achieved total hair regrowth of the scalp after treatment. No significant relationship was observed between response to treatment and gender (chi-square test, $p=0.44$) and there was no significant difference between mean age, mean weight and mean duration of the disease in patients who completely responded to treatment and those who did not (t test, $p=0.32$, $p=0.61$ and 0.93).

Out of 64 patients who achieved total hair regrowth, 28 (44.75%) still remained disease free at the end of one-year follow-up while 36 patients (56.25%) experienced relapse of the disease during the tapering of CS or within one year of discontinuing the therapy. Of these 36 patients, 20% had focal patchy relapses. No statistical difference was observed in recurrence rate of the disease between patients with AT and AU ($p=0.59$). No significant difference was found in mean age, mean duration of the disease and mean weight of the patients with and without recurrence (p-values at least 0.31).

As mentioned before, only nine patients out of 120 patients (7.5%) experienced severe adverse effects of the therapy.

Discussion

In our study, response to treatment was exclusively confined to total regrowth of scalp terminal hair. Despite this strict criterion, and in spite of the severe and chronic nature of the disease, more than half of the patients (57.7%) regained total hair regrowth and 44.75% did not experienced recurrence of the disease during the one-year follow-up. In addition, response to our protocol was higher than all previous studies using systemic CS which have reported response rates ranging from 11.4% to 47% [18-22]. This may be due to adjunctive effect of MTX, although exact conclusion warrants more specifically designed controlled clinical trials. The dose of administered oral CS in our study was lower than other studies but the response was comparable to high dose regimens of CS and expectedly, lower adverse effects were observed, too. [17, 21, 22].

In our study, response to treatment was similar in both alopecia totalis and universalis, and obviously independent of disease type. Mean weight showed a significant difference between two genders but no difference was detected in treatment response between the two groups despite predetermined fixed doses of CS and MTX used in our study.

Although the treatment protocol of our study was well tolerated and serious adverse effects were

rare, the potential side effects of long term MTX and CS should be considered and longer follow-ups are needed to detect the exact rate of late-onset and cumulative adverse effects of this treatment in AA [17, 23].

Although alopecia did not recur in almost half of the patients (44.75%) in our one-year follow-up, 56.25% of the patients experienced relapse during tapering or within discontinuation of CS, highlighting the fact that CS played the major therapeutic role in treating our patients rather than MTX and the latter only had an adjunctive and CS dose sparing effect. The recurrence rate of alopecia in our patients was comparable to other previous studies using CS which have reported relapse rates ranging from 25% to 100% within 3-15 months of ending the treatment. Considering this fact, our study may put even more emphasis on the refractory nature of the severe alopecia areata [21].

Alopecia has a heavy psychological burden on affected patients and severely impairs the quality of life of the patients. It may lead to a high lifetime prevalence rate of major depression or generalized anxiety disorder [23,25]; therefore, treating severely affected patients is obviously logical but decision regarding which patient is an appropriate candidate for long term MTX therapy is an important point to be taken into account. Furthermore, we should point out the fact that generally accepted, firmly evidence-based treatment guidelines for AA management yet remain to be developed, which warrants further investigations.

On the other hand, hair loss is a lifelong affliction and full recovery is unusual in most patients with extensive AA. In a long-term follow-up study, almost all patients with alopecia totalis/universalis still had a severe disease after 7 years of multiple therapies [25]. Therefore, leaving alopecia areata untreated and management aimed at helping patients cope with their lack of hair can be considered as a legitimate option for many patients.

In conclusion, our study suggested that MTX might be an effective and safe adjunctive drug in the treatment of severe alopecia totalis /universalis and could be used as a CS dose sparing agent, although careful monitoring of adverse effects and long-term safety data is warranted. Yet, controlled prospective clinical trials are needed to answer many of the questions regarding MTX therapy for alopecia areata.

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