Efficacy of Topical Diphencyprone in the Treatment of Alopecia Areata

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Abstract

Background: Topical immunotherapy with diphencyprone (DPCP) for the treatment of severe alopecia areata has been used since 1983 and is felt to be the treatment of choice for chronic extensive alopecia areata. Highly variable results have been reported. The purposes of this study were to evaluate the efficacy of DPCP in the treatment of chronic, extensive alopecia areata and to assess the long-term overall benefit of treatment.

Methods: In a retrospective study, 54 patients with chronic extensive alopecia areata who had used DPCP for more than 1.5 years between 2001 and 2005 were studied. Patients' information and results of treatment after every session were collected from record files.

Results: The response to treatment was excellent (76-100% terminal hair re-growth) in 40.7%, good (51-75% terminal hair re-growth) in 14.8%, moderate (26-50% terminal hair re-growth) in 14.8%, and mild (1-25% terminal hair re-growth) in 29.6% of patients. However, 33% of them had a relapse. The response to treatment was excellent and good in 62% of the patients with less than 10 years duration of alopecia areata, but in the group with the duration of more than 10 years, a good and/or excellent response was found in 25% of patients and 75% had a poor and/or moderate response (P=0.017). There was no relationship between response to treatment and sex, onset of disease, nail involvement, atopy, extent of hair loss, and family history of alopecia areata.

Conclusion: Topical immunotherapy with DPCP has proved to be an effective treatment with prolonged therapeutic results in Iranian population. Duration of disease less than 10 years is a main predictor for a good response rate. *(Iran J Dermatol 2008;11: 103-107)*

Keywords: alopecia areata, diphencyprone, immunotherapy

Introduction

Alopecia areata is a chronic inflammatory condition with an involvement of the hair follicles and sometimes the nails. It is an organ specific autoimmune disease with a genetic predisposition and environmental triggers[1-3].

The most frequent types of treatment for this disease are topical and intralesional corticosteroids, topical minoxidil, topical immunotherapy (squaric acid dibutyl ester or diphencyprone), systemic corticosteroids, psoralen-UVA irradiation and immunosuppressive agents such as methotrexate and cyclosporine[3-5].

Topical immunotherapy is defined as the induction and periodic elicitation of an allergic contact dermatitis by topical application of potent topical contact allergens. In 1983, Happle et al. first reported a therapeutic trial of DPCP in 27 patients with extensive alopecia areata, obtaining a complete response in 67% of cases[6]. Since then, the effectiveness of topical immunotherapy with DPCP in alopecia areata has been demonstrated in several reports, although the response rates varied greatly from 4% to 85%[7,8].

In the present study, we considered the clinical features and population characteristics of alopecia areata and assessed the responsiveness of the disease to topical immunotherapy with DPCP.

Patients and Methods

In a retrospective study, all patients with alopecia areata who had been treated with DPCP in DPCP therapy clinic for more than 1.5 years and were still on treatment between January of 2001 and December of 2005 were included.

The DPCP clinic protocol was as follows:

The ethics committee of Tehran University of Medical Sciences approved the study protocol and all patients signed informed consent. The patients' information was collected from medical records. Women of childbearing age were required to use a reliable form of birth control. Individuals with alopecia areata were ineligible for DPCP treatment if they presented with vitiligo, pregnancy, lactation or serious intercurrent medical illnesses. Subjects with severe alopecia areata who had stopped other topical treatments one month and systemic therapies three months before were sensitized initially with a 2% solution of DPCP in acetone; which was applied to a 5-centimeter-diameter circular area on the scalp. Treatment started two weeks after sensitization with the lowest concentration of 0.001% DPCP on the one-half of the patient's scalp. The concentration of the solution increased stepwise (0.01%, 0.1%, 0.2%, 0.5%, 1% and 2%) to maintain redness and pruritus without vesicular eruption. The patients were instructed to avoid direct sun exposure to the scalp and to not wash the scalp for 48 hours after DPCP treatment. If terminal hair growth was noted, the entire scalp was then treated under the same weekly protocol.

Efficacy evaluation was performed with both clinical examination and taking photographs in all patients. Extent of hair loss was categorized as severe (76-100% scalp involvement), moderate (26-75% scalp involvement), and mild (less than 25% scalp involvement). Response to treatment was also expressed using a percentage scale ranging from zero to 100%, as mild (1-25% terminal hair re-growth), moderate (26-50% terminal hair re-growth), good (51-75% terminal hair re-growth), and excellent (76-100% terminal hair re-growth).

The treatment was discontinued in patients who did not demonstrate any responses after 6 months.

Complete blood cell count (CBC), liver, renal and thyroid function tests and anti nuclear antibody titer were performed in all patients.

All patients who had been treated in this clinic for more than 1.5 years and were still on treatment were included.

We did not include patients who were not sensitized to DPCP; those who did not continue treatment for more than 1.5 years and patients who could not continue the treatment because of severe side effects such as generalized eczematous reactions.

Onset of disease, sex, history of atopy, positive family history, nail involvement, extent of alopecia, and results of treatment after every session were also recorded as percentages for categorical variables. The relationship between the response to treatment and other variables was assessed using One-way ANOVA statistical analysis. P values of 0.05 or less were considered statistically significant. All statistical analyses were performed using SPSS version 13 for Windows.

Results

Fifty-four patients entered the study including 38 (70.4%) females and 16 (29.6%) males. Their ages ranged from eight to 45 years (mean 23.7±9.66). The extent of hair loss was severe, moderate, and mild in 68.5%, 29.6%, and 1.9% of them, respectively. The mean age of onset of disease was 15.8±9.5 (range: 5-43) years. In addition, the mean duration of the disease was 7.8±8.1 (range: 1-36) years.

Nail involvement was found in 46.3% of patients in the form of pitting, ridging, onycholysis, and nail dystrophy. History of atopy was found in 13% of them. Family history of alopecia areata was also positive in 18.5% of patients. One patient had diabetes mellitus and five (9.3%) were hypothyroid.

A marked re-growth of the overall scalp hair (excellent) was observed in 40.7%. The response to treatment was good in 14.8%, moderate in 14.8%, and mild in 29.6% of patients.

Analysis showed that there was a positive relationship between atopy and severity of alopecia areata among patients (P=0.020). Duration of disease was related to response to treatment (P=0.017), so that 62% of patients with the duration of ≤10 years had a good and/or excellent response to treatment while 38% of them showed a poor and/or moderate response. Besides, in the group with the duration of more than 10 years, a good and/or excellent response was found in 25% of the patients and 75% had a poor and/or moderate response. There was no relationship between response to treatment and sex, onset of disease, nail involvement, atopy, extent of hair loss, and family history of alopecia areata (table 1).

During the treatment, 22 (33%) patients had a relapse, but continuation of DPCP therapy caused hair re-growth in 21 of them. No abnormalities in laboratory data were detected on baseline and follow-up in these patients. The adverse effects among patients completing the therapy were as follows: mild contact dermatitis on the face or neck (5 of 54) that resolved after topical corticosteroid application within 2 weeks, hyperpigmentation at

Table1: *The response to diphencyprone treatment in patients with alopecia areata*

		Response to treatment				P value
		0-25%	25-50%	50-75%	75-100%	
Gender						
	Male	6(37.5%)	2(12.5%)	2(12.5%)	6(37.5%)	
	Female	10(26.3%)	6(15.8%)	6(15.8%)	16(42.1%)	0.874
Family history of AA						
	Positive	2(20.0%)	2(20.0%)	0.0	6(60.0%)	
	Negative	14(31.8%)	6(13.6%)	8(18.2%)	16(36.4%)	0.315
Atopy						
	Positive	2(28.6%)	2(28.6%)	0.0	3(42.9%)	
	Negative	14(29.8%)	6(12.8%)	8(17.0%)	19(40.4%)	0.526
Hair loss severity						
	0-25%	0.0	0.0	0.0	1(100%)	
	26-75%	3(18.8%)	3(18.8%)	4(25.0)	6(37.5%)	
	76-100%	13(35.1%)	5(13.5%)	4(10.8%)	15(40.5%)	0.644
Thyroid disease						
	Positive	1(20.0%)	2(40.0%)	1(20.0%)	1(20.0%)	
	Negative	15(30.6%)	6(12.2%)	7(14.3%)	21(42.9%)	0.360
Autoimmune disease						
	Positive	1(100%)	0.0	0.0	0.0	
	Negative	15(28.3%)	8(15.1%)	8(15.1%)	22(41.5%)	0.490
Nail involvement						
	Positive	8(32.0%)	5(20.0%)	2(8.0%)	10(40.0%)	
	Negative	8(27.6%)	3(10.3%)	6(20.7%)	12(41.4%)	0.494

the sensitization site (4 of 54) and occipital lymphadenopathy (one 0f 54).

Discussion

The majority of studies believe that although topical DPCP treatment for alopecia areata is good, it may have some side effects. It is effective and well tolerated and provides prolonged remission; however, several factors as predictors for prognosis of alopecia areata and response rate of treatment have been known.

The mechanisms of DPCP remain to be elucidated and various theories have been propounded. One suggested that the mechanism is antigenic competition, where the allergic reaction stimulates suppressor T cells activation that non-specifically inhibits the autoimmune reaction against a hair follicle constituent[9]. In some other studies, changes in the ratio of peribullbar CD4+ to CD8+ T lymphocytes have been reported in the skin treated with topical sensitizer[10]. Furthermore, it has been also suggested that long-term treatment of alopecia areata patients with DPCP leads to a non-specific suppression of delayed-type hypersensitivity reactions[11].

In the present study, the response of treatment in 55.5% of patients was appropriate. This result was close to reports by Cotellessa et al.[7], who observed a 48% complete success rate in a series of 52 patients, and by Weise et al.[12] and Van Der Steen et al.[13], who detected a 40% and 50.4% complete re-growth in 124 and 139 patients, respectively. In other reports, however, the percentage of success greatly varied from 4% to 85% [7, 8]. The changes in response rates may be due to the number of patients in clinical trials; the type of alopecia areata, duration, and severity of the alopecia areata; and different methods of assessing clinical efficacy. In our study, the moderate to excellent response rate was 70.3%, whereas in two studies among similar population, the overall response rate was 81.5% and 51.1% [14, 15].

In addition, in our study, only the duration of the disease was a predictor for response rate; Avgerinou et al. found no association between duration of alopecia areata, age, gender, atopic diathesis, nail involvement and presence of thyroid antibodies with response to treatment[16]. The presence of nail changes, a personal history of atopy, a long duration of alopecia before treatment, baseline extent of alopecia, age at disease onset and duration of treatment have been considered as prognostic factors in other studies[7,12,15, 18,19,20].

In the present study, 33% of the patients had a relapse during the treatment, however, in a study by Avgerinou et al., 68.9% of patients had a relapse during follow-up and were treated again[16]. In another study by Wiseman et al., relapse (loss of more than 25 percent of re-growth) was observed in more than 60 % of patients whether maintenance therapy was used or not[17]. In addition, in Aghaei study, 50.9% of patients suffered a relapse either simultaneously on maintenance treatment of follow-up or following termination of therapy[14]. It seems that the topical immunotherapy with DPCP in the treatment of severe cases is an effective treatment[21], but with a slightly high relapse rate during treatment.

In our study, family history of alopecia was positive in 18.5% of the patients. Various studies reported familial incidences ranging from 3% to 42%[22] and it has been shown that the familial aggregation of alopecia areata supports the role of genetic factors in the development of the disease [23]. However, the genetic aspects of alopecia areata in our population are unclear and needs more studies.

The study had some limitations though: the patients who discontinued DPCP due to severe reactions, did not respond to medication or voluntary discontinued DPCP before 1.5 years were not included in the study, so there would have been a higher failure rate if these patients had been included. Additionally, we did not evaluate maintenance therapy of DPCP in this study and it seems that further studies with a long-term follow-up are necessary.

Our study shows that the response to treatment with Diphencyprone in alopecia areata in our population is good and appropriate and that a disease duration of less than 10 years is a main predictor for this response rate.

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