

DIPHENYLCYCLOPROPENONE (DIPHENCYPRONE, DPCP) IN THE TREATMENT OF CHRONIC SEVERE ALOPECIA AREATA (AA)

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SUMMARY :

■ **Background:** Diphenylcyclopropenone (DPCP) has been reported to be an effective topical immunotherapy of extensive alopecia areata (AA) with highly variable reported results.

■ **Objective:** The purposes of this study were to assess the efficacy, side effects, and adverse prognostic factors in the treatment of alopecia areata with DPCP.

■ **Methods:** 21 patients were included in the study with chronic and extensive AA. Patients were sensitized in the beginning with 2% DPCP, and the concentrations were increased gradually beginning with 0.000001% every one to two weeks for a period of 6 months.

■ **Results:** 15 patients (71.4%) had a complete or partial recovery at the end of the treatment period. Most frequent side effects were erythema at the site of application, pigmentation, and lymph node enlargement. The most important adverse prognostic factors were duration of AA, history of atopy, and presence of nail changes.

■ **Conclusion:** Treatment of AA with topical DPCP is effective. Though the treatment may have some side effects, in most cases they are tolerable and respond well to treatment.

INTRODUCTION

Alopecia areata (AA) is a dermatological disease in which the hair is lost suddenly from a well-circumscribed round or oval areas, particularly on the scalp. It is a non-scarring hair loss condition with no scales, induration, or any signs of inflammation on the skin. Any hair-bearing surface may be affected (1, 2).

The exact etiology of the disease is still unknown. Genetics, autoimmunity, infections, abnormal melanocytes or keratinocytes, and emotional stress have been investigated in the pathogenesis of AA (2-4).

All treatments for AA at present are palliative. They only control the problem but do not cure the condition. Some modalities of treatment are topical, intralesional, and systemic steroids; topical and systemic immunotherapy, anthralin, minoxidil, and photochemotherapy (2-5).

Many studies conducted showed that topical immunotherapy is the best overall treatment for chronic severe AA (i.e. more than 50% scalp hair loss) (6). It has been used for more than 10 years with various contact allergens such as dinitrochlorobenzene (DNCB), squaric acid dibutylester (SADBE) and diphenylcyclopropenone (DPCP) (7, 8).

DNCB was found to be mutagenic, whereas SADBE was expensive and unstable in acetone (6, 9-11). DPCP, on the other hand, is a potent contact sensitizer (11-13). It is stable in acetone and relatively inexpensive. Recently however, it has been shown to be photomutagenic (9, 14). Topical immunotherapy with DPCP is felt to be the treatment of choice by many dermatologists for severe AA (5-6, 15-19). The effectiveness of its use and the response rate in several reports varied greatly from 4% to 85% (9, 15-20).

We performed an open-label study to assess the efficacy and side effects of DPCP in the treatment of severe AA. In addition, we correlated the clinical response with the prognostic factors.

The study was conducted in Dubai and Al-Ain cities in the United Arab Emirates. 21 patients (6 male and 15 females) with chronic severe alopecia areata were

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enrolled in the study. Their ages ranged from 12 to 45 years (mean: 21.9 years). 17 of the patients were adults and 4 were children. The duration of alopecia ranged from 1 to 6 years (mean: 3.9 years).

Nail changes were observed in 4 of the 21 patients. A personal history of atopic dermatitis was detected in 5 patients, whereas a history of other atopic diseases were noted in 3 other patients. A history of vitiligo, diabetes mellitus, and goiter and autoimmune thyroiditis was noted in 2, 3 and 4 patients respectively (table 1). A family history of AA, vitiligo, and atopy was detected in 2, 2 and 3 patients respectively.

The inclusion criteria of our study were the following:

- presence of extensive AA (>50% scalp hair loss) for at least one year ;
- interruption of any systemic or topical therapy for AA for at least 6 months ;
- patients with stable AA with no signs of spontaneous remission ;
- co-operative and psychologically stable patients ;
- child-bearing females on contraception.

The exclusion criteria were:

- AA <50% of scalp hair loss ;
- pregnant and lactating females ;
- known allergy to DPCP ;
- uncooperative patients.

The following laboratory tests were performed for the patients: complete blood count, fasting blood sugar, blood urea and electrolytes, urinalysis, liver function tests, creatinine, pregnancy test, anti-thyroglobulin antibodies, immunoglobulin, anti-parietal antibodies, thyroid function test, RAST if needed, and L.E. profile. A written informed consent was obtained from all patients.

DPCP powder was dissolved in acetone and diluted into appropriate concentrations ranging from 0.000001% to 2%. Patients were sensitized with topical application of 2% DPCP on 1 cm² area of AA on the scalp. One week later, 0.000001% DPCP was applied and the concentration was then increased every 1 to 2 weeks to a maximum of 2%. The patients were instructed to avoid direct sun exposure of the scalp and not to wash the scalp for 48 hours after each application.

The duration of therapy lasted for at least 6 months. Photographs before treatment were taken and consequently repeated every month until the end of the therapy course. The percentage of hair regrowth was determined by comparative evaluation of other photographic series. Response to therapy was grouped into 4 categories according to regrowth of hair in the affected area, complete recovery (80-100%), excellent

results (60-79%), moderate change (30-59%), and minimal change (10-29%).

RESULTS

All the 21 patients completed the therapy for at least 6 months. 15 of them showed re-growth of terminal hair on the scalp with a response rate of 71.4%. Of these 15, 7 patients (33.3%) showed complete remission or an excellent response to therapy with regrowth of terminal hair (photos 1 and 2). No further maintenance therapy was required for these patients. The remaining 8 (38.1%), showed partial remission with moderate to minimal response to DPCP (table 1).



Photo 1.



Photo 2.

There were 6 patients (28.6%) who failed to respond to treatment. In the non-responders, the duration of AA before treatment ranged from 4 to 6 years. From these 6, 3 patients had a personal history of atopic dermatitis, and one patient had a family history of atopy. Two had a history of goiter and autoimmune thyroiditis. Family history of vitiligo was also detected in 2 patients. Nail changes were observed in 3 of the 6 non responders (table 1).

With regard to side effects of DPCP, an erythematous reaction at site of application was observed in all

patients. Severe dermatitis was observed in 6 patients, some of which even showed blistering reactions. This was managed successfully topical steroids. Headache, which could have been related to edema of the scalp, was observed in 4 patients. Change in pigmentation in the form of hyper and hypopigmentation occurred in 10 patients. In 7 patients lymph node enlargement was detected. Spread of contact dermatitis and generalized itching, treated successfully by systemic antihistamines, were observed in 3 and 4 patients respectively (table 2).

DISCUSSION

In this study, a re-growth of terminal hair on the scalp was achieved in 71.4% of the patients after a 6-month period of therapy. Our results were similar to those reported by Wisema *et al.* (20) who obser-

ved a 77.9% response rate in a series of 148 patients and with those of Pericin and Trueb (15) who achieved an overall response rate of 70.6% in 68 patients.

A complete or an excellent remission was observed in 33.3% of our patients, and partial remission in 38.1%. These results are also comparable with that of Pericin and Trueb (15) who obtained complete remission in 30.9% and partial remission in 39.7% of patients treated with DPCP.

In a study performed by Van der Steen *et al.* (21) on 139 patients complete remission was obtained in 50.4% of patients after 6 to 12 months of treatment, whereas a success rate of 40% was reported by Weise *et al.* (18) in a study on 124 patients.

In the previous reports, the response rate varied greatly from 4% to 85% (9, 13, 15-20, 22-23). These varia-

Pt. No	Age (yr)	Duration Of AA (years)	Form of AA	AD	Atopic diseases	Goiter & Auto-immune thyroiditis	DM Rate	Vitiligo	Nail changes	Fhx	Response Rate
1	20	1.5	Diffuse/ Ophiasis	-	-	-	-	-	-	Atopy/ AA	CR
2	45	2	Patchy	-	-	-	+	-	-	-	CR
3	14	6	Totalis	+	-	+	-	-	+	-	F
4	19	1	Patchy	-	-	-	-	-	-	-	CR
5	18	5	Patchy	-	-	-	-	-	-	-	Mod
6	17	5	Ophiasis	-	+	-	-	-	-	Atopy/ AA	Min
7	38	5	Patchy	-	-	-	-	-	-	-	Min
8	17	4	Universalis	-	-	-	-	+	-	-	Min
9	12	4.5	Patchy	-	-	-	-	-	-	-	Mod
10	18	5	Universalis	+	-	-	-	-	-	Vitiligo	F
11	17	5	Patchy	+	-	+	-	-	-	-	F
12	20	5	Ophiasis	-	-	-	-	-	-	Atopy	F
13	12	4	Diffuse	-	-	-	-	-	+	Vitiligo	F
14	21	3	Diffuse	-	-	-	+	-	-	-	Mod
15	16	2	Patchy	+	+	-	-	-	-	-	CR
16	28	4	Diffuse	-	-	+	-	-	-	-	CR
17	32	4	Universalis	-	-	-	-	-	+	-	Mod
18	19	3	Patchy	+	-	-	-	+	-	-	Ex
19	25	4	Diffuse	-	-	+	-	-	-	-	Mod
20	30	5	Universalis	-	+	-	-	-	+	-	F
21	22	4	Diffuse	-	-	-	+	-	-	-	Ex

Table 1 : Patients' response rate in relation to duration & form of AA, other associated conditions, & family history.

AD : atopic dermatitis

DM : diabetes mellitus

Fhx : family history.

+ : presence of the condition

- : absence of the condition.

CR : Complete recovery 80-100% (n=5)

Ex : Excellent result 60-79% (n=2)

Mod : Moderate 30-59% (n=5)

Min : Minimal 10-29% (n=3)

tions may be attributed to the number of patients in the studies; type, duration, and severity of AA; period of treatment, or the different methods of assessing the response.

Many adverse prognostic factors have been reported. Personal history of atopy, presence of nail changes and long duration and extent of AA seem to be associated with poor prognosis (9, 15, 23). In our study, all non-responders had a 4 to 6 years duration of disease before therapy. In 66.7% of them, there was a personal or family history of atopy. We observed nail changes in 50%, a history of goiter and autoimmune thyroiditis in 33.3%, and a family history of vitiligo in 33.3% of non responders. These findings suggest that the duration of AA, history of atopy, and presence of nail changes are the most important adverse prognostic factors.

The side effects that were encountered in our study are common, suspected, successfully managed and did not necessitate the cessation of therapy. According to past studies, other rare complications which can be encountered are vitiligo and erythema multiforme-like reactions (9, 24).

CONCLUSION

Diphenylcyclopropenone (DPCP) is a topical immunotherapy, which can be used in the treatment of chronic extensive AA. Due to its effectivity and good response rate, it is increasingly becoming the drug of choice by many dermatologists. Though it has many side effects, most of them are tolerable and do not indicate cessation of the treatment regimen. Many prognostic factors, however, can affect the response to therapy. These include: extent, type, and duration of AA, presence of nail changes, and personal and family history of atopy.

REFERENCES

1. Olsen E., Hordinsky M., McDonald-Hull S. *et al.* - Alopecia areata investigational assessment guidelines. *J Am Acad Dermatol* 1999 Feb; vol. 40; no. 2.
2. Madani S., Shapiro J. - Alopecia areata update. *J Am Acad Dermatol* 2000 April; vol. 42; no. 4.
3. Proceedings of the First International Research Workshop on Alopecia Areata. *J Invest Dermatol* 1999;96(Suppl):67S-98S.
4. Proceedings of the Second International Research Workshop on Alopecia Areata. *J Invest Dermatol* 1995;104 (Suppl):2S-45S.
5. Shapiro J. - Alopecia areata: update on therapy. *Dermatol Clinics* 1993;11:35-46.
6. Shapiro J. - Topical immunotherapy in the treatment of chronic severe alopecia areata. *Dermatol Clinics* 1993;11:611-617.

Pt. No.	Severe dermatitis	Generalized itching	Headache	Lymph nodes enlargement	Pigmentation	Spread of foci
1	+	+	+	+	+	-
2	+	-	+	+	+	-
3	+	-	+	+	+	-
4	-	-	-	-	-	-
5	+	-	-	-	-	-
6	-	-	-	-	-	-
7	+	-	-	+	+	-
8	-	-	-	-	+	-
9	-	-	-	-	-	-
10	-	-	-	-	-	+
11	-	-	-	-	-	-
12	-	-	-	-	-	-
13	-	-	-	-	-	-
14	-	-	-	-	+	-
15	-	+	-	+	+	-
16	-	-	-	-	-	-
17	+	+	+	+	+	+
18	-	-	-	-	-	-
19	-	-	-	-	+	-
20	-	+	-	+	+	+
21	-	-	-	-	-	-

Table 2 : Side effects encountered by the patients.

+ : presence of the condition.

- : absence of the condition.

7. Daman L., Rosenberg W., Drake L. - Treatment of alopecia areata with DNCB. *Arch Dermatol* 1978;114:1036-1038.
8. Happle R., Kalveran K.-J., Buchner U. et al. - Contact allergy as a therapeutic tool for alopecia areata: application of squaric acid dibutylester. *Dermatologica* 1980;161:289-297.
9. Rokhsar C.-K., Shupack J.-L., Vafai J.-J., Washenik K. - Efficacy of topical sensitizers in the treatment of alopecia areata. *J Am Acad Dermatol* 1998 Nov.; vol. 39, no. 5.
10. Wilkerson M., Henkin J., Wilkin J.-K., Smith R.-G. - Squaric acid and esters: analysis for contaminants and stability in solvents. *J Am Acad Dermatol* 1985;13:229-234.
11. Wilkerson M.-G., Henkin J., Wilkin J.-K. - Diphenylcyclopropenone: examination for potential contaminants, mechanisms of sensitization, and photochemical stability. *J Am Acad Dermatol* 1984 Nov.; 11 (5 pt 1):802-807.
12. Stute J., Hausen B.-M., Schulz K.-H. - Diphenylcyclopropenone a new strong contact sensitizer. *Derm Beruf Umwelt* 198;29(1):12-14.
13. Hausen B.-M., Stute J. - Diphenylcyclopropenone: a strong contact sensitizer. *Chem Industry* 1980;17:699-700.
14. Wilkerson M., Connor T.-H., Henkin J., Wilkin J.-K., Matney T.-S. - Assessment of diphenylcyclopropenone for photochemically induced mutagenicity in the Ames assay. *J Am Acad Dermatol* 1987;17:606-611.
15. Pericin M., Trueb R.-M. - Topical immunotherapy of severe alopecia areata with diphenylcyclopropenone: evaluation of 68 cases. *Dermatology* 1998;196(4):418-421.

16. Bolduc C., Shapiro J. - DPCP for the treatment of alopecia areata. *Skin Therapy Lett* 2000;5(5):3-4.
17. Shapiro J., Yan J., Ho V., Abbott F., Tron V. - Treatment of chronic severe alopecia areata with topical diphenylcyclopropenone and 5% minoxidil: a clinical and immunopathologic evaluation. *J Am Acad Dermatol* 1993;29:729-735.
18. Weise K., Kretzschmar L., John S.-M., Hamm H. - Topical immunotherapy in alopecia areata: anamnestic and clinical criteria of prognostic significance. *Dermatology* 1996;92:129-133.
19. Orecchia G., Rabbiosi G. - Treatment of alopecia areata with Diphenylcyclopropenone. *Dermatologica* 1985;171:193-196.
20. Wiseman M.-C., Shapiro J., MacDonald N., Lui H. - Predictive model for immunotherapy of alopecia areata with diphenylcyclopropenone. *Arch Dermatol* 2001 Aug.;137(8):1063-1068.
21. Van der Steen PHM., Van Baar HJM., Perret C.-M., Happle R. - Treatment of alopecia areata with diphenylcyclopropenone. *J Am Acad Dermatol* 1991;24:253-257.
22. Happle R., Hausen B.-M., Wiesner-Menzel L. - Diphenylcyclopropenone in the treatment of alopecia areata. *Acta Derm Venereol (Stockh)* 1983;63:49-52.
23. Gordon P.-M., Aldridge R.-D., McVittie E., Hunter JAA. - Topical diphenylcyclopropenone for alopecia areata: evaluation of 48 cases after 30 months' follow-up. *Br J Dermatol* 1996;134:869-871.
24. Buckley D.-A., Du Vivier A.-W. - Topical immunotherapy in dermatology. *Int J Clin Pract* 1999 March;53(2):130-137.



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