

ORIGINAL ARTICLE

Efficacy and safety of diphenylcyclopropenone among Chinese patients with steroid resistant and extensive alopecia areata

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Abstract

Background Topical immunotherapy has recently been found useful in the treatment of chronic and extensive Alopecia Areata (AA).

Objective To evaluate the efficacy and safety of diphenylcyclopropenone (DPCP) use among Chinese patients with steroid resistant and extensive AA in our institute.

Methods The medical records of 31 Chinese patients treated with DPCP were analysed retrospectively. The efficacy, adverse effects, and relapse rate of DPCP treatment were reviewed.

Results Thirty-one (16 male, 15 female) Chinese patients with extensive, steroid resistant Alopecia Areata and a mean age of 28.9 years (SE 10.4) were treated. The mean age of onset was 17.8 years (SE 8.8) with an average disease duration of 11.2 years (SE 7.7). Ten patients had a history of atopy and 4 had a history of thyroid disease. Nail changes were found in 14 patients and a family history of AA was found in 2 patients. Thirteen patients (41.9%) had experienced total hair loss. Two patients abandoned the treatment due to severe side effects. Of the remaining 29 patients, 4 (13.8%), 7 (24.1%), 5 (17.2%), and 13 (44.8%) achieved >90% complete response, >50–90% partial response, >10–50% minimal response, and <10% no response hair regrowth, respectively. Adverse effects included pruritus, erythema, vesiculation, scaling, cervical lymphadenopathy, dyspigmentation and urticarial reactions. Relapse occurred (>25% hair loss) in 69.23% of patients after 18 months of follow up.

Conclusions DPCP is an effective and tolerable treatment for Chinese patients with extensive, steroid resistant AA.

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Conflict of Interest

None declared.

Disclosure

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Introduction

Alopecia areata (AA) is an organ-specific autoimmune disease with a genetic basis.¹ It occurs in 1–2% of the general population and can be associated with traumatic childhood events.² Having a history of atopy or autoimmune diseases may increase the risk of AA.³ Clinically, patients present with asymptomatic, patchy hair loss. The scalp appears normal with hair follicles preserved and at the edges of the active lesions, characteristic ‘exclamation mark’

hairs may be found. The natural history of the disease is quite variable, with spontaneous remission occurring in a number of cases.⁴ Although the pathophysiology of AA is not well understood, cytokines like IFN-gamma, interleukins, and TNF-alpha are believed to play a major role.⁵ More recently the concept of immune privilege has been introduced.⁶

For treatment of extensive alopecia, topical immunotherapy such as Diphenylcyclopropenone (DPCP) is the treatment of

choice for adults with more than 50% scalp involvement⁷ Phototherapy such as PUVA, with and without oral steroids, has also been used with limited success.⁸ Cyclosporin is not recommended because of its long term nephrotoxicity⁹ and biologics such as efalizumab¹⁰ and etanercept¹¹ failed to show improvement in AA.

Besides DPCP, topical immunotherapy with Dinitrochlorobenzene, Squaric Acid Dibutylester have been used to treat severe and refractory AA.¹² Because Ames testing has revealed that Dinitrochlorobenzene is mutagenic and Squaric Acid Dibutylester requires a special solvent to maintain its potency, DPCP is more commonly used. The efficacy of DPCP in the treatment of Alopecia Areata has been shown in a variety of non-Chinese studies.^{13–16} Chronic, extensive Alopecia Areata; long disease duration; and the associated nail changes have been reported as poor prognosticators.¹⁷ The adverse effects of DPCP treatment are eczematous reactions,¹⁸ lymphadenopathy,¹⁹ urticaria,²⁰ vitiligo,²¹ pigmented contact dermatitis,²² and, rarely, an erythema multiforme-like reaction.²³ This retrospective study aims to evaluate the efficacy and safety of DPCP in treating extensive, steroid resistant AA among Chinese patients and to look for any prognostic factors.

Methods and patients

Study population

Patients being treated with DPCP in the Dermatology Clinic of the Prince of Wales Hospital Hong Kong SAR between June 2009 and May 2010 were retrieved for analysis. There were 31 patients in total with ages ranging from 12 to 48 years (mean age, 28.9; SE 10.4). Those treated were AA patients with 30% or more hair loss (extensive Alopecia Areata) who had been ineffectively treated with topical or intralesional steroids for at least 6 months (steroid resistant). Information regarding their age, sex, age of onset, duration of disease, personal history of atopy or thyroid disease, family history of Alopecia Areata, extent of alopecia (% of bald area) and nail changes was extracted for analysis.

Treatment regime

During their first visit, a 2×2 cm² area of each patient's scalp was sensitised with 2% DPCP (FLUKA, Sigma-Aldrich, Saint Louis, MO, USA) and the patients were asked to return two weeks later for appraisal. Those with severe skin reactions, e.g. severe bullous eruptions or generalised urticarial lesions, were excluded from the study. For those who experienced no untoward effects, DPCP in escalating concentrations (0.001%, 0.01%, 0.05%, 0.1%, 0.5%, 1.0%, and 2.0%) was applied to the whole scalp at weekly intervals. Patients were instructed to avoid direct sun exposure and wash off the DPCP 48 h after application. The target concentration was to maintain the reaction of itching and erythema in the treated areas for 48 h. Patients with no sign of hair regrowth after 6 months of therapy were considered non-responders and treatment was discontinued. Those with hair regrowth were maintained on DPCP if the patient had no objection. Written consent

for minors (those below 18 years of age) was obtained before treatment. The treatment modality was approved by the Chinese University of Hong Kong's ethics committee.

Classifications of disease severity and outcome measurements

The extent of hair loss was divided into five classes: S1 disease (no hair loss); S2 disease (26–50% hair loss); S3 disease (51–75% hair loss); S4 disease (76–99% hair loss); and S5 disease (100% hair loss). At each visit, the adverse effects of DPCP treatment and the patients' clinical hair regrowth responses were assessed. Adverse effects were graded as: (i) mild: erythema only; (ii) moderate: localized edema, blisters, and erosion; (iii) severe: widespread skin rash; and (iv) life threatening reaction: anaphylaxis, Stevens Johnson syndrome, or toxic epidermal necrosis syndrome. Clinical responses were measured as: complete response (CR): >90% regrowth; partial response (PR): >50–90% regrowth; minimal response (MR): >10–50% regrowth; and no response (NR): <10% regrowth of scalp hair. Relapse was defined as >25% hair loss after hair regrowth.

Statistical analysis

Chi-squared tests were used to correlate good response (>50% regrowth) to gender, childhood onset of disease (age of onset <18 years), chronic duration of disease (> 10 years), personal history of atopy, family history of alopecia areata, extent of alopecia (totalis vs. areata), and presence of nail changes. When the cell frequency dropped below 5, Fisher's exact test was used. A logistic regression model (forward conditional) was used to determine the independent risk factors of poor response. The Statistical Package for Social Science (SPSS version 15; Chicago, IL, USA) was used, with a *P* value of <0.05 regarded as significant.

Results

Patients' demographic and clinical features

The initial sample group for this study comprised 31 (16 male, 15 female) Chinese patients with extensive, steroid resistant AA who were being treated with DPCP. Their mean age was 28.9 years (SE 10.4). The mean age of onset was 17.8 years (SE 8.8) with average disease duration of 11.2 years (SE 7.7). Ten of the patients had a history of atopy and 4 had a history of thyroid disease. Nail changes (pitting and trachyonychia) were found in 14 patients and a family history of AA was found in 2 patients. Thirteen patients (41.9%) had S5 disease (100% hair loss), 9 patients (29.0%) had S4 disease (76–99% hair loss), 4 patients (12.9%) had S3 disease (51–75% hair loss), and 5 patients (16.1%) had S2 disease (26–50% hair loss). The clinical features, disease severity, and responses to treatment of the patients are shown in Table 1.

Treatment outcome

Two patients abandoned the treatment due to severe side effects, namely severe bullous and urticarial reactions. Of the remaining

Table 1 Clinical features, disease severity and response of patients treated with DPCP

Patient no.	Sex/Age (years)	Form of alopecia‡	Severity grading*	Duration of disease (years)	Family history of Alopecia Areata	Personal history of atopy	Presence of nail changes	Treatment response†
1	F/12	at	s5	11	no	no	yes	nr
2	M/26	at	s5	5	no	no	yes	nr
3	M/28	m	s3	14	no	no	yes	pr
4	F/39	m	s2	1	no	no	no	NA
5	M/18	m	s4	1	no	yes	no	mr
6	M/25	at	s5	4	no	no	no	cr
7	M/25	m	s4	7	no	no	no	pr
8	M/19	m	s2	7	no	yes	no	pr
9	F/38	at	s5	13	no	no	no	pr
10	F/23	m	s3	3	no	no	yes	mr
11	F/13	at	s5	12	no	yes	no	nr
12	M/24	at	s5	10	no	no	no	mr
13	F/32	at	s5	23	no	no	yes	nr
14	M/24	at	s4	3	no	no	yes	pr
15	F/37	m	s3	20	no	yes	no	nr
16	M/28	at	s5	4	no	yes	no	cr
17	M/21	au	s5	7	no	yes	yes	nr
18	F/18	m	s2	11	no	yes	no	nr
19	M/26	m	s4	19	no	yes	no	cr
20	F/44	at	s5	26	no	no	yes	nr
21	F/28	m	s4	12	no	no	yes	nr
22	M/27	at	s5	11	no	no	yes	nr
23	F/38	au	s5	20	no	no	yes	nr
24	F/16	au	s5	10	no	no	yes	nr
25	M/48	at	s4	15	no	no	no	mr
26	M/27	m	s4	15	no	no	yes	mr
27	M/32	m	s3	3	no	no	no	NA
28	M/41	m	s2	25	yes	yes	no	nr
29	F/21	m	s4	2	yes	no	no	cr
30	F/54	m	s4	20	no	no	no	pr
31	F/44	m	s2	20	no	yes	yes	pr

*S0 = No hair loss, S1 = 25%, S2 = 26–50%, S3 = 51–75%, S4 = 76–99%, S5 = 100% hair loss.

†CR, complete response; >90% regrowth; PR, partial response; >50–90% regrowth; MR, minimal response; >10–50% regrowth; NR, no response; <10% regrowth of scalp hair; NA, not applicable.

‡ m, multifocal; at, alopecia totalis; au, alopecia universalis; DPCP, diphenylcyclopropenone.

29 patients, 4 (13.8%) had CR with >90% hair regrowth; 7 (24.1%) had PR with >50–90% hair regrowth; 5 (17.2%) had MR with >10–50%, and 13 (44.8%) had NR with <10% hair regrowth within the treatment period from 6 to 18 months (Fig. 1). Of the 4 patients with CR, 4 (100%) had relapsed (>25% hair loss) and 5 out of 9 patients with PR had relapsed after 18 months. The overall relapse rate in our patients with PR and CR was 69.23%.

Adverse events

All patients complained of itching and erythema across the treated sites. These were regarded as desired reactions. More than half of the patients had eczematous reactions with scaling (55%), vesiculation, and localized bullous eruptions (76%) (Fig. 2, top left). Cervical lymphadenopathy was noted in 15 (52%) patients while



Figure 1 Patient with complete response after 6 months of diphenylcyclopropenone (DPCP) treatment.



Figure 2 Complications and side effects of diphenylcyclopropenone (DPCP) treatment. Top left: patient with vesicles, scaling and hyperpigmentation. Top right: ophiasis remains despite significant regrowth in other areas. Bottom left: induction of vitiligo. Bottom right: uneven hair regrowth could cause patient dissatisfaction.

Table 2 Adverse events encountered

Adverse event	No of patients	Percentage
Erythema	29	100%
Pruritus	29	100%
Vesicles or localized bulla	22	76%
Cervical lymphadenopathy	16	55%
Scaling	16	55%
Hyperpigmentation	13	45%
Contact urticaria	2	7%
Severe reactions	2	7%
Vitiligo	1	3%

post-inflammatory hyperpigmentation developed in 13 (45%) patients. Vitiligo (Fig. 2, bottom left) was developed by one patient over the treated area (Table 2).

Prognostic factors

Based on the 29 patients who had completed at least 6 months of DPCP treatment, chi-squared tests were used to correlate good

Table 3 Correlation of various parameters with response grade

Parameter	Response grade		P value
	Poor (NR/MR)†	Good (PR/CR)†	
Sex			
Female	10	4	0.450
Male	8	7	
Drinker			
Yes	4	1	0.356
No	14	10	
Smoker			
Yes	1	1	0.623
No	17	10	
Family history of AA			
Yes	1	1	0.623
No	17	10	
Age of onset			
Childhood onset (age<18 years)	15	4	0.015*
Adult onset (age 18 years or above)	3	7	
Duration of disease			
<10 years	6	6	0.230
10 years or above	12	5	
Nail changes			
Presence	11	3	0.082
Absence	7	8	
Extent of alopecia			
AT/AU	10	3	0.135
AA	8	8	
Recurrent disease			
Yes	7	4	0.604
No	11	7	
History of atopy			
Yes	6	4	0.589
No	12	7	

*P value of >0.05 was considered as significant

†AA, Alopecia Areata; AT, alopecia totalis; AU, alopecia universalis; NR, no response; MR, minimal response; PR, partial response; CR, complete response; DPCP, diphenylcyclopropenone.

treatment response (>50% regrowth) to gender, childhood onset of disease (<18 years), chronic duration of disease (>10 years), personal history of atopy, family history of AA, extent of alopecia (totalis vs. areata), and presence of nail changes. Childhood onset of disease ($P = 0.015$) was significantly correlated with a poor response (Table 3). This was confirmed by the logistic binomial regression model as an independent risk factor for poor treatment response ($P = 0.047$, OR = 0.160).

Discussion

Topical immunotherapy has been used since 1978²⁴ and has proven effective in treating chronic and extensive AA in those for

whom conventional therapies, such as topical and systemic steroids or immunosuppressants, had failed. Success rates vary between 5 and 85%.²⁵

Our study confirms the efficacy of DPCP in Chinese patients with extensive, steroid resistant AA. Eleven (37.9%) of our patients achieved either PR or CR, which was slightly less than a recent review of 142 patients.²⁶ This might be due to the inferior clinical profiles of our patients such as long disease duration (10.61 vs. 6 years), a large number of alopecia totalis and alopecia universalis (AU) patients (44.8% vs. 17.7%), and short treatment duration (mean 9 vs. 20 months). Two patients had ophiasis on presentation, despite achieving CR and PR in other scalp areas, and the ophiasis showed only slight regrowth (Fig. 2, top right). In addition, of the 4 patients with CR, all 4 (100%) experienced relapse (>25% hair loss) and 5 out of 9 patients with PR relapsed after 18 months. The overall relapse rate for PR and CR among our patients was 69.23%.

The different success rates reported in the literature could be due to the various reporting methods. For example, some studies adopted the MacDonald Hull and Norris grading¹⁴ while others used a 'cosmetically acceptable' measure as their end point.²⁵ A unified outcome measurement would enable future studies to be more comparable. Furthermore, for a comprehensive outcome measurement, it would be better to separate objective assessment, e.g. the percentage of hair regrowth, from patients' subjective perceptions, e.g. cosmetic acceptability. This sort of 'combined' score has been used in the study of atopic dermatitis, i.e. the 'SCORAD'. One benefit of this sort of combined score in assessing alopecia is that we can separately assess the patients' satisfaction and the dermatologists' objective assessments. Some patients will not be satisfied with significant, but uneven hair regrowth. One of our patients deliberately shaved off the regrown hair so as to remain uniformly bald (Fig. 2, bottom right). The general principles and various criteria for assessment, in particular the Severity Alopecia Tool, have been thoroughly reviewed by Olsen *et al.*²⁷

The adverse effects of DPCP treatment were usually tolerable. However, two of the patients abandoned the treatment due to severe bullous and urticarial eruptions. The former experienced a full regrowth of her hair, but it was unclear whether it was due to the 4 treatments she received or due to the natural course of the disease. One patient developed progressive vitiligo over the treated area and subsequently gave up the treatment. The vitiligo did not improve, even a year after stopping treatment. On further enquiry, the patient volunteered that she had actually had a small depigmented lesion at her left axilla before treatment which had been stable over the years. This raised the question whether patients with vitiligo should be excluded from DPCP treatment on the grounds that the risk of vitiligo complicating the treatment may be higher. All of the other adverse effects were reported by our patients to be endurable with the symptomatic use of topical steroids or oral antihistamines. One point worth noting is that the climate in Hong Kong is hot and humid, such that almost all of

our patients complained of a burning sensation after DPCP application aggravated by occlusion and sweating (due to wigs or hats). Thus, patients in hot climates should be forewarned. Furthermore, two of our patients experienced a short period of chills on the day of treatment that subsided the next day without treatment. Compared to the conventional topical and intralesional steroid therapy, topical immunotherapy must be applied weekly and hence patients must attend the clinic more frequently. These are the practical considerations that patients should consider before embarking on this modality of treatment.

In the literature, poor treatment outcomes for DPCP included the severity of alopecia at the time of presentation,²⁸ the presence of nail changes and disease duration before treatment,¹⁷ the age of onset, disease duration, and a personal history of atopy.²⁵ Taking all of these studies together, the most consistent prognosticator appears to be the extent of AA before treatment. This study used chi-squared tests to correlate treatment outcomes and clinical parameters, which showed that the childhood onset of disease (<18 years) was a significant poor prognosticator. This was further confirmed in a logistic regression model. There was no correlation between treatment responses and the extent of disease upon presentation, personal history of atopy, disease duration lasting more than 10 years, or family history of alopecia areata. Due to our study's small sample size, these correlations require further verification in a larger study.

A DPCP concentration of 2% was used for sensitisation in most previous studies and if there is no reaction after weekly challenges with increasing concentrations up to 2%, the patient would be labelled anergic. Those with initial responses who subsequently developed tolerances received a higher concentration. In one study, 5% DPCP was used for 48 months²⁹ with no untoward effect and remission was maintained in 5 patients. It would be interesting to study whether a higher response rate might be achieved using high concentrations of DPCP in similar studies. The maximum concentration of DPCP used in this study was 2%, which might account for its low efficacy in some patients. A variety of previous studies have also shown that the longer the treatment, the higher the chance of response, although the success rate decreases with time. It has been suggested that at least a 12 or 18-month period be tried before the patient is declared non-responsive.^{25,26} The question whether maintenance therapy is needed to prevent relapse remains controversial. Studies by Wiseman *et al.*²⁵ and Aghaei¹⁶ did not show any relationship between maintenance therapy and risk of relapse. In contrast, El-Zawahry²⁹ demonstrated a decrease in the relapse rate (17.9% vs 57.1%) with maintenance DPCP treatment. The relapse rate in this study was very high, approaching 70%. Only 2 of the 9 relapse cases were not on maintenance therapy. Given that some relapse cases have been successfully rescued by re-treatment with DPCP, it may be reasonable to assume that the therapeutic effects of DPCP can be maintained through continuous treatment, which would support the institution of maintenance therapy. The specific

characteristics of an ideal maintenance regime, however, remain unclear. How frequently should DPCP be applied for maintenance purposes? Would the concentration be the same as that used in the 'induction' phase? Would the purpose of maintenance therapy be to 'prolong' remission rather than prevent an inevitable relapse? In the long run, can we pinpoint who should benefit from maintenance therapy? These questions should be addressed in future studies. Furthermore, the diagnosis of alopecia areata was made clinically in this study with no pre-treatment biopsies to confirm, although most of the patients had experienced a clinical course of alopecia areata with relapse and regrowth.

Limitations of the study

This study was retrospective, with a short follow up period. The sample size was small ($n = 29$) and the highest DPCP concentration used was only 2%. In addition, most of the patients received just 6 months of treatment. As spontaneous regrowth is possible, especially in patients with limited alopecia areata, the study may be more revealing if we could treat only half of the scalp with DPCP while leaving the other half untreated.

In conclusion, our study shows that DPCP was an effective and tolerable treatment for Chinese patients with extensive, steroid resistant AA. DPCP could be considered for cases in which conventional therapy has failed or for patients who reject systemic treatment or phototherapy.

Author contributions

Nai-Ming T. Luk was responsible for writing the study proposal, making the application to the local ethics committee, carrying out the treatment, analyzing the results and writing the manuscript.

LS Chiu, M Chang and YK Lam were responsible for carrying out the treatment.

KC Lee, VWY Lee, CTS Chau and Hau-Chi S Lee were responsible for the preparation of diphenylcyclopropenone.

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