A retrospective comparative study of the efficacy and safety of two regimens of diphenylcyclopropenone in the treatment of recalcitrant alopecia areata

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Abstract

Diphenylcyclopropenone (DPCP) is an effective topical immunotherapy for recalcitrant alopecia areata (AA), which sometimes requires prolonged treatment. We developed a new treatment protocol to shorten the duration of therapy. This study aimed to compare the efficacy and safety of the new treatment protocol with the standard treatment protocol in the treatment of recalcitrant AA. We conducted a 6-year retrospective comparative study of patients with AA who received one of the DPCP treatment protocols at our institute. Patients’ information was collected and subsequent statistically analyzed. Thirty-nine patients (16 in the new treatment group and 23 in the standard treatment group) were included. There were no statistically significant differences in area of hair regrowth. Mean duration to initial hair regrowth and mean duration to significant hair regrowth in the new treatment group were significantly shorter than in the standard treatment group (P=0.002 and 0.01, respectively). Adverse effects were slightly higher in the new treatment group. The present study reveals the effectiveness and safety of the new treatment protocol, which shortens the duration of DPCP treatment and could represent an alternative regimen.

Introduction

Alopecia areata (AA) is an autoimmune disease with a genetic basis presenting with non-scarring hair loss both on the scalp and non-scalp areas. The prevalence of AA is approximately 1-2% of the general population. The disease has no sexual and age prevalence. Clinically, patients manifest with well-defined, asymptomatic, non-scarring areas of hair loss with characteristic exclamation mark hairs. The prognosis of the disease is quite variable. Spontaneous improvement within 1 year was reported in 34-50% of patients. However, in 14-25%, AA can progress to total scalp hair loss (alopecia totalis; AT) or even entire body hair loss (alopecia universalis; AU), which shows spontaneous improvement in less than 10% of cases. Even though AA is not a life threatening disease, it can greatly affect patients’ psychosocial status and quality of life. Compared with the general population, psychological disorders, such as anxiety, depression, and phobias, are more common in patients with AA. The pathogenesis of AA remains to be determined. Currently, a widely accepted theory is the autoimmune etiology. Specific T-cell lymphocytes, autoantibodies against anagen follicles, and various cytokines such as interferon-γ, interleukins, and tumor necrosis factor-α have been found to play a major role in AA. In addition, the immune privilege theory has been recently introduced and suggested to play a role in the pathogenesis. Therefore, the principle of treatment is to inhibit all the possible etiological pathways. There is currently no curative treatment for AA. Treatment modalities include corticosteroids, anthralin, cyclosporine, biologic therapy, topical immunotherapy, photochemotherapy, and 308-nm excimer laser, among other. However, treatment is still very difficult, particularly in patients with chronic and extensive AA.

Currently, topical immunotherapy using diphenylcyclopropenone (DPCP) is one interesting treatment option for recalcitrant case. This treatment was first introduced by Happle et al. in 1983. The principle of treatment is induction and repeated elicitation of an allergic contact dermatitis by application of contact allergen on affected areas. Its mechanism of action is not fully understood, but antigenic competition from induction of contact dermatitis on the scalp is believed to be a possible mechanism.

For almost 10 years, we have been performing DPCP treatment regularly in patients with AA who do not respond to other treatments within the first 6 months. The first step of treatment is sensitization of the patient to DPCP. After this is successfully completed, the lowest concentration of DPCP is initially applied to the affected area on the patient’s scalp. Then, the concentration is gradually increased every week until the optimal reaction occurs. We observed that some patients took several weeks or even months to reach the optimal reaction, which could extend the overall treatment duration.

We developed a new treatment protocol of topical immunotherapy for recalcitrant AA and have been using it in some patients since 2011. The purpose of developing the new protocol was to minimize the duration of DPCP treatment. After sensitization, multiple concentrations of DPCP were applied to the scalp in individual small areas at the same time. Then, the optimal concentration that could cause mild contact dermatitis was selected to be the first concentration applied to the patient’s scalp. We believe that our new treatment protocol could reduce the treatment duration and also reduce the cumulative treatment cost compared to the standard protocol. Therefore, to prove our hypothesis, we conducted a retrospective comparative study of patients with AA who received DPCP treatment at our institute. The objective of the study was to determine whether the new treatment protocol is superior to the standard protocol in the treatment of recalcitrant AA and to compare adverse events between the two treatment protocols.

Materials and Methods

Study design

This is a retrospective comparative study conducted at Ramathibodi Hospital, Mahidol University. Patients’ information from 2011 to 2016 was collected from medical records. The study was reviewed and
optimal eczematous reaction was main-
tained at subsequent treatments. If the con-
pruritus and mild erythema lasting not more
erable eczematous reaction, which was mild
of DPCP was titrated upward to reach a tol-
gentle shampoo. Each week, concentration
the scalp for 24 h and then washed off with
gentle shampoo. One week later, the concentra-
tion of DPCP was adjusted every
week to maintain a tolerable eczematous
reaction.

Clinical assessment
The patients were followed up weekly
for evaluation of clinical responses and side
effects. Treatment was withdrawn if there
were no signs of hair regrowth at 6 months.
If there was any clinical response, treatment
was continued until complete hair regrowth.
For patients with incomplete hair regrow-
tht at 1 year after treatment, percentage of hair
regrowth at 1 year was recorded as their
treatment outcome. All patients were fol-
lowed up monthly for 6 months after dis-
continuation of treatment.

The clinical assessment was divided
into efficacy and safety. Efficacy assess-
ment included the treatment response
reported as percentages of area of hair
regrowth, change in SALT score from base-
line, and duration of clinical responses (ini-
tial response and significant response).
The initial response was defined as appearance
of any new regrowth hair within treated
sites and significant response was defined
as greater than 75% hair regrowth. Failure
of treatment was considered when hair
regrowth was not observed after the first 6
months of treatment. Relapse was defined
as more than 25% hair loss after complete
hair regrowth. Safety information was col-
lected from the adverse effects recorded.

Sensitization to diphenylcyclo-
propene
DPCP solution was prepared by dis-
solving DPCP powder (Fluka, Sigma-
Aldrich Corp, St. Louis, MO, USA) in ace-
tone at serial dilutions of 0.0001%,
0.0005%, 0.001%, 0.005%, 0.01%, 0.02%,
0.05%, 0.1%, 0.2%, 0.5%, 1.0%, and 2.0%
and storing the dilution in dark glass vials
to prevent degradation from ultraviolet light.
At the first visit, the patient was sensitized
by application of 2% DPCP at the inner
aspect of the upper arm over a 4×4 cm² area.
DPCP was left on the sensitized area for 24
hours then washed off. After 72 h, patient
was evaluated for an eczematous reaction
to detect whether sensitization to DPCP had
occurred.

Treatment with standard regimen
Two weeks after sensitization, DPCP
treatment starting with the 0.0001% con-
centration was applied at the affected scalp
area every week. First, DPCP was left on
the scalp for 24 h and then washed off with
gentle shampoo. Each week, concentration
of DPCP was titrated upward to reach a tol-
erable eczematous reaction, which was mild
pruritus and mild erythema lasting not more
than 48 h. The concentration that produced
optimal eczematous reaction was main-
tained at subsequent treatments. If the con-
centration of DPCP on the scalp
revealed negative or below the optimal
reaction, then the concentration of DPCP
would be titrated upward. The concentra-
tion may be titrated upward or downward to
maintain the optimal eczematous reaction.

Treatment with new treatment regimen
Two weeks after sensitization, the scalp
was mapped for applying DPCP. Then, six
consecutive concentrations of DPCP
(0.0001%, 0.001%, 0.01%, 0.05%, 0.1%,
and 0.5%) were applied on the scalp over
3×3 cm² areas separated by a distance of 4
cm. DPCP was left on the scalp for 24 h and
then washed off with gentle shampoo. One
week later, the concentration that created a
mild eczematous reaction was chosen to be
the first applied. The starting concentration
was applied at the affected scalp area
and left for 24 h and then washed off. The
concentration of DPCP was adjusted every
week to maintain a tolerable eczematous
reaction.

Results
From a total of 65 patients with AA who
received DPCP treatment during the last 5
years, 39 patients were eligible and were
included in the study. Sixteen patients were
treated with the new treatment regimen
and 23 patients were treated with the standard
regimen. Epidemiological data and baseline
clinical characteristics of all patients are
compared and summarized in Table 1. The
groups were comparable in terms of age,
gender, duration of disease, underlying dis-
eease, scalp area involvement, and nail
involvement.

Table 2 demonstrates the comparison of
treatment outcomes between the 2 treatment
groups. Eight patients in the new treatment
group and 12 patients in the standard group
had >75% area of hair regrowth. Seven
patients in each group had complete hair
regrowth. Failure of treatment was reported
in 2 and 3 patients in the new and standard
treatment group, respectively. Regarding
area of hair regrowth, there were no statisti-
cally significant differences between the
two groups. For treatment duration, mean
duration to initial hair regrowth in the new
treatment group was significantly shorter
than that in the standard treatment
group (10.5±2.6 weeks and 14.2±3.9 weeks,
respectively; P=0.002). Moreover, mean
duration to >75% hair regrowth was
24.3±4.2 weeks in the new treatment
group and 29.2±6.5 weeks in the standard
treatment group, representing a statistically
significant difference (P=0.01). Regarding
relapse of AA, there was no significant dif-
fERENCE in both number of patients and
median duration to relapse between the 2
groups (P=0.81 and 0.62, respectively). Adverse
effects were slightly higher in the
new treatment group, without statistical sig-
nificance.

Discussion
Topical immunotherapy using DPCP
has been proven effective in the treatment
of patients with recalcitrant AA. This
method is recommended as first-line thera-
py in patients with AA who have more than
50% scalp area involvement.11 Its efficacy,
in terms of acceptable regrowth, has been
reported in previous studies with variable
response. A systematic review reported that
the average response rate of DPCP treat-
ment in 26 studies was 53.75%.12 Our study
reported a significant response rate of 50%
in the new treatment group and 52.1% in
the standard treatment group, which are com-
parable with the average response rate.
Previous studies reported response rates of DPCP ranging from 5 to 85%. The variability in clinical response rate between studies may be attributed to different study designs, treatment protocols, baseline disease severity, therapeutic response grading systems, and follow-up periods. To minimize this problem in future studies, clinical trials using a standardized method in clinical assessment is recommended.

Regarding percentage of hair regrowth, the present study found similar clinical response rates between the 2 groups. The data confirms that the efficacy of the new treatment protocol was not inferior in comparison with the standard treatment protocol. In addition, this retrospective study reveals the advantage of the multiple DPCP treatment protocol in shortening the duration of treatment. Our study showed that mean duration to initial response and mean duration to >75% hair regrowth in the new treatment group were significantly shorter than in the standard treatment group, which was approximately 5 weeks. Our results are comparable with a previous study using multiple concentrations of DPCP in patients with AT or AU, which revealed a benefit of shortened treatment duration.21

When comparing the treatment duration using data from the standard treatment group, the average duration to significant hair regrowth was comparable with previous studies. Chiang et al.,22 and El Khoury et al.23 reported durations to significant hair regrowth of 28 and 31.74 weeks, respectively. Therefore, the new treatment protocol could shorten the response time, which normally takes several months to reach a significant clinical response, and could be considered an alternative regimen to shorten the therapeutic period. Application of multiple concentrations of DPCP at the first treatment assisted the physician in identifying the optimal concentration in a shorter period. Reduction of the overall treatment duration could reduce the cost of treatment and other expenses such as transportation, accommodation, and income loss while undergoing DPCP treatment.

The relapse rates in each treatment group in the present study were less than that reported in previous studies, which range between 45.1 and 70%. The difference in the relapse rate may be due to different definitions of relapse and the duration of follow-up. Although the relapse rate of topical immunotherapy with DPCP is quite high, it is considered to be the most successful treatment for severe types of AA.25

Common adverse effects of DPCP treatment described in the literature are severe eczematous reaction, wide spread eczema, urticarial reaction, severe dermographism, and cervical lymphadenopathy. The present study shows that adverse effects were slightly higher in the new treatment protocol group, without statistical significance. Using a higher concentration during the early treatment period could increase the possibility of severe reactions. Fortunately, the adverse effects were tolerable and rapidly disappeared within a few days after providing symptomatic treatment. None of the patient dropped out of the treatment.

Limitations of this study are the retrospective design and small number of patients. Therefore, we were unable to assess patients’ history and clinical evaluation completely. The small sample size may account for the lack of statistically significant results. Prospective clinical trials with a large number of patients could overcome this limitation.

Conclusions

Topical immunotherapy is an effective treatment option for patients with chronic...
and extensive AA. The present study shows that the new treatment protocol is effective and safe, and could shorten the duration of DPCP treatment. Our new treatment protocol could be an alternative regimen for the treatment of AA.

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