Multi-Concentration Level Patch Test Guided Diphenyl Cyclopropenone (DPCP) Treatment in Alopecia Totalis or Alopecia Universalis

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Background: *Diphenylcyclopropenone (DPCP) has proved to be effective in alopecia areata. The present study aimed to shorten the treatment duration of DPCP for achieving optimal outcomes.*

Objective: *To evaluate the efficacy of multi-concentration level patch test guided DPCP treatment against conventional protocol by measuring percentage of hair regrowth and duration of treatment.*

Material and Method: *The scalp was divided into experimental and control sites. Conventional DPCP sensitization and experimental patch test with multi-level of DPCP concentration were applied in 20 alopecia totalis or universalis patients. The percentages of hair regrowth were evaluated.*

Results: *Five patients achieved complete response within 34 weeks. Mean duration of the experimental sites was shorter although there was no significant difference. Reported complications of both groups were vesicle formation, generalized eczema and folliculitis.*

Conclusion: *Patch test guided DPCP therapy may be a new regimen for alopecia areata treatment because of shortening treatment duration without increasing complications.*

Keywords: *Alopecia totalis, Alopecia universalis, Alopecia areata, Topical immunotherapy, Diphenylcyclopropenone, Patch test*

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Alopecia areata (AA) is one type of non-scarring alopecia that increases an incidence in children and adolescents. Clinical characteristics are usually limited alopecic patches on the scalp, excepting more severe forms may affect total scalp (alopecia totalis) or body (alopecia universalis). Alopecia areata is diagnosed by clinical presentation and tissue biopsy. At present, aetiology of alopecia areata remains unknown, whereas the biopsy specimens from affected sites commonly demonstrate activated T lymphocytes infiltrate at anagen hair follicles. Thus an autoimmune mechanism is implicated the pathologic process of disease[1].

Due to the previous study, topical immunotherapy (DPCP) has been proven to be effective in treating patients with severe and chronic alopecia areata including alopecia totalis and alopecia universalis[3-5]. Two percent DCPC sensitization is performed on scalp in the initial step and induces mild allergic contact dermatitis reactions inapplied areas. The mild allergic dermatitis reactions are expected only erythematous macules or papules with itching, but vesicle formation or serous oozing does not occur[6]. If the mild eczema reaction is shown in 2-week later, 0.0001% concentration of DPCP would be applied to target areas. Consequently, the concentration of reapplied DPCP is adjusted once a week base on the severity of previous reactions[6]. It takes several weeks for achieving the optimal concentration that stimulates hair regrowth as planned.

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Patch test is a technique that used to determine a specific substance which causes allergic inflammation on patient's skin[7]. For the purpose of the present study, this technique was adapted to identify a new initial concentration of DPCP in each patient. We expected that the duration for titrating DPCP concentrations was minimized. Consequently, the goal of treatment was accomplished faster than under normal conditions. For this reason, the study was designed to prove the hypothesis.

Material and Method

The present was a randomized-controlled trial experimental clinical study approved by the Ethics Committee of The Siriraj Institutional Review Board, Faculty of Medicine, Siriraj Hospital, Mahidol University. The study enrolled 20 alopecia totalis or alopecia universalis patients age >18 years who achieved unsatisfied outcomes with other treatments for at least one year at the Department of Dermatology, Faculty of Medicine, Siriraj Hospital, Mahidol University. The informed consents from all 20 subjects were taken after subjects received all relevant information about DPCP. None of the patients had history of topical immunotherapy treatment.

Procedure

Firstly, all of the patients were sensitized by 2% DCPC on quarter-size area on scalp and followed by one-week evaluation. After that, the patients were applied with open patch test with DPCP concentration of 0.0001%, 0.001%, 0.01%, 0.05%, 0.1%, 0.5% and 1% then, read for the result after 72 hours, (Fig. 1). The reactive concentration was defined as the concentration that had redness at 72 hours after application of DPCP.

After randomization, one side of the scalp was applied with DPCP one step lower than the reactive concentration, and the other side was applied by standard regimen which would apply DPCP from the lowest concentration of 0.0001%. Thereafter, the reaction of DPCP was followed every 4 weeks and the concentrations of DPCP of both sides were increased 1 step. Hair regrowth was evaluated as the indicator of effectiveness. In the present study, the clinical end point was defined as greater than 75% of hair regrowth. Thus the percentages of hair regrowth in each visit were recorded. Furthermore, the complication of DPCP was observed.

Statistical analysis

Data was analyzed using SPSS version 20.0. Descriptive statistics were performed to describe demographic data, duration of hair regrowth and complication. The comparison of hair regrowth area at 34 weeks between control and experimental sites of scalp after DPCP treatment was analyzed by using t-test and Kaplan-Meier test. The data were considered statistically significant when p-value <0.05.

Results

Twenty patients with an average age of 35 years (SD 15.2, range 18-71 years) were enrolled in the present study. Twelve cases were female (65%). Alopecia totalis and alopecia universalis were diag-

Table 1. The result of patch test with diphenylcyclopropenone (DPCP) demonstartedthe number of subjects who react to DPCP in different concentrations

Concentrations of DPCP	Number of the patients with DPCP reaction (%)
0.01%	4 (20%)
0.05%	4 (20%)
0.1%	5 (25%)
0.5%	6 (30%)
1%	1 (5%)

nosed in 6 and 14 patients, respectively. The average duration of alopecia areata in the present study was 1 year (range 0.17-15 years). All of the participants were sensitized with 2% DPCP and followed up eczema reactions 2 weeks later. Subsequently, patch tests with different concentration of DPCP were performed. After doing patch test, 20 patients had positive patch test at different concentration shown in Table 1.

Six patients (30%) discontinued DPCP therapy, 5 cases had with severe adverse effects, and 1 case lost follow up. Only 5 patients (25%) had complete response within 34 weeks (>75% of hair regrowth). Eight patients (40%) exhibited a partial response (<75% of hair regrowth). Average percentage of hair regrowth area in the partial response group was 29.4%. One patient had no response after DCP therapy

Table 2. The response duration of DPCP that achieved 75% of hair regrowth was demonstrated in each patient

Case	Sex (age)	Diagnosis	DPCP response	Response duration Control site (weeks)	Response duration Experimental site (weeks)
1.	female (31)	alopecia totalis	>75% hair regrowth	34	13
2.	female (71)	alopecia totalis	drop out	-	-
3.	female (29)	alopecia universalis	>75% hair regrowth	14	10
4.	female (18)	alopecia universalis	<75% hair regrowth	-	-
5.	female (18)	alopecia universalis	<75% hair regrowth	-	-
6.	male (57)	alopecia universalis	drop off	-	-
7.	male (30)	alopecia universalis	<75% hair regrowth	-	-
8.	male (55)	alopecia totalis	<75% hair regrowth	-	-
9.	female (24)	alopecia universalis	drop off	-	-
10.	female (34)	alopecia totalis	<75% hair regrowth	-	-
11.	male (25)	alopecia universalis	drop off	-	-
12.	male (34)	alopecia universalis	drop off	-	-
13.	male (28)	alopecia universalis	drop off	-	-
14.	male (37)	alopecia totalis	>75% hair regrowth	11	9
15.	female (31)	alopecia universalis	<75% hair regrowth	-	-
16.	female (22)	alopecia universalis	<75% hair regrowth	-	-
17.	female (58)	alopecia totalis	>75% hair regrowth	15	11
18.	female (35)	alopecia universalis	>75% hair regrowth	22	16
19.	male (19)	alopecia universalis	drop off	-	-
20.	female (53)	alopecia universalis	drop off	-	-

Table 3. Adverse effects of DPCP treatment by standard concentration compared to patch test guided

Adverse effects	Standard regimen	Patch test guided
vesicle formation	2 (10%)	2 (10%)
generalized eczema	0 (5%)	1 (5%)
folliculitis	1 (5%)	1 (5%)

(no regrowth of hair). Interestingly, all cases in the complete response group accomplished 100% of hair regrowth.

The median duration that achieved 75% of hair regrowth of experimental site was 11 weeks (interquartile; IQR 5, range 9-16 weeks). As for the control site, median duration that completed 75% of hair regrowth was 15 weeks (IQR 16, range 11-34), (Table 2). The result revealed that the new initial concentration suggested by patch test performing, accomplished the complete response faster than the standard regimen approximately 4 weeks, although bivariate logistic analysis showed that the comparison of both durations, including experimental and control sites indicated no statistically significant difference (p-value = 0.81), (Fig. 3). More than that, adverse effects with DPCP use were reported in experimental and control sites including vesicle formation, generalized eczema and folliculitis, as shown in Table 3.

Discussion

Topical immunotherapy with DPCP is one of the most effective treatment for severe alopecia areata group such as alopecia totalis, alopecia universalis, although the mechanism of DPCP is still unknown[3-5]. As a conventional protocol of DPCP treatment, the patients need to be prior sensitized by 2% DPCP at scalp. Thus DPCP reaction is mediated by delayed type hypersensitivity reaction. After 2 weeks, the patient will be applied DPCP at the lowest concentration 0.0001% at scalp. The early development of dermatitis after initial sensitization may be a predictor of positive outcome. The concentration will be stepped up every month until hair regrowth[6]. The disadvantage of conventional DPCP regimen is that patients need a long time to applied DPCP from many months to a few years. The principle of patch test in the present study helped to find out the effective concentration that was able to stimulate the patients' reaction in the initial step to reduce the duration for titrating DPCP concentrations. This hypothesis assumed that the overall duration of treatment should be shortened. The results showed that patch test had been positive with the concentration from 0.01 to 1% DPCP. Thirty percent of these patients responded to 0.5% DPCP as shown in Table 1.

The previous study reported that the response rate of DPCP relied on type, duration, and severity of AA. Ohlmeier MC et al. conducted a large retrospective study of 142 patients treated with DPCP and found that 51 patients (37.8%) had complete response, 20 patients (14.8%) exhibited partial response, 26 patients (19.3%) experienced minimal response and 38 patients (28.1%) had no response after DPCP therapy[8]. Pericin M and Trüeb RM. performed a study of severe AA (involved morethan 40% of scalp hair). The total response rate was 70.6%, complete remission rate was 30.9% and partial remission rate was 39.7%[9]. The response rate of the present study was 25%, consistent with the previous reports. Thus DPCP therapy is acceptable as an alternative treatment of AA. Additionally, the overall duration of DPCP treatment was the interesting point

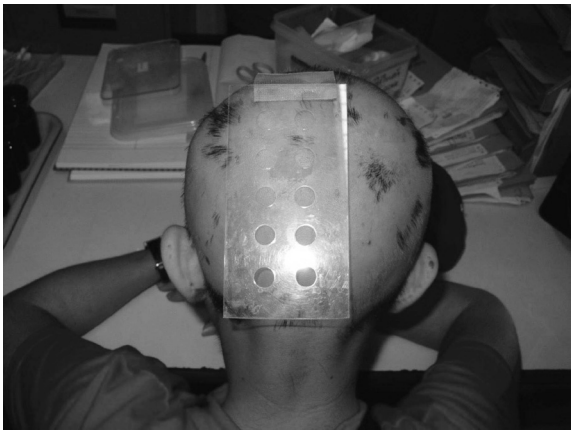

Fig. 1 The patients performed open patch test with DPCP in different concentrations at scalp.

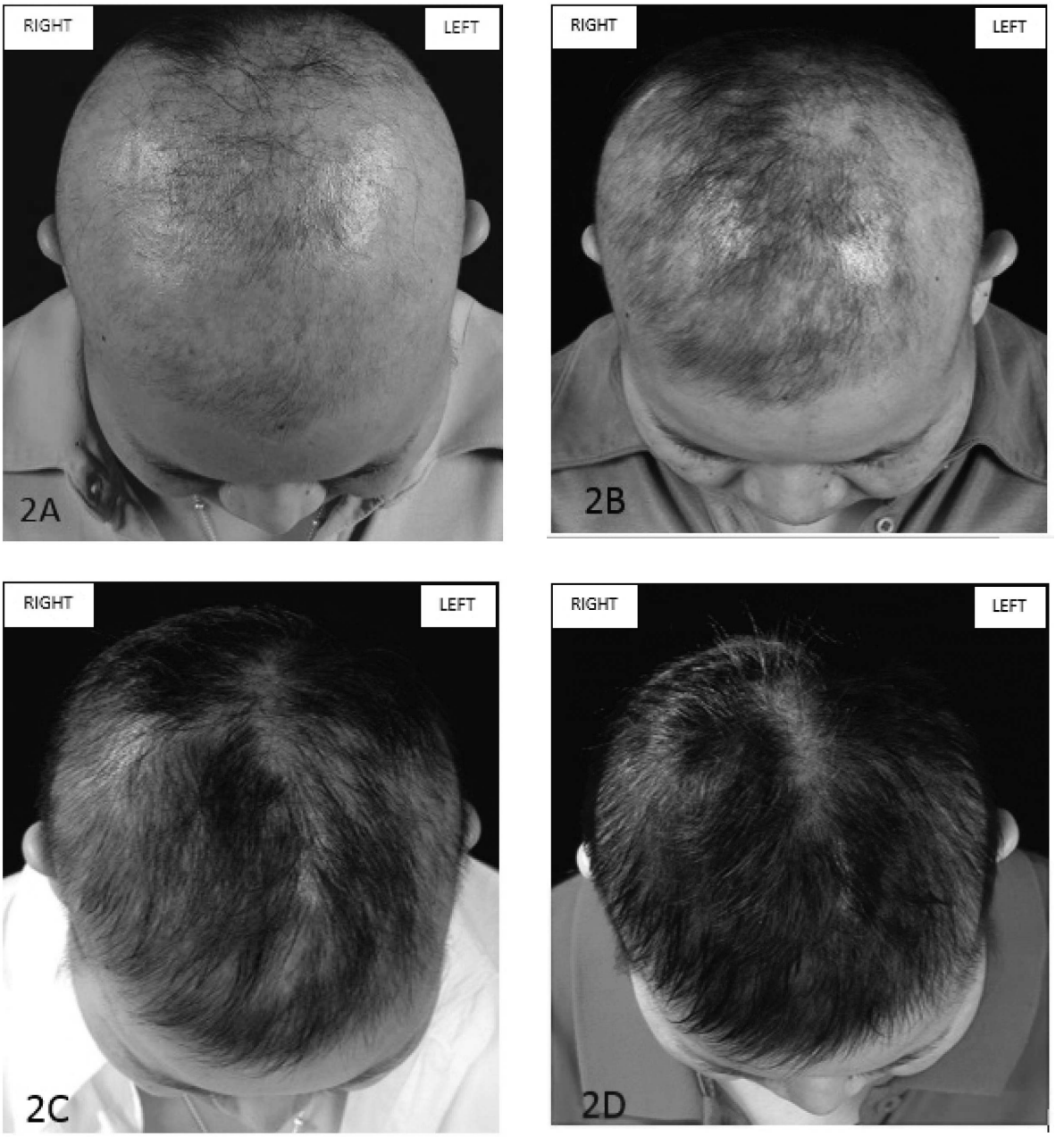

Fig. 2 The hair regrowth of alopecia totalis patient with DPCP treatment was demonstrated in control site (left) and experimental site (right).
2A: Before treatment 2B: After 10 weeks of treatment
2C: After 14 weeks of treatment 2D: After 34 weeks of treatment

in the present study because the patients were applied with the higher concentration of DPCP at beginning. The results were according to plan that the treatment duration of the experimental groups was shorter than the control groups approximately 4 weeks. It was implied that multi-concentration level patch test of DPCP performed assisted to accomplish the complete response faster than conventional protocol. Another noticeable point of the present study was the outcome of the partial response group. In this group, the aver-

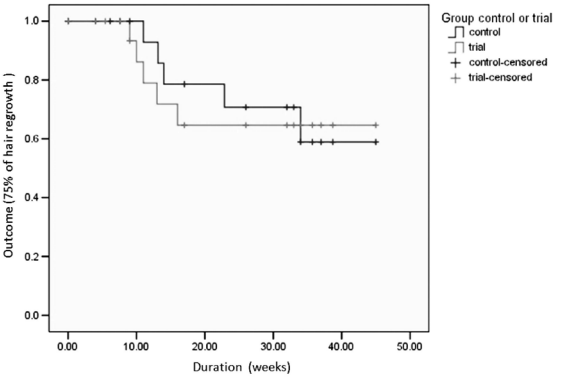

Fig. 3 The response duration that achieved 75% of hair regrowth that was illustrated by Kaplan–Meier analysis had no statistically significant difference. (p-value = 0.81).

age percentage of hair regrowth area was 29.4%. It was likely to get good response, if the treatment was continued. Prolong DPCP therapy maybe benefit to some patients who had unsatisfactory outcomes with other treatments.

In addition to the complication of DPCP therapy, the common side effects, including vesicle formation, generalized eczema and folliculitis were reported in both groups. But the incidence of complication did not increase in patch test guided regimen. Nevertheless the present study was limited by small sample size, multi-concentration level patch test guided DPCP treatment needed further study to demonstrate benefits.

Conclusion

Patch test guided DPCP therapy may be an innovative practical model in treating patients with severe, chronic alopecia areata including alopecia totalis and alopecia universalis. The reason is that the higher concentration in initial step assists to gain total regrowth of scalp hair earlier than the conventional protocol without increasing complications.

What is already known on this topic?

Topical immunotherapy, diphenylcyclopropenone (DPCP) has been proven to be efficacious in treating patients with alopecia areata. DPCP induces allergic contact dermatitis in the applied areas. However, it takes several weeks to achieve the optimal concentration that stimulates hair regrowth.

What is this study adds?

The treatment duration of patch test guided diphenylcyclopropenone (DPCP) therapy was shorten than conventional regimen. Moreover, better outcomes were demonstarted in DPCP regimen. So, it is an alternative practical regimen in alopecia totalis and alopecia universalis treatment.

Acknowledgement

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การใช้ patch test ด้วย DPCP หลายความเข้มข้นเป็นแนวทางในการรักษาโรคผมร่วงเป็นหย่อมที่ไม่ทราบสาเหตุ

รัฐพล ตวงทอง, สุเพ็ญญา วโรทัย, ดรัลพร ไตรวงศ์วรนาท, ชุดา รุจิธารณวงศ์

ภูมิหลัง: *โรคผมร่วงเป็นหย่อมที่ไม่ทราบสาเหตุเป็นปัญหาพบบ่อยในทางเวชปฏิบัติ ปัจจุบันการรักษายังเป็นปัญหายุ่งยาก การทาอิมมูโนเจนเฉพาะที่เป็นอีกวิธีการรักษาที่ได้รับการยอมรับ หลักการคือทำให้ผู้ป่วยแพ้สารอิมมูโนเจนที่จะใช้ก่อนแล้วจึงนำอิมมูโนเจนไปทาที่หนังศีรษะ เพื่อกระตุ้นให้เกิดอาการผื่นผิวหนังอักเสบซึ่งจะกระตุ้นให้ผมขึ้นได้สารอิมมูโนเจนที่ใช้บ่อยคือ diphenylcyclopropenone (DPCP) เนื่องจากวิธีการรักษามาตรฐานในขณะนี้เริ่มทาอิมมูโนเจนจากระดับความเข้มข้น 0.001% DPCP ซึ่งเป็นขนาดที่ค่อนข้างต่ำทำให้ใช้ระยะเวลานานในการปรับความเข้มข้นยาเพิ่มขึ้นจนถึงระดับที่เหมาะสมในการกระตุ้นผมขึ้นของผู้ป่วย*

วัตถุประสงค์: *เพื่อศึกษาเกี่ยวกับการทดสอบหาระดับความเข้มข้นเริ่มต้นของสาร DPCP ที่เหมาะสมกับผู้ป่วยแต่ละคนโดยอาศัยหลักการของ patch test มาประยุกต์ เพื่อเริ่มต้นการรักษาด้วยความเข้มข้นที่เหมาะสมกับผู้ป่วยแต่ละคน*

วัสดุและวิธีการ: *ผู้ป่วยโรคผมร่วงเป็นหย่อมไม่ทราบสาเหตุ (Alopecia totalis, Alopecia universalis) จำนวน 20 คนที่เข้าร่วมโครงการวิจัยจะได้รับการตรวจหนังศีรษะอย่างละเอียดเกี่ยวกับพื้นที่รอยโรค หลังจากนั้นแบ่งพื้นที่ศีรษะของผู้ป่วยแต่ละคนออกเป็น 2 ส่วน คือ (1) ส่วนควบคุมเป็นส่วนที่ได้รับการรักษาวิธีมาตรฐานคือเริ่มทาสาร DPCP ระดับความเข้มข้นต่ำ (0.001% DPCP) แล้วปรับความเข้มข้นขึ้นจนถึงระดับที่เหมาะสม (2) ส่วนทดลองเป็นส่วนที่เริ่มทาสาร DPCP ที่ระดับความเข้มข้นที่ผู้ป่วยเกิดอาการผื่นผิวหนังอักเสบจากการทดสอบ patch test ด้วย DPCP หลายความเข้มข้นแล้วประเมินผลการรักษาโดยการวัดพื้นที่ผมที่ขึ้นและระยะเวลาการรักษาระหว่างกลุ่มควบคุมและกลุ่มทดลอง*

ผลการศึกษา: *ผู้ป่วยโรคผมร่วงเป็นหย่อมไม่ทราบสาเหตุจำนวน 5 คนตอบสนองต่อการรักษาภายใน 34 สัปดาห์ โดยพบว่าระยะเวลาตอบสนองต่อการรักษาเฉลี่ยของส่วนทดลองตอบสนองเร็วกว่าส่วนควบคุมถึงแม้ว่าไม่มีนัยสำคัญทางสถิติ นอกเหนือจากนั้นภาวะแทรกซ้อนระหว่างการรักษาพบว่าเกิดขึ้นทั้งส่วนทดลองและส่วนควบคุมได้แก่ตุ่มน้ำใส ผื่นผิวหนังอักเสบและรูขุมขนอักเสบ*

สรุป: *การทดสอบหาระดับความเข้มข้นของสาร DPCP โดย patch test ก่อนเริ่มการรักษานั้นสามารถลดระยะเวลาการรักษา โดยที่ผลข้างเคียงจากการเริ่มต้นใช้สาร DPCP ความเข้มข้นสูงไม่แตกต่างจากกลุ่มที่เริ่มใช้สาร DPCP ความเข้มข้นต่ำตามวิธีมาตรฐาน ดังนั้นการประยุกต์ใช้ patch test ในการทดสอบหาระดับความเข้มข้นของสาร DPCP ที่เหมาะสมกับผู้ป่วยแต่ละราย จึงเป็นอีกวิธีหนึ่งที่ช่วยลดระยะเวลาการรักษาโรคผมร่วงเป็นหย่อมไม่ทราบสาเหตุ*