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ORIGINAL PAPER

Efficacy and safety of anthralin in combination with diphenylcyclopropenone in the treatment of alopecia areata: a retrospective case series

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Abstract

Contact immunotherapy with diphenylcyclopropenone (DPCP) and anthralin is considered the treatment option for extensive alopecia areata (AA) unresponsive to DPCP immunotherapy alone. Only one study has described the efficacy of combination therapy; therefore, we investigated whether topical DPCP and anthralin can promote hair regrowth in DPCP-non responders. In this retrospective case-series we analyzed the efficacy and side effects of DPCP with anthralin in AA patients who did not respond to several months of treatment with DPCP alone. Thirty-two DPCP-nonresponsive AA patients were treated with DPCP and anthralin for the average of 8.3 ± 3.8 (3–17) months. During the treatment, 40.62% of patients (13 patients out of 32) had terminal hair regrowth. The mean of hair regrowth rate was 41%; it was mainly as partial hair regrowth (< 50%) and 27.27% of cases achieved > 50% terminal hair regrowth. Treatment response strongly related to the duration of combination therapy (p value < 0.001), but we did not find any relation with other demographic characteristics. The first signs of response to treatment were noticed 2–12 months (5.5 ± 3.4) after initiation of combination therapy while there was a positive correlation among the duration of treatment and percentage of hair regrowth ($p < 0.001$). The most common complication was bullae (25%), and the least frequent side effect was generalized pruritus (3.1%). The combination therapy with DPCP and anthralin could be effective to treat DPCP non-responder AA patients. Additionally, the higher treatment response could be achieved by longer treatment duration.

Keywords Alopecia areata · Diphenylcyclopropenone · Anthralin · Immunotherapy · Side effects

Introduction

Alopecia areata (AA) is a non-scaring T cell lymphocyte-mediated autoimmune disorder [22] with prevalence of 1–2% in general population [22] and a calculated lifetime risk of 2% [14]. Patchy AA is the most common form of the disease and the literature was reported spontaneous hair regrowth in 34–50% of patients [1]. Also, in 14–25% of cases patchy hair loss can progress to alopecia totalis or alopecia universalis where spontaneous regrowth is rare (less than 10%) [1, 22]. The psychologically damaging consequences of AA include anxiety, depression, and phobia, which lead to personal and social related problems [11, 17].

It has been suggested that T- cell lymphocytes are major factors for hair loss in AA [16]. The role of autoantibodies against anagen follicles, and several cytokines like interferon γ (INF-γ), interleukins, and tumor necrosis factor α (TNF-α) have been established in AA pathogenesis [8].

Treatment of chronic and extensive AA is so challenging and variable treatment options have been introduced like topical and intralesional corticosteroids, minoxidil, anthralin, topical sensitizers, systemic steroids, photochemotherapy, cyclosporine, biologic therapy, and 308 nm excimer laser [6, 21].Topical sensitizers such as diphenylcyclopropenone (DPCP) are one of the most effective treatment modalities for patients with extensive disease.

Contact immunotherapy was first introduced in 1983 by Happle et al. [9]. The function of topical immunotherapy is not well-known, but mechanism like change in the

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perifollicular CD4 (+)/CD8 (+) T-lymphocyte ratio, and increased number of perifollicular CD8 (+) which leads to destruction of autoreactive T lymphocytes are postulated [10, 28]. Previous studies have reported the response rate of about 53.75% with DPCP treatment [12].

Anthralin is another option for topical immunotherapy, which induces irritant local dermatitis. The mechanism of action of anthralin is associated with modulating the expression of cytokines [16].

Some patients with chronic extensive AA may be refractory to topical immunotherapy and combination therapy is recommended for such patients. Recently, for the first time, Durdu et al. have reported the superior efficacy of combination therapy with DPCP and anthralin compared to DPCP alone. They showed that the time to onset of hair regrowth and the time to complete hair regrowth is shorter with combination therapy.

Only one study have described the efficacy of combination therapy. Therefore, we sought to clarify whether topical DPCP and anthralin would have therapeutic effects on AA patients who did not respond to treatment with DPCP alone.

Method

This study included AA patients who were under treatment in our alopecia areata clinic and were not responsive to treatment by DPCP between 2015 and 2017.

Demographic information such as age, sex, history of atopic dermatitis, medical history, and age of the patient at the onset of the disease were included in patient file at the time of admission to the Alopecia clinic. Clinical information like the type of AA, severity of scalp involvement, pattern of AA, eyebrow, eyelash, beard, body hair, and nail involvement were examined by dermatologists and recorded in each patient's file.

Severity of the scalp involvement was determined with the Severity of Alopecia Tool (SALT) scoring system. Inclusion criteria for combination treatment of anthralin with DPCP were patients who were treated with DPCP alone for at least 6 months without response to this treatment including vellus or terminal hair regrowth. Exclusion criteria were current pregnancy or lactation, liver function failure, systemic immunosuppressive or steroid therapy in the past 6 months, and history of malignancies and blood dyscrasia. This study has been performed as the thesis project for the medical degree of Dr. Azade Mirshamsi and ethical approval was provided by Tehran University of Medical Sciences ethics committee. (IR.TUMS.MEDICINE.REC.1397.154).

Treatment method

DPCP was diluted in acetone in different dilution between 0.001 and 2.0% concentrations. In the first step, 2% DPCP was applied to a 2 × 2 cm area of the scalp for sensitization. 1 or 2 weeks after sensitization, in the case of positive eczematous reaction, a 0.001% DPCP solution was applied in weekly intervals to same half of the scalp on which drug has been tested. Patients were instructed to avoid touching the scalp for 6 h. The patients were educated to cover their head for 48 h. The sensitizer was left on the scalp for 48 h and then it should be washed off with a mild shampoo. If the reaction was negative, the concentration of DPCP was increased incrementally until a low-grade dermatitis reaction (erythema, scale, and pruritus) was developed at 48 h, and the same concentration was continued weekly. If the dermatitis was not seen, the concentration of DPCP was increased gradually every 1 week. DPCP was pre-prepared in 0.001, 0.01, 0.05, 0.1, 0.5, 1.0, and 2.0% concentrations and if clinically indicated, other concentrations are made for patients.

If hair regrowth was not observed after 6 months, the patient was supposed to be a non-responder to DPCP and was candidate for combination therapy.

Treatment method with DPCP and anthralin

For the combination therapy, DPCP was left on the scalp for 48 h and for the next 5 days of week, patients used 0.5% anthralin in petroleum jelly for 15 min daily, and then washed off it with a mild cleanser. The contact time for the anthralin was increased gradually by 1–2 min every day until a mild erythematous dermatitis happened in treated area. The patients who achieved hair regrowth continued DPCP and anthralin therapy.

Assessment of efficacy

Patients were examined every 2 weeks. The SALT scoring system [2], was used for determining percentage of scalp hair loss and hair regrowth. The side effects of treatment like bullae, lymphadenopathy, pigmentation, and pruritus were recorded.

Statistical analysis

Statistical analyses was performed by SPSS version 24 (Chicago, Illinois, United States) using parametric and non-parametric tests such as student's *T* test, Chi squared test, Mann–Whitney test, and Logistic Regression. Log rank test was also used to calculate time until the hair

regrowth. The *p* value being less than 0.05 was considered as statistically significant.

Results

Patients

From a total 32 [20 (62.5%) females and 12 (37.5%) males] with DPCP-nonresponse AA patients were eligible and were included in the study. These patients did not have acceptable response to DPCP alone after mean duration of 8.23 ± 2.51 (6–15) months. The mean age of participants was 24 ± 16 years; the mean age of onset of the AA and the mean duration of the disease were 16.5 ± 15.5 years and 7.98 ± 8.38 years, respectively. Five patients (19.2%) had multifocal patches of AA; two patients (7.7%) had ophiasis type; the remaining 13 (40.62%) and 12 (37.5%) had alopecia universalis and alopecia totalis, respectively. Fourteen patients (53.8%) had nail involvement.

Two patients (6.25%) had medium hair loss, two patients (6.25%) had severe hair loss, and 28 patients (87.5%) had very severe hair loss (Table 1). The mean of hair loss rate was 89.69 ± 19.3% (32–100%).

There was a reverse correlation between the rate of hair loss and duration of the disease ($p = 0.002$, spearman rho = −0.561) while nail involvement did not associate with duration of alopecia ($p = 0.568$). The higher doses of DPCP was used for patients with more severe alopecia and the concentration of DPCP was positively associated with the rate of hair loss ($p < 0.001$, Spearman rho = 0.614).

Response to treatment

The mean duration of therapy with DPCP and anthralin was 8.3 ± 3.8 months with a minimum of 3 months and a maximum of 17 months. Thirteen patients (40.6%) responded positively (terminal hair growth), and no hair regrowth occurred in the remaining 19 patients. However, the data of regrowth rate of two responders have been missed. The mean duration of combined treatment was 11.23 ± 3.2 (6–17 months) and 6.3 ± 3 (3–14 months) in responders and non-responders to combined treatment, respectively (Table 2).

The mean hair regrowth rate was 41% ± 26.53, which varied from 3 to 90% in patients with positive response to combined treatment. Our results showed that 27.27% and 9.09% of responder patients achieved > 50% and > 75% terminal hair regrowth, respectively, while none of them had 100% response rate. The mean time to onset of terminal hair regrowth was 5.5 ± 3.4 (2–12) months (Table 2).

There was no significant difference in the meantime to onset of hair regrowth between both sexes ($p = 0.38$) or among patients with or without nail involvement ($p = 0.78$). Interestingly, there was no significant correlation between hair regrowth and the duration of alopecia, age of disease onset, gender, or severity of hair loss.

The concentration of DPCP used for responders and non-responders to combined treatment was 0.34 ± 0.4% (0.01–1.2%) and 0.74 ± 0.75% (0.005–2%), respectively. There was no significant association between concentration of DPCP and rate of hair regrowth and the mean time to onset of response. However, the percentage of hair regrowth

Table 1 Demographics and clinical characteristics of the patients with alopecia areata

	Patients treated with DPCP and anthralin
Mean ± SD age, y (range)	24 ± 16 (5–60)
Male/female, *n* (%)	12 (37.5%)/20 (62.5%)
Mean ± SD duration of first alopecia episode, y (range)	7.98 ± 8.38 (1–34)
Subtypes, *n* (%)	
Alopecia universalis	13 (40.62%)
Alopecia totalis	12 (37.5%)
Multifocal patchy	5 (19.2%)
Ophiasis	2 (7.7%)
Scalp involvement, *n* (%)	
Mild (< 25% hair loss)	0
Moderate (26–50% hair loss)	2 (6.25%)
Severe (51–75% hair loss)	2 (6.25%)
Very severe (76–100% hair loss)	28 (87.5%)
Nail involvement, *n* (%)	14 (53.8%)
Mean ± SD time of treatment with DPCP alone, months (range)	8.23 ± 2.51 (6–15)
Mean ± SD DPCP treatment concentration, % (range)	0.48 ± 0.58 (0.001–2%)

y year, *n* number, *DPCP* diphenylcyclopropenone

Table 2 Response to treatments and adverse effects

	Response to combined therapy *n* (%)	
	Yes	No
	13 (40.06%)	19 (59.3%)
Mean time of combined therapy ± SD, months (range)	11.23 ± 3.2 (6–17)	6.3 ± 3 (3–14)
Mean time to response as terminal hair, months (range) *n* (%)	5.5 ± 3.4 (2–12)	
< 3 months	5 (38.5%)	
3–6 months	4 (30.8%)	
6–9 months	1 (7.7%)	
> 9 months	3 (23.1%)	
Hair regrowth of scalp, *n* [severity] (%)		
Mild (< 25% hair regrowth)	3 (27.27%)	
Moderate (26–50% hair regrowth)	5 (45.45%)	
Good (51–75% hair regrowth)	2 (18.18%)	
Excellent (76–100% hair regrowth)	1 (9.09%)	
> 50% hair regrowth, *n* (%)	3 (27.27%)	
> 75% hair regrowth, *n* (%)	1 (9.09%)	
The mean hair regrowth rate, % ± SD (range)	41% ± 26.53 (3–90%)	
Adverse effects		
Bullae, *n* (%)	8 (25%)	
Hyperpigmentation, *n* (%)	5 (15.6%)	
Lymphadenopathy, *n* (%)	3 (9.4%)	
Generalized pruritus, *n* (%)	1 (3.1%)	

was positively correlated to the duration of combination therapy ($p < 0.001$, rh0 = 0.677).

Three patients of combination therapy (23.07%) responded to DPCP 2% concentration, one patient (7.6%) responded to DPCP 0.01, 0.5 and 1.2% concentrations, One patient responded to DPCP 0.05, two patients responded to DPCP 0.2 concentration, and four patients (30.76%) responded to DPCP 0.1% concentration (Fig. 1).

Side effects

Adverse effects were seen in 17 (53.1%) patients. The most frequent complication was bullae (25%), and the least common was generalized pruritus which was only observed in one patient (3.1%). Three cases (9.4%) and five patients (15.6%) developed lymphadenopathy and hyperpigmentation, respectively (Table 2).

Discussion

This retrospective case series shows that the combination therapy using DPCP and anthralin is effective to treat DPCP-nonresponsive AA patients without causing serious side-effects. Our findings represent that 40.6% of patients (13 patients out of 32) had 3–90% (mean = 41%) hair regrowth with combination therapy that lasts for the mean of 8.3 ± 3.8 (3–17) months. The first signs of response to treatment were noticed 2–12 months (mean = 5.5 ± 3.4 months) after initiation of combination therapy, and there was a positive correlation between the duration of treatment and percentage of hair regrowth. ($p < 0.001$, rh0 = 0.677).

Topical immunotherapy, including DPCP and anthralin, is effective in the treatment of AA due to an allergic contact dermatitis and subsequent antigenic competition and changing the milieu of immune cells surrounding hair follicles through an unknown mechanism [23]. The histopathologic evaluation of AA shows perifollicular lymphocytic infiltrates around anagen hair follicles, consisting of CD4+ and intrafollicular infiltrates of CD8+ cells. Mediators and cytokines including IFN-γ and TNF-α coordinating cyclical hair growth play major roles in the pathogenesis of the disease [8]. Beneficial effect of DPCP is mainly mediated by regulating the locally secreted cytokines. It has been reported that DPCP decreases the expression of IFN-γ and IL-1β while increasing the expression of IL-2, IL-8, IL-10, and TNF-α. DPCP also causes increase in number of infiltrating leukocytes in the bulbar and suprabulbar area of the hair follicle that act against autonomously functioning CD4+ and CD8+ cells. Moreover, DPCP decreases the ratio of CD4: CD8 from 4:1 to 1:1 in the perifollicular infiltrate [8]. Anthralin has immunomodulatory effect resulting in the inhibition of TNF-α/β and IFN-γ [24–26] while it increases the expression of interleukins

Fig. 1 Results of treatment with DPCP and anthralin in a 40-year-old woman with multifocal alopecia areata. She responded to DPCP (0.5%) concentration and anthralin after 24 weeks of treatment. **a–d** Before treatment. **e–h** Regrowth of scalp hair after 24 weeks of treatment

(IL-1 and IL-10) [24]. It has been suggested that DPCP and anthralin with different mechanisms of action synergistically improve alopecia [7].

With respect to the previous research, DPCP has the success rate ranging from 6 to 85% and is an appropriate treatment option for patients with chronic, extensive AA including AA totalis and AA universalis [20]. Anthralin in low concentration of 0.2 to 1% has been shown to induce irritant dermatitis so that could be used as a topical immunotherapy in AA patients [16]. Schmoeckel et al. [18] have shown that 75% of patients with patchy alopecia and 25% of patients with alopecia totalis responded to the anthralin. However, most of other investigators failed to demonstrate similar efficacy and overall improvement between 25 and 75% has been reported. These controversial reports could be due to inconsistent assessment of alopecia severity and treatment improvement; as well as using a varied range of drug concentration (0.1–1.25%) [16].

The therapeutic effect of DPCP is also varied among several studies [29] which could be explained by disease-associated factors, definition of hair growth and treatment-associated factors including sensitization protocol and treatment area, duration, and interval [4, 5, 15]. Treatment with DPCP has poorer outcomes in extensive and chronic AA, as well as longer disease duration [13]. In addition, some patients do not have an allergic reaction to DPCP which results in poor response [27]. Therefore, combined treatment regimens with DPCP and anthralin may be of benefit to treat AA. However, previous studies have not shown a synergistic effect with minoxidil [19] and inosine pranobex [3].

Herein, we initiated the combined therapy using DPCP and anthralin in DPCP-resistance patients who failed to respond to 6–15 (mean = 8.23) months of treatment with DPCP alone. Durdu et al. [7]. for the first time reported that the efficacy of DPCP is enhanced by combination therapy with anthralin. They retrospectively evaluated the hair regrowth in 22 patients who were treated only with DPCP, and 25 with DPCP and anthralin for at least 30 weeks. Their results have shown that 88% of the patients who received combination therapy achieved 50% or greater terminal hair regrowth, which was significantly higher than that of for DPCP alone. Mean time to onset of terminal hair regrowth with combination therapy was 8 (5–15) weeks which was shorter than with DPCP alone. In our study 27.27% of DPCP-nonresponders achieved > 50% terminal hair regrowth. It has been stated that the treatment duration for plausible hair regrowth is quite long (24 weeks) [2]. We also did not have any patients with 100% of hair regrowth with combination therapy while Durdu et al. reported such response in 18 patients (72%) [7].As we included only the DPCP-nonresponders, it seems that the combination therapy has lower efficacy and longer duration of onset of hair regrowth in such patients. In addition, AA totalis and AA universalis cases were approximately twice the same in the Durdu's study, where extensive AA at baseline is a negative prognostic factor for AA treatment [13].

Consistent with previous investigations there was no correlation between the hair regrowth and age of disease onset, duration of AA, severity of hair loss, sex, and nail involvement [7]. The response to treatment in our study was 41% that was mainly as partial hair regrowth, and we found a positive association between duration of combination therapy and the percentage of hair regrowth and treatment success so that higher treatment response could be achieved by longer treatment duration. There was no serious complication with the combination therapy as described by previous studies [7]. Bullae was the most frequent side effect and the least common was generalized pruritus.

This study had some limitations. It was a retrospective case-series with a limited sample size without control group. Hair growth information of two patients were not recorded.

Conclusion

The combination therapy with DPCP and anthralin is effective to treat AA patients who did not respond to several months of treatment with DPCP alone. Interestingly, the higher treatment response could be achieved by longer treatment duration.

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Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

Ethical approval The study was approved by the Ethics Research Committee of the School of Public Health, Tehran University of Medical Sciences. (IR.TUMS.MEDICINE.REC.1397.154).

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