Efficacy and safety of diphenylcyclopropenone alone or in combination with anthralin in the treatment of chronic extensive alopecia areata: A retrospective case series

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Background: Some patients with chronic extensive alopecia areata (AA) may be refractory to topical immunotherapy. Combination therapy is recommended for such patients. Efficacy and safety of a combination therapy with diphenylcyclopropenone (DPCP) and anthralin in chronic extensive AA is unknown.

Objective: We sought to determine whether the combination therapy of DPCP and anthralin is superior to DPCP alone in chronic extensive AA.

Methods: We retrospectively analyzed the efficacy, side effects, and relapse rates of DPCP (alone or with anthralin) in chronic extensive AA.

Results: A total of 47 patients (22 were treated only with DPCP, and 25 with DPCP and anthralin for at least 30 weeks) were evaluated. Complete hair regrowth was observed in 36.4% and 72% of the patients who received DPCP and combination therapy, respectively ($P = .01$). Hair regrowth duration was shorter with combination therapy ($P = .01$). Regrowth rates of the eyebrows, eyelashes, and beard in patients on combination therapy were higher than those in patients on DPCP ($P = .01$). Side effects such as folliculitis, hyperpigmentation, and staining of skin, hair, and clothes were more common in combination therapy group.

Limitations: The retrospective design and small number of patients are limitations.

Conclusion: Combination therapy with DPCP and anthralin is superior to DPCP alone in chronic extensive AA. (J Am Acad Dermatol 2015;72:640-50.)

Key words: adverse effects; alopecia areata; alopecia totalis; alopecia universalis; anthralin; cignolin; diphencyprone; diphenylcyclopropenone; dithranol; folliculitis.

Alopecia areata (AA) is a common T-lymphocyte-mediated autoimmune disorder.[1] Treatment is very difficult in patients with alopecia totalis (AT), alopecia universalis (AU), and widespread multifocal patches.[2]

In patients with chronic, treatment-refractory extensive AA, topical immunotherapy with squaric acid dibutylester or diphenylcyclopropenone (DPCP), also known as diphencyprone, is recommended.[2,3] The mechanism of action of topical sensitizers is not fully understood, but studies have shown that they change the perifollicular $CD4^+/CD8^+$ T-lymphocyte ratio,[4] cause antigenic

Abbreviations used:

AA:	alopecia areata
AT:	alopecia totalis
AU:	alopecia universalis
DPCP:	diphenylcyclopropenone

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competition,[5] lead to apoptosis of autoreactive T lymphocytes,[6] and modulate proinflammatory cytokines.[7] DPCP was first used in severe forms of AA by Happle et al,[8] and the authors reported a complete hair regrowth rate of 67%. Since then, numerous studies have found different hair regrowth rates ranging from 6%[9] to 85%.[10]

Anthralin, also called cignolin or dithranol, in 0.2% to 1% concentrations, induces irritant dermatitis.[2] Animal studies have shown that anthralin increases interleukin-1β secretion and inhibits tumor necrosis factor-alfa and -beta secretion.[11] In the study by Schmoeckel et al,[12] the response rate to anthralin treatment was high in patchy lesions (75%) compared with that in AT (25%). Other investigators reported a regrowth rate of 50%; cosmetic response, however, was observed in only 25% of the patients.[13] The activity of anthralin was found to be similar to that of azelaic acid,[14] but lower than topical corticosteroids.[15,16] Combination therapy with anthralin and 5% minoxidil shows a synergistic effect in treatment-resistant AA.[17]

CAPSULE SUMMARY

- Severe alopecia areata may be refractory to topical immunotherapy.
- In severe alopecia areata, regrowth rates of the hair, eyebrows, eyelashes, and beard are higher with combined diphenylcyclopropenone and anthralin therapy compared with diphenylcyclopropenone alone.
- Anthralin can be added to diphenylcyclopropenone in the treatment of severe alopecia areata.

In our clinic, we have been performing topical immunotherapy with DPCP regularly for patients with severe patchy AA, AT, and AU for the past 4 years. After observing unsatisfactory response to DPCP treatment in some of those patients, we decided to combine DPCP with anthralin in patients with severe and/or treatment-resistant AA from the outset. This retrospective case series evaluates our experience with DPCP treatment alone or combined with anthralin in those patients. To our knowledge, this is the first report comparing the efficacy and safety of combination therapy with DPCP and anthralin with those of DPCP in chronic extensive and/or treatment-resistant AA.

METHODS

Patients and study design

This study included patients with severe (>50% scalp hair loss) and/or treatment-resistant (to any other topical or systemic treatment for at least 6 months) AA who had been followed up in our department during the previous 4 years (2010-2014). The patients were examined by 2 dermatologists, and the type of AA, severity of scalp involvement, and presence of ophiasis pattern, salmon patch, or eyebrow, eyelash, beard, body hair, or nail involvement along with their medical history were recorded.

Exclusion criteria included current pregnancy or lactation, liver failure, or having received systemic immunosuppressive or corticosteroid treatment in the past 6 months. The study was approved by Başkent University Institutional Review Board (project No. KA14/235), and conducted in conformity to the 1975 Helsinki Declaration.

Treatment method with DPCP

DPCP powder (Fluka, Sigma-Aldrich Corp, St Louis, MO) was diluted in 0.001%, 0.01%, 0.05%, 0.1%, 0.5%, 1.0%, and 2.0% concentrations in acetone. In the first stage, 2% DPCP was applied to a 4-cm^2 area of the scalp. After 2 days, patients were checked to detect whether or not sensitization to DPCP has occurred. If an eczematous reaction was positive, patients were seen 2 weeks later, and a 0.001% DPCP solution was applied in weekly intervals to only half of the scalp by the dermatologist. DPCP was left on the scalp for 48 hours and then washed off with a mild shampoo. If the reaction was negative, the concentration of DPCP was increased gradually until a mild dermatitis reaction developed for 48 hours. The treatment continued weekly at the concentration that induced a mild dermatitis. A wig or hat had to be worn for 2 days to avoid photoallergic reaction. If terminal hair regrowth was noted during the first 30 weeks, DPCP was applied on entire scalp. If hair regrowth was not observed after the first 30 weeks, the patient was considered a nonresponder.[18]

Treatment method with DPCP and anthralin

Two weeks after sensitization with 2% DPCP, 0.001% DPCP was applied to right half of the scalp by the dermatologist, left on the scalp for 48 hours, and then washed off with a mild shampoo. For the next 5 days, 0.5% anthralin in petrolatum was applied to left half of the scalp for 30 minutes daily by the patient at home, and then washed off with a mild shampoo. The concentration of DPCP was increased gradually weekly until a mild dermatitis developed for 48