Imunomodelação Tópica com Difenilciclopropenona para a Alopécia Areata

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RESUMO – **Introdução**: A imunoterapia tópica com difenilciclopropenona é uma opção terapêutica em casos de alopécia areata extensa ou refratária. Este estudo teve como objetivos avaliar a eficácia clínica e tolerabilidade da terapia com difenilciclopropenona, em doentes com alopécia areata, e identificar possíveis fatores prognósticos da resposta ao tratamento. **Métodos**: Realizámos um estudo retrospetivo que incluiu todos os doentes diagnosticados com alopécia areata e tratados com difenilciclopropenona no Serviço de Dermatologia do Hospital Santo António dos Capuchos, Centro Hospitalar e Universitário de Lisboa Central. **Resultados**: Foram incluídos vinte e um doentes (15 mulheres e 6 homens). No geral, nove pacientes (42,9%) tiveram algum crescimento de cabelo com a terapia DPCP. Destes, cinco (55,6%) tiveram crescimento do pêlo terminal pigmentado, mas com áreas de alopécia persistentes. Apenas um doente atingiu mais de 90% de reponte capilar. A idade mais avançada e a maior extensão da doença à apresentação, assim como a presença de distrofia ungueal foram fatores estatisticamente significativos de mau prognóstico ($p < 0,05$). Atopia e disfunção tiroideia não foram estatisticamente significativos como preditores de pior resultado terapêutico com difenilciclopropenona. Efeitos adversos foram documentados em 15 doentes, sendo na maioria de ligeira gravidade não implicando a interrupção do tratamento. **Conclusão**: O tratamento com difenilciclopropenona é uma opção de tratamento viável em pacientes com alopécia areata extensa, embora a resposta seja parcial na maioria dos casos. As limitações deste estudo incluem a sua natureza retrospetiva e a amostra reduzida de doentes.
PALAVRAS-CHAVE – Alopécia Areata/tratamento; Ciclopropanos; Fármacos Dermatológicos; Imunoterapia.

Topical Immunomodulation with Diphenlycyclopropenone for Alopecia Areata

ABSTRACT – ***Introduction:*** *Topical immunotherapy with diphenylcyclopropenone is a treatment option for patients with refractory or extensive alopecia areata. The aim of this study was to evaluate the clinical efficacy and tolerability of diphenylcyclopropenone therapy, in patients with alopecia areata, and identify possible prognostic factors that predict response to treatment.* ***Methods:*** *We conducted a retrospective study that included all patients diagnosed with alopecia areata and treated with diphenylcyclopropenone at our Department.* ***Results:*** *Twenty one patients were included for analysis (15 females and 6 males). Overall, nine patients (42.9%) had some hair regrowth with diphenylcyclopropenone therapy. Of these, five (55.6%) achieved pigmented terminal hair regrowth but with persistent patches of alopecia. Only one patient achieved > 90% of hair regrowth. Older age at onset, broader extent of alopecia at baseline and presence of nail dystrophy were all negative prognostic factors ($p < 0.05$). Atopy and thyroid dysfunction were not statistically significant as predictors of poor treatment outcome. Adverse effects were documented in 15 patients, most of them were mild and did not lead to treatment interruption.* ***Conclusion:*** *Diphenylcyclopropenone therapy is a viable treatment option in patients with extensive alopecia areata, although the response is partial in the majority of the cases. Limitations of this study include its retrospective nature and the limited number of patients.*
KEYWORDS – *Alopecia Areata/therapy; Cyclopropanes; Dermatologic Agents; Immunotherapy.*

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INTRODUCTION

Alopecia areata (AA) is a chronic inflammatory condition primarily affecting the hair follicle, resulting in non-scaring patchy hair, ranging from limited patchy hair loss to complete loss of both scalp and body hair.[1] The exact pathophysiology of AA remains poorly understood but current evidence suggests that is an immune-mediated disease in which CD8+ T-cells specifically target the hair follicle.[2] Although AA can resolve spontaneously, it is known to be a cosmetic burden with a high impact on quality of life, therefore, effective treatment options are required. The first steps in treatment most often consist of topical or intralesional corticosteroids. Immunotherapy is one possible treatment modality and, to date, diphenylcyclopropenone (DPCP) is considered as the topical sensitizer of choice because of its stability and safety profile.[3] The mechanism of action is unclear, but an immune-deviation strategy, inducing an allergic contact dermatitis, might be involved. Its reported efficacy is variable, and the individual response cannot be predicted.[4]

MATERIALS AND METHODS

We aimed to evaluate the clinical efficacy and tolerability of DPCP therapy in patients with AA and identify possible prognostic factors that predict response to treatment. The study was retrospectively performed at the Department of Dermatology, Hospital Santo António dos Capuchos, Lisbon, Portugal, and included all patients diagnosed with AA followed at our Adnexal Skin Disorder Clinic, between 2014 and 2018.

Statistical analysis was performed with Excel and RStudio softwares. Fisher's exact test and Student's t tests were used as appropriate. Statistical significance was defined for $p < 0.05$.

All patients were first sensitized to DPCP 0.5% in acetone applied with occlusion for 48 hours. An induction phase followed with increasing concentrations of DPCP until tolerable erythema and pruritus applied directly on the scalp by a trained nurse every week. Once an acceptable response was obtained, all patients were prescribed the last concentration assessed, for treatment at home.

In our study, the grading system used to evaluate treatment response is summarized on Table 1. Observations were carried out monthly until the first year and thereafter every 3 or 6 months. Hair regrowth was correlated with clinical and evolutive data on AA, presence of nail dystrophy, personal atopy (presence of atopic dermatitis, asthma and/or rhinitis) and thyroid function (TSH, free T3 and T4, anti-TPO and anti-ATG).

RESULTS

A total of 21 patients were included for analysis (15 females and six males) with a mean age of 32 years. All patients had at least > 50% of scalp involvement, the majority of which with extensive patchy involvement. Four (19%) had AA *totalis* and five (23.8%) AA *universalis* (Table 2).

Overall, nine patients (42.9%) had some hair regrowth with DPCP therapy (grade 1-4). Of these, five patients achieved pigmented terminal hair regrowth but with persistent patches of alopecia (grade 3). Only 1 patient achieved > 90% of hair regrowth (grade 4).

These six patients with the best treatment response were younger than 40 years old. In fact, we found that the age of onset was a factor statistically significant ($p < 0.05$) of a better treatment response to DPCP. Also the extent of alopecia at baseline was a factor statistically significant when comparing responders to non-responders. None of the patients with alopecia *universalis* achieved any type of hair regrowth.

We also observed that the presence of nail dystrophy, observed in five patients (23.8%) was significantly more frequent in non-responders (5) than in responders to DPCP therapy (0) ($p = 0{,}006192$). Atopy and thyroid disfunction were not statistically significant predictors of poor treatment outcome.

Adverse effects were documented in 15 patients (71.42%). The majority of them was mild and occurred in at an early stage of the treatment. The most common side effect was mild extra-scalp eczema (38.1%) followed by blistering (33.3%). Three patients eventually stopped treatment because of severe eczema and pruritus.

DISCUSSION

The treatment of AA remains a challenge. In fact, robust evidence for many prescribed treatments is lacking. DPCP is widely considered the most effective topical immunotherapy for refractory or extensive AA, but variable response rates have been reported. Comparisons between published studies can be difficult, in part because of different definitions of treatment response and disease severity. As previously reported,[5-10] in our study both age of onset and baseline severity of hair loss were factors statistically significantly associated with poor outcome, emphasizing that these findings

Table 1 - Grading system used to evaluate the treatment response.

Grade 0	No hair growth
Grade 1	Vellus hair growth
Grade 2	Sparse terminal pigmented hair
Grade 3	Pigmented terminal hair regrowth with persistent patches of alopecia
Grade 4	90%-99% hair regrowth
Grade 5	Complete hair regrowth

Table 2 - Demographics and clinical characteristics of the study population (n=21).

DEMOGRAPHICS AND CLINICAL CHARACTERISTICS	TOTAL (min./max.)
Mean age (years)	32 (min. 8, max. 48)
Gender distribution, n (%) • Males • Females	 6 (28.6%) 15 (71.4%)
Mean duration of disease (years)	15.5 (min. 0.8; max. 37)
Type of AA, n (%) • Patchy AA with > 50% scalp involvement • AA *totalis* • AA *universalis*	 12 (57.2%) 4 (19.0%) 5 (23.8%)
Response to therapy, n (%) • Non-responders • Responders	 12 (57.1%) 9 (42.9%)
Mean time to response (months)	7.8 (min. 6; max. 11)

should be anticipated in those treated with DPCP. In contrast with other studies, atopy and thyroid dysfunction were not associated with poor disease prognosis.[10,11]

We acknowledge our small sample size, which limited the power of the statistical analysis. However, the results of this study support our belief that DPCP therapy in AA is effective and mostly well tolerated. Additionally, our results suggest that atopy and thyroid dysfunction should not be considered predictors of poor outcome.

New treatment options are needed particularly regarding patients with poor prognostic factors, such as older and with more extensive alopecia at onset.

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