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Comparison of Azelaic Acid and Anthralin for the Therapy of Patchy Alopecia Areata

A Pilot Study

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Abstract

Background: Although topical azelaic acid has been previously used for the treatment of alopecia, no controlled trials of azelaic acid for this condition have been conducted to date.

Objective: The goal of this study was to determine the efficacy, tolerability, and safety of azelaic acid treatment in patients with patchy alopecia areata (AA) in comparison with anthralin (dithranol) treatment.

Subjects and methods: This study included 31 subjects with patchy AA who did not receive any treatment for at least 1 month prior to the study. Demographic and clinical characteristics of these subjects were recorded at baseline. Subjects were randomized to apply either 20% azelaic acid (15 subjects) or 0.5% anthralin (16 subjects) for 12 consecutive weeks. In a subsequent 8-week follow-up period no cream was applied. Two independent investigators performed an efficacy evaluation with clinical examination using a terminal hair regrowth score (RGS) with a scale ranging from 0 (inadequate response) to 2 (complete response) at week 20. Partial response was accepted as score 1.

Results: Both groups were well matched for the relevant demographic and clinical indicators affecting treatment response at baseline. All subjects completed the trial. At week 20 the RGS was 1.27 ± 0.9 in the azelaic acid group versus 1.37 ± 0.8 in the anthralin group ($p > 0.05$). A complete response was observed in 53.3% of cases in the azelaic acid group (8 of 15) compared with 56.2% (9 of 16) in the anthralin group ($p > 0.05$). No serious adverse events were observed in either group during the study.

Conclusion: The present pilot study showed that the use of azelaic acid gave similar results to anthralin with regard to hair regrowth, and that it can be an effective topical therapy for patchy AA. More extensive trials are necessary, however, to reach a definitive conclusion.

Topically applied azelaic acid has been shown to be of therapeutic value in skin disorders of different etiologies. Two side effects observed during azelaic acid use are hypertrichosis (stimulation of hair growth)[1] and irritant dermatitis.[2] After noting these side effects, some people have tried to use azelaic acid to treat hair loss diseases such as androgenetic alopecia, telogen effluvium, and alopecia areata (AA).[1] While azelaic acid is not indicated for use in treating androgenetic alopecia, some dermatologists and specialists use and prescribe this product as part of the treatment for this condition, and there are a number of commercial solutions available that contain azelaic acid for the treatment of androgenetic alopecia.[3,4] However, no controlled studies have been conducted to see how effective azelaic acid is or how it might work to permit/promote hair growth in people with these conditions. Thus, in this study, we evaluated the efficacy, tolerability, and safety of azelaic acid treatment in subjects with patchy AA.

Subjects and Methods

This study included 31 subjects with patchy AA who did not receive any treatment for at least 1-month prior to the study. Patients <13 years and pregnant or lactating women were excluded. AA was usually diagnosed on the basis of history and physical findings alone but, when necessary, serologic tests were performed to exclude syphilis.

Demographic and clinical characteristics of these subjects were recorded at baseline. Informed consent was obtained from all participants. Subjects were assigned randomly to apply either 20%

azelaic acid (Azelderm®,[1] Orva, Turkey) or 0.5% anthralin dithranol [Psoraks®, Kurtsan, Turkey]. Azelaic acid was applied to the affected areas twice daily for 12 consecutive weeks. Anthralin was applied in sparing applications for a short contact time (15 minutes) for 2 weeks and then, if tolerated, was continued with 30 minutes contact for 10 weeks. In the subsequent 8-week follow-up period no cream was applied.

Subjects were observed every 4 weeks to record progress of hair regrowth, adverse effects, and compliance. Two independent investigators performed an efficacy evaluation with clinical examination using a terminal hair regrowth score (RGS) with a scale ranging from 0 (inadequate response) to 2 (complete response). We used the terms 'complete response' to denote hair growth described by two independent investigators as excellent and cosmetically acceptable (wig no longer required), 'partial response' to denote hair growth referred to as moderate to good (wig may be required) [accepted as score 1], and 'poor growth' for the growth of vellus hair, sparse pigmented or nonpigmented terminal hair if the response was considered inadequate. When the two investigators were unable to agree on the RGS score, an independent third investigator was asked to act as a referee.

SPSS® 10.0 for Windows® (a computerized statistics package program consisting of Fisher's exact test, Pearson chi-squared test, t-test, and corrected chi-squared test) was used to compare variables. Results were expressed as means ± SD. A p-value <0.05 was considered statistically significant.

Results

The number of patients' lesions varied from one to seven, and the durations of AA ranged from 1 to 12 months. At baseline, both groups were well matched for the relevant demographic and clinical indicators affecting treatment response. There were no statistically significant differences in any of the baseline characteristics between the groups. Table I shows the main demographic and clinical characteristics of the enrolled patients.

All of the 31 subjects completed the trial. Regrowth of terminal coarse hairs usually started after 8 weeks of treatment with both drugs. No correlation existed between duration of the current episode and response to treatment. Growth was uniform in individuals with multiple patches under treatment. The RGS was 1.27 ± 0.9 in the azelaic acid group and 1.37 ± 0.8 in the anthralin group at 20 weeks ($p = 0.72 > 0.05$). A complete response (RGS = 2) was observed in 53.3% (8 of 15) of the patients in the azelaic acid group compared with 56.2% (9 of 16) of the patients in the anthralin group ($p = 1.0 > 0.05$) [table II]. The efficacy of both drugs was found to be statistically equivalent in the therapy of patchy AA.

No new patches developed in cases with complete response during the study period, suggesting that the effects of treatment may not have been restricted to the area of application. The same treatment was ordered for new patches that developed in only a few of the other patients; however, their results were not included in the evaluation.

Although the average RGS of cases with multiple episodes was determined as 1 in the azelaic acid group and 0.8 in the anthralin

Table I. Demographic and prognostic characteristics in the azelaic acid and anthralin (dithranol) groups at baseline

Characteristic	Azelaic acid (n = 15)	Anthralin (n = 16)	All subjects (n = 31)
Male/female	10/5	10/6	20/11
Mean age (SD) [year]	27 (9)	24 (10)	25 (10)
Age range [year]	13–43	13–42	13–43
First episode[a]	11/15	11/16	22/31
Mean duration (SD) [mo]	5.2 (3.8)	6.3 (4.6)	5.8 (4.2)
Duration range [mo]	2–12	2–12	2–12
Mean affected area (SD) [cm^2]	8.9 (7.2)	11.6 (9.0)	10.3 (8.2)
Affected area, range [cm^2]	1–29	2–30	1–30
Single lesion	8/15	7/16	15/31
Family history of AA[a]	1/15	2/16	3/31
Nail change[a]	3/15	2/16	5/31

a Data are numbers of affected subjects/total numbers of subjects in the given group.

AA = alopecia areata.

1 The use of trade names is for product identification purposes only and does not imply endorsement.

Table II. Distribution of the terminal hair regrowth score (RGS) at week 20

RGS	Azelaic acid (n = 15) [no. (%)]	Anthralin (dithranol) [n = 16] [no. (%)]	All subjects (n = 31) [no. (%)]
0	4 (26.7)	3 (18.8)	7 (22.6)
1	3 (20.0)	4 (25.0)	7 (22.6)
2	8 (53.3)	9 (56.2)	17 (54.8)

group, statistical analysis could not be performed because of the small number of cases.

No serious adverse events were observed in either treatment group during the study. However, two patients in the anthralin and one in the azelaic acid group reported pruritus, burning, and redness in treated areas.

Discussion

AA is an organ-specific autoimmune disease with an incidence of 0.15% in the general population. It has equal distribution in females and males. Approximately 40–50% of patients develop AA before the age of 21 years and 20% develop the condition after the age of 40 years.[5] The treatment of AA primarily involves promotion of hair growth (with topical minoxidil), immunosuppression, or immunomodulation. Immunosuppression is typically performed with corticosteroids, specific immunosuppressants (e.g. cyclosporine), or phototherapy. Current methods of immunomodulation include the application of either an irritant (e.g. anthralin) or an allergic sensitizer (e.g. squaric acid dibutylester).[6,7]

Because the therapeutic options for AA are associated with specific adverse effects and limitations, other effective, more harmless forms of treatment have been sought. The possibility of spontaneous remission makes it difficult to assess efficacy, particularly in mild forms of AA. Few data exist regarding the natural evolution of the condition; for example, in patients with <40% scalp involvement a study showed no benefit with treatment (minoxidil 1% and topical immunotherapy) over placebo.[8] The high spontaneous remission rate makes it difficult to assess clearly the true efficacy of a therapy unless appropriate controls with placebo treatment are studied. Some trials have been limited to patients with severe AA where spontaneous remission is unlikely. Nevertheless, these patients tend to be resistant to all forms of treatment and the failure of a treatment in this setting does not exclude efficacy in mild AA. Few treatments have been evaluated in randomized controlled trials and there are few published data on long-term outcomes.[9]

The exact mechanism of action of irritants in the therapy of AA is not known. The local cytokine profile induced by topical irritants may also inhibit the attack of inflammatory cells on the hair follicles.[6] Topical anthralin seems to be the most useful of the various irritants in the treatment of AA. It has been reported to be successful, achieving cosmetically good results, in 75% of patients with AA and 25% of patients with alopecia totalis.[10] However, other studies have reported less successful results. For example, Fiedler-Weiss and Buys[11] reported that 29% of patients with <75% hair loss and 20% of those with >75% hair loss achieved a cosmetic response with 0.5–1% topical anthralin. However, all of these studies were uncontrolled trials.

The strong indicator of effectiveness of azelaic acid for AA is its similarity to anthralin with regard to its irritant character. Our pilot study shows comparable results for azelaic acid and anthralin in the treatment of patchy AA.

Azelaic acid is a naturally occurring saturated, nine-carbon dicarboxylic acid found in whole-grain cereals (e.g. wheat, rye, barley) and animal products. The actual concentration of azelaic acid in each individual varies considerably depending on his or her diet. Azelaic acid causes alterations in the free fatty acid composition of skin surface lipids, and significantly reduces the follicular bacterial density. Azelaic acid affects the hornification process of the epidermal cells and appears to normalize keratinization of cells in the skin and hair. Interestingly, azelaic acid has an antiproliferative and cytotoxic effect on human malignant melanocytes that is related to inhibition of mitochondrial oxidoreductase activity and DNA synthesis. Azelaic acid also appears to act as an antiandrogen by blocking the activity of 5α-reductase.[2,3,12]

The favourable adverse effect profile of naturally available azelaic acid makes it superior to alternative medications. Nevertheless, our study had two limitations. First, the study population included only patients with patchy AA, in whom no treatment is a legitimate option for many patients with mild disease.[9] Secondly, our study was not a double-sided blind patient-controlled therapeutic trial.

Conclusion

This pilot study showed that use of azelaic acid gave similar results for hair regrowth as anthralin, and that it can be an effective topical therapy for patchy AA. This study population was, however, too small to allow definite conclusions to be drawn. Future trials of treatment of AA with azelaic acid should also have an untreated control site and include patients with alopecia totalis in addition to patients with patchy AA.

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