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Double-blind Comparison of Azelaic Acid and Hydroquinone in the Treatment of Melasma

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Melasma is a macular hypermelanosis of the sun-exposed areas of the face and neck. The clinical efficacy of azelaic acid (20%) and hydroquinone creams (2%) in the treatment of this benign pigmentary disorder was compared in a randomized, double-blind study with 155 patients of Indo-Malay-Hispanic origin. The creams were applied twice daily. A broad spectrum sunscreen was used concomitantly. Over a period of 24 weeks, 73% of the azelaic acid patients, compared with 19% of the hydroquinone patients, had good to excellent overall results, as measured by the reduction of melasma pigmentary intensity and lesion size. Transient mild to moderate irritant reactions were initially seen with both test drugs.

INTRODUCTION

Melasma is an acquired facial hyperpigmentary disorder which is common among darker-skinned individuals living in countries with high solar radiation. The factors implicated in the etiology of melasma are abundant in the tropics: UV-A and UV-B light, pregnancy, racial predisposition, and the use of certain cosmetics and pharmaceuticals (1).

Current therapy often is unsatisfactory. At present the drug most frequently used is hydroquinone (HQ), alone or in combination with tretinoin and corticosteroids (2). The efficacy of topical HQ preparations is variable, depending on the concentration employed. However, higher concentrations of HQ not only increase the efficacy but also the risk of untoward effects (3, 4).

Thus there is a need for alternative treatments for this benign but nevertheless highly distressing skin problem. Azelaic acid (AA), a dicarboxylic acid, has been shown to affect hyperactive melanocytes (5). In order to investigate the clinical efficacy of AA in the treatment of melasma, this double-blind study of 155 patients was undertaken in two centres (V. V.-R.; M. G.-L.) by comparing 20% AA cream with 2% HQ cream.

MATERIAL AND METHODS

155 patients were allocated at random to treatment with azelaic acid ($n=77$) or with hydroquinone ($n=78$). Pregnant or nursing women or women taking oral contraceptives were excluded. All patients had clinical melasma, confirmed by biopsy when the diagnosis was doubtful, and were differentiated into epidermal and mixed epidermo-dermal types by Wood's light (1, 6). Melasma pigmentary intensity was rated on a 5-point grading scale in relation to the patient's normal facial skin (1: no difference, 2: slightly more pigmented 3: moderately more pigmented 4: markedly more pigmented, and 5: intensely more pigmented). The size of the lesions was measured directly using a millimetre grid scale. Ratings and measurements were made prior to treatment and at each of the follow-up visits (after 4, 9, 14, 19 and 24 weeks, respectively.) The overall response to treatment was rated at the end of the study as excellent, good, fair, or poor. Colour photographs were taken at the start, midway and at the end of the study. Side effects were monitored and treated.

The treatment regimen was twice daily application for 24 weeks of a cream containing 20% AA (SH C 441 F, Schering AG, West Berlin) or a cream containing 2% HQ (Esoterica®, Berk Pharmaceuticals Ltd., Eastbourne, Sussex, England). A broad-spectrum sunscreen (Contralum Ultra, Hermal Chemie, Hamburg, FRG) was used concomitantly by both groups. Patients were instructed to avoid strong sun exposure and to minimize the use of cosmetics.

RESULTS

The data from the two centres were pooled and analysed. The treatment groups were evenly matched (Table I). The patients were, for the most part, oriental women with skin types III–V (fair to dark brown). Their melasma, as determined by Wood's light, was both of the epidermal and of the mixed epidermodermal type; the median previous duration was 4 years. The pigmented macules were in general moderately to markedly darker than the normal facial skin and, on the average, involved about one-third of the face. Previous treatment used by approx. half of the patients included skin peeling, various HQ preparations and OTC bleaching creams.

Table I. *Baseline characteristics of the melasma patients*

The intensity of pigmentation, as compared with the unaffected facial skin, was rated on a 5-point grading scale (as described in Material and Methods)

		Azelaic acid	Hydroquinone
No. of patients		77	78
No. of patients who completed treatment		65	67
Sex		73 F/4 M	73 F/5 M
Skin type			
II		–	5
III		28	33
IV		29	19
V		20	21
Epidermal melasma		43	38
Mixed-type melasma		34	39
Median duration and range (y)		4 (1 month–17 y)	4 (10 months–30 y)
Previously treated		37	41
Initial median lesion size and range (cm^2)		69 (7–185)	57.5 (14–157)
Intensity of pigmentation	2	1	2
	3	28	34
	4	38	27
	5	10	15

65 (84.4%) of the patients using AA treatment and 67 (85.9%) of the patients using HQ completed the study. In 18 of the 23 drop-outs, treatment was terminated prematurely either for reasons not related to the study therapy (6 AA, 7 HQ) or because of poor patient compliance (2 AA, 3 HQ). Local side effects led to discontinuation in 2 cases in the AA group (cosmetic acne, marked stinging) and in one case in the HQ group (eczema).

The results of the therapeutic efficacy are summarized in Table II.

In both types of melasma, therapeutic response was achieved. No major differences between the results obtained in epidermal melasma and those obtained in the mixed epidermo-dermal type were found.

In the AA group, 48 patients had a favorable therapeutic response after 24 weeks: 37 (56.9%) achieved a good overall improvement, while 11 (16.9%) had an excellent result. In 2 of the latter cases the melasma had been present for 15 years. 2 patients were complete treatment failures, while in 15 (23%) a fair therapeutic effect was noted (Table II).

The overall results in the AA group differed significantly from those in the HQ group ($p < 0.001$; χ^2-test). Thus the majority of the HQ patients, i.e. 34 (50.8%), achieved only a fair improvement. An excellent response was seen in one case (1.5%), good results were obtained in 12 patients (17.9%), 20 patients (29.8%) were treatment failures.

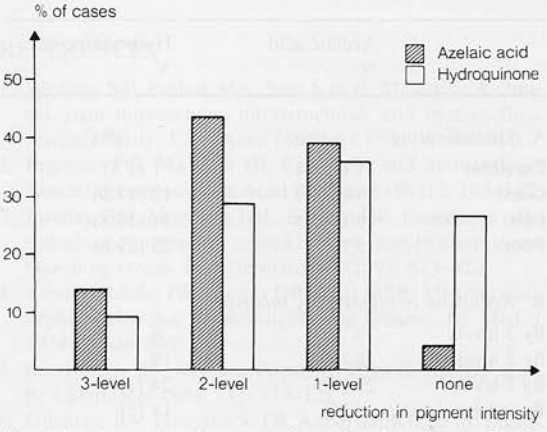

Fig. 1. Reduction in pigmentary intensity of melasma after 24 weeks. The pigmentary intensity of melasma, as compared with the unaffected facial skin, was rated on a 5-point scale, from 1 = no difference, to 5 = highly more intensive. The difference in the rating prior to treatment and after 24 weeks is shown for the patients of the azelaic acid group ($n = 65$) and of the hydroquinone group ($n = 67$).

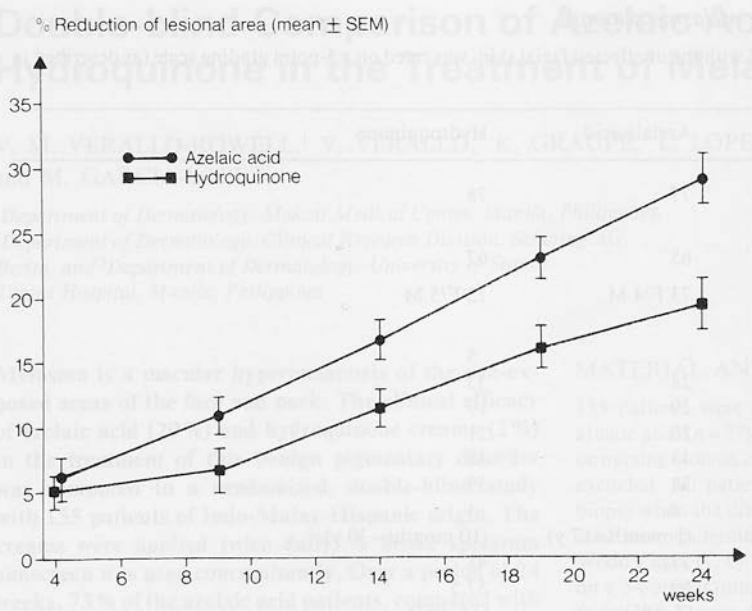

Fig. 2. Reduction in the size of the lesional area. The size of the lesional areas was determined at each visit by a millimetre grid. The mean percentages of reduction (±SEM) for the AA group (——) and the HQ group (– – –) are shown.

Table II. *Therapeutic efficacy*

A: Overall therapeutic response in the patients completing 24 weeks of treatment with AA ($n=65$) and HQ ($n=67$). A reasonable estimation of the overall efficacy in the drop-outs could not be obtained. B: Reduction of pigmentary intensity as determined from the colour intensity (see Material and Methods) prior to treatment and at the end of therapy. The numbers refer to patients completing the study, the numbers in brackets refer to drop-out patients. C: Reduction of initial lesional size. The numbers in brackets refer to drop-out patients.

	Azelaic acid *N*	Hydroquinone *N*
A. *Overall rating*	(%)	(%)
Excellent	11 (16.9)	1 (1.5)
Good	37 (56.9)	12 (17.9)
Fair	15 (23.1)	34 (50.8)
Poor	2 (3.1)	20 (29.8)
B. *Reduction in pigmentary intensity*		
By 3 levels	9	6
By 2 levels	28 [1]	19
By 1 level	25 [5]	24 [4]
By <1 level	3 [6]	18 [7]
C. *Reduction in lesion size*		
75–100%	1	–
50–75%	4	2
25–50%	36 [1]	25
<25%	24 [11]	40 [11]

The improvement was characterized by a lightening and by a resolution of parts of the pigmented macules.

Lightening of melasma was better in the AA group than in the HQ group. Judging by the 5-point grading scale employed for the pigmentary intensity over a period of 24 weeks, 57% of the AA patients had a reduction by 2 or 3 levels of intensity and 4.6% had a reduction by less than 1 level (Fig. 1, Table II). These results differed significantly ($p<0.05$; χ^2-test) from those achieved in the HQ patients, of whom 37% had a reduction by 2 or 3 levels and 27% a reduction by less than 1 level.

The reduction of lesion size was significantly greater in the AA group than in the HQ group (Fig. 2). The reduction of the initial lesion size ranged between 0 and 75.5% (median 29%) in the AA group and between −5.9% (aggravation) and 58.3% (median 20.9%) in the HQ group. In the majority of the AA cases, i.e. 36 (55.4%) a diminution by 25–50% was observed, while 40 (59.7%) of the HQ patients had a diminution by less than 25% (Table II).

Premature cessation of treatment was encountered mainly after 4–9 weeks of therapy. Since melasma will in general require an extended time of treatment and since, in addition, the patients did not return for further control visits, no judgement about the overall therapeutic efficacy was made in the drop-out cases. It was noted, however, that 6 of the 12 drop-outs in the AA group and 4 of the 11 in the HQ group had

obtained a definite lightening of their melasma (Table II), indicating a therapeutic effect of the drug employed.

Side effects

Mild, transient, local irritant sensations were reported by 11 patients in the AA group and by 9 in the HQ group. Pronounced primary irritant reactions (negative skin patch test) were noted in 5 patients on AA and in 2 patients on HQ. Ochronosis was not observed.

The symptoms mainly reported were burning, itching and/or stinging. In each group, objectively measurable local side effects, i.e. pronounced scaling or erythema, were noted in 2 and 1 case, respectively, of the above-mentioned patients. Mostly the occurrence of local side effects was related to unsuitable cleansing, i.e., by vigorous rubbing of the face with a cleanser, followed by a thicker-than-usual application and subsequent rubbing in of the test creams. When corrected, the patients were able to continue with the use of the drugs for the entire course.

In 2 instances an allergic contact dermatitis developed which, as confirmed by a positive 48-hour skin patch test, was elicited by the sunscreen. In a few patients in either group, a mild comedone formation was noted. Although in those cases no additional treatment was necessary, a change of the sunscreen preparation suggested that comedone formation was due to the prolonged use of the initially employed sunscreen.

DISCUSSION

This study shows that 20% azelaic acid cream applied topically twice daily over a period of 24 weeks and used concomitantly with a broad-spectrum sunscreen is effective in reducing or clearing melasma.

Azelaic acid cream was clearly superior to the 2% hydroquinone cream employed in the control group. In the HQ group, 19% of the patients achieved good to excellent results. This low rate, which is well in line with data reported by Pathack et al. (7), confirms that 2% hydroquinone is only moderately effective against melasma. In contrast, 73% of the patients achieved good to excellent results after 24 weeks use of the azelaic acid cream.

In order to prevent an exacerbation of melasma, a broad-spectrum sunscreen was used concomitantly during the study period. However, since the same sunscreen was employed in both treatment groups, the difference in the overall results must reflect genuine differences in the therapeutic activity of the two trial preparations.

The effect of therapy was characterized primarily by a progressive lightening of the pigmented macules. Concomitantly with the lightening, a reduction in lesion size was observed, i.e., parts of the lesions resolved completely, while other parts (though considerably lightened) were still discernible in outline. Whether this reflects inherent cellular differences in the response to treatment or simply that melasma consists of zones with different melanocytic activity is not clear.

Azelaic acid cream produced some primary irritant reactions when applied in large amounts and rubbed in vigorously. However, when the manner of application was corrected the patients were able to continue uneventful use of the test cream. Azelaic acid cream did not elicit allergic reactions. In those 2 cases in which an allergic contact dermatitis was observed, a positive patch test was found with the broad-spectrum sunscreen.

To sum up, 20% azelaic acid cream was found to be effective for the treatment of melasma in oriental women of skin type III–V. Patients should receive clear instructions regarding the proper and regular application of the cream and it should be emphasized that a continuous treatment for several months may be required in order to achieve the desired results.

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