Acta Derm Venereol (Stockh) 1989; Suppl 143: 45–48

Azelaic Acid for the Treatment of Acne

A Clinical Comparison with Oral Tetracycline

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INTRODUCTION

Azelaic acid is an aliphatic dicarboxylic acid, $HOOC-(CH_2)_7-COOH$. The inhibitory effect of this substance on the activity of abnormal melanocytes (1) has prompted investigations into its clinical potential for the treatment of hyperpigmentary disorders such as lentigo maligna (2) and melasma (3, 4).

It was incidentally discovered that in patients with melasma and coexisting acne, the use of azelaic acid cream not only led to an improvement of the melasma but also had a beneficial effect on the acne (5). Cunliffe and co-workers (6) confirmed the therapeutic effect of azelaic acid cream in acne and demonstrated that this effect must be attributed, at least in part, to an antimicrobial activity of the diacid on the cutaneous microflora (7).

In the following we summarize results of controlled clinical investigations comparing the therapeutic efficacy of 20% azelaic acid cream in inflammatory acne with that of oral tetracycline hydrochloride.

MATERIAL AND METHODS

333 patients (178 M/155 F) were admitted to a study comprising cases of predominantly papulo-pustular acne. Approximately 80% of these patients had a severity grade of II/III according to the Plewig-Kligman classification.

In a second study, 261 patients (193 M/68 F) with conglobate acne (41.8%), nodulocystic acne and acne papulopustulosa nodosa (58.2%) were included. Both clinical investigations were conducted as double-dummy, multicentre studies. Patients were allocated at random to the treatments. In the two azelaic acid groups, patients (164 and 126, respectively) were treated topically twice daily with a 20% AA cream (SH C 441 F, Schering AG, Berlin) and additionally received placebo capsules.

The patients in the tetracycline groups of the two studies (169 and 135, respectively) received oral tetracycline hydrochloride (Hostacyclin®, Hoechst AG, Frankfurt, FRG) and the cream base of the azelaic acid preparation. The dose regimen for tetracycline hydrochloride was 1 g/day during the first month of treatment, 0.75 g/day during the second month and 0.5 g/day during the third month. Thereafter the dose could be adjusted to individual demands. Following a washout period of 4 weeks, the patients in the study of moderate acne were treated for a maximum period of 5 months. Patients in the study of severe inflammatory acne were treated for 6 months.

The patients were seen at monthly intervals. At each visit the therapeutic progress was monitored by counting the number of papules, pustules, nodules, cysts, and open and closed comedones.

In the statistical analysis the Mann-Whitney U-test was employed for the lesion counts, while the χ^2-test was used for the therapeutical overall evaluation ($\alpha=0.05$). Due to the asymmetric distribution of the data, median values rather than means were employed.

RESULTS

Both studies demonstrated that a significant and clinically relevant reduction in the initial number of lesions was achieved during therapy with the azelaic acid cream, thus indicating that the drug is an effective treatment.

Moderate acne

The examination of the median numbers of facial papules and pustules in the study of moderate acne shows a similar time–response relationship in the two treatment groups (Fig. 1). During the treatment period, the median number of inflamed lesions was reduced from initially 35 to 6 in the azelaic acid group and from initially 36 to 5 in the tetracycline group. No significant difference between the treatments was found after 5 months.

When considering the total lesion counts, likewise no clinically relevant difference between treatments was observed after 5 months.

The overall efficacy was determined from the reduction of the sum of lesions. A reduction of the initial total count by more than 75% was considered to be an excellent response, a reduction by 50–75% was a good response. The rates of therapeutically

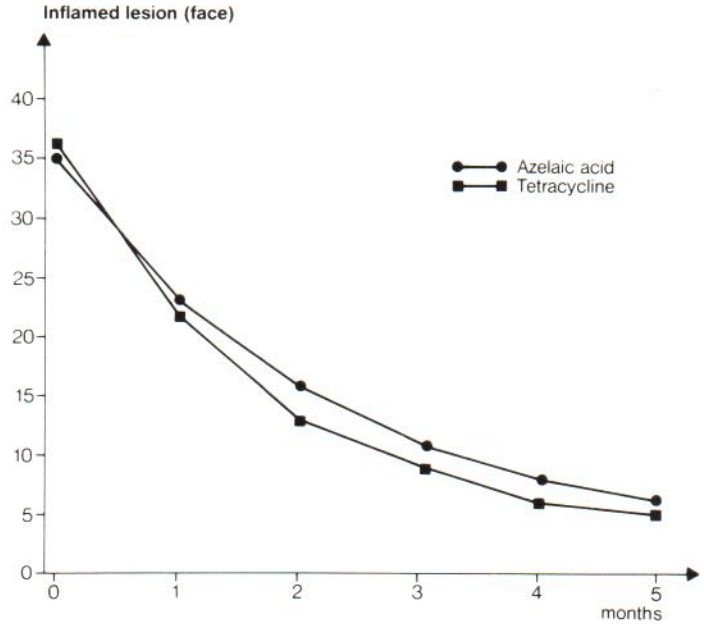

Fig. 1. Reduction of inflamed facial papules and pustules during treatment of moderate acne. The numbers at each visit are median values. Circles indicate treatment with azelaic acid ($n=164$), squares indicate treatment with tetracycline ($n=169$).

desirable results, i.e. good and excellent improvement, are shown in Fig. 2. At the final visit, 81.7% of the patients on azelaic acid treatment and 86% of the patients receiving tetracycline had achieved good or excellent overall improvements. No significant difference was found between the groups with respect to this overall rating.

Moderate–severe acne

In the study of more severe forms of inflammatory acne, the time course and the magnitude of response for the reduction of papules and pustules closely resembled that observed in the former study. Thus in the azelaic acid group a reduction of the median facial counts (Fig. 3; please note that only the lesions of one half-side of the face were counted) from initially 14.5 to 3 after 5 months of treatment is found. The corresponding percentage reduction of the initial number of papules and pustules, i.e. 79.3%, is essentially similar to that observed in the previous study of moderate acne, i.e. 82.9%. When comparing the counts of the small inflamed lesions in the azelaic acid group with those in the tetracycline group (Fig. 3), again no significant difference was observed.

The time–response curves for the deep lesions, i.e. nodes and cysts, are depicted in Fig. 4. The statistical analysis did not reveal a significant difference between the treatments at any of the visits. From Fig. 4 it would appear that the deep lesions respond more rapidly to tetracycline therapy. However, it must be emphasized that the maximum difference in the median numbers is one lesion only and that the difference disappears following the fourth month of treatment.

Nodes and cysts contribute essentially to the severity of acne. However, since they do not numerically

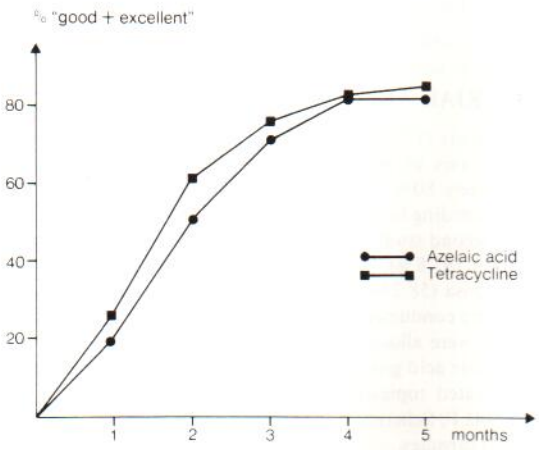

Fig. 2. Rate of overall 'good and excellent' responses during treatment of moderate acne. An 'excellent' response was defined as >75% reduction of total lesion counts, a 'good' response as 50–75% reduction. Circles indicate treatment with azelaic acid ($n=164$), squares indicate treatment with tetracycline ($n=169$).

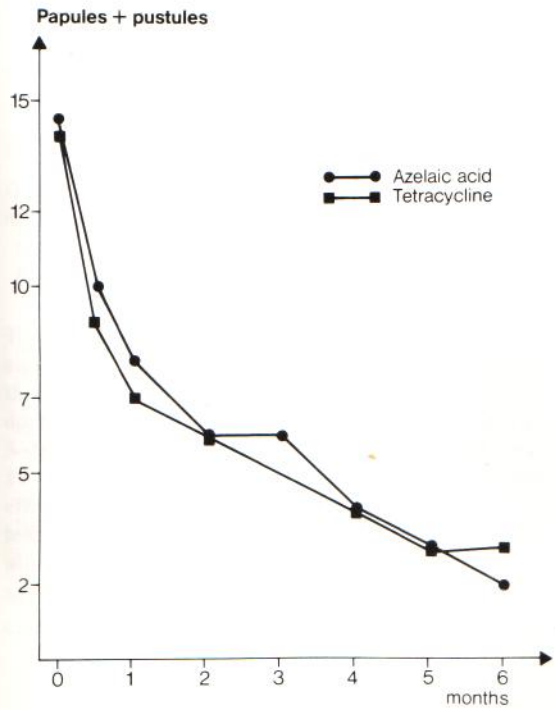

Fig. 3. Reduction of inflamed facial papules and pustules during treatment of severe acne. The numbers given at each visit are median values. Circles indicate tretment with azelaic acid ($n=126$), squares indicate treatment with tetracycline ($n=135$).

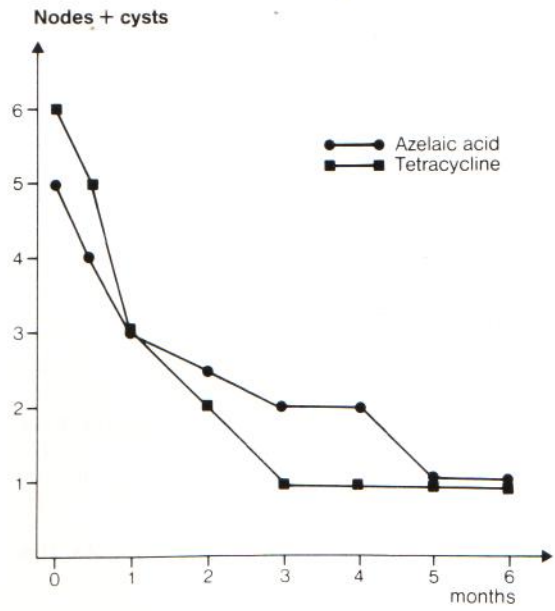

Fig. 4. Reduction of nodes and cysts during treatment of severe acne. The numbers given at each visit are median values. Circles indicate treatment with azelaic acid ($n=126$), squares indicate treatment with tetracycline ($n=135$).

constitute a major proportion of the total number of lesions, the evaluation of overall efficacy was made in terms of subjective ratings rather than by the reduction of lesion counts. Thus subjectively 62.3% of the patients treated with azelaic acid cream had achieved a good or excellent improvement, whilst in 60.7% of the patients in the tetracycline group the results were rated good or excellent.

The 20% azelaic acid cream was in general well tolerated. Local irritant effects, such as burning and/or stinging, itching and/or scaling were noted at a low incidence rate, mainly at the beginning of therapy. No allergic reactions were observed during the studies.

COMMENTS

Drugs which reduce the population density of *Propionibacterium acnes* are commonly employed in the management of inflammatory acne. Azelaic acid both in vitro and in vivo has an antimicrobial effect on the cutaneous microflora (6, 7). Under clinical conditions the topical use of azelaic acid cream significantly reduces the intrafollicular density of *P. acnes* (8).

From the present studies it is concluded that the 20% azelaic acid cream employed is an effective topical treatment for inflammatory acne, leading to a significant and clinically relevant reduction in the numbers of superficial and deep inflamed lesions. It is observed from the time–response curves that, following a clear initial effect, the major improvement was achieved after 4 months. Taking into account both the inflamed lesions and the total lesion counts as well as the rate of therapeutically meaningful overall improvements, the two studies in conjunction show that the final results achieved with 20% azelaic acid cream parallel those achieved with oral tetracycline hydrochloride. These findings are in accordance with those of Cunliffe and co-workers (6) who reported only minor differences between topical azelaic acid and tetracycline given at a dose of 1 g/day for 6 months.

The use of topical preparations in cases of extensive involvement of the back may pose practical problems and affect patient compliance. Furthermore it appears that acne lesions on the back generally respond less well to acne therapy. In those cases a combination of topical azelaic acid with a systemic treatment might be considered.

Azelaic acid has been reported to be a non-toxic and non-teratogenic substance (9). In the present clinical investigations the azelaic acid cream was well tolerated. Although some local irritant reactions occurred, no allergic contact dermatitis was observed. Gastrointestinal discomfort, candidiasis, photodynamic skin reactions, vertigo, or the development of resistant bacterial strains associated with the use of various antibiotics do not constitute a problem with azelaic acid therapy.

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