Combination of azelaic acid 5% and erythromycin 2% in the treatment of acne vulgaris

HAMIDREZA PAZOKI-TOROUDI1,2, MANSOUR NASSIRI-KASHANI1, HOSSEIN TABATABAIE1, MARJAN AJAMI2, ROUHOLLAH HABIBEY3, MOHAMMAD SHIZARPOUR1, SHAHAB BABAKOOHI1, MAKAN RAHSHENAS1 & ALIREZA FIROOZ1

1 Center for Research & Training in Skin Diseases & Leprosy, Tehran University of Medical Sciences, Tehran, Iran, 2 Nano Vichar Pharmaceutical Ltd, Tehran, Iran, 3 Department of Nutrition, Iran University of Medical Sciences, Tehran, Iran and 4 Department of Physiology, Iran University of Medical Sciences, Tehran, Iran

Abstract

Introduction: Acne vulgaris is a common problem, particularly among adolescents, which is usually resistant to monotherapy. We evaluated the efficacy and safety of a combination of azelaic acid (AA) 5% and erythromycin 2% gel (AzE) compared with AA 20% or erythromycin 2% gels in facial acne vulgaris. Methods: We conducted a 12-week, multicenter, randomized double-blind study on 147 patients with mild-to-moderate acne vulgaris. Four treatment groups were determined (placebo, erythromycin, AA and AzE) and followed in 4-week intervals for 12 weeks, except the placebo group which was changed to routine treatment after 4 weeks. Results: The combination of AA 5% and erythromycin 2% gel significantly reduced the number of papules, pustules and comedones compared with placebo (p < 0.001), erythromycin 2% (p < 0.01) or AA 20% (p < 0.05). The incidence of adverse effects observed in patients treated with AzE (27%) was less than that with erythromycin 2% (34%) and AA 20% (45%). Conclusions: The combination of AA 5% and erythromycin 2% produced more potent therapeutic effects in comparison with erythromycin 2% or AA 20% alone, and with fewer side effects.

Key words: acne vulgaris, azelaic acid, erythromycin

Introduction

Acne development is attributed to a constellation of factors including pilosebaceous follicle hyperkeratinization (plugging); increased sebaceous gland activity; increased bacterial colonization of pilosebaceous units; and perifollicular inflammation (1). No single topical agent has been developed to overcome all of these factors. So, combination therapy that often includes an antibiotic and an agent to reduce plug formation has become the mainstay of treatment of mild-to-moderate acne (2).

Azelaic acid (AA), an aliphatic dicarboxylic acid, is an effective treatment in mild-to-moderate acne vulgaris, with efficacy comparable to other approved treatments including benzoyl peroxide, erythromycin, and tretinoin (3–6). It has a predominant antibacterial activity, though is not classified classically as an antibiotic, a modest comedolytic effect, and it reduces sebum production on the forehead, chin and the cheek alone or in combination with other treatments (2,7–9).

Erythromycin is a bacteriostatic macrolide that can be used as a topical or systemic treatment for acne vulgaris (10). Topical antibiotics are often used for mild-to-moderate acne, while systemic antibiotics are reserved for moderate-to-severe inflammatory ones (11). Increasing resistance to antibiotics in Propionibacterium acnes stains has become a challenge in the further usefulness of erythromycin as a single
therapy of the patients about the severity of their acne were sought. The disease status was evaluated every 4 weeks by a dermatologist. In each session, the total numbers of lesions (papules, pustules and comedones) were counted. The photography, evaluation of adverse effects and patient satisfaction were performed in week 12 (in the case of the placebo group, these variables were evaluated at week 4 and then the patients returned to routine treatments). Patient satisfaction was rated as: 0: very unsatisfied, 1: unsatisfied, 2: moderately satisfied, 3: satisfied, 4: very satisfied. Adverse effects including scaling, pruritus, erythema, dry skin and oiliness were evaluated at each visit.

Results

A total of 106 of 127 non-placebo patients completed the study. The majority of drop-outs were due to the long distance some patients had to travel to follow-up appointments or due to the high expectations of some to see dramatic results in just a few days. The number of inflammatory lesions (papules and pustules) and non-inflammatory lesions (open and closed comedones) are shown in Table I. Within-group analysis revealed a significant reduction of papules and pustules from week 4 in all treatment groups ($p < 0.01$ for erythromycin 2%, and $p < 0.001$ for AA 20% and AzE), except placebo. The number of open and closed comedones also showed a significant reduction in these groups of patients ($p < 0.001$).

In each session, the mean number of lesions, as well as the mean change from baseline, were compared among the different groups. After 4 weeks, the number of papules, pustules and comedones were reduced significantly in all treatment groups compared with the placebo group ($p < 0.001$). The effects of AA 20% on reducing the number of papules and pustules at
weeks 8 and 12 was more than erythromycin 2% (p < 0.05), but the difference in the number of comedones became significant just after 12 weeks of treatment. In the group treated with AzE, a significant reduction in the number of all lesions (inflammatory or non-inflammatory) compared with AA 20% and erythromycin 2% was observed at weeks 4, 8 and 12 (p < 0.05 and p < 0.01, respectively).

Patient satisfaction is shown in Table II. Detailed analysis did not show a statistical difference between AA 20% and erythromycin 2%, whereas patients in group AzE showed significantly more satisfaction compared with AA 20% or erythromycin 2% (p < 0.05), with 80% of them satisfied or very satisfied.

At least one adverse effect was shown in 42% of patients (Table III): 16 (45%) AA 20% patients, 17 (54%) erythromycin 2% patients, and 11 (27%) AzE patients showed adverse effects because of treatment (Table III). Adverse effects were significantly lower in patients treated with AzE compared with other groups (p < 0.05). The most common adverse effects in the total study population were pruritus (10 patients; 9.4%) and erythema (10 patients; 9.4%). Although bothersome, the adverse effects did not lead to patients quitting treatment.

**Discussion**

To our knowledge, this is the first study evaluating the combination of AA 5% and erythromycin 2% for the treatment of acne vulgaris. The results showed that this combination was significantly more effective than AA 20% or erythromycin 2% alone in decreasing the number of comedones and inflammatory lesions. Moreover, AzE showed its effect on reducing lesions

| Table II. Patient satisfaction of treatments at week 12 of the study. |
|--------------------------|--------|---------|--------|
| Treatments               | 4     | 3       | 2      | 1      | 0      | Total  |
| Azelaic acid 20%         | 8     | (22.86)| 13     | (37.14)| 9      | (25.71)| 4      | (11.43)| 1      | (2.86)| 35     |
| Erythromycin 2%          | 7     | (22.58)| 9      | (29.03)| 9      | (29.03)| 4      | (12.90)| 2      | (6.45)| 31     |
| AzEa, b                  | 11    | (27.5)| 21     | (52)   | 6      | (15)   | 2      | (5)    | 0      | 40     |

Data are shown as the number and percent of patients belonging to each grade regarding patient judgment of the therapeutic effect of different treatments at the end of the study (week 12). 0: Very unsatisfied; 1: unsatisfied; 2: moderately satisfied; 3: satisfied; 4: very satisfied. *p < 0.05 compared with the azelaic acid 20% group and †p < 0.05 vs erythromycin 2% patients.
faster than the two other treatments. Evaluation of disease severity, side effects, and patient satisfaction confirmed there were more significant and fewer harming effects of AzE compared with the two other single treatments.

AzE reduces keratinocyte proliferation and modulates epidermal differentiation, the mechanisms that involve inhibition of DNA and protein synthesis (18). Moreover, AA possesses bacteriostatic activity and acts on both aerobic and anaerobic bacteria, including *P. acnes* (19). AA also acts as a competitive inhibitor of mitochondrial oxidoreductases (20) and has an inhibitory effect on 5-alpha-reductase, so it may be effective in acne treatment in which the role of androgenic hormones has been demonstrated previously (21,22).

The present study confirmed the results of previous clinical trials that evaluated the effects of AA 20% on acne (23,24). However, the main propose of this study was the evaluation of an AA 5% and erythromycin 2% combination to achieve an effective compound with a low rate of adverse effects. The anti-inflammatory effects of erythromycin 2% potentiated the therapeuthic properties of AA 5% as both inflammatory and non-inflammatory lesions were decreased significantly compared with each treatment alone (Table III). Previously, combination therapies with AA have demonstrated more efficacy than a single agent. Most of these combinations include AA and an antibiotic (25,26). There have also been studies carried out on a combination of erythromycin with other agents including zinc acetate (26), tretinoin (27), and benzoyl peroxide (13). The results of the present study suggest that erythromycin 2% is an effective supplement in the treatment of acne vulgaris with AA 5%. After 4 weeks an attenuated response to treatment was seen in almost all groups. Perhaps this is due to the natural course of acne in which the physician usually modifies the treatment, but in this study we continued the same treatment. This can be interpreted as necessity of exact follow-up of acne patients in order to modify the medication if the situation aggravates or reaches a plateau.

In conclusion, the present study has demonstrated that AzE effectively reduced the number of inflammatory and non-inflammatory acne lesions and was more potent and had fewer adverse effects than AA 20% or erythromycin 2% alone. AzE also gave more patient satisfaction. These results suggest that the combination of low concentrations of AA with an appropriate antibiotic may give a better clinical outcome with fewer unwanted effects in the treatment of acne vulgaris.

**Acknowledgement**

Hereby, the cooperation of medical staff of Dowlati Skin Clinic in performing this trial and the efforts of Mr Akhavan in preparing the material for this study are greatly appreciated.

**Declaration of interest:** The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

**References**

- 6. Katsambas A, Graupe K, Stratigos I. Clinical studies of 20% azelaic acid cream in the treatment of acne vulgaris:

<table>
<thead>
<tr>
<th>Side effects</th>
<th>Placebo</th>
<th>Azelaic acid 20%</th>
<th>Erythromycin 2%</th>
<th>AzE</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n = 20</td>
<td>n = 35</td>
<td>n = 31</td>
<td>n = 40</td>
</tr>
<tr>
<td>Scaling</td>
<td>–</td>
<td>4 (11.43)</td>
<td>2 (6.45)</td>
<td>1 (2.5)</td>
</tr>
<tr>
<td>Dry skin</td>
<td>–</td>
<td>2 (5.71)</td>
<td>4 (12.9)</td>
<td>3 (7.5)</td>
</tr>
<tr>
<td>Erythema</td>
<td>1 (5)</td>
<td>3 (8.57)</td>
<td>5 (16.1)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Oiliness</td>
<td>–</td>
<td>3 (8.57)</td>
<td>3 (9.68)</td>
<td>2 (5)</td>
</tr>
<tr>
<td>Pruritus</td>
<td>–</td>
<td>4 (11.43)</td>
<td>3 (9.68)</td>
<td>3 (7.5)</td>
</tr>
</tbody>
</table>

In the case of the placebo group, the signs were evaluated at week 4. In the remaining groups the signs were checked at week 12 of treatment. Percentages given in parenthesis.