Journal of the Turkish Academy of Dermatology

Research

Photographic Evaluation of 15% Azelaic Acid Gel in Acne Rosacea

Meltem ÖNDER, MD, Esra ADIŞEN,* MD

Address:
Department of Dermatology, Faculty of Medicine, Gazi University, Ankara, Turkey.
E-mail: eozsoy@gazi.edu.tr
* *Corresponding author*: Esra Adışen, MD, Gazi University Faculty of Medicine Department of Dermatology 06500 Beşevler, Ankara- Turkey

Published:
J Turk Acad Dermatol 2008;**2 (3)**:jtad82301a
This article is available from: http://www.jtad.org/2008/3/jtad82301a.pdf
Key Words: acne rosacea, azelaic acid 15% gel, topical treatment, photographic evaluation

Abstract

Objective: Acne rosacea is a difficult to treat disease and current treatments remain unsatisfactory. Our aim was to assess and present the photographic evaluation of the effectiveness and tolerability of azelaic acid 15 % gel for the treatment of acne rosacea.

Methods: Healthy male and female adult outpatients (>18 years of age) with mild to moderate acne rosacea. All patients were instructed to apply azelaic acid 15% gel to entire affected area twice daily for 4 weeks. Primary efficacy endpoints in the study included changes from baseline to the last visit (4th week) in the severity of lesions on a 4-point scale. Both patients and investigators rated the overall improvement at the end of the study.

Results: All 31 patients completed the study. The investigator assessment of rosacea revealed that azelaic acid 15% gel resulted in a statistically significant decrease in facial erythema (p=0.001) while no statistically significant change was observed with regard to changes in inflammatory lesions and telangiectasia (p>0.05). Most of the patients (58%) rated the outcome of the treatment as "moderately" to "very satisfactory". With regard to investigators' evaluation scores, 29% (n=9) of patients showed marked improvement or clearance.

Conclusion: Azelaic acid 15% gel is an effective and safe treatment for mild to moderate acne rosacea when used twice daily in combination with sunscreens.

Introduction

Acne rosacea is a chronic acneiform disorder affecting both the skin and the eyes. Clinical findings are usually limited to the face and include erythema, telangiectasia, papules and pustules, and sebaceous gland hypertrophy. It is also characterized by episodic flushing of affected areas, which may be aggravated by consumption of alcohol, hot drinks, or spicy foods. Rhinophyma is an accompanying finding [1, 2, 3].

The etiology remains unknown despite considerable research. Some of the well known hypotheses have included gastrointestinal, psychological, infectious, climatic, and immunological causes [1, 2].

Acne rosacea is a difficult to treat disease and current treatments remain unsatisfactory. Oral antibiotics, isotretinoin, topical antibiotics, metronidazole, and many other medications have been used with various success rates. Each of these agents has their own advantages and disadvantages: oral antibiotics are often limited by systemic side effects [1] and topical therapies may irritate already sensitive skin [4]. Many studies found azelaic acid to be effective in the

treatment of acne rosacea when used twice daily for 9-15 weeks [**5, 6, 7, 8, 9**]. The exact mechanism of action of azelaic acid in acne rosacea is not known. Azelaic acid is in a class of medications called dicarboxylic acids. In addition to its effects on keratinization, it exerts antimicrobial and anti-inflammatory effects [**2, 3**]. Which of these properties are involved in the treatment of acne rosacea is unclear.

More recently, studies focused on the effectiveness of a gel formulation of azelaic acid (Finacea ®, Intendis, Intendis İlaç Tic. Ltd. Şti. İstanbul, Turkey). The Food and Drug Administration approved azelaic acid 15% gel in December 2002 for the treatment of mild to moderate rosacea [**11**]. Azelaic acid 15% gel contains higher amount of the active ingredient as compared to azelaic acid cream and the vehicle of gel formulation has ability to more effectively deliver a higher azelaic acid dose fraction into the viable skin which is 25.3% for the gel and 3.4% for the cream formulation [**12**].

Herein we assessed and presented the photographic evaluation of the effectiveness and tolerability of azelaic acid topical gel for the treatment of acne rosacea. The objective was to compare the photographic results of patients treated with azelaic acid 15% gel at baseline and at the end-of four weeks of treatment.

Materials and Methods

Patients: Healthy male and female adult outpatients (>18 years of age) with mild to moderate acne rosacea defined as the presence of 15 or fewer inflammatory papules or pustules were eligible for the trial. Severe cases were excluded. Other exclusion criteria were; receiving topical or oral antibiotics during the 4 weeks prior to the study, known or suspicion of pregnancy and presence of a history of hypersensitivity to azelaic acid 15% gel. Age, sex, duration of acne rosacea, the presence or absence of rhinophyma or ocular findings were also recorded.

Study Design: This study was designed as an open clinical test and was approved by Local Ethical Committee of Gazi University, Faculty of Medicine, Ankara, Turkey. All patients were instructed to apply azelaic acid 15% gel to entire affected area twice daily for 4 weeks. Besides this, sunscreen use (SPF>30) was advised. Patients were also instructed to wash their face before treatment application, to apply agent very sparingly and spread it thoroughly by smooth massage. Other acne/acne rosacea medications such as systemic or topical antibiotics and treatments with other antimicrobial products such as those contained in shampoos and soaps were prohibited. Also, all patients were recommended avoiding sun exposure and heat. Patients were also informed not to take excessive amounts of alcohol and spicy food. The patients were evaluated at baseline and later, every two weeks. At the end of 4 weeks, the effectiveness and tolerability of the treatment was evaluated. Full-face photographs were taken at baseline and at the end of the study (4th week).

Primary efficacy endpoints in the study included changes from baseline to the last visit (4th week) in the severity of lesions (on a 4-point scale [0= 'none', 1= 'mild', 2= 'moderate', 3= 'severe']). At baseline, a dermatologist investigator assessed the degree of the erythema and telangiectasia, the inflammatory lesion and the overall rosacea severity on this 4-point scale.

In addition to this assessment, patients rated the overall improvement at the end of the study as "0" (not satisfied) to "4" (very satisfied). Investigators' evaluation was rated as "0" (no change), "1" (slight improvement), "2" (moderate improvement), "3" (marked improvement), "4" (clear).

Compliance was assessed by a treatment chart at each visit and adverse effects such as erythema, stinging, burning and dryness were recorded.

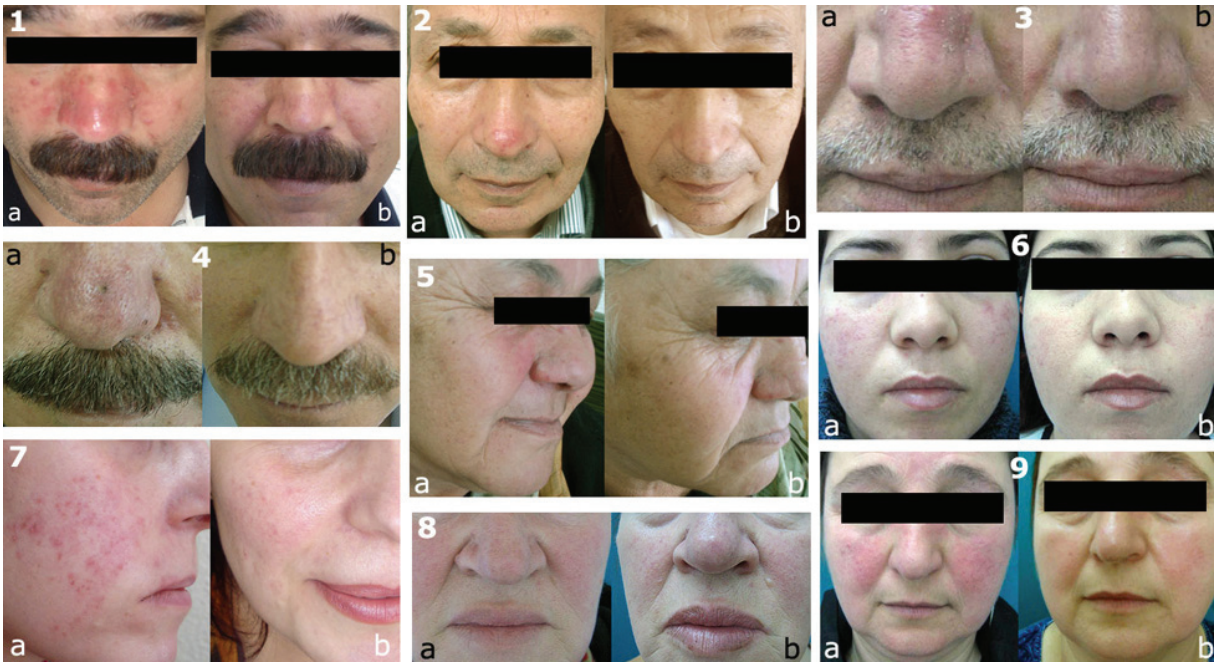
Statistical Programme for Social Sciences 11.0 (SPSS 11.0) was used for statistical analysis. Statistical analyses to evaluate differences in the scores of papulopustules, erythema and telangiectasia were carried using *Wilcoxon* signed rank test and paired t test where needed. A probability less than 0.05 was considered as significant.

Results

All 31 patients completed the study. Patients were 29-65 years of age (mean, 49.2±11.1) with a disease duration of 1-25 years (mean, 6±6.6). Nine of them were male and twenty two of them were female. Eight of 31 (25.8%) had rhinophyma and thirteen of 31 (42%) had ocular findings.

The investigator assessment of rosacea revealed that azelaic acid 15% gel resulted in a statistically significant decrease in facial erythema ($p<0.05$) and statistically significant improvement in the global rosacea severity assessment ($p<0.05$) while no statistically significant change was observed with regard to changes in inflammatory lesions and telangiectasia ($p>0.05$) (**Table 1**).

Over the course of the study erythema was



Figures 1-9. a) Before treatment; **b)** At the end of four weeks of treatment. At the end of 4 weeks, investigator's improvement evaluation revealed "clear" (**Figures 1, 2, 3 and 4**), "marked improvement" (**Figures 5 and 6**), "moderate improvement"(**Figures 7, 8 and 9**).

statistically improved from 2.3±0.8 to 1.6± 0.6 (p<0.05), therefore azelaic acid 15% gel achieved 69.5% reduction in erythema scores in 21 (68%) of the patients. Inflammatory lesions improved in 18 (58%) of the patients, but the difference was not statistically significant (p>0.05). Photographic results of some of our patients are presented in **Figures 1** to **9**.

Most of the patients (58%) rated the outcome of the treatment as "moderately" to "very satisfactory". The effectiveness of azelaic acid 15% gel was rated as "very satisfied" in 9.6% (n=3), "satisfied" in 16.1% (n=5), "moderately satisfied" in 32.2% (n=10), fairly satisfied" in 32.2% (n=10) and not satisfied in 9.6% (n=3) of the patients (**Figure 10**).

At the end of the study, with regard to investigators' evaluation scores, 29% (n=9) of patients showed marked improvement or clearance, 25.8% (n=8) showed moderate improvement, 32.2% (n=10) showed slight improvement and 12.9% (n=4) failed to response to the therapy (**Figure 11**).

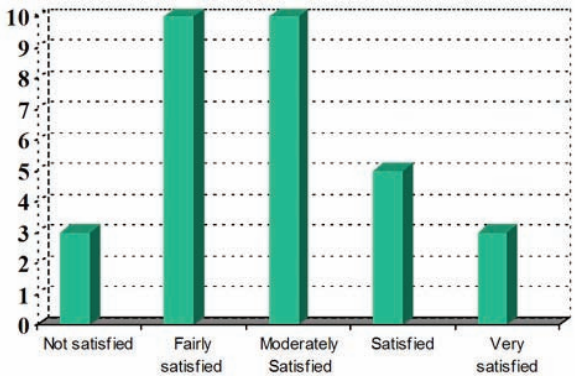
Side effects including stinging and burning sensation was observed in 11 (35.4%) of 31 patients. None of the patients discontinued due to the side effects.

Discussion

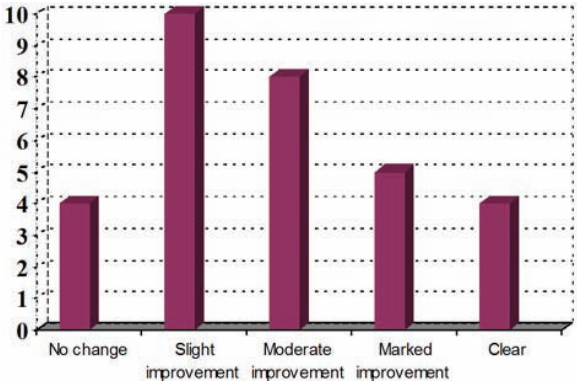
This study represented the photographic evaluation of the efficacy and safety of azelaic acid 15% gel in 31 patients with acne rosacea during a four weeks period. In our study, the severity of erythema dramatically

Table 1. Change in Investigator's Assessment of Acne Rosacea Severity Over the Treatment Period. Primary Efficacy Endpoints in the Study Included Changes From Baseline to the Last Visit (4th week) in the Severity of Lesions (on a 4-point scale [0= 'none', 1= 'mild', 2= 'moderate', 3= 'severe']).

	Baseline	Fourth weeks of therapy	p value
Erythema score	2.3±0.8	1.6±0.6	<0.05
Telangiectasia score	1.8±0.3	1.7±0.9	>0.05
Inflammatory lesion score	1.9±0.6	1.8±0.6	>0.05
Overall rosacea severity score	2.1±0.6	1.9±0.9	<0.05



Figures 10. Patients' evaluation at the end of four weeks



Figures 11. Investigator's improvement evaluation at the end of four weeks

improved over four weeks of therapy in 68% of the patients. Only after four weeks, azelaic acid 15% gel was able to provide 69.5% reduction of overall erythema. Therefore, our result may indicate that erythema is the first component of acne rosacea that improves during treatment with azelaic acid 15% gel. Improvement of erythema in our study was in consistent with other studies [**7, 8**]. *Thiboutot* et al. [**8**] compared the effectiveness and safety of twice-daily treatment with azelaic acid 15% gel with its vehicle in a total of 664 patients with moderate papulopustular acne rosacea in a vehicle-controlled study. At the end of 12 weeks, azelaic acid gel was well tolerated and achieved significantly better therapeutic rates in improving the symptoms and erythema as compared to its vehicle. A significantly higher proportion of patients (44% and 46%) treated with azelaic acid gel showed improvement in overall erythema than those treated with vehicle (29% and 28%, respectively) at the end of therapy [**8**]. In another double blind randomized clinical trial, the efficacy and safety of metronidazole 0.75% gel and azelaic acid 15% gel was compared [**7**]. A total of 251 patients with papulopustular rosacea were enrolled. After 15 weeks of therapy, 56% of the patients in the azelaic acid 15% gel group experienced improvement in erythema compared with 42% of the metronidazole group.

Elewski et al. [**7**] found that azelaic acid 15% gel twice daily for 15 weeks provided a 72.7% reduction in the mean inflammatory lesion count. In the study of *Thiboutot* et al. [8], the mean reductions of inflammatory lesions in the azelaic acid 15% gel treated patients were 58% and 51%, versus 40% and 39% in control patients at the end of 12 weeks of therapy. In 18 (58%) of the patients, improvement in the inflammatory lesions were observed in our study, but this effect was not reflected to statistical analysis. Therefore we could not demonstrate the effectiveness of azelaic acid in treating inflammatory lesions. One possible explanation of our results may have been the duration of the treatment since four weeks of treatment is short to anticipate an anti-inflammatory effect.

In our study, a five point scale was used to evaluate the patients' and investigators' assessment of the treatment. With regard to the investigator's rating, 54.8% of the patients showed "clearance" to moderately" improvement in our study, while 58% of the patients rated their treatment as "moderately" or "very" satisfactory. In previous studies with azelaic acid-treated acne rosacea patients, investigators found complete remission or marked improvement in 46% [**8**], 48% [**7**] or 51% [**8**] of the patients while 58% [**8**], 61% [**8**] or 78% [**7**] of the patients rated their overall improvement as "good" for "excellent".

The exact mechanism of action in the treatment of acne rosacea is not yet known. The antimicrobial, antikeratinization, and anti-inflammatory effects have been implicated. The antimicrobial action may be related to inhibition of microbial cellular protein synthesis. Azelaic acid is bactericidal against *Propionibacterium acnes, Staphylococcus epidermidis* and possesses bacteriostatic properties against many other aerobic microorganisms [**2, 3, 9**]. Effects of azelaic acid on neutrophil function have been studied by *Akamatsu* et al. [**13**] in 1991, and its ability to inhibit of the production of reactive oxygen species have been shown which

may contribute the anti-inflammatory effects of azelaic acid. It has been reported that azelaic acid treatment achieved a reduction in the thickness of the stratum corneum, a reduction in the number and size of keratohyalin granules, and a reduction in the amount and distribution of filaggrin in epidermal layers [**3, 14**]. Acne rosacea is a chronic inflammatory disease therefore, the beneficial effects of azelaic acid in acne rosacea have been thought to be related to the anti-inflammatory activity of the drug [**9**]. Treatment with azelaic acid had never produced any improvement in telangiectasia in any study as well as in ours [**5, 6, 7, 9**].

As shown by *Jappe* et al. [**4**] acne rosacea patients possess a heightened sensitivity to topical formulations and cosmetics that cause difficulties in treatment of the disease. Azelaic acid 15% gel was safe and well tolerated in our study. One third of the patients described side effects including stinging and burning sensation while none of these patients had discontinued the study due to these side effects. In consistent with our study, up to 40% of patients experienced burning, stinging, or itching with azelaic acid application in other studies. These side effects are considered as mild and transient in nature. Thus azelaic acid has a high local tolerability [**6, 7, 15**].

In conclusion, azelaic acid 15% gel is an effective and safe treatment for mild to moderate acne rosacea when used twice daily in combination with sunscreens. Our results show its beneficial effect in controlling erythema of acne rosacea and favor its use in cases that erythematous components of the disease predominate.

References

1. van Zuuren EJ, Gupta AK, Gover MD, Graber M, Hollis S. Systematic review of rosacea treatments. J Am Acad Dermatol 2007; 56: 107-115. PMID: 17190628
2. Gupta AK, Gover MD. Azelaic acid (15% gel) in the treatment of acne rosacea. Int J Dermatol 2007; 46: 533-538. PMID: 17472690
3. Liu RH, Smith MK, Basta SA, Farmer ER. Azelaic acid in the treatment of papulopustular rosacea: a systematic review of randomized controlled trials. Arch Dermatol 2006; 142: 1047-1052. PMID: 16924055
4. Jappe U, Schnuch A, Uter W. Rosacea and contact allergy to cosmetics and topical medicaments—retrospective analysis of multicentre surveillance data 1995-2002. Contact Dermatitis 2005; 52: 96-101. PMID: 15725288
5. Maddin S. A comparison of topical azelaic acid 20% cream and topical metronidazole 0.75% cream in the treatment of patients with papulopustular rosacea. J Am Acad Dermatol 1999; 40: 961-965. PMID: 10365928
6. Bjerke R, Fyrand O, Graupe K. Double-blind comparison of azelaic acid 20% cream and its vehicle in treatment of papulo-pustular rosacea. Acta Derm Venereol 1999; 79: 456-459. PMID: 10598760
7. Elewski BE, Fleischer AB Jr, Pariser DM. A comparison of 15% azelaic acid gel and 0.75% metronidazole gel in the topical treatment of papulopustular rosacea: results of a randomized trial. Arch Dermatol 2003; 139: 1444-1450. PMID: 14623704
8. Thiboutot D, Thieroff-Ekerdt R, Graupe K. Efficacy and safety of azelaic acid (15%) gel as a new treatment for papulopustular rosacea: results from two vehicle-controlled, randomized phase III studies. J Am Acad Dermatol 2003; 48: 836-845. PMID: 12789172
9. Nazzaro-Porro M, Passi S, Picardo M, Breathnach A, Clayton R, Zina G. Beneficial effect of 15% azelaic acid cream on acne vulgaris. Br J Dermatol 1983; 109: 45-48. PMID: 6222755
10. Draelos ZD, Graupe K. Development of a new aqueous gel formulation of azelaic acid 15% as topical therapy for moderate papulopustular rosacea.64th Annu Meet Soc Invest Dermatol (April 30-May 4, Miami Beach) 2003, Abst 0397.
11. NDA Approvals for Calender Year 2002. http://www.fda.gov/cder/rdmt/ndaaps02cy.htm. 10-14-2003.
12. Draeolos ZD. What's in a formulation? Cosmetic Dermatology 2003; 16: 56-58.
13. Akamatsu H, Komura J, Asada Y, Miyachi Y, Niwa Y. Inhibitory effect of azelaic acid on neutrophil functions: a possible cause for its efficacy in treating pathogenetically unrelated diseases. Arch Dermatol Res 1991; 283: 162-166. PMID: 1867478
14. Fitton A, Goa KL. Azelaic acid: a review of its pharmacological properties and therapeutic efficacy in acne and hyperpigmentary skin disorders. Drugs 1991; 41: 780-798. PMID: 1712707
15. Draelos ZD. Noxious sensory perceptions in patients with mild to moderate rosacea treated with azelaic acid 15% gel. Cutis 2004; 74: 257-260. PMID: 15551720