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EXPERIENCE OF AZELAIC ACID USE IN ACNE TREATMENT

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ABSTRACT

Acne treatment is one of the important problems in modern dermatology. The goal of the study was to evaluate clinical efficacy and safety of the drug «Azelik» (15% azelaic acid gel) in the treatment of patients with papulopustular acne mild to moderate in severity. **Material and Methods:** an open comparative 8-week study, which enrolled 75 patients. In order to assess the safety and efficacy of the therapy, complete blood count, blood chemistry panel, and urinalyses were performed, along with evaluation of dermatological status, measurement of pH value, levels of skin hydration and sebum production, and assessment of Dermatology Life Quality Index (DLQI) in the study participants. **Results:** 82% of the patients who were receiving treatment with Azelik gel showed clinical recovery or significant clinical improvement. **Conclusions:** The results of the study indicate the high level of safety and tolerability of the Azelik gel. Clinical results obtained during the study have proven the therapeutic efficacy of the Azelik gel in the treatment of papulopustular acne mild to moderate in severity.

KEYWORDS: papules, pustular acne, topical therapy, azelaic acid, «Azelik» gel.

INTRODUCTION

Acne vulgaris (or simply acne) is one of the most common dermatoses affecting 80%-90% of adolescents. As acne typically affects open areas of the skin, this disorder, being apermanent stress factor, can lead to aesthetic discomfort in patients, abridging them in many fields of life activities.[1]

The following factors are known to be implicated in complex etiology of acne: increased oil-sebum secretion, disbalance of lipid content in the sebaceous gland secretion, hyperkeratosis follicularis, obstruction of sebaceous gland duct, Propionibacterium acnes colonization, and initiation of inflammatory lesions within and around hair follicles.[2]

Acne treatment is one of the problems of current importance in modern dermatology. Selection of treatment strategy depends on the severity of the disease. Therapy of acne that is mild or moderate in severity is mainly based on use of topical medications including antimicrobial drugs (such as antibiotics and benzoyl peroxide) and retinoids. Treatment of severe acne usually includes combination of topical and systemic drugs (isotretinoin, antibiotics, and hormones).[3, 4] There are, however, several disadvantages of existing methods of acne treatment. In order to achieve clinical effect of antibiotics, prolonged (up to several months long) courses of therapy might be needed which can result in acquisition of antibiotic resistance in the microflora. Treatment with topical and systemic retinoids can lead to a number of side effects (such as skin irritation, skin dryness, and photosensitivity).

Medical products containing azelaic acid have proven to be well tolerable and highly effective in acne treatment.[5] Azelaic acid is a saturated C9-dicarboxylic acid of natural origin (it is found in gramineous plants, meat; can be synthetized in small amounts in the human body). Topical azelaic acid gel «Azelik®» (15% azelaic acid) is an over-the-counter medication widely used to treat acne and rosacea. Properties of azelaic acid allow it to provide the following therapeutic effects, affecting the key steps of acne development.[6, 7]

- Anti-inflammatory activity – azelaic acid inhibits metabolic processes in neutrophils and diminishes production of free oxygen radicals by these cells; as well as suppresses the release of inflammatory cytokines;
- Azelaic acid eliminates hyperkeratosis near the openings of sebaceous glands;
- Azelaic acid decreases excessive thickness of the epidermis, normalizing the differentiation of epidermal cells;
- Azelaic acid shows bacteriostatic action against Propionibacterium acnes and Staphylococcus epidermidis. Long-term treatment with azelaic acid has been shown to be effective without acquisition of resistance to this medication in the indicated bacteria species;

– Azelaic acid has been recognized to have anti-tyrosinase activity: it inhibits tyrosinase, which is a key enzyme in melanogenesis, and inhibits melanocyte activity, suggesting it may be a suitable treatment option for post-inflammatory hyperpigmentation.

Furthermore, previous years' studies have presented evidence of antimycotic properties of 1% azelaic acid. Azelaic acid has been shown to inhibit the growth of such fungi as Pityrosporum ovale and Candida albicans, as well as the growth of antibiotic-resistant strains of Staphylococcus aureus *in vitro*. Considering the fact that azelaic acid is a non-toxic medication with skin affinity and without mutagenic activity, it is not contraindicated for topical use during pregnancy and breastfeeding. Squalane, a component of the Azelik gel, restores skin barrier properties and improves tolerability of the medication. This high quality emollient agent does not exert a comedogenic effect. Squalane droplets fill spaces between the flakes of the stratum corneum of the epidermis, which leads to decrease of skin tightness, and ensures softening and deep skin moistening.[8, 9]

Thus, azelaic acid («Azelik») might be an effective option for treatment of Acne vulgaris.
The goal of the study was to evaluate clinical efficacy and safety of the drug «Azelik» (15% azelaic acid gel) in the treatment of patients with papulopustular acne mild to moderate in severity.

MATERIALS AND METHODS

The study was designed as an open comparative 8-week study, which enrolled 75 patients with papulopustular acne mild to moderate in severity. The participants were randomly distributed in two groups: group I (N=50) and group II (N=25). There were no significant differences in disease severity, gender and age of the patients between the study groups.

The patients in the group I were assigned to receive the Azelik gel as a basic topical medication twice a day. The patients in the group II were assigned to receive combination of 4% erythromycin alcoholic solution and 1, 2% zinc acetate dihydrate (Zineryt) twice a day. The study was performed at the Department of Skin and Venereal Diseases of the S.M. Kirov Military Medical Academy.

Protocol of examination of the study participants prior to the beginning of treatment included the following diagnostic procedures.

– Assessment of inclusion/exclusion criteria for each prospective participant of the study;

- Signing of informed consent;
- Obtaining a medical history (duration of the main disease, past medical history, concomitant diseases, previous therapy, history of drug allergies);
- Performing a complete blood test, an urinalysis, blood chemistry panel (levels of total protein, total bilirubin, ALT, AST, gamma glutamyl transpeptidase, alkaline phosphatase, blood glucose, urea, creatinine);
- Evaluation of dermatologic status;
- Measurements of pH value, levels of skin hydration and sebum production at 5 facial skin sites (using the instrument SKIN-O-MAT, Cosmomed, Germany);
- Photographing;
- Evaluation of quality of life of the patients using the Dermatology Life Quality Index (DLQI).

  In order to evaluate safety and efficacy of treatment, all the laboratory investigations described above, along with other procedures (evaluation of dermatologic status; measurements of the skin pH values and levels of sebum production and skin hydration; evaluation of quality of life of the study participants) were repeated in 4 and 8 weeks after the beginning of treatment. Efficacy evaluation was performed by counting inflammatory and non-inflammatory elements on one-half of the patient's face and the results were described as follows:

- Clinical recovery – complete disappearance of primary skin lesions;
- Significant improvement – healing of at least 70% of the skin lesions, as compared to the baseline data;
- Improvement –at least 25% decrease in the severity of pathological process compared to the baseline data;

Lack of effect – less than 25% decrease in the severity of pathological process compared to the baseline data Worsening – worsening of skin lesions as compared to the baseline data.

RESULTS

All 75 patients completed the therapy course. Principal study results are presented in the Tables 1-4.

Several patients pointed to development of skin dryness, erythema and burning sensation after application of the study medication (Table 1). No adverse drug reactions that led to discontinuation of the treatment were observed throughout the study. Analysis of the

laboratory results (blood tests, urinalyses, blood chemistry panel) did not reveal any deviations of indices from the normal reference ranges in both study groups.

Table 1: Characteristics of the study groups and data relating to side effects and adverse reactions

	Total	Absolute number (proportion, %)		Average age	Side effects and adverse reactions Absolute number (proportion, %)			
		female	male		Skin dryness	Erythema	Burning sensation	Other
Group I	50	24 (48%)	26 (52%)	23.2±6.5	2 (4%)	4 (8%)	6 (12%)	No
Group II	25	11 (44%)	14 (56%)	21.8±7.6	7 (28%)	2 (8%)	5 (20%)	No
Total	75	35 (46.7%)	40 (53.3%)	22.7±6.9	9 (12%)	6 (8%)	11 (14.7%)	No

All patients in both study groups showed similar improvement of skin lesions by the end of the fourth week of therapy (Table 2). Clinical recovery was achieved in 10/50 (20%) of the patients in the group I (Azelik treatment), and in 5/25 (20%) of the patients in the group II (Zineryt treatment) ($p>0.05$); significant improvement was observed in 13/50 (26.0%) and in 6/25 (24.0%) of the patients, respectively ($p>0.05$); improvement - in 19/50 (38.0%) and in 10/25 (40.0%) of the patients, respectively ($p>0.05$). Lack of improvement was observed in 8/50 (16.0%) of the patients of the group I and in 4/25 (16.0%) of the patients of the group II ($p>0.05$); there were no registered cases of worsening in either study group. Thus, no statistically significant differences were observed between the study groups after 4 weeks of treatment.

Table 2: Results of acne treatment

Result of treatment	Study groups			
	Group I (Azelik treatment), absolute number (proportion)		Group II (Zineryt treatment), absolute number (proportion)	
	4 weeks	8 weeks	4 weeks	8 weeks
Clinical recovery	10 (20.0%)	**20* (40.0%)**	6 (24.0%)	**4* (16.0%)**
Significant improvement	13 (26.0%)	21 (42.0%)	6 (24.0%)	5 (20.0%)
Improvement	19 (38.0%)	4 (8.0%)	9 (36.0%)	6 (24.0%)
Lack of effect	8 (16.0%)	**5* (10.0%)**	4 (16.0%)	**8* (32.0%)**
Worsening	0 (0%)	0 (0%)	0 (0%)	2 (8,0%)
Total	50 (100%)		25 (100%)	

Note: * statistically significant differences between the group I and the group II.

Significant changes in treatment results were observed in both groups after 8 weeks of treatment. Clinical recovery had been achieved in 20/50 (40.0%) of the patients in the group receiving Azelik (I), and in 4/25 (16%) of the patients in the group receiving Zineryt (II) ($p<0,05$); significant improvement - in 21/50 (42.0%) and in 5/25 (20.0%) of the patients, respectively ($p>0.05$); improvement - in 4/50 (8.0%) and in 5/25 (20.0%) of the patients, respectively ($p>0.05$); lack of improvement - in 5/50 (10.0%) and in 9/25 (36.0%) of the patients, respectively, ($p<0,05$). Worsening of skin lesions was not observed in the group I, whereas it was diagnosed in 2 patients (2/25; 8.0%) in the group II ($p>0.05$).

Total number of acne patients who achieved clinical recovery or significant improvement in the first group comprised 42/50(82.0%), which was higher than the corresponding number in the second group - 9/25(36.0%). ($p<0.05$).

Significant decrease in skin pH values was observed in the patients in the first group (Azelik treatment) after 8 weeks of treatment. In this group pH value decreased from 6.1 (range 5.0-6.7) to 4.9 (4.1-6.2) ($p<0.05$), whereas in the second group only slight decrease in pH values was revealed – from 6.0 (range 4.9 – 6.8) to 5.8 (4.7 - 6.9) which was not statistically significant ($p>0.05$) (Table 3). At that, after 8 weeks of treatment statistically significant differences were found in skin pH levels between the study groups:4.9 (range 4.1 – 6.2) in the first group, and 5.8 (range 4.7 – 6.9) in the second group ($p<0.05$).

Table 3 – Results of pH-metry, sebumetry and corneometry in the study groups

	Number of the examined patients	pH-metry, X ($x_{0.25}$- $x_{0.75}$)		Sebumetry, µg/cm^2, X ($x_{0.25}$- $x_{0.75}$)		Corneometry, arbitrary units, X ($x_{0.25}$- $x_{0.75}$)	
		Prior to treatment	After 8 weeks of treatment	Prior to treatment	After 8 weeks of treatment	Prior to treatment	After 8 weeks of treatment
Group I (Azelik treatment)	50	**6.1§ (5.0-6.7)**	**4.9*§ (4.1-6.2)**	162.3 (112.0-216.4)	**124.3* (84.2-166.7)**	**38.6§ (24.7-53.2)**	**61.5*§ (47.4-71.3)**
Group II (Zineryt treatment)	25	6.0 (4.9-6.8)	5.8 (4.7-6.9)	160.6 (110.2-217.1)	**174.0* (119.2-42.8)**	**37.9§ (23.1-54.9)**	**24.2*§ (10.1-21.0)**

Note: X – median, $x_{0.25}$ – lower quartile, $x_{0.75}$ – upper quartile, * statistically significant differences between the group I and the group II; § – statistically significant differences in the study group prior to treatment and after 8 weeks of treatment.

Sebum production tended to decrease in the patients receiving treatment with the Azelik gel. In the first group of patients this index decreased from 162.3 (range 112.0-216.4) µg/cm^2 to

до 144.3 (84.2-166.7) µg/cm^2 (p=0.11) after 8 weeks of therapy, while in the second group it increased from 160.6 (range 110.2-217.1) µg/cm^2 to 174.0 (range 119.2-242.8) µg/cm^2 (p>0.05).

Corneometry measurements showed increase of skin hydration in the first group (Azelik treatment) from 38.6 (24.7-53.2) arbitrary units to values within the normal range – 61.5 (47.4-71.3) arbitrary units (p<0.05) after 8 weeks of treatment; while in the second group these measurements, on the contrary, demonstrated decrease of skin hydration index from 37.9 (23.1-54.9) arbitrary units to 14.2 (10.1-21.0) arbitrary units (p<0,05). Differences between corneometry results between the study groups after 8 weeks of treatment were found to be statistically significant: 61.5 (47.4-71.3) arbitrary units and 14.2 (10.1-21.0) arbitrary units , respectively (p<0.05).

Assessment of quality of life using Dermatology Life Quality Index (DLQI) (Table 4) at the beginning of the study revealed extremely large and very large effect (score: 11-30) of the disease on quality of life in 14/50 (28%) of the patients in the first group, and in 8/25 (32.0%) of the patients in the second study group. Moderate effect (score: 6 – 10) was found in 31/50 (62.0%) and in 14/50 (56.0%) in the first and the second groups, respectively; while small effect or lack of any effect (score: 0 – 5) of the disease on the patient's quality of life was found in 5/50 (10.0%) and in 3/24 (12.0%) patients, respectively. In the group of patients who were receiving treatment with the Azelik gel, proportion of patients with extremely large or very large effect of the disease on quality of life tended to decrease throughout the study: from 14/50 (28,0%) of the patients to 6/50 (12.0%) of the patients (p=0.09). Proportion of patients with moderate effect of the disease on quality of life in the first group decreased from 31/50 (62.0%) at the beginning of the study to 13/50 (26.0%) at the end of the study (p<0.05). Proportion of patients with small or no effect of the disease on quality of life showed more than 6-fold increase in the first group: from 5/50 (10.0%) to 31/50 (62.0%) (p<0.05). Changes of DLQI over time in patients in the second group were similar to those observed in the first group: proportion of patients with extremely large and very large effect did not change significantly (8/25; 32.0%) and (10/25; 40,0%), respectively (p>0.05). Proportion of patients of the second group with moderate effect decreased from 14/25 (56.0%) to 6/25 (24.0%) (p<0,05); and 3-fold increase of proportion of patients with small or no effect of the disease on quality of life was observed in this group: from 3/25 (12.0%) to 8/25 (36.0%) (p<0.05). Analysis of DLQI scores obtained in both groups after 8 weeks of treatment

showed that the proportion of patients demonstrating extremely large and very large impact of acne on quality of life is lower in the first group (6/50; 12.0%) as compared to the patients in the second group (10/25; 40.0%) ($p<0.05$); while the proportion of patients with small or no impact of the disease on quality of life is higher in the first group (31/50; 62.0%, as compared to the patients in the second group (8/25; 36.0%) ($p<0.05$).

Table 4: Changes of DLQI in the study groups over time as a result of treatment.

DLQI scores	Study groups					
	Group I (Azelik treatment), absolute number (proportion)			Group II (Zineryt treatment), absolute number (proportion)		
	Prior to treatment	In 4 weeks	In 8 weeks	Prior to treatment	In 4 weeks	In 8 weeks
0-5 scores	**5§ (10.0%)**	19 (38.0%)	**31*§ (62.0%)**	**3§ (12.0%)**	10 (40.0%)	**8*§ (36.0%)**
6-10 scores	**31§ (62.0%)**	20 (40.0%)	**13§ (26.0%)**	**14§ (56.0%)**	7 (28.0%)	**6§ (24.0%)**
11-30 scores	14 (28.0%)	9 (18.0%)	6* (12.0%)	8 (32.0%)	8 (32.0%)	10* (40.0%)
Total	50 (100%)			25 100%)		

Note: score 0-5: there is a small or no effect of the disease on quality of life of the patient; score 11-30: there is a moderate effect of the disease on quality of life; score 11-30: there is a very large or extremely large effect of the disease on quality of life of the patient.

*statistically significant differences between the group I and the group II; § – statistically significant differences in the study group prior to treatment and after 8 weeks of treatment.

DISCUSSION

The goal of the present study was to evaluate clinical efficacy and safety of the Azelik gel in treatment of acne vulgaris. Lack of serious side effects, normal results of laboratory tests (complete blood count, blood chemistry panel) performed after the end of treatment, as well as results of subjective assessment of the medication by the study participants; provide strong evidence for high level of safety and tolerability of the Azelik gel.

According to the study design, the patients in the comparison group were receiving treatment with combination of 4% erythromycin alcoholic solution and 1,2% zinc acetate dihydrate. At the end of the treatment course, the patients in this group showed lack of changes in skin pH values and sebum production levels, along with statistically significant decrease of skin hydration. This effect was apparently due to ethanol which was a component of the lotion

used (ethanol is used as a solvent for erythromycin). Application of this medication over a long period leads to considerable skin dehydration and, therefore, decreases skin barrier properties. In the group of patients who were receiving Azelik gel, skin pH levels decreased to normal values, accompanied with increase of skin hydration levels. Restoration of skin hydration, observed by means of corneometry after the treatment with Azelik gel, is an evidence of moistening properties of its formulation owing to the presence of an emollient agent squalene. Azelik gel application decreases transepidermal water loss.

DLQI is one of the criteria used for evaluation of efficacy of treatment of any cutaneous disease. Analysis of changes of this index over time in the present study showed that topical monotherapy of acne with Azelik gel results in significant improvement of the patients' quality of life.

CONCLUSIONS

1. The results of the study suggest high level of safety and tolerability of the Azelik gel.
2. Clinical results obtained in the study have demonstrated high therapeutic efficacy of the Azelik gel in papulopustular acne treatment mild to moderate in severity.
3. The Azelik gel exerts moistening effect, and long-term treatment with the medication ensures restoration of skin hydration.
4. Acne treatment with the Azelik gel diminishes skin pH shift to the alkaline region and favors its normalization.
5. Patients receiving acne treatment with the Azelic gel show improvement in the life quality index.
6. The Azelik gel can be recommended as a drug of choice for treatment of papulopustular acne mild to moderate in severity.

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