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# Prevention and treatment of post-acne atrophic scars

© N.E. MANTUROVA[1], A.M. TALIBOVA[1,2], L.S. KRUGLOVA[2], A.G. STENKO[1,2]

[1]Institute of Plastic Surgery and Cosmetology, Moscow, Russia
[2]Central State Medical Academy of Affairs Administration of the President of the Russian Federation, Moscow, Russia

Post-acne atrophic scars most often occur in clinical practice due to the loss of the dermal matrix as a result of collagen destruction induced by inflammation, in particular due to increased expression of matrix metalloproteinases.

**Material and methods**. The study was conducted in two stages. Genetic study of the frequency distribution of *ESR1, CollA1, Col1A2, Col3A1, Col5A1, MMP1, MMP12, MMP2, MMP3, MMP7* gene polymorphism was carried out as the first stage (n = 43). At the second stage, patients with severe acne (n = 50) received systemic isotretinoin at standard dosage as the main treatment, the duration of the course was at least 6 months. After reaching IGA 0-1, patients with atrophic post-acne scars were divided into two groups. Group 1 patients (n = 24) used the fixed combination of 0.1% adapalene and 2.5% benzoyl peroxide as a topical treatment once a day for 6 months. Group 2 patients (n = 26) received no treatment.
**Results**. Comparative analysis of the polymorphism of the genes under study at stage I showed statistically significant differences in the allele distribution between the groups of patients. At stage II, there were no cases of disease recurrence in group 1. In group 2, 15.4% of patients had new inflammatory elements by the 3rd month. In 3 months, there was twice higher number of patients with clear skin in group 1; there was also 1.5-fold improvement of qualitative characteristics and relief of cicatricial deformities of moderate scars. In 6 months, there was 7-fold higher number of patients with "almost clear skin" as assessed by Scar Global Assessment (SGA) scale, while group 2 demonstrated no positive dynamics in 3 and 6 months.
**Conclusions**. The results of the study suggest that there are certain genetic predictors of formation of atrophic post-acne scars. The fixed combination demonstrates reliable prophylactic effect on formation of scars as evidenced by the absence of new secondary elements, while the proportion of patients with "almost clear skin" as assessed by SGA (barely noticeable scars) increased from 6.4% to 46.7% when using the coformulated drug and remained unchanged in the control group.

*Keywords: acne, atrophic post-acne scars, gene polymorphism, fixed adapalene/benzoyl peroxide combination.*

N.E. Manturova — Chief part-time plastic surgeon of the Ministry of Health of the Russian Federation, Head of the Department of Plastic and Reconstructive Surgery, Cosmetology, and Cell-bases Technologies of N.I. Pirogov Russian State Research Medical University, MD. Institute of Plastic Surgery and Cosmetology, Moscow, Russia. https://orcid.org/0000-0003-4281-1947
A.M. Talibova — Candidate of Medicine, Dermatovenereologist, Cosmetologist. Institute of Plastic Surgery and Cosmetology, Moscow, Russia; Central State Medical Academy of Affairs Administration of the President of the Russian Federation, Moscow, Russia
L.S. Kruglova — Doctor of Medicine, Professor, Vice-principal for Academic Affairs, Head of the Department of Dermatovenereology and Cosmetology, Federal State Institution of Additional Postgraduate Education "Central State Medical Academy" of Affairs Administration of the President of the Russian Federation. https://orcid.org/0000-0002-5044-5265
A.G. Stenko — Doctor of Medicine, Professor of the Department of Dermatovenereology and Cosmetology (Central State Medical Academy of Affairs Administration of the President of the Russian Federation, Moscow, Russia); Head of the Department of Cosmetology, Cosmetologist; Institute of Plastic Surgery and Cosmetology, Moscow, Russia. Dermatovenereologist https://orcid.org/0000-0002-6686-4253

Acne is a chronic inflammatory disease of pilo-sebaceous system of the skin characterized by formation of retentional (open and closed comedones) and inflammatory (papules, pustules, nodes) elements, which are often resolved with formation of secondary elements (post-inflammatory hyperpigmentation, scars). This dermatosis occurs almost everywhere, including 60 to 80% adolescents in Europe and America, which suggests that treatment of these patients is a socially significant problem [1]. The following factors play a leading role in the development of acne: sebaceous gland hypertrophy, follicular hyperkeratosis, hypercolonization by *Propionibacterium acnes* (possibly, certain phenotype), and inflammation, which in some cases may precede formation of retentional elements [2]. As a rule, seborrhea associated with hyperproduction of sebum and change in its qualitative composition is an underlying factor of the development of acne. Development of acne is often triggered by increased sensitivity of the receptors of sebaceous gland cells to testosterone derivatives (the so-called relative hyperandrogenism; hyperandrogenism in the form of absolute increase in the number of ovarian or adrenal androgens is less common).

The international and Russian clinical guidelines for treatment of patients with acne consider, first of all, the severity of the pathological process, localization of rash, and the presence of post-acne symptoms [3]. In this situation, special attention of specialists should be paid to improvement of patient's quality of life as a component of therapy, which is essentially the ultimate goal of therapeutic measures. The literature data and our own experience show that it is the presence of post-acne after inflammatory element resolution that is the main factor of dissatisfaction with therapy and worsening of the quality of life in this category of patients.

According to Layton A.M. et al., the incidence of scars of varying severity in patients with severe acne is

**Corresponding author:** Kruglova Larisa Sergeevna — Central State Medical Academy of Affairs Administration of the President of the Russian Federation, Moscow, Russia. kruglovals@mail.ru

95% and, according to Tan J.K. et al., they are located on the face, back, and chest in 55, 24, and 14% of cases, respectively [4,5]. In the case of severe acne, scarring as an outcome of inflammation is 3.4—6.8 times more common than in patients with milder form of acne. Further, scarring is 1.6—2.8 times more common in those who did not receive effective treatment within the first 3 years after the onset of the disease [6—8].

Post-acne symptom complex presents with the development of persistent post-inflammatory erythema, impaired pigmentation, and formation of cicatricial deformities. While the first two clinical symptoms are transient and, as a rule, are resolved spontaneously, scars require correction.

The mechanism of post-acne scarring is caused by deep inflammatory process (or mechanical injury, such as, for example, in the case of excoriated acne), when reparative and destructive changes occur in the dermal layers in response to inflammation, which may result in atrophic or hypertrophic (less often, keloid) scars, which is determined by dermal matrix reactivity [8,9]. Formation of pathological cicatricial deformities is associated with genetic predisposition (autosomal dominant or autosomal recessive inheritance), there is also an evidence of a correlation with blood group A (II). It was also noted that keloid scars are more common in dark-skinned people [9]. The predictors of post-acne scar development are as follows:

— deep inflammatory process (nodular, conglobate, and other severe clinical forms of acne);

— late or inadequate treatment of the disease, which in fact leads to deeper inflammatory process and formation of severe forms of acne;

— excoriated acne;

— mechanical removal of acne elements (deep injury when attempting unqualified removal).

Pathogenesis of scar formation reflects the equilibrium between the processes of collagen formation and temporary matrix destruction. Fibroblasts, mast cells, endothelial cells and macrophages produce special enzymes, matrix metalloproteinases involved in the restructuring and destruction processes in the dermal layers. Interferons produced by fibroblasts, T-lymphocytes, and leukocytes prevent the development of fibrosis resulting in normal healing. Impairment of one of the mechanisms of reparative processes is accompanied by pathological scarring [10]. There are several stages of scar formation: inflammation, regeneration and proliferation, epithelization, and reorganization. Inflammation (or mechanical tissue damage) is associated with production of a high amount of growth factors, which attracts neutrophils and monocytes to the lesion. Along with phagocytosis and destruction of microorganisms, the functions of neutrophils include production of inflammatory mediators, resulting in activation of keratinocytes and macrophages. Macrophages secrete growth factors that attract fibroblasts to the lesion and stimulate proliferation of keratinocytes. Healing stage begins with formation of granulation tissue characterized by high content of type I and III collagen. The number of cells is regulated by apoptosis mechanism. Formation of granulation tissue is facilitated by myofibroblasts, having the properties of both fibroblasts and smooth muscle cells, which also contain the contractile proteins actin and desmin. The role of *P. acnes*, which synthesize the collagenase enzyme, leading to destruction of collagen tissue in some cases, is considered as one of the mechanisms of the development of post-acne scars. Defective collagen fibers result in skin "slacking" and formation of atrophic scars [11,12].

According to the modern classification of post-acne scars, the following clinical forms are distinguished:

— atrophic scars involving mesodermal and hypodermal layers, 50—60% of cases:

— V-shaped (Icepick),

— M-shaped (Rolling),

— U-shaped (Boxcar);

— hypertrophic scars, 30—40% of cases of post-acne scars;

— keloids, accounting for up to 2—5%.

Atrophic scars most often occur in clinical practice due to the loss of the dermal matrix resulting from inflammation-induced collagen destruction, among other things, due to increased expression of matrix metalloproteinases [8,12,13]. The same enzymes are involved in dermal matrix remodeling. Topical retinoids can stimulate dermal fibroblasts, which results in enhanced production of procollagen [13]. This property of topical retinoids makes them potentially important for the treatment and prevention of atrophic post-acne scars.

Despite the sufficient understanding of the mechanisms of cicatricial skin changes, their correction is still a relevant problem. In particular, the question of the effectiveness of standard topical and systemic therapy of acne in terms of potential post-acne scarring is still unexplored. Both aggressive (surgical excision, laser resurfacing, medium and deep chemical peeling, sandblasting dermabrasion), and more sparing (IPL techniques, RF therapy, ultrasound therapy, EHF therapy, Bucca therapy, injections of enzymes and cytostatic drugs) methods are currently used, depending on the clinical type of scars [14—16].

It is important to take into account the fact that inappropriate or late treatment without considering the severity of the disease is one of the predictors of post-acne scars. Therefore, timely and well-chosen acne therapy is the most important factor in preventing the development of post-acne scars. The fixed combination of 0.1% adapalene and 2.5% benzoyl peroxide is the first line topical treatment for acne. Current data from the pilot study on the effectiveness of this fixed combination in terms of qualitative characteristics of post-acne atrophic scars, as well as the preventive action of the drug, are of great interest [17].

The design of the multicenter randomized blind study by Dreno V. et al. [17] using the fixed combination of 0.1% adapalene/2.5% benzoyl peroxide and gel base as a control included their separate application on two halves of the face for 6 months. Patient inclusion criteria: moderate acne, at least 10 atrophic scars, symmetrical location of lesions. The effectiveness was evaluated taking into account the number of primary elements of acne, atrophic post-acne scars, as well as the overall assessment of the severity of scars (Scar Global Assessment; SGA).

The study showed that along with high therapeutic efficacy (58% in terms of reduction of non-inflammatory elements, 72% in terms of inflammatory elements), the fixed combination of 0.1% adapalene/2.5% benzoyl peroxide has a prophylactic effect on formation of scars, as evidenced by the absence of new secondary elements (11.1 before therapy and 11.6 after therapy), while the average number of scars in the control group increased by 24.8%, from 10.9 to 13.6 ($p$= 0.036) **(Fig. 1)**. Thus, in the group of 0.1% adapalene and 2.5% benzoyl peroxide, the number of new post-acne scars after 6 months of using the drug was 5.5 times lower than in the placebo group (gel base).

At the same time, the proportion of patients with "almost clear skin" (barely noticeable scars) as assessed by SGA increased from 9.7 to 45.2% when using the combined preparation and did not change when using the gel base ($p$ =0.0032) **(Fig. 2)**.

Thus, the study showed that the use of 0.1% adapalene/2.5% benzoyl peroxide gel for 6 months reduces the risk of new atrophic post-acne scars and improves the overall condition of already formed scars. These data suggest the following possible mechanisms: arresting inflammation, which prevents formation of scars and effect (mostly of adapalene) on collagen production and dermal matrix restructuring, which can potentially improve the qualitative characteristics of scars.

It should be noted that there are only scarce data on the effectiveness of standard therapy with respect to prevention of formation and correction of post-acne scars and further studies are required, but these data suggest that it is adequate therapy in terms of timing that has the greatest potential, since it can prevent the development of scars.

## Material and methods

At the first stage of our study, we followed 43 females aged 15 to 27 years old diagnosed with acne and acne

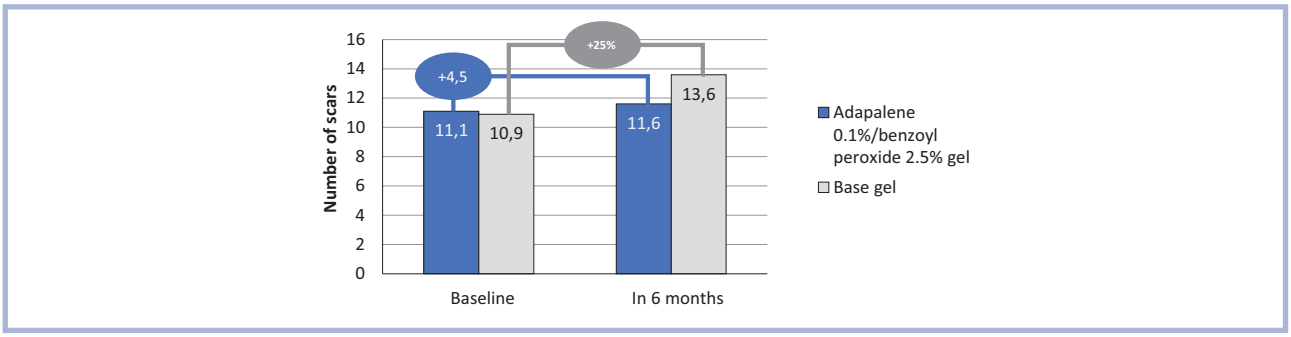


***Fig.1.*** **The comparative data on the number of post-acne scars before and after application of the 0.1% adapalene/2.5% benzoyl peroxide gel and base gel [B. Dreno et al., 2017].**

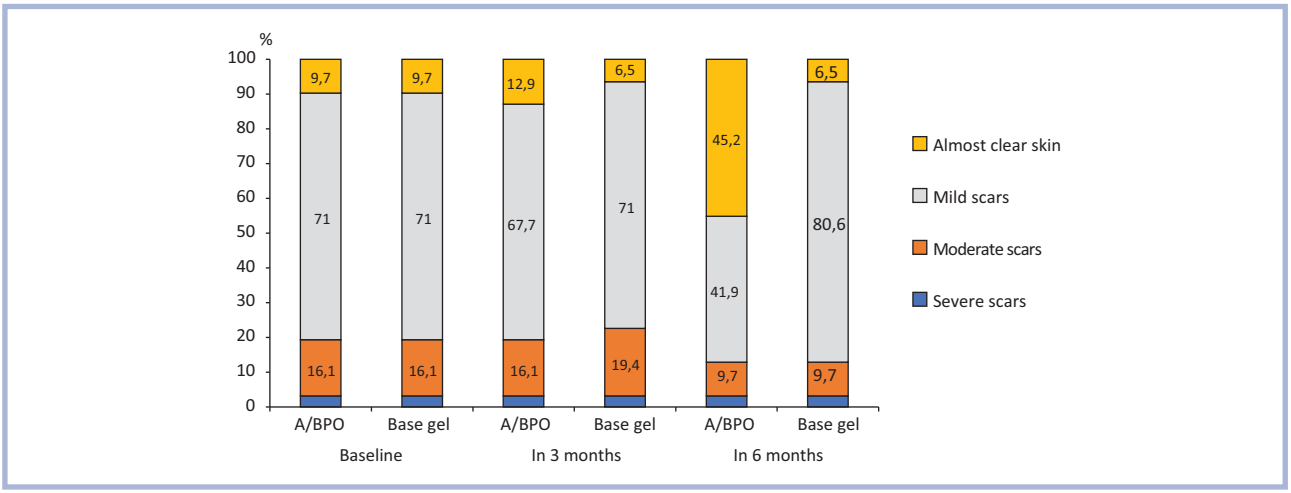


***Fig. 2.*** **The overall assessment of scars at the baseline, in 3 and 6 months: comparison of the 0.1% adapalene/2.5% benzoyl peroxide (A/BPO) gel and base gel [B. Dreno et al., 2017].**

complicated by atrophic scars. All patients were divided into two comparable groups, depending on the clinical presentation: group A included 22 patients (acne complicated by atrophic scars) and group B included 21 patients (acne). All patients underwent buccal scraping with sterile cotton swabs to collect the material for analysis followed by genetic studies of the frequency distribution of the polymorphism of *ESR1, Col1A1, Col1A2, Col3A1, MMP2, MMP3, MMP7* genes.

The results of the study were evaluated using a 3-point scale:

1 — homozygous frequent allele (normal/normal), which corresponds to the absence of increased risk of developing the condition under study (medium population risk);

2 — heterozygous (normal/mutation), which corresponds to a moderate risk of developing the condition under study;

3 — homozygous rare allele (mutation/mutation), which corresponds to a significant risk of developing the condition under study (the gene is the risk factor for the development of this condition).

At the second stage of the study, we followed 50 patients, including 28 (56%) males and 22 (44%) females with severe acne, whose average age was 15.7 ± 1.4 years. The participants received the systemic retinoid (isotretinoin) at standard dosages (initial dose 0.7—0.8 mg/kg/day followed by dose reduction to 0.4—0.5 mg/kg/day, course duration no less than 6 months) as the main treatment. After reaching IGA score of 0—1, patients with atrophic post-acne scars were divided into two groups: group 1 included 24 patients, group 2 included 26 patients. After the course of isotretinoin, group 1 patients were treated with topical fixed combination of 0,1% adapalene/2.5% benzoyl peroxide once a day for 6 months. Group 2 patients received no treatment. Clinical presentation in group 1 and 2 patients included atrophic scars, post-inflammatory pigmentation, and foci of congestive erythema. The effectiveness was evaluated taking into account the number of primary elements of acne and atrophic post-acne scars (5-point visual analogue severity scale for each element), as well as the overall assessment of the severity of scars (Scar Global Assessment; SGA).

## Results and discussion

A comparative analysis of gene polymorphisms at the first stage of the study showed a statistically significant difference in the distribution of alleles of *Col1A2, MMP3, ESR1, MMP1, MMP7* genes between the two groups of patients **(Fig. 3)**.

Group A (22 patients diagnosed with acne complicated by atrophic scars):

*Col1A2* gene — allele 3 was found in 17 (77.2%) patients, allele 2 — 3 (13.6%), allele 1 — 2 (9.1%);

*MMP3* gene — allele 3 was found in 19 (86.4%) patients, allele 2 — 2 (9.1%), allele 1 — 1 (4.5%);

*ESR1* gene — allele 3 was found in 8 (36.3%) patients, allele 2 — 12 (54.5%), allele 1 — 2 (9.1%);

*MMP1* gene — allele 3 was found in 6 (27.2%) patients, allele 2 — 14 (63.6%), allele 1 — 2 (9.1%);

*MMP7* gene — allele 3 was found in 8 (36.3%) patients, allele 2 — 13 (59.1%), allele 1 — 1 (4.5%).

Group B (21 patients diagnosed with acne):

*Col1A2* gene — allele 3 was found in 2 (9.5%) patients, allele 2 — 3 (14.2%), allele 1 — 16 (76.1 %);

*MMP3* gene — allele 3 was found in 5 (23.8%) patients, allele 2 — 7 (33.3%), allele 1 — 9 (42.8%),

*ESR1* gene — allele 3 was found in 1 (4.7%) patient, allele 2 — 2 (9.5%), allele 1 — 18 (85.7%);

*MMP1* gene — allele 3 was found in 6 (28.5%) patients, allele 2 — 5 23.8%), allele 1 — 10 (47.6%);

*MMP7* gene — allele 3 was found in 2 (9.5%) patients, allele 2 — 4 (19.1%), allele 1 — 15 (71.4%).

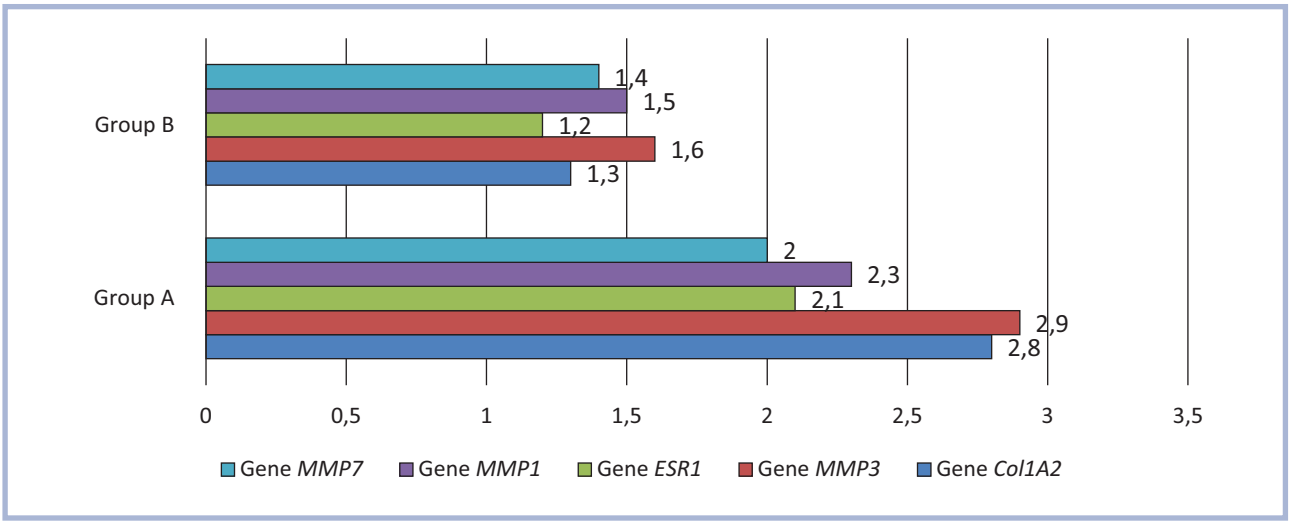


***Fig.3.*** **The average values of allele cipher of *Col1A2, MMP3, ESR1, MMP1, MMP7* genes in groups A and B.**

At the same time, in group A patients, the average value of allele cipher of *Col1A2* gene was 2.8 ± 0.1 ($p$<0.01), *MMP3* gene — 2.9 ± 0.1 ($p$<0.01), ESR1 gene — 2.1 ± 0.1 ($p$<0.01), MMP1 gene — 2.3 ± 0.1 ($p$<0.01), MMP7 gene — 2.0 ± 0.1 ($p$<0.01).

In group B patients, the average value of allele cipher of *Col1A2* gene was 1.3 ± 0.1 ($p$<0.01), *MMP3* gene — 1.6 ± 0.1 ($p$<0.01), *ESR1* gene — 1.2 ± 0.1 ($p$<0.01), MMP1 gene — 1.5 ± 0.1 ($p$<0.01), MMP7 gene — 1.4 ± 0.1 ($p$<0.01).

Accordingly, group A demonstrated high values of allele cipher of *Col1A2, MMP3* genes and medium values of allele cipher of *ESR1, MMP1, MMP7* genes; at the same time, low values for alleles of these genes were found in group *B*. Analysis of *Col1A1, Col3A1, Col5A1, MMP12, MMP2* gene polymorphism showed no statistically significant difference in distribution of alleles of these genes between the studied groups of patients. Thus, the results of the study suggest the presence of certain genetic predictors of formation of atrophic post-acne scars.

At the second stage of the study, the prophylactic and therapeutic efficacy of the fixed combination of 0.1% adapalene/2.5% benzoyl peroxide was evaluated in patients with post-acne.

There were no cases of disease recurrence when using the fixed combination in group 1 patients, which is indicative of prophylactic orientation of the drug. There was pronounced positive dynamics in terms of post-acne symptoms: post-inflammatory erythema decreased by 85%, pigmentation resolved by 70%, morphological structure, relief, and number of scars decreased by 56.1% (mostly due to mild and moderate scars) **(Fig. 4)**.

By the 3rd month, 15.4% of group 2 patients noted formation of new single inflammatory elements (papules, pustules). Significant dynamics in terms of post-inflammatory erythema and pigmentation was observed only by the 6th month, however, the severity of these symptoms decreased only by 35 and 24%, respectively. The morphological structure and relief of scars did not tend to improve, moreover, scarring continued at the sites of new lesions, and their total number increased **(Fig. 5)**.

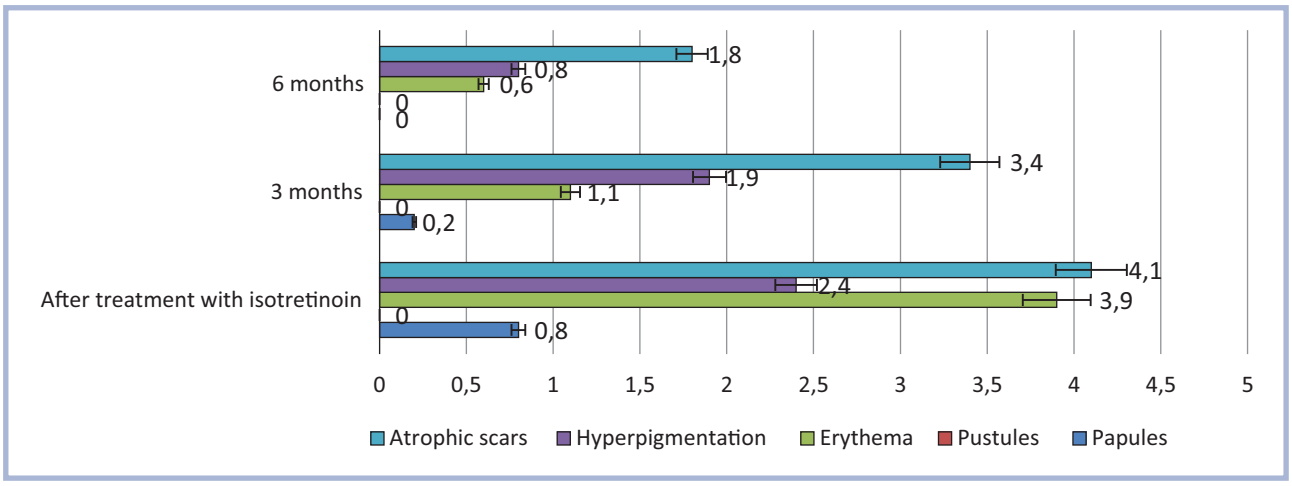


***Fig. 4.*** **General assessment of clinical symptoms of acne and post-acne at the baseline, in 3 and 6 months in group 1 patients.**

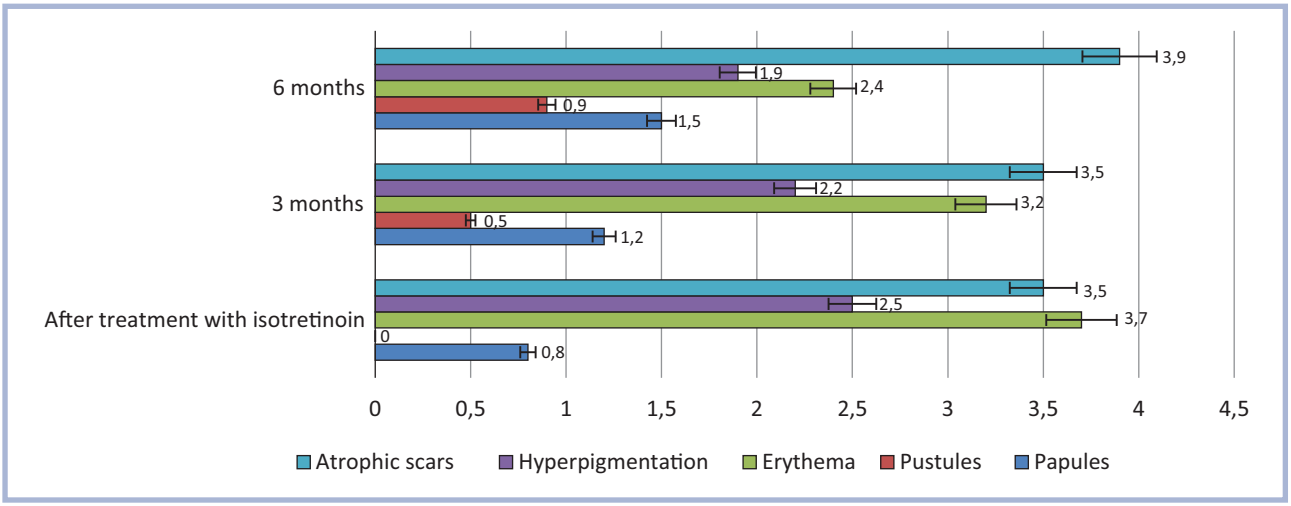


***Fig. 5.*** **General assessment of clinical symptoms of acne and post-acne at the baseline, in 3 and 6 months in group 2 patients.**

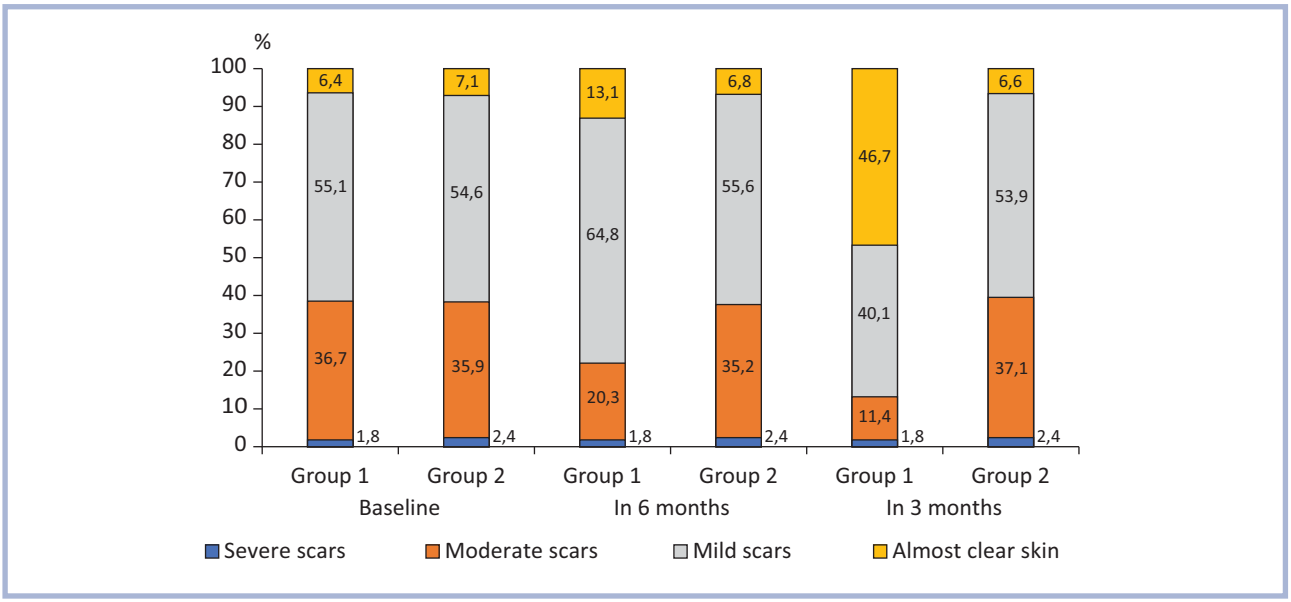


***Fig. 6.*** **General assessment of the severity of scars, taking into account the SGA score at the baseline, in 3 and 6 months in both groups of patients.**

The severity of atrophic post-acne scars was in general assessed based on the SGA scale. The number of patients with clear skin increased twofold after 3 months of application of the fixed combination of 0.1% adapalene/2.5% benzoyl peroxide, the qualitative characteristics and relief of moderate cicatricial deformities improved. In 6 months, there was 7-fold higher number of patients with "almost clear skin" in group 1, while there was no positive dynamics after 3 and 6 months in group 2. Therefore, the fixed combination of 0.1% adapalene/2.5% benzoyl peroxide has a certain prophylactic effect on the formation of atrophic scars as evidenced by the absence of new secondary elements, while the proportion of patients with "almost clear skin" (barely noticeable scars) as assessed by SGA increased from 6.4 to 46.7% when using the coformulated drug and did not change in the control group **(Fig. 6)**.

## Conclusions

The study of gene polymorphism revealed the following predictors of post-acne scar development: high values of allele cipher of *Col1A2, MMP3* genes, medium values of allele cipher of *ESR1, MMP1, MMP7* genes. The results of the study suggest the presence of certain genetic predictors of formation of atrophic post-acne scars.

The use of the fixed combination of 0.1% adapalene/2.5% benzoyl peroxide has a certain prophylactic effect on formation of post-acne scars and reduces the severity of atrophic scars, mostly mild ones.

**The authors declare no conflict of interest.**

**Authors' contributions:**

The concept and design of the study: N.E. Manturova, L.S. Kruglova, A.G. Stenko

Collecting and interpreting the data: N.E. Manturova, A.M. Talibova, L.S. Kruglova, A.G. Stenko

Statistical analysis: A.M. Talibova, L.S. Kruglova

Drafting the manuscript: A.M. Talibova, L.S. Kruglova

Revising the manuscript: N.E. Manturova, L.S. Kruglova, A.G. Stenko

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