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**ROSACEA: FEATURES OF PATHOGENESIS AND THERAPY**<sup>1</sup>Bilalova K.A., <sup>2</sup>Yusupova L.A.<sup>1</sup>*Federal State Budgetary Educational Institution of Higher Education «Kazan State Medical University» of the Ministry of Health of the Russian Federation, Kazan, e-mail: bilalowa.camilla@yandex.ru;*<sup>2</sup>*Kazan State Medical Academy – Branch Campus of the Federal State Budgetary Educational Institution of Further Professional Education «Russian Medical Academy of Continuing Professional Education» of the Ministry of Healthcare of the Russian Federation, Kazan, e-mail: yuluizadoc@hotmail.com*

The article provides information about the chronic polyethological inflammatory disease rosacea. Information about the pathogenetic mechanisms of rosacea development and adverse risk factors is disclosed. In patients with papulopustular rosacea, the efficacy of small doses of isotretinoin was studied. There were 23 patients with papulopustular rosacea under observation, who made up two subgroups. The first subgroup included patients with papulopustular rosacea who used isotretinoin 1 mg per 10 kg, patients of the second subgroup used isotretinoin 3 mg per 10 kg of weight. The course of treatment was 4.5 months. No serious adverse drug reactions were detected. The most common and easily treatable side effect was registered cheilitis (54.5%). After the treatment, it was obvious that isotretinoin 3 mg per 10 kg of weight in patients with papulopustular rosacea leads to clinical recovery and a reduction in relapses. There was a significant improvement in the quality of life of patients with papulopustular rosacea after therapy. The results of the study found that low doses of isotretinoin are a good method of treating these patients, which confirms the significant role of isotretinoin in the pathogenetic process of rosacea.

**Keywords:** rosacea, papulopustular form, clinical picture, isotretinoin, therapy, pathogenesis, risk factors

Rosacea is a common chronic skin disease of the face, the features of which include erythema, papules, pustules, telangiectasia, redness, changes in the mucous membrane and ocular manifestations [1, p. 1754]. Prevalence rates among the population vary from less than one to 22%, but these indicators are likely influenced by differences in study design, methodology, population size, geographical location, as well as cultural and social differences in the perception of the disease. In a recent systematic review, the global prevalence of rosacea was estimated at 5.5% of the adult population. In addition, it was found that men and women suffer equally, unlike previous studies, which revealed a greater prevalence in women. Rosacea is more common in people with fair skin of Celtic and Northern European origin. However, in individuals with darker phototypes, rosacea is most likely not recognized and underestimated, since erythema and telangiectasia are more difficult to recognize [2, p. 457]. Rosacea is a major medical and social health problem. The clinical picture of the disease is observed both at the age of 13-19 and in the third decade of life, mainly in persons with the first and second skin phototype [3, p. 1124]. Rosacea is a multifactorial, polyethological disease with a certain genetic predisposition. Often, unfavorable factors include dry skin, which is a favorable environment for the addition of fungal and bacterial flora. Dry skin is accompanied by hypersensitivity and increased irritability under the influence of exogenous factors [4, p. 41]. Environmental factors such as exposure to sunlight, temperature changes, alcohol consump-

tion and stimulation of inflammation by the demodex follicle may play a triggering role in the occurrence of rosacea [5]. The most frequent recurrence is caused by such adverse factors as environmental pollution, smoking, excessive insolation. Sun-damaged skin includes all the changes associated with insolation (clinical, histological and functional) [6, p. 75]. Poor sleep caused by any underlying cause can have a number of consequences, including immunological modulation and internal skin changes (such as a violation of the protection of the skin barrier and changes in the skin microbiome) that can provoke rosacea [7]. A decrease in superoxide dismutase was found in the skin in cases of inflammatory rosacea [8, p. 727]. Pathogenesis develops against the background of dysfunction of the cardiac, nervous system, innate immunity and a strong increase in the density of Demodex folliculorum (D. folliculorum), Staphylococcus epidermidis (S. epidermidis) [9, p. 26]. It can often be complicated by a secondary infection. Pyoderma is considered the most common dermatosis among all skin diseases [10, p. 19]. Bacteria associated with mites, Staphylococcus epidermidis, Chlamydia pneumonia, bacterial toxins and antimicrobial peptides as potential triggers of rosacea Demodex folliculorum, bacterial overgrowth syndrome in the small intestine and Helicobacter pylori are the most studied, studied, but also discussed in relation to their contribution to the pathogenesis of rosacea [11, p. 199]. Common forms can lead to a more severe course, up to generalized inflammation of the skin. Erythroderma can be severe with fever, severe malaise

[12, p. 6]. All this leads to a violation of the regulation of innate and adaptive immunity, aberrant neurovascular signaling, chronic inflammation and excessive growth of commensal skin organisms. With the dysfunction of innate immunity, reactive oxygen species are formed, which is a component of the mechanism of rosacea disease, since studies by a number of authors have shown increased concentrations of reactive oxygen species in this category of patients [13, p. 1]. One of the most frequent provoking causes of rosacea is the detection of ticks of the genus *D. folliculorum*. The clinical picture of rosacea creates a favorable ground for the existence of *D. folliculorum*, increasing its density of skin colonization and contributing to increased itching, burning, etc. In therapeutic tactics with variable results, several treatment methods are used, including topical drugs, lasers, light therapy and systemic drugs, including oral isotretinoin, which has been recognized as valuable for difficult-to-treat cases of rosacea [3, 14]. The response to therapy of rosacea patients plays a crucial role in determining the duration of treatment [15, p. 506].

Purpose of the study. To study the efficacy of small doses of isotretinoin in patients with papulopustular rosacea.

#### Material and methods of research

23 patients with papulopustular rosacea (PPR) of moderate severity were under observation. Rosacea was diagnosed clinically when erythema, papules, and pustules were visualized. Secondary symptoms of rosacea, such as swelling, eye symptoms, itching, burning, and others, were also detected in PPR. Rosacea was characterized by severity with the help of signs: 0 – absence of erythema, papules, pustules, peeling, 1 – insignificant, 2 – average, 3 – severe manifestation of signs. PPR consisted of two subgroups, one of which used isotretinoin 1 mg per 10 kg, the other – 3 mg per 10 kg of weight. The course of treatment was 4.5 months. The exclusion criteria were PPD during pregnancy and lactation. At the end of the course of therapy, the clinical efficacy was characterized as follows: 100% – absence of papules and pustules; reduction in the number of papules and pustules from 75 to 99% – excellent; reduction in the number of papules and pustules from 50 to 74% – good; reduction in the number of papules and pustules from 25 to 49% – controlled and without changing the clinical picture. The next stage of evaluating the effectiveness of the treatment was the tolerability of the drug, the satisfaction of the patients themselves. Side effects

(PE) were recorded as significant and not significant, as well as from mild to severe severity. Pregnancy testing was also carried out, *D. folliculorum* was determined in the laboratory. The Dermatological Quality of Life Index (DLQI) was used in the study. The use of such a scale made it possible to measure how much the problems that occurred with the skin of PPR affected their quality of life (QOL) over the past week. PPR marked the appropriate box next to the statement that is most suitable for answering the question. The interpretation of the DLQI scale included scores from 0 to 30, which were recorded before and after treatment with PPD. The mathematical calculation was recorded using the Student's t-criteria. Statistical research methods were carried out using a package for Windows.

#### Results of the research and discussions

To fulfill the tasks set in the work, 23 patients with papulopustular rosacea in the largest age group of 47 years were examined. Acne was found in 8 (34.7%) PPD, and seborrheic dermatitis was found in 2 (8.7%). Before treatment,  $7.19 \pm 5.21$  points were recorded on the DLQI scale. PPR presented many unfavorable factors that affected their quality of life. This was especially true for women to a greater extent and they had significantly lower QOL levels compared to men ( $p < 0.001$ ). At the same time, it was found that the level of QOL did not significantly affect the degree of education, whether patients were married or not, whether there was rosacea before ( $p > 0.05$ ).

Interpretation of the data of the dermatological examination of PPR was recorded in both groups before and after treatment.

According to the results of the dermatological examination, it was revealed that the overall DLQI score significantly influenced patients by gender characteristics, drug choice, the development of side effects from medications, housing conditions and the possibility of living with rosacea. In the second subgroup, there was a 39% decrease in the average overall DLQI score compared to the average DLQI scores before treatment. At the same time, a decrease of 23% was recorded in the first subgroup in comparison with the average DLQI scores before treatment. In PPR, the overall DLQI score did not significantly affect age, social aspects, as well as seasonal fluctuations and clinical changes ( $p > 0.05$ ).

Both after treatment with isotretinoin 1 mg per 10 kg and 3 mg per 10 kg of weight, there was general patient satisfaction with the results of treatment. One patient (4.3%) stopped tak-

ing isotretinoin due to side effects. However, 22 PPR fully received the planned therapy. At the same time, with long-term follow-up, rosacea passed in 68.2% of PPD, in 4 (18.2%) it was excellent, and in 1 (4.5%) it was controlled

The complete disappearance of papulopustules after therapy in the first subgroup of PPD was visualized in 27.3% of cases. Isotretinoin 3 mg per 10 kg of weight contributed to the complete disappearance of papulopustules in 40.9% of cases. Both in the first and in the second subgroup, 9.1% of PPD registered a decrease in papulopustules by 75-99%. In the first subgroup, a decrease from 50 to 74% was observed in 9.1% of patients, while no such patients were observed in the second subgroup. Controlled reduction of papulopustules by 25-49% was also recorded only in the first group and amounted to 4.5% of cases.

Side effects from the category of significant were not recorded. Ten patients (45.5%) reported the absence of any PE. Cheilitis was the most common of all PE (54.5%). The manifestations of cheilitis in PPR on the background of treatment were mild and treatable in all. At the same time, one of the PPR had more severe manifestations of cheilitis.

Dermatological examination revealed clinical manifestations of moderate severity of rosacea in the eye area in 4 (18.2%) PPD. Eye symptoms improved significantly in 3 (75.0%) of them.

The conducted observation of the comparative therapy of PPD revealed the effectiveness of the use of isotretinoin in the treatment of refractory foci of rosacea.

It was found that meteorological weather conditions (heat, wind), increased temperature of food and drink, physical activity, drinks containing alcohol, spicy seasonings, cosmetics and medicines can act as trigger factors in PPR. A significant role in pustular and ocular rosacea was assigned to *S. epidermidis*. It is known that a number of bacteria react differently even at slightly elevated temperatures. In long-term PPR sufferers, gram-negative microorganisms indicate the severity of the disease and the result of inadequate treatment with antibacterial agents.

It is known that bacterial antigens of *Bacillus oleronius* isolated from *D. folliculorum* ticks activate cells of the immune system in PPR. The most frequent localization of *D. folliculorum* in PPD was the nasal area (36.3%), the second place was the forehead area (27.2%), the third was the perioral area (22.7%). The next recorded localizations were cheeks (18.2%) and periorbital (13.6%). *D.*

*folliculorum* was observed less frequently in the chin area (9.1%) and neck (4.5%) in PPD. The density of *D. folliculorum* affects the patterns of the clinical picture, the activity of the inflammatory response in response to the presence of a tick. Already formed rosacea is a favorable environment for the existence of *D. folliculorum* and predisposes to the progression of the clinical picture of both objective and subjective symptoms.

Gastrointestinal disorders were registered in 56.5% of PPD. Rosacea may be associated with gastrointestinal tract problems through hyperproduction of vasodilation mediators. Many researchers identify *Helicobacter pylori* (*H. pylori*) bacteria in the gastrointestinal tract and associate a large number of them with the clinical activity of rosacea itself. [4, p 41]. *H. pylori* release toxins that predispose to the state of tides, predispose to the formation of vasoactive peptides. Gastrinemia may be registered in PPR with *H. Pylori* [4].

In the conducted study, 31.8% of PPD associated the manifestations of the clinical picture with disorders of the endocrine system. A decrease in lipase secretion and diabetes mellitus contributed to metabolic disorders in PPR. Disorders of the endocrine system can contribute to recurrent papulopustular rosacea.

Systematic emotional stress both in the family and at work was found in 40.9% of PPD. At the same time, only a high degree of nervousness, anxiety-depressive reactions affecting mental health cannot be only a consequence of the appearance of patients.

Vascular disorders in the facial area were associated with greater sensitivity of bradykinin receptors, which confirm the importance of provoking pathogenetic factors of rosacea formation. The localization of hot flashes in the face area is facilitated by kallikrein, produced by the salivary glands. Catecholamines are also produced by the gastric mucosa under the influence of alcohol-containing products and stress factors. Kallikrein promotes increased formation of bradykinin, which has a vasoactive effect.

Dermatological observation showed the effectiveness of isotretinoin in the treatment of PPD and a significant improvement in rosacea patterns in these patients.

Many authors have confirmed the negative effects of chemical, physical trigger factors that lead to impaired skin sensitivity, vasodilating effects. All this provokes the release of kallikrein 5 through Toll-like type 2 receptors. In this case, cathelicidin is activated, leading to clinical patterns of rosacea due to the expan-

sion of the vascular wall. The use of isotretinoin leads to a decrease in the production of the sebaceous gland, blocking secretory active cells. It is known that isotretinoin in low doses causes a shift in lipid fractions from the norm. Innate immune response via Toll-like type 2 receptor promotes lipid activation. Isotretinoin also affects the activity of antimicrobial peptides, thereby improving the condition of rosacea. This is confirmed by the present dermatological observation of PPR, where isotretinoin indirectly influenced D. folliculorum. Due to the antiangiogenic property, the use of isotretinoin somehow contributes to the normalization of the erythematous background of rosacea.

Thus, rosacea requires long-term therapy. The study showed that low doses of isotretinoin are a good alternative for PPR, which confirms the significant role of isotretinoin in the pathogenetic process in these patients.

### Conclusions

1. In patients with papulopustular rosacea who used isotretinoin 3 mg per 10 kg of weight, the complete disappearance of papulopustules after therapy (40.9%) occurred 1.5 times faster than in the subgroup treated with isotretinoin 1 mg per 10 kg (27.3%). The indicator of the quality of life index was 1.7 times lower in the subgroup of patients receiving isotretinoin 3 mg per 10 kg of weight, which confirms a significant improvement in the quality of life of patients in this subgroup.

2. The most common and easily treatable side effect was registered cheilitis (54.5%). No serious adverse drug reactions were detected.

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