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APPLICATION OF PIOGLITAZONE IN THE COMPREHENSIVE TREATMENT OF PSORIATIC PATIENTS WITH CONCOMITANT ALIMENTARY OBESITY

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Псоріаз - одне з найбільш розповсюджених хронічних рецидивуючих системних аутоімунних мультифакторних захворювань, яке характеризується залученням до патологічного процесу шкіри, суглобів та внутрішніх органів і систем організму. Незважаючи на значне поширення псоріазу та на велику кількість робіт з цієї проблеми, до сих пір немає єдиного погляду на патогенез цього дерматозу. Для об'єктивного розуміння патогенезу псоріазу необхідно враховувати недостатньо вивчену коморбідність цієї патології. Останнім часом доведений безперечний зв'язок між псоріазом і ожирінням. В літературі широко висвітлюється питання про ідентичні патогенетичні механізми запальних процесів при псоріазі і ожирінні. Враховуючи сучасні данні ролі системного запалення, що лежить в основі розвитку як псоріазу, так і ожиріння, вивчення молекулярних механізмів його розвитку та беручи до уваги роль прозапальних ядерних транскрипційних факторів патогенетично обумовленим препаратом вибору для лікування цих захворювань є тіазолідиндіони.У цьому досліджені ми визначали ефективність використання 15 мг піоглітазону 1 раз на добу протягом 6 місяців у комплексному лікуванні хворих на розповсюджений вульгарний псоріаз середнього ступеня тяжкості перебігу з супутнім аліментарним ожирінням I-II ступеня шляхом клінічного та імунологічного дослідження показників системного запалення. Аналізуючи результати проведеного дослідження було встановлено, що тривале використання піоглітазону, навіть в малих дозах, призвело до зниження показників системного запалення та сприяло до більш легкому перебігу псоріазу при повторному рецидиві захворювання.

Ключові слова: псоріаз, аліментарне ожиріння, патогенез, клініка, системне запалення, лікування.

Psoriasis is one of the most common chronic recurrent systemic autoimmune multifactorial diseases, in which the skin, joints, internal organs and systems of the body are involved in the pathological process. Despite the significant prevalence of psoriasis and a large number of studies on this problem, there is still no single view on the pathogenesis of this dermatosis. To objectively understand the pathogenesis of psoriasis, it is necessary to take into account the insufficiently studied comorbidity of this pathology. Recently, an indisputable link between psoriasis and obesity has been proven. The scientific literature widely covers the issue of identical pathogenetic mechanisms of inflammatory processes in psoriasis and obesity. Given the current data on the role of systemic inflammation underlying the development of both psoriasis and obesity, the study of molecular mechanisms of its development and taking into account the role of proinflammatory nuclear transcription factors, thiazolidinediones are the pathogenetically justified drugs of choice for treatment of these diseases. In this study, we determined the effectiveness of using 15 mg of pioglitazone once a day for 6 months in the treatment of patients with extensive psoriasis vulgaris of moderate severity and concomitant grade I-II alimentary obesity by clinical and immunological examination of systemic inflammation. Analyzing the results of the study, it was found that long-term use of pioglitazone, even in small doses, led to a decrease in systemic inflammation and contributed to a milder course of psoriasis in recurrence of the disease.

Key words: psoriasis, alimentary obesity, pathogenesis, clinical presentation, systemic inflammation, treatment.

Introduction

Psoriasis is the most common chronic, genetically determined autoimmune, polyetiological inflammatory disease with impaired epidermal proliferation, provoked by exogenous and endogenous factors, manifested on the skin by erythematous and scaly papules and plaques with the involvement of the internal organs in the patho-

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logical process. According to the results of clinical and epidemiological studies, psoriasis affects about 3-4% of the population of our planet, regardless of sex, age and ethnic group. The causes of psoriasis are immunological disorders and genetic defects. However, despite the significant prevalence of psoriasis and a large number of studies on this problem, there is still no single view on the pathogenesis of this dermatosis, which is associated with insufficiently studied comorbidity of the disease [1].

Recently, there has been a steady trend of increased comorbidity of psoriasis and obesity. Obesity develops due to disorders of metabolism and eating behavior. It is characterized by the accumulation of adipose tissue in the body. Obesity can be both an independent multifactorial disease – primary obesity (alimentary and constitutional), and a syndrome that accompanies the course of other diseases – secondary obesity (symptomatic). In the structure of morbidity, primary obesity occurs in 95% of patients, secondary – only in 5% [2]. A person is considered obese if his/her body mass index (BMI) exceeds 30 kg/m^2. According to the results of the study, alimentary obesity in patients with psoriasis leads to metabolic disorders complicating the course of dermatosis, leading to worsening of patients' DLQI, ineffectiveness of standard therapies and frequent exacerbations of psoriasis [3, 4]. Given the current role of systemic inflammation underlying the development of both psoriasis and obesity, the study of the molecular mechanisms of its development and taking into account the role of proinflammatory nuclear transcription factors (NTF), especially NFkB, activator protein-1, and the anti-inflammatory activity of other NTF receptors that are activated by PPARγ [5, 6]. Thiazolidinediones (pioglitazone) are the pathogenetically justified drug of choice for the treatment of these diseases. A large number of prospective observations have been accumulated in the scientific literature, indicating a positive effect of pioglitazone in the presence of signs of systemic inflammation. The mechanism of action of this drug is the effect on the suppression of chronic systemic delayed inflammation with low activity. The anti-inflammatory effect of PG is associated with its activating effect on PPARγ NTF. Pioglitazone binds to the PPARγ1, PPARγ2 and PPARδ receptors (double agonist PPAR$_\gamma$ – PPARδ) with high affinity, being its potent activator, which promotes the suppression of proinflammatory cytokine production in macrophages – by inhibiting the nuclear transcription factor NFkB [7].

Therefore, the prospect of further research is a more in-depth study of the effects of pioglitazone in the comprehensive treatment of patients with psoriasis and concomitant alimentary obesity.

The aim of the study is to examine the effectiveness of pioglitazone at a dose of 15 mg per day for 6 months in the comprehensive treatment of patients with extensive psoriasis vulgaris of moderate severity, progressive stage, and concomitant grade I-II alimentary obesity by clinical and immunological examination of systemic inflammation.

Materials and methods

20 examined patients were diagnosed with extensive psoriasis vulgaris of moderate severity, progressive stage, and concomitant grade I-II alimentary obesity. The study group included 14 (70%) men and 6 (30%) women aged from 35 to 65 years.

The study was approved by the decision of the Committee on Bioethics and Ethical Issues of Ukrainian Medical Stomatological Academy. All patients signed informed consent to participate in the study.

Psoriatic lesions were of extensive nature in all patients. When determining the number of recurrences of psoriasis per year, it was found that recurrence of the disease was observed once a year in 1 (5%) patient, 2 times a year in 3 (15%) patients, 3 times a year in 11 (55%) patients and 4 times a year in 5 (25%) patients. The PASI (Psoriatic Area and Severity Index) was used to assess the severity of psoriasis [8].

To assess the severity of alimentary obesity in the examined patients, we determined body mass index (BMI) [9]. Subjects with a BMI of 30-40 kg/m^2 were included in the study.

Determination of systemic inflammation was carried out at the Research Institute for Genetic and Immunological Foundations of Pathology and Pharmacogenetics of Ukrainian Medical Stomatological Academy. To assess the severity of systemic inflammation (SI) in the serum of patients, we determined the concentration of interleukin-33 (IL-33), interleukin-6 (IL-6) and high sensitive C-reactive protein (hs-CRP) by enzyme-linked immunosorbent assay on a multichannel photometer "STAT-FAX-303" (USA). For quantification of indicators, we used commercial test systems "interleukin-6-ELISA-BEST" (Russia), "CRP-ELISA-BEST" (Russia), "Human IL-33 ELISA Kit" "eBioscience™ / Affymetrix" (USA) according to the recommended methods. The obtained indicators were compared with those of the reference values recommended by the manufacturers of diagnostic test systems.

Patients received standardized conventional therapy: sedatives, detoxifiers, antihistamines, hepatoprotectors, vitamins and 1-2% salicylic ointment 2 times a day topically for 4 weeks. In order to evaluate the effectiveness of pioglitazone at a dose of 15 mg per day for 6 months in the comprehensive treatment of patients with extensive psoriasis vulgaris of moderate severity, progressive stage, and concomitant alimentary obesity, we evaluated the clinical, laboratory and anthropometric parameters before and after the treatment. Statistical processing of the obtained results was performed using the Statistica 7.0 software. The difference was considered reliable with an error probability $P<0.05$.

Results and discussion

Alimentary obesity was observed in all patients of the study group. When calculating BMI and analyzing indicators in accordance with the classification of obesity by BMI, it was found that 8 (40%) patients had grade I obesity, whereas 12 (60%) patients had grade II obesity. The average group BMI was 37.2 ± 1.7 kg / m².

Based on an objective examination of the clinical presentation, the average PASI index was calculated. It was (21.6 ± 1.5 points), which corresponds to the average severity of psoriasis.

In the study of systemic inflammation, the mean group values of hs-CRP, IL-33 and IL-6 were calculated. In the analysis of the obtained results, it was found that all patients presented with an increased hs-CRP (13.26 ± 1.5 IU / l). 19 patients presented with an increased IL-33 (73.98 ± 7.0 pg / ml), and IL-6 (12.97 ± 1.8 pg / ml), which indicates the presence of a systemic inflammatory process in all examined subjects (Table 1).

Table 1.

Indicators of systemic inflammation in patients with extensive psoriasis of moderate severity and concomitant grade I-II alimentary obesity (M ± m), n = 20

Indicator	Value	Reference value
IL-33, pg/ml	73.98±7.0	0-54.8
IL-6, pg/ml	12.97±1.8	0-10
hs-CRP, IU/l	13.26±1.5	0.068-8.2

Analyzing the results, it should be taken into account that excess fat deposition is not only an accumulation of excessive fat cells overloaded with triglycerides, but also an important element of the endocrine system, which possesses endo-, auto- and paracrine functions that cause subclinical inflammation. Obesity causes a mild chronic systemic inflammatory response, which provokes increased insulin resistance through the augmented production of inflammatory mediators by excess fat cells. Moreover, tissues remote from the adipose tissue do not demonstrate a clear inflammatory reaction, but they are exposed to elevated levels of adipokines, which are secreted by activated and hypertrophied adipocytes.

IL-33 is known to be expressed in adipose tissue by adipocytes and macrophages, and its production increases with weight gain, reflecting the close link between obesity and inflammation.

In turn, IL-33 activates mast cells, basophils, eosinophils and natural killer cells, contributing to inflammatory and autoimmune diseases. In obese patients, low-intensity chronic inflammation can be detected when plasma levels of hs-CRP and inflammatory cytokines such as interleukin-33 (IL-33) and interleukin-6 (IL-6) are elevated. The results of multicenter studies prove a threefold increase in the expression of IL-33 by subcutaneous adipose tissue in obese patients. In psoriasis, IL-33 is released during cell damage to warn the immune system and initiate the inflammatory processes by activating the NF-kB immune response [10, 11, 12].

Adipocytes and macrophages secrete IL-6 in adipose tissue. Determination of arteriovenous cytokine difference showed an increase in its serum concentration, indicating the secretion of IL-6 by adipose tissue, which produces approximately 30% of circulating IL-6 in the human body. Both leptin and IL-6 production by adipose tissue increase with weight gain [11, 12]. Circulating IL-6 is one of the most important factors determining the production of acute-phase proteins by the liver. It provides a rapid coordinated physiological response to tissue damage or infection, aimed at activating the body's defense mechanisms: the destruction of pathogenic microorganisms, removal of damaged cells and repair of damaged tissues [13]. It should be noted that hs-CRP is one of the most important proteins of the acute phase. It attaches to the membranes of damaged cells and causes their death by activating the reactions of the complement cascade. It is known that hs-CRP is a marker of the IL-6 action [14]. The production of hs-CRP in the liver is regulated by circulating IL-6. Therefore, it can be argued that this cytokine, whose concentration increases in obesity, significantly contributes to the occurrence of a chronic systemic inflammatory reaction [15].

To determine the effectiveness of the obtained treatment for patients with extensive psoriasis vulgaris, moderate severity, progressive stage, and concomitant grade I-II obesity, we studied the clinical, laboratory and anthropometric parameters before and after treatment (Tables 2, 3).

Table 2.

Dynamics of clinical and anthropometric parameters in the group of patients with extensive psoriasis vulgaris of moderate severity and grade I-II alimentary obesity, who received treatment according to the protocol (M ± m), n = 20

Indicator / Value	Before treatment	14 days after the conducted treatment	1 month after the conducted treatment	6 months after the conducted treatment
PASI, points	21.6±1.5	10.37±1.2 *	5.9±0.8 *	18.6±1.3
BMI, kg / m²	37.2±1.7	37.3±1.6	37.3±1.4	37.2±1.5

Note: statistical processing was performed by the Wilcoxon-Mann-Whitney method Hereinafter:

** - p <0.001 as compared to pre-treatment*

Table 3

Dynamics of laboratory indicators in the group of patients with extensive psoriasis vulgaris of moderate severity and grade I-II alimentary obesity, who received treatment according to the protocol (M ± m), n = 20

Indicator / Value	Before treatment	6 months after the conducted treatment
IL-33, pg/ml	73.98±7.0	47.53±6.4 *
IL-6, pg/ml	12.97±1.8	8.36±0.9 *
hs-CRP, IU/l	13.26±1.5	8.06±0.8 *

When studying the dynamics of the PASI index in patients with extensive psoriasis vulgaris of moderate severity and concomitant grade I-II alimentary obesity, it was found that for 14 days of hospital treatment the rate decreased by 52% from (21.6 ± 1.5 points) to (10.37 ± 1.2), after 1 month – by 73% from (21.6 ± 1.5 points) to (5.9 ± 0.8 points). At the same time, the reduction of the PASI 75 index was observed in 65% of patients, i.e., the obtained results indicate the effectiveness of this therapy. When the corresponding indicator was studied in 6 months, during the next recurrence of psoriasis, there was a decrease in the mean group PASI index by 3.6 points, which is 16.5% as compared to the corresponding indicator before treatment.

No statistically significant changes were observed in the BMI study throughout treatment.

After 6 months of treatment with pioglitazone 15 mg once a day, there was a statistically significant decrease in SI. The mean group value of IL-33 decreased by 26.45 pg / ml, which is 35.8%, IL-6 decreased by 4.6 pg / ml,

which is 35.5%, and hs-CRP decreased by 5.2 IU / l, which is 39.2% as compared to the corresponding indicators before treatment. Our findings are consistent with many other studies showing that thiazolidinediones reduce CRP concentration in obese patients, suppressing the production of proinflammatory cytokines in macrophages by inhibiting nuclear transcription factor NFkB and significantly reducing CRP after 6-26 weeks of treatment as compared to the initial level [16, 17].

Thus, the use of 15 mg of pioglitazone once a day for 6 months in the comprehensive treatment of patients with extensive psoriasis vulgaris of moderate severity and concomitant grade I-II alimentary obesity was effective in terms of the parameters of SI and PASI index. Further, it made it possible to achieve a more favorable course of psoriasis by reducing the PASI index during the next recurrence of the disease.

Conclusions

1. The use of 15 mg of pioglitazone once a day for 6 months in the comprehensive treatment of patients with extensive psoriasis vulgaris of moderate severity and concomitant grade I-II alimentary obesity was effective and led to a decrease in SI and PASI index in recurrence of the disease.

2. Treatment of patients with extensive psoriasis vulgaris of moderate severity and concomitant grade I-II alimentary obesity requires a personalized and comprehensive approach, taking into account the identified comorbidities.

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