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THIAZOLIDINEDIONES IN THE TREATMENT OF PSORIASIS IN PATIENTS WITH OBESITY

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Psoriasis is the most common chronic, genetically determined autoimmune polyetiologic inflammatory disease with impaired epidermal proliferation, provoked by exogenous and endogenous factors and manifested by erythematous scaly elements, papules and plaques. Despite the widespread prevalence of psoriasis and a large number of studies on this problem, there is still no single view of the pathogenesis of this dermatosis. For an objective understanding of the pathogenesis of psoriasis, it is necessary to consider the insufficiently studied comorbidity of this pathology. Recently, an undeniable link between psoriasis and obesity has been proven. Taking into account 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 determined drug of choice for the treatment of these diseases. In this study, we determined the efficacy of using 45 mg of pioglitazone once daily for six months in the complex treatment of patients with moderate vulgar psoriasis with concomitant alimentary obesity of I-II degree by clinical and immunological studies of systemic inflammation. Analyzing the study results, it was found that long-term use of 45 mg of pioglitazone was effective, led to a decrease in systemic inflammation, and contributed to a milder course of psoriasis in case of recurrent relapse of the disease.

Key words: psoriasis, alimentary obesity, systemic inflammation, treatment.

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ТІАЗОЛІДИНДІОНИ У ЛІКУВАННІ ПСОРІАЗУ У ПАЦІЄНТІВ З ОЖИРІННЯМ

Псоріаз є найбільш розповсюдженим хронічним, генетично детермінованим аутоімунним поліетіологічним запальним захворюванням з порушенням епідермальної проліферації, що провокується екзогенними і ендогенними факторами та проявляється еритематозно-лускатими елементами, папулами і бляшками. 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. 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 45 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 45 мг піоглітазону виявилось ефективним та призвело до зниження показників системного запалення і сприяло більш легкому перебігу псоріазу при повторному рецидиві захворювання.

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

The study is a fragment of the research project "Development of improved methods of diagnosis and complex treatment of chronic dermatoses and infections, which are mainly sexually transmitted, taking into account the determination of additional factors significant in the pathogenesis of these diseases", state registration No. 0119U000272.

Psoriasis is a systemic immune-associated disease of multifactorial nature with a predominance of genetic factors in the development, characterized by accelerated proliferation of epidermocytes and impaired differentiation, immune reactions in the dermis and synovial membranes, an imbalance between pro- and anti-inflammatory cytokines, chemokines, and frequent pathological changes in the musculoskeletal system.

Psoriasis affects about 3 % of the world's population [2, 8]. The highest incidence is observed in Western Europe and Scandinavia [2]. The disease is less common among representatives of black and Mongoloid races [8]. Among children, dermatosis is more common in girls than in boys. Psoriasis can occur in newborns and infants [3, 14]. Men and women are equally affected.

Immunological disorders and genetic defects play a significant role in the pathogenesis of the disease. Unfortunately, despite numerous studies of the pathogenesis of psoriatic disease, there is still no clear and unified understanding of the pathogenesis of this dermatosis. Most likely, the reason is the insufficiently studied comorbidity of this disease [1].

Recently, doctors have been increasingly inclined to believe that psoriasis and obesity are closely related. A person is considered obese if their body mass index (BMI) exceeds 30 kg/m² [4]. The bidirectional relationship is supported by scientific evidence: obesity and overweight are associated with a higher incidence of psoriasis, and people with psoriasis may be more prone to weight gain. Increased body weight (BW) in such cases is likely to be a consequence of treatment and a patient's response to systemic disease. Today, dermatologists pay more attention to BMI when evaluating the results of therapy and consider obesity as an independent risk factor for psoriasis.

Obesity can exacerbate the clinical manifestations of psoriasis or even provoke its development. The relationship between obesity and psoriasis is likely bidirectional, i.e., obese patients are more prone to developing psoriasis, and psoriasis, in turn, increases the risk of obesity. However, there are currently insufficient data to determine the initial trigger of this vicious circle (Mehta N. et al., 2010). It is known that in overweight and obese people, adipocytes secrete inflammatory cytokines that contribute to the worsening of psoriasis.

Identifying risk factors for the disease can help control it, reduce medication use, and improve its course, which is why overweight is the focus of many research studies. In addition, the impact of obesity on the severity of psoriasis is an area for current and future research. Therefore, in our opinion, thiazolidinediones are the pathogenetically determined drug of choice for treating patients with psoriasis with concomitant obesity. The mechanism of action of this drug is aimed at suppressing chronic systemic low-intensity slow inflammation [5].

The purpose of the study was to determine the feasibility of using pioglitazone at a dose of 45 mg per day for six months as part of the complex treatment of patients with moderate-to-severe widespread vulgar psoriasis, progressive stage of the course and concomitant alimentary obesity of grade I-II.

Materials and methods. We examined 60 (36 (60 %) men and 24 (40 %) women aged 35 to 65 years) patients with widespread vulgar psoriasis, progressive stage, moderate severity with concomitant nutritional obesity of I-II degree. The study was approved by the decision of the Bioethics and Ethics Committee of Poltava State Medical University. Furthermore, all patients in the observation group signed an informed consent to participate in the study. All patients had widespread psoriatic manifestations. At the beginning of the study, it was found that the disease recurred in 3 (5 %) patients once a year, in 9 (15 %) patients two times a year, in 33 (55 %) patients – three and 15 (25 %) patients – four. The PASI (Psoriatic Area and Severity Index) index was used to assess the severity of psoriasis [10]. All patients had concomitant alimentary obesity (body mass index (BMI) 30–40 kg/m²) [13].

Indicators of systemic inflammation were determined by examining the concentration of interleukin-33 (IL-33), interleukin-6 (IL-6) and high-sensitivity C-reactive protein (hsCRP) in the patient's serum. The study was conducted at the Research Institute of Genetic and Immunological Bases of Developmental Pathology and Pharmacogenetics of Poltava State Medical University using an enzyme-linked immunosorbent assay on a multichannel photometer STATFAX-303 (USA). Using commercial test systems Interleukin-6 ELISA-BEST, CRP ELISA-BEST, Human IL-33 ELISA Kit eBioscience™/Affymetrix (USA) (quantitative indicator). To determine the efficacy of the treatment and the feasibility of prescribing pioglitazone, clinical, laboratory and anthropometric parameters before and after treatment were evaluated in all patients who were subject to observation. Patients were treated according to unified clinical protocols for managing patients with psoriasis and with pioglitazone at a dose of 45 mg once daily for six months.

Statistical processing of the results was performed using the Statistica 7.0 program. The difference was considered significant at an error probability of $P<0.001$.

Results of the study and discussion. All patients in the study group had alimentary obesity. When calculating BMI and analyzing the indicators following the classification of obesity by BMI, it was found that 21 (35 %) patients had grade I obesity, while 39 (65 %) patients had grade II obesity. The mean group BMI was 36.1±2.2 kg/m². Based on an objective examination of the clinical picture, the PASI index was calculated, the average value of which was (21.8±1.6), corresponding to the moderate severity of psoriasis.

In the study of systemic inflammation, the mean group values of hsCRP, IL-33 and IL-6 were calculated. In the analysis of the results obtained, it was found that all patients had an increase in hsCRP (13.85±0.83 IU/l), IL-33 (73.92±8.45 pg/mL) and IL-6 (13.25±1.35 pg/mL), indicating the presence of a systemic inflammatory process in all patients studied. The results of other studies show that obesity causes a chronic, non-intense systemic inflammatory response due to the expression of IL-33, IL-6, and hsCRP by adipose tissue adipocytes. Thus, an increase in body mass index causes an increase in the production of proinflammatory cytokines, which reflects the close relationship between obesity and inflammation.

To determine the effectiveness of pioglitazone use in the complex treatment of patients with widespread vulgar psoriasis, moderate severity, progressive stage of the course with concomitant alimentary obesity of I-II degree, clinical, laboratory and anthropometric parameters were studied before, during and after treatment (Tables 1, 2).

Table 1

The dynamics of clinical and anthropometric indices in widespread vulgar psoriasis with concomitant alimentary obesity of the I-II degree (M±m), n=20

Index/Value	Before treatment	2 weeks after the event treatment	4 weeks after the event treatment	26 weeks after the procedure treatment
PASI, points	22.5±1.5	5.8±0.5 *	2,09±0.2 *	11.4±1.03 *
BMI, kg/m²	36.4±2.09	36.3±2.1	36.3±1.7	36.2±1.3

Note: statistical processing was carried out by the Wilcoxon-Mann-Whitney method. Here and further: *p <0.001 in comparison with indices before treatment.

Table 2

Dynamics of indices of systemic inflammation in patients with widespread vulgar psoriasis with concomitant alimentary obesity of the I-II degree(M±m), n=20

Index/Value	Before treatment	26 weeks after the treatment
IL-33, pg/ml	73.92±8.45	12.5±2.19 *
Il-6.pg/ml	13.25±1.35	3.4±0.72 *
University of SRB, MO/l	13.85±0.83	3.2±0.52 *

When studying the dynamics of the PASI index of patients with widespread, vulgar psoriasis of moderate severity with concomitant alimentary obesity of I-II degree, it was found that after two weeks of treatment in the hospital, the index decreased by 74 % from 22, 5±1.5 points to 5.8±0.5 points, after four weeks from the start of treatment by 90.7 % from 22.5±1.5 points to 2.09±0.2 points, after 26 weeks, during the subsequent relapse of psoriasis, the PASI index was 11.4±1.03 points, which is 49.3 % lower than before treatment. In the study of BMI, no statistically significant changes were observed throughout the treatment.

After 26 weeks of treatment with pioglitazone 45 mg once daily, a statistically significant decrease in systemic inflammation was observed. The mean group value of IL-33 decreased from 73.92±8.45 pg/ml to 12.5±2.19 pg/ml, which is 83.1 % lower than before treatment, the mean group value of IL-6 decreased from 13.25±1,35 pg/ml to 3.4±0.72 pg/ml, which is 74.3 % lower than before treatment, the mean group hsCRP decreased from 13.85±0.83 IU/l to 3.2±0.52 IU/l, which is 76.9 % lower than before treatment.

Analyzing the study results, it was found that all patients had systemic inflammation due to increased levels of hsCRP, IL-33 and IL-6 in the blood serum, which is consistent with the results of other studies that show a threefold increase in the expression of IL-33 in subcutaneous adipose tissue in obese patients [8, 11, 12].

Circulating IL-6 and hsCRP are acute phase proteins secreted by adipocytes and macrophages in adipose tissue. IL-6 provides a rapid, coordinated physiological response to tissue damage or infection aimed at activating the body's defence mechanisms [5]. In contrast, hs-CRP attaches to the membrane of damaged cells and causes their death by activating the complement cascade reactions. In turn, hsCRP is a marker of IL-6 action [15]. Furthermore, circulating IL-6 regulates the production of hsCRP in the liver, so it can be argued that IL-6, whose concentration increases with obesity, significantly contributes to the onset of a chronic systemic inflammatory response [3].

Our study results are consistent with the results of many studies that have shown that thiazolidinediones with prolonged treatment reduce the concentration of systemic inflammation in obese patients by suppressing the production of proinflammatory cytokines in macrophages by inhibiting the nuclear transcription factor NFkB [5, 14, 15].

Thus, the use of 45 mg of pioglitazone once daily for 26 weeks in the complex treatment of patients with moderate vulgar psoriasis with concomitant alimentary obesity of the I-II degree was effective in terms of IL-33 concentration, IL-6, hsCRP in the patients' serum and the PASI index and subsequently made it possible to achieve a more favourable course of the psoriatic disease by reducing the PASI index during the subsequent relapse of the disease.

Conclusions

1. The use of 45 mg of pioglitazone once a day for 26 weeks in the complex treatment of patients with moderate vulgar psoriasis with concomitant alimentary obesity of I-II degree was effective and led to a decrease in the level of systemic inflammation in terms of IL-33 by 83.1 %, IL-6 by 74.3 %, hsCRP by 76.9 % and PASI index by 49.3 % in the case of repeated relapse of the disease.

2. Treating patients with widespread vulgar psoriasis of moderate severity with concomitant alimentary obesity of I-II degree requires an integrated approach, considering the identified comorbidities.

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