EFFICACY AND SAFETY OF TARGETED THERAPY IN PATIENTS WITH PSORIASIS

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ABSTRACT

The pathogenesis of psoriasis is largely associated with the cytokine system (expression of proinflammatory cytokines), which served as the basis for the development of special biological drugs that are the basis of targeted therapy of this dermatosis. The predominant role of individual cytokines, in particular IL-17, in the development of psoriatic arthritis has been proven. In the treatment of 72 patients with psoriasis (vulgar and arthropathic forms of dermatosis), a selective IL-17 inhibitor, a biological drug "SCAFO" (secukinumab), was used, which in most cases allowed not only to cause regression of psoriatic rashes with long-term remission of the disease, but also significantly improve the CASPAR criteria, reflecting the clinical manifestations of osteoarticular syndrome in patients with psoriasis.

KEYWORDS: psoriasis, diagnosis, joint syndrome, treatment, biological drugs.

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INTRODUCTION

Psoriasis is considered as a chronic immune-mediated inflammatory skin disease [4,5,7,9,14]. Currently, the important role of immune mechanisms in the pathogenesis of psoriasis is recognized [4,9,11,14], and cytokines, whose biological effects are mediated through specific cellular receptor complexes, play a key role in the development of psoriasis. The properties that combine cytokines into an independent regulatory system include the interchangeability of biological action, pleiotropism, the absence of antigenic specificity of action and the formation of a cytokine network [1,9,16]. As a result of numerous studies, the presence of overexpression of various proinflammatory cytokines, such as IL-1, IL-6, IL-12, TNF-α, IL-17, IL-23, both in the skin and in the blood serum of patients with psoriasis, has been shown in psoriatic lesions [1,10,15,17]. Particular importance is attached to the cytokine IL-17, which is involved in the normal reactions of inflammation and immune response. IL-17 plays a key role in the pathogenesis of psoriasis, psoriatic arthritis (PA) and ankylosing spondylitis. In the blood of patients with plaque psoriasis, PA and ankylosing spondylitis, as well as in the cells of the affected skin areas, an increase in the concentration of IL-17 was detected, as well as an increase in the number of lymphocytes and innate immunity cells producing IL-17 [2,3]. In addition, in patients with PA, there is an increase in the number of IL-17-producing cells in the synovial fluid. These studies were the basis for the development of targeted therapy, i.e. the use of genetically engineered biological drugs in the treatment of patients with psoriasis [2,3,15,16]. TNF-α blocking agents (infliximab, adalimumab), as well as IL-12 and IL-23 blockers (ustekinumab) have found the most widespread use in the practice of dermatologists, although in some patients it is not possible to achieve the necessary clinical effect when treating with anti-cytokine drugs [6,8,10,13,17]. Special problems in treatment are created by patients suffering from PA, due to their high disability and a decrease in the quality of life of patients [4,9,10]. This circumstance makes it necessary

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to search for new approaches to prescribing anti-cytokine therapy in patients with psoriasis.

The purpose of the study: To evaluate the efficacy and safety of secukinumab in the treatment of severe forms of psoriasis.

MATERIALS AND METHODS

We observed 72 patients with various forms of psoriasis (vulgar with a PASI index of more than 20 points and PA). The age of the patients was 38.5±5.7 years and the duration of the disease ranged from 6 months to 22 years.

Immunological studies were studied using the Beckman Coulter Navios flow cytofluorimeter, which is designed to carry out qualitative and quantitative measurement of the biological and physical properties of cells, as well as other particles sequentially passing through the flow cell in a stream of compression fluid and irradiated with a laser beam.

Concentrations of pro- and anti–inflammatory cytokines in biological samples were studied using flow fluorimetry technology with a suspension of encoded microspheres - xMAP technology developed by Luminex (xMAP – Multiple Analyses Profiling). This technology refers to immunological methods, since highly specific monoclonal antibodies are used for the detection of cytokines, when it becomes possible to simultaneously determine several cytokines in one sample of biological material, quantify the concentration of cytokines in a wide range.

Using the CASPAR criteria, 29 out of 72 (40.3%) patients were diagnosed with PA. The patients underwent general clinical, laboratory and instrumental (ultrasound, MRI), enzyme immunoassay and immunological research methods. Articular syndrome was assessed by: the number of painful and swollen joints; the Ritchie index (palpatory joint soreness, in points); the intensity of joint pain by the patient according to VAS, mm; disease activity assessed by the patient and the doctor according to VAS, mm; the combined DAS activity index (Disease Activity Score); Leeds Enthesopathy Index LEI (Leeds Enthesitis Index); inflammatory back pain according to ASAS criteria (Assessment of SpondyloArthritis International Society); BASDAI Spondylitis Activity Index (Bath Ankylosing Spodylitis Activity Index); HAQ Functional Quality of Life index (Health Assessment Questionare).

To confirm the lesion of the osteoarticular apparatus in patients with psoriasis, studies were conducted to identify the allele of the 27 locus in the main human histocompatibility complex (HLA-B27) by polymerase chain reaction in real time. A set of reagents "DNA Technology" (Russia) was used for the study.

Finecare CRP – Rapid Quantitative Test (C-reactive protein), is a fluorescent immunoassay for the quantitative determination of C-reactive protein (CRP) and hs-CRP (highly sensitive C-reactive protein) in human whole blood, serum or plasma. The research is carried out on the WondfoFinecare FIA Meter measuring device (China). Normally, CRP<10.0 mg/L; hs-CRP<1.0 mg/L.

The obtained data were subjected to statistical processing on a Pentium IV personal computer using the Microsoft Office Excel-2016 software package, including the use of built-in statistical processing functions. The methods of variational parametric and nonparametric statistics were used with the calculation of the arithmetic mean of the studied indicator (M), the standard error of the mean (m), relative values (frequency, %), the statistical significance of the measurements obtained when comparing the averages was determined by the Student's criterion (t) with the calculation of the probability of error (P) when checking the normality of the distribution (by kurtosis criterion) and equality of general variances (Fischer's F-criterion). For statistically significant changes, the confidence level $p<0.05$ was taken. Statistical significance for qualitative values was calculated using the $\chi 2$-criterion.

For the treatment of patients with psoriasis, the drug "SCAFO" (secukinumab) was chosen, which is a completely human antibody (IgG1) that selectively binds and neutralizes the pro–inflammatory cytokine - IL-17A.

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Secukinumab has a targeted effect on IL-17 and inhibits its interaction with the IL-17 receptor, which is expressed by different cell types, including keratinocytes and synoviocytes. As a result, secukinumab inhibits the release of pro-inflammatory cytokines, chemokines and mediators of tissue damage and reduces the contribution of IL-17 to autoimmune and inflammatory diseases. Secukinumab reaches the skin in clinically significant concentrations and reduces the concentration of inflammatory markers. A direct consequence of treatment with secukinumab is a decrease in the severity of redness, compaction and peeling of the skin, which is observed in the lesions of psoriasis. Treatment of patients with psoriasis and PA was as follows: the recommended dose is 300 mg in the form of subcutaneous injection as an initial dose at 0, 1, 2, 3, 4 weeks, followed by monthly administration as a maintenance dose. Each dose of 300mg is administered as two separate subcutaneous injections of 150mg. With plaque psoriasis (PASI index > 20 points), patients received 10-12 injections for the course of treatment, with PA – 12-15 injections. In no case were any side effects or allergic reactions reported from the use of secukinumab.

RESULTS AND DISCUSSION

The treatment with secukinumab has shown the high effectiveness of this remedy in various forms of psoriasis, especially in PA. There was a significant decrease in the PASI index ($p<0.001$) in patients with plaque psoriasis: from 36.7±3.2 points to 5.7±0.6 points, respectively. A similar trend was observed in patients with psoriatic arthritis, which was studied by the dynamics of the CASPAR index. Observation of PA patients has shown the importance of detecting arthritis, enteritis, dactylitis and spondylitis in the diagnosis of early and late stage of PA, along with the advantage of ultrasound over X-ray in the diagnosis of early stage of joint syndrome, determining the degree of activity of the inflammatory process, monitoring and correction of therapy.

Patients with psoriasis have immunological disorders of varying severity. The results of studying the cellular link of immunity in patients with different duration of psoriasis, including PA, showed that the level of CD3+ and CD4+ cells decreased at an early stage, and with a longer course of dermatosis, their content increased. The study of another immunoregulatory population of T–suppressor cells regulating the strength and duration of the reaction to the antigen showed that at the early stages of the psoriatic process, the number of CD8+ cells was greater than at the later stages ($p<0.05$). The imbalance of the subpopulation composition of T-lymphocytes influenced the immunoregulation index, which was reduced in patients at the early stages, and increased in patients with a long course ($p<0.05$). This indicates that the disease occurs against the background of autoimmune aggression. A comparative characteristic of the content of circulating CD20+ cells showed that in the early stages of psoriasis, the level of these cells increased, but the maximum value was observed with a prolonged course of dermatosis. The relative and absolute content of NK cells in the bloodstream of psoriasis patients in the early stage of dermatosis increased by 1.5 times, in the late stage killer activity decreased by 2 times. The imbalance of immunocompetent cells and hypersecretion of humoral protection cause the risk of accumulation of abnormally high concentrations of CEC, the level of which increased by about 1.5 times in the early stages, and 4 times in the future.

Proinflammatory cytokines play a significant role in the development of psoriasis, when the level of TNF-α increased 2 times in the early stages, and 4 times higher than normal in the late stages ($p<0.001$). The production of IL-6 in patients with psoriasis significantly increased, acquiring maximum values during the prolonged course of dermatosis. In patients with PA, IL-17 is the most significant pathogenetically, the values of which were increased by about 3.2 times compared to the data of the control group and about 2 times

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higher than in patients with plaque psoriasis ($p<0.05$).

The use of secukinumab in patients with plaque psoriasis led to a significant regression of psoriatic elements after 4-5 injections of the drug. Further use of secukinumab increased the regression of psoriatic elements with the development of secondary hyperpigmentation of the skin. In 43 patients with plaque psoriasis, the PASI index before treatment was 36.7±3.2 points, after treatment – 5.7±0.6 points at $p<0.001$. The situation was more complicated in the treatment of PA patients, since a noticeable clinical effect occurred after 7-8 injections of secukinumab and was expressed in a significant decrease in the CASPAR index, as well as other indicators of joint syndrome activity: DAS, LEI, ASAS, BASDA.

It was found that changes in the immune system in PA patients depend on the clinical course and duration of the disease and it was proved that with early PA there is a decrease in the level of CD3+ and CD4+ cells and an increase in suppressor and killer activity. Late PA is characterized by an increase in helper activity and a decrease in the number of SD8+ and SD16+ cells, indicators of humoral immunity (SD20+, IgG, CEC) increase, more significantly with a prolonged course of PA. Increased levels of proinflammatory cytokines (IL-6, TNF-α, IL-17) have been proven depending on the activity and duration of the disease, joint destruction and the presence of HLA-B27 antigen in PA patients. The use of secukinumab led to a significant decrease in the concentration of proinflammatory cytokines (TNF-α and IL-17), especially in PA patients, which confirms the need for the use of this drug in PA patients.

Studies of the immune status in patients with psoriasis, including PA, revealed sharp multidirectional changes in the content of antibodies, the population composition of lymphocytes, which in turn affected the synthesis of proinflammatory cytokines [1]. A chronic disorder in the transmission pathways of inflammatory signals probably leads to long-term changes on the part of tissue immune cells of the skin and joints, which cause the severity of the characteristic clinical manifestations of the psoriatic process [12].

It should be pointed out that in the last 10 years, ultrasound has become one of the most accessible for the diagnosis of damage to the musculoskeletal system. Simplicity, safety, non-invasiveness, high information content of new ultrasound technologies have provided this method with priority among instrumental studies of joints and soft tissues. The high informative value of the method in assessing the condition of ligaments and tendons, the ability to detect changes in both periarticular and intraarticular tissues allow us to consider ultrasound as the method of choice for PA, and joint changes in the latter are characterized by polymorphism of the ultrasound picture. In patients with PA, lesions of all anatomical structures of the joints with a diverse ultrasound picture are detected. Ultrasound of joints and tendon-ligamentous apparatus in PA is a diagnostic marker. Ultrasound makes it possible to detect synovitis, enthesitis, tenosynovitis of the flexors of the fingers and feet significantly more often at an early stage of the disease than it can be done during a clinical examination and with the help of radiography.

The concentration of total IL-17 (free and secukinumab-bound) in the blood serum increases within 2-7 days due to a slowdown in the clearance of IL-17 associated with secukinumab, indicating that secukinumab selectively binds to free IL-17, which plays a key role in the pathogenesis of psoriasis. In a study in patients with psoriasis, after one to two weeks of treatment with secukinumab, the infiltration of the epidermis by neutrophils and the number of various markers associated with them, which is often increased in the affected areas of the skin in these patients, significantly decreased. Against the background of secukinumab therapy in patients with PA and axial spondyloarthritis, a decrease in the concentration of C-reactive protein (in two positions), which is a marker of inflammation, was noted for 2-3 weeks.

CONCLUSION

In certain forms of psoriasis characterized by torpidity in relation to the treatment, the prevalence and damage of the osteoarticular apparatus, including the manifestations of psoriatic onychodystrophy, it is advisable to use biological drugs, in particular, secukinumab, which allows to influence the most important pathogenetic mechanisms of dermatosis, as an IL-17 blocker. The conducted studies have shown that the treatment of patients with psoriasis with secukinumab is characterized by high safety and effectiveness, which significantly lengthens the time of clinical remission, thereby improving the quality of life of patients with this dermatosis. In cases of psoriatic arthritis, the early use of secukinumab (arthralgia stage) will allow to suspend the inflammatory reaction from the bone and joint apparatus, and therefore reduce the likelihood of developing arthropathies, which are the direct cause of the development of disability of patients.

REFERENCES

1. Arican O, Aral M, Sasmaz S, Ciragil P. Serum levels of TNF-alpha, IFN-gamma, IL-6, IL-8, IL-12, IL-17 and IL-18 in patients with active psoriasis and correlation with disease severity. Mediators Inflamm. 2005;23(2):273-279.
2. Blauvelt A. T-helper 17 cells in psoriatic plaques and additional genetic links between IL-23 and psoriasis. J Invest Dermatol. 2008;128(7):1064-1067.
3. Brown G, Malakouti M, Wang E, Koo JY. Anti-IL-17 phase II data for psoriasis: a review. J Dermatolog Treat. 2015;26(1):32-36.
4. Chandran V, Raychaudhuri SP. Geoepidemiology and environmental factors of psoriasis and psoriatic arthritis. J Autoimmun. 2010;34(5):314-321.
5. Christophers E. Psoriasis – epidemiology and clinical spectrum. Exp Dermatol. 2001;26(2):314-320.
6. Galluzzo M, Adamio SD, Campione E., Bianchi L. A safety evaluation of guselkumab for the treatment of psoriasis. Expert Opin Drug Saf. 2018;17(7):741-751.
7. Gelfand JM, Weinstein R, Porter SB. Prevalence and treatment of psoriasis in the United Kingdom – a population-based study. Arch Dermatol. 2005;141(6):1537-1541.
8. Feagan BG, Lam G, Ma C, Lichtenstein GR. Systematic review: efficacy and safety of switching patients between reference and biosimilar infliximab. Aliment PharmacolTher. 2019;49(1):31-40.
9. Kruglova LS, Lvov AN, Pishkina AV. Risks and predictors of the development of psoriatic arthritis in psoriasis and issues of the early administration of genetically engineered biological products. Russian Journal of Clinical Dermatology and Venereology=Klinicheskayadermatologiyaivenerologiya. 2020;19(3):289-296.
10. Loures MA, Alves HV, de Moraes AG, da Silva Santos T. et al. Association of TNF, IL-12, and IL-23 gene polymorphisms and psoriatic arthritis: meta-analysis. Expert Rev Clin Immunol. 2019;15(3):303-313.
11. Matikainen S, Jokiranta S, Eklund KK. Role of cytokines and their blocking in immune-mediated inflammatory diseases. Duodecim. 2016;132(4):349-354.
12. Morales CM, Gomes-Castro S, Sanchez M, Lopez R, New therapeutic targets in psoriatic arthritis. Reumatol Clin. 2012;Suppl.1:15-19.
13. No DJ, Inkeles MS, Amin M, Wu JJ. Drug survival of biologic treatments

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in psoriasis: a systematic review. J Dermatol Treat. 2018;29(5):460-466.

14. Parisi R, Symmons DP, Griffiths CE, Ashcroft DM. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Invest Dermatol. 2012;133(6):377-385.
15. Savvina NA, Sleptsova NP, Steshenko IG. Experience of using the domestic inhibitor IL (anti-IL-17A) in thr treatment of moderate-severe psoriasis. Russian Journal of Clinical Dermatology and Venereology=Klinicheskayadermatologiyaivenerologiya. 2020;19(5):739-748.
16. Torres T, Filipe P. Interleukin-17 as a therapeutic target in psoriasis. Acta Med Port. 2014;27(2):252-258.
17. Zaragoza V, Perez A, Sanchez JL, Oliver V. Long-term safety and efficacy of etanercept in the treatment of psoriasis. ActasDermosifiliogr. 2010;101(1):47-53.