

DYNAMICS OF IL-12/IL-23 LEVELS IN PSORIASIS PATIENTS TREATED WITH USTEKINUMAB

<https://doi.org/10.5281/zenodo.22052401>

**U.Yu. Sabirov, M.F. Khushvaktova, Yu.A. Alimukhamedova,
A.B. Rakhmatov**

*Republican Specialized Scientific and Practical Medical Center of Dermatovenereology
and Cosmetology, Ministry of Health of the Republic of Uzbekistan*

Summary

In the treatment of 110 psoriasis patients with a mean PASI index of 27.7 ± 3.2 , ustekinumab was administered at a dose of 90 mg subcutaneously according to a specific regimen (6 injections in total), which allowed PASI 100 to be achieved in 91.5% of patients, along with normalization of the main pathogenetic cytokines IL-12 and IL-23 by the end of targeted therapy.

Key words

psoriasis, cytokines, biological therapy, prognosis.

Introduction.

The involvement of the immune system in psoriasis has been proven, in particular that of activated T-lymphocytes and certain pro-inflammatory cytokines [1,5,6]. According to various authors, the pathological process in the skin of psoriasis patients begins with activation of keratinocytes by an unknown triggering factor (bacterial, viral, mechanical injury, stress, etc.) [5,6]. Damaged keratinocytes release cytokines (TNF- α , IL-12, IL-17, IL-23, IL-36), which activate antigen-presenting Langerhans cells [7,12,13]. The latter migrate to regional lymph nodes, where they activate T-lymphocytes, subsequently presenting them with an antigen bound to the major histocompatibility complex (HLA) through the interaction of specific ligand pairs on their surface [11,12].

Under the influence of IL-12 and IL-23, activated T-lymphocytes in the lymph nodes differentiate into Th1 and Th17 cells, which subsequently migrate to the skin, where TNF- α , produced by keratinocytes and dendritic cells, facilitates diapedesis of T-lymphocytes into the epidermis and dermis [10,12]. The synthesized cytokines act on surface receptors of keratinocytes, Langerhans cells, fibroblasts, and macrophages, in turn inducing the production of cytokines such as IL-1 β , IL-6, IL-8, IL-18, and others. This cytokine cascade leads to keratinocyte hyperproliferation and recirculation of T-lymphocytes, neutrophils, and macrophages into the skin, stimulating angiogenesis [1,2]. In response to this cytokine activation, keratinocytes and other cells produce immune mediators that stimulate and enhance the inflammatory response in the skin [2,4,7].

Among the pathogenetically significant cytokines in the development of psoriasis are the pro-inflammatory cytokines IL-12 and IL-23, secreted in regional lymph nodes by CD11+ cells [9]. These cytokines exert their immune effect through

interaction with a receptor complex expressed on the surface of CD4+ T-cells or natural killer (NK) cells. IL-23 is important for recruiting to the skin an increased population of activated CD4+ cells that produce IL-17, IL-6, and TNF- α [8,13,14]. The IL-23/Th17 complex plays a decisive role in the pathogenesis of psoriasis, and its inhibition produces a therapeutic effect.

Currently, a wide range of agents is available for the treatment of psoriasis patients, including biological drugs, which have evolved from an integrated understanding of the interaction between skin cells and the immune system and of the cytokines they produce that initiate pathological processes ultimately leading to the clinical manifestations of psoriasis [1,3,5,13]. For the treatment of patients with moderate-to-severe forms of psoriasis, the most widely used biological agent is ustekinumab, a fully human anti-IL-12/23 antibody.

Aim of the study.

To study the efficacy of ustekinumab in the treatment of psoriasis patients and to assess the dynamics of the cytokine indices IL-12 and IL-23.

The study included 110 psoriasis patients (67 men, 43 women) aged 18 to 55 years. Disease duration ranged from 3 months to over 20 years. The ustekinumab treatment regimen was as follows: a single dose of ustekinumab was 90 mg subcutaneously; injections were administered after the corresponding tests had been performed (No. 1), then after 1 month (No. 2); subsequent injections were given every 3 months (Nos. 3-4-5-6), i.e., each patient received 6 injections of ustekinumab over the course of treatment. Only emollient agents (dexpanthenol) were used topically.

The severity of the psoriatic process (PASI index) was assessed using a "Fotofinder" device. Patients with a PASI index greater than 10 points were selected for treatment with ustekinumab. The mean PASI index in the 110 patients was 27.7 ± 3.2 points. It should be noted that a significant clinical improvement of the cutaneous pathological process and disappearance of subjective sensations were already observed after the first and second injections of the drug. The results of the therapy are presented in Table 1, which shows the positive dynamics of the PASI index over the course of treatment.

Table 1.

Dynamics of the PASI index in psoriasis patients

Treatment regimen	PASI index
Before treatment	27.7 ± 3.2
After injection 1	16.2 ± 1.9
After injection 2	12.2 ± 1.2
After injection 3	11.6 ± 2.5
After injection 4	10.5 ± 1.1
After injection 5	8.6 ± 1.5
After injection 6	5.2 ± 0.9

As can be seen from the data presented, regression of psoriatic lesions was already observed after 1-2 injections (the PASI index decreased by almost half), and

this trend persisted with each subsequent injection, so that after 6 injections PASI 100 was observed in 91.5% of patients.

At the same time, the dynamics of the studied IL-12 and IL-23 indices followed a somewhat different pattern, as shown in Table 2.

Table 2.

Dynamics of IL-12/IL-23 cytokines in psoriasis patients

Observation period	IL-12 (pg/mL)	IL-23 (pg/mL)
Control group (n=22)	5.4±0.7	0.12±0.01
1 Before treatment (n=110), No.	18.5±2.7*	0.95±0.03*
After 1 month, No. 2	9.1±1.3	0.52±0.01
After 3 months, No. 3	8.2±0.9	0.44±0.03
After 3 months, No. 4	7.2±0.7	0.37±0.03
After 3 months, No. 5	7.1±0.5	0.32±0.02
After 3 months, No. 6	6.9±0.2	0.21±0.03

*Note: No. 1 – number of ustekinumab injections; * – significance of differences at $p<0.05$.*

The persistence of elevated cytokine levels in individual psoriasis patients after treatment apparently indicates the organism's predisposition to subsequent relapses of the dermatosis, which is consistent with the general concept of the psoriatic process.

Discussion and conclusion.

Thus, the cytokines IL-12 and IL-23 play an important pathogenetic role in the psoriatic process and allow the introduction of biological therapy methods aimed at suppressing the expression of these cytokines, as well as achieving PASI 100 treatment outcomes, along with a significant extension of the dermatosis remission period. Correction of IL-12 and IL-23 alone does not solve the overall problem of psoriasis; although its high efficacy allows an improvement in patients' quality of life for a certain period, it also requires consideration of further treatment and prevention strategies for the dermatosis.

REFERENCES:

1. Bakulev A.L., Samtsov A.V., Sokolovsky E.V. Targeted therapy of psoriasis. *Vestnik Dermatologii*. 2022;2:42-52.
2. Belova O.V., Arion V.Ya. Immunobiologically active substances isolated from the skin. *Vestnik RAMN*. 2010;6:8-12.
3. Znamenskaya L.F., Svishchenko S.I. First experience of using ustekinumab in the treatment of psoriasis patients in Russia. 2012;2:48-52.
4. Ketlinsky S.A., Simbirtsev A.S. Cytokines. Saint Petersburg. Foliant. 2008. 345 p.
5. Kruglova L.S., Bakulev A.L., Korotaeva T.V., Lila A.M. Psoriasis. Moscow: GEOTAR-Media. 2022. 328 p.

6. Rakhmatov A.B. Psoriatic disease. Tashkent. 2019. 238 p.
7. Albanesi C, de Pita J, Girolomoni G. Resident skin cells in psoriasis: a special look at the pathogenetic functions of keratinocytes. *Clin Dermatol*. 2007;25:581-588.
8. Boniface K, Blom B, Liu Y. From interleukin-23 to T-helper 17 cells differentiation revisited. *Immunol Rev*. 2008;226:132-146.
9. Capon F, Meglio P, Szaub J. Sequence variants in the genes for the interleukin-23 receptor and its ligand IL-12B confer protection against psoriasis. *Hum Genet*. 2007;122:201-206.
10. Kim J, Krueger J. Highly effective new treatments for psoriasis target the IL-23/Type 17 cell autoimmune axis. *Ann Rev Med*. 2017;68:255-269.
11. Koo J, Marangeli LB, Nakamura M. Depression and suicidality in psoriasis: review of the literature including the cytokine theory of depression. *J Eur Acad Dermatol*. 2017;31(12):1999-2009.
12. Langrish C, Chen Y, Blumenschein W. IL-23 drives a pathogenic T-cell population that induces autoimmune inflammation. *J Exp Med*. 2005;201:233-240.
13. Loures M, Aives H, de Moraes A. Association of TNF, IL-12, IL-23 gene polymorphisms and psoriatic arthritis: meta-analysis. *Exp Rev Clin Immunol*. 2019;15(3):303-313.
14. Luo J, Wu S, Lacy E. Structural basis for the dual recognition of IL-12 and IL-23 by ustekinumab. *J Mol Biol*. 2010;402:797-812.