® Postepy Hig Med Dosw (online), 2016; 70: 1198-1205
e-ISSN 1732-2693

www.phmd.pl
Review

Received: 2015.04.20
Accepted: 2016.06.13
Published: 2016.12.08

Anti-cytokine therapy for psoriasis – not only TNF-α blockers. Overview of reports on the effectiveness of therapy with IL-12/IL-23 and T and B lymphocyte inhibitors

Terapia antycytokinowa łuszczycy – nie tylko blokery TNF-α. Przegląd piśmiennictwa na temat skuteczności terapii inhibitorami IL-12/IL-23 oraz limfocytów T i B

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Summary

TNF-α inhibitors – infliximab, etanercept and adalimumab – can be used in the treatment of psoriasis vulgaris and psoriatic arthritis, along with other inhibitors of proinflammatory cytokines, such as interleukin-12 (IL-12) and IL-23.

This paper presents the results of research on the use of biological drugs other than the tumor necrosis factor blockers (TNF-α), namely inhibitors of IL-12 and IL-23 (ustekinumab), T-cell inhibitors (alefacept and efalizumab), B-cell inhibitors (rituximab), anti-IL-17 agents (secukinumab, ixekizumab, and brodalumab) and IL23p19 inhibitors (guselkumab and tildrakizumab).

The paper presents an analysis of the mechanism of action, recommended doses and methods of therapy, taking into account the adverse events associated with the use of anti-cytokine therapy. The use of biological drugs is discussed based on a review of the current literature.

Keywords: **psoriasis • psoriatic arthritis • therapy • biological drugs**

Full-text PDF: http://www.phmd.pl/fulltxt.php?ICID=1225953

Word count: 3695
Tables: 1
Figures: 1
References: 45

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The way to the discovery of biological drugs, that is biopharmaceuticals produced using the newest biotechnology methods, was initiated by James Watson and Francis Crick, who presented the double-helix model of DNA structure, which allowed the DNA recombination phenomenon to be observed and thereby launched the era of genetic engineering. Their research showed that the transmission of the human or animal gene into the bacterial cell enables the production of specific proteins. Thus, in the 1970s human insulin was synthesized, and in 1985 human recombinant growth hormone. These were the first biological drugs [10].

Psoriasis is an immunological skin disease, characterized by a chronic course. In the following paper the results of research on the use of biological drugs other than the tumor necrosis factor blockers (TNF-α) will be presented. In the European Union, for the treatment of psoriasis, the following biological drugs are approved, three of which are TNF-α blockers: infliximab, etanercept and adalimumab. These can be used in the treatment of psoriasis vulgaris and psoriatic arthritis, along with other inhibitors of proinflammatory cytokines, such as interleukin-12 (IL-12) and IL-23 [25,43] (table 1, fig. 1).

T-cell inhibitors (efalizumab, alefacept) are not commonly used, because of frequently occurring side effects (table 1, fig. 1).

Rituximab, an antibody that targets the CD20 antigen on B cells, is primarily used for the treatment of lymphomas. Its common use in dermatology requires further clinical trials [25] (table 1, fig. 1).

New agents – secukinumab, ixekizumab, brodalumab, guselkumab and tildrakizumab – have shown meaningful effectiveness in treatment of psoriatic arthritis and moderate to severe plaque psoriasis but still require further clinical trials.

The effectiveness of biological therapy is usually evaluated based on the Psoriasis Area and Severity Index (PASI), assessment of body surface area (BSA) and the Dermatology Life Quality Index (DLQI).

Inhibitors of proinflammatory cytokines (IL-12 and IL-23) – ustekinumab

Ustekinumab is a human IgG1 kappa monoclonal antibody, directed against IL-12 and IL-23. These cytokines play an important role in the pathogenesis of psoriasis and the development of a Th1 cell-mediated immune response. There are reports on the polymorphism of genes encoding IL-12 and IL-23 proteins and its relation with the occurrence of psoriasis [34,36]. IL-12 and IL-23 are produced by antigen-presenting cells such as macrophages and dendritic cells. Both interleukins are composed of two subunits. The p40 subunit, shared by both interleukins, binds to the interleukin-12 receptor β1 (IL-12Rβ1), located on the surface of immune cells. The IL-12Rβ1 receptor is found on the surface of Th1 and NK cells. The second subunit of IL-12 and IL-23 is p35 and p19, respectively. Through those subunits the interleukins can bind to the specific IL-12Rβ2 and IL-23R receptors [34,36].

Interleukin-12 promotes T cell differentiation into Th1 cells and has a beneficial effect on anchoring those cells into the skin by increasing the expression of cutaneous lymphocyte antigen (CLA). This cytokine is an essential factor in the accumulation of lymphocytes in the skin. Moreover, IL-12 stimulates the activity of Th1 cells causing increased secretion of pro-inflammatory cytokines such as interferon gamma (IFN-γ) and TNF-α [24].

Interleukin-23 has a similar effect to IL-12, but is characterized by its specific properties and plays a key role in the pathogenesis of psoriasis. IL-23 has an influence on undifferentiated T lymphocytes, stimulating the formation of Th17 cells that secrete interleukin-17 (IL-17) and interleukin-22 (IL-22). Thus, IL-23 is a potent stimulus for IL-17 production. IL-17 induces the release of many pro-inflammatory mediators such as chemokines, cytokines, and metalloproteinases from the epidermal cells and fibroblasts. There are multiple reports suggesting the important role of IL-17 in inflammatory joint diseases [4,6,13,27,34]. In contrast to IL-17, IL-22 inhibits the differentiation of epidermal cells. However, both cytokines enhance the antimicrobial peptide expression.

Expression of cytokines such as IL-12, IL-23, and IFN-γ is significantly increased in the skin of patients with psoriasis. This applies both to the skin lesions and lesion-free skin. In comparison with a healthy control group, plasma of patients with psoriatic arthritis showed increased levels of the p40 subunit [40].

The described mechanism of the pro-inflammatory effect suggests that ustekinumab, an IL-12 and IL-23 inhibitor, will be an effective weapon in the treatment of exacerbations of psoriatic skin and joint symptoms.

Ustekinumab is administered subcutaneously and is used at an interval of 4 weeks after the first injection, and then every 12 weeks. Body weight determines the dose: for patients with body weight less than 100 kg, 45 mg of ustekinumab is administered. For patients with a weight of 100 kg or more, 90 mg is recommended [38,39].

Table. 1. Not only TNF-α blockers in psoriasis therapy – characteristic of IL-12/IL-23, lymphocytes T and B inhibitors.

	MOLECULARY CHARACTERISTIC	ADMINISTRATION	HALF-LIFE	DOSAGE
USTEKINUMAB	human monoclonal antibody IL12/23 inhibitor	subcutaneous	~ 3 weeks	45 mg or 90 mg (weight ↑ 100 kg) at 0, 4 week; then after every 12 weeks
BRIAKINUMAB - ABT-874	human monoclonal antibody IL12/23 inhibitor	investigational On 14 January 2011, Abbott Laboratories Ltd officially notified the Committee for Medicinal Products for Human Use (CHMP) that it wishes to withdraw its application for a marketing authorisation for Ozespa, for the treatment of plaque psoriasis *		
ALEFACEPT (used in US)	fusion protein CD2-binding portion of the human leukocyte function antigen-3 (LFA-3) linked to the Fc portion of human IgG1 T cell targeted	intramuscular – i.m. intravenous – i.v.	~ 270 hours	15 mg i.m. weekly or 7,5 i.v. weekly
EFALIZUMAB (withdrawn from therapy)	CD 11a monoclonal antibody T cell targeted	subcutaneous	~72 – 132 hours	0,7 mg/kg at 0, then 1 mg/kg weekly
RITUXIMAB	chimeric monoclonal antibody against the protein CD 20	intravenous infusion only	~30 to 400 hours	1000 mg at 0, 2 week** investigational

* Ref. [44]
** Ref. [12]

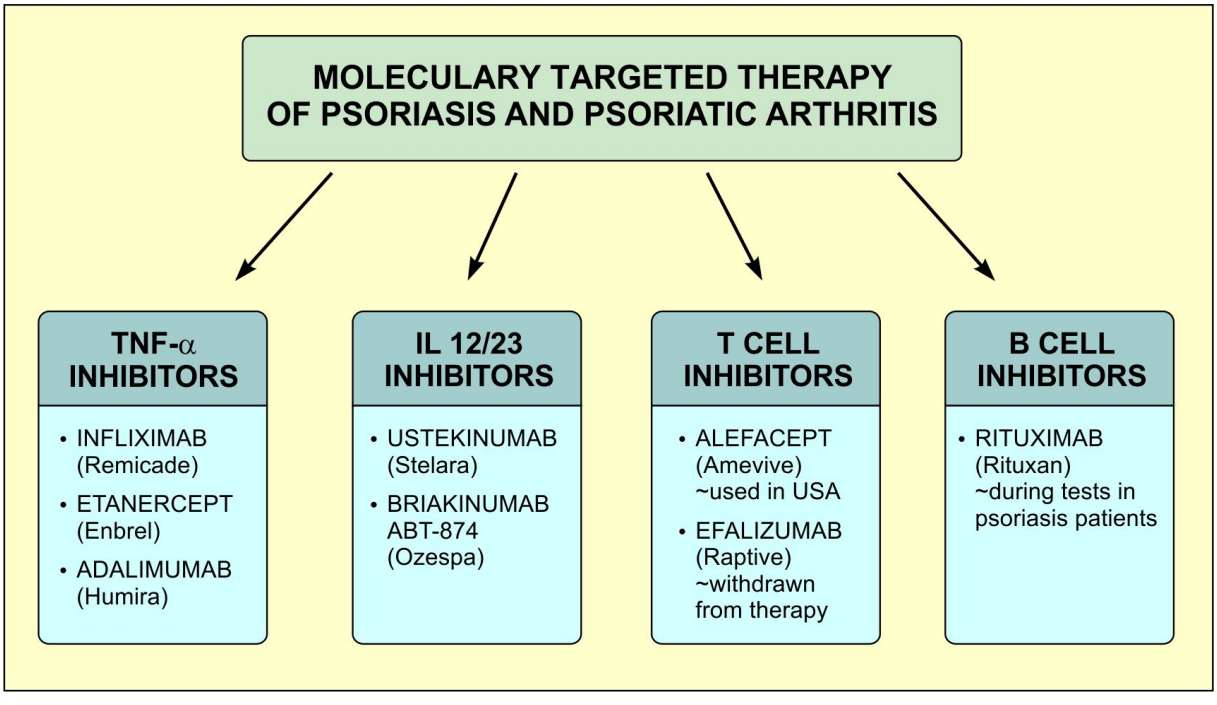

Fig. 1. Molecularly targeted therapy of psoriasis and psoriatis arthritis

Treatment with ustekinumab allows long-term remission, and drug withdrawal does not cause a rebound effect. Reintroduction of this drug has a comparable effectiveness to the therapy when used for the first time. In the case of patients who have failed to achieve a satisfactory improvement, treatment effectiveness can be achieved by administering 90 mg of ustekinumab every 8, instead of every 12 weeks. A similar relationship has not been observed for a dose of 45 mg [19,39].

Ustekinumab is used mainly in the treatment of plaque psoriasis. The results of recent studies show that it may be beneficial in psoriatic arthritis [13,16,37,39].

In a multicentre, randomized, double-blind, placebo-controlled study an analysis of the effectiveness of ustekinumab in inhibiting the progress of psoriatic arthritis was conducted. The study included patients with psoriatic arthritis who did not respond to prior conventional or biological treatment. Patients were divided into three groups: the first one received ustekinumab at a dose of 45 mg at weeks 0, 4, 12, the second group received 90 mg at the same intervals, and the third one received a placebo. After 16 weeks patients from the last group, in whom the radiological response was less than 5%, received ustekinumab at a dose of 45 mg and a standard dosage regimen. Eventually, all the other patients receiving the placebo also started ustekinumab at week 24 of the study. At week 0/24/52 of the experiment radiographs of the hands and feet were evaluated using PsA-modified van der Heijde-Sharp (vdH-S) scores. The results of the data analysis showed that patients treated with ustekinumab, regardless of dose, showed significantly less radiographic progression at week 24 of the therapy. In the placebo group no regression of joint changes was observed. Inhibition of radiographic changes and disease progression was significantly reduced among the patients who first received the placebo and then began the therapy with ustekinumab from week 16 or 24 of the study. The authors concluded that ustekinumab at a dose of 45 and 90 mg significantly inhibits the progression of joint damage in patients with active psoriatic arthritis [13].

In 2008 the largest randomized study conducted so far on the efficacy and safety of ustekinumab was published. The study involved nearly 2000 patients with moderate to severe psoriasis. The patients were followed up for 52-76 weeks and were randomized into two groups, receiving ustekinumab at a dose of 45 mg or 90 mg and to the placebo group. At week 12 the placebo patients were assigned to one of the groups receiving the active drug. The endpoint of the study was a 75% reduction in PASI score (PASI 75) at week 12. PASI 75 was reached by 66-76% of patients, significantly more than in the placebo group (3-4%). The drug is distinguished by its rapid effect; a significant improvement was noted as early as at week 2 of treatment, and the maximum effect was obtained at about 24 weeks. Quality of life measured with the DLQI index significantly improved in the group actively treated with ustekinumab. The most commonly observed adverse events were upper respiratory tract infections, arthralgias and headaches. The percentage and type of complications were at a placebo level. Anti-drug antibodies (ADA) occurred in 5.1% of patients and were generally at low levels [19,29,34].

Researchers from Macedonia presented a case of a 34-year-old female patient with plaque psoriasis who developed pustular psoriasis after ten weeks of treatment with ustekinumab. Her treatment was intensified after changing the regimen of drug administration from 12 to 8 weeks. After 28 weeks, standard intervals of treatment were restored. In addition, pustular lesions were treated with topical corticosteroids until complete remission. During an 18-month follow-up no recurrence of pustular psoriasis was noted. In this case, despite the adverse events, the therapy with ustekinumab was not discontinued and thus the therapeutic benefits were not compromised [1].

The majority of patients with psoriasis have nail changes, and their treatment is difficult. Ustekinumab improves the condition of the nails in patients with moderate to severe psoriasis. Richi et al., in a randomized clinical trial, studied 766 patients, of whom 545 (71.1%) had nail psoriasis. Patients received ustekinumab at a dose of 45 mg and 90 mg or the placebo at weeks 0 and 4. After 24 weeks the NAPSI (Nail Psoriasis Severity Index) was 46.5% and 48.7%, respectively. NAPSI improvement ranged from 29.7% in patients with PASI below 50% to 57.3% in patients with PASI above 75%. During the subsequent 1-year follow-up the nail condition significantly improved in most patients [33].

Piaserico et al. drew attention to the problem of the treatment of psoriasis in elderly patients. Treatment of these patients is often difficult, due to the impairment of immune system efficiency, the presence of comorbidities, as well as contraindications to systemic therapy. Safety and efficacy of traditional methods of systemic therapy and biological treatment were evaluated in 187 patients with psoriasis vulgaris aged >65 years. After 12 weeks of treatment, PASI 75 was achieved in 49%, 27%, 46% and 31% of patients who received, respectively, methotrexate, cyclosporine, acitretin and PUVA therapy. In the group receiving biological drugs the same response to treatment was observed in 64.1%, 64.7%, 93.3%, 57.1% and 100% of patients who received, respectively, etanercept, adalimumab, infliximab, efalizumab and ustekinumab. The use of etanercept was associated with the lowest incidence of adverse effects as compared to other methods of treatment. The study shows that in a population of elderly people conventional methods of treatment are less effective than the biological drugs, among which the best was found to be ustekinumab [30].

T CELL INHIBITORS – ALEFACEPT, EFALIZUMAB

Alefacept

Alefacept is a fusion protein, composed of the LFA-3 domain fused to a human IgG antibody. It has an immu-

nosuppressive effect through the CD2-binding portion and inhibits the activation of T cells and thus also keratinocyte proliferation.

Alefacept inhibits the activation and proliferation of T cells by blocking their binding with antigens. It also induces the apoptosis of memory-effector (CD45RO+) T cells in vitro. The drug is administered intramuscularly or intravenously.

Although alefacept was registered in 2003, it has been approved as a drug for the treatment of plaque psoriasis only in Switzerland. In other countries of the European Union alefacept has never been approved for the treatment of psoriasis due to its low efficacy (PASI 75 at 12 weeks therapy usually does not exceed 25%), and also because of the increased risk of serious adverse events [25,39].

On the other hand, Sheinfeld, a researcher from the United States, in his study on the most common adverse events of alefacept, concluded that this biological drug is safe. The most common symptoms reported by patients undergoing therapy were flu-like symptoms such as headaches, rhinitis, and fatigue, and these were transient [35]. Despite these encouraging reports, among European countries alefacept is commonly used only in Switzerland [25,39].

Lebre et al. investigated the efficacy of the drug in 11 patients with psoriatic arthritis and psoriasis vulgaris. Patients received alefacept at a dose of 7.5 mg per week for 12 weeks. The efficacy of alefacept was evaluated based on the expression of IL-20. Skin biopsies were performed before the start of the study and at weeks 1 and 6 of the treatment, while the synovial biopsies were performed before and after 4 and 12 weeks of therapy. The material was analyzed immunohistochemically in order to detect IL-20. The researchers found that the expression of IL-20 in patients with psoriasis vulgaris decreased significantly ($p = 0.04$) after 6 weeks of treatment, which correlated positively with the decrease in PASI score. In contrast, patients suffering from psoriatic arthritis did not show a decrease in IL-20 expression after treatment, which indicates the limited effectiveness of the therapy [16].

Researchers from the United States performed a meta-analysis of randomized and double-blind studies. Literature data were searched using the PubMed database. The aim of the study was to compare the effectiveness of different biological drugs in the treatment of psoriasis. The proportion of patients reaching PASI 75 at week 12 of treatment was assessed. The desired effect was achieved with infliximab, ustekinumab, adalimumab, and etanercept therapy in 78.6%, 72.1%, 70.5%, and 48.1% of patients, respectively. Alefacept was the least effective of the compared biological agents – only 21% of patients achieved PASI 75. However, available data cannot fully explain the obtained clinical response, because a longer period of follow-up may be necessary. In the selection of the most effective agent, a number of variable factors must be considered, including the patient's preferences, treatment costs, tolerance of the drug, possible side effects, dosage regimen, and route of administration [14].

Efalizumab

Efalizumab is a recombinant humanized monoclonal antibody directed against the α-subunit of leukocyte function associated antigen-1 (LFA-1; CD11a). Blocking of the adhesion molecule on T cells leads to a reduction of skin lesions in psoriasis. The drug is administered subcutaneously.

In the European Union and United States of America, efalizumab was withdrawn in 2009 from general use because of the risk of progressive multifocal leukoencephalopathy for patients in long-term treatment with this drug [39]. Despite the lack of a recommendation, it is sometimes used, although relatively rarely.

Polish researchers compared the effectiveness of different biological drugs. Efalizumab in patients with plaque psoriasis was administered by a subcutaneous injection. The first dose was 0.7 mg/kg body weight and then 1.0 mg/kg every week. After 12 weeks of efalizumab treatment, 7 out of 12 patients had a clinically significant improvement (4 patients achieved PASI 30, 2 patients PASI 50 and 1 patient PASI 75). During the treatment, after the first injection of the drug, half of the patients experienced mild to moderate headaches. The symptoms did not appear after the subsequent doses of efalizumab. Two patients after 12 weeks of treatment had severe joint pain, and in one of them, lesions were significantly exacerbated – in both patients the treatment was discontinued [41].

Lembo et al. studied the effectiveness of various biological agents, including efalizumab, by assessing the level of monocyte chemoattractant protein-1 (MCP-1). It is a chemokine, plasma concentrations of which are increased in psoriatic patients. Patients were treated with TNF-α blockers as well as with efalizumab. MCP-1 plasma level was evaluated at baseline and after 2 months of treatment. All patients receiving biologics showed a significant clinical improvement and a reduction in MCP-1 plasma concentration. The authors concluded that MCP-1 should be a potential marker of inflammation in patients with psoriasis, used to assess the severity of the disease and the effectiveness of treatment with anti-TNF-α and anti-CD11 monoclonal antibodies [18].

B cell inhibitors – rituximab

Rituximab (RTX) is an antineoplastic and immunosuppressive drug. It is a chimeric monoclonal antibody directed against the CD20 antigen. The fragment anti-

gen-binding (Fab fragment) of the immunoglobulin is of murine origin and determines the affinity to the CD20 antigen located on B cells and on the surface of pre-B cells. The binding of rituximab with the CD20 protein causes B cell depletion in one of three mechanisms: antibody-dependent cell-mediated cytotoxicity (ADCC), complement-dependent cytotoxicity (CDC), and apoptosis. ADCC appears to be the major mechanism of action of rituximab [3].

Unfortunately, bone marrow stem cells and pro-B cells do not express CD20 protein, and therefore B cell depletion is temporary and after 4-12 months the B cell count returns to the initial state. It should be noted that the number of antibody-producing plasma cells is not reduced, and thus the concentration of immunoglobulins during the therapy is unchanged. Recent studies have shown that rituximab also has an impact on the cell-mediated immune response. A significant increase in the T helper (Th) cells and cytotoxic T cells (TC) is observed during therapy [36].

Rituximab is used in oncology for the treatment of non-Hodgkin's lymphoma (NHL), chronic lymphocytic leukemia (CLL), granulomatosis with polyangitis and microscopic polyangitis. It is also used to treat autoimmune diseases such as rheumatoid arthritis and systemic lupus erythematosus. Despite the growing amount of evidence regarding the safety and efficacy of rituximab, there are increasingly reports on its side effects. Researchers from Italy describe a case of a 69-year-old patient suffering from rheumatoid arthritis, who, after 3 months of therapy, developed psoriatic lesions on her trunk and arms [8].

Jimenez-Boj et al., in a randomized prospective study, evaluated the effects of rituximab in psoriatic arthritis (PsA). Nine patients with psoriatic arthritis and 14 with rheumatoid arthritis (RA) received RTX at a dose of 1000 mg twice within 14 days. Patients were examined again after six months of treatment. The criteria for clinical improvement in psoriatic arthritis was achieved in 56% of patients. The Disease Activity Score in 28 joints (DAS28) improved from 6.2 to 4.9 (medians) in psoriatic arthritis and 6.4 to 5.2 in rheumatoid arthritis. DLQI was reduced from 1.5 to 1.0 and from 2.1 to 1.4, respectively (all $p \leq 0.05$). The Disease Activity Index for psoriatic arthritis was reduced from 52.0 to 32.5 ($p<0.05$). C reactive protein did not change significantly. RTX was well tolerated [12]. It is the first and so far the only study showing the efficacy of rituximab in the treatment of psoriatic arthritis.

New drugs

Secukinumab, ixekizumab, brodalumab, guselkumab

Recently, there has been increasing comprehension of the value of the TH17 lineage of T cells and related cytokines, including interleukin IL17 and IL23, particularly in the pathogenesis of inflammatory skin diseases. New drugs that are designed to inhibit steps in this pathway – the IL12/IL23 inhibitor ustekinumab, the IL17A inhibitors secukinumab and ixekizumab, the IL17A receptor inhibitor brodalumab and the IL23p19 inhibitors guselkumab and tildrakizumab – have shown meaningful effectiveness in treatment of psoriatic arthritis and moderate to severe plaque psoriasis [2,23,26,45].

Secukinumab, ixekizumab, and brodalumab are three anti-IL-17 medications used for psoriasis therapy, of which only secukinumab is FDA accepted; ixekizumab and brodalumab require further clinical trials [2]. The efficacy of the IL-17A inhibitors has elevated the standard care for patients with severe psoriasis to the extent that PASI 90, instead of PASI 75, should now be considered as the criterion for assessment of treatment response [23]. An example is the recent CLEAR trial, which used a primary endpoint of the PASI 90 at week 16. The results showed that secukinumab reached a PASI 90 of 79%, a significantly higher result than ustekinumab (57.6%). The AMAGINE-2 and AMAGINE-3 studies, which are similar phase III RCTs comparing brodalumab to ustekinumab, used an even more rigorous primary endpoint of PASI 100 and found that brodalumab achieved a PASI 100 of 44 and 37% in the respective studies at week 12, which was significantly better than ustekinumab (22% in AMAGINE-2 and 19% in AMAGINE-3) [26]. Results from clinical trials show that these three medications are highly effective in psoriasis therapy and seem to be as safe as other biologic treatments that are FDA approved [2,45].

Little is known about the effect of specific anti-interleukin-23 therapy for the treatment of moderate to severe plaque psoriasis. In a 52-week, phase 2, dose-ranging, randomized, double-blind, placebo-controlled, active-comparator trial, Gordon et al. compared guselkumab (CNTO 1959) – an anti-interleukin 23 monoclonal antibody – with adalimumab in patients with plaque psoriasis. A total of 293 patients were randomly assigned to receive guselkumab (5 mg at weeks 0 and 4 and every 12 weeks thereafter; 15 mg every 8 weeks; 50 mg at weeks 0 and 4 and every 12 weeks thereafter; 100 mg every 8 weeks or 200 mg at weeks 0 and 4 and every 12 weeks thereafter) for 40 weeks, placebo, or adalimumab (standard dosage for psoriasis). At week 16, patients in the placebo group crossed over to receive guselkumab at a dose of 100 mg every 8 weeks. The primary endpoint was the proportion of patients with a Physician's Global Assessment (PGA) score of 0 (indicating cleared psoriasis) or 1 (indicating minimal psoriasis) at week 16. At week 16, the proportion of patients with a PGA score of 0 or 1 was significantly higher in each guselkumab group than in the placebo group: 34% in the 5-mg group, 61% in the 15-mg group, 79% in the 50-mg group, 86% in the 100-mg group, and 83% in the 200-mg group, as compared with 7% in the placebo group ($P \leq 0.002$ for all comparisons). Moreover, the proportion was significantly higher in the 50-mg, 100-mg, and 200-mg guselkumab groups than in the adalimumab group (58%) ($P<0.05$ for

all comparisons). At week 16, the proportion of patients with at least a 75% improvement in PASI scores was significantly higher in each guselkumab group than in the placebo group (P<0.001 for all comparisons). At week 40, the proportion of patients with a PGA score of 0 or 1 remained significantly higher in the 50-mg, 100-mg, and 200-mg guselkumab groups than in the adalimumab group (71%, 77%, and 81%, respectively, vs. 49%) (P<0.05 for all comparisons). The effects of this phase 2 trial suggest that guselkumab may be an effective therapy for plaque psoriasis and allows control of psoriasis patients with a specific anti-interleukin-23 drug [5].

Conclusions

The results of the research carried out in the centers around the world seem to be very optimistic. Biological drugs have a high efficacy, as determined on the basis of the reduction of the PASI score. Most patients achieved a PASI 75 response. These drugs have a positive impact on the quality of life of patients suffering from psoriasis, as emphasized in many publications [7,11,21,31,42]. Modern biological drugs, apart from a significant efficacy, have a high safety profile [7,15,17,20,28,32].

Alternative treatments for severe psoriasis and psoriatic arthritis should also be constantly explored. Currently, there is ongoing research on new biologics such as Janus kinase (JAK) inhibitors and phosphodiesterase 4 inhibitors. Efficacy and safety of JAK pathway blockers were demonstrated in the first randomized trials. These drugs may be alternatives to monoclonal antibodies [9,22].

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The authors have no potential conflicts of interest to declare.