Risankizumab in the treatment of psoriasis – literature review

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Abstract
Risankizumab is a humanized, monoclonal antibody directed against subunit p19 of interleukin 23 (IL-23). In February 2019, risankizumab was approved for the treatment of moderate to severe psoriasis. The aim of the work is to collect up-to-date information on risankizumab and present its mechanism of action and recent clinical trials in which it was applied. This work also compares the mechanisms of action of risankizumab and ustekinumab and their importance in the treatment of psoriasis and describes the role of IL-23 in the etiopathogenesis of psoriasis. The work also refers to the effectiveness of risankizumab treatment and its safety profile. The results of molecular and histological studies that show changes in psoriatic skin after risankizumab treatment are also described.

Key words: psoriasis, antibodies, treatment, risankizumab.

Introduction
Psoriasis is a systemic, chronic inflammatory disease inseparably associated with the immune system, which is typically characterized by a cutaneous manifestation. At the present time, psoriasis is quite a challenge for modern medicine because it is often associated with a significant decrease in the quality of life and may even lead to disability [1]. In developed countries, the incidence of psoriasis is estimated at about 1–4% [2]. It should be noted that psoriasis is associated with the risk of co-morbidities such as depression, heart disease, including ischemic heart disease, metabolic syndrome, hypertension and also inflammatory bowel diseases [3].

Psoriasis can co-exist with diseases such as psoriatic arthritis, inflammatory bowel diseases and ankylosing arthritis. Psoriatic arthritis affects 5% to 42% of patients with psoriasis. Interestingly, it can overtake skin symptoms in up to 15% of patients [4].

Due to the above reasons, intensive clinical trials are underway for new drugs, including antibodies, in order to best control the disease and increase the quality of life of patients with psoriasis. In recent years, the knowledge about the etiopathogenesis of psoriasis has significantly increased. The discovery of the prominent role of the interleukin (IL) 23/IL-17 immune axis in the pathogenesis of psoriasis has given a new option for the development of new therapies [5, 6].

The aim of this study is to gather current knowledge about the recently registered antibody risankizumab, which, as clinical trials show, seems to be a promising therapeutic option in the treatment of psoriasis.

The mechanism of action of risankizumab and the role of IL-23 in the pathogenesis of psoriasis
Risankizumab is a humanized, monoclonal IgG1 class antibody whose action is based on binding to the p19 subunit of IL-23. After binding to the antibody, IL-23 is selectively blocked, thus inhibiting its pro-inflammatory activity [7].

Interleukin 23 plays an important role in the development of chronic inflammation and, as genetic research has shown, there is a relationship between the receptor for IL-23 (IL-23R) or its ligand and inflammatory diseases, including psoriasis [8]. Interleukin 23 is involved in stimulation and has an effect on the functioning of Th17 lymphocytes, which play an important role in the pathogenesis of psoriasis [9].

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The development of inflammation and the immune response in psoriasis is associated with IL-23. According to the research, lack of IL-23 is associated with stopping the development of Th17 cells at the early stage of activation, which is associated, inter alia, with a reduction in the level of pro-inflammatory IL-17 produced by stimulated Th17 lymphocytes. The lack of IL-23 was also associated with a smaller pool of Th17 lymphocytes in the lymph nodes [10]. Interleukin 23 is necessary for the full inflammatory function of Th17 lymphocytes [11]. Moreover, it is worth noting that IL-23 is involved in the induction of IL-C3 cell activity, which also has significance in the pathogenesis of psoriasis [12]. The IL-23/IL-17 axis has been identified in the study as the major signaling pathway leading to characteristic molecular, cellular and structural changes in psoriatic skin [13]. Studies in mice showed that intradermal injection of IL-23 was associated with the development of psoriatic skin lesions [14].

Considering the play of cytokines and immune pathways, IL-23 seems to be a proper target for antibodies used to treat inflammatory diseases, including psoriasis.

**The mechanism of action of ustekinumab**

It is also worth mentioning the action of ustekinumab, which in clinical trials is compared with risankizumab in terms of safety and efficacy in the treatment of psoriasis. Ustekinumab is a fully human IgG1 monoclonal antibody that works by binding to the p40 subunit, common to IL-12 and IL-23 cytokines. It is worth noting that secondary inhibition of IL-12 may weaken the anti-inflammatory effect of this antibody. There are studies that indicate that IL-12 may in some way have anti-inflammatory action and inhibit dermatitis [15]. Interleukin 12 has a protective effect against intracellular pathogens, and is also likely to be involved in immune surveillance in the development of tumors [16, 17]. Furthermore, inhibition of the p19 subunit is also associated with inhibition of IL-39, which is still a poorly studied factor [18].

Further research is needed to find out the properties and role of IL-39 in the pathogenesis of psoriasis, because it may turn out that this secondary action through the p19 subunit will render risankizumab superior to ustekinumab in the treatment of psoriasis. Bearing in mind the above reports, it may seem that the selective inhibition of IL-23 only is more beneficial and may be associated with fewer side effects during long-term treatment of psoriasis.

**Reports from the latest clinical trials**

In recent years, there have been several large clinical trials of risankizumab that have given hope of finding a new, effective drug for patients with psoriasis. Krueger [19] and others focused on the safety assessment of risankizumab compared to placebo. The study included 39 patients aged 18–75 years with moderate to severe plaque psoriasis who had been suffering for at least 6 months. It was a one-stage, multi-center, double-blind, placebo-controlled clinical trial, in which patients received 0.01 mg/kg, 0.05 mg/kg, 0.25 mg/kg, 1 mg/kg, 3 mg/kg, or 5 mg/kg of risankizumab intravenously \( (n = 18) \), 0.25 mg/kg or 1 mg/kg risankizumab subcutaneously \( (n = 13) \), or matched placebo \( (n = 8) \). The effectiveness of treatment with this antibody was also evaluated. At week 12, Psoriasis Area Severity Index (PASI) 75 was achieved in 87% of cases, PASI 90 in 58%, and PASI 100 in 16%. None of these endpoints were achieved in the placebo group. At week 24, PASI 75 was obtained in 71% of cases, PASI 90 in 48% and PASI 100 in 29% of patients, compared to 13% for PASI 75 and 0% for PASI 90 and 100 in the placebo group.

Regarding the safety profile, after 24 weeks, 20 out of 31 (65%) patients receiving risankizumab (intravenously or subcutaneously) had an adverse event, while in the placebo group this percentage was 88% (7 out of 8 patients). The severity of adverse events did not correlate with the dose of risankizumab. The most frequent adverse events were upper respiratory tract infections, rhinitis and pharyngitis, i.e. adverse reactions that occur classically during the use of biological drugs in the course of psoriasis. Four serious events occurred during risankizumab use (alcoholic pancreatitis, ischemic stroke, transient ischemic attack and polymyositis), but they did not result from the treatment.

The above study showed that risankizumab was well tolerated and was associated with rapid and sustained clinical improvement in patients with moderate to severe plaque psoriasis. It is also worth noting that the use of risankizumab was associated with a decrease in the expression of genes and proteins associated with the IL-17/IL-23 axis [20]. This study included a relatively small group of patients, which is why in subsequent months the focus was on the next, larger clinical trials of risankizumab and its role in the treatment of psoriasis.

Another study, this time comparing risankizumab and ustekinumab, was carried out by Papp et al. [20]. It was a multicenter, randomized trial in which 166 patients with moderate or severe psoriasis participated. Patients were randomly assigned to the group with subcutaneous risankizumab (single dose 18 mg or 90 mg or 180 mg at 0, 4 and 16 weeks) or ustekinumab (45 mg or 90 mg, depending on body weight, at week 0, 4, and 16). The primary endpoint for this study was the PASI 90 response or greater at week 12 of the study. At week 12, PASI 90 was achieved by 77% of patients (64 out of 84) using risankizumab at a dose of 90 mg or 180 mg. In
the ustekinumab group, this point was reached by 40% of patients (16 out of 40). PASI 100 was achieved in 45% of patients in the risankizumab 90 mg or 180 mg group, compared to 18% in the ustekinumab group. The effectiveness of treatment with risankizumab was maintained for approximately 20 weeks (the group receiving 90 mg/180 mg). It is also worth noting that patients using risankizumab reported a reduction in joint pain and nail condition improvement, which significantly affects the quality of life of patients with psoriasis [20]. This relatively short clinical trial has shown that risankizumab is more effective in the treatment of moderate to severe psoriasis compared to ustekinumab.

The next multicentre, double-blind, placebo-controlled trial compared the efficacy and safety of risankizumab in the treatment of moderate to severe plaque psoriasis. In this study, the researchers evaluated the efficacy of risankizumab compared to placebo and ustekinumab. The first phase of the study included 506 patients who were at least 18 years old and had moderate-to-severely active Crohn’s disease. It was a randomized, placebo-controlled, double-blind study with comorbidities with psoriasis, such as psoriatic arthritis – reports from recent studies

Recent clinical reports indicate that risankizumab may be an effective therapeutic option in the treatment of comorbidities with psoriasis, such as psoriatic arthritis and Crohn’s disease.

Feagan et al. [23] conducted an interesting study on the efficacy of risankizumab in patients with moderately-to-severely active Crohn’s disease. It was a randomized, double-blind, placebo-controlled study that included patients between 18 and 75 years of age, diagnosed with moderate-to-severe Crohn’s disease lasting at least 3 months. Patients were divided into three groups in a 1:1:1 ratio. Patients received intravenously risankizumab 200 mg, 600 mg or placebo. The intervention
took place at week 0, 4 and 8 of the study. The primary endpoint was clinical remission (CDAI < 150) at week 12. At week 12 of the study, 25 out of 82 patients with risankizumab (total 41 patients in 200 mg and 41 patients in the 600 mg arms) had clinical remission compared to six (15%, respectively) of the 39 patients in the placebo group. This short study shows that risankizumab was more effective than placebo in the induction of clinical remission in patients with active Crohn’s disease [23].

In subsequent clinical trials of risankizumab and its effectiveness in the treatment of Crohn’s disease, encouraging results were also obtained. 101 patients who completed the study described above were divided into three groups (33 patients in the placebo group, 34 in the 200 mg risankizumab group and 34 in the 600 mg risankizumab group). They received intravenous therapy with 600 mg risankizumab; the drug was administered every 4 weeks for 12 weeks. Remission induction was achieved in a larger proportion of patients at week 26 of the study compared to week 12: 18 (55%) compared to 6 (18%) of 33 patients in the original placebo group; 20 (59%) vs. 7 (21%) of 34 patients in the primary risankizumab group 200 mg; and 16 (47%) vs. 9 (26%) of 34 patients in the original 600 mg risankizumab group. Of the 62 patients who received subcutaneous maintenance therapy (180 mg risankizumab), at week 52, 44 patients (71%) maintained clinical remission, 50 (81%) had a clinical response, 22 (35%) had endoscopic remission, and 34 (55%) had an endoscopic response [24]. The study shows that risankizumab may be an effective therapy for patients with moderate to severe Crohn’s disease, but more studies are needed to confirm its safety and efficacy in the treatment of this disease.

Promising results have also been obtained with respect to the treatment of psoriatic arthritis. In a randomized, double-blind, 24-week study, including patients with active psoriatic arthritis (n = 185), risankizumab 150 mg administered subcutaneously significantly improved joint and skin symptoms compared to placebo. The primary endpoint was an improvement of ≥ 20% in the American College of Rheumatology (ACR20) criteria at week 16 of the study. An improvement of ≥ 20% at week 16 among risankizumab dosage groups (150 mg at weeks 0, 4, 8, 12, and 16; 150 mg at weeks 0, 4, and 16; 150 mg at weeks 0 and 12; and a 75 mg single dose at week 0) was achieved in 57.1%, 61.9%, 59.0% and 65.0% of patients, respectively, compared with 35.7% in the placebo group [25, 26]. The above studies show that risankizumab is also effective in relieving and treating psoriasis-related diseases.

Conclusions
Clinical studies indicate that risankizumab may be a good therapeutic option in the treatment of moderate to severe plaque psoriasis. What is more, it is characterized by a very good safety profile and significant efficacy in the treatment of psoriasis, which exceeds the efficacy of ustekinumab. In February 2019 risankizumab after positive assessment by the Committee for Medicinal Products for Human Use (CHMP) was approved for the treatment of psoriasis by the Committee for Medicinal Products EMA, so it is worth considering a therapeutic option using this drug [27]. The above clinical trials proved that it is a very effective and safe therapeutic option.

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