CLINICAL OBSERVATIONS

Experience with guselkumab in the treatment of patients with psoriatic arthritis in real-world clinical practice

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The article presents an analysis of literature on the efficacy and safety of a new biologic disease-modifying antirheumatic drug, the interleukin 23 inhibitor guselkumab (GUS), in the treatment of patients with psoriatic arthritis (PsA). Two of our own clinical observations of GUS therapy are described. It has been demonstrated that in PsA of moderate activity and in severe to moderate psoriasis with nail damage, the use of GUS (100 mg at weeks 0 and 4, and then every 8 weeks), allows to achieve remission of peripheral arthritis, enthesitis and psoriasis by the 20th week of treatment as in the monotherapy regimen and in combination with methotrexate. When GUS is re-prescribed (re-treatment) after a long break (10 months), its effectiveness is quickly and completely restored. The safety of GUS was confirmed in patients with comorbidities, in particular, Gilbert's syndrome, hyperuricemia, metabolic disorders (abdominal obesity).

Key words: *psoriatic arthritis; psoriasis; guselkumab; biologic disease modifying antirheumatic drugs*
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Psoriatic arthritis (PsA) is an immunoinflammatory rheumatic disease, which primarily affects the joints, spine and entheses and usually occurs in patients with psoriasis [1]. A number of highly efficient drug products (DP) called genetically engineering biological drugs (GEBD) are currently being introduced into clinical practice for the treatment of PsA. Most of these drugs are monoclonal antibodies against key cytokines such as tumor necrosis factor α (FNα), interleukin (IL) 17a, IL12/23 and IL23 [2]. The benefits of this DP class are high efficacy against primary clinical manifestations of PsA (arthritis, enthesitis, dactylitis, spondylitis, psoriasis), as well as well-controlled safety. The first GEBDs authorized for the treatment of PSA and psoriasis were TNF-α inhibitors (TNFαI), which are the most studied class of biological drugs date [3]. The GEBD spectrum is constantly expanding due to emergence of new DP classes which selectively act on certain pathophysiological stages of PsA and psoriasis. Recently, IL-23 inhibitors (IL-23i) have been actively studied and introduced into rheumatological, as well as dermatological and venereological, practice. These include guselkumab (GUS) and risankizumab. Another IL-23i, tildrakizumab, is undergoing phase III clinical trials [4].

The wide range of existing GEBD calls for a personalized approach to the choice of drugs based on the principle “the right drug for the right patient at the right time” [5]. Therefore, the value of analyzing the data of individual clinical cases which describe the use of various DPs for the treatment of PsA is increasing.

HUS is a human monoclonal antibody IgG1λ (IgG1λ) which selectively blocks IL-23 by binding to its p19 subunit. As a result, the expression of a number of other pro-inflammatory cytokines and chemokines is suppressed. Thus, the mechanism of action of this drug is based on decreasing serum concentrations of IL-17A, IL-17F and IL-22.

In 2020, GUS became the first IL-23i in the United States to be approved by the Food and Drug Administration (FDA) for active PsA. Since 2021, GUS has been authorized in the Russian Federation for the treatment of both moderate or severe psoriasis and active PsA in patients with previous failure of synthetic synthetic disease-modifying antirheumatic drug (sDMARDs). Efficacy of this DP in psoriasis and PsA was demonstrated in a number of randomized clinical trials (RCTs): VOYAGE 1, VOYAGE 2, NAVIGATE, DISCOVER-1, DISCOVER-2.

The results of preclinical and clinical studies obtained to date indicate that the IL-23/IL-17 axis plays a key role in the pathophysiology of skin and articular manifestations of PsA [6–8]. Inhibition of the IL-23 ascending signaling pathway reduces the production of cytokines, which have been shown to be involved in the pathophysiology of the disease (TNFα and IL-17) [9]. It was also recognized that an IL-23 block by transdifferentiation of Th-17 lymphocytes (apparently, key effector cells in psoriasis and PsA) into T-regulatory cells or Th-123 cell population block interrupts Th-17 differentiation pathways. Activation of these pathways contributes to the development and maintenance of chronic inflammation underlying immunopathogenesis and clinical manifestations of the group of diseases being reviewed [6, 10].

The mechanism of action of GUS is different from that of ustekinumab, which inhibits IL-23 by acting on the p40 subunit common to IL-23 and IL-12. As the protective role of IL-12 is to limit the recruitment of IL-17-producing λδ T-cells in the process of skin inflammation in psoriasis, selective targeting of IL-23 through binding its p19 subunit represents a new mechanism underlying the effective treatment of various manifestations of PsA [11].

It is also important to note the clinical rationality of the use of GEBD with different mechanisms of action in the treatment of PsA and psoriasis, since by now prolonged use of a number of drugs of this class has been proven to lead to secondary failure. In addition, the safety profile of therapy must be further improved, since the use of GEBD increases the risk of serious infections, for example, the onset/reactivation of latent tuberculosis, “paradoxical” psoriasis (more characteristic of TNFα), fungal infections or exacerbation/development of inflammatory bowel disease (reported in rare cases with IL-17Ai, according to RCTs) [12–16].

In a phase II RCT, GUS 100 mg demonstrated high efficacy in all endpoints: arthritis, enthesitis, dactylitis, psoriasis, and quality of life. A decrease in serum concentrations of IL-17A, IL-17F, and CRP along with clinical improvement was observed in patients receiving

GUS. At the same time, there were no significant differences in serum levels of IL-17A and IL-17F in patients receiving GUS and healthy controls a week after the start of treatment [17].

A. Deodhar et al. [18] recently published the results of a phase III, multicenter, double-blind, placebo-controlled RCT (DISCOVER-1), which was conducted in 86 centers in 13 countries in Asia, Australia, Europe and North America. The study included patients with active PsA with inadequate response to or intolerance of standard treatment, including the use of apremilast for at least 4 months, sDMARDs for at least 3 months, or non-steroidal anti-inflammatory drugs (NSAIDs) for at least 4 weeks. About 30% of participants may have previously received one or two TNFαI. A total of 624 patients were randomized, of which 381 were randomly assigned to three groups: patients in groups 1 (n = 128) and 2 (n = 127) initially received GUS 100 mg Q4W or Q8W, respectively, and patients in group 3 (n = 126) received placebo (PL). 362 patients continued to participate in the study at week 24. A significant number of patients in groups 1 and 2 achieved ACR20 criteria at week 24: 59% (76 out of 128) and 52% (66 out of 127), respectively, compared to only 22% patients in the PL group (28 out of 126; p <0.0001 for both comparisons). No patients in group 1, 4 (3%) patients in group 2, and 5 (4%) patients in the PL group experienced serious adverse drug reactions (ADRs) prior to Week 24 of therapy. At the same time, there was 1 death associated with heart failure and 2 cases of serious infections in the PL group before Week 24. There were no deaths or severe infections in the active treatment groups.

The aim of the DISCOVER-2 phase III study was to evaluate the efficacy of GUS in two dosing regimens in PsA patients who had not previously been treated with GEBDs. 741 patients with active PsA (more than 5 inflamed joints) were randomized [19]. By Week 24, 64% of patients receiving GUS, regardless of the treatment regimen, achieved an ACR20 response; the number of such patients in the PL group was almost 2 times less (33%). Evaluation of the data at Week 24 of the study showed that the use of GUS significantly improved the quality of life of patients with PsA. It should be noted that by this time a quarter of patients treated with GUS (versus 11% in the PL group) had reached the minimum disease activity: they experienced decreased severity of joint pain and improved physical functioning. In addition, according to the cumulative data obtained with additional statistical analysis, there were no differences in the efficacy of GUS at a dose of 100 mg Q4W or Q8W.

The DISCOVER-2 study demonstrated not only a decrease in the activity of articular manifestations of PsA during GUS therapy, but also a slowdown in the progression of structural joint damage at a dose of 100 mg Q4W [19].

Sub-analysis of data of RCTs presented above demonstrated the ability of GUS to reduce the activity of axial manifestations of PsA, including sacroiliitis diagnosed using imaging methods. However, this needs confirmation in larger studies.

The phase III RCT COSMOS evaluated the efficacy and safety of GUS in PsA patients with inadequate response to one or two TNF-αI [20]. GUS at a dose of 100 mg Q8W for 24 weeks was shown to lead to a higher ACR20 response rate (p <0.001) (44.4%) vs PL (19.8%). There were no differences in safety parameters; the incidence of ADR was similar in patients receiving GUS and PL.

The efficacy of GUS in reducing the severity and prevalence of psoriasis and its safety have been demonstrated in the VOYAGE 1/VOYAGE 2 RCT, including with long-term use of the drug (3 years or more). The incidence of serious ADRs developed by Week 156 of therapy was 5.68 per 100 patient-years; the incidence of serious infections was 1.15, the incidence of non-melanoma skin cancer was 0.28, the incidence of other cancers was 0.47, and the incidence of serious cardiovascular diseases was 0.28 [21]. The efficacy of GUS was shown to be potentially restored after temporary discontinuation and resumption of therapy [22].

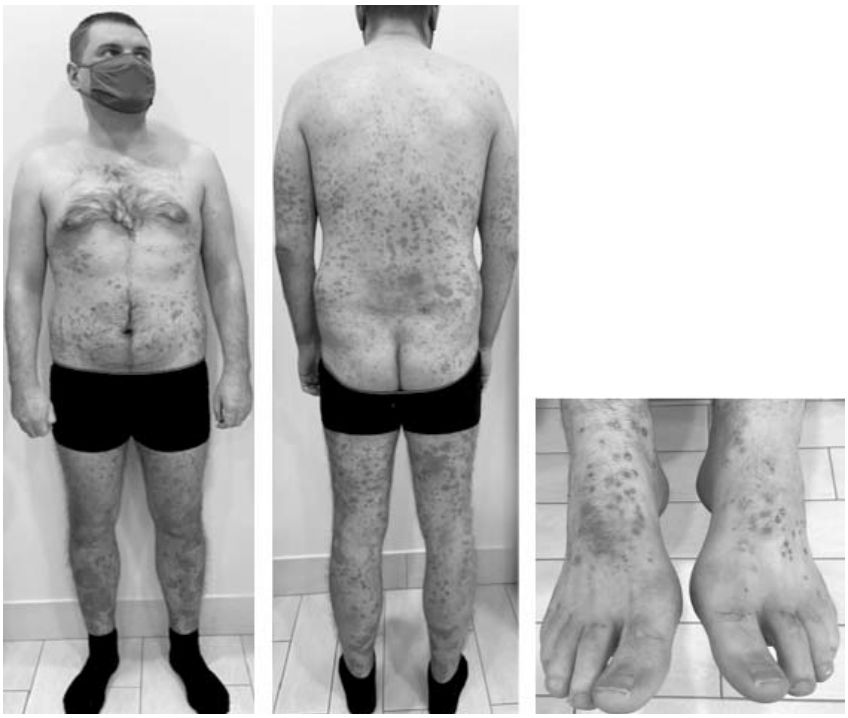

Fig. 1. *Patient G. before the start of GUS therapy: a, b – widespread severe plaque psoriasis (BSA – 40%, PASI – 36 points); c – arthritis of the left ankle joint and the 1st left metatarsophalangeal joint. Marginal onycholysis of great toes.*

Thus, the presented RCT results demonstrate high clinical efficacy and safety of GUS therapy in patients with various clinical manifestations of PsA.

Recently, the results of the GUS efficacy at Week 52 of follow-up were summarized. The portion of patients who achieved an ACR20 response by this time was 71% (173 of 245) and 75% (185 of 248) for patients randomized to receive GUS 100 mg Q4W and Q8W, respectively. The high efficacy of treatment was demonstrated, among other things, by complete resolution of dactylitis (reported in more than 70% of cases) and enthesitis (54%). Slower X-ray progression in the joints, as well as improvement in the quality of life (SF-36, HAQ-DI), were reported both at Week 52 and Week 24 of therapy [23].

There are currently no RCTs with direct comparison of clinical efficacy of GUS and other GEBDs. However, data from a recently conducted meta-analysis show that GUS is superior to other GEBDs (IL-17Ai, TNFαI) according to PASI (Psoriasis Activity and Severity Index) 75/90 and has a similar effect on articular manifestations of the disease and PASI100 response [24].

We present case reports demonstrating the efficacy and safety of GUS in real-world clinical practice.

Case report 1

Patient G., male, 33 years old, referred to FSBRI "Research Institute of Rheumatology named after V.A. Nasonova" (RIR named after V.A. Nasonova) in November 2020. He had suffered from plaque and scalp psoriasis since the age of 17. The patient was observed by a dermatologist, received topical therapy (Belosalic) and PUVA, which were ineffective. Episodes of inflammatory pain in the lumbar spine since January 2018. Pain and swelling of the first metatarsophalangeal joints (MTPJ) of the feet, exacerbation of psoriasis since the spring of 2018. In December 2019 the dermatologist prescribed subcutaneous (s/c) methotrexate (MT) (Metoject) 7.5 mg once a week for widespread active psoriasis. After three injections, there was a 5-fold increase in the activity of hepatic transaminases, as well as the level of bilirubin. As a result, MT was discontinued. Pain and swelling of the right ankle joint and right Achilles tendon since July 2020 while taking the phosphodiesterase 4 inhibitor apremilast (Otezla) 60 mg/day; the drug was started in April 2020 and discontinued in October of the same year due to lack of efficacy. The patient took nimesulide 200 mg/day, which had a short-term effect.

In June 2020, due to an increase in serum uric acid (UA) up to 542 μmol/L, allopurinol 100 mg/day was added to therapy; the dose was increased to 200 mg/day in November 2020. UA decreased down to 366.5 μmol/L. Psoriasis, arthritis and spondylitis remained active despite ongoing therapy.

Concomitant diseases: Gilbert's syndrome, hyperuricemia. Heredity: patient's father suffers from gout.

Examination: general condition is satisfactory. Height 200 cm, body weight 105 kg, body mass index (BMI) 26. Widespread plaque psoriasis of skin and scalp (Fig. 1, a, b). BSA (Body Surface Area) 40%, PASI 36 points. Marginal onycholysis of the first toes. Arthritis of the first left MTPJ and left ankle joint (Fig. 1, c). Tender joint count (TJC): 2, swollen joint count (SJC): 2, pain assessment on the visual analogue scale (VAS): 20 mm, patient/doctor assessment of disease activity: 40/40 mm according to the VAS. Achillodynia on the right. Inflammatory pain in the lumbar spine.

Blood tests: C-reactive protein 0.2 mg/L, ESR 2 mm/h, HLA-B27 negative. X-ray of the feet: Hallux valgus, suspected erosion of the first interphalangeal joint (IPJ) of the left foot, osteophyte of the first left metatarsal bone head. X-ray of the hands: narrowing of several joint spaces. X-ray of the pelvis and magnetic resonance imaging of the sacroiliac joints: no reliable radiographic or MR signs of sacroiliitis were found. X-ray of the spine revealed local calcification of the anterior longitudinal ligament in the lower thoracic region (syndesmophyte).

Diagnosis: psoriatic spondylitis of the lumbar spine, HLA-B27-negative, oligoarthritis, stage II, right achillodynia, moderately active, BASDAI (Bath Ankylosing Spondylitis Disease Activity Index) 3, DAPSA (Disease Activity in Psoriatic Arthritis) 10, functional failure (FF) 1. Common plaque psoriasis, severe (BSA 40%, PASI 36 points), M07.2. Secondary hyperuricemia. Gilbert's syndrome.

Considering the ongoing activity of PsA, the involvement of the axial skeleton, severe psoriasis, MT intolerance, the lack of efficacy of apremilast and NSAIDs, and concomitant diseases, genetically engineered biological therapy with IL-23 inhibitor GUS (Tremfya) was prescribed. The first injection of GUS 100 mg s/c was performed on December 21, 2020 in the day hospital at the RIR named after V.A. Nasonova. The drug was well tolerated, there were no adverse reactions (AR). 4 weeks before the second injection of HUS, the patient noted the disappearance of pain in the joints (except for the first MTPJ of the left foot), the absence of morning stiffness and inflammatory back pain (IBP); by the 10th day after the 1st injection, he stopped taking nimesulide. DAPSA 3.64, BASDAI 2.4. The area of psoriasis remained the same, however, the severity of hyperemia, peeling and induration of the skin decreased; PASI 21.8. ESR 2 mm/h, C-reactive protein 1.44 mg/L, UA 382 μmol/L, aspartate aminotransferase (AST) 37.9 U/L. After a diet violation, alanine aminotransferase (ALT)

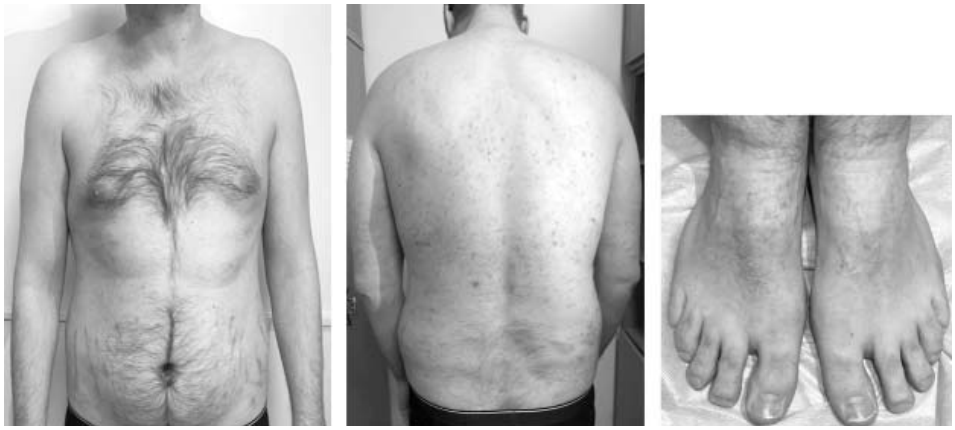

Fig. 2. *Patient D. after 12 weeks of GUS therapy: a, b – decrease in the area and severity of psoriasis (BSA – 3%, PASI – 1.4 points), c – absence of arthritis and enthesitis of the feet*

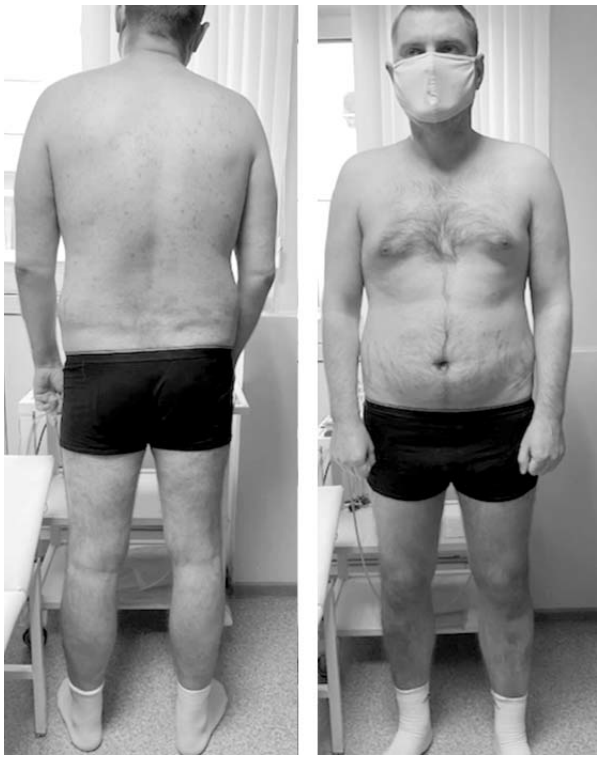

Fig. 3. *Patient G. after 20 weeks of GUS therapy: a, b – remission of psoriasis (BSA – 0.5%) and PsA (DAPSA – 0.33)*

was 86 U/L, total bilirubin was 41.4 μmol/L, direct bilirubin was 8.7 μmol/L. GUS therapy was continued with 8-week intervals between injections. 12 weeks later (before the 3rd injection): BSA 3%, PASI 1.4, no arthritis or enthesitis (Fig. 2, a – c). ESR - 2 mm/h, C-reactive protein 1.02 mg/L, UA 322 μmol/L, ALT 57.2 U/L, AST 28 U/L, total bilirubin 18.8 μmol/L, direct bilirubin 6.1 μmol/L (normal limit <5 μmol/L).

Remission was reported after 20 weeks of GUS therapy (before the 4th injection). TJC/SJC 0, no IBP, DAPSA 0.33, BASDAI 0.8, BSA 0.5% (slight peeling remained in the scalp area), single point depressions - pitting of the fourth finger nail on the right hand and oil drop signs under the nails of the first toes (Fig. 3, a, b). Blood tests: ESR 2 mm/h, C-reactive protein 1.33 mg/L, UA 383 mmol/L, slightly increased ALT 69.3 U/L, total bilirubin 42.6 mmol/L and direct bilirubin 10.7 mmol/L.

Remission of all clinical manifestations of PsA remained by Week 28 of observation; there was a slight increase in total bilirubin (up to 28 μmol/L) and direct bilirubin (up to 8.1 μmol/L), ALT values returned to normal.

Case report 2

Patient K.*, male, 34 years old, has been observed at FSBRI RIR named after V.A. Nasonova since 2013. He has suffered from psoriasis since the age of one. A dermatologist established the following diagnosis: psoriasis vulgaris, widespread, progressive stage (BSA 19%, PASI 19.7). Nail psoriasis. Nodular acne. The patient received intramuscular (i/m) MT 20, 15 mg/week for 8 months, folic acid, topical Flucinar, Dermovate; however, there was an incomplete regression of rashes. In 2014, the MT dose was increased to 25 mg/week i/m. Due to the worsening of psoriasis since October 1, 2014, the patient interrupted the treatment. Retinol therapy with palmitate (December 27, 2013 to February 21, 2014) had no effect. The patient noted joint pain, took etoricoxib (Arcoxia) 60 mg/day for a month with insufficient effect.*

Ultrasound of entheses (November 29, 2013): signs of enthesopathy of the left medial ligament, right infrapatellar bursitis in the area of the knee joints. Right foot examination revealed fluid in the cavity of the ankle joint and tarsal joints, as well as talonavicular synovitis and retrocalcaneal bursitis; signs of flexor tendovaginitis, a small amount of fluid of increased echo density in the retrocalcaneal bursa in the left foot. Ultrasound of the hands revealed developing osteophytes in the carpometacarpal joint of the thumbs of both hands, synovitis of the wrist joints, II–V metacarpophalangeal, II–V proximal IPJ of the right hand, III–IV metacarpophalangeal and II–V proximal IPJ of the left hand, flexor tendovaginitis of both hands.

In April 2015, the patient visited a rheumatologist complaining of joint pain and morning stiffness, although arthritis was not revealed at the time of examination. The following diagnosis was established: PsA, arthralgia, enthesopathy. The patient continued taking etoricoxib 60 mg/day. Since the patient suffered from widespread plaque psoriasis (BSA 19%, PASI 31.8), he was enrolled in an international clinical study of the efficacy and safety of GUS in patients with moderate to severe plaque psoriasis. GUS injections were performed according to the therapy regimen from April 28, 2015 to February 26, 2020; a good therapeutic effect was observed, psoriasis severity significantly decreased (PASI 1.8 at the last visit).

In October 2020 the patient had exacerbation of psoriasis (BSA 70%), arthritis of the right ankle joint, pain and slight swelling of some joints of the hands. On November 16, 2020, after consultation with a rheumatologist, MT was

resumed at a dose of 15 mg/week s/c, meloxicam 15 mg/day was prescribed, Diprospan was injected into and around the right ankle joint.

On December 25, 2020 GUS was again prescribed to the patient. Before starting treatment, the diagnosis was as follows: psoriatic arthritis, oligoarthritis, moderate activity (DAPSA 18.1), enthesitis (lateral epicondyle in the area of the right elbow joint). Functional class 0. Widespread plaque psoriasis (BSA 42%, PASI 15.5). Nail psoriasis.

According to the examination, the duration of psoriasis before the 1st injection of GS (Visit 1/Week 0) was 33 years, the duration of arthritis was 5 years (onset with arthralgia and enthesopathy), the patient's height was 168 cm, body weight was 92 kg, BMI was 32.6 kg/m2, waist circumference was 101 cm. TJC was 5, SJC was 0. ESR 5 mm/h, CRP 1.2 mg/L, LEI (Leeds Enthesitis Index) 1, DAPSA 18.1, severe psoriasis: BSA 42%, PASI 15.5 (Fig. 4, a, b).

The drug was injected at Weeks 0, 4, 12 and 20. The patient continued to take MT 15 mg/week s/c and meloxicam 15 mg/day. A positive effect was already observed after the 2nd injection of GUS at Week 12: TJC 1, SJC 0, ESR 12 mm/h, CRP 1.0 mg/L, LEI 0, DAPSA 5.1, psoriasis in the stage of regression, areas of skin hyperpigmentation, BSA 0.1% (Fig. 5, a, b).

Positive changes continued up to the 4th injection of GUS, at Week 20 of therapy: TJC 0, SJC 0, ESR 30 mm/h, CRP 1.0 mg/L, LEI 0, DAPSA 1.1, single small psoriatic plaques (BSA 0.1%), skin hyperpigmentation at the site of psoriatic plaques (Fig. 6, a, b).

The achieved treatment success has been maintained for 8 weeks after the 4th injection of the drug. There have been no ARs.

Conclusion. The presented case reports show that the use of GUS at a dose of 100 mg according to the standard regimen (either alone or in combination with MT) in patients with moderately active PsA and moderate to severe psoriasis with nail damage may lead to remission of peripheral arthritis, enthesitis, and psoriasis by Week 20 of treatment. When GUS is resumed (re-treatment) after a long break (10 months), its efficacy is quickly and completely restored. The safety of GUS was confirmed in patients with comorbidities, in particular, Gilbert's syndrome, hyperuricemia, metabolic disorders (abdominal obesity).

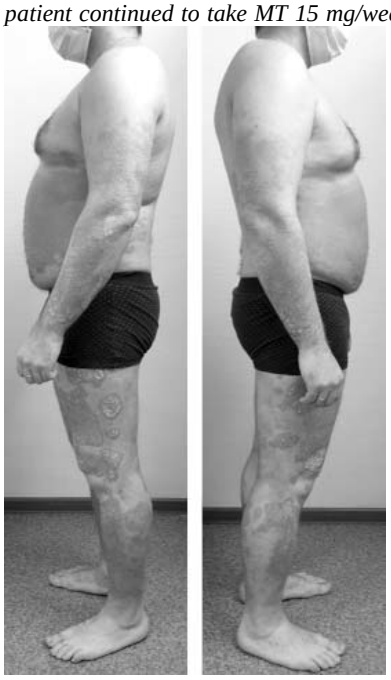

Fig. 4. *Patient K. before GUS treatment (a, b)*

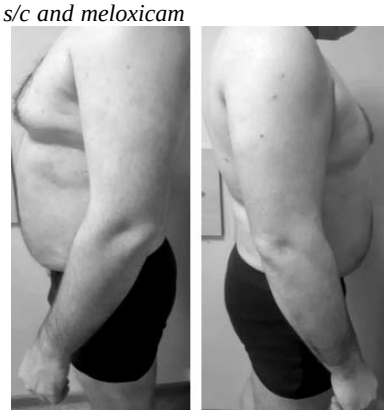

Fig. 5. *Patient K. after the 2nd injection of GUS, 12th week (a, b)*

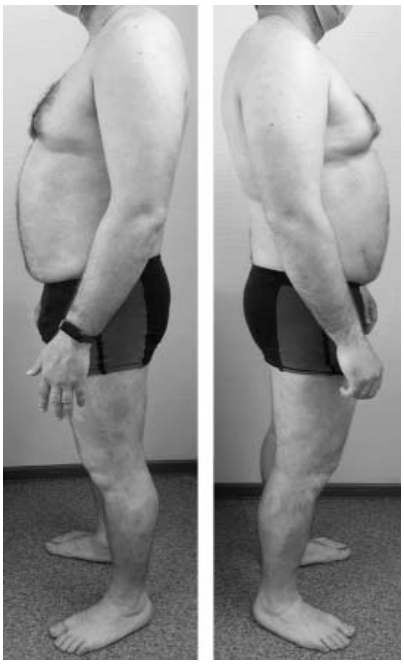

Fig. 6. *Patient K. after the 3rd injection of GUS, week 20 (a, b)*

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Conflict of Interest Statement

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