Prospects for the use of monoclonal antibodies to interleukin 23 Guselkumab in psoriatic arthritis: New data

Evgeny L. Nasonov[1,2], Tatiana V. Korotaeva[1], Stefano Rodolfi[3,4], Carlo F. Selmi[3,4]

Насонов Е.Л. – д.м.н., профессор, академик РАН, научный руководитель ФГБНУ «НИИР им. В.А. Насоновой»

Коротаева Т.В. – д.м.н., начальник отдела спондилоартритов, заведующая лаборатории псориатического артрита, ФГБНУ «НИИР им. В.А. Насоновой»

С. Родольфи – Руководитель лаборатории ревматологии и клинической иммунологии Гуманитарного клинического и научного центра (IRCCS), Милан, Италия

Селми К.Ф. – Зав. отделением ревматологии и клинической иммунологии Гуманитарного клинического и научного центра (IRCCS); доцент кафедры ревматологии Гуманитарного Университета, Милан, Италия.

[1]V.A. Nasonova Research Institute of Rheumatology 115522, Russian Federation, Moscow, Kashirskoye Highway, 34A
[2]I.M. Sechenov First Moscow State Medical University of the Ministry of Health Care of Russian Federation (Sechenov University) 119991, Russian Federation, Moscow, Trubetskaya str., 8, building 2
[3]Rheumatology and Clinical Immunology, Humanitas Clinical and Research Center (IRCCS), Rozzano, Milan, Italy
[4]Humanitas University, Department of Biomedical Sciences, Pieve Emanuele, Milan, Italy

Among the pathophysiological mechanisms of immune-mediated inflammatory diseases (IMIDs), specific attention has been paid to the abnormal activation of Th17 type immune response related to the dysregulated synthesis of cytokines forming the interleukin (IL)-23 and IL-17 axis. IL-23 blockade is an innovative approach to the treatment of psoriasis and psoriatic arthritis (PsA). Much of the interest has focused on guselkumab (GUS) (TREMFYA, Janssen, Johnson & Johnson, USA), a fully human IgG λ monoclonal antibody (mAb) targeting the p19 IL-23 subunit and the first-in-class treatment approved for patients with psoriasis and PsA. In patients with psoriasis, GUS is at least as effective as other biologic therapies for PsA and is superior to ustekinumab, an anti-IL-12/IL-23 mAb, and secukinumab, an anti-IL-17 mAb. Compared with TNF-α inhibitors, GUS therapy is less likely to cause infections and does not increase the risk of the reactivation of latent TB infection. The new GRAPPA guidelines (2021) recommend GUS (and other IL-23 inhibitors) for patients with PsA resistant to conventional disease-modifying antirheumatic drugs (DMARDs), who have peripheral arthritis, enthesitis, dactylitis, psoriatic skin and nail lesions. The paper discusses new data on the efficacy of GUS in patients resistant to TNF-α inhibitors, its benefits in patients with axial PsA, and safety during the COVID-19 pandemic.

Key words: interleukin 12, interleukin 23, psoriatic arthritis, guselkumab.
For citation: Nasonov EL, Korotaeva TV, Rodolfi S, Selmi CF. Prospects for the use of monoclonal antibodies to interleukin 23 Guselkumab in psoriatic arthritis: New data. *Nauchcno-Prakticheskaya Revmatologia = Rheumatology Science and Practice*. 2022;60(1):80–90 (In Russ.).

ПЕРСПЕКТИВЫ ПРИМЕНЕНИЯ МОНОКЛОНАЛЬНЫХ АНТИТЕЛ К ИНТЕРЛЕЙКИНУ 23 ГУСЕЛЬКУМАБА ПРИ ПСОРИАТИЧЕСКОМ АРТРИТЕ: НОВЫЕ ДАННЫЕ

Е.Л. Насонов[1,2], Т.В. Коротаева[1], С. Родолфи[3,4], К.Ф. Селми[3,4]

В спектре механизмов патогенеза иммуновоспалительных заболеваний (ИВЗ) человека особое внимание привлечено к патологической активации Th17-типа иммунного ответа, связанного с дисрегуляцией синтеза цитокинов, формирующих ось интерлейкин (ИЛ) 23 и ИЛ-17. Блокада ИЛ-23 является инновационным подходом к лечению псориаза и псориатического артрита (ПсА). Особый интерес привлекает гуселькумаб

[1]ФГБНУ «Научно-исследовательский институт ревматологии им. В.А. Насоновой» 115522, Российская Федерация, Москва, Каширское шоссе, 34а
[2]ФГАОУ ВО «Первый Московский государственный медицинский университет имени И.М. Сеченова» Минздрава России (Сеченовский Университет) 119991, Российская Федерация, Москва, ул. Трубецкая, 8, стр. 2
[3]Ревматология и Клиническая иммунология, Гуманитарный Клинический и Научный Центр (IRCCS), Роццано, Милан, Италия
[4]Гуманитарный Университет, Отделение Биомедицинских Наук, Пьеве Эмануэле, Милан, Италия

Corresponding author: Yevgeny Lvovich Nasonov; **nasonov@irramn.ru**
Контакты: Е.Л. Насонов; **nasonov@irramn.ru**

Поступила 30.04.2021
Принята 21.12.2021

(ГУС) (Guselkumab, TREMFYA, Janssen, Johnson&Johnson, США), который представляет собой полностью человеческие моноклональные антитела (мАТ) IgG-λ, взаимодействующие с p19-субъединицей ИЛ-23, и является первым препаратом этого класса, разрешенным к применению у пациентов с псориазом и ПсА. ГУС не уступает по эффективности другим генно-инженерным биологическим препаратам, использующимся для лечения ПсА, и более эффективен у пациентов с псориазом, чем мАТ к ИЛ-12/ИЛ-23 устекинумаб и мАТ к ИЛ-17 секукинумаб. По сравнению с ингибиторами фактора некроза опухоли альфа (ФНО-α) ГУС реже вызывает развитие инфекционных осложнений и не увеличивает риск реактивации латентной туберкулезной инфекции. В новых рекомендациях GRAPPA (2021) применение ГУС (и других ингибиторов ИЛ-23) рекомендуется пациентам с ПсА, резистентным к терапии стандартными БПВП, имеющим периферический артрит, энтезиты, дактилит, псориатическое поражение кожи и ногтей. Обсуждаются новые данные, касающиеся эффективности ГУС у пациентов, резистентных к ингибиторам ФНО-α, положительного влияния терапии на аксиальные проявления ПсА и безопасности применения ГУС в период пандемии COVID-19.

Ключевые слова: интерлейкин 12, интерлейкин 23, псориатический артрит, гуселькумаб
Для цитирования: Насонов ЕЛ, Коротаева ТВ, Родолфи С, Селми КФ. Перспективы применения моноклональных антител к интерлейкину 23 гуселькумаба при псориатическом артрите: новые данные. *Научно-практическая ревматология*. 2022;60(1):80–90.
doi: 10.47360/1995-4484-2022-80-90

Introduction

Among the immune mechanisms involved in the pathogenesis of immune-mediated inflammatory diseases, specific attention has been focused on the abnormal activation of Th17 type of immune response related to the imbalance in the synthesis of cytokines forming the interleukin (IL)-23/IL-17 axis that regulates mucosal immunity and barrier function of the gut, ultimately involved in the protection against bacterial and fungal infections[1]. IL-23 plays a key role in Th17 cell differentiation and proliferation and belongs to the IL-12 family of cytokines including also IL-27, IL-35, and IL-39[1], all sharing some degree of structural homology with cytokines of the IL-6 superfamily[2]. Despite belonging to the same family, IL-12 and IL-23 play different roles in the regulation of immune responses[1]. IL-12 stimulates polarization of antigen-activated T cells towards a Th1 phenotype characterized by interferon (IFN)-γ synthesis while IL-23 induces and maintains a Th17 type of immune response. The IL-17/IL-23 axis is thought to play a more important role in autoimmune pathology than IL-12/IFN-γ [3 4]. Th17 cells are characterized by a specific gene signature involving the transcription factor retinoic acid-receptor-related orphan receptor (RORγt) and induce synthesis of proinflammatory cytokines such as IL-17, IL-22, TNF-α, IL-21, and granulocyte-macrophage colony-stimulating factor (GM-CSF). Naïve T helper cells do not express the IL-23 receptor and need stimulation by transforming growth factor (TFG)-β in the presence of proinflammatory cytokines, primarily IL-6, to respond to IL-23 stimulation. This is mediated by signal transducer and activator of transcription (STAR3)-dependent activation of Th17 cell genes (*IL-23R, Rorc, IL-17*) [5]. STAR3 is also responsible for the downregulation of transcription factor forkhead box P3 (FOXP3), which normally suppresses the expression of RORγt and mediates the differentiation of naïve T cells into T regulatory cells (Tregs). This ultimately results in dysregulation of the balance between Th17/Tregs in favour of the proinflammatory Th17 phenotype[6]. Until recently, Th17 cells induced by TGF-β and IL-6 were thought to have limited pathogenetic implication however, the trans-presentation of IL-6 by dendritic cells that bind to IL-6R has been recently shown to be involved in the generation of pathogenic Th17 cells [7 8]. Although IL-23 alone cannot induce differentiation of naive CD4+ T cells into Th17 cells, it plays a fundamental role in maintaining the pathogenic pro-inflammatory phenotype of Th17 cells (*Rorc and IL17*) and their effector genes (*IL22, Csf2, Ifng*) by inducing *IL23* gene expression and inhibiting synthesis of cytokine (IL-2, IL-27, and IL-12) that suppress Th17 cell activation and differentiation [9 10]. The IL-17 family comprises marker cytokines reflecting activation of the IL-23/IL-17 axis. These include 6 cytokines: IL-17A, IL-17B, IL-17C, IL-17D, IL-17E (also known as IL-25), and IL-17F [11]. IL-17A (as well as IL-17F) bears the most potent proinflammatory activity. IL-17B, IL-17C, and IL-17D are also classified as pro-inflammatory cytokines, unlike IL-17E, which is involved in Th2 cell generation and inhibits Th17 cell activation. IL-17 acts synergistically with other cytokines (TNF-α, IL-1β, IL-22, IFN-γ, GM-CSF) to promote the induction and persistence of inflammation at the target site.

This review will focus on the role of IL-23 inhibition in psoriatic artritis (PsA), classified

as a mixed-pattern disease with interwoven autoinflammatory and autoimmune responses [1], whose key pathogenic pathways are related to activation of the IL-23/IL-17 axis [12 13]. This is supported by different lines of evidence [14 4]. First, there are increased transcript levels of IL-23 and IL-23-related cytokines IL-17A, IL-21, and chemokine ligand 13 (CXCL13) in the synovial tissue collected from patients with PsA. Second, data show a correlation between an increased number of IL-23p19 and IL-23R cells in the synovial tissue with inflammatory activity and lymphoid-myeloid and diffuse myeloid pathotypes. Third, there is the hyperexpression of IL-23R in cells from inflammatory infiltrates of joint tissues and entheses in patients with PsA; fourth, several IL-23R gene polymorphisms (IL12B, IL23A, IL23R, STAT3) are associated with the risk of developing PsA. Finally, elevated levels of IL-17 and IL-23 in the serum and synovial fluid correlate with inflammatory activity of PsA.

Literature search

We conducted a search in the MEDLINE databases (via PubMed) that included all relevant publications until December 1, 2021. The following keywords were used when searching English-language publications in PubMed: "immune-mediated diseases," or "systemic autoimmune rheumatic diseases," or "arthritis," or "psoriasis," or "psoriatic arthritis" and "biologics," or "DMARDs," or "interleukin 23 inhibitors," or "guselkumab". Out of 1665 identified papers, 71 papers focused on the use of guselkumab in immune-mediated inflammatory diseases.

Guselkumab in psoriatic arthritis

Currently, the blockade of IL-23 (along with IL-17 and TNF-α) is considered to be an effective approach to the treatment of PsA and other IMIDs associated with the activation of the IL-23/IL-17 axis [15 16]. The class of IL-23 inhibitors comprises anti-IL-12/IL-23 p40 mAbs (ustekinumab and briakinumab) and anti-IL-23 p19 monoclonal antibody (guselkumab, risankizumab, and tildrakizumab), as well as JAK inhibitors blocking the downstream signaling of this cytokine. Guselkumab (GUS) (Tremfya, Janssen, Johnson & Johnson, USA) is an human IgGλ monoclonal antibody targeting with high affinity the IL-23 p19 subunit. GUS is the first-in-class treatment approved in the United States, Europe, and Russia for patients with psoriasis and the only treatment for PsA.

GUS blocks the interaction between IL-23 and membrane IL-23R to abrogate the IL-23-mediated signaling involved in the activation of the proinflammatory cytokine cascade. In patients with PsA, decreases in C-reactive protein (CRP) and serum amyloid protein A (SSA) levels, IL-6, and Th17 effector cytokines, such as IL-17A, IL-17F, and IL-22, were noted as early as 4 weeks of GUS therapy and continued to decrease through Week 24 ($p < 0.05$). GUS therapy produced greater decreases in these cytokines compared with ustekinumab. Notably, while baseline IL-17A and IL-17F levels correlated with disease activity and response to therapy in cutaneous psoriasis in PsA, these levels were not associated with disease activity in the joints in PsA, suggesting that mechanisms responsible for musculoskeletal and skin manifestations in PsA may not be the same [17]. Maintenance of response to GUS in patients with psoriasis was associated with suppression of IL-17A, IL-17F, IL-22, and IL-21, whereas increased levels of these cytokines predicted psoriasis reoccurrence [18].

In patients with psoriasis and PsA, GUS has a linear pharmacokinetic profile (at doses up to 10–300 mg SC) [19], with the steady-state serum concentration increasing from 1.2 μg/mL to 3.8 μg/mL in a dose-proportional manner and bioavailability of 49%. In patients with psoriasis, a volume of distribution of 15.3 L, a clearance of 0.516 L/day, and a half-life of 18.1 days were derived from a population pharmacokinetic model [19 20]. Similar to native IgG, GUS is eliminated by intracellular catabolism, breaking down into amino acids and peptides. Liver and renal insufficiency, concomitant use of non-steroidal anti-inflammatory drugs (NSAIDs) or conventional DMARDs, including methotrexate (MTX), do not affect the pharmacokinetics of GUS.

Other molecules targeting IL-23 include tildrakizumab and risankizumab which provided good efficacy and safety profiles in treatment of psoriatic arthritis when compared to placebo in phase IIb[21] and phase III[22 23] double-blind trials, respectively.

Efficacy

GUS has demonstrated efficacy in treating skin disease (PASI75/90/100) in patients with psoriasis in phase 2 and 3 randomized placebo-controlled trials (RPCTs): X-PLORE (versus placebo[24]), VOYAGE 1 (versus placebo and adalimumab, an anti-TNF-α mAb)[25], VOYAGE 2 (versus placebo and adalimumab)[26], ECLIPSE (versus secukinumab, an anti-IL-17A mAb) [27 28], ORION [29], M Ohtsuki et al. [30], NAVIGATE (an inadequate response to ustekinumab, an anti-IL-12/IL-23 mAb)[31]. The efficacy of GUS in PsA has been evaluated in phase 2a [32] and 3 multicenter Randomized Placebo Controlled Trial (RPCT) DISCOVER-1 [33], DISCOVER-2 [34] (**Table 1**) and COSMOS[35].

The DISCOVER-1 and DISCOVER-2 trials enrolled patients who met the classification criteria for PsA, had ⩾ 3 swollen joints, ⩾ 3 tender joints, a CRP concentration of ⩾ 0.3 mg/dL despite standard therapy, and clinical signs of plaque psoriasis (active or a documented history). In the DISCOVER-1 trial, about 30% of the subjects had received one or two TNF-α inhibitors before randomization while the DISCOVER-2 study enrolled only biologic-naïve patients. In both RPCTs, patients were assigned to receive GUS 100 mg every 4 weeks (GUS Q4W), GUS 100 mg at week 0, 4 and then every 8 weeks (GUS Q8W), and placebo (placebo) every 4 weeks. Patients were stratified by treatment and the baseline CRP level. About 60% of patients received maintenance therapy with MTX. After a 24-week placebo-controlled period, all patients continued to receive GUS Q4W until Week 52 or Week 100 [33 34 36 37]. In both trials, regardless of the GUS regimen, patient demographics, and clinical characteristics (including severity of skin lesions and prior or concomitant therapy), significantly greater proportions of patients receiving guselkumab achieved an ACR20 response compared with placebo. Differences in efficacy between

Table 1. Efficacy of GUS in patients with PsA in the DISCOVER-1 and DISCOVER-2 studies

Patient groups	Efficacy (%)		SF-39MCS LSM mean change from baseline		SF-36-MCS
	ACR20	IGA	HAQ-DI	SF-36 PCS	
Outcomes at Week 24					
DISCOVER-1 (TNF-α-naive and treated)					
GUS 100 mg (8 weeks) (*n* = 127)	52***	57***	–0.32***	6.10***	3.20
GUS 100 mg (4 weeks) (*n* = 128)	59***	75***	–0.40***	6.87***	3.60
Placebo (*n* = 126)	22	15	–0.07	1.96	2.37
DISCOVER-2 (TNF-α-naive)					
GUS 100 mg (8 weeks) (*n* = 248)	64***	70***	–0.37***	7.39*	4.17
GUS 100 mg (4 weeks) (*n* = 245)	64***	68***	–0.40***	7.04*	4.22
Placebo (*n* = 246)	33	19	–0.13	3.42	2.14
Outcomes at Week 52					
DISCOVER-1 (TNF-α-naive and treated)					
Continued GUS 100 mg (8 weeks) (*n* = 127)	60	63	–0.4	6.6	4.4
Continued GUS 100 mg (4 weeks) (*n* = 128)	73	82	–0.50	8.6	4.3
Started GUS 100 mg (4 weeks) (*n* = 126)	56	68	–0.3	5.5	4.1
DISCOVER-2 (TNF-α-naive)					
Continued GUS 100 mg (8 weeks) (*n* = 248)	75	74	–0.5	9.0	4.3
Continued GUS 100 mg (4 weeks) (*n* = 245)	71	79	–0.5	8.6	4.4
Started GUS 100 mg (4 weeks) (*n* = 246)	64	79	–0.4	7.5	4.0

Note: *** $p < 0.0001$; ** $p < 0.001$; * $p < 0.05$; MCS, mental component summary score; PCS, physical component summary score; SF-36, 36-Item Short Form Survey; ACR20, improvement by ≥ 20% in the American College of Rheumatology response criteria; HAQ-DAI, Health Assessment Questionnaire—Disability Index; IGA, Investigator's Global Assessment; LSM, least-squares mean.

GUS and placebo were significant as early as Week 4 after treatment initiation ($p < 0.05$) in DISCOVER-2 [34] and at Week 8 in DISCOVER-1 [33]. Improvements in all individual components of ACR compared with baseline were noted after 24 weeks of GUS therapy [38]. At Week 24, significantly more patients in the GUS Q8W and GUS Q4W groups had an ACR50 response compared with the placebo group: 30%, 39%, and 9%, respectively, in DISCOVER-1, and 31%, 33%, and 14% in DISCOVER-2 ($p < 0.0001$ in all cases). In DISCOVER-1, an ACR70 response at week 24 was achieved in 12% and 20% patients in the GUS Q8W and GUS Q4W groups, respectively, versus only 6% of patients in the placebo group ($p = 0.0005$) and in 19% and 13% versus 4% in the placebo group in DISCOVER-2 ($p \leqslant 0{,}0004$) [33 34]. Consistent changes from baseline in DAS (Disease Activity Score) 28-CRP were reported. At week 24 More patients had minimal disease activity in the GUS Q8W and GUS Q4Q groups compared with the placebo group (23%, 30%, and 11%, respectively; $p \leqslant 0.012$) in DISCOVER-1 and DISCOVER-2 (25%, 19%, and 6%, respectively; $p < 0.0001$). At Week 24, greater reductions from baseline in DAS28-CRP least-squares means (LSMs) were noted in the GUS groups compared with the placebo group ($p < 0.0001$, in all cases). With longer observation periods [36 37 39 40], GUS efficacy (ACR20 response rate) continued to increase and at Week 52 was higher than at Week 24. In the GUS Q4W and GUS Q8W groups, the ACR50 response rate increased from 39% to 54% (DISCOVER-1) and from 48% to 46% (DISCOVER-2); the ACR70 response rate increased from 26% to 29% (DISCOVER-1) and from 28% to 28% (DISCOVER-2). In DISCOVER-2, the ACR20 response rates were 74% (GUS Q8W) and 76% (GUS Q4W) at Week 100. The rates of ACR50 and ACR70 responses were 55% and 36%, respectively, in the GUS Q8W group, and 56% and 35% in the GUS Q4W group.

In all GUS groups, significant improvements in all measurements of skin disease (Global Physician Assessment, IGA skin response and PASI 75%, 90%, and 100%) were noted compared with the placebo group ($p \leqslant 0.0005$, in all cases). Moreover, in a pooled analysis of DISCOVER-1 and -2, increased proportions of resolution of enthesitis were noted in all GUS groups (n = 728): 50% (GUS Q8W), 45% (GUS Q4W), and 29% of patients in the placebo group ($p < 0.05$) at week 24. Consistent findings were reported for dactylitis (n = 473), with its resolution in 59%, 64% and 42% of patients, respectively ($p < 0.05$ in all cases). Both GUS dosing regimens were associated with reductions in LSM Leeds Enthesitis Index score and dactylitis score ($p \leqslant 0.0025$).

Data on the effects of GUS therapy on the changes in sacroiliitis have particular relevance[41]. In earlier studies, ustekinumab and anti-IL-23 monoclonal antibody risankizumab failed to show benefits in patients with ankylosing spondylitis [42 43], as opposed to the high efficacy of anti-IL-17 monoclonal antibody[44 45]. It is not clear why patients with AS and axial involvement did not respond to anti-IL-23 mAb. Possible explanations include the production of IL-17 by various cells (CD8+ cytotoxic T cells, γσ T cells, innate immune cells, CD1x5+ neutrophils, mast cells, etc.) in the entheses and axial skeleton occurring independently from IL-23 [46 47 48]. A pooled (post hoc) analysis of the DISCOVER trials showed improvements in Bath Ankylosing

Spondylitis Disease Activity Index (BASDAI), back pain, and Ankylosing Spondylitis Disease Activity Index (ASDAS)-CRP scores ($p < 0.001$) in patients with PsA (n = 312) after 24 and 52 weeks of GUS treatment regardless of the dose and HLA-B27 positivity status[41]. Currently, a RPCT (NCT04929210) is being planned to evaluate the efficacy of GUS in patients with PsA and axial involvement.

GUS therapy was associated with a reduced risk of radiographic progression of arthritis assessed through changes in the van der Heijde modified Sharp score (vdHS) in DISCOVER-2 [34 39]. At week 24, significant decrease in radiographic progression was detected in the GUS Q4W group, with least squares mean changes in the vdHS score of 0.29, compared with 0.95 in the placebo group ($p = 0.011$). However, no significant difference in this variable was noted between the GUS Q8W and placebo groups (0.52 versus 0.95, p=0.072). Mean changes in the vdHS score were 0.99 (GUS Q8W) and 1.06 (GUS Q4W) from Week 0 to Week 52, and 0.46 and 0.75, respectively, from Week 52 to Week 100. In the placebo group, mean changes in the vdHS score in patients who were switched to GUS Q4W at Week 24 were 1.12 (0–24 weeks), 0.34 (24–52 weeks), and 0.13 (52–100 weeks). GUS significantly improved the patients' quality of life as measured by the Health Assessment Questionnaire—Disability Index (HAQ-DI) and Short Form-36 (SF-36) Questionnaire. Changes in the SF-36 Mental Component Summary scores in the placebo groups were not statistically significant. A pooled analysis of the DISCOVER-1 and DISCOVER-2 trials showed an improvement in fatigue represented by improvements in the Functional Assessment of Chronic Illness (FACIT-FATIGUE) score regardless of the changes in other efficacy endpoints during 1 year of GUS therapy[49].

Data from the phase IIIb RPCT COSMOS focused on the efficacy of GUS in patients with PsA who were resistant to TNF-α inhibitors are of great interest [35]. Briefly, approximately 40% of PsA patients do not achieve an ACR20 response to TNF-α inhibitors within 6 months of therapy, and subsequent switching between TNF-α inhibitors is associated with progressive loss of treatment efficacy [50 51]. Moreover, paradoxical exacerbation of psoriatic skin lesions may occur during the treatment with TNF-α inhibitors [52] as well as an increased risk of infectious complications, including opportunistic infections, compared with IL-17A inhibitors and IL-12/IL-23 inhibitors [53]. Although about one-third of patients in the DISCOVER-1 study had prior exposure to 1–2 TNF-α inhibitors, the efficacy of GUS in this subset of patients with severe PsA required specific evaluation.

The COSMOS study enrolled 285 patients with active PsA (⩾ 3 tender and swollen joints) who discontinued treatment with TNF-α inhibitors due to inadequate response or poor tolerability [35]. Patients were assigned (2:1) to receive GUS 100 mg (at Week 0, Week 4, and then every 8 weeks (Q8W)) or placebo. The duration of the trial was 44 weeks. At Week 24, patients receiving placebo were switched to GUS at week 24, 28, and then every 8 weeks (**Table 2**).

At Week 24, significantly higher response rates for both joint and skin PsA manifestations were demonstrated in the GUS arms compared with placebo. The primary outcome, identified by ACR20 response, was achieved by 44.4% of GUS-treated patients compared 19.8% of placebo-treated patients. Guselkumab was superior to placebo for each key secondary endpoint, such as mean changes in HAQ-DI, ACR50 response, mean changes in SF-36 PCS and PASI100 response (multiplicity-adjusted p<0.01).

These results were consistent across subgroups defined by sex, age, baseline tender and swollen joint counts, CRP levels, prior exposure to non-biologic DMARDs, NSAIDs, TNF-α inhibitors, and the reason for TNF-α inhibitor discontinuation

Table 2. Efficacy of GUS versus placebo in the COSMOS study with bDMARD-exposed patients with PsA.

	Week 24		Week 48	
	GUS (*n* = 189)	**placebo (*n* = 96)**	**GUS (*n* = 189)**	**placebo→GUS (*n* = 51)**
ACR20 response rate, %	44.4 $p < 0.001$	19.8	57.7	54.9
ACR50 response rate, %	19.6 $p < 0.001$	5.2	39.2	29.4
ACR70 response rate, %	7.9 $p = 0.018$	1.0	23.8	17.6
HAQ-DI (improvement by ≥ 0,35 from baseline), %	37.5 $p < 0.001$	16.1	53.4	37.0.25
SF-36 (LSM)	2.10 $p < 0.07$	0.36		
PASI75 response rate, %	59.4 $p < 0.001$	9.4	74.4	82.6
PASI90 response rate, %	51.1 $p < 0.001$	7.56	66.9	60.9
FACIT-F (change by ≥ 4 from baseline)	42.9 $p < 0.001$	20.8	55.6	51.0

Note: SF-36, 36-Item Short Form Survey; PASI75, a reduction by ≥ 75% in the Psoriasis Area and Severity Index; ACR20, an im

(inadequate efficacy or intolerance). Regarding prior use of TNF inhibitors, efficacy of GUS was maintained for patients with prior use of 1 TNFi, while results were not statistically significant for patients exposed to 2 TNFi before the study; however this might be just due to the small number of patients (5 patients in the GUS group vs 1 patient in the placebo group). In the placebo group, switching to GUS was associated with an increase in the response rate, with 55% of patients achieving an ACR20 response at week 48. Although fewer patients who failed prior TNF-α inhibitor therapy responded to GUS compared with patients without prior TNF-α inhibitor exposure, the difference in ACR20 response rate was not significant in the DISCOVER-1 trial.

No head-to-head comparison has been performed between GUS, TNF-α inhibitors, and IL-17A inhibitors in PsA patients; however, meta-analysis data suggest that all three classes of drugs have approximately equal efficacy in patients without prior exposure t o biologics [54]. Data from an indirect comparison of GUS (pooled analysis of both DISCOVER trials) and ustekinumab (PSUMMIT 1 and PSUMMIT 2 trials) [55 56 57] suggest superiority of GUS for skin (PASI90) and joint (ACR20) disease at Week 52 of the treatment [58]. As noted, GUS treatment provided greater efficacy versus secukinumab in patients with cutaneous psoriasis [59].

Safety

Treatment with GUS Q4W and GUS Q8W in patients with PsA was well tolerated and rarely caused severe adverse drug reactions [29-33,57,58]. In the pooled analysis of the DISCOVER-1 and DISCOVER-2 trials, rates of treatment-related adverse drug reactions were 48.5% (DISCOVER-1), 48.8% (DISCOVER-2), and 47.3% in the placebo group [58]. The most common adverse drug reactions were nasopharyngitis, increased liver enzyme levels (transient and without hyperbilirubinemia), and upper respiratory tract infections. The frequencies of severe adverse drug reactions were 1.9% (GUS Q4W), 2.1% (GUS Q8W), and 3.2% in the placebo group; very severe adverse drug reactions were reported in 0.8%, 0.5%, and 1.6% of patients, respectively. In these treatment groups, treatment interruptions due to an ADR were rare and occurred in 1.3%, 2.1%, and 1.9% of patients, respectively; the frequencies of injection reactions were 1.3%, 1.1%, and 0.3%, respectively. NCI CTCAE (National Cancer Institute Common Terminology Criteria for Adverse Events) Grade 1 (< LLN to 1500 cells/uL) and grade 2 (1500 to 1000 cells/uL) neutropenia were more common in both GUS groups compared with the placebo group: 5.6% and 5.9% vs 3.2%, and 1.6% and 1.6% vs 0.8%, respectively. Grade 3 and 4 neutropenia were very rare and without differences among treatment groups. Overall, neutropenia was not associated with events of infection. At least one infection event (as reported by patients) was reported in 19.5%, 21.4%, and 20.7% of patients, with at least one severe infection in 0.3%, 0.8%, and 0.8% of patients, respectively. No unexpected adverse drug reactions were reported and the frequency of adverse drug reactions did not increase during long-term follow-up for 60 weeks (DISCOVER-1; 365 patient-years)[36] and groups was 1.1 (DISCOVER-1), 1.9 per (DISCOVER-2), and 3.5% and 0.9% in the placebo group, respectively. In DISCOVER-2, 3 patients in the GUS Q8W group had opportunistic infections (fungal esophagitis, disseminated herpes), and an event of listeriosis meningitis was reported in 1 patient who was switched from placebo to GUS Q4W. In both DISCOVER trials, only 2 patients were positive for anti-drug antibodies which were neutralizing in one case; however, they were not associated with injection reactions or the loss of treatment efficacy.

Data regarding the safety of GUS therapy during the COVID-19 pandemic (COronaVIrus Disease 2019) are limited [60 61 62 63 64]. In all GUS-treated patients, COVID-19 symptoms were mild and did not require hospitalization; moreover one patient with psoriasis showed rapid clinical improvement after treatment, with rapid resolution of dyspnea and fever [60]. GUS therapy did not appear to affect IgG antibody response to severe acute respiratory syndrome-related coronavirus 2 (SARS-CoV-2)[65]. Treatment with IL-23 inhibitors was not associated with an increased risk of upper respiratory tract infections[66]. It is assumed that the class of IL-23 inhibitors does not affect the risk of SARS-CoV-2 infection [67] and the response to SARS-CoV-2 vaccination, thus GUS withdrawal is not recommended by the latest ACR recommendations for COVID-19 vaccination in rheumatic patients[68 69 70].

Conclusions

GUS is the only currently approved anti-IL-23 treatment for PsA, and its use is supported by the National Institute for Health and Care Excellence (NICE) [71]. Clinical trials of GUS treatment for Crohn's disease[72] and hidradenitis suppurativa with concomitant Crohn's disease are ongoing [73 74]. In patients with psoriasis, GUS was demonstrated superior to ustekinumab and secukinumab [28 27]. In patients with active PsA, GUS showed an efficacy profile at least equal to other biologics [54], although secukinumab showed higher response (ACR20/50) rates for joint disease in a meta-analysis of 6 RPCTs [75]. The same meta-analysis showed higher PASI75 response rates for skin disease in GUS patients though. Compared with TNF-α inhibitors, GUS is less likely to cause infections and does not increase the risk of the reactivation of latent TB infection [76]. The advantages of GUS include a very rapid onset of clinical response and lower required frequency administration, offering greater patient convenience (once every 1-2 months by subcutaneous injection).

Among patients with psoriasis and PsA (n = 3251), the proportions of adherent patients were numerically highest among those treated with GUS (59.5%), followed by ustekinumab (57%), secukinumab (47.9%), ixekizumab (47.6%), adalimumab (46.8%), etanercept (37.4%), and certolizumab (22.0%)[77]. Real life preliminary data suggest that in early PsA patient, GUS therapy is highly effective (low disease activity in 65% of patients and a remission rate of 35%) for peripheral and axial manifestations[78] and reduces the risk of PsA in patients with psoriasis carrying a high risk of PsA [79]. In perspective, these data may be crucial for the prevention of PsA in patients with psoriasis [80].

The new GRAPPA recommendations[81] envision the use of IL-23 inhibitors in patients with PsA with inadequate response to conventional DMARDs, including those with peripheral arthritis, enthesitis, dactylitis, skin and nail psoriasis. However, these recommendations do not include emerging data on the efficacy of GUS in patients with PsA who are resistant to TNF-α inhibitors (COSMOS RPCI)[35] nor the proposed effectiveness on axial disease[41]. These data will be taken into account during the preparation of a new version of the ARR (Association of Rheumatologists of Russia) recommendations for the treatment of PsA.

Study transparency

The study had no sponsor support. The authors bear full responsibility for the submission of the final version of the manuscript for print.

Declaration of financial and other interests

All authors participated in conceptualizing the article and in writing the manuscript. The final version of the manuscript was approved by all authors. The authors received no fees for the paper.

Conflicts of interest

YLN: speakers bureaus for AbbVie, Eli Lilly, Janssen, Novartis, Pfizer, R-Pharm, BIOCAD

KVT: speakers bureaus for AbbVie, BMS, Eli Lilli, MSD, Novartis, Pfizer, Janssen, BIOCAD

SR: none

CS: consu lting and speakers bureaus for AbbVie, Amgen, Alfa-Wassermann, Biogen, Celgene, Eli-Lilly, Gilead, Janssen, MSD, Novartis, Pfizer, Sanofi-Genzyme.

REFERENCES / ЛИТЕРАТУРА

1. Szekanecz Z, McInnes IB, Schett G, Szamosi S, Benkő S, Szűcs G. Autoinflammation and autoimmunity across rheumatic and musculoskeletal diseases. *Nat Rev Rheumatol.* 2021;17(10):585-595. doi: 10.1038/s41584-021-00652-9
2. Schett G, McInnes IB, Neurath MF. Reframing immune-mediated inflammatory diseases through signature cytokine hubs. *N Engl J Med.* 2021;385(7):628-639. doi: 10.1056/NEJMra1909094
3. Gaffen SL, Jain R, Garg AV, Cua DJ. The IL-23-IL-17 immune axis: From mechanisms to therapeutic testing. *Nat Rev Immunol.* 2014;14(9):585-600. doi: 10.1038/nri3707
4. Li H, Tsokos GC. IL-23/IL-17 axis in inflammatory rheumatic diseases. *Clin Rev Allergy Immunol.* 2021;60(1):31-45. doi: 10.1007/s12016-020-08823-4
5. Schinocca C, Rizzo C, Fasano S, Grasso G, La Barbera L, Ciccia F, et al. Role of the IL-23/IL-17 pathway in rheumatic diseases: An overview. *Front Immunol.* 2021;12:637829. doi: 10.3389/fimmu.2021.637829
6. McGeachy MJ, Cua DJ, Gaffen SL. The IL-17 family of cytokines in health and disease. *Immunity.* 2019;50(4):892-906. doi: 10.1016/j.immuni.2019.03.021
7. Matsuzaki G, Umemura M. Interleukin-17 family cytokines in protective immunity against infections: Role of hematopoietic cell-derived and non-hematopoietic cell-derived interleukin-17. *Microbiol Immunol.* 2018;62(1):1-13. doi: 10.1111/1348-0421.12560
8. Tait Wojno ED, Hunter CA, Stumhofer JS. The immunobiology of the interleukin-12 family: Room for discovery. *Immunity.* 2019;50(4):851-870. doi: 10.1016/j.immuni.2019.03.011
9. Najm A, McInnes IB. IL-23 orchestrating immune cell activation in arthritis. *Rheumatology (Oxford).* 2021;60(Suppl 4):iv4-iv15. doi: 10.1093/rheumatology/keab266
10. Ruiz de Morales JMG, Puig L, Daudén E, Cañete JD, Pablos JL, Martín AO, et al. Critical role of interleukin (IL)-17 in inflammatory and immune disorders: An updated review of the evidence focusing in controversies. *Autoimmun Rev.* 2020;19(1):102429. doi: 10.1016/j.autrev.2019.102429
11. Насонов ЕЛ. Новые возможности фармакотерапии иммуновоспалительных ревматических заболеваний: фокус на ингибиторы интерлейкина 17. *Научно-практическая ревматология.* 2017;55(1):68-86. [Nasonov EL. New possibilities of pharmacotherapy for immunoinflammatory rheumatic diseases: A focus on inhibitors of interleukin-17. *Nauchcno-Prakticheskaya Revmatologia = Rheumatology Science and Practice.* 2017;55(1):68-86 (In Russ.)]. doi: 10.14412/1995-4484-2017-68-86
12. Noack M, Miossec P. Th17 and regulatory T cell balance in autoimmune and inflammatory diseases. *Autoimmun Rev.* 2014;13:668-677. doi: 10.1016/j.autrev.2013.12.004
13. Hasegawa H, Mizoguchi I, Orii N, Inoue S, Katahira Y, Yoneto T, et al. IL-23p19 and CD5 antigen-like form a possible novel heterodimeric cytokine and contribute to experimental autoimmune encephalomyelitis development. *Sci Rep.* 2021;11(1):5266. doi: 10.1038/s41598-021-84624-9
14. Heink S, Yogev N, Garbers C, Herwerth M, Aly L, Gasperi C, et al. Trans-presentation of IL-6 by dendritic cells is required for the priming of pathogenic T_H17 cells. *Nat Immunol.* 2017;18(1):74-85. doi: 10.1038/ni.3632
15. Pastor-Fernández G, Mariblanca IR, Navarro MN. Decoding IL-23 signaling cascade for new therapeutic opportunities. *Cells.* 2020;9(9):2044. doi: 10.3390/cells9092044
16. Sherlock JP, Cua DJ. Interleukin-23 in perspective. *Rheumatology (Oxford).* 2021;60(Suppl 4):iv1-iv3. doi: 10.1093/rheumatology/keab461
17. Насонов ЕЛ, Коротаева ТВ, Дубинина ТВ, Лила АМ. Ингибиторы ИЛ23/ИЛ17 при иммуновоспалительных ревматических заболеваниях: новые горизонты. *Научно-практическая ревматология.* 2019;57(4):400-406. [Nasonov EL, Korotaeva TV, Dubinina TV, Lila AM. IL-23/IL-17 inhibitors in immunoinflammatory rheumatic diseases: New horizons. *Nauchcno-Prakticheskaya Revmatologia = Rheumatology Science and Practice.* 2019;57(4):400-406 (In Russ.)]. doi: 10.14412/1995-4484-2019-400-406
18. Bravo A, Kavanaugh A. Bedside to bench: defining the immunopathogenesis of psoriatic arthritis. *Nat Rev Rheumatol.* 2019;15(11):645-656. doi: 10.1038/s41584-019-0285-8

19. Silvagni E, Missiroli S, Perrone M, Patergnani S, Boncompagni C, Bortoluzzi A, et al. From bed to bench and back: TNF-α, IL-23/IL-17A, and JAK-dependent inflammation in the pathogenesis of psoriatic synovitis. *Front Pharmacol.* 2021;12:672515. doi: 10.3389/fphar.2021.672515
20. Bianchi E, Vecellio M, Rogge L Editorial: Role of the IL-23/IL-17 pathway in chronic immune-mediated inflammatory diseases: Mechanisms and targeted therapies. *Front Immunol.* 2021;12:770275. doi: 10.3389/fimmu.2021.770275
21. Sweet K, Song Q, Loza MJ, McInnes IB, Ma K, Leander K, et al. Guselkumab induces robust reduction in acute phase proteins and type 17 effector cytokines in active psoriatic arthritis: Results from phase 3 trials. *RMD Open*. 2021;7(2):e001679. doi: 10.1136/rmdopen-2021-001679
22. Gordon KB, Armstrong AW, Foley P, Song M, Shen YK, Li S, et al. Guselkumab efficacy after withdrawal is associated with suppression of serum IL-23-regulated IL-17 and IL-22 in psoriasis: VOYAGE 2 study. *J Invest Dermatol.* 2019;139(12):2437-2446.e1. doi: 10.1016/j.jid.2019.05.016
23. Zhuang Y, Calderon C, Marciniak SJ Jr, Bouman-Thio E, Szapary P, Yang TY, et al. First-in-human study to assess guselkumab (anti-IL-23 mAb) pharmacokinetics/safety in healthy subjects and patients with moderate-to-severe psoriasis. *Eur J Clin Pharmacol.* 2016;72(11):1303-1310. doi: 10.1007/s00228-016-2110-5
24. Yao Z, Hu C, Zhu Y, Xu Z, Randazzo B, Wasfi Y, et al. Population pharmacokinetic modeling of guselkumab, a human IgG1λ monoclonal antibody targeting IL-23, in patients with moderate to severe plaque psoriasis. *J Clin Pharmacol.* 2018;58(5):613-627. doi: 10.1002/jcph.1063
25. Gordon KB, Duffin KC, Bissonnette R, Prinz JC, Wasfi Y, Li S, et al. A phase 2 trial of guselkumab versus adalimumab for plaque psoriasis. *N Engl J Med.* 2015;373(2):136-144. doi: 10.1056/NEJMoa1501646
26. Blauvelt A, Papp KA, Griffiths CE, Randazzo B, Wasfi Y, Shen YK, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the continuous treatment of patients with moderate to severe psoriasis: Results from the phase III, double-blinded, placebo- and active comparator-controlled VOYAGE 1 trial. *J Am Acad Dermatol.* 2017;76(3):405-417. doi: 10.1016/j.jaad.2016.11.041
27. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: Results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. *J Am Acad Dermatol.* 2017;76(3):418-431. doi: 10.1016/j.jaad.2016.11.042
28. Reich K, Armstrong AW, Langley RG, Flavin S, Randazzo B, Li S, et al. Guselkumab versus secukinumab for the treatment of moderate-to-severe psoriasis (ECLIPSE): Results from a phase 3, randomised controlled trial. *Lancet.* 2019;394(10201):831-839. doi: 10.1016/s0140-6736(19)31773-8
29. Blauvelt A, Armstrong AW, Langley RG, Gebauer K, Thaçi D, Bagel J, et al. Efficacy of guselkumab versus secukinumab in subpopulations of patients with moderate-to-severe plaque psoriasis: Results from the ECLIPSE study. *J Dermatolog Treat.* 2021 Aug 4:1-8. doi: 10.1080/09546634.2021.1959504
30. Ferris LK, Ott E, Jiang J, Hong HC, Li S, Han C, et al. Efficacy and safety of guselkumab, administered with a novel patient-controlled injector (One-Press), for moderate-to-severe psoriasis: Results from the phase 3 ORION study. *J Dermatol Treat.* 2020;31(2):152-159. doi: 10.1080/09546634.2019.1587145
31. Ohtsuki M, Kubo H, Morishima H, Goto R, Zheng R, Nakagawa H. Guselkumab, an anti-interleukin-23 monoclonal antibody, for the treatment of moderate to severe plaque-type psoriasis in Japanese patients: Efficacy and safety results from a phase 3, randomized, double-blind, placebo-controlled study. *J Dermatol.* 2018;45(9):1053-1062. doi: 10.1111/1346-8138.14504
32. Langley RG, Tsai TF, Flavin S, Song M, Randazzo B, Wasfi Y, et al. Efficacy and safety of guselkumab in patients with psoriasis who have an inadequate response to ustekinumab: Results of the randomized, double-blind, phase III NAVIGATE trial. *Br J Dermatol.* 2018;178(1):114-123. doi: 10.1111/bjd.15750
33. Mease PJ, Gladman DD, Deodhar A, McGonagle DG, Nash P, Boehncke WH, et al. Impact of guselkumab, an interleukin-23 p19 subunit inhibitor, on enthesitis and dactylitis in patients with moderate to severe psoriatic arthritis: Results from a randomised, placebo-controlled, phase II study. *RMD Open*. 2020;6(2):e001217. doi: 10.1136/rmdopen-2020-001217
34. Deodhar A, Helliwell PS, Boehncke WH, Kollmeier AP, Hsia EC, et al.; DISCOVER-1 Study Group. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): A double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020;395(10230):1115-1125. doi: 10.1016/S0140-6736(20)30265-8
35. Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al.; DISCOVER-2 Study Group. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): A double-blind, randomised, placebo-controlled phase 3 trial. *Lancet*. 2020;395(10230):1126-1136. doi: 10.1016/S0140-6736(20)30263-4
36. Deodhar A, Gottlieb AB, Boehncke WH, Dong B, Wang Y, Zhuang Y, et al.; CNTO1959PSA2001 Study Group. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: A randomised, double-blind, placebo-controlled, phase 2 study. *Lancet*. 2018;391(10136):2213-2224. doi: 10.1016/S0140-6736(18)30952-8
37. Coates LC, Gossec L, Theander E, Bergmans P, Neuhold M, Karyekar CS, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: Results through one year of a phase IIIb, randomised, controlled study (COSMOS). *Ann Rheum Dis*. 2021 Nov 24:annrheumdis-2021-220991. doi: 10.1136/annrheumdis-2021-220991
38. Ritchlin CT, Helliwell PS, Boehncke WH, Soriano ER, Hsia EC, Kollmeier AP, et al. Guselkumab, an inhibitor of the IL-23p19

subunit, provides sustained improvement in signs and symptoms of active psoriatic arthritis: 1 year results of a phase III randomised study of patients who were biologic-naïve or TNFα inhibitor-experienced. *RMD Open*. 2021;7(1):e001457. doi: 10.1136/rmdopen-2020-001457

39. McInnes IB, Rahman P, Gottlieb AB, Hsia EC, Kollmeier AP, Chakravarty SD, et al. Efficacy and safety of guselkumab, an interleukin-23p19-specific monoclonal antibody, through one year in biologic-naive patients with psoriatic arthritis. *Arthritis Rheumatol*. 2021;73(4):604-616. doi: 10.1002/art.41553
40. Gottlieb AB, Mease PJ, Merola JF, Kollmeier AP, Hsia EC, Xu XL, et al. 15281 Effects of guselkumab on articular components of American College of Rheumatology score and skin responses in patients with active psoriatic arthritis: Results from the phase 3 DISCOVER-2 study. *JAAD*. 2020;83(Suppl 6):AB145.
41. Mease P, Helliwel PS, Efficacy of guselkumab on axial involvement in patients with active psoriatic arthritis and sacroiliitis: A post-hoc analysis of the phase 3 DISCOVER-1 and DISCOVER-2 studies. *Lancet Rheumatol*. 2021;3(10):e715-723. doi: 10.1016/S2665-9913(21)00105-3
42. Deodhar A, Gensler LS, Sieper J, Clark M, Calderon C, Wang Y, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. *Arthritis Rheumatol*. 2019;71(2):258-270. doi: 10.1002/art.40728
43. Baeten D, Østergaard M, Wei JC, Sieper J, Järvinen P, Tam LS, et al. Risankizumab, an IL-23 inhibitor, for ankylosing spondylitis: Results of a randomised, double-blind, placebo-controlled, proof-of-concept, dose-finding phase 2 study. *Ann Rheum Dis*. 2018;77(9):1295-1302. doi: 10.1136/annrheumdis-2018-213328
44. Dubash S, Bridgewood C, McGonagle D, Marzo-Ortega H. The advent of IL-17A blockade in ankylosing spondylitis: Secukinumab, ixekizumab and beyond. *Expert Rev Clin Immunol*. 2019;15(2):123-134. doi: 10.1080/1744666X.2019.1561281
45. McGonagle DG, McInnes IB, Kirkham BW, Sherlock J, Moots R. The role of IL-17A in axial spondyloarthritis and psoriatic arthritis: Recent advances and controversies. *Ann Rheum Dis*. 2019;78(9):1167-1178. doi: 10.1136/annrheumdis-2019-215356
46. Baeten D, Adamopoulos IE. IL-23 Inhibition in ankylosing spondylitis: Where did it go wrong? *Front Immunol*. 2021;11:623874. doi: 10.3389/fimmu.2020.623874
47. McGonagle D, Watad A, Sharif K, Bridgewood C. Why inhibition of IL-23 lacked efficacy in ankylosing spondylitis. *Front Immunol*. 2021;12:614255. doi: 10.3389/fimmu.2021.614255
48. Mease P, van den Bosch F. IL-23 and axial disease: Do they come together? *Rheumatology (Oxford)*. 2021;60(Suppl 4):iv28-iv33. doi: 10.1093/rheumatology/keab617
49. McInnes IB, Rahman P, Gottlieb AB, Hsia EC, Kollmeier AP, Xu XL, et al. Long-term efficacy and safety of guselkumab, a monoclonal antibody specific to the p19 subunit of interleukin-23, through 2 years: Results from a phase 3, randomized, double-blind, placebo-controlled study conducted in biologic-naïve patients with active psoriatic arthritis. *Arthritis Rheumatol*. 2021 Nov 1. doi: 10.1002/art.42010
50. Rahman P, Mease PJ, Helliwell PS, Deodhar A, Gossec L, Kavanaugh A, et al. Guselkumab demonstrated an independent treatment effect in reducing fatigue after adjustment for clinical response – Results from two phase 3 clinical trials of 1120 patients with active psoriatic arthritis. *Arthritis Res Ther*. 2021;23(1):190. doi: 10.1186/s13075-021-02554-3
51. McGonagle D, McInnes IB, Deodhar A, Schett G, Shawi M, Kafka S, et al. Resolution of enthesitis by guselkumab and relationships to disease burden: 1-year results of two phase 3 psoriatic arthritis studies. *Rheumatology (Oxford)*. 2021;60(11):5337-5350. doi: 10.1093/rheumatology/keab285
52. Mantravadi S, Ogdie A, Kraft WK. Tumor necrosis factor inhibitors in psoriatic arthritis. *Expert Rev Clin Pharmacol*. 2017;10(8):899-910. doi: 10.1080/17512433.2017.1329009
53. Merola JF, Lockshin B, Mody EA. Switching biologics in the treatment of psoriatic arthritis. *Semin Arthritis Rheum*. 2017;47(1):29-37. doi: 10.1016/j.semarthrit.2017.02.001
54. Li SJ, Perez-Chada LM, Merola JF. TNF inhibitor-induced psoriasis: Proposed algorithm for treatment and management. *J Psoriasis Psoriatic Arthritis*. 2019;4(2):70-80. doi: 10.1177/2475530318810851
55. Li X, Andersen KM, Chang HY, Curtis JR, Alexander GC. Comparative risk of serious infections among real-world users of biologics for psoriasis or psoriatic arthritis. *Ann Rheum Dis*. 2020;79(2):285-291. doi: 10.1136/annrheumdis-2019-216102
56. Mease PJ, McInnes IB, Tam LS, Eaton K, Peterson S, Schubert A, et al. Comparative effectiveness of guselkumab in psoriatic arthritis: results from systematic literature review and network meta-analysis. *Rheumatology (Oxford)*. 2021;60(5):2109-2121. doi: 10.1093/rheumatology/keab119
57. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al.; PSUMMIT 1 Study Group. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet*. 2013;382(9894):780-789. doi: 10.1016/S0140-6736(13)60594-2
58. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al.; PSUMMIT 2 Study Group. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis*. 2014;73(6):990-999. doi: 10.1136/annrheumdis-2013-204655
59. McInnes IB, Chakravarty SD, Apaolaza I, Kafka S, Hsia EC, You Y, et al. Efficacy of ustekinumab in biologic-naïve patients with psoriatic arthritis by prior treatment exposure and disease duration: Data from PSUMMIT 1 and PSUMMIT 2. *RMD Open*. 2019;5(2):e000990. doi: 10.1136/rmdopen-2019-000990
60. Diels J, Thilakarathne P, Schubert A, Hassan F, Peterson S, Noël W, et al. AB0556 Comparing efficacy of guselkumab versus ustekinumab in patients with psoriasis arthritis: An adjusted com-

parison using individual patient data from DISCOVER 1&2 and PSUMMIT trials. *Ann Rheum Diss.* 2021;80:1313.
61. Ru Y, Ding X, Luo Y, Li H, Sun X, Zhou M, et al. Adverse events associated with anti-IL-23 agents: Clinical evidence and possible mechanisms. *Front Immunol.* 2021;12:670398. doi: 10.3389/fimmu.2021.670398
62. Rahman P, Ritchlin CT, Helliwell PS, Boehncke WH, Mease PJ, Gottlieb AB, et al. Pooled safety results through 1 year of 2 phase III trials of guselkumab in patients with psoriatic arthritis. *J Rheumatol.* 2021;48(12):1815-1823. doi: 10.3899/jrheum.201532
63. Benhadou F, Del Marmol V. Improvement of SARS-CoV-2 symptoms following Guselkumab injection in a psoriatic patient. *J Eur Acad Dermatol Venereol.* 2020;34(8):e363-e364. doi: 10.1111/jdv.16590
64. Wang CJ, Truong AK. COVID-19 infection on IL-23 inhibition. *Dermatol Ther.* 2020;33(6):e13893. doi: 10.1111/dth.13893
65. Messina F, Piaserico S. SARS-CoV-2 infection in a psoriatic patient treated with IL-23 inhibitor. *J Eur Acad Dermatol Venereol.* 2020;34(6):e254-e255. doi: 10.1111/jdv.16468
66. Gisondi P, Facheris P, Dapavo P, Piaserico S, Conti A, Naldi L, et al. The impact of the COVID-19 pandemic on patients with chronic plaque psoriasis being treated with biological therapy: The Northern Italy experience. *Br J Dermatol.* 2020;183(2):373-374. doi: 10.1111/bjd.19158
67. Damiani G, Pacifico A, Bragazzi NL, Malagoli P. Biologics increase the risk of SARS-CoV-2 infection and hospitalization, but not ICU admission and death: Real-life data from a large cohort during red-zone declaration. *Dermatol Ther.* 2020;33(5):e13475. doi: 10.1111/dth.13475
68. Mintoff D, Benhadou F. Guselkumab does not appear to influence the IgG antibody response to SARS-CoV-2. *Dermatol Ther.* 2021 Dec 4:e15246. doi: 10.1111/dth.15246
69. Salvarani C, Bajocchi G, Mancuso P, Galli E, Muratore F, Boiardi L, et al. Susceptibility and severity of COVID-19 in patients treated with bDMARDS and tsDMARDs: A population-based study. *Ann Rheum Dis.* 2020;79(7):986-988. doi: 10.1136/annrheumdis-2020-217903
70. Syed MN, Shin DB, Wan MT, Winthrop KL, Gelfand JM. The risk of respiratory tract infections in patients with psoriasis treated with interleukin 23 pathway-inhibiting biologics: A meta-estimate of pivotal trials relevant to decision making during the COVID-19 pandemic. *J Am Acad Dermatol.* 2020;83(5):1523-1526. doi: 10.1016/j.jaad.2020.06.1014
71. Gelfand JM, Armstrong AW, Bell S, Anesi GL, Blauvelt A, Calabrese C, et al. National Psoriasis Foundation COVID-19 Task Force guidance for management of psoriatic disease during the pandemic: Version 2 – Advances in psoriatic disease management, COVID-19 vaccines, and COVID-19 treatments. *J Am Acad Dermatol.* 2021;84(5):1254-1268. doi: 10.1016/j.jaad.2020.12.058
72. Mikuls TR, Johnson SR, Fraenkel L, Arasaratnam RJ, Baden LR, Bermas BL, et al. American College of Rheumatology guidance for the management of rheumatic disease in adult patients during the COVID-19 pandemic: Version 3. *Arthritis Rheumatol.* 2021;73(2):e1-e12. doi: 10.1002/art.41596
73. Gresham LM, Marzario B, Dutz J, Kirchhof MG. An evidence-based guide to SARS-CoV-2 vaccination of patients on immunotherapies in dermatology. *J Am Acad Dermatol.* 2021;84(6):1652-1666. doi: 10.1016/j.jaad.2021.01.047
74. Насонов ЕЛ, Лила АМ, Мазуров ВИ, Белов БС, Каратеев АЕ, Дубинина ТВ, и др. Коронавирусная болезнь 2019 (COVID-19) и иммуновоспалительные ревматические заболевания. Рекомендации Общероссийской общественной организации «Ассоциация ревматологов России». *Научно-практическая ревматология.* 2021;59(3):239-254. [Nasonov EL, Lila AM, Mazurov VI, Belov BS, Karateev AE, Dubinina TV, et al. Coronavirus disease 2019 (COVID-19) and immune-mediated rheumatic diseases. Recommendations of the Association of Rheumatologists of Russia. *Nauchcno-Prakticheskaya Revmatologia = Rheumatology Science and Practice.* 2021;59(3):239-254 (In Russ.)]. doi: 10.47360/1995-4484-2021-239-254
75. Yang K, Oak ASW, Elewski BE. Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: A comprehensive review. *Am J Clin Dermatol.* 2021;22(2):173-192. doi: 10.1007/s40257-020-00578-0
76. Lamb YN. Guselkumab in psoriatic arthritis: A profile of its use. *Drugs Ther Perspect* 2021;37:285-293. doi: 10.1007/s40267-021-00840-3
77. Almradi A, Hanzel J, Sedano R, Parker CE, Feagan BG, Ma C, et al. Clinical trials of IL-12/IL-23 inhibitors in inflammatory bowel disease. *BioDrugs.* 2020;34(6):713-721. doi: 10.1007/s40259-020-00451-w
78. Song GG, Lee YH. Relative efficacy and safety of secukinumab and guselkumab for the treatment of active psoriatic arthritis: A network meta-analysis. *Int J Clin Pharmacol Ther.* 2021;59(6):433-441. doi: 10.5414/CP203906
79. Nogueira M, Warren RB, Torres T. Risk of tuberculosis reactivation with interleukin (IL)-17 and IL-23 inhibitors in psoriasis – Time for a paradigm change. *J Eur Acad Dermatol Venereol.* 2021;35(4):824-834. doi: 10.1111/jdv.16866
80. Xu C, Teeple A, Wu B, Fitzgerald T, Feldman SR. Treatment adherence and persistence of seven commonly prescribed biologics for moderate to severe psoriasis and psoriatic arthritis in a U.S. commercially insured population. *J Dermatolog Treat.* 2021 Jul 15:1-21. doi: 10.1080/09546634.2021.1950600
81. Pantano I, Mauro D, Romano F, Gambardella A, Valenti M, Simone D, et al. Real-life efficacy of guselkumab in patients with early psoriatic arthritis. *Rheumatology (Oxford).* 2021 Jun 21:keab509. doi: 10.1093/rheumatology/keab509
82. Zabotti A, Giovannini I, McGonagle D, De Vita S, Stinco G, Errichetti E. Arthritis interception in patients with psoriasis treated with guselkumab. *Dermatol Ther (Heidelb).* 2021 Nov 27. doi: 10.1007/s13555-021-00650-5
83. Насонов ЕЛ, Коротаева ТВ, Лила АМ, Кубанов АА. Можно ли предотвратить развитие псориатического артрита у пациентов с псориазом? *Научно-практическая ревматология.* 2019;57(3):250-254. [Nasonov EL, Korotaeva TV, Lila AM, Kubanov AA. Can the development of psoriatic arthritis be prevented in patients with psoriasis? *Nauchcno-Prakticheskaya*

Revmatologia = Rheumatology Science and Practice. 2019;57(3):250-254 (In Russ.)]. doi: 10.14412/1995-4484-2019-250-254

84. Scher JU, Ogdie A, Merola JF, Ritchlin C. Preventing psoriatic arthritis: focusing on patients with psoriasis at increased risk of transition. *Nat Rev Rheumatol*. 2019;15(3):153-166. doi: 10.1038/s41584-019-0175-0
85. Coates LC, Corp N, van der Windt DA, Soriano ER, Kavanaugh A. GRAPPA Treatment Recommendations: An Update From the 2020 GRAPPA Annual Meeting. *J Rheumatol*. 2021 Feb 15:jrheum.201681. doi: 10.3899/jrheum.201681.
86. Gossec L, Baraliakos X, Kerschbaumer A, de Wit M, McInnes I, et al. EULAR recommendations for the management of psoriatic arthritis with pharmacological therapies: 2019 update. Ann Rheum Dis. 2020;79(6):700-712. doi: 10.1136/annrheum-dis-2020-217159.

Ye.L. Nasonov *ORCID: https://orcid.org/0000-0002-1598-836*
T.V. Korotayeva *ORCID: https://orcid.org/0000-0003-0579-1131*
C. Selmi *ORCID: https://orcid.org/0000-0002-0323-0376*
S. Rodolfi *ORCID: https://orcid.org/0000-0001-8054-2843*