BioDrugs (2024) 38:61–71
https://doi.org/10.1007/s40259-023-00634-1

REVIEW ARTICLE

Targeting IL-6 or IL-6 Receptor in Rheumatoid Arthritis: What Have We Learned?

Ali Berkant Avci[1] · Eugen Feist[2] · Gerd R. Burmester[3]

Accepted: 18 October 2023 / Published online: 21 November 2023

Abstract

The use of different pathways in the treatment of rheumatoid arthritis has led to a significant decrease in the number of treatment-resistant patients. In this context, interleukin (IL)-6 inhibition has filled an important gap in rheumatoid arthritis treatment with its effectiveness and safety in both monotherapy and combinations. The process of IL-6 inhibition initiated with IL-6 receptor blockers has prompted questions regarding the potential impact and safety of different inhibitions of this pathway, such as the direct blockade of IL-6. Following the termination of the development of sirukumab because of mortality data in early studies, the investigation of olokizumab, which targets a different region of the IL-6 cytokine, has renewed the hope in this area and the safety concerns have been largely alleviated by the open-label extension data. In addition, the efficacy and safety of tocilizumab and sarilumab have led to a rapid investigation of biosimilars and new potent IL-6 receptor blockers. A comprehensive understanding of mechanisms of this pathway with further long-term clinical data and basic research may provide a decisive impact on selecting the appropriate mechanism as the first choice in personalized treatments.

1 Introduction

Rheumatoid arthritis (RA) is a chronic autoimmune disease causing articular and extra-articular damage due to tissue and organ infiltration by leukocytes and prolonged systemic inflammation driven by proinflammatory cytokines. In this regard, interleukin-6 (IL-6), which is an important cytokine in the control of the acute-phase reaction, has a key position. Interleukin-6 is crucial for both the innate and adaptive immune systems [1]. It is a pleotropic cytokine that is

Key Points

The role of the interleukin (IL)-6 pathway in the treatment of rheumatoid arthritis has the potential to progress with different inhibitions of this pathway such as IL-6 cytokine blockade and trans-signaling blockade, in addition to IL-6 receptor blockers.

The favorable efficacy/safety profile of tocilizumab has prompted the rapid development of biosimilars and new potent IL-6 receptor inhibitors.

The potential impact of modalities targeting different antigenic sites of the IL-6 cytokine on efficacy and safety data highlights the importance of both clinical and basic research in revealing the true potential of this pathway.

The efficacy demonstrated by olokizumab in phase III studies, along with its open-label extension safety data, has shown that direct IL-6 inhibitors may also have an important place in this field.

✉ Gerd R. Burmester
gerd.burmester@charite.de

Ali Berkant Avci
avcialiberkant@yahoo.com

Eugen Feist
eugen.feist@helios-gesundheit.de

[1] Department of Internal Medicine, Rheumatology, Medical Park Antalya Hospital, Antalya, Türkiye

[2] Department of Rheumatology, Helios Fachklinik Vogelsang-Gommern, Cooperation Partner of the Otto-von-Guericke University Magdeburg, Gommern, Germany

[3] Department of Rheumatology and Clinical Immunology, Charité - Universitätsmedizin Berlin, Medizinische Klinik für Rheumatologie und Klinische Immunologie, Charitéplatz 1, Berlin, Germany

also involved in hematopoietic, metabolic, and hormonal regulation [2–4]. Interleukin-6 can demonstrate its biological activities only by binding to its specific IL-6 receptor (IL-6R) and this cytokine-receptor complex associates with the gp130 IL-6R β-subunit leading to intracellular signaling [5, 6]. Two case reports that failed to show an acute-phase reaction as a result of a homozygous mutation in the IL-6R in 2019 again showcased the importance of IL-6 in acute-phase mechanisms [7].

Interleukin-6 receptor is expressed as a membrane-bound (mIL-6R) form but also as a soluble form (sIL-6R). The soluble form is proteolytically cleaved from the cell membrane by a disintegrin and metallopeptidase domain 17 (ADAM17) [8]. The pathways generated by mIL6-R and sIL-6R are different, while the cascade by mIL-6R is called 'classic signaling', the cascade by sIL-6R is called 'trans-signaling' (Fig. 1). The recent application of the sgp130Fc (olamkicept), which exclusively blocks IL-6 trans-signaling without affecting classic signaling, led to new insights in the IL-6 pathway [9]. Inhibition of trans-signaling with sgp130Fc was effective in controlling inflammation without compromising the immune response to infections, suggesting that proinflammatory effects of IL-6 occur via the trans-signaling pathway, while protection against infections and regenerative functions occurs via classic signaling [10–13]. In addition, sgp130Fc (olamkicept) has also taken its place in clinical studies in inflammatory bowel diseases with the hypothesis that it can control inflammation while affecting

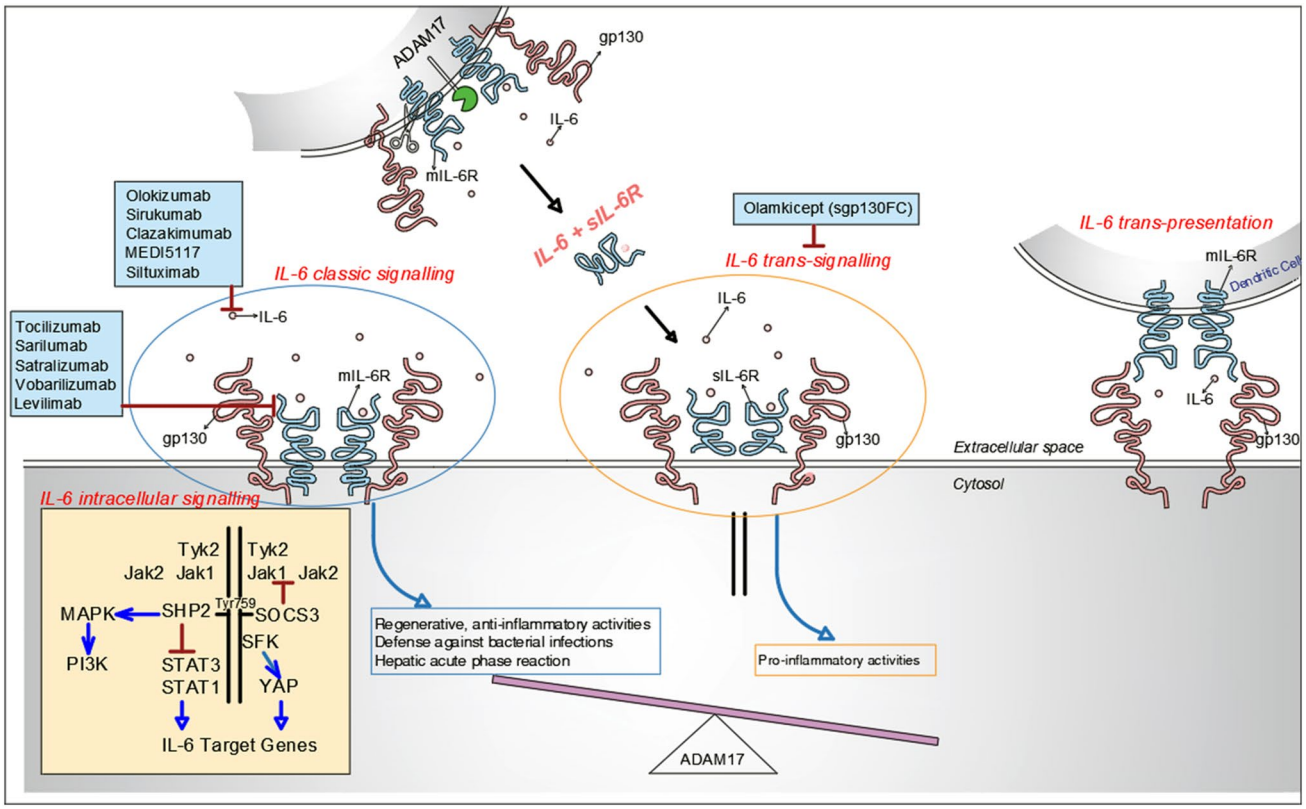

Fig. 1 Interleukin (IL)-6 signaling cascade. Interleukin-6 demonstrates its biological activities only by binding to its specific receptor, IL-6R. This cytokine-receptor complex then associates with the IL-6R β-subunit, gp130, leading to intracellular signaling. Classical IL-6 receptor signaling occurs in cells that express IL-6R and gp130. IL-6 receptor can be proteolytically cleaved from the cell membrane by ADAM17, generating sIL-6R. This mechanism of trans-signaling allows IL-6 to act on cells that lack IL-6R. Both modes of IL-6 receptor signaling lead to gp130 activation of Janus kinases 1 and 2 and tyrosine kinase 2, and a series of proximal tyrosine residues that activate the STAT1, STAT3, MAPK, and PI3K cascade. In addition to the JAK/STAT pathway, IL-6 signaling also stimulates SFK-dependent signaling, which probably leads to the activation of different transcriptional regulators including YAP. Phosphorylation of the tyrosine motif 759 in the cytoplasmic tail of gp130 is important for negative regulation of IL-6 signal transduction. SHP2 and SOCS3 bind to this phosphotyrosine and attenuate the IL-6 downstream JAK/STAT signaling. In trans-presentation, mIL-6Rα in complex with IL-6 is presented by dendritic cells and sensed by gp130 molecules expressed on T cells. *ADAM17* a disintegrin and metallopeptidase domain 17, *IL-6* interleukin-6, *IL-6R* interleukin-6 receptor, *Jak* Janus kinase, *MAPK* mitogen-activated protein kinase, *mIL-6R* membrane bound IL-6R, *PI3K* phosphatidylinositol-4,5-bisphosphate 3-kinase, *SFK* Src-family kinase, *SHP2* Src homology 2-containing protein tyrosine phosphatase 2, *sIL-6R* soluble IL-6R, *SOCS3* suppressor of cytokine signaling 3, *STAT* signal transducer and activator of transcription, *Tyk2* Tyrosine kinase 2, *Tyr759* tyrosine residue 759, *YAP* YES-associated protein

less the immune response to infections [14]. However, currently, this product is not being investigated for use in RA.

Additionally, a third mechanism of IL-6 signaling, called 'trans-presentation,' has been described in which T cells respond to IL-6 in the absence of IL-6Rα expression [15]. Here, mIL-6Rα in complex with IL-6 is presented by dendritic cells and sensed by gp130 molecules expressed on T cells. The formation of the IL-6-IL-6Rα complex occurs within the intracellular compartments of dendritic cells before being transported to the membrane. Unlike classical IL-6 signaling and IL-6 trans-signaling, anti-IL-6 antibodies fail to inhibit IL-6 trans-presentation. However, anti-IL-6Rα antibodies can neutralize trans-presentation.

In recent years, the success of the IL-6R inhibitors tocilizumab (TCZ) and sarilumab (SAR) in the treatment of RA has further highlighted the important role of this cytokine. The high efficacy even with monotherapy and the acceptable risk profile has encouraged researchers to target different points of this pathway. In addition to RA, IL-6R inhibitors have been approved for use in various other diseases such as juvenile idiopathic arthritis, polymyalgia rheumatica, giant cell arteritis, cytokine-release syndrome in CAR-T cell therapy, Castleman disease, COVID-19, and others, in all of which inflammation and the acute-phase response play an important role [16, 17]. Of note, use in systemic sclerosis-induced interstitial lung disease has also been approved by the US Food and Drug Administration (FDA) [18]. Further indications such as adult-onset Still's disease and Schnitzler's disease are also highlighting that additional research is needed to understand the full potential of IL-6 inhibition. General characteristics of biologics targeting IL-6 or IL-6R have been shown in Table 1.

Under steady-state conditions, serum levels of sIL-6R and sgp130 are roughly about 1000 times higher than IL-6 levels. In septic conditions, serum IL-6 levels can increase by more than 1000 times; however, in chronic inflammatory diseases such as rheumatoid arthritis, this elevation is more constrained, and serum levels of sIL-6R and sgp130 remain relatively consistent with serum IL-6 levels [11, 19, 20]. sIL-6R and sgp130 together serve as a buffer against high IL-6 levels and act as a barrier against inflammatory diseases. Preliminary data also suggest that there may be potential advantages of targeting the IL-6 cytokine over targeting IL-6R in the context of systemic complications associated with RA, such as depression and cardiovascular diseases [21].

Finally, on the basis of lower levels of circulating cytokine versus receptor, polymorphisms in the IL-6R gene, and the fact that the IL-6R has additional ligands, it was assumed that IL-6 inhibition may have additional advantages over IL-6R inhibition, such as lower drug load, longer half-life, and more specific and efficacious responses [22–24]. In this context, various direct IL-6 inhibitors have been investigated in clinical studies and only recently, the first drug of this class, olokizumab (OKZ) has been approved in Russia for the treatment of RA [25].

In this review, we discuss the current status of new agents targeting the IL-6 pathway in RA treatment. We also examine the emergence of TCZ biosimilars into the landscape following the broader utilization of TCZ and SAR and try to explore where we stand regarding the direct inhibition of the IL-6 cytokine.

2 IL-6 Inhibitors for the Treatment of RA

2.1 Olokizumab (OKZ)

Olokizumab came to the fore with three pivotal, phase III core publications in 2022. In a phase III study in which patients with RA whose disease was not adequately controlled with methotrexate (MTX), both OKZ 64 mg every 2 weeks (q2w) and OKZ 64 mg every 4 weeks (q4w) in combination with MTX, established a significant superiority over placebo (PBO) plus MTX in the primary efficacy outcome, American College of Rheumatology 20% (ACR20) response at week 12 (63.6%; 70.4%; 25.9%, respectively, $p < 0.0001$ for both comparisons) [26].

Table 1 General characteristics of biologics targeting IL-6 or IL-6R

Biologics	Target molecules	Antibody	Route of administration and dose	Intervals
Tocilizumab	IL-6R	Humanised	IV 8 mg/kg	4 w
			SC 162 mg	1–2 w
Sarilumab	IL-6R	Human	SC 150 mg, 200 mg	2 w
Levilimab	IL-6R	Human	SC 162 mg	1–2 w
Vobarilizumab	IL-6R	Humanised	SC 75 mg, 150 mg, 225 mg	2–4 w
Olokizumab	IL-6, site 3	Humanised	SC 64 mg	2–4 w
Sirukumab	IL-6, site 1	Human	SC 50 mg, 100 mg	2–4 w
Clazakimumab	IL-6, site 1	Humanised	SC 25 mg, 100 mg, 200 mg	Once monthly

IL-6 interleukin-6, *IL-6R* interleukin-6 receptor, *IV* intravenous, *SC* subcutaneous, *w* weeks

Additionally, the secondary endpoint of Disease Activity Score 28-joint count C-reactive protein (DAS28-CRP) < 3.2 at week 12 was met significantly higher in both OKZ dosage groups compared with the PBO group (38.7%; 33.6%; 3.5%, respectively, $p < 0.0001$ for both comparisons). The Health Assessment Questionnaire-Disability Index-based physical function also significantly improved in the OKZ groups with least-squares mean changes of 0.54, 0.56, and 0.20, respectively ($p < 0.0001$ for both comparisons). Safety was consistent with the expected range for this class of agents and the observed immunogenicity was low. Treatment-emergent adverse events (TEAEs), which were reported in 52.9% of patients, were mostly mild to moderate leading to treatment discontinuation in 3.5 and 4.9% of patients on OKZ q4w and q2w compared with 0.7% of patients on PBO. Treatment-emergent serious adverse events (TESAEs) were numerically higher in patients on OKZ q2w and q4w compared with PBO (5.6, 5.6, and 2.8%, respectively), with infections being the most common adverse event, occurring in 2.8% of the patients on OKZ q2w and 1.4% on PBO. Serious infection was not reported in the OKZ q4w group. One TEAE leading to death because of septicemia was reported in OKZ q2w group.

In another phase III study in patients with RA who did not respond to anti-tumor necrosis factor treatments, patients were randomized to OKZ 64 mg q2w, OKZ 64 mg q4w, or PBO plus MTX. All subjects in the PBO group were re-randomized to receive either OKZ 64 mg q2w or OKZ 64 mg q4w at week 16 [27]. The primary endpoint was met with ACR20 response rates of 60.9, 59.6, and 40.6%, respectively ($p < 0.01$ for both comparisons, at week 12). Additionally, the major secondary efficacy endpoint (DAS28 [CRP] < 3.2) at week 12 was significantly superior in both OKZ arms compared with PBO ($p < 0.0001$ for OKZ q2w and 0.0035 for OKZ q4w). The safety profile was similar to monoclonal antibodies to the IL-6 receptor. Most of the TEAEs were mild to moderate in severity and were reported in 64.7% of patients with 64.3% in the OKZ q2w group, followed by 59.7% group in the OKZ q4w group (up to week 44, OKZ groups including the period before and after re-randomization) compared with 50.7% in the PBO group (up to week 16) group. Prior to re-randomization, discontinuation because of TEAEs were observed in 4.1% of the OKZ q2w group and 5.4% in the OKZ q4w group compared with 1.4% in the PBO group. Up to week 16, no TESAEs were reported in the PBO group, TESAEs reported in the OKZ groups during the first 16 weeks were 6.5% in the q2w group compared with 1.9% in the q4w group. Furthermore, numerically higher TESAEs were reported in the OKZ 64-mg 2w group up to week 44. No deaths were reported.

In a head-to-head study, patients with RA with an inadequate response to MTX were randomly assigned to receive subcutaneous OKZ at a dose of 64 mg every 2 or 4 weeks, adalimumab (ADA) 40 mg q2w, or PBO while continuing background MTX [28]. At week 12, OKZ resulted in a better efficacy than PBO with respect to the primary efficacy endpoint ACR20 response, 70.3% in OKZ q2w, 71.4% in OKZ q4w, and 44.4% of the patients receiving PBO ($p < 0.001$ for the superiority of each OKZ dose to PBO) and 66.9% in patients receiving ADA. Of note, OKZ was non-inferior to ADA in both doses in terms of the percentage of patients with an ACR20 response at week 12. The rates of serious adverse events were similar among treatment groups: 4.8% in the OKZ q2w group, 4.2% in the OKZ q4w group, 5.6% in the ADA group, and 4.9% in the PBO group. Infections were the most commonly reported serious adverse events with rates of 1.3, 1.5, 3.5, and 1.6% in the respective groups. Three deaths were reported in the OKZ q2w group followed by two in the OKZ q4w group, and one in each of the ADA and PBO groups because of adverse reactions.

Following phase III core studies, patients were enrolled in an open-label extension study. During the extension period, patients on OKZ 64 mg q2w and q4w continued their medication, patients on ADA and PBO were switched to OKZ 64 mg q2w or q4w [29]. Adverse events were assessed at week 82 and safety monitoring was continued for an additional 20 weeks. In 73.5% of the patients, TEAEs were observed, with infections being the most common adverse event, occurring in 38.5% of the patients. Adverse events leading to treatment discontinuation were infections in 2.5% of the patients followed by laboratory changes such as elevated liver function tests or changes in blood counts in 2% of the patients. Serious adverse events occurred in 11.8% of patients, while serious infections occurred in 4.1%. Deaths were reported in 1.2% of patients, with similar rates in both groups. Throughout the study, the efficacy of OKZ remained consistent, and patients who were switched from PBO or ADA to OKZ treatment groups achieved similar responses to those in the initial OKZ groups and no significant difference was observed in terms of efficacy or safety among the OKZ treatment groups. Olokizumab was well tolerated and had low dropout rates. The main efficacy results of OKZ phase III trials and an overall summary of adverse events and immunogenicity in safety population were shown in Tables 2 and 3.

2.2 Sirukumab (SRK)

Sirukumab (SRK) had completed phase III studies and demonstrated similar clinical efficacy compared to TCZ and other IL-6 inhibitors [30–32]. However, death rates in the SRK arms compared with PBO, especially in the controlled period, led to the decision by the FDA not to grant approval of SRK in August 2017 and the company terminated its development program. In 2021, the long-term extension

Table 2 Main efficacy results in OKZ phase III trials

Outcomes	OKZ q2w vs OKZ q4w vs PBO (plus MTX) [MTX-IR] [26]	OKZ q2w vs OKZ q4w vs PBO (plus MTX) [aTNF-IR] [27]	OKZ q2w vs OKZ q4w vs ADA vs PBO (plus MTX) [MTX-IR] [28]
ACR20-w12 (%)	63.6/70.4/25.9	60.9/59.6/40.6	70.3/71.4/66.9/44.4
ACR50-w12 (%)	37.8/38/4.2	33.3/32.3/15.9	40.9/42.8/39.2/15.6
ACR50-w24 (%)	42/48.6/7.7	33.3/40.6	50.4/50.1/46.3/22.6
DAS28CRP < 3.2, w12 (%)	38.7/33.6/3.5	39.9/28.0/11.6	45.3/45.7/38.3/12.8
DAS28CRP < 3.2, w24 (%)	48.6/37.8/7.7	45.7/42.9	52.2/53.9/46.1/21.8
CDAI ≤ 2.8, w12 (%)	2.8/1.4/0	6.5/3.1/0	7.8/7.7/8.0/3.3
CDAI ≤ 2.8, w24 (%)	8.4/7.7/0	10.1/5.6	11.2/12.1/13/4.1

ACR American College of Rheumatology Response, *ADA* adalimumab, *aTNF-IR* anti-tumor necrosis factor inadequate responders, *CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *DAS28 (CRP)* Disease Activity Score based on CRP, *MTX* methotrexate, *MTX-IR* methotrexate inadequate responders, *OKZ* olokizumab, *PBO* placebo, *q2w* every 2 weeks, *q4w* every 4 weeks, *w* week, *w12* at week 12, *w24* at week 24, *(%)* percentage of responders

study of the SIRROUND-D and SIRROUND-T studies enrolling 1820 patients with a median exposure of 2.34 and 2.07 years in the SRK 50-mg q4w group and the 100-mg q2w group, respectively, were published [33]. The efficacy was maintained and the safety profile did not change from the reported profile in SIRROUND-D and SIRROUND-T studies. Throughout the studies, 32 deaths were reported, 27 during the primary study periods and five in the long-term extension. The death rates were 0.5/100 year (50 mg q4w) and 0.4/100 year (100 mg q2w) mainly due to serious infections and major adverse cardiovascular events. As mentioned in the discussion of the study, mortality rates were similar with long-term TCZ and SAR data [34, 35]

2.3 Other IL-6R Inhibitors

Clazakizumab (BMS945429; ALD518) is another monoclonal humanized antibody that binds to circulating IL-6 cytokine and blocks both classic and trans-signaling [36]. Although it was more potent than TCZ in in-vitro assays, and showed efficacy in phase II trials, the company stopped further development in RA and phase III trials have not been performed [37, 38]. Additionally, MEDI5117, a fully human monoclonal antibody targeting IL-6 has been developed from the progenitor anti-IL-6 human monoclonal antibody CAT6001 by variable domain engineering to achieve a higher affinity and an improved half-life; however, a phase I trial in patients with RA has been terminated because of difficulties with patient recruitment (ClinicalTrials.gov identifier NCT01559103) [39, 40]. Another recombinant humanized monoclonal antibody (gerilimzumab, GB3224) against IL-6 has been evaluated in healthy adults in a phase I study. A single-dose subcutaneous administration of gerilimzumab was well tolerated with desirable pharmacokinetics and a low immunogenicity [41]. However, a phase II study evaluating further the safety and efficacy profile in RA was not started because of a sponsor's decision (ClinicalTrials.gov identifier: NCT02795299) [42].

3 New IL-6R Inhibitors for the Treatment of RA

3.1 Levilimab (LVL)

Following the successful worldwide use of IL-6R inhibitors TCZ and SAR, results for a new IL-6R inhibitor, levilimab (LVL), were shown at the European League Against Rheumatism (EULAR) Congress 2021. Twenty-four-week results of efficacy and safety of a phase III, double-blind, PBO-controlled, randomized clinical study (SOLAR) have been mainly reported [43]. The study aimed to confirm the superiority of LVL (162 mg, subcutaneously, once weekly) plus MTX over PBO plus MTX in patients with RA resistant to treatment with MTX, in terms of ACR20 at week 12 and low disease activity at week 24. Levilimab plus MTX achieved both primary outcome points (71 vs 40% for ACR20; $p = 0.0003$ and 52 vs 6% for low disease activity; $p < 0.0001$) at the end of the study. The spectrum of adverse events observed in this period were similar to other IL-6R inhibitors without any new safety signals.

At EULAR 2022, 1-year results of the open-label period of the SOLAR study have been presented [44]. In the open-label period, patients who achieved DAS28-CRP ≤ 2.6 at week 24, were switched to a maintenance dose of LVL, every 2 weeks plus MTX. Patients with a DAS28-CRP score over 2.6 continued the weekly regimen of LVL+MTX. In the q2w LVL group, the ACR70 response, DAS28-CRP < 2.6, and ACR/EULAR2011 remission rates were 55.6, 85.2, and 25.9%, respectively at week 24. After 1 year, the rates were 63.0, 77.8, and 44.4%, respectively. The rates did not differ significantly

Table 3 Overall summary of adverse events and immunogenicity (OKZ safety population) [reproduced with permission from Feist et al. [29]]

All cases, *n* (%)	OKZ 64 mg q2w *N* = 1061	OKZ 64 mg g4w *N* = 1043
≥ 1 AE	793 (74.7)	753 (72.2)
≥ 1 AE, related to study treatment	352 (33.2)	318 (30.5)
> 1 serious AE	120 (11.3)	129 (12.4)
Serious infection	47 (4.4)	40 (3.8)
≥ 1 AE of special interest	611 (57.6)	598 (57.3)
Infections	398 (37.5)	389 (37.3)
Opportunistic infections	22 (2.1)	19 (1.8)
Malignancies	6 (0.6)	9 (0.9)
Melanoma	0	0
Basal cell carcinomas	1 (<0.1)	2 (0.2)
Hyperlipidemia	138 (13.0)	120 (11.5)
Systemic injection and hypersensitivity reactions	100 (9.4)	99 (9.5)
Anaphylactic reactions	0	0
Injection-site reactions	34 (3.2)	34 (3.3)
Gastrointestinal perforation	2 (0.2)	1(<0.1)
Cytopenias	168 (15.8)	146 (14.0)
Potential hepatotoxicity (ALT > 3 ULN)	63 (5.9)	68 (6.5)
Demyelination in the peripheral or central nervous system	1 (< 0.1)	0
Autoimmune disorders	41 (3.9)	48 (4.6)
Musculoskeletal and connective tissue disorders	30 (2.8)	34(3.3)
Rheumatoid arthritis	28 (2.6)	28 (2.7)
Rheumatoid nodule	2 (0.2)	4 (0.4)
Systemic lupus erythematosus	0	2 (0.2)
Skin and subcutaneous tissue disorders[a]	5 (0.5)	5 (0.5)
Other disorders[b]	6 (0.6)	10 (1.0)
Respiratory, thoracic, and mediastinal disorder	68 (6.4)	60 (5.8)
Pulmonary embolism	4 (0.4)	2 (0.2)
Major adverse cardiac events (adjudicated)	7 (0.7)	15 (1.4)
AE leading to discontinuation of study drug	90 (8.5)	87 (8.3)
Death[c]	13 (1.2)	13 (1.2)
Immunogenicity		
ADA OLE BL positive confirmatory results	18 (1.7)	27 (2.6)
ADA any time post-BL positive confirmatory results	34 (5.0)	17 (2.6)
Nab OLE BL positive confirmatory results	0	1 (0.1)
Nab any time post-BL positive confirmatory results	2 (0.3)	2 (0.3)

ADA antidrug antibodies, *AE* adverse event that occurred after the first dose of the open-label (OLE) study treatment, *ALT* alanine aminotransferase, *BL* baseline, *n* number of subjects, *Nab* neutralizing antibodies, *OLE* open-label extension, *q2w* every 2 weeks, *q4w* every 4 weeks, *ULN* upper limit of normal, % percentage of subjects calculated relative to the total number (*N*) of subjects in the population

[a]Psoriasis, cutaneous vasculitis, alopecia areata, hypersensitivity vasculitis, pyoderma gangrenosum, vasculitic rash, vitiligo

[b]Chronic gastritis, ulcerative keratitis, ocular myasthenia, vasculitis, rheumatoid vasculitis, autoimmune thyroiditis, type 1 diabetes mellitus, rheumatoid lung

[c]AEs leading to death by System Organ Class: infections and infestations 7 (0.3%), general disorders and administration-site conditions 5 (0.2%), cardiac disorders 3 (0.1%), neoplasms benign, malignant, and unspecified (central nervous system neoplasm, metastatic neoplasm, pancreatic carcinoma metastatic) 3 (0.1%)

in terms of the ACR70 response and DAS28-CRP remission rates and even further increased with respect to ACR/EULAR 2011 remission criteria after 52 weeks. These findings suggested the possibility of switching to a maintenance dose of LVL q2w in patients with RA who achieved remission.

Moreover, patients who could not achieve DAS28-CRP remission at week 24 and had a continued weekly regimen

Table 4 Main efficacy results and most common adverse events in levilimab phase III trials[a] [43, 44]

ACR20, w12 (%) [LEV/PBO]	71/40
DAS28(CRP) < 3.2, w24 (%) [LEV/PBO]	52/6
DAS28(CRP) < 2.6, w24 (%) [LEV/PBO]	18/0.6
Blood cholesterol increase (%)	30.3
ALT increase (%)	23.0
Lymphocyte count decrease (%)	17.1
ANC decrease (%)	16.4
Blood triglyceride increase (%)	13.8
Bilirubin increase (%)	11.2
AST increase (%)	9.9
WBC decrease (%)	9.9
IGRA with M. tb antigen positive (%)	7.2
Injection-site reactions (%)	5.9

ACR American College of Rheumatology Response, *ALT* alanine transaminase, *ANC* absolute neutrophil count, *AST* aspartate transaminase, *CRP* C-reactive protein, *DAS28(CRP)* Disease Activity Score based on CRP, *IGRA* interferon-gamma release assay, *LEV* levilimab, *M. tb* Mycobacterium tuberculosis, *PBO* placebo, *w12* at week 12, *w24* at week 24, *WBC* whole blood count, *(%)* percentage of responders or percentage of patients experiencing an adverse effect

[a]Efficacy results of first 24 weeks before re-randomization, adverse events reflect 1-year safety data of the open-label period (reported in ≥ 5% of subjects)

of LVL+MTX reached remission rates of 46.7% of DAS28-CRP and 10.7% of ACR/EULAR 2011 remission and 36% ACR70 response after 1 year, confirming the maintained efficacy of LVL+MTX in patients with active RA resistant to treatment with MTX. The safety analysis was again similar to other IL-6R inhibitors. No deaths occurred. Subsequently, LVL has been approved in Russia, but no results from real-life clinical practice have been reported so far [45]. The main efficacy results and most common adverse events in LVL phase III trials are shown in Table 4.

3.2 Vobarilizumab

ALX-0061 (vobarilizumab) is a bispecific anti-IL-6R nanobody designed to have an extended half-life in vivo by targeting human serum albumin, in combination with strong target binding using a single anti-IL-6R building block in order to inhibit the proinflammatory activities. It appears to modulate the IL-6 trans-signaling pathway in addition to the classical mIL-6R-dependent pathway [46]. Because of the small size, these nanobodies have low in-vivo toxicity and immunogenicity and can be rapidly eliminated from the body by the kidneys [47, 48]. Compared with TCZ, ALX0061 has a 2400-fold higher affinity for the sIL-6 receptor and a 17-fold higher affinity for mIL-6R. In a phase I/II study, ACR 20 response rates reached up to 84% and DAS28 remission rates up to 58% [49]. In a phase IIb monotherapy study conducted head-to-head with TCZ in 251 patients with RA, ALX0061 demonstrated comparable or superior efficacy in primary and secondary efficacy endpoints [50]. In an open-label extension study assessing the long-term efficacy and safety of ALX-0061 in RA over 104 weeks, ACR20, ACR50, and ACR70 rates reached 97, 84, and 72%, respectively [51].

3.3 Tocilizumab (TCZ) Biosimilars

The successful results of TCZ in many inflammatory conditions have brought biosimilars to the agenda after expiration of its patent period. In this regard, BAT1806/BIIB800 has been approved for use in RA by China's National Medical Products Administration and has been filed applied for approval to both at the FDA and the European Medicines Agency [52].

The results of the phase III study BAT1806/BIIB800 in patients with RA with moderate-to-severe disease activity and irresponsive to MTX were published at the EULAR Congress in 2022 [53]. With a randomization of 2:1:1, patients were divided into three groups: (1) those who received BAT1806/BIIB800 for 48 weeks; (2) those who received TCZ for 48 weeks; or (3) those who received TCZ for 24 weeks followed by BAT1806/BIIB800 for the next 24 weeks. The administrations were performed at a dose of 8 mg/kg every 4 weeks. The primary endpoints of the study were the ACR responses at week 12 and week 24. ACR20 rates in BAT1806/BIIB800 and TCZ groups were 68.97 versus 64.82% at week 12 and 69.89 versus 67.94% at week 24, respectively. The confidence intervals for the estimated differences were within the pre-defined equivalence margins. Compared to reference TCZ, BAT1806/BIIB800 exhibited comparable efficacy at both the 12th and 24th weeks of the study. Moreover, at the 24th week, the pharmacokinetic profiles, safety, and immunogenicity were similar.

The results from week 24 to week 48 were published at the American College of Rheumatology Convergence 2022 [54]. At week 48, the ACR20 rates in groups 1, 2, and 3 were 92.9, 92.2, and 93.5%, respectively. The ACR20/50/70 responses and mean changes in DAS28-erythrocyte sedimentation rate and DAS28-CRP scores from baseline were similar between the groups. No deaths occurred during this period. Safety, immunogenicity, and pharmacokinetic profiles were comparable among the three groups, and no additional safety or immunogenicity concerns were observed in the group that switched from TCZ to BAT1806. Other TCZ biosimilars such as HS628, QX003S, and MSB11456 have also been developed and entered into a clinical trial program [55–59].

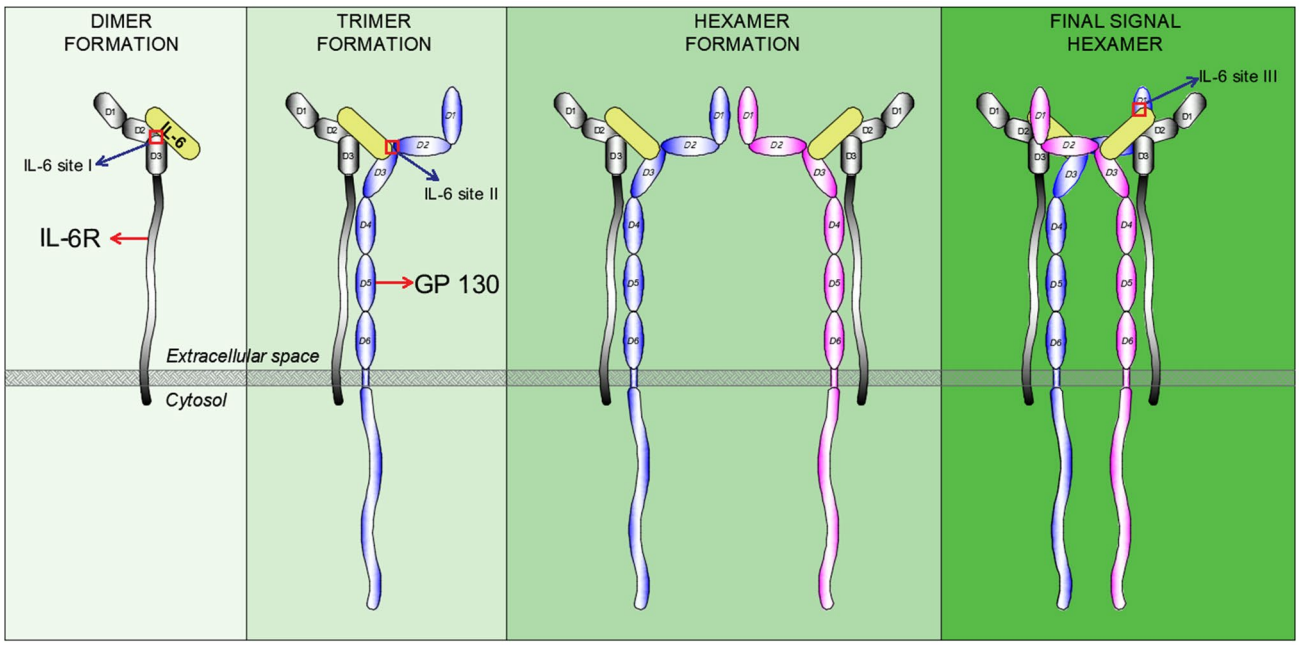

Fig. 2 Interleukin-6 inhibitors can bind to different antigenic sites on interleukin (IL)-6. Sirukumab and clazakizumab bind to site 1 and interfere with the binding of IL-6 to the IL-6 receptor (IL-6R)-α in the IL-6–IL-6R–gp130 trimolecular complex and prevents dimerization. Olokizumab binds to site 3 and blocks hexamer formation by disrupting the interaction of IL-6 and the IL-6–IL-6R dimer with the signal-transducing β-receptor subunit gp130 part of the receptor complex

4 Discussion and Conclusions

Recent advances in the treatment of RA have made significant breakthroughs, with IL-6 inhibitors playing an important role alongside other biologics in both combination therapy with MTX and as monotherapy. The combination of acceptable safety data with high efficacy has led to long-term drug survival rates in treatment with IL-6R inhibitors. The successful introduction of IL-6R inhibitors, TCZ and SAR, in therapy have led to the rapid development of biosimilars in addition to new potent and safe IL-6R inhibitors. In this context, LVL, a new IL-6R blocker such as TCZ and SAR, has exhibited a similar efficacy and safety profile reflecting the group effect in the published data so far. Furthermore, the biosimilar BAT1806/BIIB800 has completed phase III trials and has been approved for use in RA by the National Medical Products Administration and approval has been applied for both at the FDA and European Medicines Agency.

The advantages and risks of targeting different points of the IL-6 cytokine pathway, such as directly neutralizing IL-6 or inhibiting trans-signaling, have been the focus of current discussions. Despite the development of sirukumab being halted, data from extension studies of phase III trials of SRK and the successful use of another IL-6 cytokine inhibitor, OKZ, have largely alleviated safety concerns. Moreover, in a recently published network meta-analysis of randomized controlled trials, TCZ, SAR, and OKZ were compared in terms of efficacy and safety in active RA despite MTX [60]. While they were more effective than ADA in terms of efficacy, all three drugs targeting the IL-6 pathway were similarly effective and safe compared to each other.

Interleukin-6 inhibitors can bind to different antigenic sites on IL-6 [61, 62] (Fig. 2). In this regard, SRK and clazakizumab bind to site 1, interfering with the binding of IL-6 to IL-6Rα in the IL-6–IL-6R–gp130 trimolecular complex and preventing dimerization, while OKZ binds to site 3, blocking hexamer formation by disrupting the interaction of IL-6 and the IL-6–IL-6R dimer with the signal-transducing β-receptor subunit gp130 part of the receptor complex [5, 28, 63–65]. This also brings the advantage of inhibiting the binding of IL-6 and sIL-6R dimers to the membrane portion of the receptor, preventing continued cell activation [27]. Additionally, hypothetically, dimeric or trimeric complexes can still form, and the physiological buffering system continues to function, thereby facilitating better control of inflammation. Unlike SRK, OKZ demonstrated low mortality rates both in the PBO-controlled and long-term extension period. In a recent systematic review, pairwise analysis, and network meta-analysis of OKZ, both in the pairwise and the network meta-analysis, no difference was found in the incidence of any-cause mortality between different OKZ regimens and PBO, without any observed heterogeneity [66]. Therefore,

targeting different antigenic regions of IL-6 separately or simultaneously may result in different outcomes in terms of efficacy and/or safety and can be an important topic for future drug development research.

Finally, the potential clinical outcomes of new strategies, such as selective blockade of trans-signaling or trans-presentation, in contrast to IL-6 and IL-6R blockade, remain a subject of interest. In this context, the development of new drugs based on basic research and their evaluation in advanced clinical trials will contribute to the optimal therapeutic approach of this pathway's potential in translational and clinical research.

Funding Open Access funding enabled and organized by Projekt DEAL.

Declarations

Funding No sources of funding were used to support the writing of this article.

Conflict of interest Ali Berkant Avci has no conflicts of interest that are directly relevant to the content of this article. Eugen Feist has received honoraria for lectures as an advisor from AbbVie, BMS, Celgene, Galapagos, Lilly, Medac, Novartis, Pfizer, Sobi, and Sanofi. Gerd R. Burmester has received honoraria for consulting and lectures from Chugai and Sanofi.

Ethics approval Not applicable.

Consent to participate Not applicable.

Consent for publication Not applicable.

Availability of data and material This article has no associated data.

Code availability Not applicable.

Author contributions The authors have contributed sufficiently to the article (drafting and/or critical revision of the manuscript and approved the final submitted version of the manuscript) and share collective responsibility and accountability for the article.

References

1. Schett G. Physiological effects of modulating the interleukin-6 axis. Rheumatology (Oxford). 2018;57(Suppl_2):ii43–50.
2. Bethin KE, Vogt SK, Muglia LJ. Interleukin-6 is an essential, corticotropin-releasing hormone-independent stimulator of the adrenal axis during immune system activation. Proc Natl Acad Sci USA. 2000;97(16):9317–22.
3. Kraakman MJ, Kammoun HL, Allen TL, Deswaerte V, Henstridge DC, Estevez E, et al. Blocking IL-6 trans-signaling prevents high-fat diet-induced adipose tissue macrophage recruitment but does not improve insulin resistance. Cell Metabol. 2015;21(3):403–16.
4. Schett G, Elewaut D, McInnes IB, Dayer JM, Neurath MF. How cytokine networks fuel inflammation: toward a cytokine-based disease taxonomy. Nat Med. 2013;19(7):822–4.
5. Hunter CA, Jones SA. IL-6 as a keystone cytokine in health and disease. Nat Immunol. 2015;16(5):448–57.
6. Rose-John S, Winthrop K, Calabrese L. The role of IL-6 in host defence against infections: immunobiology and clinical implications. Nat Rev Rheumatol. 2017;13(7):399–409.
7. Spencer S, Kostel Bal S, Egner W, Lango Allen H, Raza SI, Ma CA, et al. Loss of the interleukin-6 receptor causes immunodeficiency, atopy, and abnormal inflammatory responses. J Exp Med. 2019;216(9):1986–98.
8. Mullberg J, Schooltink H, Stoyan T, Gunther M, Graeve L, Buse G, et al. The soluble interleukin-6 receptor is generated by shedding. Eur J Immunol. 1993;23(2):473–80.
9. Jostock T, Mullberg J, Ozbek S, Atreya R, Blinn G, Voltz N, et al. Soluble gp130 is the natural inhibitor of soluble interleukin-6 receptor transsignaling responses. Eur J Biochem. 2001;268(1):160–7.
10. Nowell MA, Williams AS, Carty SA, Scheller J, Hayes AJ, Jones GW, et al. Therapeutic targeting of IL-6 trans signaling counteracts STAT3 control of experimental inflammatory arthritis. J Immunol. 2009;182(1):613–22.
11. Nowell MA, Richards PJ, Horiuchi S, Yamamoto N, Rose-John S, Topley N, et al. Soluble IL-6 receptor governs IL-6 activity in experimental arthritis: blockade of arthritis severity by soluble glycoprotein 130. J Immunol. 2003;171(6):3202–9.
12. Sodenkamp J, Waetzig GH, Scheller J, Seegert D, Grotzinger J, Rose-John S, et al. Therapeutic targeting of interleukin-6 trans-signaling does not affect the outcome of experimental tuberculosis. Immunobiology. 2012;217(10):996–1004.
13. Hoge J, Yan I, Janner N, Schumacher V, Chalaris A, Steinmetz OM, et al. IL-6 controls the innate immune response against Listeria monocytogenes via classical IL-6 signaling. J Immunol. 2013;190(2):703–11.
14. Schreiber S, Aden K, Bernardes JP, Conrad C, Tran F, Hoper H, et al. Therapeutic interleukin-6 trans-signaling inhibition by olamkicept (sgp130Fc) in patients with active inflammatory bowel disease. Gastroenterology. 2021;160(7):2354-66.e11.
15. 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(H)17 cells. Nat Immunol. 2017;18(1):74–85.
16. Narazaki M, Kishimoto T. Current status and prospects of IL-6-targeting therapy. Expert Rev Clin Pharmacol. 2022;15(5):575–92.
17. US FDA. Sarilumab approval for polymyalgia rheumatica. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2023/761037s013lbl.pdf. Accessed 2 July 2023.
18. US FDA. Tocilizumab approval for systemic sclerosis-induced interstitial lung disease. Available from: https://www.accessdata.fda.gov/drugsatfda_docs/label/2021/125276s131lbl.pdf Accessed 9 July 2023.

19. Schaper F, Rose-John S. Interleukin-6: biology, signaling and strategies of blockade. Cytokine Growth Factor Rev. 2015;26(5):475–87.
20. Rose-John S. IL-6 trans-signaling via the soluble IL-6 receptor: importance for the pro-inflammatory activities of IL-6. Int J Biol Sci. 2012;8(9):1237–47.
21. Lazzerini PE, Capecchi PL, Guidelli GM, Selvi E, Acampa M, Laghi-Pasini F. Spotlight on sirukumab for the treatment of rheumatoid arthritis: the evidence to date. Drug Design Dev Ther. 2016;10:3083–98.
22. Robak T, Gladalska A, Stepien H, Robak E. Serum levels of interleukin-6 type cytokines and soluble interleukin-6 receptor in patients with rheumatoid arthritis. Mediators Inflamm. 1998;7(5):347–53.
23. Zhang M, Bai Y, Wang Y, Cui H, Tang M, Wang L, et al. Cumulative evidence for associations between genetic variants in interleukin 6 receptor gene and human diseases and phenotypes. Front Immunol. 2022;13: 860703.
24. Avci AB, Feist E, Burmester GR. Targeting IL-6 or IL-6 receptor in rheumatoid arthritis: what's the difference? BioDrugs. 2018;32(6):531–46.
25. Olokizumab official approval. Available from: https://grls.rosminzdrav.ru/GRLS.aspx?RegNumber=&MnnR=%d0%9e%d0%bb%d0%be%d0%ba%d0%b8%d0%b7%d1%83%d0%bc%d0%b0%d0%b1&lf=&TradeNmR=&OwnerName=&MnfOrg=&MnfOrgCountry=&isfs=0&regtype=1%2c6&pageSize=10&order=Registered&orderType=desc&pageNum=1. Accessed 7 July 2023.
26. Nasonov E, Fatenejad S, Feist E, Ivanova M, Korneva E, Krechikova DG, et al. Olokizumab, a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study. Ann Rheum Dis. 2022;81(4):469–79.
27. Feist E, Fatenejad S, Grishin S, Korneva E, Luggen ME, Nasonov E, et al. Olokizumab, a monoclonal antibody against interleukin-6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by tumour necrosis factor inhibitor therapy: efficacy and safety results of a randomised controlled phase III study. Ann Rheum Dis. 2022;81(12):1661–8.
28. Smolen JS, Feist E, Fatenejad S, Grishin SA, Korneva EV, Nasonov EL, et al. Olokizumab versus placebo or adalimumab in rheumatoid arthritis. N Engl J Med. 2022;387(8):715–26.
29. Feist E, Nasonov E, Luggen M, Fatenejad S, Grishin S, Samsonov M, et al. Long-term safety and efficacy of olokizumab in patients with rheumatoid arthritis: results of an open-label extension study [abstract]. Arthritis Rheumatol. 2022;74(Suppl. 9).
30. Takeuchi T, Yamanaka H, Harigai M, Tamamura R, Kato Y, Ukyo Y, et al. Sirukumab in rheumatoid arthritis refractory to sulfasalazine or methotrexate: a randomized phase 3 safety and efficacy study in Japanese patients. Arthritis Res Ther. 2018;20(1):42.
31. Takeuchi T, Thorne C, Karpouzas G, Sheng S, Xu W, Rao R, et al. Sirukumab for rheumatoid arthritis: the phase III SIRROUND-D study. Ann Rheum Dis. 2017;76(12):2001–8.
32. Aletaha D, Bingham CO 3rd, Tanaka Y, Agarwal P, Kurrasch R, Tak PP, et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. Lancet. 2017;389(10075):1206–17.
33. Aletaha D, Bingham CO, Karpouzas GA, Takeuchi T, Thorne C, Bili A, et al. Long-term safety and efficacy of sirukumab for patients with rheumatoid arthritis who previously received sirukumab in randomised controlled trials (SIRROUND-LTE). RMD Open. 2021;7(1): e001465.
34. Genovese MC, Rubbert-Roth A, Smolen JS, Kremer J, Khraishi M, Gomez-Reino J, et al. Longterm safety and efficacy of tocilizumab in patients with rheumatoid arthritis: a cumulative analysis of up to 4.6 years of exposure. J Rheumatol. 2013;40(6):768–80.
35. Fleischmann R, Genovese MC, Lin Y, St John G, van der Heijde D, Wang S, et al. Long-term safety of sarilumab in rheumatoid arthritis: an integrated analysis with up to 7 years' follow-up. Rheumatology (Oxford). 2020;59(2):292–302.
36. Mease P, Strand V, Shalamberidze L, Dimic A, Raskina T, Xu LA, et al. A phase II, double-blind, randomised, placebo-controlled study of BMS945429 (ALD518) in patients with rheumatoid arthritis with an inadequate response to methotrexate. Ann Rheum Dis. 2012;71(7):1183–9.
37. Zhao Q, Pang J, Shuster D, Hung C, Baglino S, Dodge R, et al. Anti-IL-6 antibody clazakizumab is more potent than tocilizumab in blocking in vitro and ex vivo IL-6-induced functions (abstract). Arthritis Rheum. 2013;65(Suppl):S1020.
38. Weinblatt ME, Mease P, Mysler E, Takeuchi T, Drescher E, Berman A, et al. The efficacy and safety of subcutaneous clazakizumab in patients with moderate-to-severe rheumatoid arthritis and an inadequate response to methotrexate: results from a multinational, phase IIb, randomized, double-blind, placebo/active-controlled, dose-ranging study. Arthritis Rheumatol. 2015;67(10):2591–600.
39. Finch DK, Sleeman MA, Moisan J, Ferraro F, Botterell S, Campbell J, et al. Whole-molecule antibody engineering: generation of a high-affinity anti-IL-6 antibody with extended pharmacokinetics. J Mol Biol. 2011;411(4):791–807.
40. Study to assess the safety and tolerability of MEDI5117 in rheumatoid arthritis patients. Available from: https://clinicaltrials.gov/ct2/results?cond=MEDI5117+rheumatoid&term=&cntry=&state=&city=&dist=. Accessed 26 Mar 2023.
41. Yan D, Niu S, Hu D, Dong W, Sun Y, Wang Q, et al. Pharmacokinetics, pharmacodynamics, safety, and immunogenicity of gerilimzumab (GB224), a recombinant humanized interleukin-6 monoclonal antibody, in healthy Chinese adults: a randomized controlled dose-escalation study. Expert Opin Invest Drugs. 2023;32(2):161–70.
42. Study evaluating gerilimzumab's safety/efficacy for patients MTX or TNFα antagonist failed in rheumatoid arthritis. Available from: https://clinicaltrials.gov/ct2/show/NCT02795299?cond=gerilimzumab&draw=2&rank=3. Accessed 26 Mar 2023.
43. Mazurov V, Korolev M, Kundzer A, Soroka N, Kastanayan A, Povarova T, et al. Efficacy and safety of levilimab in combination with methotrexate in subjects with active rheumatoid arthritis: phase III, double-blind, placebo-controlled, randomized trial. Ann Rheum Dis. 2021;80(Suppl. 1):550.
44. Mazurov V, Korolev M, Pristrom A, Kundzer A, Soroka N, Kastanayan A, et al. Efficacy and safety of levilimab in combination with methotrexate in patients with active rheumatoid arthritis: 1-year results of phase III, double-blind, placebo-controlled, randomized trial. Ann Rheum Dis. 2022;81(Suppl. 1):59645.
45. Levilimab official approval. Available from: https://grls.rosminzdrav.ru/GRLS.aspx?RegNumber=&MnnR=%d0%9b%d0%b5%d0%b2%d0%b8%d0%bb%d0%b8%d0%bc%d0%b0%d0%b1&lf=&TradeNmR=&OwnerName=&MnfOrg=&MnfOrgCountry=&isfs=0&regtype=1%2c6&pageSize=10&order=Registered&orderType=desc&pageNum=1. Accessed 7 July 2023.
46. Van Roy M, Ververken C, Beirnaert E, Hoefman S, Kolkman J, Vierboom M, et al. The preclinical pharmacology of the high affinity anti-IL-6R Nanobody(R) ALX-0061 supports its clinical development in rheumatoid arthritis. Arthritis Res Ther. 2015;17(1):135.
47. Hamers-Casterman C, Atarhouch T, Muyldermans S, Robinson G, Hamers C, Songa EB, et al. Naturally occurring antibodies devoid of light chains. Nature. 1993;363(6428):446–8.

48. Muyldermans S. Nanobodies: natural single-domain antibodies. Ann Rev Biochem. 2013;82:775–97.
49. Holz JB, Sargentini-Maier L, De Bruyn S, Gachályi B, Udvaros I, Rojkovich B, et al. Twenty-four weeks of treatment with a novel anti-IL-6 receptor nanobody (aALX-0061) resulted in 84% ACR20 improvement and 58% DAS28 remission in a phase I/II study in RA. Ann Rheum Dis. 2013;72:A64.
50. A phase IIb study for ALX-0061 monotherapy in subjects with rheumatoid arthritis. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02287922?term=ALX0061+rheumatoid&draw=2&rank=3&view=results. Accessed 2 Apr 2023.
51. An open-label extension study assessing the long-term efficacy and safety of ALX-0061 in subjects with rheumatoid arthritis. Available from: https://clinicaltrials.gov/ct2/show/results/NCT02518620?term=ALX0061+rheumatoid&draw=2&rank=1. Accessed 2 Apr 2023.
52. BAT1806/BIIB800 official approval. Available from: http://english.nmpa.gov.cn/2023-01/16/c_888726.htm. Accessed 10 Nov 2023.
53. Leng X, Leszczynski P, Jeka S, Liu S, Liu H, Miakisz M, et al. A phase III, randomised, double-blind, active-controlled clinical trial to compare BAT1806/BIIB800, a proposed tocilizumab biosimilar, with tocilizumab reference product in subjects with moderate to severe rheumatoid arthritis with an inadequate response to methotrexate therapy. Ann Rheum Dis. 2022;81(Suppl. 1):388.
54. Leng X, Leszczynski P, Jeka S, Liu S, Liu H, Miakisz M, et al. Fifty-two-week results from a phase 3, randomized, double-blind, active-controlled clinical trial to compare BAT1806/BIIB800, a proposed tocilizumab biosimilar, with a tocilizumab reference product in subjects with moderate to severe RA with an inadequate response to methotrexate [abstract]. Arthritis Rheumatol. 2022;74(Suppl. 9).
55. Miao S, Fan L, Zhao L, Ding D, Liu X, Wang H, et al. Physicochemical and biological characterization of the proposed biosimilar tocilizumab. BioMed Res Int. 2017;2017:4926168.
56. Zhang H, Li X, Liu J, Li C, Wu M, Zhu X, et al. A randomized phase-I pharmacokinetic trial comparing the potential biosimilar tocilizumab (QX003S) with the reference product (Actemra®) in Chinese healthy subjects. Ann Med. 2021;53(1):375–83.
57. Schwabe C, Illes A, Ullmann M, Ghori V, Vincent E, Petit-Frere C, et al. Pharmacokinetics and pharmacodynamics of a proposed tocilizumab biosimilar MSB11456 versus both the US-licensed and EU-approved products: a randomized, double-blind trial. Exp Rev Clin Immunol. 2022;18(5):533–43.
58. Schwabe C, Wynne C, Illes A, Ullmann M, Vincent E, Ghori V, et al. Pharmacokinetic and pharmacodynamic evaluation of a proposed biosimilar MSB11456 versus both the US-licensed and EU-approved tocilizumab: results of a randomized, double-blind, parallel-group, single-dose trial in healthy adults. Ann Rheum Dis. 2021;80(Suppl. 1):1121.
59. Tomaszewska-Kiecana M, Ullmann M, Vincent E, Petit-frere C, Monnet J, Illes A. Pharmacokinetics, safety, tolerability, and immunogenicity of a proposed tocilizumab biosimilar (MSB11456) versus US-licensed tocilizumab: results of a randomized, double-blind, parallel-group, single-intravenous dose study in healthy adults (APTURA II) [abstract]. Arthritis Rheumatol. 2022;74(Suppl. 9).
60. Ho Lee Y, Gyu Song G. Comparison of the efficacy and safety of tocilizumab, sarilumab, and olokizumab in patients with active rheumatoid arthritis: a network meta-analysis of randomized controlled trials. Z Rheumatol. 2023. https://doi.org/10.1007/s00393-022-01315-0
61. Kang S, Tanaka T, Narazaki M, Kishimoto T. Targeting interleukin-6 signaling in clinic. Immunity. 2019;50(4):1007–23.
62. Veverka V, Baker T, Redpath NT, Carrington B, Muskett FW, Taylor RJ, et al. Conservation of functional sites on interleukin-6 and implications for evolution of signaling complex assembly and therapeutic intervention. J Biol Chem. 2012;287(47):40043–50.
63. Genovese MC, Fleischmann R, Furst D, Janssen N, Carter J, Dasgupta B, et al. Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised phase IIb study. Ann Rheum Dis. 2014;73(9):1607–15.
64. Takeuchi T, Tanaka Y, Yamanaka H, Amano K, Nagamine R, Park W, et al. Efficacy and safety of olokizumab in Asian patients with moderate-to-severe rheumatoid arthritis, previously exposed to anti-TNF therapy: results from a randomized phase II trial. Mod Rheumatol. 2016;26(1):15–23.
65. Feist E, Chohan S, Fatenejad S, Grishin S, Korneva E, Nasonov EL, et al. P131 Efficacy and safety of olokizumab in a phase III trial of patients with moderately to severely active RA inadequately controlled by methotrexate: placebo and active controlled study. Rheumatology. 2021;60: keab247.126. https://doi.org/10.1093/rheumatology/keab247.126.
66. Abuelazm M, Ghanem A, Mahmoud A, Brakat AM, Elzeftawy MA, Mamdouh Fayoud A, et al. The efficacy and safety of olokizumab for rheumatoid arthritis: a systematic review, pairwise, andnetwork meta-analysis. Clin Rheumatol. 2023;42(6):1503–20.