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REVIEW

Understanding the Role of Interleukin-6 (IL-6) in the Joint and Beyond: A Comprehensive Review of IL-6 Inhibition for the Management of Rheumatoid Arthritis

Ennio G. Favalli

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ABSTRACT

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disorder involving inflammation and progressive destruction of the joints, affecting up to 1% of the population. The majority of patients with RA have one or more comorbid conditions, the most common being cardiovascular disease, osteoporosis, and depression, the presence of which are associated with poorer clinical outcomes and lower health-related quality of life. RA pathogenesis is driven by a complex network of proinflammatory cells and cytokines, and of these, interleukin-6 (IL-6) plays a key role in the chronic inflammation associated with RA. Through cell signaling that can be initiated by both membrane-bound and soluble forms of its receptor, IL-6 acts both locally to promote joint inflammation and destruction, and in the circulation to mediate extra-articular manifestations of RA, including pain, fatigue, morning stiffness, anemia, and weight loss. This narrative review describes the role of IL-6 in the pathogenesis of RA, its comorbidities, and extra-articular systemic manifestations, and examines the effects of the IL-6 receptor inhibitors sarilumab and tocilizumab on clinical endpoints of RA, patient-reported outcomes, and common comorbidities and extra-articular manifestations.

Keywords: Antirheumatic agents; Comorbidity; C-reactive protein; Inflammation; Interleukin-6; Rheumatoid arthritis

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E. G. Favalli (✉)
Department of Rheumatology, ASST Gaetano Pini-CTO Institute, University of Milan, Milan, Italy
e-mail: enniofavalli@me.com

INTRODUCTION

Key Summary Points

Interleukin-6 (IL-6) plays an important role in the development of rheumatoid arthritis (RA) disease state within the joint.

Beyond the joint, IL-6 is also linked to extra-articular manifestations and common comorbidities in patients with RA.

Interleukin-6 receptor (IL-6R) blockade treatment with the humanized monoclonal antibody (mAb) tocilizumab, and more recently with the human mAb sarilumab, has been shown in clinical studies to be an important advancement for treating RA-associated disease manifestations within and beyond the joint.

The benefits of IL-6R blockade seem to extend to improvements in many of the extra-articular manifestations of the condition, such as pain, fatigue, and anemia, as well as potentially beneficial effects on certain comorbidities, such as improvements in glycemic control in patients with RA and comorbid diabetes, improvements in bone mineral density in patients with RA prone to osteoporosis, and improvements in mood disorders.

Rheumatoid arthritis (RA) is a chronic, debilitating autoimmune disorder affecting up to 1% of the population [1]. While RA is characterized by inflammation of the synovial joint tissues, it has also been linked to a variety of extra-articular systemic manifestations including pain, fatigue, morning stiffness, anemia, weight loss, and common comorbidities such as osteoporosis, cardiovascular (CV) disease (CVD), diabetes, infection, malignancies, depression, sleep disturbances, and other mood/mental disorders. The pathogenesis of RA is driven by a complex network of proinflammatory cells and cytokines, which in the past two decades have become the target of biotechnologic drugs. The expanding number of available targeted drugs in the therapeutic armamentarium of RA has progressively increased the need for predictive factors useful to drive the prescription of the right therapy for the right patients according to a personalized approach [2]. In this scenario, a better understanding of the pathways leading to disease development can be the key for population stratification according to the heterogeneous manifestations of RA in different patients [3–6].

Among the actors involved in the network of RA, interleukin-6 (IL-6) seems to be the most pleiotropic cytokine with the greatest number of downstream influences [7, 8] (major IL-6 influences are detailed in Fig. 1). This narrative review describes the role of IL-6 in the pathogenesis of RA, and in the associated extra-articular systemic manifestations and comorbidities often observed in clinical practice, as well as the beneficial effects of the IL-6 receptor (IL-6R) blockers sarilumab and tocilizumab from the perspectives of both the physician and the patient. This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors. The peer-reviewed primary articles used as a basis for this review were obtained from PubMed or from literature reviews.

IL-6 INHIBITION: WHICH OPTIONS?

IL-6 inhibitors target either the IL-6 ligand itself or the IL-6R [9, 10]. In contrast to the disappointing study status for the IL-6 ligand inhibitors (sirukumab, the most advanced anti-IL-6 ligand, completed phase III trials but was rejected for approval by the US Food and Drug Administration due to safety concerns, olokizumab is in phase III, clazakizumab has not progressed from phase II, and development of gerilimzumab seems to have been halted), two agents targeting IL-6R have shown impressive results in clinical studies and are now available

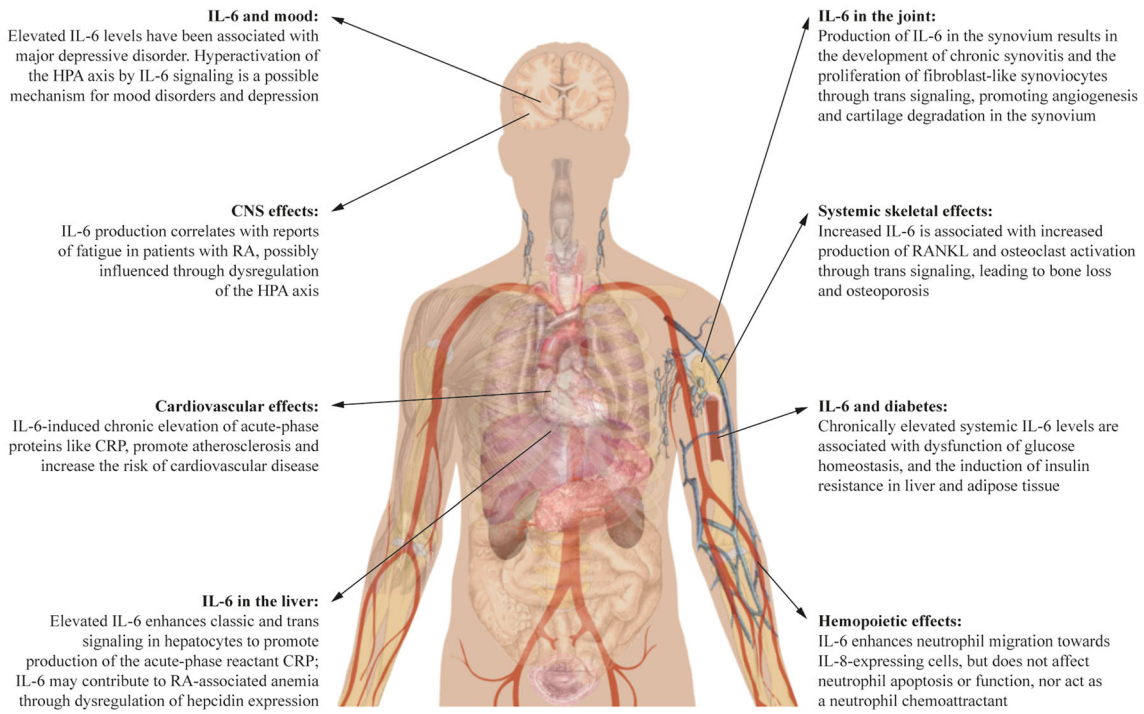

Fig. 1 IL-6 as a pleiotropic cytokine. *CNS* central nervous system, *CRP* C-reactive protein, *HPA* hypothalamic–pituitary–adrenal, *IL-6* interleukin-6, *IL-8* interleukin-8, *RA* rheumatoid arthritis, *RANKL* Receptor Activator of Nuclear Factor-κB Ligand. Body image, Mikael Häggström https://commons.wikimedia.org/w/index.php?curid=15298838

clinically. Tocilizumab is a humanized monoclonal antibody (mAb) targeting IL-6R, first approved for RA as an intravenous (IV) formulation in 2009 in Europe [11] and in 2010 in the USA [12], and then approved as a subcutaneous (SC) formulation. Sarilumab is a human mAb targeting IL-6R, which was more recently approved (2017) in the USA and the EU [13, 14] for SC administration. Tocilizumab and sarilumab target both membrane-bound IL-6R (mIL-6R) and soluble IL-6R (sIL-6R), and both are indicated in combination with conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or as monotherapy [9, 10].

The recommended starting doses for tocilizumab are different in Europe and the USA [11, 12]. In the USA, IV tocilizumab should be started at 4 mg/kg every 4 weeks (Q4W), followed by an increase to 8 mg/kg Q4W based on clinical response; SC tocilizumab should be started at 162 mg every 2 weeks (Q2W), followed by an increase in dosing frequency to weekly (QW) based on clinical response (except in patients ≥ 100 kg who should start on the more frequent administration schedule) [12]. In Europe, IV tocilizumab should be started at 8 mg/kg body weight Q4W with a reduction of dose to 4 mg/kg for laboratory abnormalities, and SC tocilizumab should be started at 162 mg QW with a reduction to a less frequent Q2W dosing schedule for laboratory abnormalities [11]. The recommended sarilumab dose is the same in Europe and the USA: 200 mg Q2W administered as an SC injection, with a reduction of dose to 150 mg Q2W recommended for the management of neutropenia, thrombocytopenia, and liver enzyme elevations [13, 14].

Why IL-6 Blockade for RA?

IL-6 is a soluble mediator originally cloned in 1986 [15], and subsequently named IL-6 in 1989 [16]. The effects of IL-6 are brought about by

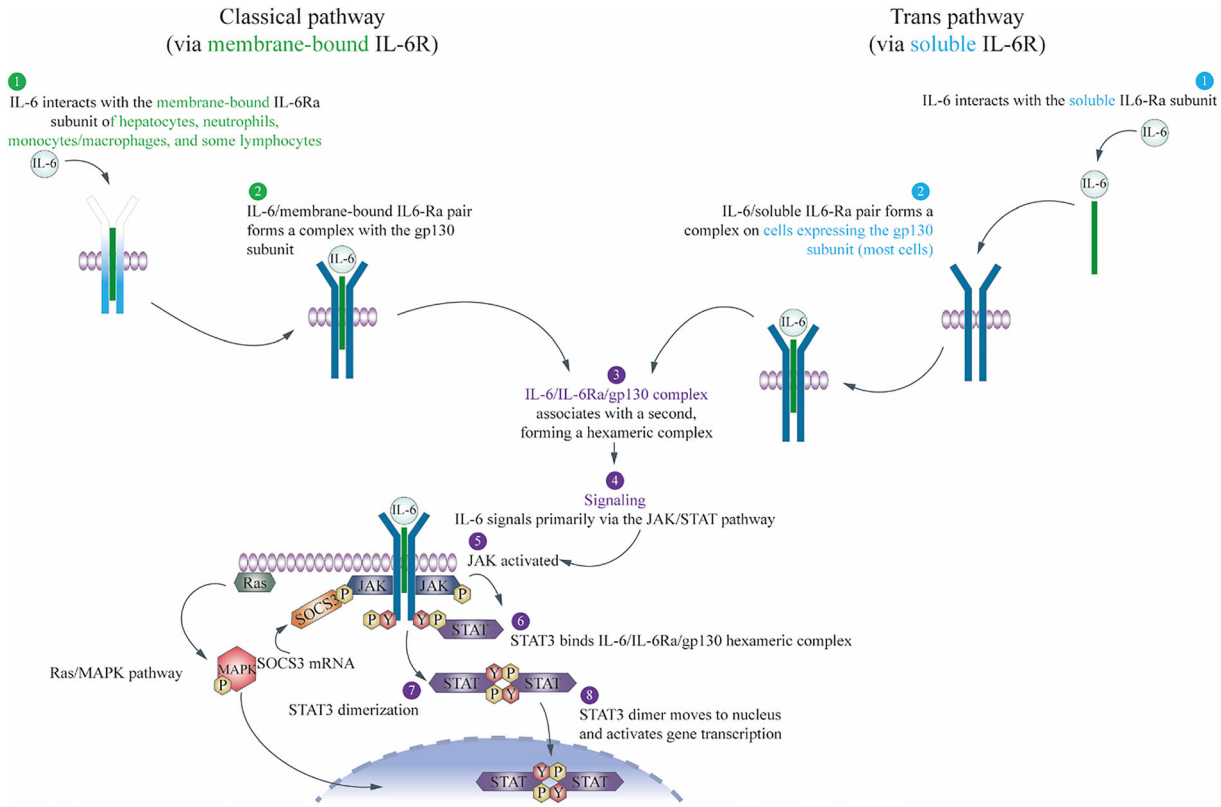

Fig. 2 The classical (or *cis*-) and *trans*-signaling pathways of IL-6. *gp130* glycoprotein 130, *IL-6* interleukin-6, *IL-6Rα* interleukin-6 receptor alpha, *JAK* Janus kinase, *MAPK* mitogen-activated protein kinase, *P* phosphate, *SOCS3* suppressor of cytokine signaling 3, *STAT3* signal transducer and activator of transcription 3, *Y* tyrosine

two mechanisms known as classical (or *cis*-) signaling and *trans*-signaling, as reviewed previously by many authors [17–20], and described below and in Fig. 2.

IL-6 activates cells via a signaling mechanism that requires two receptor components, an 80-kDa IL-6-binding alpha chain (IL-6Rα) and a 130-kDa signal-transducing beta chain, glycoprotein 130 (gp130) [17]. First, IL-6 interacts with the IL-6Rα subunit and then this IL-6/IL-6Rα pair forms a complex with the gp130 subunit (IL-6 does not bind directly to the gp130 subunit). The high-affinity IL-6/IL-6Rα/gp130 complex associates with a second high-affinity complex, forming a hexameric complex consisting of two members of each protein (IL-6/IL-6Rα/gp130), which is required to induce signal transduction [18].

IL-6Rα is expressed on only a few cell types, including hepatocytes, monocytes/macrophages, neutrophils, and some T cell subsets [21]. In classical signaling, IL-6 first binds to its membrane-bound receptor mIL-6Rα, to form an IL-6/mIL-6Rα pair and initiate the signaling as described above in this narrow range of cells [19, 21]. In *trans*-signaling, IL-6 first forms a pair with the circulating sIL-6Rα and this pair then forms a complex with membrane-bound gp130, which is ubiquitously expressed on many cell types. The IL-6/sIL-6R/gp130 complex then dimerizes as described above to initiate signaling in a much wider range of cells [19, 21].

Activation of the receptor complex leads to signaling through Janus kinase, which binds to membrane-proximal regions of activated gp130,

and phosphorylates specific tyrosine residues on gp130 and other target substrates, including the transcription factor signal transducer and activator of transcription 3 (STAT3) [22]. Phosphorylated STAT3 then translocates to the nucleus, and binds to specific DNA response elements and initiates the transcription of specific genes [22]. IL-6 also activates the Ras/mitogen-activated protein kinase and phosphoinositide 3-kinase/Akt pathways [23, 24].

Classical *cis*-signaling is thought to mediate normal homeostatic effects, while *trans*-signaling predominantly mediates systemic proinflammatory effects including monocyte recruitment, macrophage differentiation, and T cell recruitment and differentiation [19, 25]. Soluble gp130 can specifically inhibit IL-6 *trans*-signaling by binding to the IL-6/sIL-6R pair, thus preventing the pair from binding membrane-bound gp130. During inflammation, IL-6 levels are sufficiently high to overcome this protective mechanism and *trans*-signaling predominates [19, 25].

RA PATHOGENESIS: THE IMPACT OF IL-6 ON AUTOIMMUNITY AND JOINT INFLAMMATION

In RA, under the right set of risk factors, including genetic background and environmental factors, an immune response develops, autoantibodies are generated, and self-tolerance is lost [26–28]. The first steps in the development of RA have been considered akin to the normal adaptive immune response [29]. The transition from normal immunity to the beginnings of the RA pathogenic process happens when autoimmunity occurs [28, 30, 31]. Dysregulated citrullination resulting in the autoimmune production of antibodies for citrullinated proteins is key to disease development, and is stimulated by genetic predisposition and environmental factors, such as smoking or *Porphyromonas gingivalis* oral infections [28].

The IL-6R is expressed on both osteoclasts and osteoblasts [22], and IL-6 is known to be a central mediator of osteoclast activity [32]. In models of early RA, in the absence of glucocorticoid treatment, IL-6 increases bone resorption, resulting in bone loss [33, 34]. IL-6 also increases osteoblast Receptor Activator of Nuclear Factor-κB (RANK) Ligand (RANKL) production, induces RANKL messenger ribonucleic acid (mRNA) expression, and increases bone resorption through the RANK/RANKL/osteoprotegerin (OPG) interaction [35]. In addition, IL-6 acts indirectly on bone, mediating the bone resorption-inducing effects of tumor necrosis factor α (TNFα) and interleukin-1 (IL-1) [36]. The resulting erosion of bone and cartilage, accompanied by the inflammation and thickening of the synovial membranes, causes irreversible damage to the joint as the pannus develops [36].

From early in the disease process (preclinical RA), IL-6 binds to various cell types and causes migration of neutrophils into the joints, contributing to the subsequent transition from acute to chronic inflammation, alterations in B cell differentiation, T cell differentiation, and angiogenesis [37]. Circulating levels of IL-6 are normally low, but are increased in response to infection or trauma [37]. After IL-6 is synthesized in a local lesion in the initial stage of inflammation, it moves to the liver through the bloodstream and stimulates hepatocytes to produce acute-phase reactants such as C-reactive protein (CRP), a marker of systemic inflammation, fibrinogen, and serum amyloid A [38]. The increased production of these then leads to heightened activation of the adaptive immune system, which allows continued chronic inflammation and associated joint destruction, and is a major contributor to the advancement of RA disease pathogenesis in the joint [38].

EFFECT OF SARILUMAB AND TOCILIZUMAB ON CLINICAL ENDPOINTS IN RA

Given the pivotal role of IL-6 in the destruction of the joint, there is a strong scientific rationale for the beneficial effects observed on key endpoints as listed (Table 1) for the phase III studies of IV and SC tocilizumab, and SC sarilumab, and summarized in this section.

Table 1 Overview of phase III studies with tocilizumab IV and SC, and sarilumab SC, on individual clinical endpoints

	Study population	Treatment arms	ACR response	CRP	ESR	DAS28-CRP	DAS28-ESR	CDAI	Radiographic outcomes
Sarilumab combination studies									
MOBILITY [39] https://clinicaltrials.gov/ct2/show/NCT01061736	MTX-IR (n = 1197) Patients also received MTX	S 150 mg SC S 200 mg SC Placebo SCQ2W 52 weeks	Co-primary endpoint: ACR20 W24 Secondary endpoint: ACR50, ACR70 W24, W52	Secondary endpoint	Not reported	Secondary endpoints: proportion with DAS28-CRP $\leq$ 2.6 W24, W52; change from baseline in DAS28-CRP W24, W52	Not reported	Secondary endpoints: change from baseline W24, W52; proportion with CDAI remission $\leq$ 2.8 W24, W52	Co-primary endpoint: vdH-mTSS W52 Secondary endpoints: erosion and JSN score change W24, W52 vdH-mTSS W24
TARGET [40] https://clinicaltrials.gov/ct2/show/NCT01709578	TNF-IR (n = 546) Patients also received csDMARDs	S 150 mg SC S 200 mg SC Placebo SCQ2W 24 weeks	Co-primary endpoint: ACR20 W24 Secondary endpoints: ACR50, ACR70 W24	Secondary endpoint: change from baseline W12, W24	Not reported	Secondary endpoints: change from baseline W24; proportion with DAS28-CRP < 2.6 W24	Not reported	Secondary endpoint: change from baseline in CDAI W24	Not reported
Sarilumab monotherapy studies									
MONARCH [41] https://clinicaltrials.gov/ct2/show/NCT02332590	MTX-IR (n = 369)	S 200 mg SC A 40 mg SC Placebo SCQ2W 24 weeks	Secondary endpoints: ACR20, ACR50, ACR70 W24	Secondary endpoint: change from baseline W24	Secondary endpoint: change from baseline W24	Secondary endpoints: proportion with DAS28-CRP $\leq$ 2.8 and $\leq$ 3.3 W24; change from baseline in DAS28-CRP W24	Primary endpoint: change from baseline W24 Secondary endpoint: proportion with DAS28-ESR < 2.6 W24	Secondary endpoint: change from baseline W24 proportion with CDAI remission $\leq$ 2.8 W24	Not reported

Table 1 continued

	Study population	Treatment arms	ACR response	CRP	ESR	DAS28-CRP	DAS28-ESR	CDAI	Radiographic outcomes
SC tocilizumab combination studies									
SUMMACTA [42] https://clinicaltrials.gov/ct2/show/NCT01194414	csDMARD-IR (n = 1262)	T 162 mg SC QW T 8 mg/kg IV Q4W 24 weeks	Primary endpoint: ACR20 W24 Secondary endpoints: ACR50, ACR70 W24; ACR20, ACR50, ACR70 W97	Not reported	Not reported	Not reported	Secondary endpoint: proportion with < 2.6 W24, W97	Additional endpoint of CDAI remission ≤ 2.8 W24	Not reported
BREVACTA [43] https://clinicaltrials.gov/ct2/show/NCT01232569	csDMARD-IR (n = 656)	T 162 mg SC Placebo SC Q2W 24 weeks	Primary endpoint: ACR20 W24 Secondary endpoints: ACR50, ACR70 W24	Secondary endpoint: change from baseline W24	Secondary endpoint: change from baseline W24	Not reported	Secondary endpoint: change from baseline W24; proportion with < 2.6 W24; proportion with ≤ 3.2 W24	Not reported	Secondary endpoint: change from baseline in vdH-mTSS W24
IV tocilizumab combination studies									
LITHE [44] https://clinicaltrials.gov/ct2/show/NCT00106535	MTX-IR (n = 1196) Patients also receive MTX	T 4 mg/kg IV T 8 mg/kg IV Placebo IV Q4W 52 weeks	Co-primary endpoint: ACR20 W24 Secondary endpoints: ACR20 W52; ACR50/70 W24, W52, W104	Secondary endpoint: change from baseline W24, W52, W104	Secondary endpoint: change from baseline W24, W52, W104	Not reported	Secondary endpoints: change in DAS28-ESR W24, W52, W104; proportion with DAS28 ≤ 3.2 and DAS28 < 2.6, W24, W52, W104	Not reported	Co-primary endpoint: change from baseline in total G-mTSS W52, W104 Secondary endpoints: change from baseline in erosion and JSN W24, W52, G-mTSS W24; proportion with no progression of the total erosion or JSN W24

Table 1 continued

	Study population	Treatment arms	ACR response	CRP	ESR	DAS28-CRP	DAS28-ESR	CDAI	Radiographic outcomes
OPTION [45] https://clinicaltrials.gov/ct2/show/NCT00106548	csDMARD-IR (n = 623) Patients also receive MTX	T 8 mg/kg IV T 4 mg/kg IV Placebo IV Q4W 24 weeks	Primary endpoint: ACR20 W24 Secondary endpoints: ACR50, ACR70 W24	Laboratory measure: change from baseline W24	Laboratory measure: change from baseline W24	Secondary endpoint: change from baseline W24; proportion with DAS28 < 2.6 W24		Not reported	Not reported
TOWARD [46] https://clinicaltrials.gov/ct2/show/NCT00106574	csDMARD-IR (n = 1220) Patients also receive csDMARDs	T 8 mg/kg IV Placebo IV Q4W 24 weeks	Primary endpoint: ACR20 W24 Secondary endpoints: ACR50, ACR70 W24	Additional endpoint: change from baseline W24	Additional endpoint: change from baseline W24	Not reported	Additional endpoint: DAS28-ESR W24	Not reported	Not reported
RADIATE [47] https://clinicaltrials.gov/ct2/show/NCT00106522	TNF-IR (n = 499) Patients also receive MTX	T 8 mg/kg IV T 4 mg/kg IV Placebo IVQ4W 24 weeks	Primary endpoint: ACR20 W24 Secondary endpoints: ACR50, ACR70 W24	Not reported	Not reported	Not reported	Not reported	Not reported	Not reported
IV tocilizumab monotherapy studies									
U-ACT-EARLY [48] https://clinicaltrials.gov/ct2/show/NCT01034137	Newly diagnosed DMARD-naïve (n = 317)	T 8 mg/kg IV + MTX Q4W 104 weeks	Secondary endpoints: ACR20, ACR50, ACR70 W12, W24, W52, W104	Secondary endpoint: change from baseline at W12, W24, W52, W104	Not reported	Secondary endpoint: DAS28-CRP W24, W52, W104	Primary endpoint: proportion with < 2.6 sustained Secondary endpoint: DAS28-ESR W24, W52, W104	Secondary endpoint: change from baseline W24, W52, W104	Secondary endpoint: change from baseline in vdH-mTSS W52, W104

Table 1 continued

	Study population	Treatment arms	ACR response	CRP	ESR	DAS28-CRP	DAS28-ESR	CDAI	Radiographic outcomes
FUNCTION [49] https://clinicaltrials.gov/ct2/show/NCT01007435	MTX-naïve patients with early progressive RA (n = 1162)	T 8 mg/kg IV T 8 mg/kg IV + MTX T 4 mg/kg + MTX Q4W 104 weeks	Secondary endpoints: ACR20, ACR50, ACR70 W24 and W52	Not reported	Not reported	Not reported	Primary endpoint: proportion with < 2.6 W24 Secondary endpoint: proportion with < 2.6 W52	CDAI remission (< 2.8)	Secondary endpoints: change from baseline vdH-mTSS W52, change from baseline vdH erosion score W52, change from baseline JSN W52, proportion with no progression W52, W104
ACT-RAY [50] https://clinicaltrials.gov/ct2/show/NCT00810199	MTX-IR (n = 556)	T 8 mg/kg IV + MTX T 8 mg/kg IV 104 weeks	Secondary endpoints: ACR20, ACR50, ACR70, ACR90 W24, W52, W104 (and time to each)	Secondary endpoint: change from baseline W24, W52	Secondary endpoint: change from baseline W24, W52	Not reported	Primary endpoint: proportion with < 2.6 W24 Secondary endpoint: proportion with < 3.2 W24 change from baseline W24, W52	Not reported	Secondary endpoint: change from baseline G-mTSS W24, W52, W104
ADACTA [51] https://clinicaltrials.gov/ct2/show/NCT01119859	MTX-INT (n = 326)	T 8 mg/kg IV Q4W A 40 mg SC Q2W 24 weeks	Secondary endpoints: ACR20, ACR50, ACR70 W24	Not reported	Not reported	Not reported	Primary endpoint: change from baseline W24 Secondary endpoint: proportion with ≤ 3.2 and < 2.6 W24	Not reported	Not reported

A adalimumab, *ACR20/50/70/90* American College of Rheumatology 20%/50%/70%/90% response, *CDAI* Clinical Disease Activity Index, *CRP* C-reactive protein, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28* 28-Joint Disease Activity Score, *DMARD* disease-modifying antirheumatic drug, *ESR* erythrocyte sedimentation rate, *G-mTSS* Genant-modified Total Sharp Score, *INT* intolerant, *IR* inadequate response, *IV* intravenous, *JSN* joint space narrowing, *mTSS* modified Total Sharp Score, *MTX* methotrexate, *n* number of patients, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *QW* weekly, *RA* rheumatoid arthritis, *S* sarilumab, *SC* subcutaneous, *T* tocilizumab, *TNF* tumor necrosis factor, *vdH* van der Heijde, *vdH-mTSS* van der Heijde-modified Total Sharp Score, *W* week

Sarilumab or Tocilizumab in Combination with csDMARDs/Methotrexate (MTX)

American College of Rheumatology (ACR) Responses

While rheumatologists agree that ACR 20% response (ACR20) is not high, it was routinely used in the phase III trials of all licensed biologic drugs, including sarilumab and tocilizumab (Table 2) [52]. For sarilumab, ACR20 was a co-primary endpoint in both MOBILITY and TARGET. In MOBILITY, patients who had an inadequate response (IR) to MTX received SC sarilumab + MTX compared with placebo + MTX. In TARGET, patients who had IR (92.3%) to anti-TNFα biologic DMARDs (bDMARDs), or who were intolerant (INT) to anti-TNFα bDMARDs (7.7%), received sarilumab + csDMARDs [39, 40]. In both cases, sarilumab produced statistically significant improvements in the signs and manifestations of RA as defined by ACR20 at week 24, which was sustained throughout treatment [39, 40]. ACR20 was also the primary endpoint in SUMMACTA (which compared SC and IV tocilizumab) and BREVACTA (which compared SC tocilizumab with placebo) in csDMARD-IR populations [43, 53]. As measured by ACR20, SC tocilizumab 162 mg Q2W was superior to placebo [43] and SC tocilizumab 162 mg QW demonstrated comparable efficacy to IV tocilizumab 8 mg/kg [42]. Prior to this, IV tocilizumab had shown consistent improvements in ACR20 across clinical studies, including in combination with csDMARDs in MTX-IR and TNF-IR/INT patients, and as monotherapy (Table 2) [44–47].

CRP and Erythrocyte Sedimentation Rate (ESR), and 28-Joint Disease Activity Score (DAS28)-CRP and DAS28-ESR

The acute-phase reactants, CRP and ESR, comprise one aspect of the composite ACR measure described above and, in both MOBILITY and TARGET, CRP was the acute-phase reactant evaluated, with baseline levels 20–31 mg/l across the different randomization groups [39, 40]. In MOBILITY, mean change from baseline in CRP at week 24 was − 17 mg/l with SC sarilumab 200 mg Q2W [39] compared with 0.0 mg/l with placebo, and in TARGET, mean change from baseline in CRP at week 24 was − 23.3 mg/l with SC sarilumab 200 mg Q2W compared with − 3.6 with placebo [40]. In sarilumab clinical studies, similar results with the DAS28 based on CRP (DAS28-CRP) have been observed. Changes from baseline in DAS28-CRP, and the proportions of patients achieving DAS28-CRP < 2.6 or < 3.2 at week 24, were secondary endpoints of MOBILITY and TARGET [39, 40]. In both MOBILITY and TARGET, significantly more patients treated with sarilumab achieved a DAS28-CRP score < 2.6 at week 24 compared with patients receiving placebo (MOBILITY: 34% with sarilumab 200 mg Q2W compared with 10% with placebo [39]; TARGET: 29% with sarilumab 200 mg Q2W compared with 8% with placebo [40]).

Data from the SUMMACTA and BREVACTA trials have expanded what was known from studies evaluating IV tocilizumab administration. Data showed that mean reductions from baseline in CRP and ESR were comparable for the QW SC tocilizumab 162-mg dose and Q4W IV tocilizumab 8-mg/kg regimens, but less pronounced when SC tocilizumab was administered Q2W [55]. Reductions in CRP and ESR were rapid (by week 2 or 4) and sustained through 24 and 97 weeks of treatment [55].

In BREVACTA, the proportions of patients achieving DAS28 based on ESR (DAS28-ESR) < 2.6 by week 24 were similar with SC tocilizumab 162 mg QW and IV tocilizumab 8 mg/kg (38% and 36%, respectively) [43], and by week 24 in SUMMACTA, 32% of patients treated with SC tocilizumab 162 mg Q2W achieved DAS28-ESR < 2.6 (compared with 4% of patients receiving placebo) [53]. Across the previous clinical studies of IV tocilizumab, the proportion of patients achieving DAS28-ESR < 2.6 was 28–34% in patients receiving tocilizumab compared with 1–12% of control patients at 24 weeks [44–46].

Clinical Disease Activity Index (CDAI)

Given the massive effect of IL-6 inhibition in decreasing CRP levels and the high impact of CRP in the calculation of DAS28-CRP, the CDAI is considered to be the most valuable index for

the evaluation of the clinical response in patients treated with sarilumab or tocilizumab. Both MOBILITY and TARGET included CDAI as a secondary efficacy endpoint, evaluating the change from baseline in TARGET and the proportion of patients achieving remission (≤ 2.8) in MOBILITY [39, 40]. After 24 weeks of treatment with sarilumab 200 mg Q2W in MOBILITY [39], 14% of patients achieved CDAI remission (compared with 5.0% on placebo), and in TARGET [40], CDAI decreased by − 26.1 (compared with − 16.4 with placebo). A 2-year update from MOBILITY showed that the initial reduction in CDAI obtained with sarilumab was maintained [56], and with 5 years of treatment, 40% of patients (observed cases) achieved CDAI remission [57].

For SC tocilizumab, CDAI was evaluated in SUMMACTA but not BREVACTA and showed, after 24 weeks of treatment, that 14–15% of patients treated with either SC or IV tocilizumab achieved CDAI ≤ 2.8 [53]. CDAI was not routinely evaluated in the IV tocilizumab clinical program, but the results of FUNCTION showed numerically higher remission rates with IV tocilizumab compared with placebo at week 24 [49].

Structural Damage

Data on structural damage currently exist for SC sarilumab (from the MOBILITY study) and IV, but not SC, tocilizumab [39]. In the MOBILITY study (using the van der Heijde-modified Total Sharp Score [mTSS]), sarilumab was shown to have a significant effect on reducing pathologic radiographic progression compared with placebo: after 52 weeks, mean change in mTSS was 0.25 with sarilumab 200 mg Q2W and 2.78 with placebo [39]. In a 5-year follow-up of MOBILITY [57], early treatment with sarilumab 200 mg Q2W was associated with reduced radiographic progression versus patients who received placebo for 52 weeks and then switched to sarilumab 200 mg Q2W (mean change from baseline in mTSS score of 1.46 vs. 3.68, respectively), and almost 50% of patients had no progression of radiographic damage (mTSS change from baseline ≤ 0). Post hoc analysis of the MOBILITY clinical studies showed that patients with high IL-6 levels had more joint damage at baseline compared with patients with normal IL-6 levels, and had greater response in mTSS to sarilumab than patients with normal IL-6 levels [58].

Although radiographic progression has not been evaluated with SC tocilizumab, several studies have evaluated the effects of the IV formulation on structural damage. In the LITHE study [44], 84% of patients had no progression of structural joint damage (defined as change in Genant-mTSS ≤ 0 from baseline to week 52), compared with 67% of patients receiving placebo after 1 year of treatment with tocilizumab + MTX; between weeks 52 and 104, 93% had no progression [59]. In less-established disease, the FUNCTION study showed that tocilizumab treatment for 1 year resulted in up to 83% of patients exhibiting no radiographic progression (by change from baseline in van der Heijde-mTSS), compared with 73% with placebo, in patients with early RA of ≤ 2 years' duration who had not previously received MTX or bDMARDs [49]. Similar results were seen in the Dutch U-ACT-EARLY study of patients with early RA of ≤ 1 year's duration who were DMARD-naïve; radiographic joint damage progression was low in all treatment arms, but significantly less with tocilizumab + MTX than with MTX alone [48].

Monotherapy with Sarilumab or Tocilizumab

International guidelines recommend using bDMARDs in combination with csDMARDs, and as monotherapy when the combination with a csDMARD is not possible [60]. MTX is the most commonly used csDMARD and results in an ACR20 at 1 year of 54–67% [61]; however, many MTX-treated patients complain of headaches, fatigue, feeling "wiped out," and describe an "MTX fog." Other patients experience nausea, which can be lessened by evening administration or SC rather than oral administration [62, 63]. On MTX, patients should be closely monitored for bone marrow, liver, lung, and kidney toxicities: acute elevations of liver enzymes are frequent and acute MTX-induced lung disease may occur at any time during therapy [62, 63]. Diarrhea and

Table 2 Overview of the primary outcomes of the phase III studies with tocilizumab IV and SC, and sarilumab SC

	Primary endpoint/s	Outcome
Sarilumab combination studies		
MOBILITY [39] MTX-IR (n = 1197)	Co-primary endpoints:	
	ACR20 W24	S 150 mg SC: 58% ($p < 0.0001$ vs. placebo)
		S 200 mg SC: 66.4% ($p < 0.0001$ vs. placebo)
		Placebo SC: 33.4%
		Q2W
	vdH-mTSS W52	S 150 mg SC: 0.90 ($p < 0.0001$ vs. placebo)
		S 200 mg SC: 0.25 ($p < 0.0001$ vs. placebo)
		Placebo SC: 2.78
		Q2W
TARGET [40] TNF-IR (n = 546)	Co-primary endpoints:	
	ACR20 W24	S 150 mg SC: 55.8% ($p < 0.0001$ vs. placebo)
		S 200 mg SC: 60.9% ($p < 0.0001$ vs. placebo)
		Placebo SC: 33.7%
		Q2W
	HAQ-DI change from baseline W12	S 150 mg SC: − 0.46 ($p = 0.0007$ vs. placebo)
		S 200 mg SC: − 0.47 ($p = 0.0004$ vs. placebo)
		Placebo SC: − 0.26
		Q2W
Sarilumab monotherapy studies		
MONARCH [41] MTX-IR (n = 369)	DAS28-ESR change from baseline W24	S 200 mg SC: − 3.28 ($p < 0.0001$ vs. A)
		A 40 mg SC: − 2.20
		Q2W
SC tocilizumab combination studies		
SUMMACTA [42] csDMARD-IR (n = 1262)	ACR20 W24	T 162 mg SC QW: 69.4%
		T 8 mg/kg IV Q4W: 73.4%
BREVACTA [43] csDMARD-IR (n = 656)	ACR20 W24	T 162 mg SC: 60.9% ($p < 0.0001$ vs. placebo)
		Placebo SC: 31.5%
		Q2W
IV tocilizumab combination studies		
LITHE [44] MTX-IR (n = 1196)	Co-primary endpoints:	
	HAQ-DI AUC change from baseline	T 4 mg/kg IV: − 128.4 ($p < 0.0001$ vs. placebo)
		T 8 mg/kg IV: − 144.1 ($p < 0.0001$ vs. placebo)
		Placebo IV: − 58.1
		Q4W
	Radiographic outcome change from baseline in total G-mTSS W52, W104	T 4 mg/kg IV: 0.34 ($p < 0.0001$ vs. placebo)
		T 8 mg/kg IV: 0.29 ($p < 0.0001$ vs. placebo)
		Placebo IV: 1.13
		Q4W
OPTION [45] csDMARD-IR (n = 623)	ACR20 W24	T 4 mg/kg IV: 48% ($p < 0.0001$ vs. placebo)
		T 8 mg/kg IV: 59% ($p < 0.0001$ vs. placebo)
		Placebo IV: 26%
		Q4W

Table 2 continued

	Primary endpoint/s	Outcome
TOWARD [46] csDMARD-IR (n = 1220)	ACR20 W24	T 8 mg/kg IV: 61% ($p < 0.0001$ vs. placebo) Placebo IV: 25% Q4W
RADIATE [47] TNF-IR (n = 499)	ACR20 W24	T 4 mg/kg IV: 30.4% ($p < 0.001$ vs. placebo) T 8 mg/kg IV: 50% ($p < 0.001$ vs. placebo) Placebo IV: 10.1% Q4W
IV tocilizumab monotherapy studies		
U-ACT-EARLY [48] Newly diagnosed DMARD-naïve (n = 317)	DAS28-ESR proportion with < 2.6 sustained	T 8 mg/kg IV + MTX: 86% ($p = 0.06$ vs. MTX) T 8 mg/kg IV: 88% ($p = 0.0356$ vs. MTX) MTX: 77% Q4W
FUNCTION [54] MTX-naïve patients with early progressive RA (n = 1162)	DAS28-ESR proportion with < 2.6 W24	T 4 mg/kg + MTX: 31.9% ($p < 0.0001$ vs. MTX) T 8 mg/kg IV: 38.7% ($p < 0.0001$ vs. MTX) T 8 mg/kg IV + MTX: 44.8% ($p < 0.0001$ vs. MTX) MTX: 15.0% Q4W
ACT-RAY [50] MTX-IR (n = 556)	DAS28-ESR proportion with < 2.6 W24	T 8 mg/kg IV + MTX: 40.4% ($p = 0.19$ vs. T) T 8 mg/kg IV: 34.8%
ADACTA [51] MTX-INT (n = 326)	DAS28-ESR change from baseline W24	T 8 mg/kg IV Q4W: − 3.3 ($p < 0.0001$ vs. A) A 40 mg SC Q2W: − 1.8

A adalimumab, *ACR20* American College of Rheumatology 20% response, *AUC* area under the curve, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DAS28* 28-Joint Disease Activity Score, *ESR* erythrocyte sedimentation rate, *G-mTSS* Genant-modified Total Sharp Score, *HAQ-DI* Health Assessment Questionnaire-Disability Index, *INT* intolerant, *IR* inadequate response, *IV* intravenous, *mTSS* modified Total Sharp Score, *MTX* methotrexate, *n* number of patients, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *QW* weekly, *RA* rheumatoid arthritis, *S* sarilumab, *SC* subcutaneous, *T* tocilizumab, *TNF* tumor necrosis factor, *vdH* van der Heijde, *vdH-mTSS* van der Heijde-modified Total Sharp Score, *W* week

ulcerative stomatitis require interruption of therapy to reduce the risk of hemorrhagic enteritis, and death from intestinal perforation and serious, potentially fatal opportunistic infections may occur [62–64]. Consequently, patients may discontinue MTX therapy because they cannot tolerate it [62, 63], while those who are able to continue MTX may not be fully adherent [65, 66]. Hence, a bDMARD monotherapy solution may be necessary. In such cases, an anti-IL-6R may be a better approach than an anti-TNFα therapy [60].

Sarilumab Monotherapy

The efficacy of sarilumab 200 mg Q2W in monotherapy was assessed in the MONARCH study [41] and compared with adalimumab 40 mg Q2W over a 24-week randomized treatment period. Sarilumab outperformed adalimumab across key endpoints: at week 24, DAS28-ESR was decreased − 3.28 compared with − 2.20 (27% vs. 7% of patients achieving DAS28-ESR ≤ 2.6), and more patients achieved ACR20 responses (71.7% vs. 58.4%) as well as ACR 50% and 70% (ACR50/70) responses. Additionally, by week 24, the rate of CDAI remission and low disease activity (LDA) was higher in the sarilumab group (7% and 42%, respectively) than in the adalimumab group (3% and 25%, respectively). Structural damage was not evaluated. Analysis of the open-label period of MONARCH, where patients were initially randomized to adalimumab for 24 weeks and then switched to sarilumab monotherapy, showed that (despite the improvements described above in the randomized portion of the study) adalimumab patients who switched to sarilumab achieved additional clinically meaningful improvements in disease activity primarily within 12 weeks of switching [67].

Tocilizumab Monotherapy

Evidence regarding the efficacy of the anti-IL-6R class was first published a decade ago, with the AMBITION study comparing IV tocilizumab 8 mg/kg Q4W to MTX over 24 weeks [68]. The study, conducted in patients with relatively early active RA for whom previous treatment with MTX or bDMARDs had not failed, showed better ACR20 response with tocilizumab (70% vs. 53%; $p < 0.001$) and a higher rate of DAS28-ESR < 2.6 (34% vs. 12%). Subsequently, ADACTA (a comparable study to MONARCH, comparing IV tocilizumab to SC adalimumab) was published and showed the benefits of anti-IL-6R over anti-TNFα monotherapy [51]. Mean change from baseline in DAS28-ESR was − 3.3 with tocilizumab, compared with − 1.8 with adalimumab after 24 weeks of treatment; 40% of patients in the tocilizumab group achieved DAS28-ESR < 2.6, compared with 11% of patients in the adalimumab group. ACR response rates were also significantly higher with tocilizumab compared with adalimumab. The FUNCTION and U-ACT-EARLY studies also had monotherapy arms. FUNCTION [49] demonstrated that changes from baseline to week 52 in mTSS were smaller with IV tocilizumab 8 mg/kg (mean 0.26) than with MTX (1.14). U-ACT-EARLY [48] demonstrated a trend toward better protection against structural progression with IV tocilizumab compared with MTX at week 52 (change from baseline in van der Heijde-mTSS of 0.79 vs. 0.96) that was significant after 2 years (1.45 vs. 1.53). While the effects of sarilumab and tocilizumab on the clinical efficacy endpoints leading to their approvals are well established, it is the emerging effects of IL-6 and IL-6R inhibition beyond the joint that are of increasing interest and are described below.

IL-6 BEYOND THE JOINT: EXTRA-ARTICULAR MANIFESTATIONS OF RA

RA and Anemia

"Anemia of chronic disease" and "anemia of inflammation" are terms that are used interchangeably, and refer to a condition that is common in RA, being observed in 33–66% of patients with RA [69, 70]. Clinically, patients with anemia of chronic disease are more likely to experience increased disease severity and duration than patients who have chronic disease without anemia; in patients with RA and associated anemia, disease is typically more severe, outcomes are poorer, and there is greater radiographic progression [71]. As described by Weiss and Schett in their 2013 review [72], in systemic inflammatory diseases such as RA, anemia is considered to be mainly an immune-driven disorder caused by alterations of iron homeostasis (largely mediated by hepcidin), impaired erythroid progenitor proliferation, reduced biologic activity of erythropoietin, and a decrease in erythrocyte half-life.

Hepcidin has been shown to inhibit the absorption of iron in the small intestine and the release of recycled iron from macrophages, effectively decreasing the delivery of iron to maturing erythrocytes in the bone marrow [73]. IL-6 results in increased transcription of the human antimicrobial peptide gene that encodes hepcidin in liver cells [74], and has also been shown to mediate anemia through decreasing saturation of transferrin, the primary transporter delivering iron to the bone marrow for erythropoiesis [75].

IL-6R Blockade and Anemia

Recently, a post hoc analysis showed that treatment with sarilumab resulted in larger reductions in hepcidin compared with adalimumab (− 36% compared with − 28%, respectively, at week 2, but not measured thereafter) and significantly larger increases in hemoglobin levels compared with adalimumab (least squares mean change from baseline 0.528 vs. 0.119 g/dl at week 12 and 0.591 vs. 0.075 g/dl at week 24, respectively) [76]. Consequently, there were fewer patients with anemia (hemoglobin < 12 g/dl for females or < 13 g/dl for males) with sarilumab compared with adalimumab (10.9% vs. 16.3%) after 24 weeks of treatment and compared with 25% of patients in both arms at baseline [76]. Furthermore, a separate analysis exploring markers of chronic inflammation in patients with RA showed larger increases in hemoglobin in patients treated with sarilumab 200 mg and 150 mg compared

with placebo at week 2 (68.5, 64, and 40.2% of patients with change > 0 g/dl from baseline, respectively) that were sustained over 52 weeks (83.8, 76.6, and 44.12% of patients with change > 0 g/dl from baseline, respectively, at week 52) [77]. Similar effects of IL-6R blockade have been shown with tocilizumab in a post hoc analysis of a placebo-controlled study [78] and in a small prospective study versus adalimumab [70].

RA and Fatigue and Morning Stiffness

Fatigue may affect up to 80% of patients with RA and is severe in up to 40% of patients [79, 80]. Fatigue must not be mistaken for simple tiredness, since patients describe far-reaching effects permeating various aspects of life: not just physical activities, but emotions, relationships, and social activities [81]. In a small, but interesting, study of patient perspectives, most patients did not discuss fatigue with their doctors, but when they did, they felt the symptom was largely dismissed [81]. For many patients, their fatigue is "extreme" and "unresolving" [81]. Assessing fatigue in RA clinical trials was initially recommended in 2007 by the OMERACT group [82], but to this day, it is not routinely measured in interventional studies. It would be naïve to think that anemia and poor sleep, discussed elsewhere in this review, do not impact fatigue in patients with RA, but there is also increasing evidence implicating the involvement of IL-6 and the hypothalamic–pituitary–adrenal (HPA) axis, and dysfunction of the HPA axis (particularly regarding glucocorticoid and cortisol levels) in chronic fatigue [83, 84, 85].

Morning stiffness is another common symptom of RA, with variable intensity, timing (not just associated with the morning), location, and duration [86]. Most importantly, perhaps, stiffness is frequently described as impacting patients' daily activities, including getting dressed, driving, cooking, and the ability or desire to socialize [86]. Despite its importance, morning stiffness is seldom assessed in clinical practice and usually only the duration of morning stiffness is measured in the research setting [86]. Debates concerning whether the intensity, timing, and/or location of morning stiffness should also be assessed in clinical trials are ongoing [86].

As major RA manifestations, such as joint pain and stiffness, are most pronounced in the morning, it is postulated that this may be due to circadian rhythms of cytokine and hormone levels [87]. Significant circadian variation in levels of IL-6 has been identified: peaks in the morning, and low levels in the afternoon and evening [88]. Indeed, associations between IL-6 and the duration of morning stiffness have been identified [89].

IL-6R Blockade, Fatigue, and Morning Stiffness

The positive effect of IL-6R blockade on fatigue and morning stiffness in patients with RA is described in "The importance of IL-6R blockade from a patient's perspective" section below.

RA and Pain

In RA, pain is often reported as the patient's most important symptom, and often persists despite RA control [90, 91]. Since the pain in RA arises from multiple mechanisms, including inflammation, and peripheral and central pain processing, it also has a wide range of characteristics in terms of attributes, location, duration, and temporal occurrence [92]. Pain is also strongly associated with the patient's quality of life, including functional capacity, emotional health, and sleep [93, 94].

Neurons, glial cells of the spinal cord, and dorsal root ganglia express gp130, permitting IL-6/sIL-6R *trans*-signaling to occur [95]. Animal studies have shown that injections of IL-6 or IL-6/sIL-6R into normal knee joints cause increased responses of spinal neurons to mechanical stimulation [96], and a long-lasting sensitization of nociceptive C-fibers to mechanical stimuli [97]. Utilizing a rat model of antigen-induced arthritis, and soluble gp130 to bind and inactivate IL-6, Boettger et al. [98] showed antinociceptive effects in the knee joint, which were greater when administered locally than systemically, and normalized weight-bearing, gait measures, and locomotion.

These pain-relieving effects could be achieved after a single administration of gp130 and in the absence of effects on joint inflammation. The culmination of these studies indicates that IL-6 has direct actions on the nociceptive system, and pain-relieving effects that are additional to anti-inflammatory and immunomodulatory effects.

IL-6R Blockade and Pain

The positive effect of IL-6R blockade on pain in patients with RA is described in "The importance of IL-6R blockade from a patient's perspective" section below.

RA, Weight, and Body Composition

While being overweight or obese can increase the risk of developing RA, rheumatoid cachexia (low muscle mass with or without weight loss), sarcopenia (both low muscle mass and muscle function), or sarcopenic obesity can occur in patients with RA. A recent meta-analysis showed a prevalence of rheumatoid cachexia of 15–32%, according to different diagnostic criteria [99]. Utilization of dual-energy X-ray absorptiometry to evaluate visceral adipose tissue has shown that chronic, high inflammatory activity is associated with both lower muscle and fat mass (including visceral adipose tissue), while moderate inflammatory activity is associated with greater visceral adipose tissue, which is associated with increased CV risk [100].

Recent claims are that IL-6 supports healthy weight maintenance in a normal physiologic state [101], and while the causes of rheumatoid cachexia are multifactorial, the excess of proinflammatory cytokines is considered to be a central feature [102]. Anorexia and body-weight loss are common complications of inflammatory states, and IL-6, along with the proinflammatory cytokines TNFα and IL-1β, has previously been found to be implicated in anorexia of inflammation and infection [103, 104]. In animal studies, IL-6 − / − mice develop spontaneous mature-onset obesity, increased body weight, SC fat, and dysregulation of glucose metabolism [105]. Furthermore, centrally administered IL-6 (into the parabrachial nuclei) reduces food intake and increases brown adipose tissue thermogenesis in lean and obese rats (by increasing thyroid and sympathetic outflow to the adipocytes), and interacts with leptin to reduce feeding [106].

IL-6R Blockade and Weight

There is some evidence of weight gain with IL-6R blockade with tocilizumab [12, 107]. Tournadre et al. reported the first study of the impact of IL-6 inhibition on body composition in patients with RA [108] and showed that a gain in weight after 1 year of treatment was likely to be related to a significant increase in muscle mass, as no change in fat mass was detected, and favorable fat redistribution toward peripheral and SC fat was observed. Serum levels of leptin were significantly decreased after 6 months of tocilizumab treatment compared with pretreatment levels, and the authors suggest a proinflammatory IL-6-mediated effect on leptin, as leptin is a key regulator of appetite, inducing the expression of anorexigenic factors and inhibiting the production of orexigenic peptides. Therefore, IL-6R blockade may have utility in underweight patients with RA.

In contrast to IL-6R blockers, TNFα inhibitors have been shown to be associated with poor RA remission rates in obese patients with RA [109]. Gremese et al. [109] showed that disease remission according to the proportion of patients with DAS28 < 2.6 in long-standing receivers of TNFα inhibitors (adalimumab, etanercept, or infliximab) was 15% in obese patients (> 30 kg/m^2), compared with > 30% in patients with a non-obese body mass index (BMI) (≤ 30 kg/m^2). Increased adipose tissue in an obese state may cause increased expression of TNFα, leading to a more inflammatory and therapy-resistant state [109]. Consequently, high BMI in patients with RA is a potential driver toward treatments with mechanisms of action other than anti-TNFα, such as IL-6R blockade [109].

IL-6 BEYOND THE JOINT: COMMON COMORBIDITIES OF RA

RA can be complicated by several disorders that are more common in patients with RA than in

the healthy population [110]. The majority of these comorbidities are deeply interconnected with RA through shared pathogenic pathways leading to chronic inflammation or to the increased presence of traditional risk factors, such as smoking [111]. Indeed, a genetic association with a non-synonymous variant of the IL-6R may underpin the pathogenic processes that connect RA and conditions such as CVD and type 1 diabetes [112] (T1D). This allele, Asp358A1a, is associated with decreased membrane-bound IL-6R and increased sIL-6R and is protective for RA, CVD, and T1D. It was demonstrated that reduced levels of IL-6R on the surface of immune cells resulted in functional impairment of classical IL-6R signaling and dampening of IL-6R-mediated inflammation. This observation supports a role for IL-6R signaling in RA beyond the inflammatory processes found in the joints, which may overlap with the pathogenic processes underpinning other diseases with an inflammatory component [112].

The impact of comorbidities on the treatment of RA can be bidirectional. In one way, the increased prevalence of comorbidities can contribute to worsening the long-term prognosis and compromising the life expectancy in patients with RA [110, 113]. Additionally, a poorer clinical response has been observed in patients with RA carrying a great burden of comorbid disorders [114]. The most common comorbidities observed in patients with RA are osteoporosis [115], CVD [116] and pulmonary disease [117], infections [118, 119], depression [120], type 2 diabetes (T2D) [121], and malignancies [122].

RA and Osteoporosis

Osteoporosis has long been recognized as one of the most common comorbidities associated with RA [115, 123, 124]. It is prevalent in 10–50% of patients with RA depending on the population studied, and has been shown to be over twice as common in patients with RA than in age- and sex-matched controls [115, 123, 124]. The consequences of this comorbidity are important. It is well known that the use of glucocorticoids, commonly used in RA, is associated with reduced bone mineral density (BMD) due to a reduction in bone formation (rather than an increase in bone turnover) [125]; however, the risk of fracture in patients with RA is increased irrespective of glucocorticoid use [126–128].

The systemic effect of IL-6 on bone integrity (as described above) can be considered as a manifestation of RA outside the joints. Serum levels of IL-6R are increased in osteoporosis and variants of the IL-6R gene are associated with differential BMD, supporting the link between the cytokine and the pathologic process [129–131].

IL-6R Blockade, Bone Turnover, and BMD

The effects of tocilizumab and, more recently, sarilumab on markers of bone metabolism (specifically, markers of bone formation: osteocalcin, OPG, RANKL, and N-terminal propeptide of type I collagen [P1NP]; and of bone resorption: C-terminal telopeptide of type I collagen [CTX-I] and CTX-I generated by matrix metalloproteinases [ICTP]) have been reported from randomized controlled trials. Most recently, in a monotherapy study of sarilumab versus adalimumab, after 24 weeks of treatment, blockade of IL-6R with sarilumab treatment significantly increased concentrations of P1NP and resulted in a numeric increase in osteocalcin compared with adalimumab. In addition, reductions in total RANKL compared with adalimumab were observed as early as week 2 and persisted through week 24 [132]. This was consistent with other studies that had shown that sarilumab produced an early (week 2) decrease in total RANKL levels and the soluble RANKL:OPG ratio through week 24 [133, 134]. In previous studies, tocilizumab was shown to provide overall improvement in net bone biomarker balance as measured by a 25% decrease in the CTX-I:osteocalcin ratio after 16 weeks of treatment [135], to produce small (up to 15%) decreases in the bone degradation markers CTX-I and ICTP after 24 weeks of treatment [136], and to increase osteocalcin > 100% after 52 weeks of treatment [137].

In animal models of collagen-induced arthritis, the reduction in the number of

osteoclast precursors in bone marrow with IL-6R blockade contributes to the prevention of bone loss and protection against the reduction in bone strength [138, 139]. Clinical studies in patients with RA on the effects of IL-6R blockade on BMD have also been encouraging, although randomized trials are lacking. In several recent, but relatively small, open-label studies of patients treated with tocilizumab (n = 76–145), BMD was stable over the long term and, in patients who were anti-citrullinated protein antibody-positive and/or had osteopenia at baseline, BMD increased [140–142]. In addition, considering the glucocorticoid-sparing effects of anti-IL-6R bDMARDs [143], there are various routes through which this class of agents can have beneficial effects on bone metabolism in patients with RA.

RA and CVD

CVD is the leading cause of mortality in patients with RA, and the risk of CVD is increased up to twofold in patients with RA compared with the general population [116, 144–146]. Additionally, the use of glucocorticoids > 7.5 mg/day or at a cumulative dose of 40 g is associated with a considerable increased risk of CV mortality [147]. After adjusting for traditional CV risk factors, such as hypertension, smoking, and lipid abnormalities, RA itself (or rather the high systemic inflammatory burden associated with it) is an independent risk factor for CVD [148, 149]. Furthermore, a large CV study in > 15,000 individuals showed a clear link between CRP and CV risk [150], providing support for the central role of inflammation in the initiation and progression of atherothrombosis, and the prompting of CV events. Elevated ESR levels are also associated with increased CV risk [151].

The chronic systemic inflammatory burden in patients with RA is thought to explain, in part, what is known as the "lipid paradox": the phenomenon where patients with RA are at an increased risk of CVD and associated mortality, despite lower levels of total cholesterol or low-density lipoprotein cholesterol (LDL-C), or the ratio of total:high-density lipoprotein cholesterol (HDL-C), which would traditionally be considered to indicate low risk [151]. High levels of lipoprotein(a) (Lp(a)), which is atherogenic in nature, have also been reported in patients with RA [152].

The mechanisms by which inflammation confounds the association of cholesterol and CVD remain somewhat unclear, but are likely due to a myriad of factors. Given that increased CRP and ESR levels are linked to increased CVD rates, and the hepatic synthesis of CRP is largely regulated by IL-6, the direct and indirect links between IL-6 and CVD are clear, particularly in patients with inflammatory conditions such as RA. Adipose tissue is one of the main sources of inflammatory mediators, including IL-6, and animal studies have suggested that adipose tissue-derived IL-6 may affect adipose tissue-specific gene expression, suppressing total adiponectin release from human adipocytes [153], triglyceride release [154], and lipoprotein lipase activity [155]. It has also been shown in humans that coronary calcification mediated by IL-6 also contributes to the development of atherosclerosis [156]. Therefore, it is unsurprising that, in a large meta-analysis, elevated IL-6 was associated with an increased risk of coronary heart disease after adjusting for several classic vascular risk factors and correcting for within-person variability [157]. In another meta-analysis, the presence of an IL-6R variant (Asp358Ala), with effects consistent with IL-6R blockade, conferred a decreased risk of coronary heart disease [158].

IL-6R Blockade, Lipid Levels, CV Risk, and Events

The IL-6R blockers are of interest with respect to CVD risk because of their observed effects on lipid profiles in phase III studies. Across phase III studies, both sarilumab and tocilizumab treatment was associated with increases in total cholesterol, LDL-C, and HDL-C (whereas the HDL:LDL ratio remained generally stable). Consequently, prescribing guidelines recommend that physicians assess lipid parameters 4–8 weeks following initiation of treatment with IL-6R, and at regular intervals thereafter.

A recent analysis of the phase III MONARCH study, which compared the effects of sarilumab

with the anti-TNFα bDMARD adalimumab, showed significantly greater reductions in Lp(a) after 24 weeks of treatment with sarilumab compared with adalimumab, and normalization of Lp(a) occurred in a numerically greater percentage of patients treated with sarilumab [132]. In a much smaller study, inhibition of IL-6 signaling with tocilizumab decreased Lp(a) serum levels, indicating a beneficial effect of IL-6R blockade on CV risk [159]. Other small studies have shown that IL-6R blockade improves endothelial function and/or reduces arterial stiffness [160, 161].

Because of the effects of tocilizumab on lipid levels, and because it was the first anti-IL-6R bDMARD, regulatory authorities requested a phase IV trial comparing the CV safety of tocilizumab with an anti-TNFα bDMARD in patients with RA [162]. The study, with a follow-up period of 3.2 years, showed that tocilizumab did not increase the rate of major CV events compared with etanercept (hazard ratio 1:1). This finding is consistent with the integrated safety analyses of the phase III studies of both anti-IL-6R bDMARDs. Fleischmann et al. [163] recently published a report with 9000 years of patient exposure to sarilumab, which showed that the exposure-adjusted incidences of major CV events with sarilumab combination and monotherapy (0.5 and 0.2/100 patient-years [PY], respectively) were no greater than those reported in the general RA population. Similar reports have been shown previously with tocilizumab [164].

RA, Diabetes, and the Metabolic Syndrome

The incidence of T2D is at least twice that in patients with RA compared with the general population, and there is an increased risk for CVD in patients with both conditions relative to patients with either RA or T2D alone [121, 165]. The coexistence of RA and T1D is less common than that of RA and T2D (Bao et al. [166] reported that 2% of > 150,000 patients with T1D in the USA have RA), but the risk of more than one autoimmune disease in the same patient is an established phenomenon.

Elevated circulating levels of IL-6 have been associated with dysfunctional glucose metabolism, and the induction of insulin resistance in the hepatocytes and adipocytes of obese patients with and without T2D [167, 168]. Furthermore, increased levels of IL-6 have been associated with increased risk for the development of T2D [169, 170]. Additionally, pharmacologic management of T2D and RA can be complicated by the potential effects of RA treatments on glucose levels. In particular, oral glucocorticoids (especially higher doses and longer treatment durations) increase the risk for T2D [171].

While T2D is associated with insulin resistance, T1D is characterized by insulin deficiency caused by immune-mediated selective destruction of beta cells in the islets of Langerhans. T1D can therefore be considered an inflammatory disease of the pancreatic islets, in which beta cell apoptosis results through the interaction of activated T cells and proinflammatory cytokines in the immune infiltrate [172]. In vitro and in vivo research in animals has implicated IL-6 in T1D, identifying that, in addition to a possible role in regulating pancreatic beta cell function (inhibiting glucose-stimulated insulin secretion from pancreatic islets), IL-6 produced by pancreatic beta cells may act as a co-stimulator for autoreactive B and T lymphocytes in T1D [173, 174].

IL-6R Blockade, Insulin Sensitivity, and Glycosylated Hemoglobin

In recent post hoc analyses, the decreases in hemoglobin A1c (HbA1c) were greater in sarilumab groups than placebo or adalimumab groups at week 24 (n = 20) among patients with RA, both without and with T2D, as identified by medical history or use of antidiabetic medication [175]. Similar reductions in HbA1c were shown in a small open-label study of patients with active RA (n = 10 with T2D and HbA1c ≥ 6.4%) treated with IV tocilizumab 8 mg/kg Q4W for 24 weeks [176], and in an observational study where tocilizumab decreased HbA1c levels in patients with RA to a greater extent than anti-TNFα bDMARDs [177]. Tocilizumab has also been shown to improve insulin sensitivity as determined by the Homeostatic

Model Assessment of Insulin Resistance (HOMA-IR) index and the leptin:adiponectin ratio in non-diabetic patients with rheumatoid disease [159].

To date, there are limited data on the effects of IL-6R blockade in patients with T1D, but the results of a clinical trial to assess the potential efficacy of anti-IL-6 therapy on beta cell responses in children and adolescents with new-onset T1D are awaited with interest (https://www.extendstudy.org/about-extend).

RA and Mood and Sleep Disturbances

Many patients with RA suffer from mood disorders, particularly depression and anxiety [120]. A meta-analysis of 72 studies in > 13,000 patients with RA found the prevalence of depression to be 38% [120], and despite the clinical focus on depression among people with arthritis, anxiety can be more common than depression [178]. In RA, mood disorders are associated with pain, disability, and impaired quality of life, and can even adversely affect adherence to therapy [93, 179, 180].

Although the link between mood disorders and RA is certainly multifactorial, evidence points toward IL-6 being one of these key factors. Dowlati et al. [181] performed a meta-analysis that showed significantly higher serum concentrations of TNFα and IL-6 in patients with major depression compared with control subjects. An updated meta-analysis by Haapakoski et al. [182] continued to show higher mean levels of IL-6 in patients with major depression compared with non-depressed controls, but found that the association between TNFα and risk of depression was uncertain due to heterogeneity in study-specific estimates and inconsistencies between subgroups. In healthy individuals, low serum levels of IL-6 predict earlier resolution of negative mood following psychosocial distress, and administration of IL-6 results in significantly depressed self-reported mood [183, 184]. A "low-IL-6" synthesizing genotype associated with lower levels of depression has also been identified [185], and animal studies have shown that IL-6R blockade can induce long-lasting antidepressant effects in susceptible mice after social-defeat stress [186].

The HPA axis is the major endocrine system regulating the physiologic response to stress, and although the mechanisms by which IL-6 affects mood have not been fully elucidated, effects on the HPA axis have been implicated [187, 188]. Positive temporal correlations between plasma levels of IL-6 and HPA hormones, adrenocorticotropic hormone, and cortisol have been demonstrated [187, 188]. Given that dysregulation of the HPA axis has been associated with both depressive and anxiety disorders in RA and other conditions, such as cancer [188, 189], the IL-6–HPA axis interaction is a plausible explanation for the clinical effects on mood that are seen.

Another prevalent complaint of patients with RA is poor sleep quality, which has been associated with depression, pain, fatigue, and functional disability [190, 191]. Polysomnographic studies have also confirmed that chronic pain is associated with poor sleep continuity and reduced total sleep time in other populations, although it is also hypothesized that sleep disturbance might drive RA-related pain [192].

In healthy subjects, elevated IL-6 is negatively correlated with sleep quality and positively correlated with ineffective interrupted sleep [190, 191]. IL-6 is also involved in normal sleep regulation. In healthy individuals, quantity of sleep correlates negatively with the overall daytime secretion of IL-6, and individuals deprived of sleep have daytime oversecretion of IL-6 [193]. SC administration of IL-6 into healthy individuals significantly alters sleep structure, and promotes manifestations of somnolence and fatigue [183, 193]. Research has implicated the link between IL-6 and the HPA axis in poor sleep; IL-6-induced HPA axis activation in patients with RA results in transient hypercortisolemia during the early hours of sleep, which may explain the poor sleep quality during this period [194].

IL-6R Blockade and Effects on Mood Disorders and Sleep

In patients with RA, IL-6R blockade with tocilizumab and sarilumab has previously been

reported to be associated with improvements in sleep. Most recently, in a subanalysis of Italian data from the TOZURA multicenter phase IIIb/IV trial, Bazzichi et al. [195] reported a significant improvement in sleep quality after 24 (but not 12) weeks of tocilizumab treatment using the Pittsburgh Sleep Quality Index questionnaire. Previously, Strand et al. [196] reported a clinically significant improvement in sleep after 24 weeks of sarilumab treatment using a sleep visual analog scale (VAS), with a decrease in score of − 16.9 from a baseline of 54.1.

Evidence indicating that IL-6R blockers have positive effects on mood in patients with RA is discussed in more detail in "The importance of IL-6R blockade from a patient's perspective" section below.

RA and Infections

Disease activity associated with RA is a risk factor for infection explained by the pathobiologic immune system disturbances of RA itself, the impact of chronic comorbid conditions, and sequelae of immunosuppressive treatment. Individuals with RA have a twofold increased adjusted risk of hospitalized infection compared with those without, an observation that was first identified over 50 years ago and has been confirmed in recent years [118, 119]. Upper and lower respiratory tract infections are often the most common infections, and a history of serious infections and/or comorbidities, increased glucocorticoid dose, and older age are important risk factors of serious infections in patients treated with bDMARDs.

The risk of serious infections with bDMARDs targeting TNFα is higher compared with the use of csDMARDs, particularly during the first 6 months of treatment [197–199], and the addition of MTX to bDMARDs does not appear to increase the risk of serious infection [200]. However, it is interesting to note that the risk of sepsis or mortality may be lower in patients exposed to bDMARDs compared with csDMARDs at the time of serious infection [201], which suggests that successful immunosuppression may prevent the unregulated host response to serious infection. Further research is obviously warranted, but such findings highlight the complexity of the mechanisms involved in immunomodulation and infection.

IL-6R Blockade and Infection in RA

Given the increased infection risk with other bDMARDs, and since IL-6 has a pivotal role in the recruitment and antiapoptosis of T lymphocytes, and in B and T cell differentiation, the impact of IL-6R blockade on the risk of infections is of considerable interest. In the clinical studies MOBILITY, TARGET, and MONARCH, and in the recently published integrated safety analysis of 2887 patients receiving sarilumab in combination with csDMARDs or as monotherapy (8188 and 812 PY, respectively), the risk of infections was found to be increased compared with placebo but in line with other bDMARDs [39–41, 163]. IL-6 blockade with tocilizumab and sarilumab has been shown to cause a decrease in neutrophil levels [163, 202–204]. However, the reduction in absolute neutrophil count (ANC) observed with sarilumab is not associated with an increased risk of infection or serious infection in clinical studies, and a "margination" hypothesis has been described to explain these observations [205] (discussed further in the "Safety and tolerability of IL-6 blockade" section of this article).

RA and Malignancy

The association between RA and cancer has been a clinical concern, and focus of research efforts, since links between RA and cancer (as well as between RA treatments and cancer) were first identified. Epidemiologic studies have generally demonstrated that hematopoietic, lung, and skin cancers can be increased in patients with RA, while breast and colon cancers are decreased, and that there is a very slight overall increase in all cancers [206–208]. There have been various hypotheses for the differences in the increased risk of certain malignancies in patients with RA. Inflammatory responses play pivotal roles in cancer development, including tumor initiation, promotion, progression, and metastasis [122]. Inflammation is believed to play a key role in the risk of

lymphoma in particular, and evidence suggests that it is the disease activity associated with RA that confers the risk of lymphoma [122].

IL-6 is highly upregulated in many cancers, and considered one of the most important cytokines associated with tumorigenesis and metastasis [209]. A high serum concentration of IL-6 is a prognostic indicator of poor outcome in patients with various cancers, including gastric, pancreatic, melanoma, breast, colorectal, myeloma, and lung cancers [209]. As well as acting directly on tumor cells, IL-6 can act on other cells within the complex tumor microenvironment to sustain a protumor setting, and acting through STAT3, IL-6 also supports tumor cell survival [210]. The role of IL-6 signaling in the activation of downstream pathways in cancer has been reviewed extensively [211–215] and is therefore not further expanded here.

IL-6R Blockade and Malignancy in RA

Unlike some other DMARDs used to treat RA, the prescribing information for IL-6R blockers does not have a warning regarding malignancies [11–14]. It is acknowledged that malignancies have been reported in clinical studies, but analyses indicate that IL-6 blockade with sarilumab and tocilizumab does not increase cancer risk significantly compared with treatment-naïve groups [163, 164, 216]. The overall rates of malignancy of 0.7/100 PY for sarilumab combination therapy, 0.6/100 PY for sarilumab monotherapy [163], and 1.1–1.2/100 PY with tocilizumab [164, 216] are comparable with the rate of 1.3/100 PY observed in a contemporary large US cohort of patients with RA (> 40,000 PY), in which > 60% of patients were treated with anti-TNFα bDMARDs [217].

RA and Interstitial Lung Disease

Interstitial lung disease (ILD) is the most common pulmonary complication in patients with RA, with a reported lifetime risk of developing ILD of 7.7% for patients with RA compared with 0.9% for those without RA. [117] There has been growing interest in the overlap of these two conditions in recent years, particularly since prognosis is so poor, with a mean of 2.6 years' survival after diagnosis [117]. Indeed, certain drugs used to treat RA, such as MTX and potentially (although data are conflicting) anti-TNFα bDMARDs, have been associated with the development or progression of ILD [117].

A recent report has shown that active RA is associated with an increased risk for developing RA-ILD, with a hazard ratio of 2.22 for patients with moderate/high disease activity compared with those with LDA or in remission [218], thus providing the link with systemic inflammation, of which IL-6 is a key driver. However, while elevated levels of serum IL-6 (> 7.67 pg/ml) have been shown to be predictive of negative outcomes in ILD associated with systemic sclerosis (SSc-ILD) [219], and elevated serum interleukin-18 levels have recently been shown to be associated with the presence of ILD in patients with RA [220], there is a paucity of research investigating the role of IL-6 in RA-ILD [221, 222].

IL-6R Blockade and ILD

Although primary endpoints were not met in the phase II faSScinate [223] and phase III focuSSced trials conducted in patients with SSc-ILD, there was some evidence of reduced lung function decline with the anti-IL-6R agent tocilizumab. In addition, case series have also reported modest effects in patients with SSc-ILD, with approximately 50% of patients achieving an improvement or stabilization of pulmonary function [224]. However, to date there is limited information on the effects of IL-6 blockade on ILD in patients with RA, with evidence limited to case reports describing anecdotal benefits regarding the off-label use of tocilizumab in patients with RA and ILD [225–227].

THE IMPORTANCE OF IL-6R BLOCKADE FROM A PATIENT'S PERSPECTIVE

While the clinical endpoints (discussed in the "Effect of sarilumab and tocilizumab on clinical endpoints in RA" section above) are valuable

from a clinical perspective and help guide treatment decisions, they are of little direct relevance to patients themselves. In fact, RA is no different from other conditions in that there is often a disconnect between the treatment goals of patients and those of their physicians. In surveys conducted between 2014 and 2016, of approximately 1800 patients with RA whose RA was primarily managed by a rheumatologist and a similar number of physicians managing patients with RA, while 90% of physicians were satisfied with their communication with their patients regarding RA treatment, 61% of patients felt uncomfortable raising concerns or fears with their physician [228]. Over one-half of patients responding felt that improved dialogue/discussion with their physician would optimize their RA management, and over two-thirds of physicians wished that they and their patients talked more about RA goals and treatment [228]. The European League Against Rheumatism (EULAR) 2016 RA treatment recommendations were designed, in part, based on recognition of a need for improved dialogue surrounding RA manifestations [60], such as is reported here. As such, the first overarching principle is that best care for patients must be aimed for, and that such care should be based on shared decisions made between the patient and their rheumatologist [60].

Indeed, factors influencing treatment decisions differ between rheumatologists and patients [229]. Physicians are more likely to escalate treatment based on DAS28 scores, the number of swollen joints, levels of CRP, and progression of joint erosion, while patients rate the number of painful joints, fatigue, morning stiffness, and level of physical function as more important factors [230]. A recent review of patient perspectives also highlighted routes of administration as an important attribute influencing treatment preferences [231]. Studies have documented a preference for newer autoinjectors over prefilled syringes, consistent with high satisfaction rates with the sarilumab autoinjector pen [232].

Table 3 lists the key phase III studies for IV and SC tocilizumab, SC sarilumab, and patient-reported outcomes investigated [233], and the following sections describe how these measures provide more information on the beneficial effects of anti-IL-6R bDMARDs on some of the comorbid conditions and extra-articular manifestations associated with RA.

Combination Therapy with Sarilumab and Tocilizumab

Physical Functioning

The Health Assessment Questionnaire Disability Index (HAQ-DI) is often the measure used to assess the physical disability component of the ACR core set and, for sarilumab, was evaluated in MOBILITY at week 16 [39] and TARGET at week 12 [40], with change from baseline included as co-primary endpoints (Table 2). In the MOBILITY study, significant improvement was observed at weeks 16, 24, and 52 of the study, and in the TARGET clinical study, the mean change in HAQ-DI score after week 12 of the study was significantly increased versus the placebo groups [39, 40]. Treatment with tocilizumab has also been found to cause improvements in HAQ-DI scores. In the SUMMACTA study, mean HAQ-DI score improvements with SC tocilizumab were observed to be maintained at approximately − 0.6 compared with baseline values from week 24 through to week 97 [53]. In the LITHE study, the proportion of patients receiving treatment who maintained a HAQ-DI improvement score of ≥ 0.3 from the baseline level to week 24 of the study was numerically higher with IV tocilizumab than in the untreated control group [44]. At week 24 in the TOWARD study [46], 60% of treated patients were reported to exhibit clinically meaningful HAQ-DI score improvements compared with 34% in the untreated control group, with baseline mean change also significantly greater in the tocilizumab-treated versus the control group. The RADIATE study reported that HAQ-DI values improved by − 0.31 and 0.39 (tocilizumab 4 mg/kg and 8 mg/kg doses, respectively) versus − 0.05 in treated compared with control groups [47].

Effects of Sarilumab and Tocilizumab on Mood and Depressive Manifestations

In post hoc analyses, approximately 60% of patients enrolled into MOBILITY and TARGET were classified at baseline as having probable

Table 3 Overview of phase III studies with tocilizumab IV and SC, and sarilumab SC, on individual patient-reported outcome endpoints

	Study population	Treatment arms	HAQ-DI	SF-36	Fatigue	Pain	Morning stiffness
Sarilumab combination studies							
MOBILITY [39] https://clinicaltrials.gov/ct2/show/NCT01061736	MTX-IR (n = 1197) Patients also received MTX	S 150 mg SC S 200 mg SC Placebo SC Q2W 52 weeks	Co-primary endpoint: change from baseline W16	Not reported	Not reported	Secondary endpoint: change from baseline VAS W24	Not reported
TARGET [40] https://clinicaltrials.gov/ct2/show/NCT01709578	TNF-IR (n = 546) Patients also received csDMARDs	S 150 mg SC S 200 mg SC Placebo SC Q2W 24 weeks	Co-primary endpoint: change from baseline W12 Secondary endpoint: change from baseline W24	Secondary endpoints: change from baseline SF-36 physical W24; change from baseline SF-36 mental W24	Secondary endpoints: change from baseline FACIT-F W24; also measured in RAID domain (change from baseline W12, W24)	Secondary endpoints: change from baseline VAS W24; also measured in RAID domain (change from baseline W12, W24)	Secondary endpoint: change from baseline VAS W24
Sarilumab monotherapy studies							
MONARCH [41] https://clinicaltrials.gov/ct2/show/NCT02332590	MTX-IR (n = 369)	S 200 mg SC A 40 mg SC Placebo SC Q2W 24 weeks	Secondary endpoint: change from baseline W24	Secondary endpoints: change from baseline SF-36 physical W24; change from baseline SF-36 mental W24	Secondary endpoints: change from baseline FACIT-F W24; also measured in RAID domain (change from baseline W24)	Secondary endpoints: change from baseline VAS W24; also measured in RAID domain (change from baseline W24)	Secondary endpoint: change from baseline VAS W24
SC tocilizumab studies							
SUMMACTA [42] https://clinicaltrials.gov/ct2/show/NCT01194414	DMARDs-IR (n = 1262)	T 162 mg SC QW T 8 mg/kg IV Q4W 24 weeks	Secondary endpoint: proportion with $\geq$ 0.3 change HAQ-DI $\geq$ 0.3 W24, W97	Not reported	Not reported	Not reported	Not reported
BREVACTA [43] https://clinicaltrials.gov/ct2/show/NCT01232569	DMARDs-IR (n = 656)	T 162 mg SC Placebo SC Q2W 24 weeks	Secondary endpoint: change from baseline W24; proportion with $\geq$ 0.3 change W24, W97	Secondary endpoint: change from baseline SF-36 W24	Not reported	Secondary endpoint: change from baseline VAS W24	Not reported

Table 3 continued

	Study population	Treatment arms	HAQ-DI	SF-36	Fatigue	Pain	Morning stiffness
IV tocilizumab combination studies							
LITHE [44] https://clinicaltrials.gov/ct2/show/NCT00106535	MTX-IR (n = 1196) Patients also receive MTX	T 4 mg/kg IV T 8 mg/kg IV Placebo IV Q4W 52 weeks	Co-primary endpoint: change from baseline in AUC W52, W104; proportion with $\geq$ 0.3 change W104	Secondary endpoint: change from baseline SF-36 W24, W52, W104	Secondary endpoints: change from baseline FACIT-F W24, W52, W104	Secondary endpoint: change from baseline VAS W52, W104	Not reported
OPTION [45] https://clinicaltrials.gov/ct2/show/NCT00106548	csDMARD-IR (n = 623) Patients also receive MTX	T 8 mg/kg IV T 4 mg/kg IV Placebo IV Q4W 24 weeks	Additional endpoint: change from baseline W24	Additional endpoint: difference from placebo group SF-36 physical W24; SF-36 mental W24	Additional endpoint: FACIT-F score, difference from placebo group W24	Additional endpoint: change from baseline VAS W24	Not reported
TOWARD [46] https://clinicaltrials.gov/ct2/show/NCT00106574	csDMARD-IR (n = 1220) Patients also receive csDMARDs	T 8 mg/kg IV Placebo IV Q4W 24 weeks	Secondary endpoint: change from baseline W24	Secondary endpoint: change from baseline SF-36 W24	Secondary endpoint: change from baseline FACIT-F W24	Not reported	Not reported
RADIATE [47] https://clinicaltrials.gov/ct2/show/NCT00106522	TNF-IR (n = 499) Patients also receive MTX	T 8 mg/kg IV T 4 mg/kg IV Placebo IV Q4W 24 weeks	Additional endpoint: change from baseline W24; proportion with $\geq$ 0.22 change W24	Additional endpoint: change from baseline SF-36 physical and mental W24	Additional endpoint: change from baseline FACIT-F W24	Additional endpoint: change from baseline; patient's assessment of pain by VAS W24	Not reported
IV tocilizumab monotherapy studies							
U-ACT-EARLY [48] https://clinicaltrials.gov/ct2/show/NCT01034137	Newly diagnosed DMARD-naïve (n = 317)	T 8 mg/kg IV + MTX T 8 mg/kg IV Placebo + MTX Q4W 104 weeks	Not reported	Secondary endpoint: change from baseline SF-36 W12, W24, W52, W104	Secondary endpoint: change from baseline FACIT-F W12, W24, W52, W104	Secondary endpoint: change from baseline; patient's assessment of pain by VAS W12, W24, W52, W104	Not reported

Table 3 continued

	Study population	Treatment arms	HAQ-DI	SF-36	Fatigue	Pain	Morning stiffness
FUNCTION [49] https://clinicaltrials.gov/ct2/show/NCT01007435	MTX-naïve patients with early progressive RA (n = 1162)	T 8 mg/kg IV + MTX T 8 mg/kg IV T 8 mg/kg + placebo Placebo + MTX Q4W 104 weeks	Secondary endpoint: change from baseline W24, W52	Secondary endpoint: change from baseline SF-36 physical and mental W24, W52	Not reported	Not reported	Not reported
ACT-RAY [50] https://clinicaltrials.gov/ct2/show/NCT00810199	MTX-IR (n = 556)	T 8 mg/kg IV + MTX T 8 mg/kg IV 104 weeks	Secondary endpoint: change from baseline W24, W52	Not reported	Not reported	Not reported	Not reported
ADACTA [51] https://clinicaltrials.gov/ct2/show/NCT01119859	MTX-INT (n = 326)	T 8 mg/kg IV Q4W A 40 mg SC Q2W 24 weeks	Not reported	Change from baseline W24	Change from baseline W24	Not reported	Not reported

A adalimumab, *AUC* area under the curve, *csDMARD* conventional synthetic disease-modifying antirheumatic drug, *DMARD* disease-modifying antirheumatic drug, *FACIT-F* Functional Assessment of Chronic Illness Therapy-Fatigue, *HAQ-DI* Health Assessment Questionnaire Disability Index, *INT* intolerant, *IR* inadequate response, *IV* intravenous, *MTX* methotrexate, *n* number of patients, *Q2W* every 2 weeks, *Q4W* every 4 weeks, *QW* weekly, *RA* rheumatoid arthritis, *RAID* rheumatoid arthritis impact of disease, *S* sarilumab, *SC* subcutaneous, *SF-36* Short Form (36 item) Health Survey, *T* tocilizumab, *TNF* tumor necrosis factor, *VAS* visual analog scale, *W* week

major depressive disorder (PMDD; according to the Short Form [36-item] Health Survey [SF-36] mental health [MH] domain score ≤ 56), and approximately 50% were classified as having probable depressed mood and anhedonia (PDMA; score ≤ 10 on both items of the MH domain: "Have you felt downhearted and depressed?" and "Have you felt so down in the dumps that nothing could cheer you up?"). In both studies, sarilumab provided clinically meaningful improvements in most domains of health status compared with placebo. In particular, MH scores for PMDD and PDMA subgroups were higher (better) for sarilumab 200 mg Q2W versus placebo [234].

Outside the phase III studies, tocilizumab use has been associated with decreased depressive manifestations (using the Hospital Anxiety and Depression Scale, which comprises two subscales [one measuring depression and the other anxiety] of seven items) in a small study of patients with RA [235].

Effect of Sarilumab and Tocilizumab on Fatigue

In MOBILITY, 24 weeks' treatment with sarilumab 200 mg Q2W resulted in improvement from baseline by week 24 in Functional Assessment of Chronic Illness Therapy-Fatigue (FACIT-F) scores that were clinically meaningful and persisted until week 52 [236]. In TARGET, improvements in the FACIT-F scores with sarilumab 200 mg Q2W were seen 2 weeks after the start of treatment, and greater improvements versus placebo at week 12 were maintained at week 24 [237]. Similar results have been seen with tocilizumab in the OPTION [45] and TOWARD studies [46].

Effect of Sarilumab and Tocilizumab on Pain

Improvements in the pain VAS with sarilumab 200 mg Q2W were approximately double those obtained with placebo in MOBILITY and TARGET by week 12 (− 30 vs. − 15) [39, 40]. Overall, with sarilumab 200 mg Q2W in MOBILITY and TARGET, pain was improved by ≥ 30% in 50–60% of patients [39, 40]. A recent post hoc analysis reported the proportions of patients achieving ≥ 30%/ ≥ 50%/ ≥ 70% pain VAS improvements and median time to first pain VAS ≥ 50% improvement in MOBILITY and TARGET [238]. Median time to first pain ≥ 50% improvement was 12 weeks in patients receiving sarilumab 200 mg Q2W compared with 24 weeks in patients receiving placebo [238].

Effect of Sarilumab and Tocilizumab on Morning Stiffness

The effects of sarilumab on morning stiffness were measured using a VAS in TARGET, and showed an improvement in scores of − 30 at week 12 (versus − 13 with placebo) and − 34 at week 24 (versus − 22 with placebo) [237]. Morning stiffness was not measured in the tocilizumab phase III program, but in a German open-label study (TAMARA), major improvements in morning stiffness were observed in the first 4 weeks of treatment with IV tocilizumab 8 mg/kg Q4W, with further improvement until week 24 [239].

Monotherapy with Sarilumab or Tocilizumab

Sarilumab Monotherapy

The MONARCH study compared the effects of sarilumab 200 mg Q2W and adalimumab 40 mg Q2W on a variety of patient-reported outcomes [240]. After 24 weeks of treatment, and compared with adalimumab, sarilumab resulted in significantly greater improvements in HAQ-DI (decreases from 1.6 at baseline of − 0.61 and − 0.43, respectively). By week 24, 65% of patients had an improvement of HAQ-DI ≥ 0.22 and 62% had an improvement ≥ 0.3 (54% and 48% with adalimumab, respectively). Sarilumab also resulted in larger improvements in Patient Global Assessment, pain VAS, and SF-36 Physical Component Score (PCS), although, overall, between-group differences in FACIT-F and SF-36 Mental Component Score (MCS) were not significant. Improvements in four of eight SF-36 domains were significantly greater with sarilumab than with adalimumab (physical functioning, body pain, and role-physical, and social functioning). Greater changes were also reported for sarilumab versus adalimumab in RA impact of disease, a measure with seven

weighted domains covering pain, functional disability, fatigue, emotional well-being, sleep, coping, and physical well-being [241]. A recent post hoc analysis of MONARCH reported that the median time to first pain ≥ 50% improvement in MONARCH was 12 weeks in patients receiving sarilumab 200 mg Q2W, compared with 24 weeks in patients receiving placebo [238]. Morning stiffness was also evaluated using a VAS severity scale (0 mm [no problem] to 100 mm [major problem]) [240]. At week 24, improvements in morning stiffness VAS were greater with sarilumab treatment than with adalimumab, and more patients (73.9% vs. 62.2%) reported improvements greater than or equal to the morning stiffness minimal clinically important differences (MCID) of ≥ 10 units.

Tocilizumab Monotherapy

The effects of IV tocilizumab monotherapy on patient-reported outcomes have been reported from AMBITION (compared with MTX) and ADACTA (compared with adalimumab) over 24 weeks [242]. In AMBITION, tocilizumab-treated patients reported significantly greater mean improvements in FACIT-F (8.7 vs. 5.7; SF-36 PCS: 9.8 vs. 7.8) and five SF-36 domains (physical functioning, bodily pain, vitality, social functioning, and mental health) than with MTX [242].

The proportions of patients reporting improvements above the MCID depended on the outcome measured. In AMBITION, 24–44% of tocilizumab-treated patients reported scores at least equal to normative values across HAQ-DI, FACIT-F, and SF-36 PCS/MCS, and 30–52% across SF-36 domains at week 24 compared with 15–42% and 21–45% of MTX-treated patients, respectively [242].

In ADACTA, tocilizumab-treated patients reported significantly greater improvements in Patient Global Assessment (− 42.3 vs. − 31.8), pain (− 40.1 vs. − 28.7), SF-36 MCS (7.9 vs. 5.0), and three SF-36 domains than with adalimumab (role-physical, vitality, and social functioning) [242]. Overall, 58–83% of tocilizumab-treated patients reported improvements at least equal to the MCID. The proportion of tocilizumab-treated patients reporting scores at least equal to normative values ranged between 22–49% for HAQ-DI, FACIT-F, and SF-36 PCS/MCS (14–38% with adalimumab), and 23–41% across SF-36 domains at week 24 (17–33% with adalimumab).

SAFETY AND TOLERABILITY OF IL-6 BLOCKADE

Overall safety profiles of sarilumab and tocilizumab are consistent with IL-6R blockade and the route of administration, and in ASCERTAIN, no clinically meaningful differences in adverse events were seen between SC sarilumab and IV tocilizumab over 24 weeks [204]. The most useful clinical perspectives on the safety of any pharmacologic intervention develop over time after the completion of the phase III studies, and more patients are treated for longer periods of time in clinical practice in addition to clinical studies. For sarilumab, Fleischmann et al. [163] have reported an integrated safety analysis of 9000-PY exposure to sarilumab: the overall incidence rates of serious adverse events were 9.4/100 and 6.7/100 PY, respectively, in the combination and monotherapy groups. For tocilizumab, similar integrated and long-term analyses have also been published [164, 243]. Mohan et al. [243] showed that the overall rate of serious adverse events in the integrated clinical trial population of > 22,000 PY was 14.2/100 PY, and in a global postmarketing population included > 600,000 patients; the overall spontaneous reporting rate of adverse events of special interest was 9.4 cases/100 patients.

In addition to the insights from these post-marketing studies, a number of real-world and registry-based studies provide additional insight into the safety profile of these agents in the wider population of patients with RA. While data from some registries have suggested an increased risk of infections, including serious infections, with agents that inhibit IL-6 signaling [244–247], a comparative head-to-head analysis of the safety of tocilizumab and TNF inhibitors in the Japanese REAL registry did not find a higher risk for serious adverse events or serious infections with tocilizumab compared

with TNF inhibitors after adjustment for potentially confounding factors. The use of oral corticosteroids in patients receiving tocilizumab, however, was a significant risk factor for both serious adverse events and serious infections [248].

In a Japanese 26-week, real-world observational study among > 1000 patients with RA, the safety profile of SC tocilizumab was consistent with that in clinical trials and for IV tocilizumab. Infections and infestations were the most commonly reported adverse events (7.4% of patients) and accounted for the majority of serious adverse events (1.7% of patients; 2 cases of pneumonia and 2 cases of bacterial pneumonia) [249].

The most frequent laboratory parameter changes reported in sarilumab/tocilizumab trials were decreased ANC and increases in liver transaminase levels (aspartate aminotransferase [AST] and alanine aminotransferase [ALT]) [163, 164], hence it is recommended that ANC counts, AST/ALT levels, and platelet counts are monitored after starting therapy and regularly thereafter. Lipid changes are also observed as described in the "RA and CVD" section above, although there is no increased risk of major CV events with IL-6R blockade versus anti-TNFα bDMARDs [162]. Therefore, lipid parameters should be assessed 4–8 weeks following initiation of treatment and regularly thereafter.

As highlighted in the "RA and Infections" section above, the risk of infections is an ongoing clinical consideration in all patients with RA, irrespective of treatment mechanism of action. Patients should therefore be closely monitored for the development of signs and manifestations of infection during treatment with IL-6R. This is particularly true in elderly patients, in whom more infections are seen in general, irrespective of disease or treatment [250]. IL-6R blockers should not be administered during an active infection, and if a serious infection develops, the IL-6R blockers should be temporarily discontinued until the infection is controlled [11–14].

Sarilumab studies have shown that neutropenia is not associated with a higher incidence of infections, including serious infections [163], and a margination hypothesis has been postulated [205]. In this model, "margination" is explained as the redistribution of the neutrophils from the vascular compartment into the vascular wall or other tissues (such as bone marrow), without change in their functionality. The marginated neutrophils remain available in case of an infection and can "demarginate" to mount a host response. Lok et al. [202] showed that tocilizumab did not affect neutrophil function, activation, or apoptosis ex vivo and, using radiolabeled neutrophils injected into human subjects, that tocilizumab affects neutrophil trafficking to the bone marrow.

Gastrointestinal (GI) perforation has been reported primarily as a complication of diverticulitis in patients with RA. An integrated safety analysis reported 26 cases of GI perforation (2.8/1000 PY) in patients who received tocilizumab compared with no cases in control csDMARD groups; 18 of these perforations occurred in the colon [164]. An analysis of the global postmarketing database for tocilizumab, which included data for 606,937 patients, identified 632 cases of GI perforation translating to a rate of 0.1 cases/100 patients [243]. An integrated analysis of sarilumab reported an incidence of GI perforation of 0.1/100 PY with sarilumab in combination with csDMARDs, but no cases with sarilumab monotherapy with 812 PY follow-up [163].

Hypofibrinogenemia has been noted as a potential adverse effect during tocilizumab treatment in a small case series of seven patients [251]. This small group of patients (median age 60 years) received tocilizumab 8 mg/kg over a 1-year period and all exhibited low levels of plasma fibrinogen despite normal routine coagulation tests and no evidence of liver failure or disseminated intravascular coagulation (DIC). The authors suggest that, while low fibrinogen levels in the context of normal coagulation tests do not warrant discontinuation of treatment, liver function tests are warranted to rule out DIC or hemophagocytic lymphohistiocytosis.

All bDMARDs have the potential to induce an immunogenic response resulting in the formation of antidrug antibodies (ADAs). ADAs to mAbs may be neutralizing or non-neutralizing, or demonstrate a transient or persistent

response; those that are neutralizing and persistent ADAs are more likely to be clinically relevant than transient and/or non-neutralizing ADAs [252]. ADA incidences cannot be compared across different bDMARDs, partly because of the different assays needed for different products; however, the development of ADAs has been reported with sarilumab [41] and tocilizumab [253] treatment. Any impact of an ADA can be compared with different agents and, importantly, unlike infliximab and adalimumab, with IL-6R inhibitors the presence of ADAs has not been associated with a lack or loss of efficacy relative to ADA-negative patients [254].

CONCLUSIONS

RA is a chronic, debilitating autoimmune disorder characterized by inflammation of the synovial joint tissues. RA pathogenesis is driven by a complex network of proinflammatory cells and cytokines, and among the actors involved in the network of RA, IL-6 seems to be the most pleiotropic cytokine with the greatest number of downstream influences. IL-6 can bind to various cell types around the body, and increased production of IL-6 can lead to heightened activation of cells within the joint, contributing to the RA disease state. However, beyond the joint, IL-6 is also known to contribute to various extra-articular manifestations and life-threatening comorbidities tightly linked to an existing RA condition.

IL-6R blockade treatments have been shown to cause clinically important improvements in RA clinical endpoints in patients with mild to severe active RA. The leading approved IL-6R inhibitors, sarilumab and tocilizumab, have produced statistically significant improvements in the signs and manifestations of RA when used as monotherapy or in combination with csDMARDs, as defined by the ACR, CRP and ESR, CDAI, and radiographic progression measures, cementing IL-6R blockade as a robust treatment option for RA. However, beyond the joint, the extra-articular manifestations linked to RA including anemia, morning stiffness, pain, weight and body composition, and comorbidities linked to RA that include osteoporosis, CVD and pulmonary disease, infections, depression, T2D, and malignancies have also previously been investigated as IL-6 treatment targets. Clinical evidence in a range of clinical studies has indicated that use of IL-6R blockade with sarilumab or tocilizumab can improve these IL-6-linked conditions to varying extents, to ultimately improve patient disease states and quality of life. To this end, such findings indicate that sarilumab and tocilizumab can be supported as important treatments for certain extra-articular manifestations and comorbidities of RA, in addition to manifestations within the joint. The impacts of IL-6R blockade treatment effects can be observed when explored from both a clinician's perspective through clinical efficacy outcome measures, and also when viewed from a patient's perspective through the use of patient-reported outcome assessments, which measure variables including pain, physical functioning, and sleep disturbance.

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