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Review

Neuroendocrine and neurophysiological effects of interleukin 6 in rheumatoid arthritis

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Abstract

RA is a chronic, systemic, autoimmune disease characterized by inflammation and degradation of the joints, causing significant negative impact on quality of life. In addition to joint disease, symptoms and co-morbidities associated with RA—namely pain, fatigue and mood disorders—are often as debilitating as the disease itself. The pro-inflammatory cytokine IL-6 plays a critical role in RA-associated pathology. However, a greater understanding of the translational effects of IL-6 outside of the immune system is needed. This review discusses our current understanding of emerging aspects of IL-6 in RA-associated pain, fatigue and mood disorders such as depression and anxiety. This review also describes the clinical effects of IL-6 inhibition on these symptoms and co-morbidities in patients with RA.

Key words: IL-6, rheumatoid arthritis, tocilizumab, sarilumab, sirukumab

REVIEW

Rheumatology key messages

- Ubiquitous expression of *gp130* and the IL-6 trans-signalling mechanism supports pleiotropic effects of IL-6 in RA.
- IL-6 may have translational effects on RA-associated pain, fatigue and mood disorders.
- Inhibition of IL-6 has demonstrated positive effects on patient-reported pain, fatigue and mood in RA.

Introduction

RA is a common chronic, inflammatory, autoimmune disease affecting ~1% of the world population [1]. For patients with RA, the ability to perform daily activities and health-related quality of life are significantly negatively affected [2]. Furthermore, patients with RA of >10 years duration experience increased mortality compared with the general population [3]. Although RA is a disease primarily affecting the joints, its systemic symptoms and co-morbidities can also be considered part of the syndrome [4]. Extra-articular manifestations of RA affect most organ systems, including the cardiovascular, nervous, pulmonary and skeletal systems [1]. Moreover, RA-associated symptoms and co-morbidities are often intercorrelated. For example, the physical symptoms of RA, including pain, inflammation and fatigue, have important implications on mental health [5]. These chronic physical symptoms can adversely affect mental health by altering neural processing [5]. Various studies have demonstrated significant and positive correlations between pain, fatigue and mood in patients with RA [6–9]. These symptoms are recorded as patient-reported outcomes (PROs) and are vital assessments when measuring RA treatment response in clinical trials. Despite the growing interest in patient-centred outcomes in rheumatology, most domains of health assessed by PROs are not frequently reported in clinical trials [10]. Among 96 randomized controlled trials (RCTs) conducted in RA and published between 2012 and 2014, the PROs of pain, fatigue and mood were assessed in only 34, 17 and 5 trials, respectively [11].

It is well established that pro-inflammatory cytokines, particularly IL-6, are both elevated and involved in RA pathogenesis [12]. IL-6 is a pleiotropic cytokine with substantial effects on non-immunological tissues [13]. Beyond the immune system, IL-6 has been shown to affect vascular disease, lipid metabolism, insulin resistance, mitochondrial activities, the neuroendocrine system and neuropsychological behaviour [14]. It is considered one of the most important cytokines that mediates the rapid interplay between the immune system and CNS function in states of health and disease [13]. The purpose of this literature review is to investigate the translational effects of IL-6 in the presence of RA, specifically in pain, fatigue

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and mood disorders. Peer-reviewed primary articles for this review were obtained from PubMed or from literature reviews published since 2005. We focused on phase 2 or higher clinical trials reporting pain, fatigue or mood and pre-clinical mechanistic studies. Search terms included, but were not limited to RA, IL-6, pain, fatigue, mood disorders, depression, anxiety, hypothalamic–pituitary–adrenal (HPA) axis, tocilizumab, sarilumab and sirukumab.

IL-6 Signalling

IL-6 is composed of 184 amino acids and forms a four-helix protein [15]. Nearly all stromal cells and immune cells produce IL-6 [14]. The IL-6 receptor (IL-6R) consists of an α-chain, CD126, and two chains of glycoprotein 130 (gp130) [15–17]. Expression of IL-6R is largely restricted to hepatocytes, leucocytes and megakaryocytes [14]. Binding of IL-6 to its receptor alone does not result in signal transduction, as this requires recruitment and association with the gp130 protein [15]. Universally expressed, gp130 is a 130 kDa signal-transducing β-receptor subunit, also known as CD130 [14]. When IL-6/IL-6R are bound, gp130 is recruited and dimerizes and signalling is initiated (Fig. 1) [18–23].

This process of IL-6 binding to membrane-bound IL-6R and signalling through the Janus kinase–signal transducer and activator of transcription (JAK-STAT) pathway is known as classical signalling [15]. However, many cells, particularly non-immune cells (i.e. endothelial, smooth muscle and neural cells), do not express the IL-6R α-chain but can still respond to IL-6 via binding of soluble IL-6Rα to membrane-bound gp130, a process called trans-signalling [15, 24, 25]. The ability to inhibit trans-signalling using a soluble fusion protein has led to the development of a model that suggests IL-6 classical signalling is responsible for regenerative and protective functions, whereas IL-6 trans-signalling is involved in the pro-inflammatory activity of IL-6 inflammation [19, 25]. For in-depth reviews of IL-6 signalling, see Rose-John [15] and Calbrese and Rose-John [20].

As a multifunctional cytokine, IL-6 plays an important role in many physiological responses, such as acute-phase response, fever induction, angiogenesis, B and T cell differentiation and lipid and iron metabolism [26]. Under normal conditions, circulating levels of IL-6 are low; however, in patients with RA, serum and SF levels of IL-6 and IL-6R are much higher [27–29]. While IL-6 trans-signalling is involved in the maintenance of several chronic disease states, it plays a key role in RA pathogenesis [12]. The combined ubiquitous expression of gp130 and the trans-signalling pathway enable IL-6 to have pleiotropic effects in RA. Because neuronal cells express gp130 and can therefore be activated via IL-6 trans-signalling, IL-6 may have a direct effect on CNS-related RA symptoms and co-morbidities, such as pain, fatigue and mood, which are discussed below [24, 30].

Translational effects of IL-6 in RA

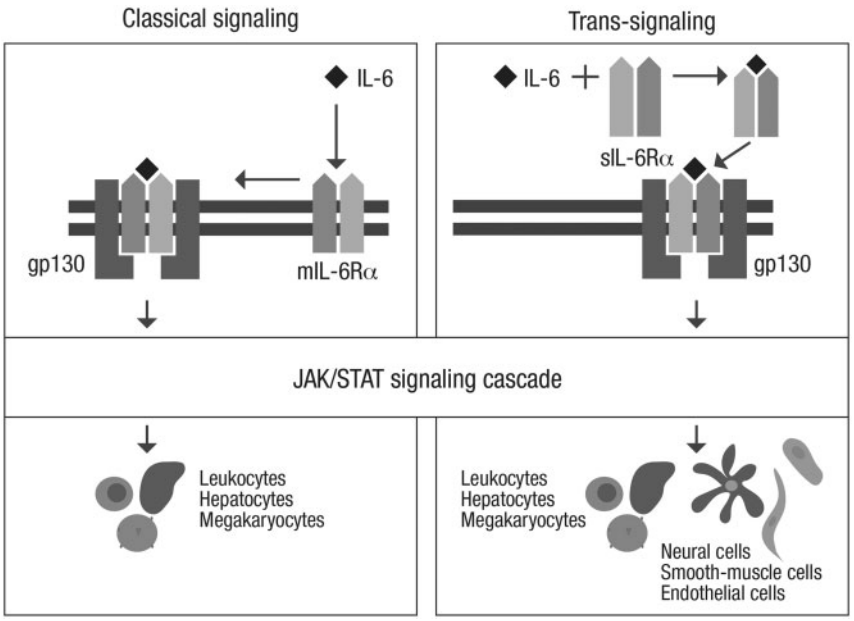
Pain

Pain is the primary reason that patients with inflammatory arthritis seek care from a rheumatologist and it is the RA-associated symptom for which most patients desire effective treatment and meaningful improvement [31, 32]. Despite an ever-growing understanding of pathological pain mechanisms, pain management still presents a major challenge in clinical practice. Typical arthritic pain may be experienced as ongoing pain in the absence of stimulation, in response to mechanical stimuli (i.e. movements in the working range and joint palpation) or from normally non-painful warm or cold stimuli, which are all states of hyperalgesia [29]. Furthermore, while both inflammation and joint damage can cause peripheral pain, some patients with arthritis complain of more severe pain than the degree of inflammation and joint damage, while others may complain of joint pain in the absence of inflammation and damage, a mechanism known as central pain [33, 34].

Pain mechanism

Hyperalgesia is the result of sensitization of the nociceptive (pain) system, wherein the excitement threshold (pain elicitation) for nociceptive neurons is lowered [29]. By targeting the nociceptive system, certain cytokines have a direct role in the development of hyperalgesia by acting on neurons themselves [29]. An increasing body of preclinical evidence suggests that IL-6 plays a dominant role in pain mechanisms [35]. Neurons and glial cells of the spinal cord, as well as dorsal root ganglia (DRG), all express gp130, thereby making these cells susceptible to IL-6/soluble IL-6R (sIL-6R) trans-signalling [29, 36, 37]. The IL-6 signal transducer gp130 in afferent neurons is a key regulator of the induction and maintenance of mechanical hypersensitivity associated with cancer, inflammation and nerve injury [38]. Using electrophysiological recordings from nociceptors of rat knee joints, IL-6 or IL-6/sIL-6R injections into normal knees caused a long-lasting sensitization of nociceptive C-fibres for mechanical stimuli applied to the joint [39]. In a rat model of antigen-induced arthritis, soluble gp130 (sgp130) injections significantly attenuated pain-related behaviour [40]. Knockout mice lacking gp130 specifically in sensory DRG neurons (SNS gp130$^{-/-}$) showed reduced inflammation-induced pain [41]. Application of IL-6/sIL-6R either into rat knee joints or topically to the spinal cord increased responses of spinal neurons to mechanical stimulation of the knee and other parts of the leg, including an expansion of the receptive field size of the neurons, showing the potential of IL-6 to induce central sensitization [42]. Furthermore, development of rat knee inflammation evoked significant spinal release of IL-6 and spinal application of sgp130 attenuated the generation of spinal hyperexcitability during the development of inflammation [42]. Collectively these preclinical studies demonstrate that IL-6 is a key mediator of pain through direct action on the nociceptive system.

Fig. 1 Signalling of IL-6 via the classical and trans-signalling pathways



In classical signalling, IL-6 binds membrane-bound receptors on a few peripheral cells, including hepatocytes and leucocytes. The IL-6/IL-6R complex does not result in signalling, as association with the ubiquitously expressed transducing protein gp130 is required to initiate signalling. In trans-signalling, membrane-bound IL-6R is made soluble by cleavage with metalloproteases. Soluble IL-6R binds IL-6 to form the IL-6/IL-6R complex, which then binds membrane-bound gp130. This form of trans-signalling does not require membrane-bound IL-6R and can therefore occur in any cell type that expresses membrane-bound gp130, including cells of the CNS, neurons, astrocytes and microglia. gp130: glycoprotein 130; JAK: Janus kinase; STAT: signal transducer and activator of transcription; mIL-6Rα: membrane-bound IL-6 receptor alpha; sIL-6Rα: soluble IL-6 receptor alpha.

Anti-IL-6 agents and pain

The positive effects of IL-6 inhibition on patient-reported pain have been demonstrated (as secondary or exploratory endpoints) in phase 3 trials of the IL-6R antagonists tocilizumab, sarilumab and sirukumab in patients with moderate to severe RA (Table 1). Tocilizumab, sarilumab and sirukumab are mAbs that target both soluble and membrane-bound receptors for IL-6, thereby preventing both classical and trans-signalling [43–45]. Although there is no gold standard for pain measurement, in rheumatology populations, pain is often measured on a visual analogue scale (VAS), a single-item unidimensional measurement of pain intensity that has been shown to be reliable, simple and applicable to a variety of populations and settings [46]. The VAS scale (in millimetres) is generally anchored by no pain (0) to worst imaginable pain (100) and patients report current pain or pain within the last 24 h [46].

In the Tocilizumab Pivotal Trial in Methotrexate Inadequate Responders (OPTION) and Tocilizumab Safety and the Prevention of Structural Joint Damage (LITHE) studies, patients with RA experienced significant improvement in pain, as measured by improvement in mean VAS scores, with tocilizumab 4 and 8 mg/kg every 4 weeks (q4w) plus MTX at both 24 and 52 weeks [47, 48]. Improvements in mean VAS scores were also modestly maintained through 104 weeks with tocilizumab [49]. The Tocilizumab and DMARDs: Achievements in Rheumatoid Arthritis (TAMARA) study, a real-world study of patients with RA treated with tocilizumab plus a DMARD, reported modest improvements from baseline in pain within the first 4 weeks of treatment, which were sustained through week 24 [50]. However, when tocilizumab monotherapy was compared with MTX monotherapy in the Actemra Versus Methotrexate Double-blind Investigative Trial in Monotherapy (AMBITION) study, only a slight improvement in pain was reported at week 24 [51].

In the Evaluation of Sarilumab (SAR153191/REGN88) on Top of Methotrexate in Rheumatoid Arthritis Patients (MOBILITY) study, patients with RA treated with sarilumab 150 or 200 mg every 2 weeks (q2w) plus MTX reported a significant improvement in pain compared with placebo plus MTX at 2 weeks of treatment that was sustained through weeks 24 and 52 [52]. Similarly, in the To Evaluate the Effect of SAR153191 (REGN88) Added to Other RA Drugs in Patients With RA Who Are Not Responding to or Intolerant of Anti-TNF Therapy (TARGET) study, patients with RA treated with sarilumab 150 or 200 mg q2w plus conventional synthetic DMARDs (csDMARDs) also reported a significant improvement in pain *vs* placebo at both 12 and 24 weeks [53]. Sarilumab monotherapy also led to a significant improvement in the VAS score compared with adalimumab monotherapy at 24 weeks [54].

Table 1 PROs of pain in studies of anti-IL-6R agents in moderate to severe RA[a]

Drug	Study	Treatment	*n*	Pain (VAS)		
				Baseline	Treatment visit	
Tocilizumab					Week 24	
	OPTION [47]	4 mg/kg q4w + MTX qw	213	60.7 (21.0)	−25.0**	NR
		8 mg/kg q4w + MTX qw	205	59.9 (22.4)	−29.8*	
		Placebo q4w + MTX qw	204	57.3 (22.2)	−14.0	
					Week 24	
	AMBITION [51]	8 mg/kg q4w	268	58.7 (22.9)	−31.9	NR
		MTX qw	262	61.5 (20.6)	−29.9	
					Week 4	Week 24
	TAMARA [50]	8 mg/kg q4w + DMARD	286[b]	60.4 (21.5)	36.0 (26.7)	23.6 (26.3)
					Week 52	Week 104[c]
	LITHE [48, 49]	4 mg/kg q4w + MTX qw	399	NR	−23.1***	−26.6 (25.4)
		8 mg/kg q4w + MTX qw	398		−26.2*	−28.9 (25.5)
		Placebo q4w + MTX qw	393		−15.1	−25.6 (24.4)
Sarilumab					Week 24	Week 52
	MOBILITY [52]	150 mg q2w + MTX qw	400	65.4 (21.4)	−28.5 (1.4)*	−32.7 (1.4)*
		200 mg q2w + MTX qw	399	66.7 (21.4)	−31.8 (1.3)*	−33.1 (1.4)*
		Placebo q2w + MTX qw	398	63.7 (19.9)	−15.4 (1.4)	−19.3 (1.6)
					Week 12	Week 24
	TARGET [53]	150 mg q2w + csDMARDs	181	71.0 (19.3)	−26.9 (1.9)*	−31.9 (2.1)**
		200 mg q2w + csDMARDs	184	74.9 (18.4)	−30.6 (1.9)*	−33.7 (2.0)*
		Placebo q2w + csDMARDs	181	71.6 (18.2)	−15.1 (1.9)	−21.3 (2.3)
					Week 24	
	MONARCH [54]	200 mg q2w	184	70.9 (18.8)	−36.2 (1.8)**	NR
		Adalimumab 40 mg q2w	185	70.3 (19.3)	−27.4 (1.8)	

Values given as mean (s.d.). [a]Only phase 3 clinical trials reporting patient-reported pain were included in this table. [b]Data presented are for patients with inadequate response to conventional DMARDs; *n* for this specific population is not given in the source. [c]At week 104, $n = 228$, 248 and 137 for tocilizumab 4 mg/kg, tocilizumab 8 mg/kg and placebo, respectively. $^{*}P \leqslant 0.0001$, $^{**}P < 0.001$, $^{***}P < 0.05$. NR: not reported; qw: every week; q2w: every 2 weeks; q4w: every 4 weeks.

Sirukumab, a mAb that binds IL-6, demonstrated a dose–response improvement in pain in the A Study of CNTO 136 (Sirukumab), a Human Anti-IL-6 Monoclonal Antibody, Administered Subcutaneously, in Patients With Active Rheumatoid Arthritis Despite Anti-TNF-Alpha Therapy (SIRROUND-T) study in patients with active RA, with the lowest dose (50 mg q4w) providing a 26.7% improvement in the VAS score and the highest dose (100 mg q2w) providing a 30.5% improvement at week 24 compared with a 1.5% improvement with placebo [55]. This was maintained at 52 weeks for both sirukumab 50 and 100 mg (28.8 and 38.7% improvement, respectively) [55].

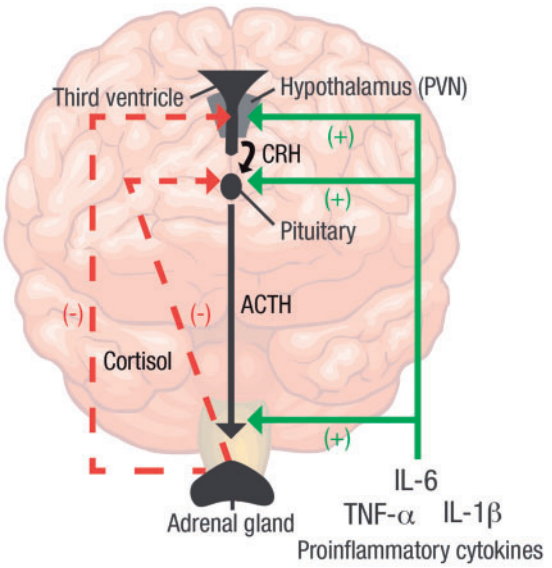
Fatigue

Like pain, fatigue is a debilitating symptom that is nearly universally experienced by patients with RA (>80%), often daily, and is typically rated as impactful and as important as pain [7, 56]. According to the US Food and Drug Administration, persistent severe fatigue occurs in 40% of patients with RA [57]. Qualitative interview data from patients with RA found that fatigue is a common, often severe experience, with consequences affecting every aspect of daily life [56]. They reported trying different self-management strategies with variable success, and most did not discuss their symptoms with their doctors or felt that the topic was dismissed if they did [56]. In a recent systematic review of RA-associated fatigue, 42 relevant studies were identified, generating 25 possible predictors of fatigue [58]. The three variables with the highest probability of being involved with RA-associated fatigue were mood disorders (depression/depressive mood), pain and disability/diminished physical functioning [58].

Fatigue and the HPA axis

Whereas the causality of RA-associated fatigue is likely multidimensional, involving inflammation, pain, anaemia, poor sleep and psychosocial factors, there is a growing body of evidence implicating the involvement of IL-6 and the HPA axis (Fig. 2) [27, 56, 59]. The HPA axis is a primary component of the stress system that is involved in the maintenance or reinstatement of homeostasis in response to physical (e.g. injury or infection) or physiological (e.g. anticipation of pain) stressors [60, 61]. Dysfunction of the HPA axis, specifically mediated by low circulating levels of cortisol, has been associated with chronic fatigue [62]. Briefly, perceived stress initiates a signal within the paraventricular nucleus of the hypothalamus. Neurons then secrete corticotropin-releasing hormone (CRH), which binds to specific receptors in the anterior pituitary [63]. This then stimulates the synthesis and release of adrenocorticotropic hormone from the anterior pituitary into the

Fig. 2 The HPA axis in RA



Pro-inflammatory cytokines such as IL-6, TNF-α and IL-1β stimulate cortisol and CRH release by acting at all three levels of the HPA axis (solid green lines). As a result, glucocorticoids regulate their own production through negative feedback on the upper levels of the HPA axis, including CRH in the PVN of the hypothalamus and ACTH in the anterior pituitary (dashed red lines). ACTH: adrenocorticotropic hormone; CRH: corticotropin-releasing hormone; PVN: paraventricular nucleus.

circulatory system [63]. This complex HPA axis relies on bidirectional communication between the neuroendocrine and immune systems [60]. Inflammatory cytokines, particularly TNF-α, IL-1β and IL-6, can stimulate the HPA axis alone or synergistically [64]. Among these, IL-6 plays one of the more dominant roles in immune stimulation of the HPA axis, particularly during chronic inflammatory stress such as in RA [64]. In fact, administration of IL-6 into humans stimulates the HPA axis even more potently than high doses of CRH [65].

Growing evidence suggests that the HPA axis stress response, via its dysfunction, plays an important role in RA, particularly in its interaction with the immune system [66]. Untreated patients with RA have hypersecretion of adrenocorticotropic hormone without the reciprocal increase in cortisol [66]. The HPA axis and IL-6 plasma levels were assessed in a study of 50 patients with RA of variable duration, ranging from recent onset (<1 year) to long-standing (>5 years) active disease [27]. Compared with healthy controls, patients with RA had impaired activity of the HPA axis, with significantly decreased cortisol levels and elevated IL-6 [27]. It is hypothesized that altered adrenal activity in RA may be responsible for decreased cortisol; however, the failure of elevated levels of IL-6 to stimulate cortisol suggests a possible hypothalamic defect as well [27]. The complexity of this system and these observations underscore the ability of hormones and cytokines to influence each other.

IL-6 is also involved in normal sleep regulation [13, 67]. Healthy individuals deprived of sleep had daytime oversecretion of IL-6, and s.c. administration of IL-6 into healthy individuals significantly altered sleep structure and promoted symptoms of fatigue [67, 68]. Clinical studies suggest a model wherein IL-6 secretion and HPA axis activation together result in fatigue and poor sleep [69]. For example, IL-6-induced HPA axis activation in patients with RA resulted in transient hypercortisolemia during the early hours of sleep, which may explain the poor sleep quality during this period [70]. In addition to its effect on the HPA axis, IL-6 may also exacerbate RA-associated fatigue through its involvement in disease-associated anaemia [13]. This may be because IL-6 drives hepcidin, which blocks ferroportin-mediated transfer of cellular iron [13].

Anti-IL-6 agents and fatigue

Assessing fatigue in RA clinical trials was initially recommended in 2007 by the OMERACT group, but as of 2015, this measure has only been specifically reported in ~18% of RCTs [11]. The Functional Assessment of Chronic Illness Therapy–Fatigue (FACIT-F) scale is a 13-item PRO questionnaire commonly used in RCTs of RA that has demonstrated reliability, validity and sensitivity for rating the severity of fatigue symptoms [11, 71]. In RA, the FACIT-F is scored on a scale of 0–52, with higher scores reflecting less fatigue and a minimally important difference requiring a 3–4 point change [71]. In the recent Cochrane Review of biologic interventions for fatigue in RA, 32 studies (20 anti-TNF and 12 non-anti-TNF biologic agents, including the anti-IL-6 agent tocilizumab) were included in the meta-analysis [72]. Overall, the study found a statistically significant reduction in fatigue in patients with RA when treated with biologics [standardized mean difference (SMD) −0.43 (95% CI −0.49, −0.38); $P < 0.00001$]. Anti-TNF agents had an SMD of −0.42 and non-anti-TNF agents had an SMD of −0.46 [72]. After a median of 24 weeks of treatment, the SMD in FACIT-F scores between anti-TNF and non-anti-TNF biologic agents and control groups was 6.3 and 6.9 U, respectively [72]. The authors were unable to pool data on pain or mood for the meta-analysis because of a lack of assessment or reported data [72].

The positive effects of IL-6 inhibition on symptoms of fatigue by tocilizumab, sarilumab and sirukumab in patients with moderate to severe RA, as assessed by FACIT-F, have been demonstrated in phase 3 clinical studies (Table 2). In the OPTION study, patients experienced a significant reduction of fatigue with tocilizumab 4 and 8 mg/kg q4w plus MTX compared with placebo plus MTX at 24 weeks [47]. In the TAMARA study, tocilizumab reduced fatigue within 4 weeks and improvement continued over 24 weeks [50]. Fragiadaki *et al*. [73] reported significant improvement of self-reported sleepiness, sleep quality and fatigue in 15 patients with active RA receiving tocilizumab 8 mg/kg q4w (mean FACIT-F improvement over baseline at 6 months = 17.7; $P < 0.00001$). In a phase 4 study of 325 patients with RA,

TABLE 2 PROs of fatigue in studies of anti-IL-6R agents in moderate to severe RA[a]

Drug	Study	Treatment	*n*	Fatigue (FACIT-F)		
				Baseline	Treatment visit	
Tocilizumab					Week 24	
	OPTION [47]	4 mg/kg q4w + MTX qw	213	27.0 (11.5)	7.3**	NR
		8 mg/kg q4w + MTX qw	205	27.7 (10.6)	8.6*	
		Placebo q4w + MTX qw	204	26.7 (11.1)	4.0	
					Week 24	
	ADACTA [74]	8 mg/kg q4w	163	NR	11.4	NR
		Adalimumab 40 mg q2w	162		8.9	
Sarilumab					Week 24	Week 52
	MOBILITY [52]	150 mg q2w + MTX qw	400	26.3 (9.8)	8.6 (0.5)*	9.1 (0.5)*
		200 mg q2w + MTX qw	399	25.9 (10.4)	9.2 (0.5)*	9.2 (0.5)*
		Placebo q2w + MTX qw	398	27.2 (10.4)	5.8 (0.5)	6.1 (0.5)
					Week 12	Week 24
	TARGET [53]	150 mg q2w + csDMARDs	181	23.5 (10.6)	8.0 (0.7)***	9.9 (0.8)***
		200 mg q2w + csDMARDs	184	23.1 (10.8)	9.5 (0.7)*	10.1 (0.8)***
		Placebo q2w + csDMARDs	181	23.7 (10.8)	5.6 (0.7)	6.8 (0.9)
					Week 24	
	MONARCH [54]	200 mg q2w	184	23.6 (8.9)	10.2 (0.7)	NR
		Adalimumab 40 mg q2w	185	24.4 (10.3)	8.4 (0.7)	
Sirukumab					Week 24	Week 52
	SIRROUND-T [55]	50 mg q4w	292	NR	6.6 (10.8)*	7.5 (10.1)
		100 mg q2w	292	NR	5.6 (9.1)*	7.0 (10.4)
		Placebo q2w	294	NR	1.9 (8.8)	

Values given as mean (S.D.). [a]Only phase 3 clinical trials reporting patient-reported fatigue were included in this table. $^{*}P \leqslant 0.0001$, $^{**}P < 0.01$, $^{***}P < 0.05$. NR: not reported; qw: every week; q2w: every 2 weeks; q4w: every 4 weeks.

tocilizumab monotherapy was associated with a modest improvement in fatigue from baseline compared with adalimumab monotherapy at 24 weeks [74].

In the MOBILITY study, patients receiving sarilumab demonstrated a significant improvement in FACIT-F scores as early as 2 weeks that were sustained through 52 weeks compared with placebo [52]. Similarly, in the TARGET study, patients receiving sarilumab plus csDMARDs reported a significant improvement in FACIT-F scores *vs* placebo at both 12 and 24 weeks [53]. Sarilumab monotherapy also led to a modest improvement in FACIT-F scores compared with adalimumab monotherapy at 24 weeks [54]. Alleviation of fatigue appears to be one of the first beneficial effects that patients with RA may experience when using biologic therapies that block IL-6 signalling [13].

In the SIRROUND-T study, patients receiving sirukumab 50 mg q4w or 100 mg q2w demonstrated a significant improvement in FACIT-F scores at 24 weeks compared with placebo [55]. Improvement was also observed at 52 weeks [55].

Mood disorders

More than one-third of patients with RA suffer from mood disorders, particularly depression and anxiety [5, 75, 76]. Depression (defined as past or current symptoms) was the most commonly observed co-morbidity among 3920 patients with RA as assessed by rheumatologists during face-to-face interviews and medical records review in the Comorbidities in Rheumatoid Arthritis (COMORA) cross-sectional study [4]. A recent systematic review and meta-analysis of 72 studies in >13 000 patients with RA found the prevalence of depression to be ~38% [76]. Despite its prevalence and effect on quality of life, mental health co-morbidity is rarely measured in rheumatology research or in clinical practice, with minimal published research reporting mental health as an outcome [77].

Mood disorder mechanism

Although there may be several proposed mechanisms underlying the relationship between RA and mood disorders, a strong link to IL-6 has been made. Animal models lacking IL-6 or those treated with IL-6-blocking antibody were found to be resilient to social stress, suggesting a potentially important role for the cytokine in the development of depression or anxiety [78]. In healthy individuals undergoing psychosocial distress, low peripheral IL-6 levels can predict earlier resolution of negative mood [79]. Conversely, administration of IL-6 into healthy individuals significantly depressed self-reported mood [68]. Both clinical studies and recent meta-analyses have indicated that IL-6 is the most consistently elevated cytokine in the blood of patients with major depressive disorder [80–82]. Although there is limited understanding of the mechanism(s) by which IL-6 signalling may contribute to manifestations of depression, a few hypotheses exist [83]. One hypothesis is that genetic polymorphisms may contribute to psychopathological symptoms since a functional single-nucleotide polymorphism in the promoter region of the IL-6 gene has been shown to be associated with decreased IL-6 expression and plasma

Table 3 PROs of mood in studies of anti-IL-6R agents in moderate to severe RA[a]

Drug	Study	Treatment	*n*	Mood (SF-36 MCS)		
				Baseline	Treatment visit	
Tocilizumab					Week 24	
	OPTION [47]	4 mg/kg q4w + MTX qw	213	40.1 (11.8)	5.7****	NR
		8 mg/kg q4w + MTX qw	205	40.9 (10.6)	7.3***	
		Placebo q4w + MTX qw	204	39.1 (11.0)	2.7	
					Week 24	
	ADACTA [74]	8 mg/kg q4w	163	NR	7.9****	NR
		Adalimumab 40 mg q2w	162		5.0	
Sarilumab					Week 24	Week 52
	MOBILITY [52]	150 mg q2w + MTX qw	400	39.0 (11.3)	5.7 (0.6)****	7.1 (0.6)
		200 mg q2w + MTX qw	399	38.7 (12.0)	8.2 (0.6)*	8.4 (0.6)**
		Placebo q2w + MTX qw	398	38.9 (11.4)	3.9 (0.6)	5.5 (0.7)
					Week 12	Week 24
	TARGET [53]	150 mg q2w + csDMARDs	181	38.6 (11.4)	5.1 (0.8)	6.3 (0.8)
		200 mg q2w + csDMARDs	184	39.1 (11.4)	6.5 (0.7)****	6.8 (0.8)
		Placebo q2w + csDMARDs	181	38.5 (12.6)	3.5 (0.7)	4.7 (0.9)
					Week 24	
	MONARCH [54]	200 mg q2w	184	36.4 (10.4)	7.9 (0.8)	NR
		Adalimumab 40 mg q2w	185	36.9 (11.6)	6.8 (0.8)	
Sirukumab					Week 24	Week 52
	SIRROUND-T [55]	50 mg q4w	292	NR	3.9 (10.7)**	4.7 (10.1)
		100 mg q2w	292	NR	4.1 (9.3)**	4.9 (10.5)
		Placebo q2w	294	NR	1.1 (8.9)	

Values given as mean (S.D.). [a]Only phase 3 clinical trials reporting patient-reported mood were included in this table. $^{*}P \leqslant 0.0001$, $^{**}P < 0.001$, $^{***}P < 0.01$, $^{****}P < 0.05$. NR: not reported; qw: every week; q2w: every 2 weeks; q4w: every 4 weeks.

concentrations [84]. A prospective study in patients receiving pegylated IFN-α for treatment of hepatitis C, designed on the basis of previous studies that showed a correlation between increased plasma IL-6 during IFN-α treatment and psychopathological symptom severity, found that a low IL-6 synthesizing genotype was significantly associated with fewer symptoms of depression ($P = 0.002$) [84, 85]. Cytokines may also cause depression through hyperactivation of the HPA axis. Dysregulation of the HPA axis has been associated with psychopathologies such as depression, panic disorder and anxiety [63, 86]. Chronic stress has been shown to activate IL-6 and signal through the JAK-STAT3 pathway in the hypothalamus of rats as well as induce a sustained corticosterone response [86].

Anti-IL-6 agents and mood

A common measure of mental health symptoms such as depression used in clinical trials of RA is the mental component summary (MCS) of the 36-item Short Form Health Survey (SF-36). The MCS is calculated by positively weighting the psychological subscales (vitality, social function, role emotional and mental health) and negatively weighting the physical subscales (physical function, role physical, bodily pain and global health) of the SF-36 [87]. The minimally important change in the SF-36 MCS for RA is 3.1 [11]. A study investigating the accuracy of SF-36 MCS scores in identifying the presence of mood disorders (major depressive disorder or anxiety) in patients with RA found that optimal use of the subscale required a threshold of ⩽38 [87]. Positive effects of IL-6 inhibition on patient-reported mental health, as assessed by the SF-36 MCS score, have been demonstrated in several phase 3 studies of tocilizumab, sarilumab and sirukumab in patients with moderate to severe RA (Table 3).

Patients experienced significant improvement in mean SF-36 MCS scores with tocilizumab 4 and 8 mg/kg q4w plus MTX compared with placebo plus MTX at 24 weeks in the OPTION study [47]. In a 24 week phase 4 study, tocilizumab monotherapy was associated with significant improvement in SF-36 MCS scores compared with adalimumab monotherapy [74].

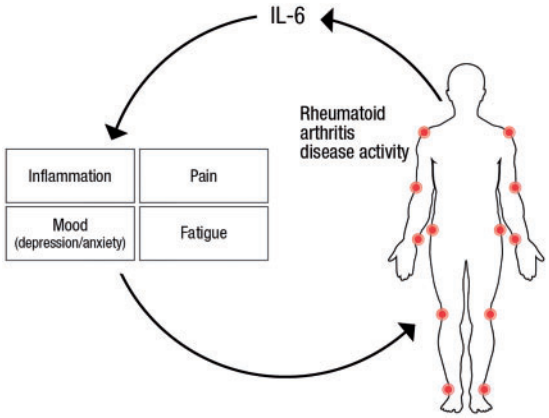
In the MOBILITY study, patients treated with sarilumab 150 and 200 mg q2w plus MTX reported a significant improvement in SF-36 MCS scores at 24 and 52 weeks [52]. In the TARGET study, patients treated with sarilumab plus csDMARDs also reported improvement in SF-36 MCS scores at both 12 and 24 weeks *vs* placebo [53]. Treatment with sarilumab monotherapy showed a trend toward greater improvement in SF-36 MCS scores *vs* adalimumab monotherapy at 24 weeks [54].

In the SIRROUND-T study, patients receiving sirukumab 50 mg q4w or 100 mg q2w demonstrated significant improvements in SF-36 MCS scores at 24 weeks *vs* placebo [55]. Improvement was also observed at 52 weeks [55].

Discussion

Whereas RA primarily involves the joints, co-morbidities and systemic extra-articular symptoms such as pain, fatigue and mood disorders are often just as debilitating

Fig. 3 Conceptual model of interactions between fatigue, pain and mood in RA



RA disease activity is associated with widespread inflammation, largely mediated by the pro-inflammatory cytokine IL-6. Pain, fatigue and inflammation act as stressors that may influence both mental health and hyperalgesia/central sensitization. In some patients these manifestations can have major implications for mood, thereby negatively impacting quality of life.

and important to patients—so much so that their utility as clinical trial endpoints, in the form of PROs, is increasingly becoming a priority among rheumatology organizations and advocacy groups. The substantial overlap and positive correlation between pain, fatigue and mood suggest the possibility of a common underlying mechanism (Fig. 3) [88]. IL-6 has long been viewed as playing a dominant role in the pathogenesis of RA because of its pro-inflammatory effects; however, the far-reaching translational effects of IL-6 in RA are beginning to be appreciated. These effects are supported by the ubiquitous expression of gp130 and the IL-6 trans-signalling mechanism. Expression of gp130 throughout the nervous system, particularly on neurons, glial cells and DRG, enables IL-6 to mediate pain by directly acting on the nociceptive system. In addition to data supporting the role of IL-6 in RA-associated pain, converging lines of evidence also support the role of IL-6 in other pathological pain conditions, including bone cancer, chemotherapy-induced peripheral neuropathy, peripheral nerve injury and spinal cord injury [35].

Data generated from both animal and human studies support the hypothesis that the HPA axis plays a critical role in RA [89]. Deficiencies in the HPA axis, particularly in glucocorticoid and cortisol levels, may result in a wide range of clinical effects, including the exacerbation of acute to chronic RA [27]. Fatigue and mood alterations, presenting as depression, anxiety or both, are also influenced by the HPA axis. A dysfunctional HPA axis that results in alterations of cortisol production is the basis of many sleep conditions. IL-6 has been described as a putative sleep factor because of its circadian secretion correlation [69]. In addition to RA-associated fatigue, systemic IL-6 levels are also upregulated in several sleep disorders, such as chronic fatigue syndrome, narcolepsy and obstructive sleep apnoea [62, 69]. Altered HPA axis activity is observed in several neurodegenerative conditions that have a high incidence of co-morbid depression, such as Alzheimer's disease, Parkinson's disease and Huntington's disease [63].

The hypothesis that IL-6 contributes to RA-associated symptoms and co-morbidities through its effects on the HPA axis is currently only supported by preclinical data. Functional and clinical data are needed to support a mechanism of action for IL-6 as a modulator of HPA axis activity. Furthermore, there is an ever-growing body of evidence supporting a link between psychosocial functioning, disease activity and associated pain in RA [66]. Teasing apart the underlying mechanisms remains a challenge as the interrelationships between psychosocial, neuroendocrine and immune variables, and their potential effects on RA exacerbation, are complex (Fig. 3).

Inhibitors of IL-6 reduced pain and fatigue and improved mood. Currently it is unclear whether this is due to suppression of inflammation and RA or a direct effect of inhibiting IL-6. Further translational research is needed to understand whether IL-6 inhibition confers additional advantages in alleviating these symptoms, particularly whether patients with hyperalgesia, severe fatigue or concomitant depression will derive greater benefits from IL-6 inhibition.

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