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Jarlborg, Matthias; Gabay, Cem

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Systemic effects of IL-6 blockade in rheumatoid arthritis beyond the joints

Matthias Jarlborg [a,b], Cem Gabay [a,*]

[a] Division of Rheumatology, University Hospital of Geneva, and Department of Pathology and Immunology, University of Geneva School of Medicine, Geneva, Switzerland
[b] VIB-UGent Center for Inflammation Research and Ghent University, Ghent, Belgium

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ABSTRACT

Interleukin (IL)-6 is produced locally in response to an inflammatory stimulus, and is able to induce systemic manifestations at distance from the site of inflammation. Its unique signaling mechanism, including classical and *trans*-signaling pathways, leads to a major expansion in the number of cell types responding to IL-6. This pleiotropic cytokine is a key factor in the pathogenesis of rheumatoid arthritis (RA) and is involved in many extra-articular manifestations that accompany the disease. Thus, IL-6 blockade is associated with various biological effects beyond the joints. In this review, the systemic effects of IL-6 in RA comorbidities and the consequences of its blockade will be discussed, including anemia of chronic disease, cardiovascular risks, bone and muscle functions, and neuro-psychological manifestations.

1. Introduction

Interleukin (IL-) 6 is a pleiotropic pro-inflammatory cytokine which plays an important role in rheumatoid arthritis (RA) and its comorbidities. As a chief stimulator of the production of most acute-phase proteins, IL-6 is involved in acute inflammation [1]. IL-6 is also a key player in immune regulation, including the transition between acute and chronic inflammation [2]. Since the discovery of its role as a T-cell factor for B cell differentiation [3] and its identification in 1986 [4], IL-6 targeting has considerably improved the management of numerous inflammatory rheumatic diseases, and in particular RA [5].

IL-6 expression is up-regulated by various transcription factors, including NF-κB which is activated by other proinflammatory cytokines (such as IL-1β, TNFα and IL-17) [6], and by Toll-like receptors (TLRs)-mediated signals [7]. In response to cellular stress signals, most leucocytes and stromal cells are able to produce IL-6. The pleiotropic effects of this cytokine can be explained by its peculiar signaling pathway, engaging an heterodimer receptor formed by 1) its specific receptor, IL-6R, expressed in a restricted manner and 2) the co-receptor, the glycoprotein gp130 that is ubiquitously expressed in different cell types and also used by other members of the IL-6 family of cytokines [8]. The receptor IL-6R exists indeed in both transmembrane (IL-6R) and soluble (sIL-6R) forms [9,10]. The *classic signaling* involves binding to membrane-bound IL-6R. This receptor is only present in some cell types such as hepatocytes, neutrophils, monocytes, and some lymphocytes. The binding to IL-6R is followed by its dimerization with gp130 which, in turn, allows signal transduction. Most importantly, the co-receptor gp130 can also be activated by binding to soluble IL-6-sIL-6R complexes (a process called *trans-signalization*). This signaling pathway leads to a major extension in the number of cell types that can respond to IL-6. Indeed, when circulating IL-6 levels exceed circulating sgp130 levels, IL-6 can bind to sIL-6R and acts systemically like a hormone. Both *classic* and *trans-signaling* pathways lead to signal transduction through the Janus kinase (JAK) signal transducer and activator of transcription 3 (STAT3) pathway, as well as the mitogen-activated protein kinase (MAPK) cascade [11,12].

IL-6 has numerous metabolic and homeostatic effects distant from the site of inflammation. The use of anti-IL-6R drugs in rheumatoid arthritis (RA) for more than a decade [13] has led to a better understanding of the broad spectrum of action of this cytokine. RA is a frequent autoimmune disease, characterized by a chronic and progressive inflammation of various organs, mostly the joints, and immune dysregulation. Many cytokines, including IL-6, are involved in the pathogenesis and maintenance of the disease [14]. Recently, the new concept of signature cytokine hub considers IL-6 together with TNF-α as critical cytokines node in RA [15]. In addition, RA is associated with an increased risk of developing comorbid conditions in which IL-6 is also directly involved [16]. These comorbidities include cardiovascular diseases, infections, osteoporosis, depression, neoplasia, anemia (among others), and are associated with higher morbidity and mortality [17]. In this narrative review, we will discuss the key roles of IL-6 in most RA comorbidities, namely anemia of chronic disease, cardiovascular risks,

* Corresponding author.
E-mail address: cem.gabay@unige.ch (C. Gabay).

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bone and muscle dysfunctions, and neuro-psychological manifestations. First, an overview of the effects of IL-6 in systemic inflammation and in systemic manifestations associated with RA will be exposed. The subsequent consequences of its blockade beyond the joints will be then discussed, whether beneficial or detrimental.

2. IL-6 and systemic inflammation

IL-6 plays a major role in systemic inflammation and immunity. It is rapidly synthesized and released by myeloid cells in response to various danger signals and cytokines such as IL-1 and TNF-α. From the local site of inflammation, IL-6 is able to reach key organs through the bloodstream and induces systemic responses. This process is referred to as the acute-phase response [18]. With other cytokines, such as TNF-α, IL-1 and IFN-γ, IL-6 acts synergistically to induce inflammatory systemic responses [19]. However, IL-6, also known as *hepatocyte-stimulary factor,* seems to have stronger and broader effects, especially on hepatocytes [20].

Acute-phase response is accompanied by changes in plasma concentrations of multiple proteins [1], known as the acute-phase proteins, the circulating levels of which change by at least 25% during inflammation. More specifically, the levels of positive acute-phase proteins increase, while plasma concentrations of negative acute-phase proteins decrease (eg. albumin, transthyretin, fibronectin) during the acute-phase response. Hepatocytes express both IL-6R and gp130 allowing a prompt response to IL-6 through the *classical signaling pathway* [21]. Positive acute-phase proteins include C-reactive protein (CRP), complement factors and mannose-binding lectin, serum amyloid A (SAA), fibrinogen, ferritin, and hepcidin (among others). Their increase in the bloodstream facilitates the elimination of pathogens and damaged cells. Commonly used as a biomarker of inflammation, CRP has also biologic effects: it participates to complement activation, and functions as a pattern recognition molecule able to opsonize pathogens or damaged cells [22]. In addition to promote inflammation, acute-phase proteins – such as fibrinogen and haptoglobin - are involved in coagulation and healing. Mice deficient for IL-6 exhibit severely impaired acute phase protein production, and are unable to develop optimal responses to trauma and certain types of pathogens [23]. Moreover, IL-6 and acute phase response are also associated with changes in many physiological and behavioral processes (such as fever, pain; hematopoietic and metabolic perturbations; anorexia and somnolence). Fig. 1 summarizes some of the numerous systemic effects of IL-6.

As mentioned in the introduction, IL-6 is not only involved in acute inflammation, but also prepares the transition to chronic and adaptive responses. The first steps of inflammation are characterized by the influx of neutrophils to the site of injury or infection. Their accumulation induces the release of high amounts of IL-6 but also of sIL-6R by shedding of its membrane-bound form [24,25]. The complex IL-6-sIL-6R-gp130 is then able to stimulate stromal cells, mostly endothelial and smooth muscle cells, but also synoviocytes [26]. Notably, *trans-signaling pathway* of IL-6 is involved in endothelial activation and production monocyte chemoattractant protein (MCP)-1 favoring transition from neutrophil to monocyte recruitment [27]. In other terms, IL-6 *trans-signaling* promotes secondary accumulation of monocytes to the site of inflammation, which is the hallmark of chronic inflammation [2]. IL-6 is also involved in the healing process by promoting differentiation of bone marrow-derived monocytes towards macrophages and pro-resolving M2-like responses [28,29]. Furthermore, IL-6 has anti-inflammatory properties. Notably, it stimulates the production of IL-1 and TNF-α antagonists such as IL-1Ra and soluble p55 respectively [30].

Trans-signaling pathway has a pivotal role on lymphocytes and adaptive immunity. IL-6 is involved in the differentiation of T helper (Th) CD4+ cells. Depending on the local microenvironment and together with TGF-β and IL-23, IL-6 promotes Th17 polarization and inhibits regulatory T cell (Treg) differentiation, favoring pro-inflammatory responses and mucosal immune defense [31,32]. IL-6 *trans-signaling* has also been shown to induce a rapid activation of effector functions in cytotoxic CD8+ T cells [33]. In addition, IL-6

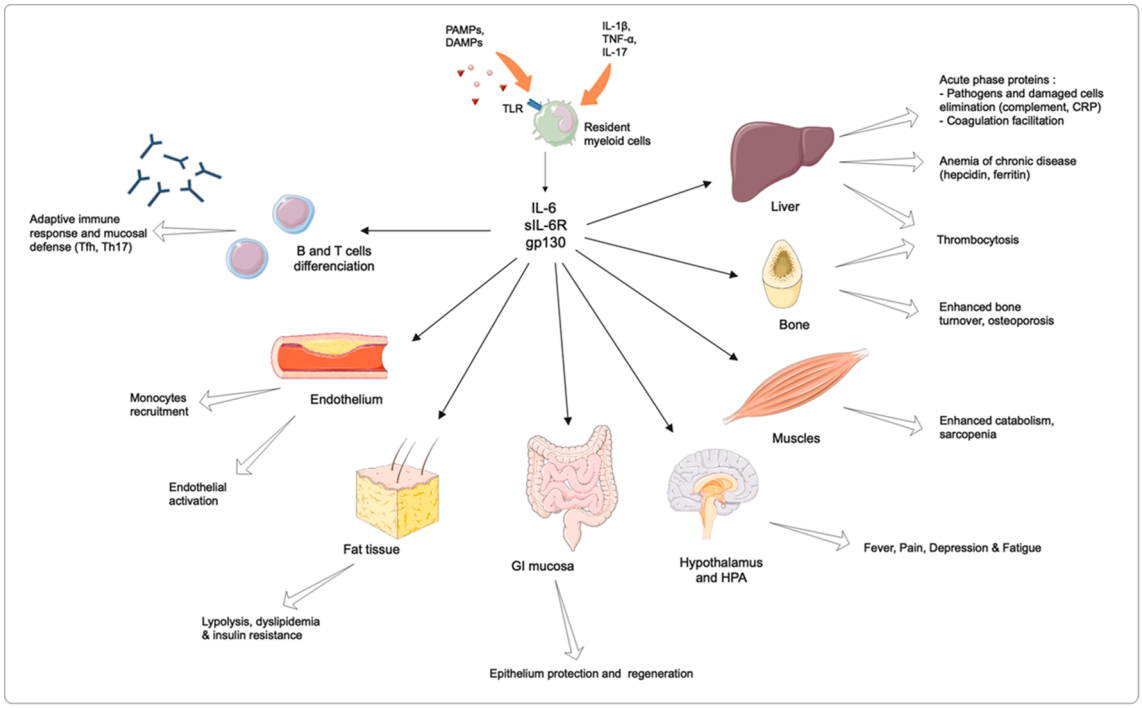

Fig. 1. This figure summarizes the pleiotropic effects of IL-6 on various organs and tissues. The complexes formed by IL-6, its soluble receptor (sIL-6R) and by glycoprotein (gp) 130 are able to induce various systemic effects distant from the initial site of inflammation. Abbreviation: CRP (C-reactive protein), DAMPs (damage-associated molecular patterns), HPA (hypothalamic–pituitary-adrenal axis), IFN-γ (interferon gamma), PAMPs (pathogen-associated molecular patterns), Tfh (follicular helper T cells), Th17 (T-helper 17 cell), TNF-α (Tumor necrosis factor-alpha). This figure is made with illustrations obtained from https://smart.servier.com/.

contributes to B cells differentiation and activation. In association with IL-2 and IL-10, IL-6 induces the maturation of plasmablasts into early plasma cells [34]. Originally described as a *B cell stimulatory factor*, IL-6 promotes the production of immunoglobulins *in vitro* [35]. In transgenic mice, overexpression of IL-6 induces plasmocytosis with hypergammaglobulinemia [36]. Together with IL-21 and IL-23 [37,38], IL-6 is indeed necessary for the differentiation of follicular helper T cells (Tfh) which, in turn, can activate B cells in germinal centers [39,40,41]. Some recent data suggest that gp130/STAT3 signaling is involved in the development of tertiary lymphoid structures [42]. These ectopic lymphoid tissues are particularly important in the pathogenesis of autoimmune diseases and autoantibodies production [43].

Hence, IL-6 orchestrates the immune response from its first innate steps to the late adaptive stages, including its resolution. Dysregulation and persistent IL-6 production leads to a chronic inflammation state as seen in many inflammatory and autoimmune diseases, as well as in cancers. IL-6-producing cardiac myxoma illustrates the clinical consequences of its overexpression with development of fever, increased acute-phase proteins, lymph node enlargement and autoimmune features including polyarthritis and autoantibody production [44]. High levels of IL-6 are also observed in the rheumatoid synovium [45], in hyperplastic lymph nodes from Castleman's disease [46], or in multiple myeloma [47]. These findings led to the development of treatments targeting IL-6. The first clinical trials were conducted in patients with multiple myeloma, with mitigated results [48]. Later, a humanized anti-IL-6R antibody (tocilizumab) was successfully used to treat chronic inflammatory symptoms in Castleman's disease [49]. Since the late 2000 s, IL-6R inhibitors, including tocilizumab and sarilumab have been licensed for the management of RA refractory to conventional synthetic disease modifying anti-rheumatic drugs (DMARDs). The use of IL-6R inhibitors was associated with improvement of composite scores of disease activity as well as with inhibition of structural damage [50–53]. Both tocilizumab and sarilumab were superior to adalimumab, a TNF antagonist, in the control of inflammatory manifestations when used as monotherapy [54–57]. More recently, tocilizumab was proven efficacious in the treatment of other inflammatory diseases, including systemic juvenile idiopathic arthritis, adult onset-Still's disease, and giant cell arteritis [58–60]. In addition to their beneficial effects in the control of inflammatory manifestations, IL-6 inhibitors are characterized by their ability to suppress acute-phase proteins. A rapid and sustained normalization of CRP levels is indeed observed upon IL-6R inhibition [61,53,62]. This is associated with clinical improvement and the reduction of many biomarkers of disease severity [63–65]. Tocilizumab suppresses fever and CRP in RA patients undergoing surgery [66]. Thus, by masking CRP elevation, IL-6 blockade rises major concerns regarding interpretation of inflammatory markers dependent on the acute-phase response [67]. Besides improvements of systemic and joint inflammation, IL-6 blockade is also associated with significant benefits on RA comorbidities. In the following sections, we will discuss the role of IL-6 in RA comorbidities and the consequences of its blockade beyond the joints.

3. Systemic benefits of IL-6 blockade in rheumatoid arthritis

3.1. Hematological effects of IL-6

The changes in blood cell count accompanying inflammation are driven by cytokines, including IL-6 [68]. Anemia is the most frequent extra-articular manifestation associated with RA. It affects 16% of newly diagnosed RA patients in a British cohort [69] and has a lifetime prevalence of up to 60% according to older publications [70]. In addition to its contribution to fatigue, anemia is an independent predictor of disease severity and radiographic progression in RA [71]. Moreover, low hemoglobin levels are associated with higher Health Assessment Questionnaire (HAQ) scores, indicative of physical disability [72]. Anemia of chronic diseases (ACD, or inflammatory anemia) is the main presentation of anemia that occurs together with RA [73]. ACD is typically normochromic, normocytic, and is due to iron sequestration. IL-6 stimulates hepatocytes to produce proteins involved in iron metabolism, mainly hepcidin [74], and ferritin [75]. Hepcidin, a hormone-like peptide, inhibits intestinal iron absorption by binding to the ferroportin channel and promoting its internalization and degradation [76,77]. Similarly, hepcidin inhibits the release of iron from reticuloendothelial cells. Serum hepcidin levels correlate with RA disease activity, and are associated to RA comorbidities such as coronary atherosclerosis and osteoporosis [78,79]. The increased ferritin levels also participate to iron sequestration. Altogether, lower transferrin saturation and lower serum iron concentrations result in ACD [80]. The decrease in iron availability seems to be a general defense mechanism against many pathogens [81]. Both anemia and increased fibrinogen levels contribute to the elevation of erythrocyte sedimentation rate (ESR) observed during inflammation [82].

IL-6R inhibition counteracts the effects of IL-6 on iron metabolism leading to greater iron availability. Tocilizumab induces a rapid and sustained reduction of hepcidin levels in patients with Castleman disease [83]. This has also been observed in RA, with improvement of anemia [84]. In a cohort of RA patients treated with either tocilizumab or infliximab (a TNF-inhibitor, TNFi), IL-6 blockade was more efficient to reduce hepcidin levels and to improve anemia [85]. Hashimoto et al. have demonstrated that tocilizumab is an independent factor associated with the increase of hemoglobin levels [86]. In a post-hoc analysis of the MONARCH study, sarilumab resulted in larger increase in hemoglobin levels at week 12 and 24 compared to adalimumab. This effect was associated with a larger decrease of hepcidin levels in the sarilumab group. Correlations between hepcidin levels and disease activity (including patient-reported outcomes) have been reported in RA, and hepcidin appears to be a predictor of treatment efficacy of both sarilumab and adalimumab at 24 weeks [65]. Thus, these studies suggest that IL-6R inhibitors are treatments of choice for RA patients with ACD.

Thrombocytosis is involved in the promotion of hemostasis but also in inflammation, host defense and healing [87]. Inflammatory thrombocytosis is also a direct consequence of IL-6 signaling. IL-6 stimulates megakaryocytopoïeses through enhancement of thrombopoietin (TPO) expression by hepatocytes [88,89]. Moreover, IL-6 has direct effects on megakaryocytes differentiation *in vitro* [90]. In a mouse model, high IL-6 production resulted in thrombocytosis, and IL-6 blockade was followed by platelet count normalization [91]. In RA, thrombocytosis correlates with IL-6 levels and disease activity [92,93]. Of note, platelet count decreases to a greater extent in RA patients treated with tocilizumab compared to adalimumab [54]. In this clinical trial, low grade thrombocytopenia occurred also more frequently in the tocilizumab group compared to adalimumab (9.3% vs 3.1%). However, no thrombocytopenia-related complications (severe thrombocytopenia or bleeding) were reported. Likewise, high platelet count together with low hemoglobin levels seem to be good predictors for IL-6R inhibitor efficacy [94].

Neutrophils are closely involved in IL-6 biology since they express IL-6R and can secrete its soluble form in large amount, allowing *trans-signaling* [24]. Data on the direct effects of IL-6 on neutrophils remain however conflicting. Clinical studies demonstrated that IL-6 blockade induces a transient but significant neutropenia [95]. Wright et al. showed that tocilizumab does not induce an increase of neutrophil apoptosis, neither affects neutrophil function [96]. Thus, one explanation could be that IL-6R inhibitors increase neutrophil margination or alter neutrophil trafficking [97]. Fortunately, there is no evidence for a higher risk of serious infection secondary to tocilizumab induced-neutropenia [98].

3.2. Effects of IL-6 on cardiovascular risks

RA is associated with excess of mortality compared to general population. The standardized mortality ratio (SMR) is estimated between

1.27 and 2.26, depending on populations studied [99,100]. Presence of extra-articular manifestations constitutes the strongest predictor of mortality [99]. Despite the significant decline in mortality in general population, the death rate in the paired cohort of RA patients appeared to stay relatively flat [101]. A more recent study in a large Korean cohort still confirms the excess of mortality in RA, with a SMR of 1.65 (95% CI 1.44–1.87). Cardiovascular disease (CVD) accounted for 14.2% of the causes of death in this study [102]. It is estimate that up to 50% of premature deaths in RA are attributable to CVD [103].

RA confers a significantly higher risk of coronary heart disease (CHD) and congestive heart failure compared to general population [104–106]. RA patients have a 1.5 to 2-fold increased risk of CV events, similar to the magnitude of risk in type 2 diabetes mellitus (DM) [107]. Recently, a large retrospective study showed a similar decline in 10-year risk of acute myocardial infarction in both RA and non-RA populations, indicating that the excess risk of CV events still persists [105].

Four major factors contribute to CV risk in RA. 1) The usual CV risks factors (notably smoking, dyslipidemia, hypertension, obesity and DM) coexist with a higher prevalence in RA [108,109]. 2) The use of some treatments such as glucocorticoids and non-steroidal anti-inflammatory drugs, is associated with an increased CVD risk [110,111]. 3) The presence of anti-citrullinated peptide antibodies (ACPAs) and rheumatoid factors (RFs) appeared to be independent risk factors for CVD and CV mortality [112–114]. 4) Finally, elevated RA disease activity with persistent inflammation represents an independent and major risk factor for CVD [115,116].

In this context, IL-6 plays a role on several levels. Systemic inflammation and the acute phase response – assessed by CRP levels and ESR – are indeed associated with atherosclerosis. There are also clear links between IL-6 and CVD [117,118]. A meta-analysis showed that one standard deviation increase in IL-6 levels is associated with an adjusted relative risk of 1.25 (1.19–1.32) of non-fatal myocardial infarction or CHD death [119]. Using Mendelian randomization analysis, a study showed that single nucleotide polymorphisms of *IL6R* gene leading to a decrease in CRP levels were associated with a decreased odd of CHD events in the general population [120]. Indeed, IL-6 directly influences endothelium homeostasis and promotes the progression of atheroma. Elevated serum IL-6 levels were associated with higher coronary artery calcifications [121]. While favoring endothelial activation and monocyte recruitment to the atheroma, IL-6 together with angiotensin II influence atheroma stability [122–124].

The increased CV risk in RA is paradoxically associated with a decrease of total cholesterol levels [125]. This phenomenon – called *lipid paradox* – is probably due to the effects of IL-6 on lipid metabolism [126]. IL-6 is involved in adipose tissue metabolism [127]. Notably, high IL-6 levels are associated with an increased expression of lipoprotein(a) (Lp(a)), a known risk factor for premature atherosclerosis [128–130]. In RA, Lp(a) concentrations are elevated, and associated with disease activity and inflammatory biomarkers [131]. Resident macrophages and adipocytes are important sources of IL-6 in adipose tissue of obese patients, and contribute to insulin resistance [132,133]. A recent cohort study of RA patients showed that IL-6 was independently associated with the incidence of type 2 DM [134].

In mice, IL-6 treatment induced an increase of very-low-density lipoprotein receptor in various tissues, and decreased circulating total cholesterol and triglyceride levels. In the same mice, anti-IL6R antibody reversed these lipid level changes [135]. In RA patients, low-density lipoprotein cholesterol (LDL-C) and high-density lipoprotein cholesterol (HDL-C) increased more with tocilizumab compared to adalimumab. However, known lipid and lipid-associated CV-risk biomarkers (including HDL-SAA, secretory phospholipase A2 IIA and Lp(a)) decreased more with tocilizumab than with adalimumab [136]. Another study, comparing levels of biomarkers associated with CVD in RA patients whose disease was insufficiently controlled by TNF inhibitors, showed a similar effect of different biological treatments on CV risk-associated biomarkers. However, tocilizumab was associated with a better improvement of Lp(a) level and leptin/adiponectin ratio [137].

Regarding insulin resistance, an observational study demonstrated a significant reduction of glycosylated hemoglobin (HbA1c) in RA patients treated with tocilizumab and TNFi. This decrease was numerically higher for tocilizumab compared to TNFi [138]. Sarilumab was also associated with decreased HbA1c levels in a post hoc analysis regrouping three placebo-controlled phase III studies [139].

The overall effects of IL-6 blockade on CV outcomes appear favorable. A *meta*-analysis concluded that tocilizumab had a CV safety profile similar to that of other biological agents, despite the increase in cholesterol levels [140]. A retrospective post-hoc study in tocilizumab-treated RA patients showed that the risk of major cardiac events was not related to changes of lipid levels over the first 24 months of therapy, but rather to the control of disease activity [141]. Long-term exposition to tocilizumab was associated with a decreased incidence of serious infections and serious cardiac dysfunctions [142]. The development of acute myocardial infarction in RA patients using tocilizumab tends to be low, even compared to patients with TNFi and abatacept [143]. Long term safety of sarilumab showed comparable results [144].

Moreover, IL-6 blockade seems to have some beneficial effects on cardiovascular system. A pilot study showed an improvement of vascular endothelial function (assessed by brachial artery flow-mediated vasodilatation and carotid to femoral pulse wave velocity) in RA patients after 3 and 6 months of tocilizumab treatment [145]. In RA patients without cardiac symptoms, tocilizumab improved cardiac ejection fraction assessed by cardiac magnetic resonance [146]. Apart from rheumatologic conditions, a large cohort of patients with heart failure showed that circulating levels of IL-6 were significantly increased in more than half of patients with heart failure, and were associated with poorer outcome [147]. These data support the use of IL-6 blockade in RA patients with CV disease, and more generally, suggest that IL-6 inhibition could offer interesting perspectives in individuals with CV disease.

3.3. *Influence of IL-6 on neuroendocrine system*

Patient-reported outcomes (PROs) include symptoms related to pain, function and global assessment of disease activity, overlapping with the concept of health-related quality of life [148]. RA is frequently associated with symptoms such as pain, fatigue and mood disorders that all have a significant impact on the quality of life [149–151]. Thus, PROs remain as relevant for disease activity assessment as traditional outcomes based on less subjective variables [152–155].

Fatigue and sleep disturbance are very common in RA, with a prevalence 4 to 8-times higher than in the general population [156]. The causal factors of fatigue are multifactorial and appear to be related more to pain and impaired function than to inflammation itself [157,158]. Pain accompanying RA is also multifactorial, involving local inflammation and joint damage, but also peripheral and central nociception [159,160]. Same observations can be made for depression and mood disorders that readily accompany RA [161]. Furthermore, fatigue, pain and mood are influencing each other, leading to mutual amplification of these symptoms [162,163].

Neurohormonal perturbations are partly responsible for these symptoms in RA, and are also driven by inflammatory processes. It is now well established that IL-6 is associated with neuroendocrine effects [164,165]. Interestingly, increased IL-6 levels have been observed in major depression [166,167]. In animal model, IL-6 knockout mice exhibit abnormal behaviors characterized by a resistance to stress [168]. Neural cells are indeed able to respond to IL-6 through *trans-signaling* [169–171]. Cytokines, including IL-6, can activate the hypothalamic–pituitary-adrenal (HPA) axis, resulting in increased levels of the stress hormone, cortisol [172,173]. However, patients with RA have decreased circulating cortisol concentrations, despite elevated IL-6 levels [174]. This may be due to hyporesponsive adrenal glands or to an altered HPA response to IL-6 [175]. In human and rat, there are some evidences that IL-6 and its circadian pattern of secretion are involved in

sleep regulation [176]. In addition, cerebral structures such as the hypothalamus, are able to produce IL-6 and increase its plasma concentrations in response to stress [177]. Thus, interactions between IL-6 and neuroendocrine responses are occurring in both directions. For instance, it has been shown that the emotional state during a noxious stimulus influences IL-6 levels [178]. IL-6 is also involved in nociceptive pathways, and seems to play a role in hyperalgesia. Neurons of the dorsal root ganglions express gp130 and exposure to IL-6 increases their responsiveness to painful stimuli [179]. Electrophysiological experiments in rats demonstrated that IL-6 is able to induce sensitization of C-fibers to mechanical stimulation [180]. Other experiments on rats also deciphered the role of IL-6 in central nociception through spinal cord neurons [181]. Thus, IL-6 is involved in both central (spinal and supra-supraspinal) and peripherical levels of nociception.

For these reasons, many studies have investigated the effects of IL-6R inhibitors on PROs. The RADIATE randomized controlled study was designed to investigate the effects of tocilizumab versus placebo on PROs in RA refractory to TNFi. Tocilizumab was clearly superior to placebo already after 2 weeks on several PROs, notably on pain (measured with a visual analogue scale), disability (assessed with the health assessment questionary, HAQ) and fatigue (evaluated by the Functional Assessment of Chronic Illness Therapy, FACIT, score) [182]. The adjunction of sarilumab to methotrexate also improved PROs in patients with inadequate response to methotrexate [183] or TNFi [184]. In the head-to-head MONARCH trial, sarilumab monotherapy was associated with a better improvement of PROs compared to adalimumab monotherapy [57]. The superiority of tocilizumab was also demonstrated for the composite PROs 7-domain score, RA Impact of Disease (RAID score) [185]. Regarding psychosocial symptoms, the randomized OPTION trial demonstrated a significant improvement of the mental component summary (MCS) score in the tocilizumab group compared to placebo [186]. The superiority of tocilizumab compared to adalimumab on same score was also observed in the ADACTA trial [54]. A cohort study showed improvement of scores reflecting depression (Hamilton Depression Score) and anxiety (Hamilton Anxiety Score) after tocilizumab introduction [187]. An observational study confirmed that tocilizumab use was associated with decreased depressive symptoms in RA patients compared to other biological agents [188]. However, a recent study, conducted in patients with planned allogenic hematopoietic stem cell transplantation, showed that a single dose of tocilizumab was not able to improve depressive symptoms. On contrary, it resulted in a significant worsening of multiple PROs [189]. This illustrates our still partial knowledge of the effects of IL-6 on the neuroendocrine system. Nevertheless, the vast majority of studies showed that IL-6 blockade is associated with improvement on pain, fatigue and mood disorders that accompany RA.

3.4. Role of IL-6 on muscle and bone homeostasis

IL-6 has also been described as a myokine that participates in the crosstalk between skeletal muscle and bone during exercise. IL-6 is indeed released upon muscle contraction with a marked increase in bloodstream during physical exercise [190]. It is hypothesized that the rapid release of IL-6 acts in a paracrine, autocrine and endocrine way to induce the metabolic adaptations in response to exercise (such as the induction of lipolyze/glycogenolysis and catabolism, activation of HPA axis, and bone turnover stimulation) [191]. Although IL-6 is known to be associated with insulin resistance, a study demonstrated that acute IL-6 treatment enhances glucose uptake by skeletal muscles [192]. On bone, IL-6 promotes osteocalcin bioactivation which further participates to the physiological adaptations to exercise [193]. It has been suggested that IL-6 release during exercise promotes also anti-inflammatory effects through induction of IL-10 and IL-1Ra [194]. However, IL-6 overproduction in inflammatory diseases such as RA has detrimental effects on both bone and muscle. Interestingly, transgenic mice overexpressing IL-6 present an amyotrophic phenotype that is reversed by IL-6R antibody treatment [195]. It is believed that age-related skeletal muscle wasting is in part due to the increase of plasmatic IL-6 levels during aging [196,197].

The effects of IL-6 on bone remodeling have been better studied. Chronic overexpression of IL-6 in transgenic mice induces important alterations in cortical and trabecular microarchitecture, and precludes the normal development of bone in prepubertal mice [198]. The same group showed that mice expressing high levels of IL-6 during the post-birth period developed growth impairment with a reduced level of insulin-like growth factor-I [199,200]. This finding enlightens mechanism of stunted growth that can be seen in systemic juvenile rheumatoid arthritis. Human trochanteric bone reverse transcription-polymerase chain reaction (RT-PCR) analysis showed increased expression of IL-6 and RANK mRNA in patients with femoral neck fragility-fracture compared to healthy bone obtained from cadavers [201]. IL-6 and its soluble receptor are able to induce the expression of receptor activator of nuclear factor-κB ligand (RANKL) by fibroblast-like synoviocytes, leading to osteoclast activation and bone resorption [26]. IL-6R *trans*-signaling also appears to be involved in postmenopausal osteoporosis [202].

Musculoskeletal manifestations of RA are not limited to the joints. The disease commonly affects muscle and bone compartments, notably osteoporosis and sarcopenia [203,204]. Patients with RA have a 2- fold increased risk of osteoporotic fractures compared to a matched control-population [205]. The origin is multifactorial, including disease duration and activity, and the use of some treatments such as glucocorticoids, opioids and selective-serotonin reuptake-inhibitors [206,207]. Despite marked improvement in RA management, the risk of vertebral fracture remains high in RA [208]. Osteoporosis is indeed still frequent, with a prevalence around 30% in a RA cohort [209]. However, analysis from the German National Database confirmed a decrease of osteoporosis prevalence in RA compared to the previous decade, indicating a beneficial effect of the use of more recent RA treatments [210]. Regarding muscle mass, a recent meta-analysis reported a 31% prevalence of sarcopenia in RA (i.e. 3 times higher than in the general population) [211]. In this study, disease activity was a predictive factor for sarcopenia, as well as the use of glucocorticoids [212]. In addition, sarcopenia is also associated to vertebral fractures in RA, having a synergistic effect with osteoporosis [213].

To date, there is no evidence that IL-6 blockade protects against fragility fractures. A recent cohort study did not find any difference in the risk of fractures between the different biologics used in RA [214]. However, in the MONARCH trial, procollagen type 1 N-terminal propeptide (P1NP), a marker of bone formation, increased more in the sarilumab group compared to adalimumab. Similarly, patients treated with sarilumab had a greater reduction of RANKL compared to those treated with adalimumab [65]. In a prospective study, tocilizumab was associated with a decrease of C-terminal cross-linking telopeptide of type I collagen (CTX), another biomarker of bone resorption, and with increased bone mineral density after 2 years in ACPA-positive RA patients [215]. Less is known about the effect of IL-6 blockade on skeletal muscle. The use of tocilizumab in RA is associated with weight gain [216]. A recent study showed that this observation was partly related to muscle gain (with a reduction of sarcopenia prevalence) [217]. Overall, there are indirect evidences that IL-6 blockade is associated with improved muscle and bone function in RA.

4. Systemic adverse effects of IL-6 blockade in rheumatoid arthritis

Considering IL-6 broad spectrum of activities, IL-6 blockade is obviously associated with a variety of adverse effects. As for other biologic (bDMARDs) or conventional synthetic (cs)DMARDs, the major safety concern of IL-6 inhibitors is the occurrence of serious infections due to their immunosuppressive effects [218,219]. The role of IL-6 in host defense against infections has been reviewed elsewhere [220]. In

addition, RA confers an increased risk of serious infections, which is associated with higher mortality rate compared to the general population [221,16,17]. This increased risk appears to be related to disease activity [222]. Biological DMARDs are also associated with an increased risk compared to csDMARDs [223].

A large US multi-database cohort showed no difference in the risk of serious infections between RA patients treated with tocilizumab compared to other biologics or tofacitinib, a Janus kinase inhibitor. But, when used as a first line therapy, tocilizumab was associated with an increased risk for serious bacterial infections, including skin and soft tissue infections as well as diverticulitis compared to TNFi and abatacept [224]. A British prospective observational study also demonstrated an increased risk of tocilizumab compared to etanercept (hazard ratio (HR) of 1.22, with a 95% confidence interval (CI) between 1.02 and 1.47) [225]. The better safety profile of TNFi compared to tocilizumab was not confirmed in a Japanese cohort study adjusting for covariates [226]. Sarilumab had the same safety profile as tocilizumab regardless of the route of administration [227,228]. After a follow-up of 5 years, safety profile of sarilumab in RA refractory to TNFi remained unchanged. The most frequent adverse events were neutropenia with an incidence of 15.3 cases per 100 patients-years (PY) [229]. The incidence of serious infection was 3.9 per 100 PY, comparable to other bDMARDs. In a cumulative safety analysis, most frequent serious infections were pneumonia (with an incidence rate of 1 per 100 PY), followed by gastroenteritis and urinary tract infection [230]. In this study, tocilizumab was also associated with a slight increased risk of opportunistic infections (0.23 per 100 PY), with no case reported in the control group. These infections included mycobacterial (with 8 cases of *Mycobacterium Tuberculosis)*, and fungal (C*andidiasis*, P*neumocystis Jiroveci*, and C*ryptococcus*) infections.

Hepatic and gastrointestinal adverse events have been associated with IL-6 blockade. Indeed, IL-6 pathways are involved in liver homeostasis and regeneration [231,232]. Mice deficient for IL-6 are more prone to develop alcoholic and non-alcoholic fatty liver disease [233]. Thus, IL-6 inhibitors have been associated with significant transaminase elevations (with an estimated incidence of 1.3/100 PY), particularly when associated to other hepatotoxic drugs [230,234]. Results from an observational study showed that the increase of transaminase levels is more frequent among patients treated with tocilizumab than with TNFi [235]. However, these hepatic perturbations are reversible, and do not appear to be associated with long-term hepatic lesions [236,237]. In particular, no increase in malignant hepatic neoplasm was observed in patients treated with tocilizumab compared to other biologics [238]. Some case reports and post-approval studies identified also pancreatitis as a potential adverse effect of IL-6 blockade, possibly due to increased levels of triglycerides [239]. More importantly, RA patients receiving tocilizumab have a 2- fold higher risk of lower intestinal perforation compared to those receiving a TNFi [240]. An increased risk of intestinal perforation was confirmed with an adjusted HR of 4.5 (95% CI 2.01–9.99) [241]. One explanation could be the protective effect of IL-6 on intestinal mucosa. Indeed, experimental data have shown that IL-6 inhibits enterocytes cell death, and is involved in epithelial regeneration [242,243]. The fact that IL-6 blockade precludes the interpretation of acute phase biomarkers is also a potential factor that could delay recognition of serious infections or diverticulitis. Table 1 summarizes some of the main systemic side effects of IL-6 blockade. In general, real world registries tend to show that IL-6R inhibitors induce a rapid and long-term improvement of RA with a good safety profile [235,244,245,142]. A recent *meta*-analysis including 88 randomized controlled trials found that tocilizumab was associated with a better

Table 1
This table summarizes the effects of IL-6 on most RA comorbidities. The subsequent systemic effects associated to its blockade, whether beneficial or detrimental, are also presented. Abbreviation: ANC (absolute neutrophil count), bDMARD (Biologic Disease-modifying Antirheumatic Drug), CRP (C-reactive protein), ESR (erythrocyte sedimentation rate), GI (gastro-intestinal), LDL (low-density lipoprotein), TB (Tuberculosis).

RA comorbidities	IL-6 effects	Consequences of IL-6 blockade	Management of IL-6 blockade sides effects
Infections	Key regulator cytokine of both innate and adaptative immunity. Participates to the defense against bacterial and fungal pathogen [220]	**Beneficial**: Good safety profile compared to other bDMARD. Long-term use is associated with a decreased incidence of serious infections [142]. **Detrimental**: Suppression of fever and CRP [66,67]. Increase risk of serious bacterial infections, skin and soft tissue infections, and diverticulitis. Rare opportunistic infections (TB, fungi) [229,230].	Caution with CRP and ESR interpretation. Treatment interruption during active infection [252]. Perioperative interruption (>3 weeks before surgery) [253]. Avoid glucocorticoid co-medication. TB screening prior treatment initiation. Avoid IL-6 blockade if latent TB [254].
Cardiovascular diseases	Involved in endothelial activation and homeostasis; acceleration of atheroma [119-124]. Participates to lipid and glucide metabolism [125-134].	**Beneficial**: Good safety profile [140]. Reduction of glycosylated hemoglobin (HbA1c) [138,139]. Improvement of endothelial and cardiac function [146,147]. **Detrimental**: Increase of total cholesterol, LDL-cholesterol and triglyceride levels	Assessment of lipid profile at therapy initiation, and regular monitoring thereafter. Consider posology reduction [252], or concomitant use of statin [255].
Hematological	Stimulates hepatocytes to produce proteins involved in iron metabolism [74,75]. Stimulates thrombopoietin expression [88,89]. Interacts with neutrophil trafficking [97].	**Beneficial**: Reduction of hepcidin levels, leading to improvement of anemia of chronic disease [64,84,85]. **Detrimental**: Neutropenia (most often transient) [95]. Thrombocytopenia [54].	Neutrophils and thrombocytes monitoring: treatment interruption if ANC 0.5–1 $\times 10^9$/l. Discontinuation if ANC $< 0.5 \times 10^9$/l. Avoid initiation in patients with ANC $< 2 \times 10^9$/l [98]
Hepato-gastrointestinal	Involved in liver homeostasis and regeneration [231-234]. Protective effects on intestinal mucosa [242,243].	**Detrimental**: Elevated transaminases (reversible, and most often moderate) [235-237]. Increase risk of GI perforation [241].	Avoid concomitant use of other hepatotoxic drugs. Regular monitoring with dose adjustment if persistent transaminases elevation [237]. Caution in patients at risk for GI perforation (older age, comorbidities such as diabetes and diverticulitis, use of high dose glucocorticoids) [240].
Fatigue, pain and mood disorders	Activation and alteration of the hypothalamic–pituitary-adrenal (HPA) axis [172-177]. Central and peripherical pain control [178-181].	**Beneficial**: Improvement of patient reported outcome [182-187]. Decreased depressive symptoms in RA patients compared to other biological agents [188].	
Osteoporosis and sarcopenia	Osteoclast activation and bone resorption [26]. Chronic elevation of IL-6 promotes muscle wasting [195-197].	**Beneficial**: Improvement of biomarkers of bone resorption [214,215]. Potential muscle gain [216,217].	

improvement of disease activity with same safety profile compared to other bDMARDs and Janus kinase inhibitors in RA patients with inadequate response to at least one DMARD [246].

5. Conclusions

Originally named *B-cell stimulatory factor-2* but also *hepatocyte-stimulary factor* or *interferon-β2*, IL-6 is characterized by a wide spectrum of action mediated by its two signaling pathways. Having both pro- and anti-inflammatory properties, IL-6 is a key regulator of inflammation and immunity. Its involvement in the pathogenesis of RA comorbidities illustrates its pleiotropic effects. IL-6 is indeed associated with multiple biological activities distant from the site of inflammation. Likewise, IL-6 blockade has consequences far beyond the joints. The recent data on RA suggest beneficial effects of IL-6R inhibitors on many comorbidities. Overall, IL-6 inhibition is associated with improvement of several systemic manifestations, including anemia of chronic disease, CV events, bone and muscle functions, and neuro-psychological manifestations as assessed by PROs (mainly fatigue, mood disorders and pain). Importantly some of these systemic effects are not necessarily dependent on the clinical efficacy of IL-6 inhibition on joint inflammation.

Furthermore, IL-6R inhibitors and new antibodies directly targeting IL-6 have increasing therapeutic applications beyond inflammatory rheumatic diseases [247]. For instance, sirukumab, an IL-6 neutralizing antibody, is tested in patients with major depressive disorder in a phase II study. Recently, a prospective study showed improvement in periodontal status in patients with RA-associated periodontal disease [248]. Specific *trans-signaling* inhibition showed promising effect of olamkicept in patients with active inflammatory bowel disease in a phase 2 study [249]. Finally, as IL-6R inhibition was already approved for treatment of cytokine release syndrome [250], several retrospective studies and randomized trials were conducted to test IL-6 inhibition in severe acute respiratory syndrome associated to Covid-19 [251].

IL-6 biology, notably *trans-signaling* pathway and its systemic effects, remains only partially elucidated yet. The therapeutic potential of IL-6 blockade goes far beyond joints, and is probably still in early stages.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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