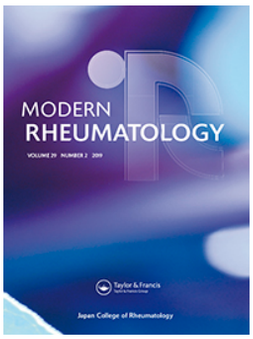

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REVIEW ARTICLE

IL-6 inhibitor for the treatment of rheumatoid arthritis: A comprehensive review

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ABSTRACT

Tocilizumab (TCZ) is an interleukin-6 (IL-6) inhibitor used for the treatment of rheumatoid arthritis (RA). It was developed in 2008, and its effectiveness is supported by evidence from all over the world based on its first decade of use. Although the overall efficacy and safety profiles of TCZ are similar to those of tumor necrosis factor (TNF) inhibitors, TCZ displays certain differences. The most notable advantage of TCZ is its usefulness as a monotherapy. Additionally, TCZ is favorable in the improvement of systemic inflammatory symptoms such as anemia and fatigue. The low immunogenicity of TCZ contributes favorably to long-term drug retention. Due to frequent relapse after TCZ cessation, TCZ use should be tapered beyond remission. During TCZ therapy, C-reactive protein (CRP) is unable to recognize disease activity and the severity of infection. The most common adverse events (AEs) are infection and abnormalities in laboratory findings including dyslipidemia, neutropenia, thrombocytopenia, and abnormality of liver enzymes. TCZ obscures the symptoms of infection. Therefore, stealth infections without obvious CRP elevation can sometimes cause severe damage to patients. Lower intestinal perforation is an uncommon but serious AE in TCZ therapy. Further clinical investigations will continue to refine the IL-6 inhibitory strategy.

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Interleukin-6; rheumatoid arthritis; tocilizumab; sarilumab; sirukmab

Introduction

Interleukin-6 (IL-6) is a major pro-inflammatory cytokine with pleiotropic functions [1]. Rheumatoid arthritis (RA) is a chronic autoimmune disorder, and IL-6 is a key player of immune activation and inflammation in RA. Therefore, IL-6 inhibition is a compelling strategy to control RA. Recently, several IL-6 inhibitors have become available for clinical use. Here we overview the recent advances in the IL-6 inhibition strategy for RA treatment.

Pathogenic role of IL-6 in RA

Increased levels of IL-6 have been detected in the sera and synovial fluid (SF) of RA patients [2]. Relatively higher IL-6 concentrations in SF indicated that the source of IL-6 was inflamed synovium caused by RA. Normal synovium consists of the intimal lining layer and the synovial sub-lining. In RA, thickening of the intimal lining layer, lymphocytic infiltration, formation of lymphoid follicles, and increased blood vessels can be observed in the synovium's so-called pannus formation [3]. The normal intimal lining is comprised of bone marrow-derived macrophages known as type A synoviocytes and resident fibroblast-like type B synoviocytes (FLSs). Type A synoviocytes mainly produce tumor necrosis factor (TNF), and FLSs mainly produce IL-6 [4,5]. The growth and activation of FLSs is autocrinally stimulated by TNF and IL-6. Such tumor-like FLS proliferations generate thickening of the intimal lining layer. Activated FLS also produces many bioactive substances including MMP, RANKL, VEGF, GM-CSF, and IFN. These, in turn, generate arthritic symptoms including joint pain, swelling, bone erosion, and cartilage destruction. IL-6 is released systemically and generates systemic symptoms including fatigue, anemia, and acute phase reactions. IL-6 also induces immune activation [6] and triggers the vicious circle of escalating RA disease activity. Figure 1 summarizes the role of IL-6 in RA pathogenesis.

As an animal arthritis model, SKG mice spontaneously develop T cell-mediated chronic autoimmune arthritis because of a mutation in ZAP-70, which is a key signal transduction molecule in T cells. In SKG mice, an IL-6 deficiency completely inhibits arthritis [7]. In collagen-induced arthritis (CIA), which is one of the most commonly used models of RA, blockades of both TNF and IL-6 inhibit arthritis [8,9]. By contrast, a blockade of TNF but not of IL-6 inhibited collagen antibody-induced arthritis, which eliminates the immune reaction of anticollagen antibody development [10]. These findings indicate that IL-6 is a particularly important autoimmune factor in RA.

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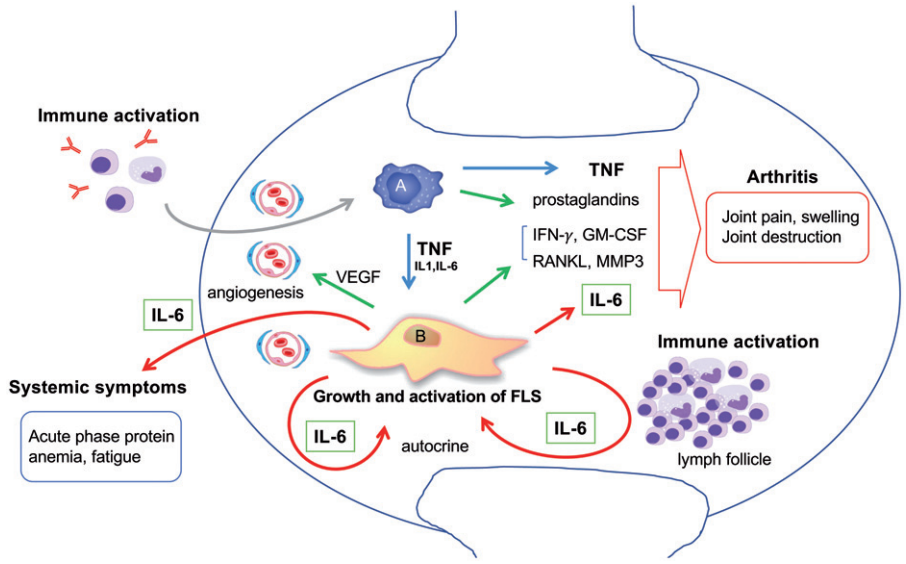

Figure 1. The pathogenic role of IL-6 in RA synovitis. There are the two main cellular components in the synovium. Type A synoviocytes are bone marrow derived macrophage-like cells. Type B synoviocytes are residential fibroblast like cells also known as FLS. In the rheumatoid synovium, FLS mainly contributes to arthritis by producing IL-6, RANKL, MMP3, GM-CSF, IFN-γ, and VEGF. TNF and IL-6 stimulate FLS autocrinally and induce tumor-like proliferation of FLS. Local arthritic symptoms are generated by the collaboration of IL-6 with TNF- and FLS-derived cytokines. Systemic symptoms are caused by IL-6. IL-6 also contributes to immune activation and leads to synovitis, resulting in a vicious circle.

Efficacy of the IL-6 inhibitor in RA

A humanized IL-6R antibody, tocilizumab (TCZ), was developed by collaborative research between the Chugai Pharmaceutical Company and Osaka University in Japan [11]. After seven major randomized clinical trials (RCTs), an intravenous formulation of TCZ (TCZ-IV) was approved for RA treatment in Japan in 2008, in Europe in 2009, and in the USA in 2010 [12]. Recently, a subcutaneous formulation of TCZ (TCZ-SC) was developed in consideration of patients' preferences. After a non-inferiority study of TCZ-SC and TCZ-IV [13], TCZ-SC was approved in Japan and the USA in 2013 and in Europe in 2014.

As shown in Table 1, TCZ displays a favorable efficacy in many RA patients, including disease-modifying anti-rheumatic drug (DMARD) naïve patients and patients with an inadequate response to conventional synthetic DMARDs (csDMARDs), methotrexate (MTX), or TNF inhibitors (TNFi) [12]. The overall efficacy including clinical responses and the radiographic damage progression of TCZ was comparable to that of other biological DMARDs (bDMARDs) such as TNFi [14,15]. The favorable efficacy of TCZ was also confirmed in real world clinical practice [16].

IL-6 particularly affects psychosomatic functioning, sleep-related symptoms, and fatigue [17,18]; therefore, TCZ improves sleep quality and fatigue [19,20]. The symptoms of sleep disturbance and fatigue are significantly correlated with diminished patient quality of life. Moreover, TCZ improved patient-reported outcomes according to the modified Health Assessment Questionnaire (mHAQ) including reduced morning stiffness and favorable EQ-5D responses [21,22]; it also ameliorated work impairment [23].

The amelioration of iron metabolism by IL-6 contributes to anemia associated with chronic inflammation. IL-6 induces the production of hepcidin, which is a liver-made peptide, proposed to be a central regulator of intestinal iron absorption and iron recycling by macrophages [18]. IL-6 also decreases transferrin, which is the primary iron transporter that delivers iron to the bone marrow for erythropoiesis [24]. Therefore, TCZ inhibits anemia associated with chronic inflammation [25]. In addition, TCZ improves insulin resistance [26] and may reduce HbA1c levels in diabetic patients with RA [27]. Given that IL-6 induces the serum amyloid A (SAA) protein [28], longstanding IL-6 production can evoke amyloid A amyloidosis, which is a serious renal complication in RA patients [29]. TCZ inhibits SAA production and eliminates amyloid deposition in amyloid A amyloidosis [30].

After TCZ therapy, inflammatory markers such as C-reactive protein (CRP) rapidly normalize. However, clinical symptoms improve gradually. Normal CRP is not directly correlated with clinical improvement of arthritic symptoms during TCZ therapy. The discordance between the improvement of inflammatory markers and clinical symptoms causes some confusion. Notably, normal CRP is only a marker of reaching a sufficient concentration of TCZ to inhibit IL-6 function; it is not a disease activity marker [31]. Therefore, inflammatory marker-containing composite measures, such as disease activity score-28 joints (DAS-28) or the simple disease activity index, may be unreliable for disease monitoring. A composite measure that does not contain any inflammatory markers such as the clinical disease activity index may be reliable for TCZ efficacy monitoring.

At the start of TCZ administration, serum IL-6 levels increase temporally. Therefore, the cessation of TCZ sometimes induces a disease flare. The so-called "Bathtub theory" illustrates the mechanism [12,31]. Given that TCZ does not inhibit IL-6 production directly, interfering with IL-6 binding to its receptor causes unbound IL-6 to accumulate in the serum. After the abrogation of immune activation, IL-6 serum levels gradually decrease. Thus, decreased CRP levels are not directly correlated with decreased IL-6 levels in TCZ therapy.

Table 1. The efficacy of TCZ in clinical study.

Study	Population	Evaluation	Treatment arms	*n*	ACr20 (%)	Remission (%)	Ref
AMBITION	MTX naïve	24 W	TCZ-IV (8 mg/kg)	286	70	34	37
			MTX	284	53	12	
SAMURAI	DMARDs-IR	52 W	TCZ-IV (8 mg/kg)	157	78	59	38
			DMARDs	145	34	3	
SATORI	MTX-IR	24 W	TCZ-IV (8 mg/kg)	61	80	43	39
			MTX	64	25	2	
TOWARD	DMARDs-IR	24 W	TCZ-IV (8 mg/kg) + DMARDs	803	61	30	40
			DMARDs	413	25	3	
RADIATE	TNFi-IR	24 W	TCZ = IV (4 mg/kg) + MTX	161	30	8	41
			TCZ-IV (8 mg/kg) + MTX	170	50	30	
			MTX	158	10	2	
OPTION	MTX-IR	24 W	TCZ-IV (4 mg/kg) + MTX	186	48	13	42
			TCZ-IV (8 mg/kg) + MTX	191	59	27	
			MTX	189	47	1	
LITHE	MTX-IR	52 W	TCZ-IV (4 mg/kg) + MTX	394	47	30	43
			TCZ-IV (8 mg/kg) + MTX	398	56	47	
			PBO	393	26	8	
MUSASHI	All DMARDs-IR	24 W	TCZ-SC (152mg q2w)	159	79	50	44
			TCZ-IV (8 mg/kg)	156	89	62	
SUMAACTA	All DMARDs-IR	24 W	TCZ-SC (162 mg qw) + DMARDs	572	69	37	45
			TCZ-IV (8 mg/kg) + MTX	564	74	38	
BREVACTA	All DMARDs-IR	24 W	TCZ-SC (162 mg q2w) + DMARDs	437	61	32	46
			PBO + DMARDs				
SHIOBI	TCZ-SC q2w-IR	12 W	TCZ-SC (162 mg qw)	21	52	19	47
			TCZ-SC (162 mg q2w)	20	20	10	

TCZ: tocilizumab; TCZ-IV: intravenous TCZ; TCZ-SC: subcutaneous TCZ; qw: every week; q2w: every other week; q4w: every 4 week; IR: inadequate response; MTX: methotrexate; DMARDs: disease modifying anti rheumatic drugs; ACR20: American college of rheumatology.

The efficacy of TCZ is dose dependent. The standard dose of TCZ for RA treatment is 8 mg/kg every 4 weeks (q4w). However, massive and continuous IL-6 producing diseases such as Castleman's disease or systemic juvenile idiopathic arthritis require TCZ-IV every 2 weeks (q2w). In RA patients who have high levels of IL-6 (high body weight or high disease activity), the efficacy of TCZ-SC q2w is sometimes insufficient, so reducing the interval between TCZ administrations, such as once a week, is preferable for disease control [32]. By contrast, a prolonged dose interval of TCZ-IV or TCZ-SC can sustain remission in RA patients who have low levels of IL-6 production [33,34].

The low necessity of MTX for maximizing the efficacy of TCZ is notable. Monotherapy with etanercept and adalimumab did not show superiority to MTX in the TEMPO and PREMIRE studies, which suggests the essential role of MTX in TNFi for RA treatment [35,36]. By contrast, TCZ monotherapy was superior to MTX in the AMBITION, SAMURAI, and SATORI studies [37–39]. Overall efficacy of TCZ was summarized in Table 1 [37–47]. In the ACT-RAY study, no clinically relevant superiority of the TCZ combination with csDMARDs over TCZ monotherapy for established RA patients was observed [48]. In the SURPRISE study, TCZ combination therapy with csDMARDs suppressed inflammation more rapidly than TCZ monotherapy, but the protocols became comparable at week 52 [49]. In the FUNCTION study, TCZ was similarly effective as monotherapy and in combination with MTX for the treatment of early (≤2-year disease duration) MTX-naïve RA [50]. In the U-ACT-Early study, TCZ with or without MTX was similarly more effective for sustained remission without an increased safety risk compared to MTX for the treatment of newly diagnosed csDMARD-naïve early RA [51]. These studies suggest that MTX is not essential for the antirheumatic effect of TCZ. Recently, a head-to-head comparative study of TNFi monotherapy and TCZ monotherapy was performed. The ADACTA study demonstrated that TCZ monotherapy was superior to adalimumab monotherapy [52]. However, the radiographic progression was inhibited to a greater degree in TCZ combination therapy with csDMARDs compared to TCZ monotherapy [49,53]. The combination of csDMARDs may have an additive effect with TCZ. Based on these accumulated findings, the 2016 update of The European League Against Rheumatism recommendations for the management of RA stated that "IL-6 pathway inhibitors may have some advantage in patients who cannot use csDMARDs as comedication" [54].

The antigenicity of TCZ is low [55]. Therefore, the overall drug survival of TCZ is favorable [56,57]. The drug survival of TCZ may be longer than that of TNFi [58]. Termination primarily occurs because of adverse events (AEs) rather than a lack of efficacy. The sustainability of TCZ-free remission was examined. In the DREAM study, 13.4% of patients maintained low disease activity for one year after TCZ (monotherapy) cessation [59]. In the ACT-RAY study, 8.6% of the add-on arm group (MTX + TCZ) and 3.1% of the switch arm group (TCZ without MTX) maintained remission at 52 weeks after TCZ cessation [60]. In the SURPRISE study, sustained remission rates of 24% for the add-on arm group (MTX + TCZ) and 14% for the switch arm group (TCZ without MTX) were reported one year after TCZ cessation [61]. These findings indicate that long-term TCZ-free remission is difficult to maintain. Although most patients eventually experienced flares, the restart of TCZ led to rapid improvement in disease activity [60,62]. By contrast, the dose reduction of TCZ [26,27] and the cessation of comedications such as corticosteroids or MTX displayed success in sustaining remission in RA patients [63,64]. The strategy after achieving remission remains unclear, but tapering TCZ may sustain remission to

Table 2. AEs of TCZ.

Rate/100 PY		Observation	Phase	Total AE	Serious AE	Serious infection	Refs.
TCZ-IV q4w combo	Pooled RCT	8,580 PY	III	278.2	14.4	4.7	65
TCZ-IV q4w mono	Pooled	2,188 PY	IV	465.1	–	6.2	66
TCZ-IV q4w mix	Japan (2008–2010)	3,831.8 PY	PMS	168.6	27.4	4.3	16
TCZ mix	Global (2008–2015)	22,394 PY	PMS	–	14.2	4.3	67
TCZ-IV q4w combo	ACT-SURE	767.7 PY	IIIb	593.0	7.8	5.1	68
TCZ-IV q4w combo	ACT-RAY (24 w)	118.32 PY	IV	491	21	6	48
TCZ-IV q4w mono	ACT-RAY (24 w)	116.4 PY	IV	467	14.4	4.7	48
TCZ-SC q2w mono	MUSASHI	561.71 PY	III	498.3	16.9	5.3	35
TCZ-SC q2w combo	BREBACTA	615.95 PY	III	332.8	11.2	3.3	69
TCZ-SC qw combo	SUMMACTA	298.82 PY	III	602.8	11.7	3.1	45
TCZ-SC combo	TOZURA	943.3 PY	IV	622.4	14.6	3.6	70
TCZ-SC q2w mix	Japan (2013–2016)	$N = 1,003$	PMS	94.4	13.9	4.5	71

TCZ: tocilizumab; TCZ-IV: intravenous TCZ; TCZ-SC: subcutaneous TCZ; AE: adverse events; combo, combination with DMARDs; RCT: randomized controlled trials; PY: patient years.

a greater degree in patients who achieved remission with TCZ therapy.

Safety of the IL-6 inhibitor in RA

The overall safety outcomes are summarized in Table 2 [16,45,48,65–71]. The most common AEs are infection and abnormal laboratory findings including neutropenia, thrombocytopenia, hyperlipidemia, and abnormality of liver enzymes such as alanine aminotransferase (ALT) and aspartate aminotransferase (AST). The network meta-analysis of controlled trials and open-label studies demonstrated that the safety profiles of TCZ were comparable to those of TNFi [72,73]. However, daily clinical practice including post-marketing surveillance (PMS) in Japan suggests that the incidence of AEs during TCZ therapy appears to have increased compared to other biologics in clinical practice [16,74]. One possible explanation is the incidence of stealth infections, which can cause severe damage to patients because TCZ obscures the symptoms of infection [75]. Overlooking early symptoms of infection such as cough, sputum, nasal discharge, or sore throat when receiving TCZ therapy in daily clinical practice is a problem. However, most patients experience the above-mentioned signs or symptoms of infection before developing a serious infection [76]. Since the symptoms of infection are relatively mild during TCZ therapy, patients may postpone hospitalization; however, the increasing severity of the infection can significantly harm the patients. Patient education and accuracy of safety management in daily clinical practice is important.

A previous report demonstrated that bDMARDs in RA are associated with an increased risk of opportunistic infections (OIs), such as tuberculosis (TB) and herpesvirus-related infections, particularly in long-lasting disease [77]. There is no convincing evidence for the increased risk of *Pneumocystis jirovecii* pneumonia (PCP) or fungal infections [77]. The overall rate of OIs did not differ significantly between TCZ and TNFi therapies [78]. Among RA patients, the rates and adjusted hazard ratios of herpes zoster were similar among biologics, including TCZ [79]. The risk of reactivation of latent TB is not increased during TCZ treatment [80]. TB antigen-induced IFN-γ production is inhibited by TNFi but not by TCZ [81], suggesting that TB immunity may not inhibited by TCZ. Therefore, TCZ therapy may be safer than TNFi therapy in Tb infection. The incidence of PCP was similar among biologics, including TCZ [82]. The risk of reactivation of the hepatitis B virus (HBV) by TCZ is controversial [83,84]. Latent HBV infection, however, should be treated before TCZ therapy to prevent de novo hepatitis.

Neutropenia is frequently observed in RA patients undergoing TCZ therapy. However, neutropenia in patients taking TCZ does not appear to be associated with serious infections [85]. Although IL-6 can stimulate stem cell proliferation and the formation of multilineage blast cell colonies, IL-6 knockout mice displayed normal steady-state hematologic parameters [86]. TCZ does not directly affect neutrophil functions [87]. By contrast, IL-6 mobilizes neutrophils into the circulating pool from the marginated pool, which includes the lymph nodes and spleen [88]. Therefore, neutropenia induced by TCZ may reflect a shift of neutrophils to the marginated pool rather than myelosuppression. Although neutrophil recruitment to inflammation sites may be delayed, the overall host defense to infection is not significantly compromised by TCZ-induced neutropenia.

Thrombocytopenia is also frequently observed during TCZ therapy. Baseline platelet production is dependent on thrombopoietin (TPO), and IL-6 stimulates thrombopoiesis through TPO induction [89]. Therefore, mice lacking TPO or its receptor c-Mpl are profoundly thrombocytopenic whereas IL-6 deficient mice are not thrombocytopenic [90]. In normal physiology, platelets are continuously produced by megakaryocytes via an IL-6 independent process of platelet formation. Therefore, TCZ-induced thrombocytopenia was not associated with serious bleeding events in clinical trials.

Dyslipidemia is a common AE in TCZ therapy. In general population, dyslipidemia is associated with higher cardiovascular (CV) risk. However, this adverse alteration in the lipid profile by TCZ administration does not increase CV risk. Recent reports have demonstrated that the CV risk of TCZ were comparable to that of TNFi which reduce the risk for acute coronary syndrome [91–93]. In RA, reductions in high-density lipoprotein-cholesterol, low-density lipoprotein-cholesterol, and total cholesterol have been reported. Despite the reduction of lipids in the sera, RA patients have an increased CV risk, and the dampening of inflammation increases lipid moieties and reduces the risk of CV disease in RA patients [94]. Inflammation is linked with accelerated atherosclerosis

and associated with a paradoxical inversion of the relationship between CV risk and lipid levels in patients with untreated RA, recently coined the lipid paradox. IL-6 may up-regulates the expression of scavenger receptors, promotes foam cell formation, and enhances atherogenesis [95,96]. TCZ inhibits lipid uptake to atherosclerotic lesions, and non-uptake lipids may overflow into the serum.

Transaminase (AST and ALT) elevations induced by TCZ are frequent, but serious liver enzyme abnormalities are rare [97]. Most of the transaminase elevations occurred during the first year of treatment, and the incidence of liver enzyme abnormalities increased in patients who received MTX/DMARDs. In most cases, the serious increase in transaminase levels returns to normal after TCZ termination, and this elevation rarely repeats. The abundant expression of IL-6R on hepatocytes may reflect the direct liver damage caused by TCZ. However, TCZ does not have antibody-dependent cellular cytotoxicity activity. In addition, the incidence of elevated liver enzymes by the IL-6 ligand antibody Sirukumab is similar to that of TCZ [98], suggesting that the cause of liver damage is interfering with the IL-6 signal rather than direct toxicity. The main function of IL-6 in the liver is the induction of acute phase proteins such as CRP and SAA [28,99]. IL-6 also helps protect against liver damage and participates in regeneration of the liver [100]. Therefore, TCZ may interfere with recovery from liver injuries, such as those caused by MTX.

Gastrointestinal (GI) perforation is an uncommon but serious AE in TCZ therapy. The incidence of GI perforation was significantly increased in TCZ therapy compared to all other treatments [101,102]. In particular, the risk of lower GI tract perforation was significantly elevated with TCZ therapy. Physicians must be aware that lower GI perforation under TCZ treatment may not present typical symptoms such as acute abdominal pain. Diverticulitis or other GI conditions and corticosteroids are risk factors. In mice, IL-6 stimulates intestinal epithelial proliferation, decreases intestinal injury, and improves barrier function following ischemia reperfusion of the small bowel [103,104]. IL-6 null mice exhibited impaired recovery following massive enterectomy and increased apoptosis [104]. Therefore, TCZ may interfere with recovery from intestinal injuries caused by diverticulitis or other GI conditions. We should be aware that lower GI perforation may occur with only mild symptoms and without CRP elevation during TCZ therapy [102].

The incidence of malignancies in patients who were treated with TCZ is comparable to that of general RA patients. It is well known that the risk of lung and lymphocyte malignancies is increased in RA patients compared to the general population [105]. The incidence of all malignancies from TCZ therapy combined, excluding non-melanoma skin cancer (NMSC), was slightly increased compared to the general population, but the incidence of overall or site-specific malignancies was not increased [106]. The risks of malignancy excluding NMSC in RA patients who are initiating TCZ therapy versus TNFi are comparable [107]. IL-6 plays a prominent role in tumorigenesis and metastasis [108]. The modulation of immune cell function by IL-6 causes dysfunction of innate and adaptive immunity against tumors [109]. Therefore, the IL-6 targeting approach may desensitize and prevent the dysfunction of innate and adaptive immunity against tumors. Additionally, an IL-6 blockade does not affect CD19 chimeric antigen receptor (CAR) T cell-driven antileukemic cytotoxicity [110]. Therefore, TCZ is the mainstay pharmacologic therapy for cytokine release syndrome, which is a systemic inflammatory response caused by cytokines released by CAR T cell therapy [111].

IL-6 deficient mice displayed significantly delayed cutaneous wound healing compared to wild-type control animals [112]. This characteristic occurred because IL-6 is a growth factor of epidermal keratinocytes [113]. The American College of Rheumatology guidelines recommend five-week TCZ-IV holding and two-week TCZ-SC holding prior to surgery in patients undergoing arthroplasty; moreover, TCZ should be restarted after careful assessment of the patient's wound status and surgical and nonsurgical site infections [114]. However, no increase in complications of superficial or deep infections or delays in wound healing after joint surgery were reported in patients who ceased TCZ-IV administration two weeks prior to surgery and restarted TCZ two weeks after surgery [115]. The incidence of delayed wound healing in TCZ-treated RA patients was higher in patients with foot and spinal surgeries [116]. We should be aware that mild injuries often cause phlegmon without obvious symptoms during TCZ therapy. Wounds must be disinfected to prevent phlegmon development.

There is limited information on pregnancy outcomes in women exposed to TCZ. In an analysis of global pregnancy-related reports, an increased preterm birth rate was observed [117]. In Japan, the spontaneous abortion rate of TCZ-exposed women is comparable to the rate in the general population [118]. Both reports demonstrated no indication of a substantially increased malformation risk [117,118]. Although IL-6 plays important roles in reproductive performance, embryonal development, parturition, and postnatal development, IL-6 signal blockade with a rat antimouse IL-6 receptor antibody (MR16-1) and IL-6-deficient mice revealed no biologically important effects on fertility, embryonic implantation, or prenatal/postnatal development [119,120]. However, the expression of IL-6 is reduced in the endometrium of women with recurrent miscarriage and in the fetal-placental tissue of abortion prone CBA × DBA/2 mice, suggesting that insufficient local IL-6 levels may contribute to fetal loss [121]. We must be cautious regarding the administration of TCZ therapy during pregnancy.

Recent advancements in IL-6 inhibitors

A fully human monoclonal antibody against IL-6R, Sarilumab (SAR), was developed by Regeneron and Sanofi. SAR was approved in Japan, the US, and the EU in 2017. The affinity of SAR for the human IL-6R is greater than that of TCZ, and it has a prolonged half-life. The overall efficacy and safety of SAR seems to be comparable with TCZ in standard clinical doses [122,123]. By contrast, a fully human anti-IL-6 monoclonal antibody, Sirukumab (SIR), was withdrawn in 2017 because it increased overall mortality. The most commonly

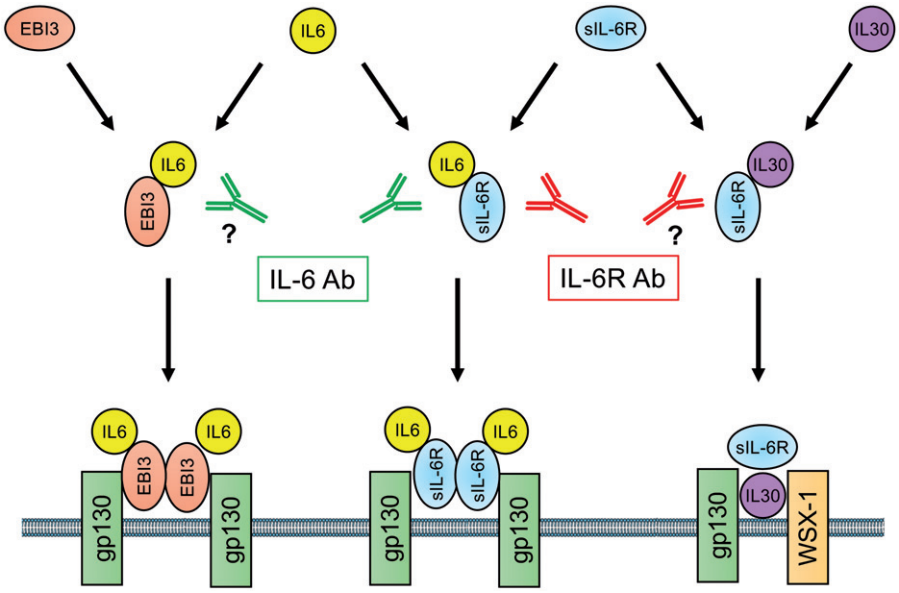

Figure 2. Differential inhibitory function of IL-6 signaling pathways by IL-6 and IL-6R antibody; a possible mechanism of action. Complexes of IL-6/IL-6R, IL-30/IL-6R, and IL-6/EBI3 can activate gp130, a cell surface signal transduction molecule. IL-6R antibody inhibit IL-6/IL-6R and IL-30/IL-6R but not IL-6/EBI3 dependent signal, whereas IL-6 antibody inhibits IL-6/IL-6R and IL-6/EBI3 but not IL-30/IL-6R dependent signal. IL-6: Interlukin-6; IL-6R: interleukin-6 receptor; IL-30: Interleukin-30; EBI3: Epstein-Barr virus-induced 3; WSX-1: interleukin-27 receptor α.

reported causes of death ($n = 30$) were major adverse CV events (MACE) (13/29), infection (7/29), and malignancies (4/29). Although IL-6 has a possible protective effect on cardiac ischemia reperfusion injury [124,125], there was no previous association with MACE with IL-6 inhibitors [66].

Interestingly, a recent report demonstrated that IL-6 can activate the MAPK cascade without sIL-6R in cardiomyocytes [126]. If so, the IL-6 inhibitor but not the IL-6R inhibitor may reduce MAPK activation, which is associated with the cardioprotective effect of IL-6. Attritionary wound healing and dextran sodium sulfate-induced colitis were also interfered in IL-6 deficient mice but not in IL-6R deficient mice [127,128]. These results suggest the existence of alternative IL-6 signaling pathways that do not use IL-6R. A recent report demonstrated that the Epstein-Barr virus-induced gene 3 (EBI3), which is a subunit of the composite cytokines IL-27, IL-35, and IL-39, can mediate IL-6 trans-signaling to gp130 [129]. This pathway does not use IL-6R: the IL-6 inhibitor, but the not IL-6R inhibitor, may interfere with EBI3-dependent signaling. In addition, IL-30, the p28 subunit of the heterodimeric cytokine IL-27, binds IL-6R and modulates inflammatory responses [130,131]. The IL-6R inhibitor, but not the IL-6 inhibitor, may interfere with IL-30 signaling. These characteristics can distinguish between the effects of the IL-6 inhibitor and the IL-6R inhibitor (Figure 2).

Conclusion

The IL-6 signaling inhibitory strategy for RA treatment is efficacious and tolerable. Features of the IL-6 inhibitors have been elucidated by many studies assessing TCZ treatment. There are currently multiple IL-6 inhibitors from which to choose (TCZ-IV, 4 or 8 mg/kg q4w; TCZ-SC, 162 mg qw/q2w; and SAR, 150 mg/200 mg q2w). The proper use of IL-6 inhibitors requires further determination. Future clinical investigations will help us determine the best use of IL-6 inhibitors.

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Conflict of interest

AO received honoraria for speech from Chugai Pharmaceutical Co, Asahi Kasei Pharm Co, Sanofi KK, Janssen Pharmaceutical KK, Pfizer Co, Bristol-Myers Squibb Co, Eisai Co, GlaxoSmithKline KK, Novartis Co, AYUMI Pharmaceutical Co, and consultant fee from Chugai Pharmaceutical Co. YK and SH have no conflicts of interest to disclosure. KY is a patent holder on the applied patent for the clinical use of tocilizumab on Still's disease. KY also received lecture fee from Chugai Pharmaceutical Co.

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