Targeting of Interleukin-6 for the Treatment of Rheumatoid Arthritis: A Review and Update

Tosho Tanaka1,2*, Atsushi Ogata1,2 and Tadamitsu Kishimoto3

1Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, Osaka University, Osaka, Japan
2Department of Immunoopathology, WPI Immunology Frontier Research Center, Osaka University, Osaka, Japan
3Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Osaka University, Osaka, Japan

Abstract

Rheumatoid Arthritis (RA) is a chronic inflammatory disease, characterized by persistent joint inflammation, systemic inflammation and immunological abnormalities. Since IL-6 plays a major role in the development of these characteristics, its targeting could reasonably be expected to constitute a novel therapeutic strategy for the treatment of RA. Tocilizumab, a humanized anti-human IL-6 receptor monoclonal antibody, has demonstrated its outstanding efficacy and tolerable safety profile in phase II clinical trials for RA patients, resulting in its worldwide approval for moderate-to-severe active RA. Post-marketing clinical trials have confirmed its efficacy. This success led to the development of various other IL-6 inhibitors. Further clinical studies including head-to-head comparative studies, and clarification of the mechanisms through which tocilizumab exerts its clinical effects can be expected to identify RA patients who should be treated with tocilizumab as a first-line biologic. In addition, recent case reports and pilot studies indicate that therapies targeting IL-6 will be widely applicable to the treatment of various intractable immune-mediated diseases.

Keywords: Rheumatoid arthritis; Interleukin-6; A humanized anti-interleukin-6 receptor antibody; Tocilizumab

Introduction

Rheumatoid Arthritis (RA), a chronic disease affecting 0.5-1% of adults, is characterized by persistent synovitis, systemic inflammation and immunological abnormalities. Uncontrolled active RA causes joint damage, disability, diminished quality of life and cardiovascular and other comorbidities [1,2]. Interleukin 6 (IL-6), a typical cytokine featuring redundancy and pleiotropic activity, plays a key role in the development of RA [3-7]. IL-6 promotes the imbalance between Th17 cells and regulatory T cells (Treg) and the production of autoantibodies such as Rheumatoid Factor (RF) and Anti-Citrullinated Peptide Antibody (ACPA). It also promotes synovial inflammation and cartilage and bone destruction as well as systemic features including cardiovascular, psychological and skeletal disorders. In this review article, we highlight the rationale for strategies targeting IL-6 for the treatment of RA, current evidence of efficacy and safety of tocilizumab, and discuss its place in the treatment of RA, current evidence of efficacy and safety of tocilizumab, a humanized anti-IL-6 receptor antibody, and discuss its place in the biological treatment of RA and assess the possibility of its widespread use for the treatment of various other immune-mediated diseases.

The Pathological Role of IL-6 in RA

Biological activity of IL-6 related to pathogenesis of RA

IL-6 was originally cloned in 1986 as a B cell stimulatory factor 2 that induces activated B cells to produce immunoglobulin [8]. Subsequent in vitro studies using recombinant IL-6 have demonstrated that IL-6 is a multifunctional cytokine [3,9,10]. RA is characterized by synovial inflammation and hyperplasia, immunological abnormalities leading to autoantibody production such as RF and ACPA, cartilage and bone destruction and systemic features [1,2]. Although the precise cause of RA remains unknown, it has been hypothesized that a multistep progression is required for the development of RA [2]. For the first step, environment-gene interactions promote loss of tolerance to self-proteins that contain a citrulline residue. This is followed by localization of the inflammatory response in the joints and synovitis, which is initiated and perpetuated by positive feedback loops, and in turn promotes systemic disorders. IL-6 appears to play a key role in all these steps in the progression of RA [4-7].

IL-6 contributes to the production of autoantibodies such as RF or ACPA by acting on plasmablasts [11]. Alternatively, IL-6 in the presence of transforming growth factor (TGF)-β promotes Th17 differentiation but inhibits TGF-β-induced Treg from CD4+ naïve T cells [12,13], leading to imbalance between Th17 and Treg. This imbalance is recently considered to contribute to the development of immunological abnormalities in RA [1,2,4-7].

Systemic inflammatory symptoms, signs and laboratory findings related to RA include fever, malaise, sleep disturbance, muscle weakness, anemia, thrombosis, C-reactive protein (CRP) elevation, hypercoagulability and hypoalbuminemia, and these are mostly mediated by IL-6. When IL-6 acts on hepatocytes, it induces a broad spectrum of acute phase proteins including CRP, Serum Amyloid A (SAA), haptoglobin, antichymotrypsin, fibrinogen and hepcidin, whereas it reduces the production of albumin, fibronecctin, transferrin and cytochrome p450 (CYPY) [14,15]. High levels of hepcidin induced by IL-6 block iron transporter ferroportin 1 on macrophages, hepatocytes and gut epithelial cells, leading to hypoferremia and anemia associated with chronic inflammation [16]. Long-term high concentrations of SAA lead to amyloid A amyloidosis, a serious complication of RA, in which amyloid fibril deposition causes progressive deterioration in various organs [17]. RA patients often suffer from thrombocytosis, also mediated by IL-6, which promotes the differentiation of megakaryocytes into platelets [18]. Furthermore, IL-6 reduces the activity of CYP and CYP3A4 isozyme in particular. Simvastatin is a CYP3A4 substrate, so that clinicians should exercise caution when

*Corresponding author: Tosho Tanaka, Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita City, Osaka 565-0871, Japan, Tel: +81-6-6879-3838; Fax: +81-6-6879-3839; E-mail: tanakai@med3.med.osaka-u.ac.jp

Received April 18, 2013; Accepted June 05, 2013; Published June 17, 2013


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co-prescribing IL-6 inhibitors and CYP-metabolized drugs such as simvastatin [19]. Cardiovascular events are the major determinants of poor prognosis for RA [20] and increased IL-6 expression is associated with the development of atherosclerosis and cardiovascular diseases such as obesity, myocardial infarction and type II diabetes [21,22]. IL-6 is also an important messenger molecule that connects peripheral regulatory processes with the central nervous system and affects sleep-related symptoms and fatigue, while changes in sleep duration and quality stimulate an increase in IL-6 concentrations in the circulation [23]. In addition, high levels of IL-6 reportedly increase the risk of muscle mass and strength loss [24,25].

IL-6 has been demonstrated to play a major role in local inflammation causing joint destruction by inducing endothelial cells to produce IL-8 and monocyte chemoattractant protein-1, and to activate expression of adhesion molecules and recruitment of leukocytes to involved joints [26,27]. Moreover, synoviocytes can produce IL-6 [28], while IL-6 can induce synoviocyte proliferation [29] and osteoclast differentiation through Receptor Activator of NF-kappa B Ligand (RANKL) expression [30,31]. This stimulation by IL-6 is also associated with the development of osteoporosis and fractures [32,33]. Enhanced angiogenesis and vascular permeability of synovial tissue are pathological features of RA resulting from the excess production of Vascular Endothelial Growth Factor (VEGF), which is induced by IL-6 in synovial fibroblasts [34,35]. Finally, IL-6 and IL-1 synergistically enhance the production of matrix metalloproteinases (MMPs) from synovial cells, which may lead to cartilage and joint destruction [36,37]. Therefore, IL-6 plays a key role in the induction of immunological abnormalities and in the development of joint and systemic inflammation of RA as well as its complications.

IL-6 expression and gene polymorphisms of IL-6 and IL-6 receptor in patients with RA

Elevated IL-6 levels were found in serum and synovial fluid of patients with RA [38-40]. These levels correlated with clinical symptoms such as morning stiffness, the number of involved joints and laboratory indices of disease activity [41-43]. Moreover, treatment with Disease-Modifying Antirheumatic Drugs (DMARDs) has been shown to be associated with reduced IL-6 serum concentrations and reduction of IL-6 during the first 12 months is reportedly a prognostic marker for clinical outcome [44].

Genetic polymorphisms (-622 or -174) in the IL-6 gene promoter, in which the -174 polymorphism was found to affect IL-6 levels [45], did not appear to increase susceptibility to RA [46]. However, a recent meta-analysis of nine studies regarding the association between IL-6 gene polymorphisms and RA showed that the -174 polymorphism might confer susceptibility to RA in Europeans [47]. Moreover, this polymorphism is reportedly associated with an increase in radiographic damage of joints in RA patients who were RF- or ACPA- positive [48] or with disease activity [49].

A single nucleotide polymorphism (rs8192284A>C) located at the proteolytic cleavage site of the IL-6 receptor (IL-6R) has been identified, which results in an amino acid substitution from aspartic acid to alanine (Asp358Ala) [50], while carriage of the C allele has been shown to correlate with higher levels of soluble IL-6R (sIL-6R) in Japanese [51] and Caucasian populations [52]. Although the positive association of plasma sIL-6R concentrations with the number of C alleles in RA patients is generally agreed upon [53], the results regarding the association between this IL-6R polymorphism and RA appeared complicated. It was previously demonstrated that concentrations of sIL-6R as well as IL-6 were higher in the serum of RA patients than in healthy controls [40] and that synovial levels of sIL-6R and IL-6 were significantly higher in RA than in osteoarthritic patients and correlated with the severity of joint damage [30]. On the other hand, it was demonstrated that the C allele frequency was not higher but lower in RA patients than in controls, which suggests that lower sIL-6R levels could be a risk factor for RA [54]. Moreover, two recent articles reported that the polymorphism of IL-6R, which results in higher serum concentrations of sIL-6R, is associated with a lower risk of coronary heart disease [55,56]. This has led to the hypothesis that the point mutation leads to an increased cleavage of the transmembrane IL-6R from the cell surface of hepatocytes, monocytes and macrophages and consequently to less IL-6-induced signaling by these cells [57]. Another hypothesis is that the reduced risk of coronary heart disease is due to a more efficient buffering of secreted IL-6 by the sIL-6R/soluble gp130 system and consequently to lower overall IL-6 activity [58].

Findings from RA animal models

Various RA models have been used for the pathological analyses of RA and for determining therapeutic targets, and evidence in support of the key role of IL-6 in the development of RA has come from many studies of RA animal models.

Collagen-Induced Arthritis (CIA) is the most well-known animal model of RA, in which injection of mice with type II collagen produces an immune response directed at connective tissues. In the CIA model, IL-6 has been shown to perform a major role in the development and progression of joint destruction since the incidence and severity of arthritis is reduced in mice with IL-6 gene deficiency or IL-6 blockade by means of anti-IL-6R antibody (Ab) [59-61]. Moreover, immunization with type II collagen predominantly increased the frequency of Th17 cells in the CIA model, while treatment of the mice with anti-IL-6R Ab during the priming markedly suppressed the induction of Th17 cells and arthritis development. However, treatment with the Ab on day 14 failed to suppress Th17 differentiation and arthritis [62].

IL-6 gene knockout mice with Antigen-Induced Arthritis (AIA), an immune complex model of RA, did not develop joint swelling, while CD4+ T lymphocytes from these mice showed reduced antigen-induced proliferation and produced less IL-17 and RANKL [63,64].

SKG mice spontaneously develop autoimmune arthritis with ageing due to a spontaneous mutation in the zeta-chain-associated protein kinase-70 (ZAP-70) gene, resulting in autoreactive peripheral T cells that cause arthritis [65]. Synovial fluids of arthritic mice were found to contain large amounts of IL-6, while IL-6 gene deficiency completely inhibited the development of arthritis, and 20% of tumor necrosis factor (TNF)-α-deficient mice developed arthritis [66]. Moreover, IL-6-deficient SKG mice completely lacked IL-17 producing CD4+ T cells, whereas TNF-α-deficient SKG mice possessed equivalent numbers of IL-17 producing CD4+ T cells as did intact SKG mice [67].

Human adult T cell leukemia virus (HTLV)-1 Tax transgenic mice constitute a genetically modified arthritis model and spontaneously develop arthritis [68]. IL-6 expression was found to be high in these mice [69], while IL-6 deficiency prevented the development of arthritis but TNF deficiency did not. Knock-in mice, known as F759 mice, with substitution of a mutation at position tyrosine-759 for phenylalanine in IL-6 family cytokine receptor subunit gp130, which is a binding site of the src homology 2 domain-bearing protein tyrosine phosphatase (SHIP)-2, spontaneously and age-dependently developed an RA-like joint disease featuring an increased number of autoreactive T cells and autoantibodies,
indicating that constitutive activation of IL-6 signaling is involved in the development of RA-like features [70]. The IL-6 amplifier loop, which features an age-dependent increase in Th17 cells, excessive IL-6 production, and is a positive feedback loop for NF-kB signaling, as well as a signal transducer and activator of transcription (STAT3) activation in non-immune cells, has been shown to be responsible for the development of arthritis in ageing F759 mice [71-73].

Arthritis of anti-type II collagen Ab-induced arthritis (CAIA) is another arthritis model but in this model the priming phase of T cell dependent Ab generation is skipped. Although IL-6 is also elevated in this model, arthritis is suppressed in TNF- but not IL-6-deficient mice, indicating that TNF plays a more significant role than IL-6 in joint inflammation in CAIA [74].

In a glucose-6-phosphate isomerase (GPI)-induced arthritis model, administration of anti-IL-6R Ab on day 0 or 3 suppressed Th17 differentiation and protected against arthritis induction while injection of the Ab on day 14, at the peak of arthritis, did not bring about any improvement in arthritis [75].

Stimulation of murine naïve CD4+ T cells with IL-6 and TGF-β, which are essential for the induction of Th17, induced a marked expression of the aryl hydrocarbon receptor (Ahr) [76], which is known as a dioxin receptor. Ahr is present in cytoplasm and, upon binding with a ligand, translocates to the nucleus and dimerizes with the Ahr nuclear translocator (Arnt). The resultant Ahr-Arnt complex binds to specific sequences, designated as xenobiotic responsive elements and exerts a variety of biological effects [77]. The experiments demonstrated that Ahr interacts with and negatively regulates both STAT1 and STAT5 activation, thus leading to the augmentation of Th17 differentiation. As expected, Ahr deficiency in T cells showed a significant reduction in Th17 [76] and suppressed the development of collagen-induced arthritis [78], pointing to the importance of the pathological IL-6-Ahr-Th17 axis in the RA model.

These observations obtained from various models of RA clearly indicate that IL-6 is essential for the induction of immunological abnormalities and the development of arthritis and that the pathological role of IL-6 is different from that of TNF-α which predominantly acts on the development of joint inflammation.

**Clinical Efficacy and Safety of Tocilizumab, a Humanized Anti-IL-6 Receptor Antibody for RA**

The findings described in the preceding section have led to expectations that targeting of IL-6 could be a novel treatment strategy for RA. IL-6 transmits its signal through binding to transmembrane IL-6R or sIL-6R [3,79-81]. After binding of IL-6 to IL-6R, the resultant IL-6/transmembrane IL-6R complex or IL-6/sIL-6R complex associates with gp130 and induces homodimerization of gp130, which triggers a signal transduction system [82,83]. Tocilizumab (TCZ) is a humanized anti-human IL-6R monoclonal Ab of the IgG1 class that was generated by grafting the complementarity-determining regions of a mouse anti-human IL-6R Ab onto human IgG1 [84]. TCZ blocks IL-6-mediated signal transduction through inhibition of IL-6 binding to transmembrane IL-6R and sIL-6R.

**Phase I/II clinical trials**

A randomized, double-blind, placebo-controlled, dose-escalation phase I trial was performed in the UK with 45 patients with active RA [85]. Patients were sequentially allocated to receive a single intravenous (IV) injection of 0.1, 1, 5 or 10 mg/kg of TCZ or placebo. At week 2, a significant difference was observed between the patients treated with 5 mg/kg of TCZ and with the placebo, with five patients (55.6%) in the TCZ cohort and none in the placebo cohort showing a 20% improvement according to the American College of Rheumatology (ACR) standards.

An open label phase I/II clinical study was performed in Japan with 15 patients with active RA [86]. Patients received IV administration of 3 doses (2, 4 or 8 mg/kg) of TCZ biweekly for 6 weeks with pharmacokinetic assessment. Safety and efficacy of the drug were evaluated after continuation of the TCZ treatment for 24 weeks. The treatment was found to be well tolerated at all doses with no severe adverse events (AEs). Although there was no statistically significant difference in efficacy among the three different dose groups, 9 of 15 patients (60%) achieved ACR20 response at week 6, while 86% achieved ACR20 and 33% ACR50 at week 24.

In a multicenter, double-blind, placebo-controlled trial, 164 patients with refractory RA were randomized to receive either TCZ (4 or 8 mg/kg) or placebo [87]. TCZ was administered IV three times every 4 weeks (q4w). After 12 weeks, ACR20 response was observed in 78%, 57% and 11% of RA patients treated with TCZ 8, 4 mg/kg and placebo, respectively.

The CHARISMA study was a phase II, double-blind, randomized, placebo-controlled, multicenter trial of TCZ with European RA patients who had showed an incomplete response to methotrexate (MTX) [88]. The 359 patients with active RA enrolled in this study were randomized to one of the following seven treatment arms: TCZ at doses of 2, 4 or 8 mg/kg, either as monotherapy or in combination with MTX, or MTX plus placebo. ACR20 response at week 16 was attained by 61% and 63% of the patients receiving 4 mg/kg and 8 mg/kg of TCZ as monotherapy, respectively, and by 63% and 74% of the patients receiving the same doses of TCZ plus MTX, respectively, compared with 41% of the patients receiving placebo plus MTX. Statistically significant ACR50 and ACR70 responses were observed in patients receiving combination therapy with either 4 mg/kg or 8 mg/kg of TCZ plus MTX.

**Phase III clinical trials**

Subsequent to phase I and II studies, seven phase III clinical trials of TCZ proved its efficacy either as monotherapy or in combination with MTX or other DMARDS for adult patients with moderate-to-severe active RA [89-97].

The SAMURAI study was the first phase III, double-blind, placebo-controlled, multicenter trial of TCZ to evaluate the ability of TCZ monotherapy to inhibit progression of structural joint damage [89]. The 306 patients with active RA of less than 5 years duration enrolled in this study were allocated to receive either TCZ monotherapy at 8 mg/kg q4w or conventional DMARDS for 52 weeks. At week 52, the TCZ group showed statistically significantly less radiographic change in the van der Heijde-modified Total Sharp Score (mTSS) (mean 2.3, 95% Confidence Interval (CI): 1.5 to 3.2) than the DMARD group (mean 6.1, 95% CI: 4.2 to 8.0, p<0.01). Signs and symptoms also improved with TCZ monotherapy.

The phase III, double-blind, placebo-controlled, multicenter TOWARD study was conducted to observe the effect of TCZ added to a stable dosage of conventional DMARDS for moderate-to-severe active RA in 1,220 patients with an inadequate response to DMARDS [90]. Patients remained on stable doses of DMARDS and received TCZ 8 mg/kg or placebo q4w for 24 weeks. At week 24, the percentage of patients attaining ACR20 response was significantly higher for the TCZ plus DMARD group than for the placebo group (61% vs. 25%, p<0.0001).
The RADIATE study examined the efficacy and safety of TCZ for patients with RA refractory to TNF inhibitor therapy [91]. A total of 499 patients with an inadequate response to one or more TNF inhibitors were randomly assigned to receive 8 mg/kg, 4 mg/kg TCZ or placebo with stable MTX for 24 weeks. ACR20 response was attained at week 24 by 50.0% of the patients in the 8 mg/kg, 30.4% in the 4 mg/kg, and 10.1% in the control group. 28-joint disease activity score (DAS28) remission rates (DAS28<2.6) at week 24 were clearly dose-related, being attained by 30.1%, 7.6% and 1.6% of the 8 mg/kg, 4 mg/kg and control group, respectively.

The aim of the multicenter double-blind, randomized, placebo-controlled, parallel group phase III OPTION study was to observe the therapeutic effect of TCZ added to a stable dosage of MTX on moderate-to-severe active RA of patients with an inadequate response to MTX [92]. For this study, 623 patients were randomized to receive TCZ (4 or 8 mg/kg) or placebo q4w, with MTX continued at stable pre-study doses (10-25 mg/week). Rescue therapy with TCZ (8 mg/kg) was offered at week 16 to patients with less than 20% improvement in both swollen and tender joint counts. The primary endpoint was the proportion of patients with ACR20 response at week 24, which was achieved by 59%, 48% and 26% of the patients in the TCZ 8 mg/kg, 4 mg/kg and control group, respectively. In the OPTION study, serum biochemical markers of bone formation (osteocalcin and N-terminal propeptide of type 1 collagen [PINP]), bone resorption (C-terminal crosslinking telopeptide of type I collagen [CTX-I] and CTX-I generated by matrix metalloproteinase [ICTP]), cartilage metabolism (N-terminal propeptide of type II collagen [PIANP] and collagen helical peptide [HELIIX―II]), and MMP-3 were measured [93]. At 4 weeks, TCZ had induced marked dose-dependent reductions in PIAINP, HELIX-II and MMP-3 levels, which were associated with enhancement of bone formation marker, PINP. TCZ also induced significant reductions in the bone degradation markers such as CTX-I and ICTP, indicating the beneficial effect of TCZ on bone turnover.

The SATORI study investigated the clinical efficacy and safety of TCZ monotherapy for active RA patients with an inadequate response to low dose MTX [94]. For this study, 125 patients were allocated to receive TCZ 8 mg/kg q4w plus MTX placebo or TCZ placebo plus MTX 8 mg/week for 24 weeks. At week 24, the ACR20 response rate was 80.3% for the TCZ and 25.0% for the MTX group. In fact, the ACR response of the TCZ group was superior to that of the MTX group at all time points.

The LITHE trial confirmed the efficacy of TCZ for preventing the progression of joint destruction. This study was a three-arm, randomized double-blind, placebo-controlled study [95]. Patients were randomized to receive TCZ (4 or 8 mg/kg q4w) plus MTX placebo or TCZ placebo plus MTX 8 mg/week for 24 weeks. At week 24, the ACR20 response rate was 60% for the TCZ and 20% for the MTX group. In fact, the ACR response of the TCZ group was superior to that of the MTX group at all time points.

The ACT-SURE trial was a phase IIIb, open-label, single-arm, 6-month study, which was conducted with a patient population resembling one to be expected in clinical practice [96]. Patients, who trial, 673 patients were randomized to receive either TCZ 8 mg/kg q4w, MTX starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks or placebo for 8 weeks followed by TCZ 8 mg/kg. Results for TCZ were better than for MTX treatment with a higher ACR20 response (69.9% vs. 52.5%, p<0.0001) and DAS28 remission rate (33.6% vs. 12.1%) at week 24.

The above trial data demonstrate the outstanding therapeutic efficacy of TCZ for adult patients with moderate-to-severe active RA. Outcomes attained in the seven phase III studies are summarized in Figure 1. TCZ has demonstrated its superior efficacy for the treatment of RA, either as monotherapy or in combination with MTX or other DMARDs, in comparison with control groups. As a result, TCZ has now been approved for the treatment of RA in more than 100 countries worldwide [4-7]. The recommended posology of TCZ is 8 mg/kg q4w in Japan and the EU. In the United States, the recommended starting dose is 4 mg/kg q4w followed by an increase to 8 mg/kg depending on clinical response.

Phase IIIb and IV clinical trials and clinical practice

In addition, the efficacy of TCZ was confirmed in subsequent clinical trials and actual medical practice.

The Rose study showed rapid improvement in clinical outcomes [98]. It was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter phase IIIb clinical trial. Patients were randomly assigned at a 2:1 ratio to administration of TCZ 8 mg/kg (n = 412) or placebo (n = 207) while background administration of DMARDs was continued for both groups. The primary efficacy endpoint, that is, the percentage of patients achieving ACR50 response at week 24, was higher for the TCZ than for the placebo group (30.1% vs. 11.2%, p<0.0001). A substudy examining early response to therapy showed improvement in patients’ global assessment of disease activity, pain and DAS28 for treatment with TCZ by day 7.

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Figure 1: The efficacy of tocilizumab in seven phase III trials. Tocilizumab as monotherapy or in combination with disease modifying antirheumatic drugs (DMARDs) or methotrexate (MTX) has shown superior efficacy compared with control in the treatment of RA. The percentages of ACR20, 50, 70 and remission responses evaluated at week 52 in SAMURAI and LITHE trials or at week 24 in other clinical trials are shown. TCZ: tocilizumab, IR: inadequate response.
were categorized as TNF inhibitor-naïve (never received TNF inhibitor), TNF inhibitor-previous (TNF inhibitor therapy discontinued for more than 2 months) or TNF inhibitor-recent (TNF inhibitor discontinued for less than 2 months), received open-label TCZ 8 mg/kg q4w with or without DMARDs for 24 weeks. A total of 1,681 patients (976 TNF inhibitor-naïve, 298 TNF inhibitor-previous and 407 TNF inhibitor-recent) were treated. Of the TNF inhibitor-naïve patients, 70.5% had attained ACR20, 51.9% ACR50 and 31.8% ACR70 responses at week 24, while for the patients with TNF inhibitor-previous the corresponding findings were 60.7%, 35.2% and 17.8%, and 62.7%, 42.3% and 19.7% for those with TNF inhibitor-recent.

The ACT-STAR study was a 24-week, prospective, open-label study conducted in the USA [100]. Of the 886 patients enrolled, 163 were assigned to monotherapy with TCZ 8 mg/kg. The remaining 723 patients were assigned to receive combination therapy, with 363 randomized to receive a starting dose of TCZ 4 mg/kg plus DMARDs and 360 a starting dose of TCZ 8 mg/kg plus DMARDs. The dosage for 152 patients (41.9%) of the initial TCZ 4 mg/kg plus DMARDs group was increased to TCZ 8 mg/kg plus DMARDs at week 8 and for 68 patients (18.7%) after 8 weeks. Overall, the 24-week study was completed by 82.5% of patients. By week 24, 49.7% of the patients in the 8 mg/kg TCZ plus DMARDs group had attained ACR20, 27.1% ACR50 and 10.3% ACR70, while the corresponding values for the patients in the 8 mg/kg TCZ monotherapy group were 47.9%, 24.5% and 7.4%. The efficacy of TCZ monotherapy and combination therapy with DMARDs was thus similar, while the safety profiles for the two groups were also similar.

For the TAMARA study conducted in Germany, 286 patients, 41.6% of whom had been previously treated with TNF inhibitors, were registered to determine the effectiveness and safety of TCZ [101,102]. Of the intention-to-treat patients, 57% attained the primary end point of low DAS (DAS<3.2), 47.6% showed DAS remission and a European League Against Rheumatism (EULAR) good response was attained by 54.9%, while ACR50/70 response rates at week 24 were 50.7% and 33.9%, respectively. Remission rates determined with the new ACR/ EULAR Boolean-based criteria for clinical studies were 15.0% after 12 weeks and 20.3% after 24 weeks, while the clinical disease activity index (CDAI) and simplified disease activity index (SDAI) remission rates were 24.1% and 25.2%, respectively.

In the nationwide registry of biological therapies established in Denmark, DANBIO, 178 patients with RA treated with TCZ have been identified, 93% of whom had previously received one or more TNF inhibitors [103]. The disease activity in these patients decreased at all time points, with DAS28 remission rates of 39% for TCZ treatment after 24 weeks and 58% after 48 weeks. EULAR good or moderate response rates were 88% at week 24 and 84% at week 48. These response rates were comparable to those for patients switching to their second TNF inhibitors as well as to those previously observed in phase III clinical trials.

In Japan, 229 patients were registered in the REACTION study to evaluate the efficacy and tolerability of TCZ in daily clinical practice for RA patients in Japan [104,105]. In this study, 55% of the patients received MTX concomitantly with TCZ and 63% had previously received anti-TNF treatment. Average DAS28 significantly decreased from 5.70 to 3.25 after 24 weeks of therapy. EULAR good response and DAS 28 remission response was attained after 24 weeks by 57.4% and 40.7% of the patients, respectively. After 52 weeks, clinical remission was observed in 43.7% of the patients, radiographic non-progression in 62.8% and functional remission in 26.4%. The retention rates at 24 and 52 weeks were 79.5% and 71.1%, respectively.

The ACT-RAY trial compared TCZ plus MTX therapy with TCZ monotherapy in a setting that closely resembled real-life clinical practice [106]. The trial was a double-blind, 2-year study in which patients whose RA had remained active in spite of MTX administration were randomly assigned to either continue MTX with the addition of TCZ 8 mg/kg q4w or switch to TCZ plus placebo. Of the 556 randomly assigned patients, 512 (92%) completed 24 weeks of the trial. ACR20/50/70 response rates were 71.5%, 45.5% and 24.5% for the TCZ plus MTX group and 70.3%, 40.2% and 25.4% for the TCZ plus placebo group, respectively, showing that TCZ plus MTX combination therapy was clinically not superior to TCZ monotherapy.

The Effect of tocilizumab on extra-articular symptoms and complications of RA

As described elsewhere, IL-6 also plays a role in the development of systemic inflammatory symptoms and complications related to RA, so that TCZ treatment was expected to ameliorate such symptoms and/or prevent the development of the complications.

Assessment of functional disability according to the Health Assessment Questionnaire Disability Index (HAQ-DI) [95,96,107] or of health status according to the Arthritis Impact Measurement Scale 2 (AIMS-2) and Short Form-36 (SF-36) showed improvements in patients with RA treated with TCZ [108]. Moreover, sleep quality assessed according to the Pittsburgh Sleep Quality Index (PSQI) improved while daytime sleepiness measured on the Epworth Sleepiness Scale and fatigue according to the Functional Assessment of Chronic Illness Therapy Fatigue Scale (FACIT-FS) significantly decreased after TCZ treatment [109].

Increased production of hepcidin induced by IL-6 was found to lead to anemia associated with chronic inflammation [16]. A significant improvement at week 12 in hemoglobin levels from 11.3 g/dL to 12.8 g/dL in patients with RA patients treated with TCZ [87] was perhaps due to down-regulation of hepcidin, which was seen in patients with multicentric Castleman disease treated with TCZ [110].

Amyloid A amyloidosis is a serious complication of RA and amyloid fibril deposition causes progressive deterioration in various organs [17]. Since the activation of the SAA gene depends primarily on IL-6 [111,112], TCZ injection promptly reduces serum concentrations of SAA, just as in the case of CRP, and the suppressive effect of TCZ on serum levels of SAA appeared to be more powerful than that of TNF inhibitors [113]. Case reports and series studies to date have demonstrated the prominent ameliorative effect of TCZ on gastrointestinal symptoms [114-116], cardiac disease [117] or renal dysfunction [118], due to amyloid A amyloidosis complicated with RA, and amyloid fibril deposits were found to have been eliminated in two cases after three injections of TCZ [114,116]. Moreover, a recent retrospective study demonstrated that TCZ was of greater clinical utility than TNF inhibitors in patients with amyloid A amyloidosis complicated with RA, evaluated by the ability to suppress SAA levels and the changes in the estimated glomerular filtration rate [119].

Cardiovascular events constitute the major determinant of poor prognosis for RA [20]. Lipid parameters such as high-density lipoprotein cholesterol, low-density lipoprotein cholesterol and triglyceride are often elevated during TCZ treatment but whether the increase is atherogenic remains to be determined [120]. In contrast, improvements due to TCZ treatment in serum biological markers related to atherosclerosis have been reported. IL-6 is reportedly involved in insulin resistance and development of type 2 diabetes mellitus [22,121,122], and we observed that TCZ treatment caused
a reduction in HbA1c levels in diabetic patients with RA [123]. The average HbA1c level of diabetic patients (n=10) significantly decreased from 7.2% to 6.4% before steroid tapering and one month after tocilizumab treatment and to 6.0% after 6 months. Insulin resistance indices, such as the Homeostasis Model of Assessment-Insulin Resistance (HOMA-IR) index and the leptin-to-adiponectin ratio, also improved in non-diabetic patients with RA after a 3-month treatment with TCZ [124]. RA patients treated with TCZ showed significantly lower levels of reactive oxygen metabolites than those treated with DMARDs or TNF inhibitors (infliximab or etanercept) [125]. Moreover, endothelial dysfunction and aortic stiffness of RA patients were recently found to have improved as a result of TCZ treatment [126,127]. The causal relationship between IL-6R gene polymorphism and coronary heart disease [55,56] as mentioned earlier and the findings reported here indicate that long-term TCZ treatment may offer protection against cardiovascular events. A randomized, open-label, parallel-group, multicenter study is in progress to evaluate the frequency of cardiovascular events following treatment with TCZ compared to that with etanercept for patients with RA.

These findings indicate the TCZ is efficacious for suppression of not only joint inflammation but also of systemic inflammation, thus leading to better prognosis.

**Safety profile of tocilizumab**

The safety profiles of TCZ monotherapy for Japanese RA patients were obtained from six initial trials and five long-term extensions [128]. For these studies, 601 patients with a total exposure to TCZ of 2,188 patient years (pt-yr) were enrolled. The median treatment duration was 3.8 years. The incidence of AEs, including abnormal laboratory test findings, was calculated as 465/100 pt-yr, with infections being the most common serious AEs (6.2/100 pt-yr). The results of an interim analysis of a post-marketing surveillance of all patients treated with TCZ in Japan were also reported [129]. This analysis comprised 3,881 patients who received 8 mg/kg of TCZ q4w and were observed for 28 weeks. Occurrence of a total of 3,004 AEs for 1,641 patients (167/100 pt-yr) and 490 serious AEs for 361 patients (27/100 pt-yr) were recorded. The most frequent AE and serious AE was infection at 31/100 pt-yr and 9/100 pt-yr, respectively, with the majority of infections being pneumonia and cellulitis. Abnormalities in laboratory test findings, such as increases in lipid and liver function parameters were common and total and serious AEs associated with laboratory test abnormalities were 35/100 pt-yr and 2/100 pt-yr, respectively. While white blood cell and neutrophil counts usually decreased just after TCZ injection, the Th17/Treg imbalance [13,146,147], which is thought to be a causal relationship between IL-6R gene polymorphism and coronary heart disease [55,56] as mentioned earlier and the findings reported here indicate that long-term TCZ treatment may offer protection against cardiovascular events. A randomized, open-label, parallel-group, multicenter study is in progress to evaluate the frequency of cardiovascular events following treatment with TCZ compared to that with etanercept for patients with RA.

The reactivation of tuberculosis is a major concern during anti-TNF treatment [131], but there is no medical consensus regarding the effect of IL-6 blockade on tuberculosis. Okada et al. examined the effects of IL-6 and TNFα blockade on the development of tuberculosis infection in mice and observed that there was less tuberculosis infection for anti-IL-6R Ab than for anti-TNFα [132]. In addition, we were able to show that tuberculosis antigens-induced interferon (IFN)-γ production was suppressed by the addition of TNF inhibitors (infliximab and etanercept) but not of TCZ [133]. Although it seems likely that the incidence of reactivation of tuberculosis is lower during TCZ treatment than that during anti-TNF treatment, more detailed studies will be needed for further clarification.

Although dysregulated persistent production of IL-6 plays a pathological role in the development of RA, IL-6, when transiently produced in response to environmental stress such as infections and injuries, contributes to host defense [3-7,9,10]. Previously it was found that cutaneous wound healing in IL-6 gene-deficient mice was significantly slower than that in wild type control mice [134-136]. It was found that gene expression enhancement of IL-1, chemokines, adhesion molecules, TGF-β1 and VEGF at the wound sites was significantly reduced in IL-6-deficient mice [136]. Moreover, reduction of the wound area was delayed due to attenuated leukocyte infiltration, re-epithelialization, angiogenesis and collagen accumulation. IL-6 is also important for tendon [137], bone fracture [138] and intestinal wound healing [139]. These findings indicate that TCZ treatment may result in delayed wound healing [140]. The TOPP study examined 161 Japanese orthopedic surgery cases during TCZ treatment [141] and found that infection rates of patients treated with TCZ were not noticeably high whereas incidence of delayed wound healing was indeed significantly higher in cases having undergone surgical interventions such as foot and spinal surgeries. Moreover, in patients treated with TCZ, the normal postoperative rise in temperature and CRP were both suppressed, thus potentially masking signs and symptoms of infection [142,143]. These observations suggest that, for reasons of safety, elective surgery needs planning for at least 2-3 weeks after the last administration of TCZ and a 2-week waiting period before restarting TCZ, since TCZ has an 11-13 day half-life depending on dose.

**Mechanisms involved in the efficacy of tocilizumab**

TCZ treatment led to improvements in serological or urinary markers related to bone and cartilage metabolisms [93,144,145]. The treatment also reduced circulating RANKL and VEGF concentrations [34,94] as well as RANKL expression in bone marrow tissues [145]. Moreover, several immunological analyses have been performed to clarify the mechanisms through which TCZ exerts its efficacy. Of particular importance is to determine whether TCZ can repair the Th17/Treg imbalance [13,146,147], which is thought to be a fundamental immunological abnormality in RA. It was recently shown that after three injections of TCZ in 15 patients with active RA, levels of Th17 (CD4+IL-17+) cells in peripheral blood decreased while the tocilizumab treatment led to reductions in circulating RANKL and VEGF concentrations [93,144,145]. The results reported for a Japanese cohort study of RA. The results of this analysis thus indicated that the safety profile of TCZ is acceptable for clinical settings.

The same post-marketing surveillance found seven cases of gastrointestinal (GI) perforation in six patients. In the worldwide Roche clinical trials, 26 (0.65%) cases of GI perforation were found among patients with RA treated with TCZ for a rate of 1.9/1,000 pt-yr and most cases appeared to be complications of diverticulitis [130]. This rate is intermediate between the GI perforation rates of 3.9/1,000 pt-yr for corticosteroids and 1.3/1,000 pt-yr for anti-TNFα agents reported in the United Health Care database.

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Effect of TCZ on the B-cell compartment and found that it induced a significant reduction of peripheral pre-switch and post-switch memory B cells [151]. In addition, TCZ but not a TNF inhibitor (etanercept) significantly reduced somatic hypermutation in immunoglobulin gene rearrangements in pre-switch memory B cells [152], suggesting that modulation of memory B cells may be another possible target for TCZ.

Place of Tocilizumab in Biological Treatment of RA

A number of biologics are now available for the treatment of RA. These include TNF inhibitors (infliximab, etanercept, adalimumab, golimumab and certolizumab pegol), an IL-1 antagonist (anakinra), a B-cell depleter (rituximab) and a T-cell costimulation inhibitor (abatacept) as well as an IL-6R blocker (TCZ) [4]. It has not yet been determined which of these biologics should be selected for a given patient. Currently, one of the TNF inhibitors is recommended as a first-line biologic [153-155], but between 14 and 38% of patients show no or little response to anti-TNF treatment, with as many as 40% of patients discontinuing these drugs within a year and 50% within 2 years. As mentioned earlier, the RADIATE trial showed that RA patients who had previously discontinued TNF inhibitors achieved ACRO20/50/70 responses of 50%, 28.8% and 12.4%, respectively, in response to TCZ [91]. In addition, the ACT-SURE [99], TAMARA [101,102], DANBIO [103] and REACTION [104,105] trials also showed that TCZ was efficacious for patients with RA who had been previously treated with TNF inhibitors. At present, TCZ is likely to be prescribed as a second-line biological therapy and will have to overcome significant competition from established anti-TNF therapies to be accepted as a first-line biologic. Meta-analyses of indirect comparisons of the efficacy of TCZ and other biologics have demonstrated that the efficacy of TCZ for patients with established RA is comparable to that of other biologics, including TNF inhibitors, abatacept and rituximab [155-159]. A comparison of AEs associated with these biologics in a review by Cochrane showed that the frequency of AEs, serious AEs and serious infections occurring during TCZ treatment was comparable to that for other biologics [160].

Biological treatment for RA patients is recommended to be initiated when patients show an inadequate response to MTX or to MTX combined with other DMARDs, and TNF inhibitors are currently positioned as the first biologic in combination with MTX [153,154]. On the other hand, patients who cannot tolerate sufficient doses of MTX could be treated with TCZ because TNF inhibitors need MTX to achieve their full efficacy [161-163], whereas the effect of TCZ monotherapy, as shown in the ACT-RAY trial, is not inferior to that of combination therapies using MTX [106]. Moreover, a clinical trial was recently performed involving a head-to-head comparison of biologics. The ADACTA study compared the monotherapeutic efficacy of TCZ with that of adalimumab [164]. 325 patients were randomly assigned to receive TCZ 8 mg/kg q4w intravenously plus placebo subcutaneously, with that of adalimumab [164]. 325 patients were randomly assigned to receive TCZ 8 mg/kg q4w intravenously plus placebo subcutaneously. After 25 weeks, ACR20 response rates were 37.5%, 83.3% and 91.7% for 81 mg qw, 162 mg qw and 162 mg q2w, respectively.

The MUSASHI study was a Japanese phase III study of TCZ-SC monotherapy [166]. Patients with RA who had responded inadequately to DMARDs or biologics except for TCZ were randomized to receive TCZ-SC 162 mg q2w or IV injection of TCZ (TCZ-IV) 8 mg/kg q4w without any DMARDs. The primary endpoint was to assist whether TCZ-SC was inferior or not to TCZ-IV in terms of ACR20 response rate at week 24 in per protocol patients. The non-inferiority margin was predefined at 18% (based on the SATORI study of monotherapy). A total 346 patients were enrolled (173 in TCZ-SC and 173 in TCZ-IV). Baseline demographics of the TCZ-SC and TCZ-IV groups were comparable, including body weight (53.8 ± 8.7 kg for TCZ-SC and 54.4 ± 10.1 kg for TCZ-IV). At week 24, 79.2% (95% CI: 72.9-85.5%) of the TCZ-SC patients and 88.5% (95% CI: 83.4-93.5%) of the TCZ-IV patients had attained an ACR20 response for a difference of -9.4% (95% CI: -17.6 to -1.2), thus confirming the non-inferiority of TCZ-SC to TCZ-IV. ACR50/70 response and DAS28/CDAI/Boolean remission rates were also similar for the two groups. Although safety profiles were also comparable, anti-TCZ Abs were detected more frequently in the TCZ-SC than in the TCZ-IV group. However, this anti-TCZ Abs did not affect the efficacy and were not related to anaphylactoid reaction.

The SUMMACTA study is a 2-year phase III study including a 24-week double-blind period, followed by a 72-week open-label phase. Patients were assigned to receive TCZ-SC 162 mg qw or TCZ-IV 8 mg/kg q4w, in combination with traditional DMARDs [167]. The primary end point to determine whether TCZ-SC was inferior or not to TCZ-IV was the percentage of patients in each group having met the ACR20 improvement criteria at week 24. The 1,262 patients enrolled in this study were stratified by body weight. Mean baseline characteristics of the TCZ-SC and TCZ-IV group were similar. The Supposition of the non-inferiority of TCZ-SC was tested by means of 95% CI and with the supposition of the non-inferiority of TCZ-SC to TCZ-IV was predefined at 18% (based on the SATORI study of monotherapy). A total 346 patients were enrolled (173 in TCZ-SC and 173 in TCZ-IV). Baseline demographics of the TCZ-SC and TCZ-IV groups were comparable, including body weight (53.8 ± 8.7 kg for TCZ-SC and 54.4 ± 10.1 kg for TCZ-IV). At week 24, 79.2% (95% CI: 72.9-85.5%) of the TCZ-SC patients and 88.5% (95% CI: 83.4-93.5%) of the TCZ-IV patients had attained an ACR20 response for a difference of -9.4% (95% CI: -17.6 to -1.2), thus confirming the non-inferiority of TCZ-SC to TCZ-IV. ACR50/70 response and DAS28/CDAI/Boolean remission rates were also similar for the two groups. Although safety profiles were also comparable, anti-TCZ Abs were detected more frequently in the TCZ-SC than in the TCZ-IV group. However, this anti-TCZ Abs did not affect the efficacy and were not related to anaphylactoid reaction.

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parallel-group study [168]. A total of 656 patients were randomized to receive TCZ-SC 162 mg q2w or placebo-SC for 24 weeks, combined with stable doses of pre-study DMARDs. Significantly more patients receiving TCZ-SC had attained an ACR20 response at week 24, compared to those in the placebo-SC group (60.9% vs. 31.5%). Mean change in mTSS from baseline at week 24 was also significantly less for the former than the latter (0.62 ± 2.7 vs. 1.23 ± 2.8, p=0.0149). Injection site reactions occurred more frequently in the TCZ-SC group but hypersensitivity reactions were similar for the two groups. These studies demonstrated that subcutaneous administration of TCZ was efficacious for RA.

Furthermore, a new fully human Ab against IL-6R (SA237), generated from TCZ by means of Ab structural optimization technology, has been developed and this IgG2 class Ab significantly improved the pharmacokinetics and duration of CRP inhibition in cynomolgus monkeys [169].

The success of the clinical indication of TCZ for the treatment of RA has made it clear that targeting of IL-6 could be a new treatment strategy for RA, so that other IL-6 inhibitors are now being developed [170]. These include fully human anti-IL-6R Ab (REGN88/SAR153191 [sarilumab]), anti-IL-6R nanobody (ALX-0061), anti-IL-6 Ab (CNTO 136 [sirilumab]), ALD518 [BMS-945429], CDP6038 [olokizumab], and MED15117 and soluble gp130-Fc fusion protein (FE301) (Table 1).

Sarilumab (REGN88/SAR153191) is a fully human monoclonal Ab directed against IL-6R. The phase II MOBILITY study, part A, involved 306 patients, who were randomized to a 12-week administration of sarilumab 100 mg qw, 150 mg qw, 100 mg q2w, 150 mg q2w, 200 mg q2w or placebo added to stable MTX [171]. An ACR20 response after 12 weeks was seen in 49.0% of the patients receiving the lowest sarilumab dose regime and in 72.0% of the patients receiving the highest dose regime compared to 46.2% of those treated with placebo and MTX. The types and incidence of AEs were consistent with those previously reported for TCZ. The phase III MOBILITY study, part B, for RA (SARIL-RA-MOBILITY) is ongoing.

ALX-0061 is a 26kD bi-specific IL-6R targeting nanobody with monovalent binding to IL-6R and serum albumin. Nanobodies are therapeutic proteins based on the smallest functional fragments of heavy chain antibodies, naturally occurring in Camelidae, which possess a high degree of homology to human Ig VH domains. In a phase I/II trial of ALX-0061, 28 patients with active RA were included [172]. Patients were assigned to receive ALX-0061 3 mg/kg qw, 6 mg/kg q2w or placebo added to stable MTX therapy for 24 weeks. ACR20/50/70 response rates were 80%/50%/10% for the 3 mg/kg q4w group, 56%/56%/44% for the group receiving 6 mg/kg qw of ALX-0061 and 17%/0%/0% for the placebo-injected group.

Sirukumab (CNTO 136) is a human monoclonal Ab with high affinity and specificity for binding to IL-6. After completion of a phase I trial [173,174], 151 patients were enrolled in a phase II study [175]. The patients were randomized equally to receive SC injections of placebo q2w for weeks 0-10 and sirukumab 100 mg 2qw for weeks 12-24, and sirukumab 100 mg q2w, 100 mg q4w, 50 mg q4w or 25 mg q4w for weeks 0-24. At week 12 (pre-crossover), more patients receiving sirukumab were in remission than those given the placebo according to both Boolean- and SDAI-based ACR/EULAR criteria (2% vs. 0% and 6% vs. 3%). At week 24, high remission rates determined with ACR/EULAR or DAS28 (CRP) criteria had been attained with sirukumab at SC dose regimes ranging from 25-100 mg q2w-q4w. The types and incidence of AEs were consistent with those previously reported for TCZ [176]. A phase III trial of sirukumab for RA (the SIRROUND study) is ongoing.

Olokizumab (CDP6038) is a humanized monoclonal anti-IL-6 Ab. A phase I study demonstrated that olokizumab was tolerated at single doses of up to 3 mg/kg SC and 10 mg/kg IV with a median half-life of 31.1 days [178]. In a phase II trial to evaluate the efficacy and safety of olokizumab administered SC for 12 weeks, 220 patients were enrolled in this randomized, double-blind, placebo-controlled, dose-ranging study with TCZ as an active comparator. Patients were randomized to receive olokizumab 60 mg q2w, 60 mg q4w, 120 mg q2w, 120 mg q4w, 240 mg q4w or placebo. All patients received concomitant MTX treatment. A significant reduction in DAS28 at week 12 was observed for all olokizumab-treated groups relative to the placebo group. The exploratory analyses of these data suggest that the efficacy and safety of olokizumab and TCZ are comparable. A trial to determine the long-term tolerability of 120 mg SC olokizumab is also ongoing.

Another human anti-IL-6 Ab, MED15117, was developed in China. This IL-6 inhibitor was generated by means of variable domain engineering to achieve sub-picomolar affinity for IL-6 and with Fc engineering to enhance its pharmacokinetic half-life [179]. A phase I trial of IV injection of MED15117 (30 mg, 100 mg, 300 mg or 600 mg) for RA is in progress.

FE301, a fusion protein consisting of the extracellular region of gp130 and the Fc part of a human IgG1 Ab (sgp130-Fc) selectively inhibits IL-6 trans-signaling without affecting responses via the membrane-bound IL-6R [180]. Trans-signaling of IL-6 (signaling via soluble IL-6R) mainly activates various inflammatory cells, which do not express transmembrane IL-6R but express gp130, whereas classical-signaling via transmembrane IL-6R, which is expressed on cells limited to monocytes, macrophages and hepatocytes, mainly activates immune response [170]. FE301 can therefore be expected to prove to be an anti-inflammatory agent, which does not affect immunosuppression nor interferes with acute phase response. The clinical utility of FE301 is as yet unknown.

**Widespread Use of Tocilizumab for Various Immune-Mediated Diseases**

TCZ is now used as an innovative drug for RA in more than 100 countries worldwide and in several countries for systemic juvenile diseases.
idiopathic arthritis, polyarticular juvenile idiopathic arthritis and Castleman’s disease [4-7,181]. Because of the pathological role of IL-6 in various immune-mediated diseases, TCZ is expected to be used widely for the treatment of these and other diseases and favorable results of recent clinical trials and case reports have suggested that this is indeed a realistic expectation [146,147,182]. These other diseases include systemic autoimmunity diseases such as systemic lupus erythematosus, systemic sclerosis, polymyositis, vasculitis syndrome, relapsing polychondritis and Cogan syndrome in addition to organ-specific autoimmune diseases including autoimmune hemolytic anemia, acquired hemophilia A, and neumyelitis optica, as well as chronic inflammatory diseases such as adult-onset Still’s disease, Crohn’s disease, polymyalgia rheumatica, relapsing seronegative, symmetrical synovitis with pitting edema, graft-versus-host disease, Behcet’s disease, uveitis, Schnitzler syndrome, TNF-associated periodic syndrome, chronic infantile neurological cutaneous and articular syndrome, pulmonary arterial hypertension, as well as sciatica and atopic dermatitis. Some case studies have reported that TCZ was efficacious for spondyloarthritides such as ankylosing spondylitis. Many clinical studies have proved that IL-6 blockade treatment is efficacious for the treatment of RA and TCZ, a humanized anti-IL-6R Ab, is being used worldwide as an innovative drug for RA patients. Since several other biological agents have also been approved, the place of TCZ in biological treatment needs to be clarified. Present evidence suggests that TCZ can be recommended for RA patients who cannot tolerate sufficient doses of MTX, but further clinical studies are needed to clarify the best use of TCZ. Moreover, in view of the pleiotropic activity of IL-6, the strategy of targeting IL-6 can be expected to be applicable to the treatment of a wide variety of immune-mediated diseases and a number of clinical trials to verify this potential are in progress.

Conclusion

Many clinical studies have proved that IL-6 blockade treatment is efficacious for the treatment of RA and TCZ, a humanized anti-IL-6R Ab, is being used worldwide as an innovative drug for RA patients. Since several other biological agents have also been approved, the place of TCZ in biological treatment needs to be clarified. Present evidence suggests that TCZ can be recommended for RA patients who cannot tolerate sufficient doses of MTX, but further clinical studies are needed to clarify the best use of TCZ. Moreover, in view of the pleiotropic activity of IL-6, the strategy of targeting IL-6 can be expected to be applicable to the treatment of a wide variety of immune-mediated diseases and a number of clinical trials to verify this potential are in progress.

Acknowledgement

T. Tanaka has received grant and payment for lectures including service on speaker’s bureaus from Chugai Pharmaceutical Co, Ltd. A. Ogata has received a consulting fee as a medical adviser, grant, and payment for lectures including service on speaker’s bureaus from Chugai Pharmaceutical Co, Ltd. T. Kishimoto holds a patent for tocilizumab and has received royalties for Actemra.

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