Journal of
Clinical & Cellular Immunology

Tanaka and Kishimoto, J Clin Cell Immunol 2011, S6
DOI: 10.4172/2155-9899.S6-001

Review Article Open Access

Immunotherapy of Tocilizumab for Rheumatoid Arthritis

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Abstract

Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterized by persistent joint inflammation, systemic inflammation and immunological abnormalities. Because IL-6 plays a major role in the development of these characteristics, IL-6 blockade may reasonably be expected to constitute a novel therapeutic strategy for the treatment of RA. Phase III clinical trials of a humanized anti-human IL-6 receptor monoclonal antibody, tocilizumab, have demonstrated its outstanding clinical efficacy, either as monotherapy or in combination with disease-modifying antirheumatic drugs, for moderate to severe active RA patients. Although tocilizumab is currently recommended as a second-line biologic for RA patients whose response to one or more of TNF inhibitors is inadequate, further clinical studies including head-to-head comparative studies, and clarification of the mechanisms through which tocilizumab exerts its clinical effects are sure to identify RA patients who should be treated with tocilizumab as a first line biologic.

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

Abbreviations: VEGF: Vascular endothelial growth factor; RANKL: Receptor activator of NF-kB ligand; CRP: C-reactive protein; Treg: Regulatory T cells; RF: Rheumatoid factor; ACPA: Anti-citrullinated peptide antibody

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]. Interleukin 6 (IL-6) plays a key role in the development of RA by promoting local and systemic inflammation and by inducing immunological abnormalities which lead to the production of auto antibodies (in particular rheumatoid factor and anti-citrullinated peptide antibody) and to imbalance between Th17 and regulatory T cells (Treg). In this review article, we highlight the rationale for IL-6 blockade for the treatment of RA, current evidence of the efficacy of IL-6 blockade strategy as well as future possibilities.

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 differentiation factor that induces activated B cells to produce immunoglobulin [2]. Subsequent in vitro studies have shown that IL-6 is a multifunctional cytokine [3-5]. RA is characterized by immunological abnormalities as well as joint and systemic inflammation while IL-6 plays a key role in the development of these characteristics (Figure 1). IL-6 contributes to the production of auto antibodies such as rheumatoid factor (RF) or anti-citrullinated peptide antibody (ACPA), and generates autoreactive T cells by causing an imbalance between Th17 and Treg. IL-6 in the presence of transforming growth factor (TGF)-β promotes differentiation of $CD4^+$ naïve T cells into Th17 cells but inhibits TGF-β-induced Treg from $CD4^+$ naïve T cells [6,7]. The pathogenic mechanisms driving RA remain poorly defined. The imbalance between Th17 and Treg has recently been thought to contribute to the development of immunological abnormalities in RA [8,9]. Systemic inflammatory symptoms, signs and findings related to RA such as fever, malaise, anemia, thrombosis, C-reactive protein (CRP) elevation and hypoalbuminemia are mostly mediated by IL-6 [10]. When IL-6 acts on hepatocytes, it induces a broad spectrum of acute-phase proteins including CRP, serum amyloid A (SAA), haptoglobulin, antichymotrypsin, fibrinogen, and hepcidin, whereas it reduces the production of albumin, fibronectin, transferrin, and cytochrome p450 [10,11]. High levels of hepcidin induced by IL-6 block iron transporter ferroportin 1 on macrophages, hepatocytes, and gut epithelial cells, leading to low serum iron levels (hypoferremia) and anemia associated with chronic inflammation [12]. 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 [13]. RA patients often suffer from thrombocytosis, also mediated by IL-6, which promotes the differentiation of megakaryocytes into platelets [14].

IL-6 also plays a major role in local inflammation causing joint destruction by activating endothelial cells to produce IL-8, monocyte chemoattractant protein, expression of adhesion molecules, and recruitment of leukocytes to involved joints [15]. Moreover, IL-6 can induce synoviocyte proliferation [16] and osteoclast differentiation through receptor activator of NF-kappa B ligand (RANKL) expression [17-19]. Enhanced angiogenesis and vascular permeability of synovial tissue are pathologic features of RA, which result from the excess production of vascular endothelial growth factor (VEGF), which is induced by IL-6 in synovial fibroblasts [20]. Finally, IL-6 and IL-1 synergistically enhance the production of matrix metalloproteinases from synovial cells, which may lead to cartilage and joint destruction [21].

Findings from RA animal models

Evidence in support of the key role of IL-6 in the development

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Received October 17, 2011; **Accepted** November 17, 2011; **Published** November 19, 2011

Citation: Tanaka T, Kishimoto T (2011) Immunotherapy of Tocilizumab for Rheumatoid Arthritis. J Clin Cell Immunol S6:001. doi:10.4172/2155-9899.S6-001

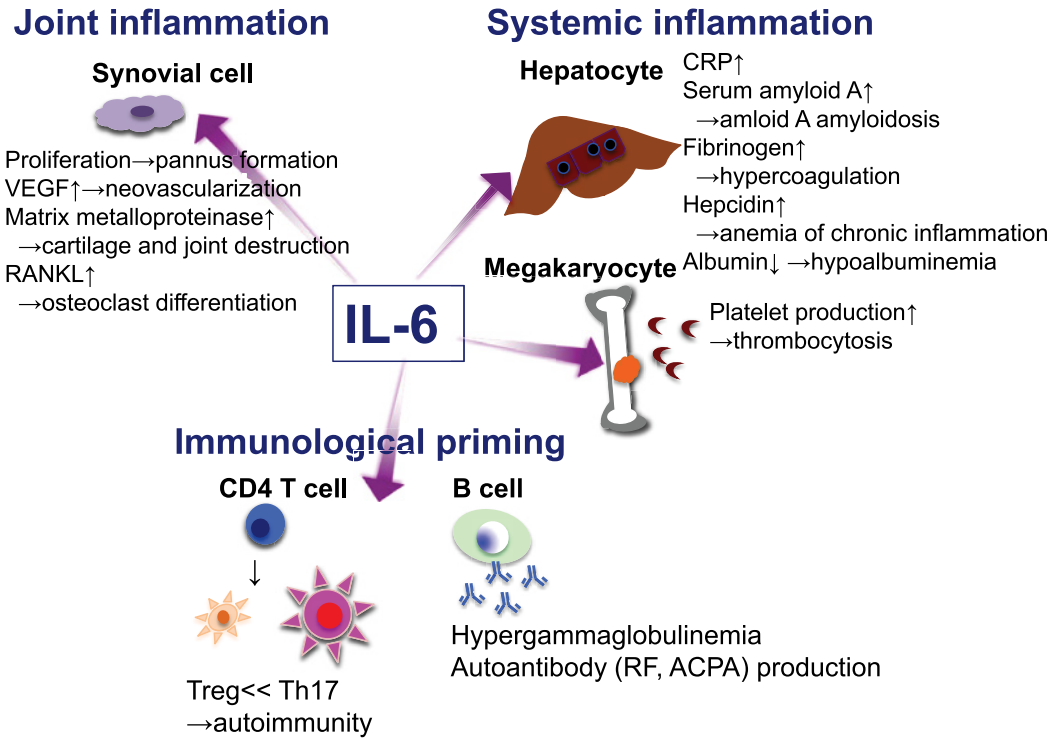

Figure 1: Pathologic role of IL-6 in development of rheumatoid arthritis. Rheumatoid arthritis (RA) is a chronic inflammatory disease, characterized by immunological abnormalities, and systemic and joint inflammation. IL-6 performs a key function in the development of these characteristics. In the priming phase, IL-6 contributes to the imbalance between Th17 and Treg and the production of autoantibodies such as RF and ACPA. IL-6 also generates systemic inflammatory symptoms, signs and findings, and persistent joint inflammation through acting on multiple cells.

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 collagen type II primes for an immune response to articular cartilage. In the CIA model, IL-6 has been shown to perform a major role in the development and progression of joint destruction because IL-6 gene deficiency or IL-6 blockade by means of anti-IL-6 receptor antibody reduces the incidence and severity of arthritis [22-24]. In antigen-induced arthritis (AIA), an immune complex model of RA, IL-6 gene knockout mice failed to develop joint swelling and $CD4^+$ T lymphocytes from the IL-6 deficient mice had reduced antigen-induced proliferation and produced less IL-17 and less RANKL [25,26].

SKG mice spontaneously develop autoimmune arthritis with aging 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 [27]. Synovial fluid of arthritic mice was found to contain large amounts of IL-6 and IL-6 gene deficiency completely inhibited the development of arthritis, whereas 20% of tumor necrosis factor (TNF)-α deficient mice developed arthritis [28]. Moreover, IL-6 deficient SKG mice were completely devoid of IL-17 producing $CD4^+$ T cells, whereas TNF-α deficient SKG mice harbored equivalent numbers of IL-17 producing $CD4^+$ T cells as intact SKG mice [29].

Human adult T cell leukemia virus (HTLV)-1 tax transgenic mice are genetically modified arthritis model and spontaneously develop arthritis [30]. The expression of IL-6 was high [31] and IL-6 deficiency in these mice did not develop arthritis while TNF deficient did. Knock-in mice with a mutation at position Tyr-759 in IL-6 family cytokine receptor subunit gp130, which is a binding site of the src homology 2 domain-bearing protein tyrosine phosphatase (SHP)-2, spontaneously develop an RA-like joint disease featuring an increased number of autoreactive T cells and autoantibodies and demonstrating the critical role of IL-6 in spontaneous autoimmune diseases including RA [32].

Arthritis of anti-type II collagen antibody-induced arthritis (CAIA) is another arthritis model but in this model the priming phase of T cell dependent antibody generation is skipped. Although IL-6 is also elevated in this model, arthritis is suppressed in TNF deficient but not IL-6 deficient mice, indicating that TNF plays a more significant role than IL-6 in the joint inflammation in CAIA [33].

In the CIA model, immunization with type II collagen predominantly increased the frequency of Th17 cells, while treatment of the mice with anti-IL-6 receptor antibody during the priming markedly suppressed the induction of Th17 cells and arthritis development. However, treatment with the antibody on day 14 failed to suppress Th17 differentiation and arthritis [34]. Similarly, in a glucose-6-phosphate isomerase (GPI)-induced arthritis model, administration of anti-IL-6 receptor antibody on day 0 or 3 suppressed Th17 differentiation and protected against arthritis induction while injection of the antibody on day 14, at the peak of arthritis, did not bring about any improvement in arthritis [35].

These observations clearly indicate that IL-6 is essential for the immunological priming for the development of arthritis in several models of RA and that the pathologic role of IL-6 in the development is

different from that of TNF.

IL-6 expression in patients with RA

Elevated IL-6 levels were found in serum and in synovial fluid of patients with RA [36-38]. The levels correlated with clinical symptoms including morning stiffness, number of involved joints and laboratory indices of disease activity [39-42]. Moreover, treatment with disease-modifying antirheumatic drugs (DMARDs) for 20 RA patients is 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 [43].

Genetic polymorphisms (-622 or -174) in the IL-6 gene promoter, of which the -174 polymorphism was shown to affect IL-6 levels, did not appear to increase susceptibility to RA [44] but the -174 polymorphism is reported to be associated with an increase in radiographic damage of joints in RA patients who were RF or ACPA positive [45] or with active disease [46].

Clinical efficacy and safety of tocilizumab for RA

The findings above have led to expectations that IL-6 blockade could be a novel treatment strategy for RA. IL-6 transmits its signal through binding to transmembrane or soluble IL-6 receptors [47,48]. After binding of IL-6 to IL-6 receptor, the resultant IL-6/IL-6 receptor complex associates with gp130 and induces homodimerization of gp130, which triggers a signal transduction system [49,50]. Tocilizumab is a humanized anti-human IL-6 receptor monoclonal antibody of the IgG1 class that was generated by grafting the complementarity-determining regions of a mouse anti-human IL-6 receptor antibody onto human IgG1. Tocilizumab blocks IL-6-mediated signal transduction through inhibition of IL-6 binding to transmembrane and soluble IL-6 receptors.

Phase I/II clinical trials

A randomized, double-blinded, placebo-controlled, dose-escalation phase I trial was performed in 45 patients with active RA in the United Kingdom (UK) [51]. Patients were sequentially allocated to receive a single intravenous dose of either 0.1, 1, 5, or 10 mg/kg of tocilizumab or placebo. At week 2, a significant treatment difference was observed between the 5 mg/kg of tocilizumab and placebo, with five patients (55.6%) in the tocilizumab cohort and none in the placebo cohort achieving the American College of Rheumatology (ACR) 20% improvement.

An open label phase I/II clinical study was performed in 15 patients with active RA in Japan [52]. Patients were intravenously administered 3 doses (2, 4, or 8 mg/kg) of tocilizumab biweekly for 6 weeks, and pharmacokinetics were assessed. After continuation of the tocilizumab treatment for 24 weeks, the patients were then assessed for safety and efficacy of the drug. The treatment was well tolerated at all doses with no severe adverse events (AEs). Although there was no statistically significant difference in efficacy among 3 dose groups, nine of 15 patients achieved ACR20 at week 6, and 86% and 33% of patients achieved ACR 20 and ACR 50, respectively at week 24.

In a multicenter, double-blind, placebo-controlled trial, 164 patients with refractory RA were randomized to receive either tocilizumab (4 or 8 mg/kg) or placebo [53]. Tocilizumab was administered intravenously every 4 weeks for a total of 3 months. At week 12, ACR20 response was observed in 78%, 57% and 11% of RA patients treated with tocilizumab 8, 4mg/kg and in the control groups, respectively.

The CHARISMA (**C**hugai **h**umanized **a**nti**r**heumatic **i**nterleukin **s**ix **m**onoclonal **a**ntibody) study was a phase II, double-blind, randomized controlled, multicenter trial of tocilizumab in European patients with RA who had an incomplete response to methotrexate (MTX) [54]. 359 active RA patients were randomized to one of the following seven treatment arms: tocilizumab 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 achieved by 61% and 63% of patients receiving 4 mg/kg and 8 mg/kg of tocilizumab as monotherapy, respectively, and by 63% and 74% of patients receiving the same doses of tocilizumab plus MTX, respectively, compared with 41% of 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 tocilizumab plus MTX.

The STREAM (Long-term **s**afety and efficacy of **t**ocilizumab, an anti-IL-6 **re**ceptor **m**onoclonal antibody, in monotherapy, in patients with rheumatoid arthritis) study was an open-label, long-term extension trial following an initial 3-month randomized phase II trial [55]. This study evaluated the safety and efficacy of 5 years, long term tocilizumab monotherapy (8 mg/kg) administered every 4 weeks for RA patients. Concomitant therapy with non-steroidal anti-inflammatory drugs (NSAIDs) and/or oral prednisolone (10 mg daily maximum) was permitted. Of the 143 patients enrolled in this trial, 94 (66%) patients completed the 5-year and were analyzed. 32 patients (22%) withdrew from the study due to AEs and one patient (0.7%) due to unsatisfactory response. The serious AE rate was 27.5 events per 100 patient-years (pt-yr), with 5.7 serious infections per 100 pt-yr, based on a total tocilizumab exposure of 612 pt-yr. At 5 years, 84.0%, 69.1% and 43.6% of the patients achieved ACR20 ACR50, and ACR70 improvement criteria, respectively. Remission defined as Disease Activity Score (DAS) 28 less than 2.6 was 55.3%. These findings proved the sustained long-term efficacy and generally good safety profile of tocilizumab monotherapy.

Phase III clinical trials

Subsequent to phase I and II studies, seven phase III clinical trials of tocilizumab demonstrated its efficacy either as monotherapy or in combination with DMARDs for adult patients with moderate to severe RA [56-62].

The SAMURAI (**S**tudy of **a**ctive controlled **m**onotherapy **u**sed for **r**heumatoid **a**rthritis, an IL-6 **i**nhibitor) study was a first phase III, double-blind, placebo-controlled, multicenter trial of tocilizumab to evaluate the ability of tociliumab monotherapy to inhibit progression of structural joint damage [56]. 306 patients with active RA of less than 5 years' duration were allocated to receive either tocilizumab monotherapy at 8 mg/kg every 4 weeks or conventional DMARDs for 52 weeks. At week 52, the tocilizumab group showed statistically significantly less radiographic change in total van der Heijde's modified Sharp score (mean 2.3; 95% 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 tocilizumab monotherapy. Theoverall incidences of AEs were 89% and 82%, of serious AEs 18% and 13% and of serious infections 7.6% and 4.1% for the tocilizumab and DMARD groups, respectively.

The phase III, double-blind, placebo-controlled, multicenter TOWARD (**to**cilizumab in combination **w**ith traditional DM**ARD** therapy) study was conducted to observe the effects of tocilizumab added to a stable dosage of conventional DMARDs for moderate-to-

severe RA in 1,220 patients with an inadequate response to DMARDs [57]. Patients remained on stable doses of DMARDs and received tocilizumab 8 mg/kg or placebo (control group) every 4 weeks for 24 weeks. At week 24, the proportion of patients achieving ACR20 was significantly greater in the tocilizumab plus DMARD group than in the control group (61% versus 25%; P<0.0001).

The RADIATE (**R**esearch on **A**ctemra **d**etermining eff**i**cacy after **a**nti-**T**NF failur**e**s) study examined the efficacy and safety of tocilizumab for patients with RA refractory to TNF antagonist therapy [58]. 499 patients with inadequate response to one or more of TNF antagonists were randomly assigned to receive 8 mg/kg or 4 mg/kg tocilizumab or placebo with stable MTX for 24 weeks. ACR20 was achieved at 24 weeks by 50.0%, 30.4% and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively. DAS28 remission rates at week 24 were clearly dose-related, being achieved by 30.1%, 7.6% and 1.6% of the 8 mg/kg, 4 mg/kg and control groups, respectively. Most AEs were mild or moderate.

The multicenter double-blind, randomized, placebo-controlled, parallel group phase III OPTION (T**o**cilizumab **p**ivotal **t**rial in methotrexate **i**nadequate resp**on**ders) study was conducted to observe the therapeutic effects of tocilizumab added to a stable dosage of MTX in moderate to severe active RA in patients with an inadequate response to MTX [59]. 623 patients were randomized to receive tocilizumab (4 or 8 mg/kg) or placebo intravenously every 4 weeks, with MTX continued at stable pre-study doses (10-25 mg/week). Rescue therapy with tocilizumab (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 tocilizumab 8 mg/kg, 4 mg/kg and control groups, respectively.

The SATORI (**S**tudy of **a**ctive-controlled **to**cilizumab monotherapy for **r**heumatoid arthritis patients with an **i**nadequate response to methotrexate) study investigated the clinical efficacy and safety of tocilizumab monotherapy for active RA patients with an inadequate response to low dose MTX [60]. 125 patients were allocated to receive either tocilizumab 8 mg/kg every 4 weeks plus MTX placebo or tocilizumab placebo plus MTX 8 mg/week for 24 weeks. At week 24, ACR20 response rate was 80.3% and 25.0%, respectively, for the tocilizumab and MTX groups. In fact, the ACR response of the tocilizumab group was superior to that of the MTX group at all time points.

The LITHE (Toci**li**zumab safety and **the** prevention of structural joint damage) trial confirmed the efficacy of tocilizumab in preventing the progression of joint destruction. This study was a three-arm, randomized double-blind, placebo-controlled one year study [61]. Patients were randomized to receive tocilizumab (4 or 8 mg/kg, once every 4 weeks) plus MTX or placebo plus MTX. Stepwise rescue therapy starting at week 16 was allowed if patients did not respond. At 1 year, patients treated with tocilizumab (8 mg/kg) had 3 times less progression of joint damage evaluated by Genant's modified Sharp score method, compared to those treated with MTX alone. The change of health assessment questionnaire of disability index (HAQ-DI) showed significant improvement in physical function of patients treated with tocilizumab 4 mg/kg and 8 mg/kg.

The 24-week, double-blind, double-dummy, parallel-group AMBITION (**A**ctemra versus **m**ethotrexate double-**b**lind **i**nvestigative **t**rial **i**n m**on**otherapy) study was conducted to determine the efficacy and safety of tocilizumab monotherapy versus MTX for patients with active RA who had not failed previous treatments with MTX/biological agents [62]. 673 patients were randomized to either tocilizumab 8 mg/kg every 4 weeks, or MTX, starting at 7.5 mg/week and titrated to 20 mg/week within 8 weeks, or placebo for 8 weeks followed by tocilizumab 8 mg/kg. Results for tocilizumab were better than for MTX treatment with a higher ACR20 response (69.9% versus 52.5%; p<0.001), and DAS28 remission rate (33.6% versus 12.1%) at week 24. The incidence of serious AEs with tocilizumab was 3.8% versus 2.8% with MTX (p = 0.50), and 1.4% versus 0.7% for serious infections.

The ACR improvement and DAS remission criteria include an acute-phase reactant component. There was therefore concern that the effect of tocilizumab evaluated with these criteria might be overestimated. However, it was found that, even when criteria such as the Simplified Disease Activity Index (SDAI) and Clinical Disease Activity Index (CDAI) were used, remission rates for patients treated with tocilizumab were in the same range as those for patients treated with TNF inhibitors [63,64].

The Rose (**r**apid **o**nset and **s**ystemic **e**fficacy) study showed rapid improvement in clinical outcomes [65]. It was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicentre phase IIIb clinical trial. Patients were randomly assigned 2:1 to tocilizumab 8 mg/kg (n=412) or placebo (n=207) every 4 weeks while continuing background DMARDs in both groups. The primary efficacy endpoint, percentage of patients achieving ACR50 response at week 24, was higher in the tocilizumab group than that in the placebo group (30.1% versus 11.2%; p<0.0001). A substudy examining early response to therapy showed improved patient global assessment of disease activity, pain and DAS28 with tocilizumab versus placebo at day 7.

The above trial data demonstrate the therapeutic efficacy of tocilizumab in adult patients with moderate-to-severe RA. As a result, tocilizumab has now been approved for the treatment of RA in more than 90 countries worldwide [66].The recommended dose of tocilizumab is 8 mg/kg, every 4 weeks in Japan and the EU. In the United States, the recommended starting dose is 4 mg/kg administered once every 4 weeks followed by an increase to 8 mg/kg depending on clinical response.

In actual medical practice

In the TAMARA (**T**ocilizumab **a**nd D**M**ARDs: **a**chievements in **r**heumatoid **a**rthritis) study conducted in Germany, 286 patients,41.6% of whom had previously been treated with TNF inhibitors, were registered to determine the effectiveness and safety of tocilizumab [67,68].Of the intention-to-treat patients, 57% attained the primary end point of low disease activity score (LDAS; 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, and CDAI and 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 tocilizumab have been identified [69], 93% of whom had previously received one or more TNF inhibitors. The disease activity decreased at all time points, with remission rates for tocilizumab treatment of 39% 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 and to the response rates previously observed in phase III clinical trials.

In Japan, 229 patients were registered in the REACTION (**Re**trospective **Act**emra (tocilizumab) **i**nvestigation for **o**ptimal **n**eeds of RA patients) study to evaluate the efficacy and tolerability of tocilizumab for RA patients seen in daily clinical practice in Japan [70,71]. In this study, 55% of the patients concomitantly received MTX 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 remission 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. These three reports convincingly demonstrate the efficacy of tocilizumab for the treatment of RA in actual medical practice.

Safety profile of tocilizumab

The safety profiles of tocilizumab monotherapy for Japanese RA patients were obtained from six initial trials and five long-term extensions [72]. For these studies, 601 patients with a total exposure to tocilizumab of 2,188 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 tocilizumab in Japan were recently reported [73]. This analysis comprised 3,881 patients who received 8 mg/kg of tocilizumab every 4 weeks, 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 reported. 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 cellulits. 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 tocilizumab injection, this was not related to the incidence of infection. Twenty-five patients died for a standardized mortality ratio of 1.66, which was similar to the results reported for a Japanese cohort study of RA. The results of this analysis thus demonstrated that the safety profile of tocilizumab is acceptable in the actual clinical setting.

Seven cases of gastrointestinal (GI) perforation in six patients were reported in this post marketing surveillance. In the worldwide Roche clinical trials 26 (0.65%) cases of GI perforation were found among patients with RA treated with tocilizumab for a rate of 1.9/1,000 pt-yr and most cases appeared to be complications of diverticulitis [74]. 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.

The reactivation of tuberculosis is a major concern during anti-TNF treatment [75], 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-6 receptor antibody than for anti-TNFα [76]. 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 tocilizumab [77]. Although it seems likely that the incidence of reactivation of tuberculosis is lower during tocilizumab treatment than that during anti-TNF treatment, more detailed studies will be needed to clarify this point.

Status of Tocilizumab for the Treatment of RA and Future Possibilities

A number of biologics are available for the treatment of RA. These include TNF inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab), an IL-1 antagonist (anakinra), a B-cell depletor (rituximab), an IL-6 receptor blocker (tocilizumab), and a T-cell activation blocker (abatacept) [63]. These biological modifiers target different molecules and B cells, leading to different clinical effects and causing different adverse effects. Since no head-to-head comparative studies have been made of the efficacy of these various agents, it has not yet been determined which of these biologics should be selected for a given patient. Currently, one of the anti-TNF drugs is chosen as a first-line biologic, and tocilizumab is recommended for RA patients with an inadequate response to one or more of TNF inhibitors. As mentioned above, since IL-6 contributes to fundamental immunological dysfunctions and to systemic and joint inflammation in RA, it is anticipated that tocilizumab, as an IL-6 receptor blocker, will be selected as a first-line biologic for RA patients with certain conditions. Amyloid A amyloidosis is a serious complication of RA and amyloid fibril deposition causes progressive deterioration in various organs [13]. Since the activation of the SAA gene depends primarily on IL-6 [78,79], tocilizumab injection promptly reduces serum concentrations of SAA, just as in the case of CRP [80]. Three case studies recently reported the clinical ameliorative effect of tocilizumab on gastrointestinal symptoms due to intestinal amyloidosis [81-83] and amyloid A fibril deposits were found to have been eliminated in two cases after three injections of tocilizumab [81,83]. This suggests that tocilizumab may be suitable as a first-line drug for RA patients who are complicated with, or at high risk of, developing amyloid A amyloidosis. Similarly, anemia of chronic inflammation is mediated by excess production of hepcidin, whose expression is regulated by IL-6. Dysregulated continuous IL-6 production also induces a hypercoagulable state and thrombocytosis. So, it is more rational for RA patients presenting with systemic inflammatory symptoms and findings to be treated with tocilizumab than with anti-TNFs.

During tocilizumab treatment, improvements in serum biological markers related to atherosclerosis have been reported. IL-6 is involved in insulin resistance and development of type 2 diabetes mellitus [84,85], and we observed that tocilizumab treatment caused a reduction in HbA1c levels in diabetic patients with RA [86]. The average HbA1c level of diabetic patients (n=10) significantly decreased from 7.17% to 6.35% before steroid tapering and one month after tocilizumab treatment and to 6.00% after 6 months. Insulin resistance indexes 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 treated with tocilizumab for 3 months [87]. Patients with RA treated with DMARDs, TNF inhibitors (infliximab or etanecept) or tocilizumab showed significantly low levels of reactive

oxygen metabolites (ROMs) in patients treated with tocilizumab [88]. Although increases in total cholesterol and triglycerides in the blood were seen in some patients during tocilizumab treatment, these findings raise the possibility that long-term tocilizumab treatment offers protection against cardiovascular events, which is now a major cause of mortality and morbidity for RA patients [89]. Indeed, endothelial dysfunction and aortic stiffness of RA patients were recently shown to improve as a result of tocilizumab treatment [90,91].

As reported elsewhere, of particular importance is that tocilizumab may be able to repair the Th17/Treg imbalance [7,11], which is considered to be a fundamental immunological abnormality in RA. Alternatively, Roll et al. examined 16 RA patients for the in vivo effect of tocilizumab on the B-cell compartment and found that it induced a significant reduction of peripheral pre-switch and post-switch memory B cells [92]. Moreover, tocilizumab but not a TNF inhibitor (etanercept) significantly reduced somatic hypermutation in immunoglobulin gene rearrangements in pre-switch memory B cells [93], suggesting that modulation of memory B cells may be another possible target for tocilizumab. Further clinical studies and clarification of mechanisms through which tocilizumab exerts its clinical efficacy are essential to achieve the optimal use of tocilizumab for RA patients.

Funding

Supported by the grant of the Program of Fundamental Studies in Health Sciences of the National Institute of Biomedical Innovation.

Disclosures

Tadamitsu Kishimoto holds a patent for tocilizumab and receives royalties for Actemra. Toshio Tanaka declares no conflict of interest.

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This article was originally published in a special issue, **Immunotherapies and Rheumatoid arthritis** handled by Editor(s). Dr. Hongkuan Fan, Medical University of South Carolina, USA