Introduction

Interleukin (IL)-6 was originally cloned as a B cell differentiation factor that promotes B cell differentiation into antibody-producing cells.[1] Subsequent in vitro studies and analysis of IL-6 transgenic mice have shown that IL-6 acts not only on B cells but also on T cells, hepatocytes, hematopoietic progenitor cells and various other cells.[2–4] One of the important functions of IL-6 is induction of the differentiation of CD4+ naïve T cells into effector cells. IL-6 promotes naïve T cell differentiation into Th17 cells in the presence of transforming growth factor (TGF)-β, while it inhibits TGF-β-induced regulatory T cell (Treg) differentiation.[5] IL-6 is also reported to be able to induce the switching of Treg into Th17 cells. An imbalance between Th17 and Treg is considered to be the primary pathogenesis of several autoimmune diseases.[6] Based on these findings, it was anticipated that IL-6 blockage would constitute a novel treatment strategy for autoimmune and inflammatory diseases.[4,7–9] Tocilizumab (TCZ) was developed to this end. TCZ is a humanized anti-IL-6 receptor (IL-6R) monoclonal antibody (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. TCZ blocks all IL-6-mediated signals by inhibiting IL-6 binding to transmembrane and soluble IL-6Rs.

Mechanism of Action, Metabolism and Pharmacokinetic Profile

Rheumatoid arthritis (RA) is a chronic, progressive inflammatory disease of the joints and surrounding tissues accompanied by intense pain, irreversible joint destruction and systemic complications such as fatigue, anemia and fever.[10] Within joints, inflammatory cells invade the synovium, which is accompanied by neovascularization. Synoviocyte hyperplasia then forms synovitis, the so-called pannus. Activated synovitis causes destruction of cartilage and erosion of the adjacent bone. Increased IL-6 levels in the sera and synovium of RA patients and proinflammatory activities of IL-6 such as augmentation of synovial fibroblast proliferation, osteoclast differentiation, and the production of matrix metalloproteinase (MMP) and vascular endothelial growth factor (VEGF) indicate that IL-6 is involved in the pathogenesis of RA.[11–16]

Induction of type II collagen-induced arthritis (CIA) requires CD4 T cells and leads to the production of anti-type II collagen IgG. The incidence and severity of arthritis of CIA was reduced following IL-6 blockade, which was achieved by gene knockout or by administration of an anti-IL-6R Ab.[17–22] In contrast, the arthritis of another arthritis model termed anti-type II collagen antibody-induced arthritis (CAIA) has skipped the priming phase of T cell dependent antibody generation. Although IL-6 is elevated in both models, CAIA was profoundly suppressed in tumor necrosis factor (TNF) -/- mice but not in IL-6-/- mice, indicating that TNF might play a more significant role in the development of CAIA than IL-6.[23] This observation suggests that, in this model, IL-6 is required for activation of T cell responses and for the production of antibodies specific for joint components (priming phase) and that TNF is necessary for the generation of arthritis (effector phase).[24] We found that TCZ was not effective for two patients with psoriatic arthritis.[25] This type of arthritis, unlike rheumatoid arthritis, does not appear to require immune activation for its development. Figure 1 shows the pathologic role of IL-6 in the development of RA. IL-6 contributes to immune activation of RA and systemic inflammation while TNF mainly contributes to arthritis and joint destruction.

Recommended TCZ dosing regimens differ depending on the area. In European countries and Japan TCZ is administered intravenously at a dose of 8 mg/kg every 4 weeks. In the USA, it is recommended that TCZ should be initially administered at a dose of 4 mg/kg every 4 weeks and it is then permitted to increase the dose up to 8 mg/kg every 4 weeks if clinically indicated. At steady state, the elimination half-life of TCZ at a dose of 4 mg/kg and 8 mg/kg is 11 days and 13 days, respectively.[26] Serum TCZ levels of more than 1 μg/mL are recommended to maintain sufficient efficacy. The level of serum CRP is a good marker for titration of TCZ. Thus, if serum concentrations of TCZ exceed 1 μg/mL at the trough level, this means that IL-6 function is blocked in vivo and therefore CRP levels are within the normal range. An increase in CRP level suggests that inhibition of IL-6 function by TCZ is not complete. Although at the present time it is not indicated, dose-up or interval shortening of TCZ administration might produce better outcome. TCZ administration at

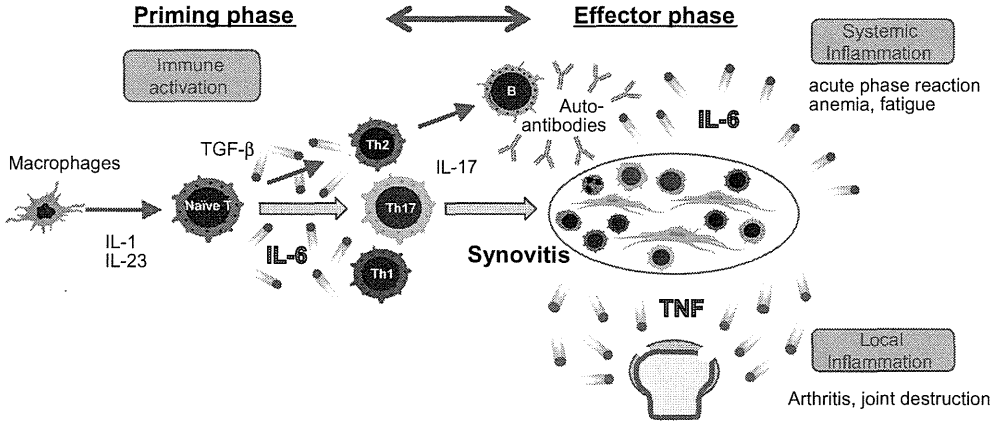

Figure 1. The pathological role of IL-6 in RA.
Notes: The pathogenesis of rheumatoid arthritis is composed of a priming phase and an effector phase. In the priming phase, IL-6-induced Th17 development and the induction of autoantibodies such as rheumatoid factor (RF) are important. Th17-dependent immune activation generates active synovitis. Synovitis is an epicenter of the inflammation of RA. Systemic inflammation (production of acute phase protein, anemia and fatigue) is mainly mediated by IL-6. Local inflammation (arthritis) such as arthralgia, swelling, and joint destruction is mainly mediated by TNF.

2-week intervals is approved in Japan for treatment of Castleman's disease and systemic juvenile idiopathic arthritis, in which a large amount of IL-6 in the sera was found. In addition to its effect on the amount of IL-6 production, the rate of TCZ degradation also influences the efficacy of TCZ. We found that more TCZ is required when patients have splenomegaly.[27] Studies of TCZ tissue distribution in cynomolgus monkeys demonstrated that high levels of TCZ remain not only in synovial fluid and plasma but also in spleen for up to 28 days after TCZ administration. Excessive accumulation of TCZ in spleen may reduce the anti-rheumatic effect of TCZ.

During TCZ therapy, the serum IL-6 concentration temporarily increases. The so-called "bathtub theory", as shown in Figure 2, illustrates this phenomenon.[28] TCZ does not directly inhibit the production of IL-6. As long as free TCZ is detectable, soluble IL-6R is saturated with TCZ and IL-6 signaling is completely inhibited. Free serum IL-6 increases because IL-6R mediated binding of IL-6 is inhibited by the unavailability of TCZ-free IL-6R. Although systemic inflammation is immediately blocked by TCZ, IL-6 production is not inhibited until immune stabilization is induced by TCZ. Normalization of serum IL-6 level suggests repair of the immunological abnormality and indeed clinical remission is achieved in such RA patients.

Phase I-III Clinical Trials

Phase I and II clinical trials of TCZ have been performed and were reported between 2002 and 2006. Summaries of phase I/II trials are shown in Table 1. The first trial was performed in the UK[29] using single administration of a placebo or TCZ at a dosage of 0.1, 1, 5 or 10 mg/kg. Patients who were treated with 5 mg/kg or 10 mg/kg of TCZ showed significant improvement at week 2. After pharmacokinetic assessment,[30] a study for dose setting trial was performed in Japan.[31] Patients were administered TCZ (4 or 8 mg/kg) monotherapy or placebo every 4 weeks. Both doses of TCZ were effective but the 8 mg/kg dose group showed a greater improvement than the 4 mg/kg dose group.

The CHARISMA study (Chugai Humanized Anti-Rheumatic Interleukin Six Monoclonal Antibody) was performed in Europe.[32] Active RA patients with an inadequate response (IR) to methotrexate (MTX) were randomly divided into one of the following seven treatment arms: TCZ at a dose of 2, 4 or 8 mg/kg that was administered either as monotherapy or in combination with MTX, or MTX plus a placebo. At week 16, the American College of Rheumatology (ACR) criteria for 20% improvement (ACR20) response was better in the 4 mg/kg and 8 mg/kg TCZ groups with or without MTX than in the group of patients that received the placebo plus MTX. Anti-TCZ antibodies were produced in approximately 25% of the TCZ 2 mg/kg monotherapy group.

To investigate the long-term safety and efficacy of TCZ, the STREAM study (the Long-term Safety and Efficacy of Tocilizumab, an Anti-IL-6 Receptor Monoclonal Antibody, in Patients with Rheumatoid

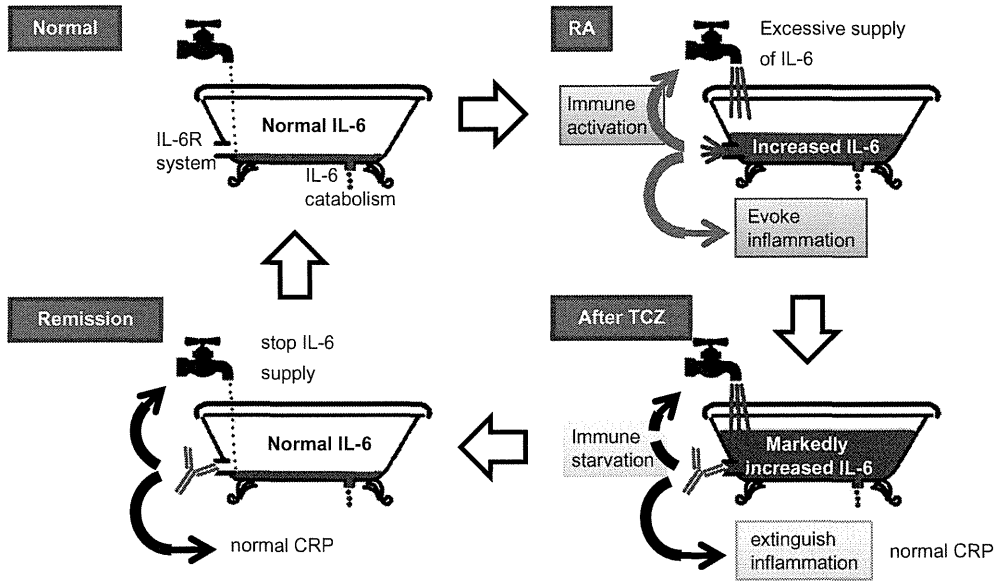

Figure 2. Mechanism of action of tocilizumab in RA (bathtub theory).
Notes: The mechanism of tocilizumab (TCZ) in rheumatoid arthritis was illustrated as the bathtub theory by Nishimoto et al.[28] The faucet (immune cells) supplies IL-6 into the bathtub (blood). Under normal conditions, the supplied IL-6 is completely cleared by soakaway (catabolism), there is no IL-6 overflow into the IL-6 receptor system (drain) and there is no IL-6 function. In RA, the faucet is fully opened and soakaway cannot completely eliminate the increased production of IL-6. Therefore IL-6 overflows into the drain and IL-6 acts pleiotropically. This IL-6 induces immune activation and systemic inflammation through the IL-6R system. After TCZ therapy, the drain is blocked. However, IL-6 is not eliminated from the blood. Although the IL-6 cannot act through its receptors, the serum IL-6 level is increased because soakaway cannot completely eliminate IL-6. Thus, IL-6 function is blocked by TCZ and inflammation is suppressed. Immune starvation by TCZ gradually closes the faucet (clinical remission). The IL-6 supply is stopped and serum IL-6 levels revert to normal. Compete starvation of immune activation may lead to cessation of TCZ treatment (drug-free remission).

Arthritis) was performed in Japan.[33] Patients received TCZ monotherapy (8 mg/kg) that was administered every 4 weeks over a 5-year period. Overall, 32 patients (22%) withdrew from the study due to adverse events (AEs). After 5 years, 84.0, 69.1 and 43.6% of the patients met improvement criteria for ACR20, ACR50 and ACR70, respectively.

As shown in Table 2, seven phase III randomized clinical trials (RCTs) under various clinical situations have been conducted to evaluate the efficacy and safety of TCZ therapy of RA patients. In these studies, the TCZ dose was set as monthly administration at a dose of 4 or 8 mg/kg, based on the results of phase I and II studies.

The AMBITION trial (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) demonstrated that TCZ monotherapy is better than MTX monotherapy, showing rapid improvement in RA signs and symptoms, and a favorable benefit-risk, in patients for whom treatment with MTX or biological agents had not previously failed.[34]

The OPTION trial (Tocilizumab Pivotal Trial in Methotrexate Inadequate RespONders) demonstrated that TCZ in combination with MTX was effective and well tolerated in patients with moderate to severe active RA that had an inadequate response to MTX.[35,36]

The TOWARD trial (Tocilizumab in cOmbination With traditional DMARD therapy) demonstrated that TCZ combined with any of the disease modifying antirheumatic drugs (DMARDs) (MTX, chloroquine, gold, sulphasalazine, azathioprine or leflunomide) was safe and effective in reducing articular and systemic symptoms in patients with an inadequate response to these DMARDs.[37]

The RADIATE trial (RheumAtoiD ArthrItis study in Anti-TNF failurEs) demonstrated that TCZ plus MTX was effective in achieving rapid and sustained improvements in signs and symptoms in patients with an adequate response to TNF antagonists and had a manageable safety profile.[38]

The LITHE trial (TociLIzumab Safety and THE Prevention of Structural Joint Damage) demonstrated that TCZ plus MTX had superior ACR20 responses at 24 weeks compared with controls treated with placebo plus MTX and significantly inhibited radiographic

Table 1. Phase I and II clinical trials of tocilizumab.

Study	Population studied	Administration duration	N	Treatment arm	Conclusion	Ref.
Phase I (UK)	DMARDs-IR	2 weeks	45	0.1, 1, 5, 10 mg/kg, TCZ or PBO	Well tolerated and efficacious at doses of 5 and 10 mg/kg TCZ	29
Phase I/II (Japan)		6 weeks	15	TCZ (8 mg/kg) monotherapy	Well tolerated and efficacious	30
Phase II (Japan)		2 years	162	TCZ (4 mg/kg, e.4.w) monotherapy TCZ (8 mg/kg, e.4.w) monotherapy PBO	TCZ (8 mg/Kg) > TCZ (4 mg/Kg)	31
CHARISMA Phase II (Europe)	MTX-IR	16 weeks	359	TCZ (4 mg/kg, e.4.w) monotherapy TCZ (8 mg/kg, e.4.w) monotherapy TCZ (4 mg/kg, e.4.w) + MTX TCZ (8 mg/kg, e.4.w) + MTX PBO	Well tolerated and efficacious TCZ (8 mg/Kg) > TCZ (4 mg/Kg) MTX combination > monotherapy	32
STREAM long term extension (Japan)	Phase I/II patients in Japan	5 year extension	143	TCZ (8 mg/kg, e.4.w) monotherapy	Well tolerated and efficacious	33

Abbreivations: MTX, methotrexate; TCZ, tocilizumab; IR, inadequate response; DMARDs, disease modifying antirheumatic drugs; PBO, placebo; wk, week; e.4.w, every 4 weeks.

Table 2. Phase III randomized clinical trials of tocilizumab.

Trial	Population studied	Administration duration	N	Treatment arm	ACR20	DAS28 < 2.6	Change of TSS	Ref.
AMBITION	MTX or Biologics without failure	24 weeks	286 284	TCZ (8 mg/kg, e.4.w) + PBO MTX + PBO	70% 53%	34% 12%		34
OPTION	MTX-IR	24 weeks	214 205 204	TCZ (8 mg/kg, e.4.w) + MTX TCZ (4 mg/kg, e.4.w) + MTX PBO + MTX	59% 48% 26%	27% 13% 1%		35,36
TOWARD	DMARDs-IR	24 weeks	803 413	TCZ (8 mg/kg, e.4.w) + DMARDs PBO + DMARDs	61% 25%	30% 3%		37
RADIATE	aTNF-IR	24 weeks	161 170 158	TCZ (8 mg/kg, e.4.w) + MTX TCZ (4 mg/kg, e.4.w) + MTX PBO + MTX	50% 30% 10%	30% 8% 2%		38
LITHE	MTX-IR	24 weeks	395 398 393	TCZ (8 mg/kg, e.4.w) + MTX TCZ (4 mg/kg, e.4.w) + MTX PBO + MTX	56% 47% 25%	47% 30% 8%	0.29 0.34 1.13	39
SAMURAI	DMARDs-IR	52 weeks	157 145	TCZ (8 mg/kg, e.4.w) DMARDs	78% 34%	59% 3%	2.3 6.1	40
SATORI	MTX-IR	24 weeks	61 64	TCZ (8 mg/kg, e.4.w) + PBO MTX + PBO	80% 25%	43% 2%		41

Abbreivations: MTX, methotrexate; TCZ, tocilizumab; IR, inadequate response; DMARDs, disease modifying antirheumatic drugs; aTNF, TNF inhibitor; PBO, placebo; ACR20, ACR criteria for 20% improvement; e.4.w, every 4 weeks; TSS, total sharp score.

progression at 52 weeks in patients with an inadequate clinical response to MTX.[39]

The SAMURAI (Study of Active Controlled Monotherapy Used for Rheumatoid Arthritis, an IL-6 inhibitor) trial demonstrated that TCZ monotherapy is generally well tolerated and provides radiographic benefit at 52 weeks in patients with an inadequate response to DMARDs.[40]

The SATORI trial (Study of Active Controlled TOcilizumab Monotherapy for Rheumatoid Arthritis Patients with an Inadequate Response to Methotrexate) demonstrated that TCZ monotherapy showed superior ACR response criteria compared with MTX plus placebo treatment for patients with an inadequate response to MTX.[41]

Phase IIIb/IV Clinical Studies

Following phase III clinical trials, a number of additional studies (TAMARA, DANBIO registry, REACTION, ROSE, ACT-RAY, ACT-SURE, and ACT-STAR) were conducted to investigate the efficacy of TCZ in clinical trials and daily clinical settings (Table 3).

Compared with the EU and Japan, the recommended initial dosing of TCZ is low (4 mg/kg) in the USA. As shown in Figure 3, Cochrane review demonstrated that the efficacy of 4 mg/kg TCZ was inferior to that of 8 mg/kg TCZ under monotherapy condition.[42] Therefore, dose-escalation of TCZ is often necessary in real life medical practice. A dose-escalation study in a clinical practice setting was therefore conducted in the US. The dose of TCZ for DMARDs inadequate response (IR) and TNF-IR patients who did not achieve adequate response to 4 mg/kg TCZ at 16 weeks was escalated to 8 mg/kg TCZ. These patients showed significant improvement when evaluated at 24 weeks.[43]

In Germany, 286 patients were registered for the TAMARA (Tocilizumab And DMARDs: Achievements in Rheumatoid Arthritis) study, which analyzed the effectiveness and safety of TCZ.[44,45] Of these patients, 41.6% had been previously treated with TNF inhibitors. The percentage of patients that achieved DAS remission and a European League Against Rheumatism (EULAR) 'good response' was 47.6% and 54.9%, respectively. ACR50/70 response rates at week 24 were 50.7% and 33.9%, respectively. The new ACR/EULAR Boolean-based criteria were 15.0% after 12 weeks and 20.3% after 24 weeks. Clinical Disease Activity Index (CDAI) and Simplified Disease Activity Index (SDAI) remission rates were 24.1% and 25.2%, respectively.

In Denmark, 178 patients with RA that were treated with TCZ were identified in the DANBIO (The Danish Registry for Biologic Therapies in Rheumatology) registry.[46] After 48 weeks, 64% of these patients were still being treated. Among patients with available response data, DAS28 was 5.4, 2.9 and 2.5 at baseline, week 24 and week 48, respectively. The remission rates at weeks 24 and 48 were 39% and 58%, respectively and EULAR good or moderate response rates were 77% and 84%, respectively. These response rates were comparable to those found in patients switching to a second TNF inhibitor and to the response rates previously demonstrated in phase III clinical trials.

In Japan, 229 patients were registered in the REACTION (Retrospective Actemra Investigation for Optimal Needs of RA) study, which analyzed TCZ effectivity.[47–49] DAS28 remission (DAS28 < 2.6) rates at 24, 52 and 104 weeks were 54%, 59% and 71%, respectively. CDAI remission (CDAI ≤ 2.8) rates at 24, 52, 104 weeks were 15%, 22%, and 37%, respectively. Structural remission (total sharp score ≤ 0.5) and functional remission (health assessment questionnaire ≤ 0.5) at 104 weeks were 53% and 38%, respectively. Thus, not only clinical remission but also structural and functional remission was maintained long-term.

These studies confirm both the short-term efficacy and the long-term tolerability of TCZ not only in RCTs but also in real life clinical care. In the DAMBIO registry, the 2-year drug survival of patients treated with TCZ and TNF inhibitors was 70% and 40%–60%, respectively.[46,50] We also demonstrated drug continuation rate of TCZ.[51] The median survival of patients treated with TCZ, infliximab (IFX), etanercept (ETN) and adalimumab (ADA) was 2.7, 1.7, 2.2 and 1.1 years, respectively. The survival rate of patients treated with TCZ was significantly higher than that of patients treated with TNF inhibitors ($P < 0.001$). These results indicate that survival following treatment with TCZ is superior to that following TNF inhibitor treatment.

In the USA, 619 patients were registered in the ROSE (The Rapid Onset and Systemic Efficacy)

Table 3. Phase IIIb, IV and open-label clinical trials of tocilizumab.

Study	Population studied	Design (country)	Administration duration	N	Treatment arm	Conclusion	Ref.
TAMARA (Phase IIIb)	DMARDs-IR	RCT (Germany)	24 weeks	286	TCZ (8) monotherapy TCZ (8) + DMARDs	TCZ was effective in daily clinical practice	44,45
DAMBIO (Phase IV)	DMARDs-IR or aTNF-IR	Retrospective cohort (Denmark)	48 weeks	178		TCZ was effective in daily clinical practice	46
REACTION	DMARDs-IR or aTNF-IR	Retrospective cohort (Japan)	2 years	229		TCZ was effective in daily clinical practice	47–49
ROSE (Phase IIIb)	DMARDs-IR	RCT (USA)	24 weeks	619	TCZ (8) monotherapy PBO	TCZ monotherapy was effective	52
Japanese PMS (Phase IV)	DMARDs-IR or aTNF-IR	Retrospective cohort (Japan)	28 weeks	7901		TCZ was effective in daily clinical practice	66,67
Post hoc analysis of clinical data	Patients of LITHE, OPTION, RADIATE study	Observational open-label (International)	Start at week 16 end at week 24	714	TCZ (4) IR→TCZ (8) TCZ (8) IR→continues TCZ (8)→continues	Dose escalation to 8 mg/kg was effective in TCZ 4 mg/kg IR	43
ACT-RAY (Phase IIIb)	MTX-IR	RCT (International)	2 years	556	TCZ (8) monotherapy TCZ (8) + MTX	TCZ monotherapy was not inferior to combined therapy with MTX	53–55
ACT-SURE (Phase IIIb)	DMARDs-IR or aTNF-IR	Observational open-label (International)	6 months	1681	TCZ (8) monotherapy TCZ (8) + DMARDs	TCZ monotherapy was not inferior to combined therapy with DMARDs	56,57
ACT-STAR	aTNF-IR	Observational open-label (USA)	24 weeks	886	TCZ (4/8) + DMARDs TCZ (8) + DMARDs TCZ (8) monotherapy	TCZ monotherapy was not inferior to combined therapy with DMARDs	58,59
DREAM	Remission after TCZ monotherapy	Retrospective cohort (Japan)	12 weeks	187	Cessation of TCZ	Cessation of TCZ was possible	61
RESTORE	Recurrence after TCZ cessation	Retrospective cohort (Japan)	12 weeks	187	Retreatmentof TCZ	Retreatment with TCZ was acceptable	62

Abbreviations: MTX, methotrexate; TCZ, tocilizumab; IR, inadequate response; DMARDs, disease modifying antirheumatic drugs; aTNF, TNF inhibitor; PBO, placebo; ACR20, ACR criteria for 20% improvement; TCZ (8), 8 mg/kg TCZ every 4 weeks; TCZ (4), 4 mg/kg TCZ every 4 weeks.

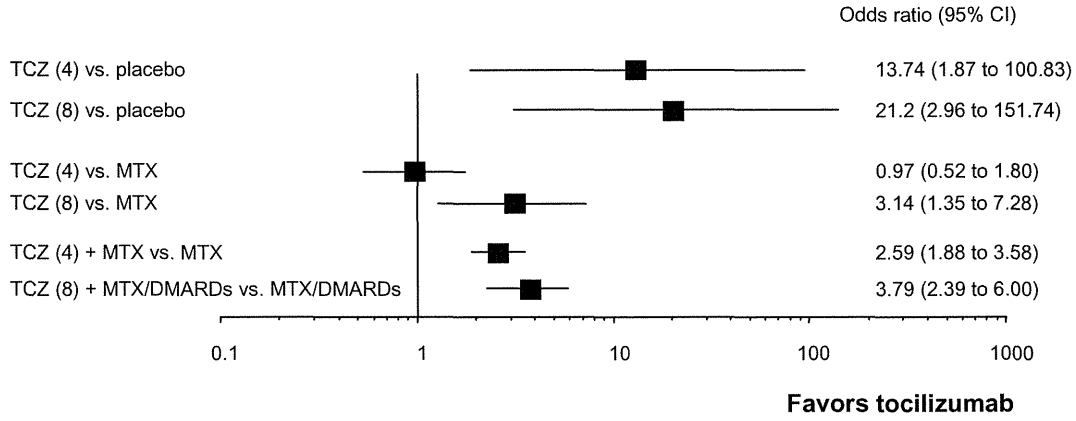

Figure 3. The summary of the efficacy of tocilizumab in phase III randomized controlled trials in RA patients.
Notes: Cochrane review summarized the efficacy of tocilizumab (TCZ) from eight randomized controlled trials.[42] These forest plots demonstrate odds ratio of achieving ACR 50 response rate. Efficacy of 8 mg/kg TCZ as monotherapy or in combination with MTX was significantly better than placebo or MTX in achieving ACR 50 response rates. Although the efficacy of 4 mg/kg TCZ monotherapy was not superior to MTX, that of 4 mg/kg with MTX can overcome MTX.

study for analysis of the efficacy and safety of TCZ.[52] This study was a 24-week, randomized, double-blind, placebo-controlled, parallel-group, multicenter phase IIIb clinical trial. The percentage of ACR20 and ACR50 responders was significantly higher for TCZ-treated versus placebo-treated patients as early as week 4 and continued up to week 24. Compared to the placebo-treated patients, more patients in the TCZ group achieved ACR70 responses beginning at week 8 ($P < 0.01$). Safety findings were consistent with the known TCZ safety profile. Rapid improvement in clinical outcomes was demonstrated as early as week 1 as shown by DAS28 scores, patient measures and CRP levels.

The ACT-RAY study was a double-blind 2-year phase IIIb study.[53–55] In this study, 556 patients who were on stable doses of oral weekly MTX were randomly divided into groups that were treated with either 8 mg/kg TCZ plus continued MTX (TCZ + MTX group) or were switched to 8 mg/kg TCZ (TCZ + placebo group). Treatment efficacy was evaluated at week 24. Five hundred and twelve patients (92%) completed the initial 24-week period. Of the TCZ + MTX group, 71.8%, 45.1% and 24.7% achieved ACR20, 50 and 70 responses, respectively and 40.4% achieved DAS remission. Of the TCZ + placebo group, 70.7%, 46.9% and 25.7% achieved ACR20, 50 and 70 response, respectively, and 34.8% achieved DAS remission. There were no differences in the ACR scores and DAS remission rates between the two groups. The onset of drug efficacy was rapid. Rates of AEs, serious AEs, and serious infections per 100 patient-years (PY) were 491, 21, and 6 for the TCZ + MTX group and 467, 18, and 6 for the TCZ group, respectively, with the most frequent AEs and serious AEs being infection. This study also analyzed X-ray and MRI changes after TCZ therapy. Structural analysis also indicated no difference between TCZ monotherapy and TCZ combined with MTX therapy.

The ACT-SURE study was a phase IIIb, open-label, single-arm, 6-month study.[56,57] In this study, 1,681 patients with inadequate responses to DMARDs or TNF inhibitors were registered. Patients were randomly divided into groups that were treated with 8 mg/kg TCZ alone every 4 weeks (TCZ monotherapy group) or 8 mg/kg TCZ in combination with DMARDs (TCZ + DMARDs group) and were evaluated at 24 weeks. Of the TCZ monotherapy group, 43.5% and 23.8%, achieved ACR50 and 70 responses, respectively, and 57.9%, 18.6% and 21.3% achieved DAS, CDAI and SDAI remission, respectively. Of the TCZ + DMARDs group, 47.2% and 26.8% achieved ACR50 and 70 responses, respectively and 49.8%, 20.0% and 21.5% achieved DAS, CDAI and SDAI remission, respectively. Thus, TCZ as monotherapy showed the same efficacy as TCZ + DMARDs.

The ACT-STAR study was a 24-week, prospective, open-label study that was performed in the US. In this study,[58,59] 886 patients with moderate-to-severe active RA who had an inadequate response to current biologic or nonbiologic DMARDs were registered and divided into random groups that were treated with 4 mg/kg

TCZ + DMARDs, 8 mg/kg TCZ + DMARDs or 8 mg/kg TCZ monotherapy. At week 8, patients treated with 4 mg/kg TCZ + DMARDs who did not achieve ACR20 had their TCZ dose increased to 8 mg/kg. For patients on 8 mg/kg TCZ + DMARDs, the dose could be decreased any time for safety reasons. Seven hundred and thirty one (82.5%) patients completed the study. Over half of the 4 mg/kg TCZ-treated patients were eventually switched to 8 mg/kg TCZ. Of the 4 mg/kg TCZ + DMARDs subgroup, 43.1%, 22.8% and 6.9% achieved ACR20, 50 and 70 responses, respectively at week 24 and 17.6% achieved DAS remission. In the 8 mg/kg TCZ + DMARDs subgroup, 48.9%, 22.6% and 8.1% achieved ACR20, 50 and 70 responses, respectively at week 24 and 22.8% achieved DAS remission. In the 8 mg/kg TCZ monotherapy subgroup, 47.3%, 20.9%, 8.1% achieved ACR20, 50 and 70 responses, respectively at week 24 and 15.8% achieved DAS remission. Safety profiles and efficacy were similar for the TCZ monotherapy and TCZ-combination with DMARDs groups.

Remission has recently become the current treatment goal for RA. An increased number of patients have achieved this goal in clinical trials.[60] The duration of TCZ efficacy after cessation of TCZ treatment following DAS28 remission was demonstrated in the DREAM (Drug free Remission after cessation of Actemra Monotherapy) study.[61] Efficacy following cessation of TCZ treatment was 35.1% and 13.4% at 24 and 52 weeks, respectively. Serum levels of IL-6 and MMP-3 are useful markers for identifying patients who may be able to discontinue TCZ without acute disease flare-up. In addition, the result that TCZ could induce remission again following recurrence after TCZ cessation was demonstrated by the RESTORE (Retreatment Efficacy and Safety to Tocilizumab in patients with rheumatoid arthritis at Recurrence) study.[62]

Safety

Cochrane review summarized the safety profile of TCZ from 8 RCTs (3,334 participants; 2,233 treated with TCZ and 1,101 controls).[42] It is demonstrated that patients treated with TCZ are 1.2 times more likely to have any AE (absolute%; 74% vs. 65%) and 0.6 times less likely to be withdrawn from treatment for any reason (absolute%; 8.1% vs. 14.9%). Nishimoto et al also reported the safety profile of TCZ monotherapy including 6 initial RCTs and 5 long-term extension studies in Japan.[63] For these studies, 601 patients with a total exposure of 2,188 PY were enrolled. The medial treatment duration was 3.8 years. The incidence of AEs, including abnormal laboratory test results, was calculated as 465.1/100 PY. Infection is the most common serious AE (6.22/100 PY). Furthermore, a systematic literature review to assess the risk of AEs for RA patients treated with TCZ reported that pooled odds ratios (ORs) indicated a statistically significant increased risk of AEs for patients treated with 8 mg/kg of TCZ plus methotrexate compared with controls (OR = 1.53; 95%CI = 1.26–1.86) in addition to a heightened risk of infection (OR = 1.30; 95%CI = 1.07–1.58). However, no increase in the incidence of malignancy or hepatitis was detected.

The safety profile of TCZ combination therapy was reported in 2011.[64] This analysis included 5 core phase III RCT, 2 ongoing extension trials, 1 clinical pharmacology study and 2 patient populations; a control population (4,199) and a TCZ-treated population (4,009). Overall AE and serious AE rates were 278.2/100 PY and 14.4/100 PY, respectively. These events included serious infections (4.7/100 PY), opportunistic infections (0.23/100 PY), gastrointestinal perforations (0.28/100 PY), malignancy (1.1/100 PY), myocardial infarction (0.25/100 PY) and stroke (0.19/100 PY). Another report demonstrated that analysis of the pooled ORs revealed a statistically significant increased risk of AEs in the 8 mg/kg TCZ with MTX group compared with controls (OR = 1.53; 95%CI = 1.26–1.86). The risk of infection was significantly higher in the 8 mg/kg TCZ with MTX group compared with controls (OR = 1.30; 95%CI = 1.07–1.58). In contrast, no increased incidence of malignancy, tuberculosis reactivation or hepatitis was seen.[65]

The safety profile of TCZ in real life medical-care in Japan was reported in 2011.[66,67] In Japan, all patients treated with TCZ were registered in the all-patient postmarketing surveillance (JPMS-TCZ) program and were observed for 28 weeks. From April 2008 to August 2010, 12,799 patients were registered in JPMS-TCZ. The interim analysis of 3,881 patients has been published[66] and the final analysis of the 7,901 patients of JPMS-TCZ was presented in ACR2011.[67] The incidence of total AEs and serious AEs was 43.9% and 9.6%, respectively. Infections and infestation

were the most frequent AEs (11.1%) and serious AEs (0.5%). The incidence of serious AEs was higher in the patients whose disease duration was ≥10 years. The DAS and Boolean remission rate was higher in patients whose disease duration was <2 years and the remission rate was higher in TNF inhibitor-naïve patients. Combining MTX with TCZ did not influence the remission rates. Surprisingly the serious AEs of TCZ monotherapy were slightly higher than those of TCZ and MTX combination therapy. The standard mortality ratio of TCZ (1.15; 95%CI = 1.12–2.46) was comparable with that of a standard Japanese patient cohort (between 1.46; 95%CI = 1.32–1.60 and 1.90; 95%CI: 1.75–2.07).[68]

Long-term safety was also analyzed in RCTs.[69] Rates of serious AEs, serious infections, and cardiovascular events have remained stable with continued exposure to TCZ in long-term clinical trials. Infection was the most frequent serious AE. The most commonly reported infections in RCT were pneumonia (0.9/100PY) and skin or soft tissue infections (0.9/100PY). The rates of serious infections remained stable for 5 years indicating that continued administration of TCZ did not increase the risk of such infections.

In the JPMS-TCZ study, the rate of serious respiratory infections was 1.77/100 PY in the TCZ cohort and 0.53/100 PY in a standard Japanese patient cohort.[70] The standardized incidence ratio (SIR) of serious respiratory infection in the TCZ cohort was 2.35 (95%CI = 1.66–3.24), standardized for age, sex and corticosteroid use. This risk was comparable with that associated with TNF inhibitors. As with other biologics, careful observation is necessary during administration of TCZ. In particular, TCZ has a strong down-regulatory effect on acute-phase reactants such as CRP. As a result, the consensus opinion issued a special caution that CRP cannot be used as a diagnostic indicator for early infections in patients treated with TCZ.[71] White blood cell count and neutrophil counts are usually decreased, especially just after TCZ injection, but this decrease was not related to the incidence of infection.[72]

Tuberculosis and opportunistic infections have been observed in clinical trials of TCZ (0.3/100PY).[70] However, half of these events were reported as non-serious infections. The reactivation of tuberculosis is a major concern during TNF inhibitor treatment.[73] In a mouse model, anti-IL-6R Ab-treated mice survived for more than 200 days after TB challenge, whereas the anti-TNF-α Ab-treated mice all died between 120 and 181 days.[74] In addition, interferon (IFN)-γ induction by the tuberculosis antigen was suppressed in the presence of TNF inhibitors (IFX and ETN) but not in the presence of TCZ.[75] Although it seems likely that the incidence of reactivation of tuberculosis is lower during TCZ treatment, further detailed study will be needed to clarify this point. The consensus opinion recommended that patients should be screened for tuberculosis. Some cases of localized Herpes zoster infection occurred in clinical trials, but the relationship between TCZ administration and these infections was unclear. Patients with active hepatitis C or B were excluded from the clinical trials, so no data has been reported regarding TCZ and HBV or HCV infections.

Clinical trials and the above-mentioned combined-analysis showed that the rate of gastrointestinal perforation following TCZ treatment was 0.26/100 PY.[69] In the JPMS-TCZ study, 7 gastrointestinal perforations were reported in 6 patients.[66] In the worldwide Roche clinical trials, 26 (0.65%) cases of gastrointestinal perforation were found among patients with RA treated with TCZ at a rate of 1.9/1,000 PY and most cases appeared to be complications of diverticulitis.[76] This rate lies between the reported rate of gastrointestinal perforations for corticosteroids (3.9/1,000 PY) and TNF inhibitors (1.3/1,000 PY) in the United Health Care database. The concomitant use of corticosteroids or non-steroid anti-inflammatory drugs with TCZ may increase this risk. The consensus opinion states that TCZ should be used in caution in patients with history of GI perforation, intestinal ulcers or diverticulitis.

Increases in mean fasting levels of plasma lipids such as total cholesterol, low-density lipoprotein, triglycerides and high-density lipoprotein, were seen in 20%–30% of patients treated with TCZ. The increase in lipid level resulting from TCZ treatment is perhaps mediated by an affect on lipoprotein receptor expression, since it has been recently shown that overproduced IL-6 decreases blood lipid levels via upregulation of the very-low-density lipoprotein (VLDL) receptor.[77] The consensus opinion recommended that lipid levels be monitored 1–2 month after initiation of treatment and then every 6 months. In spite of the elevation of lipids, combined analysis

of the data of clinical trials showed no apparent increase in cardiac events in a follow-up of up to 5 years. In the analysis, rates of myocardial infarction (0.3/100 PY) and stroke (0.2/100 PY) did not exceed the expected rates of RA patients.[69] In contrast, oxidative stress was extremely low in patients with RA treated with TCZ.[78] Moreover, hemoglobin (Hb) A_{1c} levels and insulin sensitivity were improved by TCZ treatment.[79,80]

Combined-analysis showed that the overall ratio of malignancy occurrence during TCZ treatment was 1.2/100 PY.[69] This ratio did not increase with the duration of TCZ treatment over a median duration of 3.6 years. Furthermore, the SIR for malignancy was 1.1/100 PY, which was considered to be within the range expected of RA patients. Although there is no report regarding increased incidences of malignancy during TCZ therapy, the use of TCZ for treatment of RA patients with malignancy cannot be recommended.

Many patients treated with TCZ have shown a decrease in absolute neutrophil count. This decrease usually occurs early after administration and is transient. There was no clear relationship between this neutropenia and an increase in infections.[72] The consensus recommended that complete blood counts should be monitored regularly (every 4–8 weeks).

Hepatic aminotransferase such as L-aspartate aminotransferase (AST) and L-alanine aminotransferase (ALT) and bilirubin elevations may occur in patients treated with TCZ. In the JPMS-TCZ study, abnormal hepatic function was observed in 8.5% and 5.5% of TCZ-treated patients with or without MTX.[66,67] Bilirubin elevations, mostly indirect, may occur independently. Liver function should be monitored regularly.

Serious infusion reactions related to TCZ treatment are rare. In the combined analysis, 8 out of a total of 4,009 patients showed anaphylactic infusion reactions.[69] Most of infusion reaction of TCZ occurs the beginning of TCZ therapy.

The safety of surgical intervention in patients with RA treated with TCZ has been reported.[81] Postoperative surgical site infections were not increased during TCZ therapy. TCZ is recommended to be withheld at least 14 days before major surgical procedures.[69]

There are no data available regarding the safety of TCZ treatment during pregnancy and lactation. Although IL-6-deficient mice are perfectly viable,[82] IL-6 was reported to reduce recurrent abortion in an animal model.[83] However, the effect of TCZ on embryonic and fetal development is unknown. At present the use of TCZ throughout pregnancy cannot be recommended.

Place in Therapy

A number of biologics are currently available for the treatment of RA, including TNF inhibitors (infliximab; IFX, etanercept; ETN, adalimumab; ADA, golimumab; GOL, and certolizumab pegol; CEL), an IL-1 antagonist (anakinra; ANK), a B-cell depletor (rituximab; RTX), an IL-6 receptor inhibitor (TCZ), and a T-cell activation blocker (abatacept; ABA). While all of these biologics have proven effectiveness in RCTs, very limited head-to-head comparative studies are available. Recently, meta-analysis has allowed indirect comparisons between TCZ and other biologics. Bergman et al reported such an indirect comparison of TCZ and other biologics.[84] The effectiveness of TCZ appeared to be comparable to that of other biologics (ABA, ADA, ETN, IFX and RTX) in terms of ACR20 and ACR50 responses. Turkstra et al reported a mixed treatment comparison of the short-term efficacy of nine biologics (ABA, ADA, ANK, CEL, ETN, GOL, IFX, RTX, and TCZ) in patients with established RA.[85] As shown in Figure 4, the ACR50 response rate of TCZ at 6 months is comparable to that of ABA, ADA, ETN, GOL, IFX and RTX. ANK is inferior to TCZ and CEL may be superior to TCZ. Salliot et al reported an indirect comparison of the efficacy of TCZ in RA patients with inadequate response to TNF inhibitors (ADA, ETN and IFX).[86] No significant difference was found between TCZ and other biologics (ABA, GOL, and RTX). A comparison of AEs of nine biologics was reported in Cochrane review.[87] As shown in Figure 5, serious AEs of TCZ were comparable to those of other biologics except for ABA and ANK. These indicate that the efficacy and tolerability of TCZ is comparable to TNF inhibitors. Although TNF inhibitors are now recommended as first-line biologics,[88] TCZ also has a potential capacity as a first-line biologic for RA patients who cannot use sufficient MTX, or is appropriate for the treatment of RA patients with secondary failure of TNF inhibitors. In the real world of rheumatology practice, there are RA patients who cannot use sufficient MTX because of AEs. TEMPO[89] and PREMIER[90] studies demonstrated no substantial differences in clinical responses between TNF inhibitors used as

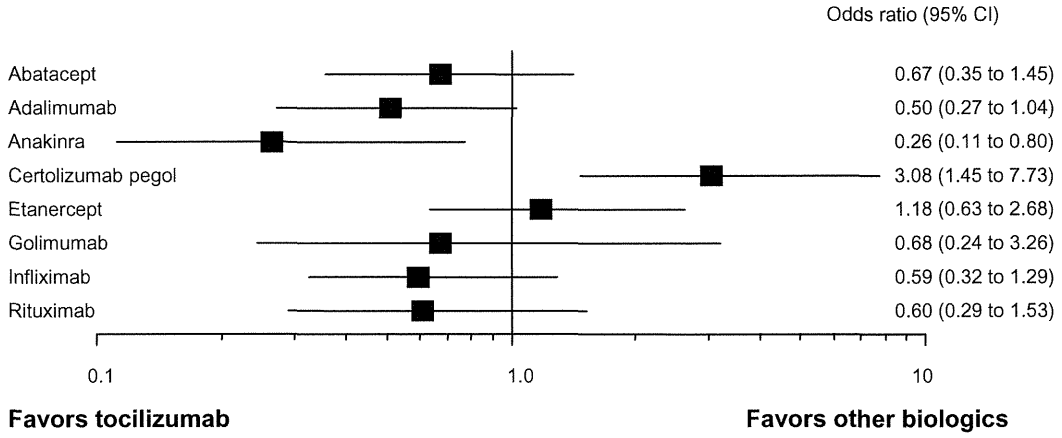

Figure 4. Indirect comparison of the efficacy of toclizumab and other biologics in RA.
Notes: Indirect comparison of ACR50 response rate at 6 months-treatment of biologics (tocilizumab vs. 8 other biologics).[85] The efficacy of tocilizumab is comparable to other biologics except for certolizumab pegol and anakinra. Other analyses of the efficacy (tocilizumab vs. TNF inhibitors) show similar results.[84,86]

monotherapy (ETN and ADA) and MTX.[91] British Society for Rheumatology Biologics Register (BSRBR) also concluded better responses of TNF inhibitors, when used in combination with MTX, than those used as monotherapy.[92] In contrast, ACT-RAY, ACT-SURE and ACT-STAR indicated that there was no difference of the efficacy between TCZ monotherapy and that with MTX.[53–59] These results suggest that TCZ has advantage for the treatment of RA patients who are not tolerable to receive MTX, since TCZ provides the excellent efficacy even without concomitant use of MTX.

In the real world of rheumatology practice, there are also RA patients who fail to respond to TNF inhibitors (primary failure) or lose response to them (second failure).[93] In such case, the switching of biologics is required. However, the probability of responding to a second TNF inhibitor is lower than that of responding to the first one.[94] For patients with primary failure it is conceivable that TNF may not be a major effector cytokine, so that change of target from TNF to non-TNF molecules including IL-6 is reasonable. TCZ is also efficacious for patients with second TNF failure.[38,44,45,56–59] These findings indicate TCZ is a good indication for the treatment of RA patients who are intolerable to MTX or non-responders to TNF inhibitors. Finally, it is worthy of describing here that clinical trial of subcutaneous injection of TCZ is currently undergoing. If the subcutaneous TCZ injection will bring the similar efficacy to the intravenous one, it would be convenient for patients.

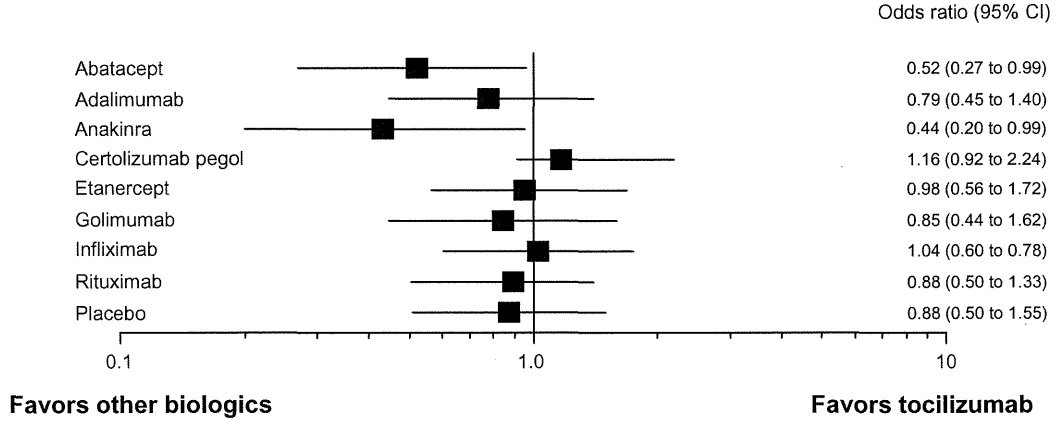

Figure 5. Indirect comparison of serious adverse events of tocilizumab and other biologics in RA.
Notes: Indirect comparison of serious adverse events of biologics (tocilizumab vs. 8 other biologics and placebo).[87] The safety profile of tocilizumab is comparable to other biologics except abatacept and anakinra.

Conclusion

IL-6 is a key cytokine in immune activation and inflammation. TCZ exerts a blocking effect on IL-6 function and exhibits excellent efficacy and tolerability for RA treatment. Because of limited evidence of TCZ in the USA, at the present time the ACR recommendations for the treatment of RA does not recommend TCZ as a first-line biologic. However, recent advance indicates that TCZ has a certain advantage for patients who cannot use MTX or fail to respond to TNF inhibitors. We believe that TCZ possesses a capacity as a first-line biologic for the treatment of RA patients, although further clinical experience of TCZ will be required.

Conflict of Interest

A.O. has received a consulting fee, as a medical adviser from Chugai Pharmaceutical Co., Ltd. The other authors declare no conflict of interest.

Disclosures and Ethics

As a requirement of publication author(s) have provided to the publisher signed confirmation of compliance with legal and ethical obligations including but not limited to the following: authorship and contributorship, conflicts of interest, privacy and confidentiality and (where applicable) protection of human and animal research subjects. The authors have read and confirmed their agreement with the ICMJE authorship and conflict of interest criteria. The authors have also confirmed that this article is unique and not under consideration or published in any other publication, and that they have permission from rights holders to reproduce any copyrighted material. Any disclosures are made in this section. The external blind peer reviewers report no conflicts of interest.

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Review Article

Tocilizumab for the Treatment of Rheumatoid Arthritis and Other Systemic Autoimmune Diseases: Current Perspectives and Future Directions

Atsushi Ogata and Toshio Tanaka

Department of Respiratory Medicine, Allergy and Rheumatic Diseases, Osaka University Graduate School of Medicine, Suita City, Osaka 565-0871, Japan

Correspondence should be addressed to Toshio Tanaka, ttanak@imed3.med.osaka-u.ac.jp

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Interleukin (IL)-6 is a cytokine featuring redundancy and pleiotropic activity. While IL-6, when transiently produced, contributes to host defense against acute environmental stress, continuous dysregulated IL-6 production plays a significant pathological role in several systemic autoimmune diseases. In response to the expectation that IL-6 blockade would constitute a novel therapeutic strategy for the treatment of these diseases, tocilizumab, a humanized anti-IL-6 receptor antibody, was developed. Clinical trials have verified the efficacy and the safety of tocilizumab for patients with rheumatoid arthritis, resulting in approval of this innovative biologic for the treatment of rheumatoid arthritis in more than 90 countries worldwide. Pathological analyses of the effect of IL-6 on the development of autoimmune diseases and a considerable number of case reports and pilot studies have also indicated the beneficial effects of this antibody on other systemic autoimmune diseases, including systemic lupus erythematosus, systemic sclerosis, polymyositis, and large-vessel vasculitis.

1. Introduction

Interleukin (IL)-6 is a cytokine featuring redundancy and pleiotropic activity. It was successfully cloned in 1996 as a B-cell differentiation factor, which promotes B-cell differentiation into antibody-producing cells [1]. Subsequent in vitro studies and analysis of IL-6 transgenic mice have shown that IL-6 acts not only on B cells but also on T cells, hepatocytes, hematopoietic progenitor cells, and various other cells [2–4]. One of the important functions of IL-6 is the differentiation of $CD4^{positive}$ naïve T cells into effector cells. IL-6 in the presence of TGF-β promotes naïve T-cell differentiation into Th17 cells, while IL-6 inhibits TGF-β-induced regulatory T-cell (Treg) differentiation [5], causing imbalance between Th17 and Treg, which is a primary pathogenic factor in several autoimmune diseases [6].

IL-6 transmits its signal through its binding to transmembrane receptors or the soluble IL-6 receptor (IL-6R) [7, 8]. After binding of IL-6 to IL-6R, the resultant IL-6/IL-6R complex associates with gp130 and induces homodimerization of gp130, which triggers signal transduction system [9].

The pathological significance of IL-6 for diseases was first demonstrated in a case of cardiac myxoma [10]. The culture fluid obtained from the myxoma tissues of a patient who presented with fever, arthritis with positivity for antinuclear factor, increased C-reactive protein (CRP) levels and hypergammaglobulinemia and was diagnosed with undifferentiated connective tissue disease, contained a large quantity of IL-6, which suggested that IL-6 might contribute pathologically to chronic inflammation and autoimmunity. Subsequent studies have shown that dysregulation of IL-6 production is implicated in the pathogenesis of Castleman's disease [11], rheumatoid arthritis (RA) [12], and various other autoimmune, inflammatory, and malignant diseases [2–4].

Because of the biological activities of IL-6 and its pathological role in diseases, it was anticipated that IL-6 blockage would constitute a novel treatment strategy for autoimmune and inflammatory diseases [4, 13–15]. To this

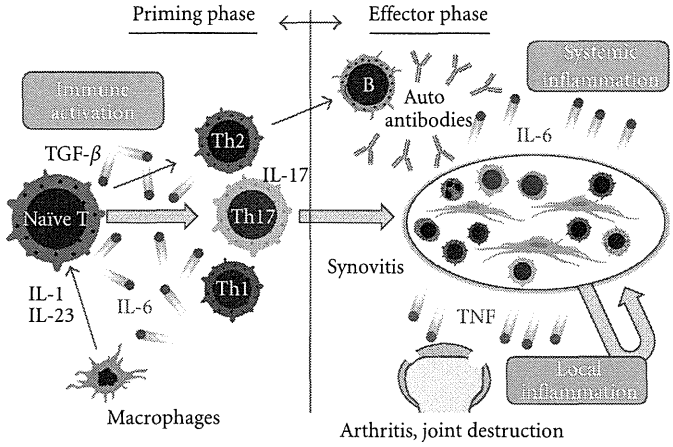

FIGURE 1: Pathological role of IL-6 in rheumatoid arthritis. IL-6 is important for development of Th17 and induction of autoantibodies such as rheumatoid factor. Activated Th17 cells and autoantibodies generate pannus in combination with activated fibroblastic synoviocytes, macrophages, and lymphocytes. Inflamed synovitis such as pannus is a major source of inflammatory cytokines including IL-6, and systemic inflammation (resulting in production of acute phase protein, anemia, and fatigue) is mainly mediated by IL-6. Tumor necrosis factor (TNF) plays a major role in the progression of local types of inflammation (arthritis) such as arthralgia, swelling, and joint destruction but plays a minor role during the priming phase.

end, tocilizumab was developed, which is a humanized anti-IL-6R monoclonal antibody (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. Tocilizumab blocks IL-6-mediated signal transduction by inhibiting IL-6 binding to transmembrane and soluble IL-6R.

2. Approval of Tocilizumab for the Treatment of Rheumatoid Arthritis

2.1. Pathological Role of IL-6 in Rheumatoid Arthritis. RA is a chronic, progressive inflammatory disease of the joints and surrounding tissues accompanied by intense pain, irreversible joint destruction, and systemic complications such as fatigue, anemia, and fever [16]. At the local level, inflammatory cells invade the otherwise relatively acellular synovium leading to neovascularization, synoviocyte hyperplasia, and formation of pannus tissue, which in turn causes destruction of cartilage, erosion of the adjacent bone, and, ultimately, loss of function of the affected joint. The biological activities of IL-6 such as proinflammatory activity, augmentation of synovial fibroblast proliferation, osteoclast differentiation, matrix metalloproteinase (MMP), and vascular endothelial growth factor (VEGF) production, as well as lymphocyte differentiation and its elevation in both serum and synovial fluids of patients with RA [17–22] indicate that IL-6 is one of the key cytokines involved in the development of RA.

It has been demonstrated in animal model of RA, that are type II collagen-induced arthritis (CIA), and antigen-induced arthritis, IL-6 performs a major role in the development and progression of joint destruction, while IL-6 deficiency generated by gene knockout or IL-6 blockade by means of anti-IL-6R Ab reduces the incidence and severity of arthritis in these models [23–28]. In the CIA model, immunization with type II collagen predominantly increased the frequency of Th17 cells and treatment of mice with anti-IL-6R Ab during priming markedly suppressed the induction of Th17 cells and arthritis development, while treatment with anti-IL-6R Ab on day 14 failed to suppress both Th17 differentiation and arthritis [29]. Similarly, 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 anti-IL-6R Ab on day 14, at the peak of arthritis, did not bring about any improvement in arthritis [30]. 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, CAIA was profoundly suppressed in $TNF^{-/-}$ mice but not in $IL\text{-}6^{-/-}$ mice [31], indicating that TNF may play a more significant role in the development of CAIA than IL-6. These observations suggest that in the priming phase IL-6 is a required factor for the activation of T cell response and production of antibodies specific for joint components and that in the effector phase TNF is the main generator of arthritis [32]. We found that tocilizumab was not effective for clinical improvement in the condition of two patients with psoriatic arthritis, for whose development immune activation does not appear to be required [33]. The clinical antiarthritic effect of tocilizumab is slower than that of TNF inhibitors, which may be due to the different pathological roles of IL-6 and TNF in the development of RA (Figure 1).

2.2. Efficacy of Tocilizumab in Randomized Controlled Trials. As shown in Table 1, seven phase III clinical trials of tocilizumab subsequent to phase I and II studies demonstrated its efficacy either as monotherapy or in combination with disease-modifying antirheumatic drugs (DMARDs) for adult

Table 1: Phase III randomized controlled trials of tocilizumab for RA patients. Summary of the results of seven phase III randomized controlled trials of tocilizumab. DMARDs: disease modifying antirheumatic drugs, IR: inadequate response, TCZ: tocilizumab, anti-TNF: anti-tumor necrosis factor inhibitor, MTX: methotrexate.

Study	Reported year	Population	Week at evaluation	Treatment arms	Patient (n)	Response rates (%)			Remission rate (%)	Radiological progression		
						ACR20	ACR50	ACR70	DAS28< 2.6	TSS: Total Sharp score	ES: Erosion score	JSNS: Joint space narrowing score
SAMURAI	2007	DMARDs IR	52 W	TCZ (8)	157	78	64	44	59	2.3	0.9	1.5
				DMARDs	145	34	13	6	3	6.1	3.2	2.9
TOWARD	2008	DMARDs IR	24 W	TCZ (8) + DMARDs	803	61	38	21	30			
				DMARDs	413	25	9	3	3			
RADIATE	2008	Anti-TNF IR	24 W	TCZ (4) + MTX	161	30	17	5	8			
				TCZ (8) + MTX	170	50	29	12	30			
				placebo + MTX	158	10	4	1	2			
OPTION	2008	MTX IR	24 W	TCZ (4) + MTX	186	48	31	12	13			
				TCZ (8) + MTX	191	59	44	22	27			
				placebo + MTX	189	26	11	2	1			
SATORI	2009	MTX IR	24 W	TCZ (8)	61	80	49	30	43			
				MTX	64	25	11	6	2			
AMBITION	2010	MTX, anti-TNF naïve	24 W	TCZ (8)	286	70	44	28	34			
				MTX	284	53	34	15	12			
LITHE	2011	MTX IR	52 W	TCZ (4) + MTX	394	47	29	16	30	0.34	0.21	0.13
				TCZ (8) + MTX	398	56	30	20	47	0.29	0.17	0.12
				MTX	393	25	10	4	8	1.13	0.71	0.42

Table 2: Reevaluation of antirheumatic effects of tocilizumab in actual medical practice. Summary of the contents of the three actual medical practice of tocilizumab for rheumatoid arthritis.

Study	Country	Patient number	Registry	Evaluation
TAMARA	Germany	286	Sep. 2008~Sep. 2009	Disease activity EULAR response ACR response Adverse events 2011 ACR/EULAR remission
DAMBIO	Denmark	178	~April 2010	Disease activity EULAR response Drug survival
REACTION	Japan	229	April 2008~March 2009	Disease activity EULAR response Adverse events Drug survival

patients with moderate to severe RA [34–40]. A Cochrane database systematic review concluded that tocilizumab-treated patients taking concomitant methotrexate were four times more likely to achieve American College of Rheumatology (ACR) 50 improvement (absolute %, 38.8% versus 9.6%) and 11 times more likely to achieve Disease Activity Score (DAS) remission (30.5% versus 2.7%) than patients taking a placebo [41]. Furthermore, the SAMURAI [34] and LITHE studies [40] proved that radiological damage of joints was significantly inhibited by the treatment. The findings of the RADIATE trial showed that, among RA patients who had previously discontinued TNF inhibitors 50% achieved ACR20, 28.8% ACR50, and 12.4% ACR70 responses [36]. The ACR improvement and DAS remission criteria include an acute-phase reactant component, so that there was 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 [42, 43].

2.3. Efficacy of Tocilizumab in Actual Medical Practice. On the basis of the excellent results obtained for the efficacy of tocilizumab, it was approved in April 2008 for the treatment of RA in Japan. The recommended posology of tocilizumab (proprietary name, Actemra) is 8 mg/kg, every 4 weeks. Subsequently, the European Medicines Agency approved tocilizumab (proprietary name, RoACTEMRA) for RA in January 2009 at a recommended dose of 8 mg/kg. In the United States, it was approved for RA in January 2010, but 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. While the dosage differs among countries, tocilizumab has now been approved for the treatment of RA in more than 90 countries worldwide [14].

In addition to clinical trials, the efficacy of tocilizumab was reconfirmed in actual medical practice. The finding by the three recent studies, the German phase IIIb real-life study (TAMARA study) [44, 45], the Danish nationwide cohorts of RA patients (DANBIO registry) study [46], and the multicenter retrospective real-life study (REACTION study) [47, 48] are shown in Table 2. In the TAMARA study, 286 patients were registered for an analysis of the effectiveness and safety [44, 45], 41.6% of whom had previously been treated with TNF inhibitors. ACR50 and ACR70 response rates at week 24 were 50.7% and 33.9%, respectively, while 47.6% of the patients achieved DAS remission and 54.9% the European League Against Rheumatism (EULAR) good response. Remission rates 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. For the DANBIO registry in Denmark, 178 patients with RA treated with tocilizumab were identified [46]. 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% and 84%, respectively. These response rates were comparable to those found 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 study for an analysis of the effectiveness of tocilizumab [47, 48]. Clinical remission at week 52 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, and were the same for those with or without previous anti-TNF treatment. These results indeed show the efficacy of tocilizumab for the treatment of RA in actual medical practice.

2.4. Safety Profile of Tocilizumab. The safety and tolerability profiles of tocilizumab monotherapy for Japanese RA patients obtained from six initial trials and five long-term extensions have been published [49]. For these studies, 601 patients with a total exposure to tocilizumab of 2,188 patient-years (pt-yr) were enrolled. The medial treatment duration was 3.8 years. The incidence of adverse events

(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). Of the patients treated more than 5 years, 59.7% met the DAS28 remission criteria at 5 years, which demonstrates the excellent tolerability and high efficacy of tocilizumab. In addition, a systemic literature review to assess the risk of AEs for RA patients treated with tocilizumab reported that pooled odds ratios (ORs) indicated statistical significance for an increased risk of AEs for patients treated with 8 mg/kg of tocilizumab plus methotrexate compared with controls (OR = 1.53; 95%CI = 1.26–1.86), as well as a heightened risk of infection (OR = 1.30; 95%CI = 1.07–1.58) [50]. However, no increases in the incidence of malignancy or hepatitis were detected.

The results of an interim analysis of a postmarketing surveillance of all patients treated with tocilizumab in Japan were recently reported [51]. This analysis comprised 3,881 patients who received 8 mg/kg of tocilizumab every 4 weeks, and was observed for 28 weeks. Occurrence of a total of 3,004 AEs in 1,641 patients (167/100 pt-yr) and 490 serious AEs in 361 patients (27/100 pt-yr) was reported. The most frequent AE and serious AE were infection at 31/100 pt-yr and 9/100 pt-yr, respectively, with the majority of infections being pneumonia and cellulitis. Cardiovascular events were observed in 0.9% (myocardial infarction in 4 patients or 0.1%). 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. The increased lipid level resulting from tocilizumab administration is perhaps mediated by its effecting on lipoprotein receptor expression, since it was recently shown that overproduction of IL-6 reduces blood lipid levels via upregulation of very-low-density lipoprotein receptors [52]. In contrast, we and others observed that HbA1c levels and insulin sensitivity improved as a result of tocilizumab treatment [53, 54]. 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 tocilizumab is acceptable in the actual clinical setting.

Seven cases of gastrointestinal (GI) perforation in six patients were reported in this postmarketing 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 [55]. This rate is intermediate between the rates of GI perforations 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 [56], 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 Ab [57]. In addition, we showed that tuberculosis antigens-induced interferon (IFN)-γ production was suppressed by the addition of TNF inhibitors (infliximab and etanercept) but not of tocilizumab [58]. Although it seems likely that the incidence of reactivation of tuberculosis is lower during tocilizumab treatment than that during anti-TNF treatment, further detailed studies will be needed to clarify this point.

2.5. The Place of Tocilizumab in Rheumatoid Arthritis Treatment. A number of biologics are available for the treatment of RA. These include anti-TNF blockers (infliximab, etanercept, adalimumab, golimumab, and certolizumab), an IL-1 antagonist (anakinra), a B-cell depletor (rituximab), an IL-6 receptor inhibitor (tocilizumab), and a T-cell activation blocker (abatacept). 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, 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. The findings of the RADIATE trial showed that RA patients who had previously discontinued TNF inhibitors, mainly due to their inefficacy, achieved ACR20/50/70 responses of 50%, 28.8%, and 12.4%, respectively, when tocilizumab was administered at 8 mg/kg every four weeks [36]. At present, tocilizumab is likely to be prescribed as a second-line biologic therapy but will have to overcome significant competition from established anti-TNF therapies.

It is anticipated that tocilizumab will be selected as a first-line biologic for moderately to severely active RA patients with certain complications. AA amyloidosis is a serious complication of RA, and amyloid fibril deposition causes progressive deterioration in various organs [59, 60]. Since the gene activation of serum amyloid A, a precursor protein of amyloid A fibril, depends primarily on IL-6 [61, 62], tocilizumab administration was found to promptly reduce serum concentrations of SAA, just as in the case of CRP [60]. Three case reports showed the clinical ameliorative effect of tocilizumab on gastrointestinal symptoms due to intestinal amyloidosis [63–65], and amyloid A fibril deposits were found to have disappeared in two cases after three injections of tocilizumab [63, 65]. This suggests that tocilizumab may be suitable as a first-line drug for RA patients who are complicated with or are at high risk of developing AA amyloidosis.

2.6. Drug-Free Remission Rate. Remission induction is the current goal for RA, and with the development of biological modifiers, a growing number of RA patients has been able to achieve this goal [66]. The long-term efficacy after cessation of tocilizumab followed by DAS28 remission was demonstrated in the DREAM (drug-free remission after cessation of actemra monotherapy) study [67]. The continuous rate

of tocilizumab-free efficacy was 35.1% at 24 weeks and 13.4% at 52 weeks. Serum levels of IL-6 and MMP-3 are useful markers for identifying patients who may be able to discontinue tocilizumab without risk of recurrence. In addition, the RESTORE study (retreatment efficacy and safety to tocilizumab in patients with rheumatoid arthritis at recurrence) demonstrated that retreatment of all relapsed patients with tocilizumab resulted in re-remission [68].

3. Therapeutic Implications of Tocilizumab for Other Systemic Autoimmune Diseases

3.1. Systemic Lupus Erythematosus. Systemic lupus erythematosus (SLE) is a multisystem autoimmune disorder with a broad spectrum of clinical presentations of unknown etiology that mainly affects young women [69]. The pathogenesis of SLE remains unclear, but the concept of apoptosis goes some way towards explaining how the immune system may recognize mainly intracellular antigens. Defects in the clearance of apoptotic cells have been recognized in SLE patients, leading to aberrant uptake by macrophages, which then present intracellular antigens to T and B cells, thus driving the autoimmune process [70]. Cytokine dysregulation is pervasive, and its expression profiles may serve as a marker of disease activity and severity. Recent findings have highlighted type I interferon pathway [71] or Th17 cell activation [72] in the pathogenesis of SLE.

Levels of CRP have been shown to rise in acute illness but not in SLE flares, indicating that IL-6, a major regulator of CRP production, has a minor role in SLE development. However, recent findings suggest that CRP dysregulation also plays a part in the pathogenesis of SLE [73] and SLE may well be a potential target for IL-6 blockade [74]. Serum IL-6 levels of SLE patients were elevated [75–77]. Urinary excretion and renal expression of IL-6 was elevated in SLE patients with active proliferating lupus nephritis [76, 78–81], as were IL-6 levels in the cerebrospinal fluid of SLE patients with central nervous system involvement [82]. Compared to healthy controls, SLE patients had significantly more IL-6 secreting peripheral blood mononuclear cells [83, 84]. Lymphoblastoid cells isolated from SLE patients produced higher levels of IL-6 and blocking of IL-6 inhibited anti-double-stranded DNA (dsDNA) Ab production in vitro [85, 86], indicating that IL-6 is involved in autoantibody production. In murine SLE models, age-associated increases in serum IL-6, soluble IL-6R, and abnormal expression of IL-6R have been detected in MRL/lpr mice [87–89]. In old NZB/W mice, anti-IL-6 Ab reduced and exogenous IL-6 increased production of IgG dsDNA Ab by B cells [90, 91]. Furthermore, IL-6 administration exacerbated glomerulonephritis [92, 93], while IL-6 blockade by means of anti-IL-6R or anti-IL-6 Ab prevented the onset and progression of the disease [94, 95]. Mice with epidermal loss of JunB reportedly developed an SLE phenotype linked to increased epidermal IL-6 secretion, and facial skin biopsies of SLE patients displayed low levels of JunB protein expression, high IL-6, and activated STAT3 levels within lupus lesions [96]. These findings led to an open-label phase I dosage-escalation study of tocilizumab (2 mg/kg, 4 mg/kg or 8 mg/kg, every 2 weeks for 12 weeks) with an enrollment of 16 SLE patients with mild-to-moderate disease activity [97]. Significant improvement in the modified Safety of Estrogens in Lupus Erythematosus National Assessment version of the Systemic Lupus Erythematosus Disease Activity Index score was observed in 8 of the 15 evaluable patients, accompanied by a median reduction in anti-dsDNA Ab levels of 47%. The percentage of $CD38^{high}CD19^{low}IgD^{negative}$ plasma cells in the peripheral blood, which was higher for SLE patients than for normal controls (mean 5.3% versus 1.2%), was significantly reduced to 3.1% at 6 weeks. These results indicate that tocilizumab represents a promising therapeutic biologic for SLE.

3.2. Systemic Sclerosis. Systemic sclerosis (SSc) is a connective tissue disease, characterized by fibrosis of the skin and internal organs, vasculopathy, and immune abnormalities [98]. IL-6 is a definite therapeutic target in SSc [99]. IL-6 in the serum of SSc patients was reportedly elevated and the level correlated with the skin severity score [100–104]. Moreover, the culture supernatants of peripheral blood mononuclear cells and skin tissues from SSc patients contained higher concentrations of IL-6 than those from controls [105–109]. In vitro studies demonstrated that IL-6 may contribute to fibrosis by inducing collagen production [110] and induce α-smooth muscle actin (α-SMA) expression by dermal fibroblasts [111], leading to their differentiation into myofibroblasts. On the other hand, anti-IL-6 Ab suppressed procollagen type 1 production in fibroblasts derived from SSc patients in vitro [112]. SSc serum mediated largely by IL-6 was found to induce endothelial cell activation and apoptosis in endothelial cell-neutrophil cocultures [113]. IL-6 is also associated with humoral and cellular immunological abnormalities in SSc [98, 99]. IL-6 is thus thought to play a significant role in producing the characteristics of SSc. Moreover, in a SSc model mouse, induced by immunization with topoisomerase I and complete Freund's adjuvant, loss of IL-6 expression could ameliorate skin and lung fibrosis [114]. We also examined the clinical effect of tocilizumab on two diffuse SSc patients who had been resistant to conventional treatment regimens [115]. Six months after the treatment, both patients showed softening of the skin with reductions of 50.7% and 55.7% for the total z-score determined with the Vesmeter, a novel device for measuring the physical properties of the skin [116], and of 51.9% and 23% for the modified Rodnan total skin score. Histological examination showed thinning of the collagen fiber bundles and reduction of the number of α-SMA positive cells in the dermis. Since there are few therapeutic drugs for SSc at the present time [117], these improvements suggest that tocilizumab appears to be a promising biologic for the treatment of SSc.

3.3. Polymyositis. The inflammatory myopathies encompass a group of heterogenous muscle diseases which share the common clinical features of slowly progressive symmetrical muscle weakness, decreased muscle endurance, and