

Monoclonal antibodies in rheumatoid arthritis: comparative effectiveness of tocilizumab with tumor necrosis factor inhibitors

Toshio Tanaka^{1,2}
Yoshihiro Hishitani³
Atsushi Ogata^{2,3}

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

Abstract: Rheumatoid arthritis (RA) is a chronic inflammatory disease characterized by persistent joint inflammation, systemic inflammation, and immunological abnormalities. Because cytokines such as tumor necrosis factor (TNF)- α and interleukin (IL)-6 play a major role in the development of RA, their targeting could constitute a reasonable novel therapeutic strategy for treating RA. Indeed, worldwide clinical trials of TNF inhibiting biologic disease modifying antirheumatic drugs (bDMARDs) including infliximab, adalimumab, golimumab, certolizumab pegol, and etanercept as well as the humanized anti-human IL-6 receptor antibody, tocilizumab, have demonstrated outstanding clinical efficacy and tolerable safety profiles, resulting in worldwide approval for using these bDMARDs to treat moderate to severe active RA in patients with an inadequate response to synthetic disease modifying antirheumatic drugs (sDMARDs). Although bDMARDs have elicited a paradigm shift in the treatment of RA due to the prominent efficacy that had not been previously achieved by sDMARDs, a substantial percentage of patients failed primary or secondary responses to bDMARD therapy. Because RA is a heterogeneous disease in which TNF- α and IL-6 play overlapping but distinct pathological roles, further studies are required to determine the best use of TNF inhibitors and tocilizumab in individual RA patients.

Keywords: interleukin-6, rheumatoid arthritis, adalimumab, biologic

Introduction to rheumatoid arthritis (RA) and the development of targeted therapies

RA, a chronic disease affecting 0.5%–1% of adults, is characterized by persistent synovitis, systemic inflammation, and immunological abnormalities.^{1,2} Uncontrolled active RA causes joint damage, disability, diminished quality of life, and cardiovascular and other comorbidities. Although its exact pathogenesis is not fully understood, a multi-step progression has been proposed for the development of RA.¹ Environment–gene interactions promote a loss of tolerance to self-antigens that contain a citrulline residue generated by posttranslational modification, leading to an anticitrulline response by both T-cells and B-cells. Thereafter, the inflammatory response becomes localized in the joints and synovitis is initiated and perpetuated by positive feedback loops, promoting systemic disorders. Lymphocytes, other inflammatory cells, and their products contribute to the development of RA. For instance, many cytokines have been implicated in the pathogenesis of RA, including tumor necrosis factor (TNF)- α , interleukin (IL)-1, IL-6, IL-7, IL-15, IL-17A, IL-17F, IL-18, IL-21, IL-23, IL-32, IL-33, and granulocyte-macrophage colony stimulating factor.¹

Because TNF- α is an important mediator responsible for joint inflammation and destruction, it was the first cytokine to be targeted in the treatment of RA.^{2,3}

Correspondence: Toshio Tanaka
Department of Clinical Application of Biologics, Osaka University Graduate School of Medicine, 2-2 Yamada-oka, Suita City, Osaka 565-0871, Japan
Tel +81 6 6879 3838
Fax +81 6 6879 3839
Email ttanak@imed3.med.osaka-u.ac.jp

TNF- α is overexpressed in the synovial fluid of patients with RA. Moreover, TNF- α transgenic mice spontaneously develop arthritis. The first biologic disease modifying anti-rheumatic drugs (bDMARD) generated was infliximab (IFX), a chimeric monoclonal antibody (mAb) to TNF- α . Clinical trials of IFX proved that TNF blockade is highly efficacious in the treatment of RA and led to the development of other TNF inhibitors.

Another cytokine that has been targeted in the treatment of RA is IL-6, a typical cytokine featuring redundancy and pleiotropic activity that plays a key role in the development of RA.⁴⁻⁶ IL-6 promotes the development of an imbalance between Th17 and regulatory T (Treg) cells and the production of autoantibodies, such as rheumatoid factor and anti-citrullinated peptide antibody. IL-6 also promotes synovial inflammation and cartilage and bone destruction and has systemic effects in cardiovascular, psychological, and skeletal disorders. The first generated bDMARD targeting IL-6 was tocilizumab (TCZ), a humanized anti-IL-6 receptor antibody. Now, other IL-6 inhibitors are also being developed and clinical trials for these agents are in progress.⁶ These include fully human anti-IL-6 receptor mAb (REGN88/SAR153191 [sarilumab]), anti-IL-6 receptor nanobody (ALX-0061), anti-IL-6 Abs (CNTO136 [sirukumab], ALD518 [BMS-945429], CDP6038 [olokizumab], and MEDI5117). In this review, we highlight current data regarding the comparative efficacy and safety of TCZ and TNF inhibitors. We also discuss the positions of these agents in the treatment of RA.

Differential pharmacology of TCZ, adalimumab (ADA), and other TNF inhibitors

Several bDMARDs are currently available for the treatment of moderate to severe active RA, including five TNF inhibitors (IFX, ADA, golimumab [GOL], certolizumab pegol [CEP], and etanercept [ETA]), an IL-6 blocker (TCZ), a T-cell stimulator blocker (abatacept), a B-cell depletory

(rituximab), and an IL-1 receptor antagonist (anakinra).^{4,6} The characteristic features of TCZ and five TNF inhibitors are shown in Table 1.

TCZ is a humanized IgG1 class anti-IL-6 receptor mAb that was generated by grafting the complementarity determining regions of a mouse antihuman IL-6 receptor antibody (Ab) into human IgG1.⁷ TCZ blocks IL-6 mediated signal transduction by inhibiting the binding of IL-6 to both transmembrane and soluble IL-6 receptors. TCZ can be administered intravenously or subcutaneously.

IFX was the first TNF inhibitor developed and it is a chimeric immunoglobulin (Ig) composed of a murine variable region and a human constant region against TNF- α . Due to immunogenicity and response failure issues, IFX is licensed to be used with methotrexate (MTX) by intravenous injection. ADA and GOL are fully human mAbs to TNF- α and can be used subcutaneously every 2 weeks and every 4 weeks, respectively. CEP is a humanized Fab fragment conjugated to polyethylene glycol (PEG). The attachment of PEG prolongs the drug's half-life, whereas the absence of an Fc fragment prevents effector functions such as Ab-dependent cellular cytotoxicity and complement-dependent cellular cytotoxicity, as well as active transfer of CEP across the placenta during pregnancy. CEP is used subcutaneously every 2 weeks.

In contrast to these TNF inhibitors, ETA is a fusion protein consisting of two TNF receptor 2 (also known as p75TNF receptor) extracellular domains and a human Fc fragment of the IgG1 class. As TNF- α and lymphotoxin binds to TNF receptor 2, ETA neutralizes the biological activity of both cytokines. ETA is administered subcutaneously once or twice weekly.

Comparative efficacy studies of TCZ, ADA, and other TNF inhibitors

TCZ

The efficacy of TCZ administered alone or in combination with MTX or other synthetic disease modifying antirheumatic

Table 1 Characteristics of tocilizumab and tumor necrosis factor inhibitors

	Tocilizumab	Infliximab	Adalimumab	Golimumab	Certolizumab pegol	Etanercept
Target molecule	IL-6R	TNF- α	TNF- α	TNF- α	TNF- α	TNF- α
Structure	Humanized Ig	Chimeric Ig	Fully human Ig	Fully human Ig	Humanized Fab-pegol	Lymphotoxin
Injection route	IV, SC	IV	SC	SC	SC	P75TNFR-Fc
Activity						SC
ADCC	+	+	+	+	—	+
CDCC	+	+	+	+	—	±

Abbreviations: ADCC, antibody-dependent cellular cytotoxicity; CDCC, complement-dependent cellular cytotoxicity; Ig, immunoglobulin; IL-6R, interleukin-6 receptor; IV, intravenously; SC, subcutaneously; TNF- α , tumor necrosis factor- α ; TNFR, TNF receptor.

drugs (sDMARDs) was verified for active RA in seven Phase III trials. The three Phase III trials AMBITION, SAMURAI, and SATORI were designed to examine the efficacy of TCZ monotherapy.^{8–10} The AMBITION trial⁸ involved active RA patients for whom previous treatment with MTX and TNF inhibitors had not failed. The SAMURAI trial⁹ involved patients with an inadequate response to sDMARDs, and the SATORI trial¹⁰ involved patients with an inadequate response to MTX. In all three studies, patients treated with TCZ had superior American College of Rheumatology (ACR) 20 responses and lower disease activity score (DAS) 28 at 24 weeks than controls treated with MTX or other sDMARDs.

Four Phase III trials were performed to evaluate the efficacy of TCZ combination therapy with MTX or another sDMARD. The OPTION trial was designed to evaluate the efficacy of TCZ in combination with MTX, and the results showed that combination therapy is effective for moderate to severe active RA.¹¹ The TOWARD trial demonstrated that TCZ combined with a sDMARD such as MTX, chloroquine, gold, sulphasalazine, azathioprine, or leflunomide is effective for reducing RA disease activity in patients with an inadequate response to monotherapy with any one of the sDMARDs.¹² The RADIATE trial proved that TCZ plus MTX is effective for achieving rapid and sustained improvements in signs and symptoms in patients whose RA is refractory to TNF inhibitors.¹³ Moreover, the LITHE trial, which was designed to evaluate not only disease activity but also structural joint damage, demonstrated that TCZ plus MTX is efficacious at suppressing disease activity.¹⁴ Radiographic evidence from the LITHE trial showed that progression of joint destruction is significantly inhibited after 52 weeks of combination treatment.¹⁴ All of these studies enrolled patients with an inadequate response to all previous treatments, including MTX, TNF inhibitors, or other sDMARDs, and all of the studies showed that TCZ combination therapy is effective for these patient populations.

ADA

The efficacy and safety of ADA was examined in the ARMADA trial.¹⁵ A total of 271 patients with active RA who had an inadequate response to MTX were randomized to continue MTX in combination with either placebo or ADA (20, 40, or 80 mg subcutaneously every other week). ACR20 responses at week 24 were 47.8, 67.2, and 65.8% in the 20, 40, and 80 mg groups, respectively, whereas the response rate was 14.5% for the placebo group. Subsequently, the PREMIER study, which involved 799 patients with early and

aggressive RA who had no previous MTX use, confirmed that ADA plus MTX combination therapy is vastly superior to either MTX alone or ADA alone in improving clinical signs and symptoms, inhibiting radiographic progression of joint destruction, and effecting clinical remission.¹⁶

IFX

In the Phase III trial ATTRACT, 428 RA patients with active disease activity and an inadequate response to MTX were randomized to receive MTX with either placebo or IFX (3 mg/kg every 4 weeks, 3 mg/kg every 8 weeks, 10 mg/kg every 4 weeks, or 10 mg/kg every 8 weeks).¹⁷ At week 30, patients in the IFX treated groups achieved an ACR20 response rate of 50%–58%, versus an ACR20 response rate of only 20% in the placebo group. Structural damage was also assessed with the modified van der Heijde-Sharp score at week 102.¹⁸ Compared with the MTX only regimen, erosion and joint space narrowing scores from baseline to week 102 with early RA patients decreased significantly with each of the IFX dose regimens.

GOL

In the Phase III trial GO-FORWARD, 444 active RA patients who had an inadequate response to MTX were randomly assigned to receive placebo subcutaneous injections plus MTX, GOL 100 mg plus placebo capsules, GOL 50 mg plus MTX, or GOL 100 mg plus MTX.¹⁹ The proportion of patients who achieved an ACR20 response at week 14 was 33.1% in the placebo plus MTX group, 44.4% ($P=0.059$) in the GOL 100 mg plus placebo group, 55.1% ($P=0.001$) in the GOL 50 mg plus MTX group, and 56.2% ($P<0.001$) in the GOL 100 mg plus MTX group. At week 24, median Health Assessment Questionnaire Disease Index (HAQ-DI) score improvements from baseline for the placebo plus MTX, GOL 100 mg plus placebo, GOL 50 mg plus MTX, and GOL 100 mg plus MTX groups were 0.13, 0.13 ($P=0.240$), 0.38 ($P<0.001$), and 0.50 ($P<0.001$), respectively.

CEP

In the Phase III trial Rapid-1, 982 active RA patients were randomized to receive subcutaneous CEP at an initial dose of 400 mg given at weeks 0, 2, and 4, with a subsequent dosage of 200 or 400 mg every 2 weeks plus MTX, or placebo plus MTX.²⁰ At week 24, the ACR20 response rates were 13.6%, 58.8%, and 60.8% for the placebo, CEP 200 mg, and CEP 400 mg groups, respectively. At week 52, mean radiographic progression from baseline was reduced in patients treated with CEP 200 mg (0.4 Sharp units) or 400 mg

(0.2 Sharp units), compared with placebo treated patients (2.8 Sharp units, $P<0.001$).

ETA

In a Phase II study, 234 active RA patients who had an inadequate response to previous treatment regimens including MTX were randomly assigned to receive twice weekly subcutaneous injections of ETA (10 or 25 mg) or placebo for 24 weeks. At week 24, the ACR20 response rates were 51%, 59%, and 11% in the ETA 10 mg, ETA 20 mg, and placebo groups, respectively.²¹ In the subsequent Phase III TEMPO trial, 682 patients with active RA were randomly allocated to treatment with ETA 25 mg (subcutaneously twice weekly), oral MTX, or the combination.²² The numeric index of the ACR response area under the curve over the first 24 weeks was significantly greater in the combination group than the ETA alone or MTX alone groups ($P<0.0001$). Moreover, at week 52, the combination was more efficacious than ETA alone or MTX alone in protecting against joint damage (mean total Sharp score: -0.54 versus 0.52 , $P=0.0006$; -0.54 versus 2.80 , $P<0.0001$, respectively).

Indirect comparisons of the efficacy of TCZ and TNF inhibitors

As indicated above, the efficacy of TCZ and TNF inhibitors in treating moderate to severe RA in patients who experienced an inadequate response to MTX has been demonstrated in separate studies. Although several systematic reviews have indirectly compared the efficacy of TCZ and TNF inhibitors in treating RA, only one trial, the ADACTA, has directly compared the efficacy of these agents.²³

Bergman et al conducted a systematic literature review of double blind, randomized, placebo-controlled trials that spanned an 18-year period and investigated the effectiveness of TCZ (three trials; OPTION, LITHE, and TOWARD) and TNF inhibitors ADA, IFX, and ETA (total 11 trials) in treating RA in patients who experienced an inadequate response to sDMARDs.²⁴ The effectiveness of TCZ is comparable to that of each of the TNF inhibitors with respect to ACR20 and ACR50 responses, but greater than that of the TNF inhibitors with respect to ACR70 response. Another systematic review of selected clinical trials involving combination therapy with MTX concluded that there was no difference in efficacy on the basis of ACR50 response criterion at 24/30 weeks between TNF inhibitors and TCZ.²⁵ Turkstra et al reported a mixed treatment comparison of the short-term efficacy of nine bDMARDs, including TNF inhibitors and TCZ in patients with established RA.²⁶

They found that the ACR50 response rate of TCZ at 6 months is comparable to that of ADA, ETA, GOL, and IFX. In an indirect comparison, Salliot et al found no significant difference in the efficacy of TCZ and GOL in treating RA patients who had an inadequate response to TNF inhibitors (ADA, ETA, and IFX).²⁷ Orme et al reported the results of a network meta-analysis of the efficacy of bDMARDs with or without sDMARDs.²⁸ Odds ratios (covariate analysis) of ACR20/50/70 responses for ADA plus sDMARDs and TCZ plus sDMARDs versus sDMARDs alone were 3.374/4.203/4.58 and 4.363/5.797/9.23, respectively. In contrast, odds ratios (fixed effect) of ACR20/50/70 responses for ADA and TCZ versus placebo were 4.95/4.82/11.42 and 26.17/46.94/55.54, respectively. Pierreisnard et al also reported that there were no significant differences between the various TNF inhibitors and TCZ in terms of clinical efficacy (ACR50) in patients who had an inadequate MTX response.²⁹ Jones et al summarized the evidence regarding radiographic damage with bDMARDs, either alone or in combination with MTX.³⁰ For biologic monotherapy, TCZ, ADA, and ETA were significantly better than MTX, with TCZ ranking first, whereas GOL had no significant effect (Figure 1). For a bDMARD in combination with MTX compared with MTX alone, TCZ and all TNF inhibitors were effective at slowing X-ray progression. Taken together, the evidence from these indirect comparisons indicates that the efficacy of TCZ is comparable to that of TNF inhibitors when used in combination with MTX and that TCZ monotherapy is superior to TNF inhibitor monotherapy.

Direct comparisons of the efficacy of TCZ and ADA

The head-to-head ADACTA trial compared the efficacy of TCZ with that of ADA as monotherapy for RA.²³ A total of 325 patients were randomly assigned to receive either TCZ 8 mg/kg intravenously every 4 weeks plus placebo subcutaneously every 2 weeks or ADA 40 mg subcutaneously every 2 weeks plus placebo intravenously every 4 weeks for 24 weeks. At week 24, patients treated with TCZ had a greater decrease in DAS28 than patients treated with ADA (-3.3 versus -1.8 ; $P<0.0001$). The proportion of patients attaining DAS28 remission was 39.9% with TCZ and 10.5% with ADA. ACR20, ACR50, and ACR70 response rates were achieved in 65% and 49.4% ($P<0.01$), 47.2% and 27.8% ($P<0.01$), and 32.5% and 17.9% ($P<0.01$) of patients treated with TCZ and ADA, respectively. These results demonstrated the overall superiority of monotherapy with TCZ compared with monotherapy with ADA for the treatment

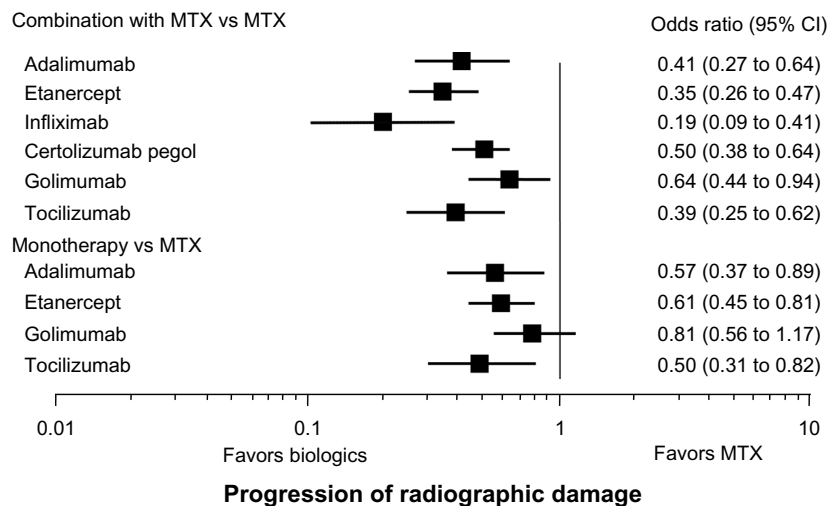


Figure 1 Indirect comparisons of the suppressive effects of tocilizumab and tumor necrosis factor inhibitors on radiographic damage.

Notes: Copyright © 2012. Adapted from Dove Medical Press. Jones G, Darian-Smith E, Kwok M, Winzenberg T. Effect of biologic therapy on radiological progression in rheumatoid arthritis: what does it add to methotrexate? *Biologics*. 2012;6:155–161.³⁰ In combination with methotrexate (MTX) compared with MTX alone, tocilizumab and all tumor necrosis factor inhibitors are effective at slowing X-ray progression. As monotherapy, adalimumab, etanercept, and tocilizumab are significantly better than MTX, whereas golimumab had no significant effect. The x-axis shows progression of radiographic damage.

Abbreviations: CI, confidence interval; MTX, methotrexate.

of RA. Clinical evidence demonstrated that coadministration of TNF inhibitors and MTX is more efficacious than administration of TNF inhibitors alone in treating RA.³¹ In contrast, the findings of the ACT-RAY trial comparing the efficacy of TCZ plus MTX therapy with that of TCZ monotherapy in a setting that closely resembled a real life clinical practice showed that TCZ monotherapy is not clinically inferior to TCZ combination therapy,³² indicating that as monotherapy, TCZ appears to be more effective than TNF inhibitors at suppressing disease activity.

In a Japanese cohort, the Tsurumi Biologics Communication Registry, the proportion of patients who achieved low disease activity, clinical remission, and a moderate or good European League Against Rheumatism (EULAR) response at 24 weeks was determined following treatment with ADA or TCZ.³³ A total of 120 patients were treated with ADA (77% of patients in combination with MTX), while 99 patients were treated with TCZ (36% of patients in combination with MTX). There was no significant difference between ADA and TCZ treated patients with respect to the proportion of low disease activity and remission, but a higher proportion of patients treated with TCZ achieved a moderate or good EULAR response.

Comparative safety and tolerability studies

The integrated safety of TCZ was evaluated in clinical trials through comparisons of adverse events (AEs) between

a control population (4,199) and a TCZ treated population (4,009), and the results were reported in 2011.³⁴ Total exposure to TCZ was 8,580 patient-years (PYs), and the total duration of observation was 9,414 PYs. Overall AE and serious AE rates were 278.2/100 PYs and 14.4/100 PYs, respectively. AEs included serious infection (4.7/100 PYs), opportunistic infection (0.23/100 PYs), gastrointestinal perforation (0.28/100 PYs), malignancy (1.1/100 PYs), myocardial infarction (0.25/100 PYs), and stroke (0.19/100 PYs).

In another systematic review in which the total duration of observation was 12,293 PYs, infections were also the most common AE and serious AE identified, and the rate of serious infections was 4.5/100 PYs.³⁵ The short-term (28 weeks) safety of TCZ was monitored in a postmarketing surveillance study in Japan involving 7,901 patients.³⁶ The incidence of total AEs and serious AEs was 43.9% and 9.6%, respectively. Infection and infestation were the most frequent (11.1%) and serious (0.5%) AEs. Analysis of long-term clinical trial safety data showed that rates of serious AEs, serious infections, and cardiovascular events remained stable during continued exposure to TCZ. Infection was identified as the most frequent serious AE. The most common infections reported in randomized controlled trials (RCTs) were pneumonia (0.9/100 PYs) and skin or soft tissue infections (0.9/100 PYs). These results led to the conclusion that infections are the most frequent AEs associated with TCZ. A meta-analysis comparing the safety

profile of TCZ with those of TNF inhibitors (7–9/100 PYs) showed similar rates of serious infections,^{37,38} although among TNF inhibitors, an increased risk of serious infection was observed with IFX.

As TNF- α plays a crucial role in the host defense against intracellular pathogens (eg, TNF- α activates macrophages and stimulates the formation and maintenance of granulomas to protect against *Mycobacterium tuberculosis* infection), TNF inhibitors increase the risk of tuberculosis reactivation, as evidenced by clinical trials showing an incidence of 0.4% with IFX.³⁹ Within the anti-TNF biologic cohort, IFX and ADA are associated with a 3- to 4-fold higher risk of reactivation than ETA.⁴⁰ It seems likely that the incidence of reactivation of tuberculosis is lower during TCZ treatment than during anti-TNF treatment, as there are only six reported cases in the worldwide TCZ clinical trials database, which covers >10,000 PYs of exposure.⁴¹ Moreover, according to QuantiFERON assay data, TNF inhibitors (but not TCZ) influence tuberculosis-antigen-induced IFN- γ production,⁴² suggesting that TCZ may be safer than TNF inhibitors with respect to reactivation of latent tuberculosis.

In contrast to TNF inhibitors, gastrointestinal perforation appears to be an AE specific to TCZ, with an incidence rate of 1.9–2.8/1,000 PYs.^{34,43} This rate is between the 3.9/1,000 PYs for corticosteroids and 1.3/1,000 PYs for TNF inhibitors, as indicated in the United Health Care database.⁴³ A total of 17 of 29 (59%) reported events involved colonic diverticular perforation, suggesting that TCZ should not be used in patients with a history of diverticulitis.

Increases in mean fasting levels of plasma lipids, such as total cholesterol (TC), low-density lipoprotein (LDL), triglycerides, and high-density lipoprotein (HDL), occur in 20%–30% of patients treated with TCZ, which appeared higher in patients treated with TNF inhibitors.^{34,36} A 24-week, double blind, randomized, multicenter, two part, Phase III trial followed by an 80-week open label trial (MEASURE) evaluated lipid and lipoprotein levels, HDL particle composition, markers of coagulation, and thrombosis in 132 patients with RA receiving either TCZ or placebo.⁴⁴ At week 12, median TC, LDL-cholesterol (LDL-C), and triglyceride levels increased in TCZ recipients versus placebo recipients (12.6% versus 1.7%, 28.1% versus 2.2%, 10.6% versus –1.9%, respectively; all $P < 0.01$). There were no significant differences in the concentrations of mean small LDL, mean oxidized LDL, or total HDL-C, but the HDL associated serum amyloid A

(SAA) content decreased in TCZ treated patients. TCZ also induced reductions (>30%) in secretory phospholipase A2-IIA, lipoprotein (a), fibrinogen, and D-dimers and an elevation in the level of paraoxonase (all $P < 0.0001$ versus placebo). These data constitute detailed evidence that TCZ modulates lipoprotein particles and other surrogates of vascular risk.

Comparisons of drug survival with TNF inhibitors have been reported in some registries. In the Consortium of Rheumatology Researchers of North America registry, the 24-month persistence for biologically naive patients on the new anti-TNF treatments IFX, ETA, and ADA was 63%, 53%, and 53% respectively.⁴⁵ The Lombardy Rheumatology Network registry reported 2.5-year treatment continuation rates for IFX, ETA, and ADA of approximately 56%, 72%, and 57%, respectively.⁴⁶ The Swiss Clinical Quality Management for Rheumatoid Arthritis registry reported 2.5-year drug survival rates for IFX, ETA, and ADA of approximately 51%, 58%, and 61%, respectively.⁴⁷ An Italian study group (Gruppo Italiano di Studio sulle Early Arthritides registry) reported 2.5-year continuation rates for IFX, ETA, and ADA of approximately 52%, 65%, and 52%, respectively.⁴⁸

There are few reports describing TCZ drug survival. The Danish Nationwide Rheumatological Database registry reported 48-, 96-, and 144-week TCZ adherence rates of 61%, 54%, and 47%, respectively.⁴⁹ In contrast, the Danish Nationwide Rheumatological Database registry reported 48-month drug survival rates for IFX, ETA, and ADA of 41%, 56%, and 52%, respectively.⁵⁰ The Japanese Osaka University Biologics for Rheumatic Diseases registry reported 1-year drug continuation rates for TCZ, IFX, ETA, and ADA of 89%, 73%, 86%, and 78%, respectively, and 2.5-year rates of 79%, 47%, 78%, and 55%, respectively.⁵¹ In this registry, the continuation rates for TCZ and ETA are significantly higher than those for IFX and ADA. The most frequent reasons given for discontinuation are AEs for TCZ and a lack of efficacy for ADA and IFX. The Registry of Japanese Rheumatoid Arthritis Patients for Long-term Safety reported significantly lower discontinuation rates due to lack of efficacy for patients taking ETA compared with patients taking IFX or TCZ.⁵² Finally, the Cohort of Arthritis Biologic Users at Kameda Institute registry reported that the drug survival and safety profiles of TCZ are similar to those of TNF inhibitors (IFX, ETA, and ADA).⁵³ The results regarding tolerability are summarized in Table 2. These reports indicate that tolerability of TCZ is comparable to or better than that of TNF inhibitors.

Table 2 Comparative tolerability of tocilizumab with tumor necrosis factor inhibitors

Registry name	Retention period	Drug survival rate (%)			
		TCZ	IFX	ETA	ADA
CORRONA ⁴⁵	24 months		63	53	53
LOHREN ⁴⁶	2.5 years		56	72	57
SCQM-RA ⁴⁷	2.5 years		51	58	61
GISEA ⁴⁸	2.5 years		52	65	52
DANBIO ^{49,50}	96 weeks	54			
	48 months		41	56	52
BiRD ⁵¹	2.5 years	79	47	78	55

Abbreviations: ADA, adalimumab; BiRD, Biologics for Rheumatic Diseases; CORRONA, Consortium of Rheumatology Researchers of North America; DANBIO, Danish Nationwide Rheumatological Database; ETA, etanercept; GISEA, Gruppo Italiano di Studio sulle Early Arthritides; IFX, infliximab; LOHREN, Lombardy Rheumatology Network; SCQM-RA, Swiss Clinical Quality Management for Rheumatoid Arthritis; TCZ, tocilizumab; TNF, tumor necrosis factor.

Comparative patient focused perspectives, such as quality of life, patient satisfaction/acceptability, adherence, and uptake

In all Phase III trials modified HAQ-DI scores significantly improved with TCZ treatment. Moreover, based on functional assessment of chronic illness therapy (FACIT), the OPTION and TOWARD studies reported that TCZ had an ameliorative effect, and the Short-Form (SF)36 Health Survey indicated both mental and physical (SF36-mental and SF-physical) effects.^{11,12} In addition, the RADIATE study found that at week 24 versus placebo, TCZ treatment at 8 mg/kg was associated with significantly greater improvements in HAQ-DI, FACIT, and SF36-physical, and that TCZ treatment at 4 mg/kg was associated with greater improvements in HAQ-DI and SF36-physical.⁵⁴ Components of the Arthritis Impact Measurement Scale 2 (AIMS-2) (eg, physical score, symptom, and affect score) and those of SF36 (eg, bodily pain, general health, vitality, and mental health) improved in 39 patients in a clinical practice after 4 weeks of TCZ therapy, but there was no improvement in the social interaction component of AIMS-2 after 24 weeks of treatment.⁵⁵

The Tocilizumab and DMARDs: Achievements in Rheumatoid Arthritis study reported improvements in diary documented fatigue, pain, and morning stiffness with TCZ treatment.⁵⁶ The mean FACIT-Fatigue score increased from 28.8±11.2 at baseline to 35.3±11.5 at week 4 and to 37.4±12.2 at week 24, and the mean HAQ-DI score decreased from 1.48±0.65 to 1.15±0.68 at week 4 and to 1.00±0.75 at week 24 or the last visit. Favorable mean changes from baseline to week 24 or the last visit were also observed in each of the domains of the SF36, especially in the physical domains. The Treatment Satisfaction Questionnaire for Medication,

which was completed at the end of the study, showed a high level of patient agreement/satisfaction for each of the derived domains: “effectiveness” (69.4%), “side effects” (88.7%), “convenience” (72.4%), and “global satisfaction” (74.7%).

Fatigue represents an important symptom for patients with RA. Chauffier et al assessed the effect of biotherapies on fatigue based on data from ten RCTs involving patients with established RA.⁵⁷ Unfortunately, with respect to fatigue, they found that the overall effect size of all bDMARDs versus placebo at week 24 of treatment is small in established RA. In inadequate responders to sDMARDs, the effect size is similar for TNF inhibitors and nonanti-TNF bDMARDs including TCZ. Strand et al reported that ADA plus MTX significantly improved physical function and health-related quality of life in patients with early RA after 2 years of treatment.⁵⁸ However, no clinically meaningful differences between patients on ADA monotherapy or MTX were observed. In a recent meta-analysis, Callhoff et al studied the impact of bDMARDs including five TNF inhibitors but not TCZ on the physical function of patients with RA, as evaluated by Health Assessment Questionnaire.⁵⁹ Overall, bDMARDs produced greater improvement in physical function than sDMARDs, with an Health Assessment Questionnaire standardized mean difference of 0.44 (95% confidence interval [CI]: 0.38, 0.50). No significant differences between TNF inhibitors were observed.

Huynh et al examined patient treatment preference.⁶⁰ The most frequent reason given for choosing intravenous treatment was “safety” (62%), followed by “easy to manage” (39%). The two most frequent reasons given for choosing self-injection at home were “time constraints” and “easy to manage” (both 57%). The majority of RA patients already treated with bDMARDs in that study preferred the route of administration they were used to. The majority of the patients not currently treated with a bDMARD preferred subcutaneous treatment at home. A feeling of safety was important to patients who preferred intravenous treatment. Health professionals as a group may be biased toward the use of subcutaneous treatment. It is now possible to administer TCZ subcutaneously as well as intravenously.^{61,62} Although subcutaneous injection of TCZ is disadvantageous in heavy patients, the fact that patients can now choose the administration route is a positive development.

Comparison of the cost-effectiveness of TCZ and TNF inhibitors

Although demonstrations of the outstanding efficacy of TNF inhibitors and TCZ have led to a paradigm shift with respect

to the management of RA, the relatively high cost of these drugs imposes a large burden on both patients and society.⁶³ The Swedish Early Interventions In Rheumatoid Arthritis project demonstrated that drug costs increased primarily due to the introduction of biologics.⁶⁴ Sick leave decreases during the first year, but disability pensions increase, resulting in no change in indirect costs. Over the following years, disability pensions increase further and indirect costs also increase. In the 6 years after diagnosis of early RA, drug costs are partially offset by decreasing outpatient visits, but indirect costs remain unchanged and total costs increase. Therefore, the cost of bDMARDs is a significant problem. bDMARDs significantly increase the quality-adjusted life years (QALYs) gained when compared to MTX alone. QALY is a measure of disease burden affecting the quality and quantity of the life lived. In Finland, TCZ plus MTX was found to be more cost-effective than ADA plus MTX or ETA plus MTX in comparison with MTX alone.⁶⁵ A QALY gained with retail priced (wholesale priced) TCZ plus MTX costs Euro (€)18,957 (€17,057) more than MTX alone. Diamantopoulos et al reported the cost utility of TCZ in RA patients with an inadequate response to sDMARDs from a payer's perspective in Italy.⁶⁶ Replacement of TNF inhibitors (ADA, ETA, and IFX) with TCZ reduces total costs over a patient's lifetime (base-case analysis, TCZ: €141,100 versus TNF inhibitors: €143,500). Patients receiving TCZ realize more QALYs than patients receiving standard of care (9.8881 QALYs versus 9.3502 QALYs). When TCZ is added to standard of care without replacing TNF inhibitors, the incremental cost-effectiveness ratio becomes €17,100 per QALY.

In the ADACTA study, economic evaluation of the cost per response or remission of TCZ versus ADA was reported for Spain.⁶⁷ The cost per ACR20/50/70 response is lower with TCZ than with ADA (€8,105/11,162/16,211 versus €11,553/20,529/31,882). The cost of attaining DAS28 remission with TCZ and ADA is €13,204 and €54,352, respectively. Treatment with TCZ was dominant in all scenarios analyzed. Similar economic evaluation of TCZ versus ADA from the ADACTA trial was conducted in Australia.⁶⁸ TCZ monotherapy was found to result in lower total treatment costs (in Australian dollars [\$]) per patient over 24 weeks compared with ADA monotherapy (\$9,739 versus \$10,722).

In the UK, the addition of TCZ in combination with MTX to treat severe active RA in patients with an inadequate response to sDMARDs was found to produce a gain of 1.17 QALYs per patient, at an incremental cost of UK pound (£)23,253.⁶⁹ This equates to an incremental cost-effectiveness ratio (ICER) of £19,870. The addition of TCZ in combination

with MTX to the current Scottish standard of care in adult TNF inhibitor-inadequate responders with moderate to severe active RA produces a gain of 1.234 QALYs per patient, at an incremental cost of £27,465.⁷⁰ This equates to an ICER of £22,254. Tanaka et al reported the cost-effectiveness of TCZ in Japan.⁷¹ The lifetime cumulative costs and QALYs were 35.4 million Japanese yen (¥) and 11.7, respectively, in the TCZ group and ¥23.3 million and 9.3, respectively, in the MTX group. The ICER for TCZ was ¥4.94 million, with a 66.2% probability of falling below the allowable threshold based upon probabilistic sensitivity analysis. These findings suggest that TCZ is more cost-effective than TNF inhibitors, including ADA, ETA, and IFX.

Conclusion and place in therapy

The property of TCZ and TNF inhibitors is summarized in Figure 2. Based upon recent findings, the EULAR recommendations for the management of RA were updated in 2013.⁷² In patients responding insufficiently to MTX and/or other sDMARDs, with or without glucocorticoids, use of bDMARDs should commence with MTX. First line bDMARDs include TNF inhibitors, abatacept, and TCZ, and under certain circumstances, rituximab. If biologic monotherapy must be initiated, only TCZ has supportive evidence. However, TCZ, TNF inhibitors, and other bDMARDs do not produce beneficial effects in all active RA patients. Therefore, to determine the optimal strategy for using particular bDMARDs in individual RA patients, the characteristic features of these drugs should be clarified.⁷³

RA animal models have provided some clarification. The most well-known animal model of RA is collagen-induced arthritis, which involves injection of mice with type II collagen to produce an immune response directed at connective tissues. Both IL-6 and TNF- α have been shown to play a major role in the development and progression of joint destruction in the collagen-induced arthritis model. Immunization with type II collagen in this model primarily increases the frequency of Th17 cells. Treatment of immunized mice with anti-IL-6 receptor Ab during priming leads to marked suppression of both the induction of Th17 cells and arthritis development, whereas administration of soluble TNF receptor-Fc fusion protein from day 0 to 14 fails to suppress Th17 differentiation and arthritis development.⁷⁴ Anti-type II collagen Ab-induced arthritis (CAIA) is a model in which the priming phase of T-cell dependent Ab generation is skipped. Although TNF- α and IL-6 are also elevated in this model, arthritis is suppressed in TNF- α - but not in IL-6-deficient mice, indicating that TNF- α plays a more significant role than IL-6 in joint

	Tocilizumab		TNF inhibitors
Efficacy (with MTX) on disease activity	Excellent	=	Excellent
Efficacy (as monotherapy) on disease activity	Excellent	>	Good
Safety profile	Tolerable		Tolerable
Incidence of AEs			
Overall infections		=	
Reactivation of TB		<	
Elevation of T-CHO		>	
GI perforation		>	
Tolerability	Good	> or =	Good
Effects on acute-phase proteins (CRP, SAA, Hepcidin)	Excellent	>	Good
Cost-effectiveness		>	

Figure 2 Properties of tocilizumab and tumor necrosis factor inhibitors in the management of rheumatoid arthritis.

Abbreviations: AEs, adverse events; CRP, C-reactive protein; GI, gastrointestinal; MTX, methotrexate; SAA, serum amyloid A; TB, tuberculosis; T-CHO, total cholesterol.

inflammation in CAIA.⁷⁵ These findings suggest that IL-6 is essential for the induction of immunological abnormalities and the development of arthritis and that the pathological role of IL-6 is different from that of TNF- α , which is primarily involved in the development of joint inflammation.

Analyses of various markers during biologic treatment are also helpful to clarify the characteristics of bDMARDs. Both TNF inhibitors and TCZ lead to improvements in serological and urinary markers related to bone and cartilage metabolism. Several immunological studies have sought to clarify the mechanisms underlying the effects of TCZ. Of particular importance is to determine whether TCZ can correct the Th17/Treg imbalance, which is thought to be a fundamental immunological abnormality in RA.⁷⁶ The results of preliminary studies suggest that inhibition of IL-6 function by TCZ corrects the imbalance between Th17 and Treg cells in the peripheral CD4-positive T-cell population.^{77,78} In contrast, TNF- α suppresses Treg function by dephosphorylating serine 418 in the C-terminal DNA-binding domain of the forkhead box P3, whereas anti-TNF therapy can restore Treg cell function.⁷⁹ Moreover, a study involving eight patients with RA demonstrated that 6 months of treatment with TCZ

causes a selective decrease in IL-21 production by memory/activated T-cells.⁸⁰ IL-21 is known to promote plasma cell differentiation and induce IgG4 production, and TCZ treatment leads to a reduction in the serum levels of IgG4-specific anticitrullinated peptide antibody, indicating the presence of a pathway involving IL-6, IL-21, and IgG4 autoantibodies in RA. In another study, Roll et al examined the in vivo effect of TCZ on the B-cell compartment in 16 RA patients and found that TCZ induces a significant reduction in peripheral preswitch and postswitch memory B-cells.⁸¹ In addition, TCZ (but not ETA) significantly reduces somatic hypermutation in immunoglobulin gene rearrangements in preswitch memory B-cells,⁸² suggesting modulation of memory B-cells as a possible mechanism for TCZ. Further evaluation is required to clarify the effects of bDMARDs in treating the immunological abnormalities associated with RA.

IL-6, which was found to be identical to hepatocyte-stimulating factor, induces the expression of various acute phase proteins, such as C-reactive protein, hepcidin, SAA, and fibrinogen, indicating that IL-6 plays a role in the development of systemic inflammatory symptoms, signs, and complications. TCZ treatment is expected to

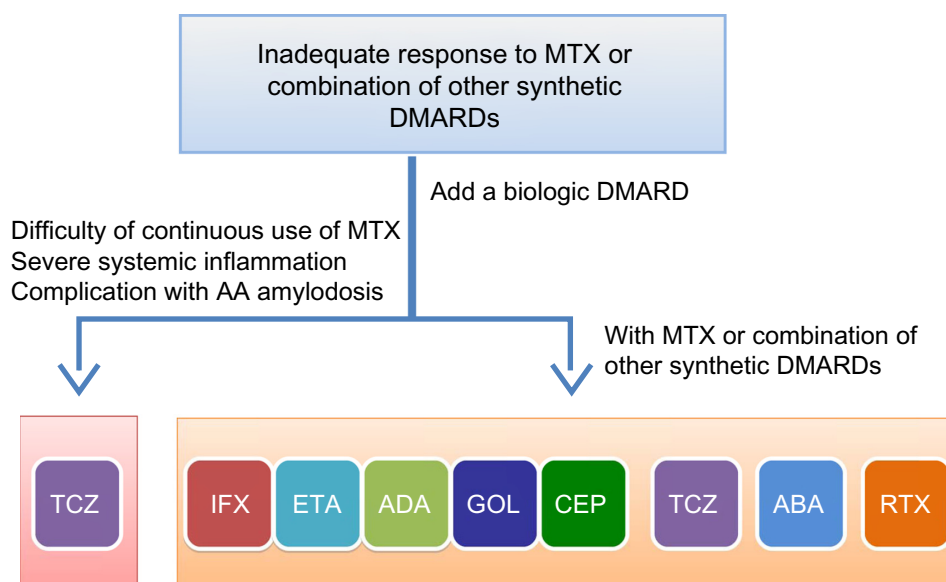


Figure 3 Selection of biologic disease modifying antirheumatic drugs.

Notes: Rheumatoid arthritis patients who fail to respond to methotrexate (MTX) alone or in combination with other synthetic disease modifying antirheumatic drugs (DMARDs) need to be treated with a biologic DMARD. For patients who can continue to receive MTX, any of the seven biologic DMARDs should be selected. These include five tumor necrosis factor inhibitors (infliximab, etanercept, adalimumab, golimumab, and certolizumab pegol), the IL-6 receptor blocker tocilizumab, the T-cell stimulation blocker abatacept, and the B-cell depletory rituximab. Rituximab is recommended to be used for patients who have certain contraindications for other agents such as a recent history of lymphoma, latent tuberculosis with contraindications to the use of chemoprophylaxis, live in a tuberculosis endemic region, or a previous history of demyelinating disease. Tocilizumab may be selected for patients who 1) cannot continue treatment with MTX or other synthetic DMARDs, 2) present with severe inflammatory findings, and 3) have or who are at high risk of developing amyloid A amyloidosis.

Abbreviations: ABA, abatacept; ADA, adalimumab; CEP, certolizumab pegol; DMARDs, disease modifying antirheumatic drugs; ETA, etanercept; GOL, golimumab; IFX, infliximab; MTX, methotrexate; RTX, rituximab; TCZ, tocilizumab.

ameliorate the inflammatory effects and inhibit the development of complications. Increased production of hepcidin predominantly induced by IL-6 leads to anemia associated with chronic disorders.⁸³ A comparative evaluation of the effects of TCZ and TNF inhibitors on serum hepcidin and anemia found that significant improvement in anemia and reduction in serum hepcidin levels are more pronounced in the TCZ treated patients than in TNF inhibitor treated patients.⁸⁴ Amyloid A amyloidosis is a serious complication of RA, as amyloid fibril deposition causes progressive deterioration in various organs,⁸⁵ although due to a marked progression of antirheumatic treatment, the incidence of amyloid A amyloidosis has recently decreased.^{86,87} SAA is an amyloid fibril precursor protein. Because the synthesis of SAA depends primarily on IL-6, TCZ injection promptly reduces the serum concentration of SAA, just as in the case of C-reactive protein, and the suppressive activity of TCZ on the serum SAA level is more powerful than that of TNF inhibitors.^{88,89} Case reports and series studies published to date have demonstrated the marked ameliorative effect of TCZ on gastrointestinal symptoms and renal dysfunction caused by amyloid A amyloidosis.^{90–92}

On the basis of these findings, we suggest that TCZ can be selected as the first line biologic for patients who

1) cannot continue treatment with MTX or other sDMARDs, 2) present with severe inflammatory findings, and 3) have or who are at high risk of developing amyloid A amyloidosis (Figure 3). Moreover, medication adherence and cost-effectiveness appears to favor TCZ in comparison with TNF inhibitors. However, further evaluation and clarification of the characteristic features of bDMARDs are essential to determine the optimal treatment for individual RA patients.

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