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The Role of Tocilizumab in the Treatment of Rheumatoid Arthritis

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1. Introduction

The characteristic pathophysiology in rheumatoid arthritis (RA) is the destruction of bone and cartilage due to persistent synovitis of unknown etiology. Pro-inflammatory cytokines, including tumor necrosis factor alpha (TNF α), interleukin-1 (IL-1), and interleukin-6 (IL-6), are overproduced in inflamed synovial membranes, and are critically involved in the spread and persistence of the inflammation. IL-6, which was identified as a B-cell stimulatory factor in 1986, is a multifunctional cytokine (Hirano, 2010), and a key mediator in the pathological processes of RA, especially in the activation of immune cells and osteoclasts (Cronstein, 2007). For RA drug therapy, therefore, inhibition of IL-6 signaling is suitable for shutting down both inflammation and bone destruction. Tocilizumab (TCZ) is a humanized monoclonal antibody (human IgG₁ κ subclass) against IL-6 receptor (IL-6R). The data from the recent clinical studies on TCZ suggests that TCZ has several advantages over other anti-rheumatic drugs (Bergman et al., 2010).

2. Pharmacological properties

2.1 Pharmacodynamics

Human IL-6 binds to human IL-6 R with a dissociation constant (K_d) of 5.5 nM, and this low affinity complex subsequently recruits a gp130 molecule to form a high-affinity complex (IL-6/IL-6R/gp130 ternary complex) with a K_d of 50 pM (Hibi et al, 1990). TCZ binds selectively and competitively to both soluble IL-6R (sIL-6R) and membrane bound IL-6R (mIL-6R) with a K_d of 0.71 nM and 2.54 nM, respectively (Japan Pharmacists Education Center, 2008; Mihara et al., 2005). TCZ suppressed the binding of IL-6 (10 ng/mL) to sIL-6R in a dose dependent manner at of a concentration between 0.002 and 4 μ g/mL and completely inhibited at concentrations of > 4 μ g/mL. Moreover, TCZ was able to dissociate IL-6/sIL-6R preformed complex which was made by mixing IL-6 (200 ng/mL) and sIL-6R (40 ng/mL). The percentage binding of IL-6 to sIL-6R fell in a TCZ concentration-dependent manner, and was less than 10% of the binding seen in the presence of TCZ at concentrations of > 1 μ g/mL. On the other hand, the binding of TCZ to sIL-6R rose in a concentration-dependent manner and reached a plateau at 0.1 μ g/mL (Mihara et al., 2005). *In vitro*, 100 μ g/mL of TCZ completely inhibited cell growth of IL-6 dependent KT-3 cells in the presence of up to 0.32 ng/mL IL-6. Cell growth inhibition by TCZ was dose-dependently decreased

by IL-6 at concentrations of > 0.32 ng/mL, and no inhibition of cell growth by TCZ was observed in the presence of 1 μ g/mL IL-6 (Australian Government, 2011). *In vivo*, serum levels of IL-6 and sIL-6R markedly increased after TCZ treatment in patients with RA. While free TCZ concentration remains 1 μ g/mL or more, serum C-reactive protein (CRP) is normalized, indicating that sIL-6R is saturated with TCZ and IL-6 signaling is completely inhibited (Nishimoto et al., 2008).

2.2 Pharmacokinetic properties

PK data were based on a population PK analysis of 1793 patients with RA who received a 1 hour infusion of TCZ 8mg/kg every 4 weeks for 24 weeks (Frey et al., 2010). The $t_{1/2}$ of TCZ was concentration-dependent. The effective $t_{1/2}$ decreased with decreasing concentrations of TCZ within a dosing interval from 14 days to 8 days. After administration of TCZ, the predicted steady-state the mean area under the concentration-time curve (AUC), maximum concentration (C_{max}), the steady-state volume of distribution, and the trough concentration (C_{min}) values were 35.0 mg·h/mL, 183 μ g/mL, 6.4 L, and 9.7 μ g/mL, respectively. The C_{min} value is 91 fold higher than the K_d of TCZ for the binding at the sIL-6R (K_d is 0.71 nM = 0.10 μ g/ml). Therefore, IL-6R was completely occupied even at the end of each 8 mg/kg dosing interval in most of the patients. Age, gender and ethnicity did not affect the PK of TCZ.

TCZ is not excreted via the renal or biliary route. Instead, TCZ is predominantly eliminated via catabolism including degradation in plasma and distribution to tissues. TCZ undergoes biphasic elimination from the circulation. Total clearance is concentration dependent and includes linear at higher TCZ concentrations and non-linear clearance at low TCZ concentration. No formal studies on the effect of renal or hepatic impairment on the PK of TCZ have been conducted. Mild renal impairment (creatinine clearance based on Cockcroft-Gault < 80 ml/min and ≥ 50 ml/min) did not affect the PK of TCZ.

Nor is the clearance of TCZ affected by concomitant use of methotrexate (MTX), nonsteroidal anti-inflammatory drugs (NSAIDs), or corticosteroids. TCZ may normalize the expression of hepatic cytochrome P450 (CYP) isozymes which are suppressed by IL-6 (Oldfield et al., 2009). Therefore, administration or discontinuation of TCZ may affect the serum concentrations of drugs metabolized via CYP3A4, CYP1A2, CYP2C9 or CYP2C19 (e.g., omeprazole, dextromethorphan, atorvastatin, simvastatin, calcium channel blockers, cyclosporine, and warfarin).

3. Therapeutic efficacy

3.1 Clinical studies

In a 12-week, multicenter, randomized, double-blind, placebo-controlled phase I/II study, 164 Japanese patients with refractory RA were randomly administered either placebo, or 4 mg/kg or 8 mg/kg TCZ (Nishimoto et al., 2004). A dose-dependent reduction in the American College of Rheumatology (ACR) 20 response was observed. At 3 months, 78% of patients in the 8 mg/kg group, 57% in the 4 mg/kg group, and 11% in the placebo group achieved an ACR20 response. This study was extended to evaluate the long-term efficacy and safety of TCZ 8 mg/kg monotherapy for five years and designated STREAM (long-term Safety and efficacy of Tocilizumab, an anti-interleukin-6 REceptor monoclonal Antibody, in Monotherapy, in patients with rheumatoid arthritis) (Nishimoto et al., 2009a). A total 143 patients were enrolled, and 94 patients completed 5 years. At 5 years, 84.0%, 69.1%, and

43.6% of the patients achieved ACR20, ACR50, and ACR70 responses, respectively. Remission (the 28-joint disease activity score using erythrocyte sedimentation rate (DAS28ESR) <2.6) was achieved in 55.3% of the patients.

The CHARISMA (the Chugai Humanized Anti-human Recombinant Interleukin-Six Monoclonal Antibody) study was a 16-week, multicenter, randomized, double-blind, placebo-controlled phase II trial in 359 European patients in whom the response to MTX was inadequate (Maini et al., 2006). ACR20 response was achieved by 61% and 63% of patients receiving 4 mg/kg and 8 mg/kg of TCZ as monotherapy, respectively.

There are seven phase III studies (Table 1). SAMURAI (Study of Active controlled Monotherapy Used for Rheumatoid Arthritis, an Interleukin-6 inhibitor) was a randomized, 52-week, multicenter, x-ray reader-blinded, controlled phase III trial to evaluate the ability of TCZ monotherapy to inhibit progression of structural joint damage in patients with RA of <5 years' duration (Nishimoto et al., 2007). A total 306 Japanese patients were randomly assigned to two groups: (i) TCZ 8 mg/kg (n = 158) and (ii) conventional disease-modifying anti-rheumatic drug (DMARD) therapy (n = 148). At week 52, the TCZ group showed statistically less radiographic change in modified Total Sharp Score (mTSS) (mean 2.3) than the DMARD group (mean 6.1). The TCZ group also showed significantly better results than the DMARD group in ACR20, 50, and 70 responses, DAS28ESR, and Modified Health Assessment Questionnaire (MHAQ) scores.

	Population Size (n=)	Subject	Control arm	Primary endpoint	Duration
SAMURAI (Nishimoto et al., 2007)	refractory to DMARDs n=306	TCZ	DMARDs	ACR, DAS28ESR, mHAQ, and mTSS at week 52	52 w
SATORI (Nishimoto et al., 2009b)	refractory to MTX n=125	TCZ+ placebo	MTX+ placebo	ACR at week 24	24 w
RADIATE (Emery et al., 2008)	refractory to anti-TNFs n=498	MTX+ TCZ	MTX+ placebo	ACR at week 24	24 w
OPTION (Smolen et al., 2008)	refractory to MTX n=623	MTX+ TCZ	MTX+ placebo	ACR at week 24	24 w
TOWARD (Genovese et al., 2008)	refractory to DMARDs n=1220	DMARDs+ TCZ	DMARDs+ placebo	ACR at week 24	24 w
AMBITION (Jones et al., 2010)	MTX-naïve or MTX-free for ≥6 months n=673	TCZ	MTX	ACR at week 24	24 w
LITHE (Kremer et al., 2011)	refractory to MTX n=1196	MTX+ TCZ	MTX+ placebo	ACR at week 24; mTSS and HAQ at week 52	2 y

Table 1. Phase III trials of TCZ in patients with RA

SATORI (Study of Active controlled Tocilizumab mOnotherapy for Rheumatoid arthritis patients with an Inadequate response to metotrexate) was a 24-week, multicenter, randomized, double-blind, placebo-controlled phase III trial in patients with RA in whom the response to MTX was inadequate (Nishimoto et al., 2009b). A total 125 Japanese patients were randomly assigned to one of two groups: (i) TCZ 8 mg/kg plus MTX placebo (n = 61)

and (ii) TCZ placebo plus MTX (n = 66). At week 24, 25.0% in the MTX group and 80.3% in the TCZ group achieved ACR20 response. Additionally, serum vascular endothelial growth factor (VEGF) levels were significantly decreased by TCZ treatment, but not by MTX treatment.

RADIATE (Research on Actemra Determining efficacy after Anti-TNF failurEs) was a 24-week, multicenter, randomized, double-blind, placebo-controlled, parallel-group phase III trial to evaluate the efficacy and safety of TCZ in patients with active RA refractory to TNF antagonist therapy (Emery et al., 2008). A total 498 US and Western Europe patients were randomly assigned to three groups: (i) TCZ 8 mg/kg plus MTX (n = 175), (ii) TCZ 4 mg/kg (n = 163) plus MTX, and (iii) TCZ placebo plus MTX (n = 160). ACR20 was achieved at 24 weeks by 50.0%, 30.4% and 10.1% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively. Patients responded regardless of most recently failed anti-TNF or the number of failed treatments.

OPTION (tOcilizumab Pivotal Trial in methotrexate Inadequate respONders) was a 24-week, multicenter, randomized, double-blind, placebo-controlled phase III trial in patients with active RA in whom the response to MTX was inadequate (Smolen et al., 2008). A total 623 patients from 17 countries were randomly assigned to three groups: (i) TCZ 8 mg/kg plus MTX (n = 205), (ii) TCZ 4 mg/kg (n = 214) plus MTX, and (iii) placebo plus MTX (n = 204). ACR20 achieved at 24 weeks by 59%, 48%, and 26% of patients in the 8 mg/kg, 4 mg/kg and control groups, respectively. Significantly greater numbers of patients receiving TCZ showed ACR50/ACR70 responses or clinical remission (DAS28ESR <2.6) at week 24 than did those receiving placebo. In patients receiving TCZ, there were greater improvements in HAQ-DI score, the Short-Form 36 Health Survey (SF-36), and Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue assessment indicating that TCZ treatment significantly improves physical and mental function.

TOWARD (Tocilizumab in cOmbination With traditional DMARD therapy) was a 24-week, multicenter, randomized, double-blind, placebo-controlled phase III trial to evaluate the efficacy and safety of TCZ combined with conventional DMARDs in patients with active RA (Genovese et al., 2008). A total 1220 patients from 18 countries were randomly assigned to two groups: (i) TCZ 8 mg/kg plus DMARD (n = 805) and (ii) TCZ placebo plus DMARD therapy (n = 415). ACR20 achieved at 24 weeks 61% for TCZ 8 mg/kg versus 25% for placebo. Similar to the results of OPTION, the TCZ group showed significantly better results than the placebo group in ACR50/ACR70 response, clinical remission rate (DAS28ESR <2.6), HAQ-DI, SF-36 and FACIT-Fatigue assessment.

AMBITION (Actemra versus Methotrexate double-Blind Investigative Trial In mONotherapy) was a 24-week, multicenter, randomized, double-blind, double-dummy, placebo-controlled phase III trial evaluating the efficacy and safety of TCZ monotherapy versus MTX in patients with active RA (Jones et al., 2010). A total of 673 patients from the US, Canada, and Israel were randomly assigned to three groups: (i) MTX (escalating dose regimen: initial dose 7.5 mg/week, increasing to 15 mg/week at week 4 and 20 mg/week at week 8) for 24 weeks (n = 284), (ii) TCZ 8 mg/kg for 24 weeks (n = 288), and (iii) TCZ placebo for 8 weeks then TCZ 8 mg/kg for 16 weeks (n = 101). The intention-to-treat analysis demonstrated that TCZ was better than MTX treatment with a higher ACR20 response (69.9 vs 52.5%; p<0.001) and rate of DAS28ESR <2.6 (33.6 vs 12.1%) at week 24. The superiority of TCZ to MTX was observed in the intention-to-treat population from week 2 and throughout this study. The proportion of ACR50 (44%) and ACR70 (28%) responders at week 24 was also statistically superior for TCZ

compared with MTX (weighted difference between treatments: 0.12 for ACR50 (95% confidence interval (CI) 0.04 to 0.20; $p = 0.002$); and 0.14 for ACR70 (95% CI 0.07 to 0.22; $p < 0.001$). The superiority of TCZ to MTX was also shown in improvement of HAQ-DI at week 24. No significant difference was seen in the incidence of serious adverse events between TCZ treatment (3.8%) and MTX treatment (2.8%) ($p = 0.50$).

LITHE (tociLizumab safety and THE prevention of structural joint damage) is a 2 (or 3)-year, multicenter, randomized, double-blind, placebo-controlled phase III trial evaluating the ability of TCZ add-on therapy to inhibit progression of structural joint damage and improve physical function in patients with moderate to severe RA who respond inadequately to MTX. A total of 1196 patients from 14 countries were randomly assigned to three groups: (i) placebo plus MTX ($n = 393$), (ii) TCZ 4 mg/kg plus MTX ($n = 399$), and (iii) TCZ 8 mg/kg plus MTX ($n = 398$). Results from year 1 were reported (Kremer et al., 2011). Mean change in the total Genant-modified Sharp score was 0.29 and 0.34 with TCZ 8 mg/kg plus MTX and 4 mg/kg plus MTX, respectively, versus 1.13 with placebo plus MTX ($P < 0.0001$). Additionally, the HAQ-DI significantly decreased in the groups of TCZ (8 mg/kg and 4 mg/kg) add-on treatment compared with the group with placebo plus MTX.

3.2 Additional remarks

MTX has the highest efficacy among conventional DMARDs and has been used as an anchor drug in the treatment of RA. The AMBITION study and the SATORI study demonstrated that TCZ monotherapy is superior to MTX monotherapy. Several studies have demonstrated that MTX monotherapy is equivalent or superior to TNF inhibitor monotherapy (Donahue et al., 2008). Comparison of TCZ with abatacept demonstrated that the rate of withdrawal due to no effect in TCZ treatment was lower than that in abatacept treatment (Leffers et al., 2011). A meta-analysis revealed that the effectiveness of TCZ appeared to be greater for ACR70 (Bergman et al., 2010). Thus, TCZ is superior to MTX, TNF inhibitors, and abatacept in the case of monotherapy. The superiority between TCZ monotherapy and TCZ plus MTX treatment has not yet been established. Yamanaka et al. (2011) reported that the improvement of DAS28ESR and HAQ-DI in TCZ plus MTX treatment was better than that in TCZ monotherapy. Nakashima et al. (2010) reported that there was no significant difference in the improvement of DAS28ESR between TCZ monotherapy and TCZ plus MTX treatment. Data from the ACT-RAY study demonstrated that TCZ provided clinical benefit, regardless of whether it was given in combination with MTX or as a monotherapy (Dougados et al., 2011).

4. Safety and tolerability

Infections are the most frequent adverse events during therapy with TCZ and other biologics or DMARDs. In the AMBITION study, TCZ monotherapy was compared with MTX monotherapy (Jones et al., 2010). Infection rates per patient year were similar (TCZ 1.06 vs MTX 1.09). In both groups, nasopharyngitis and upper respiratory tract infection were common. The common serious infections were pneumonia. Neither opportunistic infections nor tuberculosis were reported in the patients receiving TCZ. Similar results were observed in a meta-analysis of TCZ monotherapy in Japanese patients (Nishimoto et al., 2010). Long-term exposure did not increase the incidence of serious infections. TCZ may not

increase the risk of de novo infection of tuberculosis. TCZ did not affect the humoral response to influenza vaccination (Tsuru et al., 2008).

Infusion reactions (any adverse event occurring during, or within 24 h after infusion) occurred in 5.6% of patients with TCZ (Jones et al., 2010). The majority occurred during the first two infusions, and no serious infusion reactions were reported. In the meta-analysis of TCZ monotherapy, total 133 infusion reactions were observed in 93 patients (Nishimoto et al., 2010). Most of them occurred within the first four infusions. Headache, increased blood pressure, and pruritus were common. Anaphylactic reactions were observed in 3 patients.

In worldwide Roche clinical trials, the rate of malignancies in patients receiving TCZ was 11.6 events per 1000 patient-years while the rate in the patients receiving synthetic DMARDs was 17.7 events per 1000 patient-years (van Vollenhoven et al., 2010). As it usually takes several years before a malignant neoplasm grows to be clinically recognized after the appearance of the first malignant cell, TCZ may not have been involved in the carcinogenesis of the malignancies found during TCZ treatment to date.

Decreases in the neutrophil count were commonly observed in patients receiving TCZ. In the meta-analysis of TCZ monotherapy, grade 2 (<1500–1000/ μ L) and grade 3 neutropenia (<1000–500/ μ L) were observed in 92 (15.3%) and 36 patients (6.0%), respectively (Nishimoto et al., 2010). However, the decreases were not progressive, and neither febrile neutropenia nor agranulocytosis occurred. There was no obvious association between decreases in neutrophils and the occurrence infections. Decreases in the neutrophil are probably due to inhibition of the biological effects of IL-6 on recruitment of neutrophils into peripheral blood, not due to myelosuppression. Transient or intermittent elevations of alanine aminotransferase (ALT) or aspartate aminotransferase (AST) have often been observed in patients receiving TCZ. The incidence of elevations of AST or ALT in patients treated with TCZ monotherapy was no more than that in patients treated with MTX monotherapy (Jones et al., 2010). Prolonged exposure to TCZ therapy did not appear to be associated with an increased likelihood of developing increases in ALT or AST because the numbers of patients developing increased ALT or AST values was highest in the first 6 months of treatment (Australian Government, 2011). Mean total cholesterol (T-cho) rose upon treatment with TCZ, but showed no continuous increase. As high-density lipoprotein (HDL) also increased, the atherogenic index [(T-cho - HDL)/HDL] did not change. Small low-density lipoprotein (LDL), which may be proatherogenic, did not increase with TCZ treatment while both large very low density lipoprotein (VLDL) and small HDL increases were observed (McInnes et al., 2010). Inhibition IL-6 signaling decreases lipoprotein A serum levels which correlate with coronary heart disease (Schultz et al., 2010; Daneshet al., 2000). Treatment with TCZ may not increase the risk of cardiovascular disease.

Gastrointestinal (GI) perforation occurred in 26 cases out of 4009 patients treated with TCZ in worldwide Roche clinical trials (van Vollenhoven et al., 2009). The rate of GI perforations was 2.8 events per 1000 patient-years with TCZ therapy while the rate in patients with RA who were exposed to corticosteroids was 3.9 events per 1000 patient-years. The majority of the patients who experienced GI perforations treated with TCZ were also receiving corticosteroids, NSAIDs, and MTX. GI perforations occur mainly in lower GI tract, and 16 of the 18 patients with colonic perforations had diverticulitis. Prevention of constipation is important not only to reduce the incidence of colonic perforations but also to improve quality of life. A case of multiple ulcers in the small and large intestines during TCZ therapy has been reported (Iwasa et al., 2011). In mice, Il-6 signal is necessary for the development of

lamina propria T_H17 cells which may play a role in the maintenance of intestinal mucosal homeostasis (Atarashi et al., 2008). A causal relationship between TCZ and gastrointestinal perforation/ulceration should be addressed in future studies.

Experience with TCZ use in human pregnancy is very limited. Thirty-three pregnancies were reported in 32 patients (19 to 42 years) (Rubbert-Roth et al., 2010). Of the 32 patients, 26 received TCZ + MTX and 6 received TCZ monotherapy or TCZ + DMARD other than MTX. In patients who continued their pregnancies, TCZ and MTX were discontinued when the pregnancy was discovered. Of 11 term deliveries (2 received TCZ monotherapy, 9 received TCZ + MTX), 10 were of healthy newborns. One infant died of ARDS 3 days after emergency cesarean section. It is difficult to evaluate the safety of TCZ during pregnancy from the current data.

In conclusion, clinical trials demonstrated that TCZ was generally well tolerated in patients with active RA. The incidence of adverse events of TCZ monotherapy is no more than that of MTX monotherapy. Also, the risk of adverse events is comparable with that of other biologics and the risk of serious infection may be less than that for TNF inhibitors (Campbell et al., 2011). There was no increase in the frequency of adverse events with long-term treatment with TCZ (Nishimoto et al., 2010).

5. The advantages, and potential advantages, of TCZ

5.1 Synovitis

The characteristic pathophysiology of RA is the destruction of bone and cartilage due to “persistent” synovitis; however, the mechanism of this “persistence” is not yet clear. It is reported that an IL-17A-triggered positive-feedback loop of IL-6 expression is present in fibroblasts (Ogura et al., 2008). Moreover, IL-6 stimulates megakaryocytes to increase platelet counts and induces platelet activation (Oleksowicz et al., 1994; Kaser et al., 2009), while platelet-derived microparticles in turn prominently elicit IL-6, not TNF, from synovial fibroblasts (Boilard et al., 2010). These phenomena may be involved in “persistent” inflammation. TCZ is the only drug that can directly cut these positive-feedback loops.

5.2 Insulin resistance

IL-6 is involved in the pathology of type II diabetes mellitus related insulin resistance (Fève & Bastard, 2009). The expression of IL-6 was markedly increased (up to 15-fold) in human fat cells from insulin-resistant individuals (Rotter et al., 2003). Inhibition of IL-6 signaling affects insulin resistance in a positive way (Schultz et al., 2010). A significant decrease of HbA1c was observed at only 1 month after TCZ treatment (Ogata et al., 2011a). Thus, TCZ may help to resolve insulin RA patients.

5.3 Malignancies

TCZ was originally planned as an anti-myeloma drug because TCZ suppressed growth of the IL-6-dependent myeloma cell line, KPMM2 (Mihara et al., 2005). In fact, in an RA patient with IgA-kappa type multiple myeloma, TCZ not only improved RA symptoms dramatically but also stabilized serum IgA levels for 13 months (Matsuyama et al., 2011). TCZ decreases the serum levels of VEGF (Nishimoto et al., 2009b). This effect may interfere with the angiogenesis and growth of tumors. For example, the antitumor effect of TCZ for oral squamous cell carcinoma has been reported (Shinriki et al., 2009). Targeting of the IL-6 system may be beneficial in the treatment of malignancies (Hong et al., 2007).

5.4 Mycobacterium infection

The TNF α -/- mice or the IL-6 -/- mice demonstrated that TNF is critical for initiation of the granulomatous response, and IL-6 plays a key role in the granuloma maintenance response (Welsh et al., 2008). Unlike IL-6 -/- mice, TCZ does not completely inactivate the IL-6 system because TCZ works as a competitive inhibitor of IL-6. Moreover, TCZ, unlike TNF inhibitors, does not inhibit *M. tuberculosis* antigen-induced interferon gamma (IFN- γ) production (Ogata et al., 2010b). TNF inhibitors increase the risk of infection or reactivation of *M. tuberculosis* while TCZ does not in clinical practice. Of course, TCZ should not be used in the patients with active mycobacterium infection. However, TCZ may be a candidate for intractable RA patients with mycobacterium infection which is treated. A patient with intractable RA was treated with TCZ without aggravation of *M. avium* infection which had been treated in advance (Nakahara et al., 2010).

5.5 Anemia

IL-6 increases the production of hepcidin, which is an iron-regulatory peptide secreted from liver cells, inhibits the signal transduction of erythropoietin, and causes anemia (Ganz and Nemeth 2009). Therefore, inhibition of IL-6 signaling by TCZ significantly improves anemia caused by chronic inflammation and benefits patients' general physical condition (Song et al., 2010).

5.6 Amyloidosis

Secondary amyloidosis is a life-threatening complication of RA. Mortality, amyloid burden, and renal prognosis significantly correlate with serum amyloid A (SAA) concentration. As amyloid deposits regressed in 60% of patients who had a median SAA concentration of less than 10 $\mu\text{g/ml}$, normalization of the SAA concentration not only prevents but also treats secondary amyloidosis (Lachmann et al., 2007). TCZ treatment almost completely normalizes the serum SAA level because IL-6 signal is essential for the expression of SAA (Hagihara et al., 2005). Therefore, TCZ is very useful for the treatment of secondary amyloidosis (Sato et al., 2009; Inoue et al., 2010).

5.7 Osteoporosis

IL-6 levels are significantly higher (30 to 1000-fold) in synovial fluid than in sera (Desgeorges et al., 1997), and IL-6 drives osteoclastogenesis (Le Goff et al., 2010). Since osteoclasts are primarily involved in bone resorption, reduction in their number would be anticipated to reduce bone loss. This expectation is supported by the results of Axmann et al (2009) who demonstrated that blockade of IL-6R dose dependently decreased the joint osteoclast count and the number of bone erosions. They concluded that the mechanism for this effect was that blockade of IL-6R negatively affects osteoclast differentiation (Axmann et al., 2009).

6. Improving clinical outcomes

6.1 Strategies for improving clinical outcomes

The response rate and the speed of improvement basically depend on the ratio between the target cytokine and the biological agent which traps the target cytokine. To lessen the amount of the target cytokine, it is very important that any comorbidity (e.g., infectious

diseases, lifestyle diseases, etc.) is treated or controlled as well as possible before and during administration of biological agents. This not only stops stimulation of the production of inflammatory cytokines from factors other than RA, but also serves to reduce adverse events, which results in better efficacy and safety. This also directly improves physical function irrespective of disease activity (Radner et al., 2010).

The standard dosage of TCZ for the treatment of RA is 8 mg/kg every 4 weeks. The serum TCZ concentrations 4 weeks after 3 doses are greater than 1 mg/mL, which is an effective dose, in about 80% of patients. However, this means that the serum TCZ concentrations are not sufficiently high in approximately 20% of patients. In these patients, increasing the dosage of TCZ and/or shortening the dosage interval may improve efficacy. Indeed, during clinical trials, it was observed that arthritis improved following the first dose but returned after 3 weeks in several patients. This suggested that the blood level could not be maintained over the 4-week period. I thus decided to give the second dose after an interval of 3 weeks following the first. By doing this, none of the patients suffered repeat deterioration by the time of the second dose in symptoms that had improved following the first, and no additive adverse effects were observed. A shorter dose interval at the start may be thought to be perfectly reasonable in terms of maintaining blood levels of biologics. In practice, this administration method is used for infliximab and abatacept.

6.2 Clinical efficacy and safety in our experience

6.2.1 Patients

The subjects of this analysis were patients who met the 1987 revised criteria for the classification of RA from ACR. Patients were included in the analysis if they started treatment with TCZ for the first time after 16 April 2008 (the date of insurance approval in Japan) (Table 2). This is an extension of a previous study (Hirabayashi et al, 2010). Data were collected until 20 March 2010. More than 23 and 51 weeks had elapsed since the first administration of TCZ in all 101 and in 70 patients, respectively. To reduce adverse events, any comorbidity was treated or controlled as well as possible before giving TCZ. All patients had a thoracic CT scan and were tested for the tuberculin reaction (or QuantiFERON®), anti-streptolysin O (ASO), anti-streptokinase (ASK), treponema pallidum haemagglutination (TPHA), hepatitis B surface antigen (and anti-hepatitis B core antigen antibody), anti-hepatitis C virus antibody, and β -D-glucan in order to screen for infections. If tooth plaque or caries were present, I arranged for assessment and treatment by a dentist. If chronic rhinorrhea or nasal blockage was seen, the patient was assessed and treated by an otolaryngologist. Patients were asked whether they had hemorrhoids. Patients were required to abstain from smoking.

Among the various therapies being used by the patients in the three months before they received TCZ, infliximab was discontinued at least one month before, adalimumab at least one week before, and etanercept at least 4 days before the new treatment commenced. Salazosulfapyridine, bucillamine, sodium aurothiomalate and mizoribine were discontinued upon initiating TCZ. The patients continued on MTX, tacrolimus and steroids at the same dose levels as before at least until dose 3 of TCZ. Then, MTX and tacrolimus were tapered off until 6 months after. The steroid dose was decreased slowly to avoid steroid withdrawal syndrome. There were no users of auranofin, D-penicillamine, hydroxychloroquine, minocycline or lobenzarit disodium.

Patient Characteristics

Age, mean \pm SD, median (min - max), years	60.6 \pm 12.7, 61 (23 - 82)
Male : Female	20 : 81
Duration of disease, mean, years	11.3
Steinbrocker Class (I, II, III, IV) : Stage (I, II, III, IV)	37, 49, 15, 0 : 16, 19, 15, 53
DAS28ESR, mean \pm SE	4.60 \pm 0.12
Previous medications	No. of patients treated
Prednisolone	71 (mean dosage: 3.9 mg/day)
TNF inhibitors (IFX, ETA, ADA)	11 (8, 2, 1)
MTX	38
Tacrolimus	11
Other DMARDs	48
No DMARDs for 3 months prior to TCZ treatment	20

Table 2. Patient demographics, clinical characteristics, and previous medications at baseline. SD: standard deviation. SE: standard error. 'Previous medications' denotes drugs used in the 3 months before administration of TCZ. IFX: Infliximab, ETA: etanercept, ADA: adalimumab. 'Other DMARDs' were sodium aurothiomalate, bucillamine, salazosulfapyridine, and mizoribine.

6.2.2 Clinical efficacy

The mean DAS28ESR at the start of TCZ treatment in all 101 patients was 4.60 ± 0.12 (mean \pm standard error of the mean (SEM)). Mean DAS28ESR had fallen below the remission threshold (<2.6) to 2.20 ± 0.10 after two doses and had further improved to 1.61 ± 0.08 at 23 weeks (intention-to-treat with last observation carried forward (ITT-LOCF)) and 1.50 ± 0.09 at 51 weeks (ITT-LOCF). The clinical response was evaluated using the European League Against Rheumatism (EULAR) response criteria. At 51 weeks (ITT-LOCF), 64 out of 70 patients (91.4%) had achieved remission with treatment response of good in 91.4%, moderate in 7.1% and one case of no response. The no response seen beyond five doses was due to a rise in DAS28ESR associated with a temporary deterioration in symptoms due to factors other than RA and did not represent secondary non-response. To date, no patient has discontinued the treatment due to lack of response.

Next, the patients were classified based on DAS28ESR into a high-activity group at >5.1 , a moderate-activity group at $3.2-5.1$ and a low-activity group at <3.2 . Although mean DAS28ESR had been 5.84 ± 0.13 ($n=36$) in the high-activity group before treatment with TCZ, this improved rapidly to below the remission threshold to 2.31 ± 0.20 after 3 doses (after 11-12 weeks; Fig. 1a). Mean DAS28ESR further improved to 1.92 ± 0.15 at 23 weeks and 1.66 ± 0.17 at 51 weeks. TCZ proved to be very effective regardless of baseline disease activity. Also, patients were classified based on disease duration into three groups (≥ 10 years, $2 \leq <10$, <2). Although mean DAS28ESR had been 4.57 ± 0.21 ($n=30$) in the ≥ 10 years group before treatment, this improved rapidly to below the remission threshold to 2.30 ± 0.17 after 2 doses (after 7 weeks; Fig. 1b). Mean DAS28ESR further improved to 1.60 ± 0.14 at 51 weeks. TCZ proved to be effective regardless of disease duration. However, in the ≥ 10 years group, the number of swelling joints rapidly decreased while the number of joints with tenderness decreased slowly, indicating that inflammation had subsided rapidly but that tenderness at the damaged joints was prolonged.

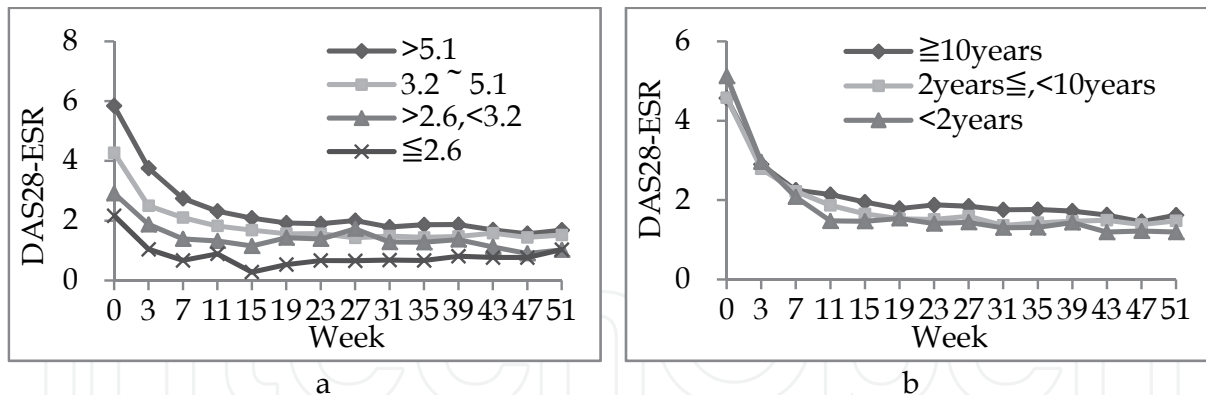


Fig. 1. Change in DAS28ESR by disease activity at baseline (a) and by duration of disease (b). Mean values shown. The criteria for exclusion from the analysis set were as follows: (i) autoimmune disease comorbidities except Sjögren's syndrome and Hashimoto's disease, (ii) functional class IV based on the Steinbrocker criteria, (iii) presence of active infection, (iv) pregnancy, (v) drug poisoning, including alcohol, (vi) lymphocyte count ≤ 500 cells/mL, and (vii) positive serum β -D-glucan. The method of administering TCZ that has received insurance approval in Japan is continuous infusion of a dose of 8 mg/kg over a period of at least 1 hour once every 4 weeks. The interval between infusions was shortened to 3 weeks between the first and second infusions only, and an interval of 4 ± 1 weeks was used thereafter. Treatment was continued unless there were adverse events requiring discontinuation or the patient requested that treatment be stopped.

6.2.3 Safety

A total of 72 adverse events occurred in 64 of the 101 patients and these are listed in Table 3. The adverse events seen during infusion were transient bone pain (back pain, lumbar discomfort and ischial pain). These all appeared a few minutes into infusion and disappeared within a few minutes. Infections were the most frequent adverse events. Nasopharyngitis (common cold) was most frequent among the infections; however, the frequency was similar to that in normal individuals. A total of 10 serious adverse events requiring hospitalization occurred in 8 patients. Three patients developed pneumonia. A 60-year-old woman with old tuberculosis and bronchiectasis as comorbidities showed a slight rise over her previous level of hemoptysis, and bacterial pneumonia appeared subsequently. An 80-year-old woman was suspected of having pneumonia due to *Chlamydia pneumoniae*. Both recovered with treatment. A 67-year-old man developed *pneumocystis carinii* pneumonia followed by cytomegalovirus pneumonia and died. MTX was administered concurrently to only this person due to scleritis suggesting vasculitis. A 68-year-old man had chronic pancreatitis as a comorbidity with several episodes of acute exacerbations before exposure to TCZ. He died of an acute exacerbation of chronic pancreatitis. One patient who died due to cerebellar infarction was elderly, at 82 years of age, and had once suffered strokes in the past. A patient with malignant lymphoma discovered as a left axillary mass underwent PET-CT scan to assess the activity of interstitial pneumonia before being treated with TCZ. Accumulation was picked up in the left axillary lymph nodes. Tiny lymphadenopathy was found at the same site by CT scan. Retrospectively, it may be inferred that the accumulation seen by PET had been the early stages of malignant lymphoma. A patient who had developed colitis probably due to viral infection recovered quickly.

PT (MedDRA Ver13.0)	a	b
Adverse drug reactions		
Bone pain	2	5
Total	2	5
Events possibly related to TCZ		
Nasopharyngitis	13	15
Sinusitis	4	4
Pneumonia*	1	2
Cystitis	3	3
Periodontitis	2	2
Otitis media	3	3
Paronychia	1	1
Infection	1	1
Bronchitis	1	2
Pneumocystis jiroveci	1	1
Pneumonia*		
Gastroenteritis	1	1
Pneumonia chlamydial*	1	1
Herpes zoster	1	1
Total	33	37

	a	b
Events hardly related to TCZ		
Rhinitis allergic	2	2
Diarrhoea	3	3
Haemorrhoids	2	2
Rash	2	2
Conjunctivitis allergic	1	1
Abdominal pain upper	1	1
Platelet count decreased	1	1
Asthma	1	1
Ileus	1	1
Pancreatitis acute*	1	2
Cough	1	1
Colitis*	1	1
Dizziness	1	1
Total	18	19
Events unrelated to TCZ		
Liver disorder	3	3
WBC count decreased	1	1
Lymphoma*	1	1
Cerebral infarction*	2	2
Hypoglossal nerve disorder	1	1
Toxic skin eruption	1	1
Bowen's disease	1	1
Compression fracture	1	1
Total	11	11

Table 3. Adverse events. *serious adverse events requiring hospitalization, a: No. of patients, b: No. of events. WBC: white blood cell.

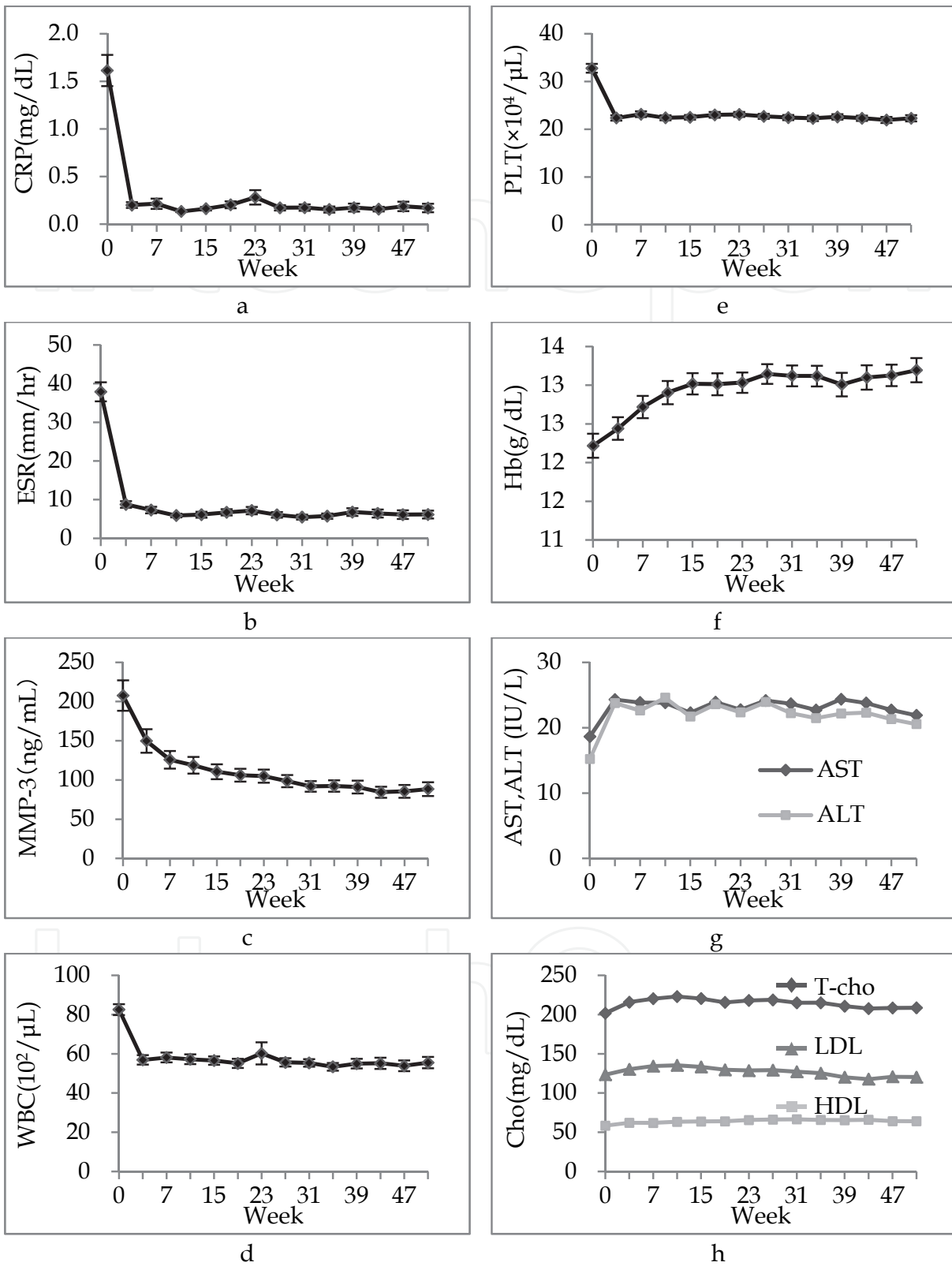


Fig. 2. Change in laboratory findings. a: CRP, b: ESR. c: MMP-3, d: WBC, e: PLT, f: Hb, g: AST and ALT, h: T-cho, HDL, and LDL. Mean values shown. Bars indicate SE.

Changes in laboratory findings are shown in figure 2. CRP virtually normalized in all patients after the first dose of TCZ ($1.61 \pm 0.16 \rightarrow 0.20 \pm 0.03$ mg/dL) (Fig. 2a). Erythrocyte sedimentation rate (ESR) likewise normalized quickly after the first dose ($37.9 \pm 2.47 \rightarrow 8.8 \pm 0.85$ mm/h) (Fig. 2b). Both followed a normal course afterwards as well. The level of matrix metalloproteinase-3 (MMP-3) gradually decreased from 207.7 ng/ml at baseline to 88.4 ± 8.79 ng/ml at 51 weeks (Fig. 2c). The mean leukocyte count was 8260 ± 278 /mL at baseline; however, this decreased to approximately 5500 /mL after the first dose. There was no progressive fall as seen in myelosuppression and no significant increase in infections (Fig. 2d). Likewise, the mean platelet count of 328000 ± 9100 /mL at baseline decreased to approximately 220000 /mL after the first dose (Fig. 2e). The hemoglobin (Hb) level rose gradually and anemia improved after treatment with TCZ began (Fig. 2f). Figure 2g shows changes over time in AST and ALT as an index of liver function. Even though abnormal values for AST or ALT were seen, these were transient and all were of grade I based on the National Cancer Institute Common Toxicity Criteria. Mean total T-cho at baseline was 201.7 ± 3.46 mg/dL. Upon treatment with TCZ, it rose to approximately 220 mg/dL and then decreased to 210 mg/dL (Fig. 2h). I provided lifestyle guidance and monitored the clinical course without administering drug treatment at least until dose 3. Several patients whose level nevertheless exceeded 280 mg/dL were treated with a HMG-CoA reductase inhibitor. HDL and LDL at baseline were 58.4 ± 1.55 mg/dL and 123.5 ± 3.08 mg/dL, respectively. HDL rose to approximately 65 mg/dL. LDL transiently rose to approximately 130 mg/dL but returned to baseline thereafter (Fig. 2h). I encountered no laboratory test abnormalities so severe that treatment with TCZ could not continue. TCZ was generally well tolerated, as was observed in clinical trials.

7. Impact of TCZ on the treatment strategy for rheumatoid arthritis

Examination by MRI of RA patients has revealed that in approximately half of the patients, bone destruction in joints had begun within 4 months of the onset of inflammation (McQueen et al., 1998). It is, therefore, important to achieve remission within 4 months of the onset of RA to reduce the chances of bone destruction. In treatment with the conventional DMRADs including MTX and with TNF inhibitors, patients who do not respond or who show insufficient response are often encountered. In these patients, bone destruction often progresses whilst disease activity remains uncontrolled. Medically, there is no reason why MTX or TNF inhibitors must be used initially. Therefore, to achieve tight control, and to reduce the number of such unfortunate patients, TCZ monotherapy is recommended from the beginning in new onset patients because it shows high efficacy and response rates. After tight control is achieved, how long to continue TCZ treatment and what treatment to use after completion of TCZ treatment are topics for future study.

8. References

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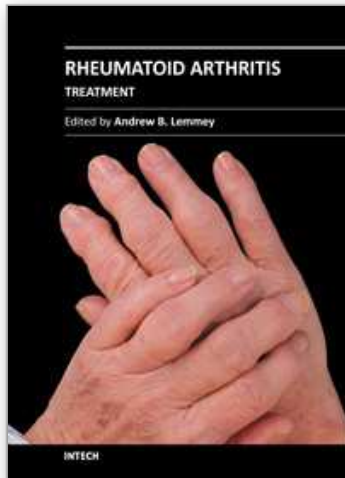
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The purpose of this book is to provide up-to-date, interesting, and thought-provoking perspectives on various aspects of research into current and potential treatments for rheumatoid arthritis (RA). This book features 17 chapters, with contributions from numerous countries (e.g. UK, USA, Canada, Japan, Sweden, Turkey, Bosnia and Herzegovina, Slovakia), including chapters from internationally recognized leaders in rheumatology research. It is anticipated that Rheumatoid Arthritis - Treatment will provide both a useful reference and source of potential areas of investigation for research scientists working in the field of RA and other inflammatory arthropathies.

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