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ORIGINAL ARTICLE

Safety and efficacy profiles of tocilizumab monotherapy in Japanese patients with rheumatoid arthritis: meta-analysis of six initial trials and five long-term extensions

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Abstract We present safety and efficacy data from Japanese clinical studies on monotherapy with tocilizumab (TCZ), a humanized anti-interleukin 6 receptor monoclonal antibody, in which 601 patients with moderate to severe rheumatoid arthritis, with a total of 2188 patient-years (pt-yr) exposure, were enrolled. The median treatment duration was 3.8 years. The incidence of adverse events (AEs), including abnormal laboratory test results, was calculated as 465.1 per 100 pt-yr. The most common serious adverse events (SAEs) were infections (6.22 per 100 pt-yr). There was no increase in the frequency of AEs or SAEs with long-term treatment. Abnormalities in the laboratory test results, such as increases in lipid parameters or abnormal liver function parameters, were common, but most were mild and there were no SAEs related to them. At baseline, 546 patients (90.8%) were taking corticosteroids; of these, 77.8% were able to decrease their corticosteroid dose during the study period, while 35.2% discontinued corticosteroids altogether. In the patients treated longer than 5 years, 91.3, 73.0, and 51.3% met the ACR20, ACR50, and ACR70 response criteria, respectively, and 59.7% met the DAS remission criterion (DAS28 <2.6) at 5 years. In conclusion, based on these results, TCZ has shown good tolerability and high efficacy during long-term treatment.

Keywords Clinical trial · Interleukin-6 · Meta-analysis · Rheumatoid arthritis · Tocilizumab

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Introduction

Rheumatoid arthritis (RA) is a common autoimmune disease characterized by persistent synovitis and progressive destruction of cartilage and bone in multiple joints [1]. The affected joints exhibit hyperplasia of inflamed synovium infiltrated with a range of immune cells; the inflamed synovium in turn forms pannus tissue that invades cartilage and bone [2]. Interleukin 6 (IL-6) is a multifunctional cytokine produced by various cell types, including T cells, B cells, monocytes, fibroblasts, and endothelial cells. It binds to membrane-expressed or soluble IL-6 receptors (IL-6R), and the resulting IL-6/IL-6R complex then binds to gp130, a common signal transduction molecule for cytokines of the IL-6 family, resulting in signal transduction to the cell nucleus [3]. Most of the clinical abnormalities seen in RA can be explained in terms of the dysregulated hyperproduction of IL-6. High levels of IL-6 are present in synovial fluid from affected joints of patients with active RA, and the IL-6 level correlates with the degree of radiological joint damage [4, 5].

Tocilizumab (TCZ) is a humanized anti-human IL-6R monoclonal antibody that inhibits IL-6 binding to IL-6R [6]. It was humanized by grafting the complementarity-determining regions from a murine anti-IL-6R antibody into human immunoglobulin (Ig) G1, thereby creating a functioning antigen-binding site in a reshaped human antibody and reducing the antigenicity of the antibody in

humans. We have demonstrated that treatment with TCZ improves the signs and symptoms of RA and also prevents joint damage [7–11]. TCZ has been developed as an anti-rheumatic agent. It was first approved in Japan in April 2008 and in the European Union in January 2009. Many other countries, including Brazil and India, have also approved its use in the clinical setting.

Here we present our meta-analysis of long-term safety and efficacy data from Japanese clinical studies of TCZ in patients with disease-modifying antirheumatic drugs (DMARD)-refractory RA.

Patients and methods

Patients

The eligibility criteria and study design for each study have already been reported [7–11]. Briefly, eligible patients were ≥20 years of age and fulfilled the 1987 American Rheumatism Association criteria for RA [12] with a disease history of >6 months (with the exception of the SAMURAI study, in which the eligible disease duration was restricted to between 0.5 and 5 years). All subjects failed to respond satisfactorily to treatment with at least one DMARD, including methotrexate (MTX) or immunosuppressants. At enrollment in the initial trials, the patients had active RA, as defined as the presence of six or more swollen joints, and tender joints. Patients receiving steroids (≤10 mg/day as prednisolone) and/or non-steroidal anti-inflammatory drugs (NSAIDs) were eligible if the dose had not increased during the 1-month washout period. Sexually active premenopausal women were required to have a negative urine pregnancy test at entry and periodically thereafter and to use effective contraception during the study period. There was no requirement to screen patients for exposure to tuberculosis (TB) or to have a Mantoux test before enrollment; the prophylactic use of anti-TB drugs was also not required.

Study protocols

We report here our meta-analysis of six clinical studies of TCZ in RA, all of which were conducted in Japan, and their five uncontrolled long-term extensions. The patient population for this meta-analysis consisted of all those individuals who received at least one dose of TCZ within the framework of the six clinical studies and/or extension studies. The initial clinical studies examined in this meta-analysis were a phase I/II open-label dose escalation study [7], a phase II double-blind dose finding study [8], a phase III open-label randomized study (SAMURAI) [9], a phase III double-blind study (SATORI) [10], a drug–drug interaction study, and a renal failure study (Fig. 1). All study protocols were approved by the Ministry of Health, Labor and Welfare of Japan and by the Ethics Committee of each institute, and the patients all gave their written informed consent. All patients received either placebo or 2, 4, or 8 mg/kg body weight of TCZ in the initial study and 8 mg/kg body weight of TCZ in the extension study. Patients receiving a corticosteroid dose of ≤10 mg/day (as prednisolone) at entry to the initial study were permitted to continue corticosteroid treatment. Surgical treatment and concomitant use of NSAIDs and corticosteroids was allowed, but concomitant use of DMARDs and immunosuppressive treatments was excluded.

Serious adverse events (SAEs) were defined as AEs that were fatal or life-threatening, resulting in permanent or significant disability or requiring prolonged inpatient hospitalization. SAEs and AEs were classified using MedDRA (Medical Dictionary for Regulatory Activities) ver. 8.0 (published by the Maintenance and Support Services Organization). Any abnormality in laboratory test results was graded by the common terminology criteria for AEs ver. 3.0 (National Cancer Institute, Bethesda, MD).

Clinical response was measured using the American College of Rheumatology (ACR) response criteria, the Disease Activity Score in 28 joints (DAS28), and the DAS28-based European League against Rheumatism (EULAR) criteria. Remission was defined, in accordance with the EULAR definition, as DAS28 <2.6 [13]. Functional disability was self-assessed by patients using the modified Health Assessment Questionnaire (mHAQ).

Statistical analysis

All data from the first dosing of TCZ to the last observation time for each patient were analyzed. Where appropriate, initial study data were combined with extension study data (matching on patient number). No imputation or estimation methods were used for missing data during the study.

The baseline time point for patient demographics, disease history, exposure, and AEs was the time of the first received dose of TCZ, which was either at the first dose in the initial controlled study or the first dose in the extension study. A Kaplan–Meier plot displaying time to withdrawal was produced. Patients were censored at the data cut-off time (if they had not already withdrawn). Data on AEs were summarized as the number of incidents per 100 patient-years (pt-yr).

A paired *t* test was used to detect statistically significant differences in disease activity and functional disability compared to baseline. Statistical analyses were performed using SAS ver. 8.2 TS2M0 (SAS Institute, Cary, NC).

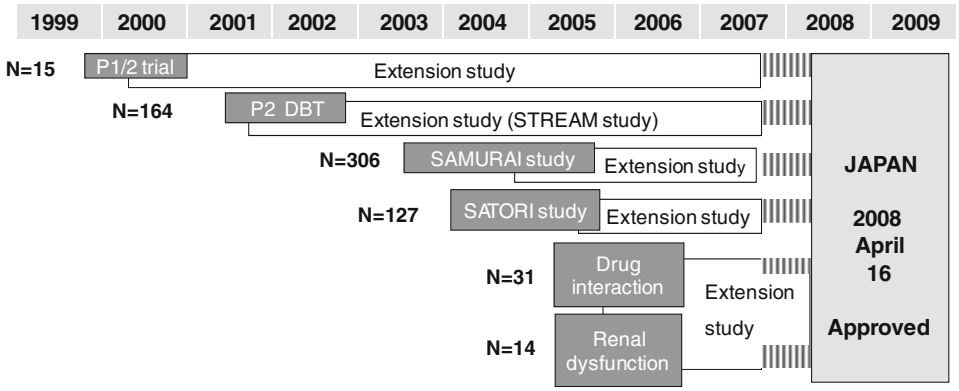

Fig. 1 Overview of clinical studies of tocilizumab (TCZ) in Japan. In total, 657 patients were enrolled in the initial studies and 601 patients received TCZ in the initial studies or the extensions. *DBT* Double-blind trial

Results

Patient characteristics

In total, 657 RA patients were initially enrolled and 601 were ultimately treated (i.e., received at least one dose of TCZ) in the clinical trials surveyed here (Fig. 1). The 56 patients who were not treated had been enrolled in the placebo group in the controlled studies but withdrew before they were enrolled in the extension studies. The mean age of the treated patients at baseline was 53.1 years (range 21–80 years), 80.5% were women, and the mean duration of RA was 6.5 years (range 0.4–52.8 years). The mean number of DMARDs previously administered was 3.5; 485 patients (80.8%) had previously received MTX, and 542 (90.8%) were taking corticosteroids (prednisolone-equivalent dose: mean 6.7 mg/day, range 0–10 mg/day) (Table 1).

The median duration of TCZ treatment was 3.8 years (range 0.1–9.0 years), and the total exposure was 2188 pt-yr. Only 27.6 and 35.7% of the patients had withdrawn from these studies at the 3- and 5-year data cut-off time point, respectively (Fig. 2). Of the treated patients, 118 (19.6%) withdrew due to AEs. Only eight patients (1.3%) withdrew due to an unsatisfactory response.

Safety

All AEs and adverse drug reactions (ADRs, that is, AEs at least possibly related to TCZ) are summarized in Table 2 according to the MedDRA system organ class (SOC). There were 10,176 AEs in 596 (99.2%) of the 601 patients administered TCZ (465.1/100 pt-yr). There was no increase in the incidence of AEs with long-term treatment. The SOCs in which AEs occurred frequently (>30 events/100 pt-yr) were "infections and infestations", "investigations", "gastrointestinal disorders", and "skin and subcutaneous tissue disorders". Among the category

Table 1 Demographics and baseline clinical characteristics of rheumatoid arthritis patients who received tocilizumab in clinical studies in Japan

Demographics and baseline clinical characteristics	Value
Total patients treated with TCZ (*n*)	601
Total exposure (patient-years) (*n*)	2188
Demographics	
Age (years)	53.1 ± 11.4
Median (years, range)	54.0 (21–80)
Women (% of patients)	80.5
Body weight (kg)	54.2 ± 20.1
Clinical characteristics	
Duration of RA (years)	6.5 ± 7.1
Median duration (years)	4.1
Previous DMARDs (*n*)	3.5 ± 1.8
Previous biologics (%)	2.5
Concomitant oral steroid (% of patients)	90.8%
Dose (mg/day)	6.7 ± 2.5
RA stage[a] (%, at I/II/III/IV)	4.7/36.4/32.3/26.6
RA classification[b] (%, at I/II/III/IV)	8.2/72.2/19.6/0.0
Tender joint count, 0–49 joints	16.1 ± 9.2
Swollen joint count, 0–46 joints	12.9 ± 7.6
ESR (mm/h)	63.0 ± 30.6
CRP (mg/dL)	4.0 ± 3.0
DAS28	6.3 ± 1.0

Values are given as the mean ± standard deviation (SD) unless stated otherwise

Calculated from patient data at first infusion of active tocilizumab, i.e., baseline of the initial trial (TCZ groups) or extension (placebo group in initial trial)

DMARDs Disease-modifying antirheumatic drugs, *TCZ* tocilizumab, a humanized anti-interleukin-6 receptor antibody, *RA* rheumatoid arthritis, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *DAS28* Disease Activity Score in 28 joints

[a] RA stage determined by Steinbrocker's criteria

[b] RA functional status determined by the American College of Rheumatology (ACR) response criteria

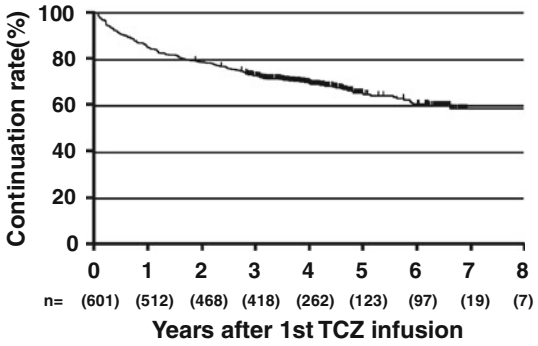

Fig. 2 The retention rate of patients treated with tocilizumab in the studies analyzed (Kaplan–Meier analysis). Treatment time was calculated from first infusion of TCZ at any dose, excluding time receiving placebo in an initial study. Patients are treated as a censored case if the patients finished a study with the completion of that study

"infections and infestations", the common AEs were upper respiratory infection, tinea, urinary tract infection, bronchitis, gastroenteritis, and pneumonia (Table 3).

In total, 133 infusion reactions were observed in 93 patients (15.5%), mostly within the first four infusions, among which headache, pruritus, and increased blood pressure were the most common. No patients were withdrawn due to infusion reactions. Anaphylaxis or anaphylactic reactions occurred in three patients; there were no serious infusion reactions due to the production of anti-TCZ antibodies.

There were 506 SAEs in 261 patients (23.1/100 pt-yr) and 223 serious ADRs in 133 patients (10.2/100 pt-yr) (Table 4). There were five deaths, giving a mortality rate of 0.23/100 pt-yr. The SOC with the most common SAEs was "infections and infestations" (6.22/100 pt-yr); this was followed by "musculoskeletal and connective tissue disorders" (5.53/100 pt-yr), which mostly related to joint surgery and were classified as unrelated to TCZ. Long-term exposure to TCZ did not increase the incidence of SAEs.

The common serious infections were pneumonia (28 events, 1.28/100 pt-yr), herpes zoster (14 events, 0.64/100 pt-yr), and cellulitis (13 events, 0.59/100 pt-yr). For

Table 2 Classification of adverse events and adverse drug reactions among patients receiving tocilizumab according to system organ class

SOC	Adverse events		Adverse drug reactions	
	Number of events	Events/100 patient-years	Number of events	Events/100 patient-years
Total	10176	465.1	6681	305.4
Infections and infestations	2696	129.2	2266	103.6
Neoplasms benign, malignant, and unspecified	61	2.78	41	1.87
Blood and lymphatic system disorders	56	2.56	32	1.46
Immune system disorders	64	2.93	32	1.46
Endocrine disorders	10	0.45	7	0.32
Metabolism and nutrition disorders	54	2.47	37	1.69
Psychiatric disorders	81	3.70	24	1.10
Nervous system disorders	463	21.2	295	13.5
Eye disorders	267	12.2	141	6.40
Ear and labyrinth disorders	68	3.10	32	1.46
Cardiac disorders	87	3.98	46	2.10
Vascular disorders	121	5.53	90	4.11
Respiratory, thoracic, and mediastinal disorders	511	23.4	400	18.3
Gastrointestinal disorders	1046	47.8	594	27.2
Hepatobiliary disorders	72	3.29	46	2.10
Skin and subcutaneous tissue disorders	984	45.0	461	21.1
Musculoskeletal and connective tissue disorders	426	19.5	119	5.44
Renal and urinary disorders	71	3.23	32	1.46
Reproductive system and breast disorders	77	3.52	41	1.87
Congenital familial and genetic disorders	7	0.33	0	0
General disorders and administration site conditions	297	13.6	203	9.28
Investigations	2207	100.9	1723	78.8
Injury, poisoning, and procedural complications	448	20.5	19	0.87
Surgical and medical procedures	2	0.09	0	0

SOC Medical Dictionary for Regulatory Activities (MedDRA) system organ class (MedDRA ver. 8.0)

Table 3 Major infections and infestations (≥1.0 events/100 pt-yr)

PT	Adverse events	
	Number of events	Events/ 100 patient-years
Total	2696	123.2
Nasopharyngitis	1402	64.1
Pharyngitis	89	4.07
Cystitis	85	3.88
Gastroenteritis	69	3.15
Tinea infection	67	3.06
Herpes simplex	61	2.79
Bronchitis acute	60	2.74
Pneumonia	56	2.56
Dental caries	53	2.42
Upper respiratory tract infection	53	2.42
Herpes zoster	50	2.29
Paronychia	41	1.87
Bronchitis	34	1.55
Tinea pedis	33	1.51
Urinary tract infection	32	1.46
Sinusitis	30	1.37
Cellulitis	29	1.33
Influenza	25	1.14
Purulence	22	1.01

PT MedDRA preferred term according to MedDRA (ver. 8.0)

pneumonia, 48% of the AEs were reported as serious events. Long-term exposure did not increase the incidence of serious infections (Fig. 3a). The onset of pneumonia tended to increase in the winter, while the onset of urinary tract infection increased in the summer (Fig. 3b, c). When the incidences of infections were analyzed using pooled data from three randomized controlled studies (one phase II study and two phase III studies [8–10]), the incidence in the TCZ-treated patients (41.9%) was not significantly higher than that in the control group (37.6%). Two cases of TB were reported (one pulmonary, one miliary TB); these developed 1.5 and 2.5 years after TCZ treatment initiation, respectively. One patient had a positive PPD skin test (no prophylaxis reported), and the other had, in retrospect, a suspicious chest X-ray during the pre-treatment period. Thus, reactivation of existing TB may have occurred. Both patients improved with the appropriate treatment, but they withdrew from the studies after developing TB.

Gastrointestinal perforation occurred in five patients, and a causal relationship with TCZ could not be ruled out in three cases. All patients improved after receiving the appropriate treatment. Nineteen malignancies were reported in 19 patients (3.2%, 0.8/100 pt-yr), with breast cancer and colon carcinoma observed in more than two patients, respectively (Table 5). No patients developed systemic lupus erythematosus or any other additional autoimmune disease.

Most of the abnormal laboratory test results were minor. Decreases in the leukocyte count to the low normal range were observed a few days after TCZ administration. Although grade 2 (<1500–1000/μL) and grade 3 neutropenia (<1000–500/μL) were observed in 92 (15.3%) and 36 patients (6.0%), respectively, these events were all transient, and no patients experienced febrile neutropenia or withdrew from a study due to neutropenia. Transient liver function disorders were also reported. Alanine aminotransferase (ALT) increased to grade 3 [>5.0–20.0 × ULN (upper limit of normal)] in 16 patients (2.7%), to grade 2 (>2.5–5.0 × ULN) in 31 patients (5.2%), and to grade 1 (>ULN–2.5 × ULN) in 221 patients (36.8%). Aspartate aminotransferase (AST) increased to grade 3 (>5.0–20.0 × ULN) in seven patients (1.2%), to grade 2 (>2.5–5.0 × ULN) in 17 patients (2.8%), and to grade 1 (>ULN–2.5 × ULN) in 180 patients (30.0%). There were no grade 4 (>20.0 × ULN) ALT or AST values and no serious liver function disorders, such as fulminant hepatitis, during the TCZ treatment. Total bilirubin increased to grade 3 (>3.0–10.0 × ULN) in three patients (2.7%), to grade 2 (>1.5–3.0 × ULN) in 32 patients (5.3%), and to grade 1 (>ULN–1.5 × ULN) in 186 patients (30.9%). There were no severe AEs related to these abnormal values. Mean non-fasting total blood cholesterol (TC) increased soon after treatment initiation and then stabilized (185 mg/dL at baseline; 215 mg/dL at 1 year; 210 mg/dL at 5 years) (Fig. 4a, b). As high-density lipoprotein cholesterol (HDLC) followed a similar pattern, the atherogenic index [(TC – HDLC)/HDLC] did not change (Fig. 4c, d). In total, 173 patients (28.8%) received statin treatment after starting TCZ therapy. Mean values of total and low-density lipoprotein cholesterol (LDLC) levels at baseline were higher in the statin-treated group than in the untreated group, suggesting that the former may have had risk factors before initiating the TCZ treatment. Lipid abnormalities were controllable by statin treatment (Fig. 5).

Efficacy

The ACR response rates rapidly increased during the first year of TCZ treatment. The ACR20 (20% improvement according to the ACR criteria) then became stable, while the ACR50 and ACR70 (50 and 70% improvement) continued to increase (Fig. 6a). At 5 years, 91.3, 73.0, and 51.3% of patients had achieved ACR20, ACR50, and ACR70, respectively, and 59.7% of the patients had achieved DAS28 remission (Fig. 6b). At 6 months, >90% of patients had achieved a DAS28 EULAR moderate or good response (Fig. 6c), and this level was maintained during the study period. The mHAQ score also improved during the study period (Fig. 6d). Although ACR response

Table 4 Major serious adverse events (≥0.2 events/100 pt-yr)

SOC/PT	Adverse events		Adverse drug reactions	
	Number of events	Events/ 100 patient-years	Number of events	Events/ 100 patient-years
Total	506	23.1	223	10.2
Infections and infestations	136	6.22	109	4.98
Pneumonia	28	1.28	27	1.22
Herpes zoster	14	0.64	13	0.59
Cellulitis	13	0.59	13	0.59
Pyelonephritis	6	0.27	4	0.18
Gastroenteritis	5	0.23	3	0.14
Bronchitis acute	5	0.23	3	0.14
Neoplasms benign, malignant and unspecified	21	0.96	18	0.82
Blood and lymphatic system disorders	6	0.27	5	0.23
Immune system disorders	5	0.23	1	<0.1
Psychiatric disorders	6	0.27	–	–
Nervous system disorders	33	1.51	9	0.41
Eye disorders	14	0.64	–	–
Cataract	13	0.59	–	–
Cardiac disorders	15	0.69	8	0.37
Vascular disorders	7	0.32	5	0.23
Respiratory, thoracic and mediastinal disorders	20	0.91	10	0.46
Gastrointestinal disorders	33	1.51	14	0.64
Hepatobiliary disorders	13	0.59	6	0.27
Hepatic function abnormality	5	0.22	3	0.14
Skin and subcutaneous tissue disorders	12	0.55	3	0.14
Musculoskeletal and connective tissue disorders	121	5.53	1	<0.1
Joint distraction	65	2.97	–	–
Toe deformity	11	0.50	–	–
Rheumatoid arthritis	7	0.32	1	<0.1
Arthralgia	6	0.27	–	–
Osteoarthritis	7	0.32	–	–
Renal and urinary disorders	6	0.27	1	<0.1
General disorders and administration site conditions	7	0.32	2	0.09
Investigations	31	1.42	28	1.28
Injury, poisoning and procedural complications	67	3.06	1	<0.1
Tendon rupture	18	0.82	–	–
Joint dislocation	10	0.46	1	<0.1
Femoral neck fracture	6	0.27	–	–
Humerus fracture	5	0.22	–	–
Spinal compression fracture	5	0.22	–	–

rates and the mHAQ score appeared to fluctuate after 5 years, the fluctuations were not statistically significant.

Most patients showed low hemoglobin (Hb) levels at baseline (Hb 11.3 ± 0.02 mg/dL, mean ± SE). TCZ significantly improved anemia, and the mean Hb level rose to 13.1 ± 0.1 mg/dL at year 5 (Fig. 6e).

At baseline, 546 patients (90.8%) were taking corticosteroids; of these, 78% were able to decrease their corticosteroid doses during the study period, and 35.2% discontinued corticosteroids. The mean dose of corticosteroid in these patients (as prednisolone) fell from 6.7 mg/day (median 4.0 mg/day) at baseline to 2.3 mg/day (median 0.5 mg/day) at 5 years (Fig. 6f).

TCZ showed greater efficacy in recent-onset RA patients (RA duration <2 years) than in those with a longer disease duration. At 6 months, the ACR50 and ACR70

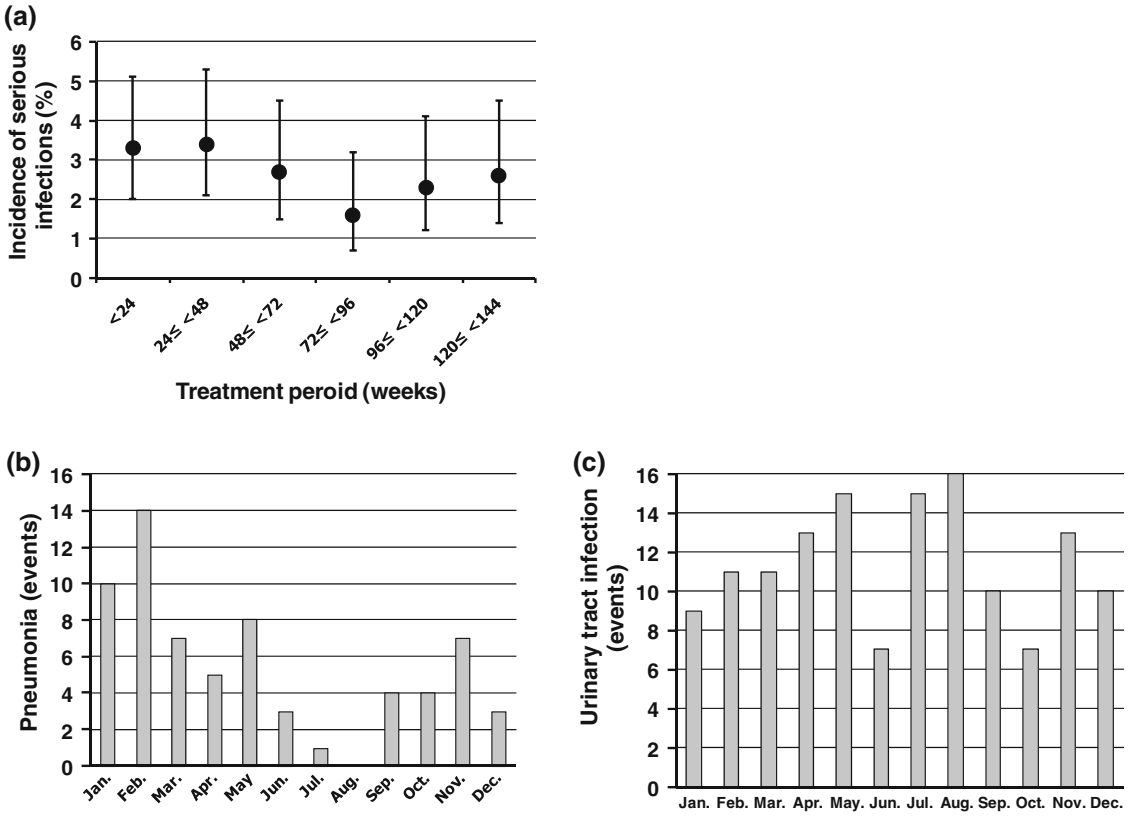

Fig. 3 Onset of serious infection and seasonal onset of pneumonia and urinary tract infection during TCZ treatment. **a** Onset of serious infection by 24-week time point. *Filled circles* and *bars* Mean and 95% confidence interval, respectively. **b** Onset of pneumonia by month. **c** Onset of urinary tract infection by month

Table 5 Malignancies observed among the patient cohorts

Malignancies	Number of patients	Percentage of patients
Total	19	3.16
Breast cancer	4	0.67
Colon carcinoma	3	0.50
Bladder cancer	2	0.33
Malignant lymphoma (NHL or HL)	2	0.33
Gastric cancer	1	0.17
Gallbladder cancer	1	0.17
Pancreatic carcinoma	1	0.17
Lung cancer	1	0.17
Cervical carcinoma	1	0.17
Colon cancer	1	0.17
Papillary thyroid cancer	1	0.17
Ovarian epithelial cancer	1	0.17

NHL, *HL* Non-Hodgkin lymphoma and Hodgkin lymphoma, respectively

response rates were >60 and >40%, respectively, in recent-onset patients. These values were almost twofold higher than the response rates seen in patients with disease duration of ≥10 years (ACR50 and ACR70 30 and 16%, respectively). At 6 months, the remission rate according to the DAS28 was 49.6% in recent-onset patients compared with only 21% in patients with the disease for ≥10 years. More than 70% of recent-onset patients, but only 38% of patients with disease for ≥10 years had EULAR good responses (Fig. 7a, b). It is noteworthy that even in the patients with longer disease duration, the clinical efficacy was significantly augmented at 1 year of treatment compared with that at 6 months.

Discussion

We report a meta-analysis of Japanese trials of TCZ in RA using data from six initial studies and their five long-term extensions. In general, the results show a good safety profile and excellent efficacy, with a total of 2188 pt-yr, as also evidenced by the high retention rate at 5 years. In particular, only 1.3% of 601 patients withdrew due to unsatisfactory response, indicating that loss of efficacy was very rare during the long-term treatment.

Long-term treatment with TCZ was well tolerated. The mortality rate of 0.23/100 pt-yr is numerically lower than

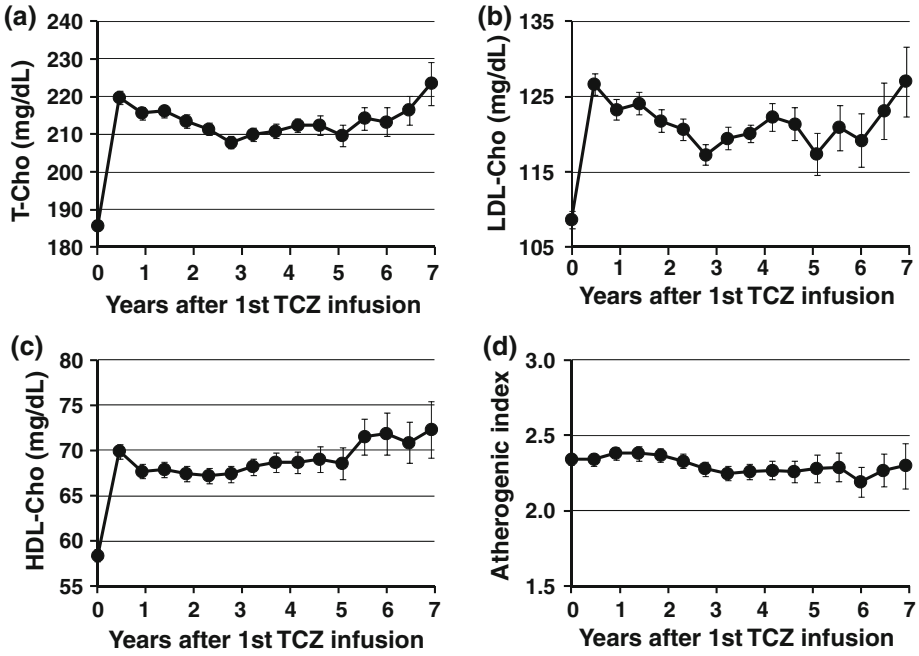

Fig. 4 Serum total, low-density lipoprotein (*LDL*) and high-density lipoprotein (*HDL*) cholesterol (*Cho*), and atherogenic index during TCZ treatment. **a** Total cholesterol, **b** LDL cholesterol, **c** HDL cholesterol, **d** atherogenic index. *T-cho* Total cholesterol. *Filled circles* and *bars* Mean ± standard error (SE), respectively

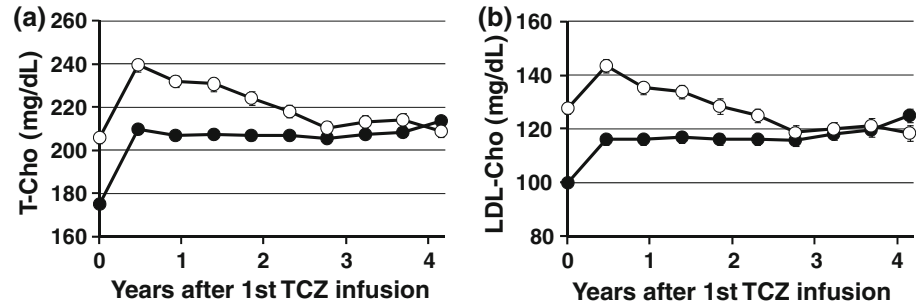

Fig. 5 Effects of statin in hypercholesterolemic patients during tocilizumab treatment. Total cholesterol (**a**) and LDL cholesterol (**b**) in patients who received statin treatment (*open circle*) and those who did not (*filled circle*). *Circles (filled and open)* and *bars* Mean ± SE

that observed with other biologics [14, 15]. Long-term exposure did not increase the incidence of SAEs, and most AEs were mild and acceptable relative to the benefits provided. TCZ did not increase the incidence of infections compared to the control groups in the phase II and III controlled studies. In addition, the incidence of serious pneumonia was comparable to that in patients treated with anti-tumor necrosis factor (TNF) drugs. However, careful monitoring must be undertaken during TCZ treatment because IL-6R inhibition can suppress acute-phase reactions (fever, C-reactive protein increase, etc.), thereby obscuring the signs and symptoms associated with infection, possibly resulting in a delayed detection of the infection itself [16].

In patients treated with anti-TNF drugs, most TB cases were reported to occur in the first 6 months [17–19]. TNF is considered a key cytokine for TB control, by a mechanism increasing anti-TB macrophage phagocytic capacity and by increasing granuloma formation [20]. Anti-TNF therapy may suppress these actions and thereby increase the risk of TB reactivation. IL-6 has no such anti-TB activities and TCZ does not inhibit granuloma formation. Even though 2 TB cases were reported after 1.5 and 2.5 years of TCZ treatment, the mechanism responsible for TB development during TCZ treatment likely differs from anti-TNF treatment. Although the incidence of TB is comparable to that observed in Japanese RA cohorts receiving conventional DMARDs [21], patients on TCZ should be carefully monitored for TB, as for other infections.

Gastrointestinal perforation occurred in five patients. A causal relationship with TCZ was not ruled out in three of these. Intestinal perforation appeared to be related to diverticulitis. At the present time we do not know whether this incidence is comparable to that in the general RA population or to other biologics users [22].

Nineteen malignancies were reported in 19 patients. Yamanaka et al. [23] compared the incidence of malignancies in three cohorts of Japanese RA patients: (1) those who received TCZ in Japanese clinical trials; (2) an observational cohort of RA patients (IORRA cohort, Institute of Rheumatology, Tokyo Women's Medical

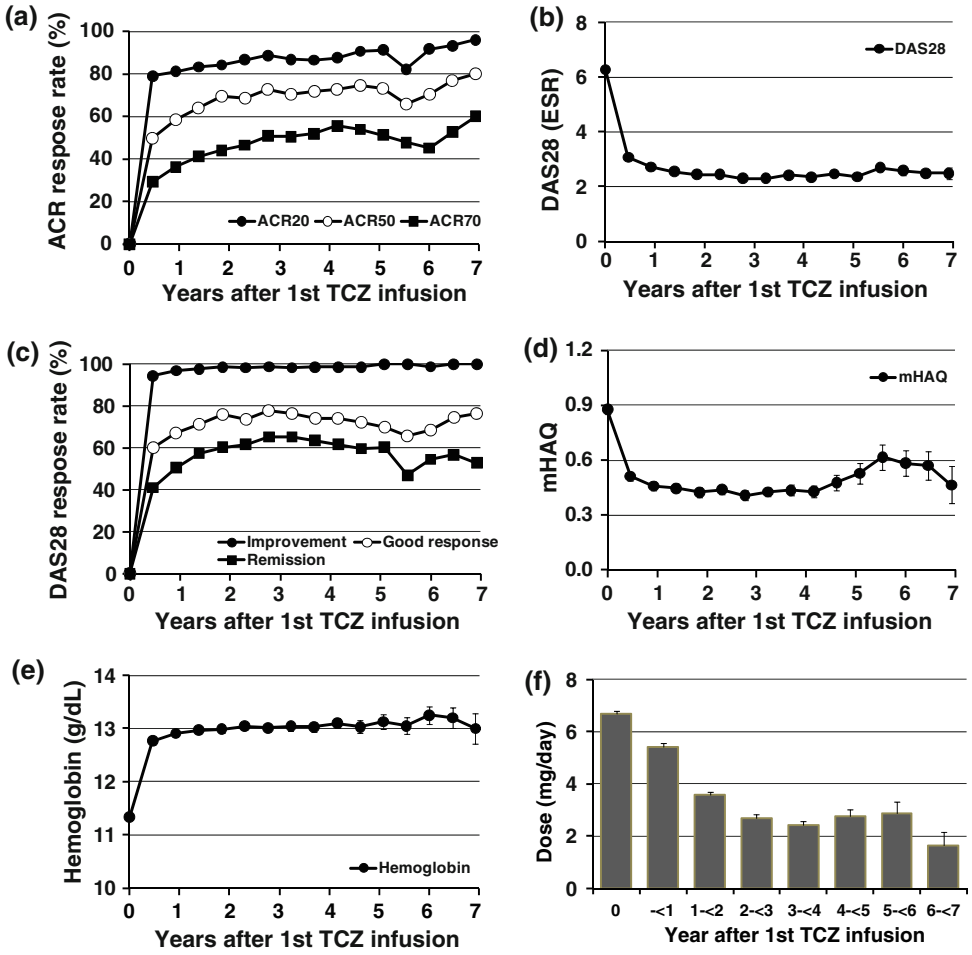

Fig. 6 Indicators of disease activity during tocilizumab treatment. **a** ACR20, -50, and -70 improvement rates [rates of 20, 50, and 70% improvement according to American College of Rheumatology (*ACR*) criteria], **b** mean of Disease Activity Score for 28 joints (*DAS28*), **c** DAS remission rate (DAS28-ESR <2.6) and European League against Rheumatism (*EULAR*) good and good + moderate response rates, **d** mean of modified Health Assessment Questionnaire (*mHAQ*) score, **e** mean of serum hemoglobin (indicator of anemia), **f** average dose of oral corticosteroid (as prednisolone) in patients who received oral prednisolone at baseline. *ESR* Erythrocyte sedimentation rate, *Circles (filled and open)* and *bars* Mean ± SE

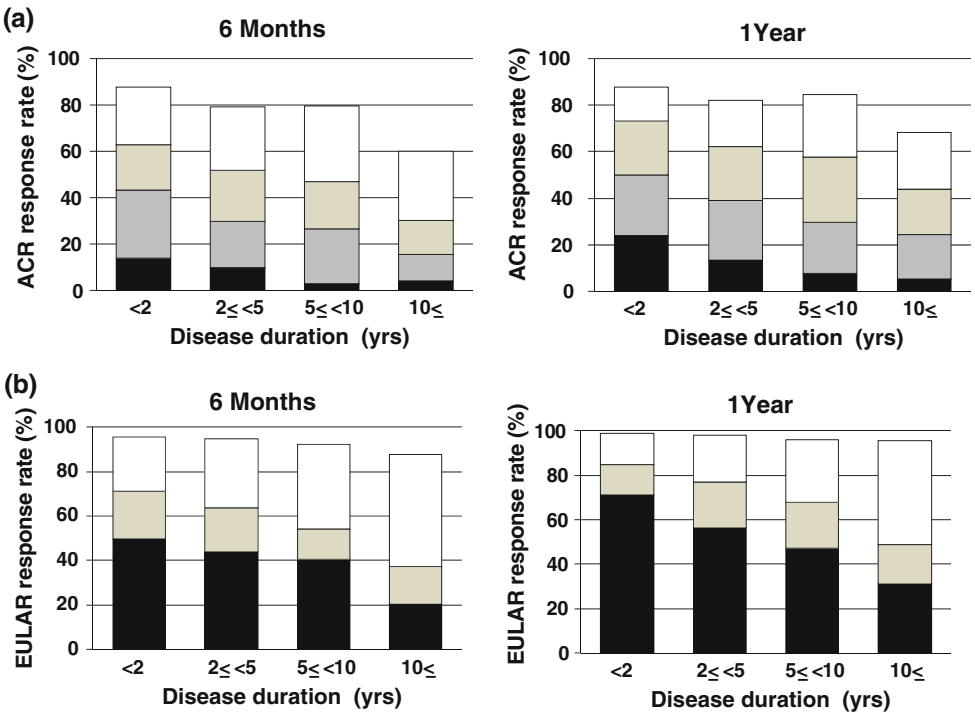

Fig. 7 Relationship between efficacy of TCZ and disease duration. **a** ACR20, -50, -70, and -90 response rates at 6 months and 1 year after first tocilizumab infusion according to disease duration. *Filled bars* ACR90 rate, *dark-shaded bars* ACR70 rate, *light-shaded bars* ACR50 rate, *open bars* ACR20 rate. **b** EULAR moderate and good response rates and DAS remission rate (DAS28-ESR <2.6) at 6 months and 1 year after first tocilizumab infusion according to disease duration. *Filled bars* DAS remission rate, *shaded bars* Good response rate, *open bars* moderate response rate

University); (3) a Japanese population database. The incidences of malignancies were almost the same in these three populations. Further study of a much larger population of TCZ-treated RA patients will be required to evaluate whether TCZ treatment affects the incidence of malignancies.

Total cholesterol, HDL cholesterol, and LDL cholesterol levels increased in our patient cohort during the first year of TCZ treatment, but did not continue to increase during the extension studies. The atherogenic index remained stable throughout 5 years of treatment. Therefore, the increase in total cholesterol may not indicate an increased risk of cardiovascular disease. Because IL-6 is thought to play a causative role in atherosclerosis, IL-6R inhibition may actually decrease the incidence of cardiovascular events, as has been postulated with respect to TNF blockade [24]. Further investigation will be required to evaluate the relationships between TCZ treatment and the risk of ischemic heart disease. At this time, therefore, treatment should follow the usual guidelines for cholesterol management.

Abnormal results were observed for neutropenia and liver function tests, but most were transient. Since IL-6 induces demargination of intravascular neutrophils and shortens their transit in the marrow [25], neutropenia may occur through an inhibition of IL-6 action; similar events have been observed during intravenous infusion of high-dose immunoglobulin [26]. An increased sensitivity of IL-6-deficient mice to chemical hepatotoxic injury has been reported [27], suggesting that IL-6 inhibition may influence the abnormalities observed in the liver function test results. It is noteworthy that the incidence of such abnormal test results in TCZ monotherapy were lower than those reported in the international clinical trials where a TCZ–MTX combination was used [28–30]. This may represent an advantage of TCZ monotherapy.

The ACR response rates and improvement in the DAS28 score and in individual components of the ACR core set were all sustained during long-term TCZ monotherapy. Indeed, at 5 years, about 59% of the patients met the criteria for ACR70, and 60% had achieved clinical remission (DAS28 <2.6). Recent-onset RA patients showed a greater clinical improvement: the ACR response rates and the DAS remission rate were almost twofold higher in patients with an RA duration <2 years than in those with a long disease duration.

A corticosteroid-sparing effect is an additional benefit of TCZ therapy. Corticosteroid use is often associated with AEs such as infection and osteoporosis. Therefore, reduced corticosteroid use is expected to contribute to an improved safety profile. Together with improvement in the HAQ score and hemoglobin levels, these effects contribute to the RA patient's improved quality of life.

For TNF inhibitors, combination treatment with MTX is needed for maximum efficacy [14, 31], but in our analysis, long-term TCZ monotherapy showed a good and sustained effect. Therefore, TCZ has considerable clinical benefits for patients who cannot tolerate MTX. The safety and efficacy of TCZ in combination with MTX or DMARDs has been investigated only in relatively short-term studies [28–30, 32]. Further studies are required to determine the long-term safety and efficacy of such combinations.

In conclusion, this study demonstrates that TCZ monotherapy has an excellent long-term efficacy and a generally good safety in patients with active RA.

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Conflict of interest statement NN has served as a consultant to and received honoraria from the Chugai Pharmaceutical Co., Ltd., the manufacturer of TCZ. NN also works as a scientific advisor to F. Hoffmann-La Roche, which is developing TCZ in collaboration with Chugai Pharmaceutical Co., Ltd. KI and NT are employees of Chugai Pharmaceutical Co., Ltd.

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