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

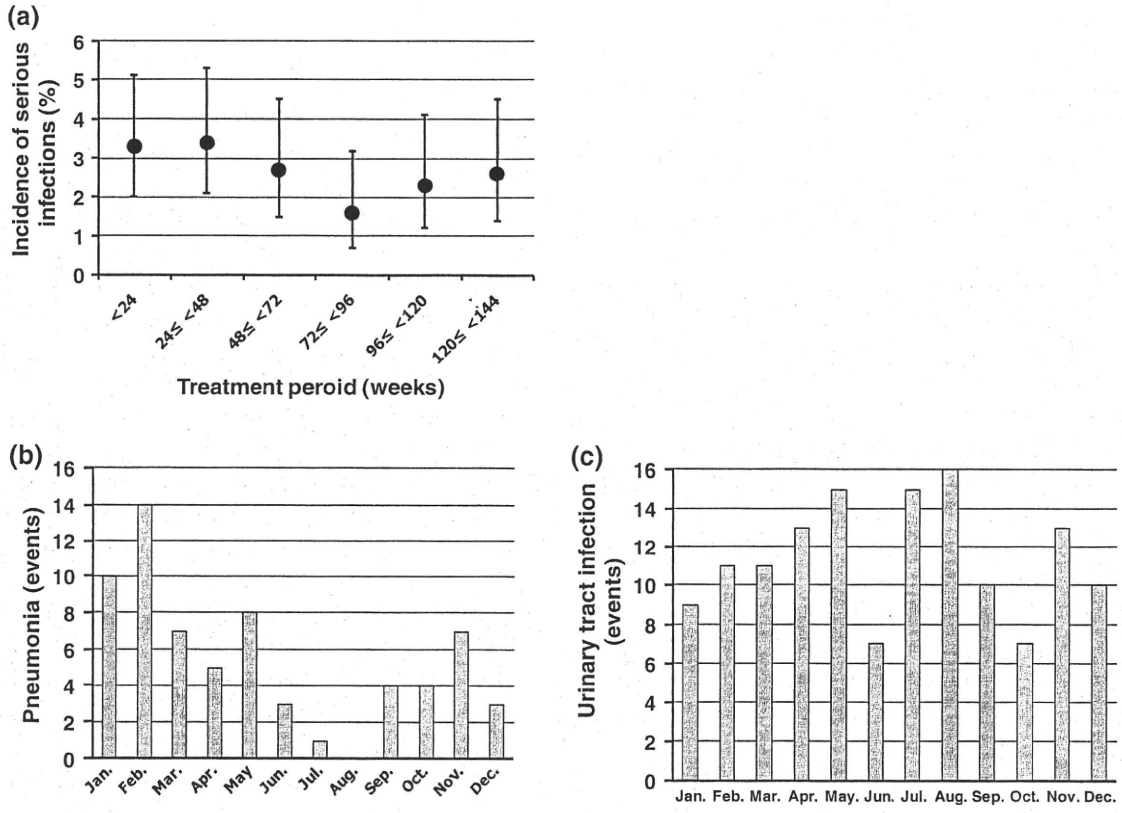

Fig. 3 Onset of serious infection and seasonal onset of pneumonia and urinary tract infection during TCZ treatment. **a** Onset of serious infection by 24-week time point. *Filled circles* and *bars* Mean and 95% confidence interval, respectively. **b** Onset of pneumonia by month. **c** Onset of urinary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

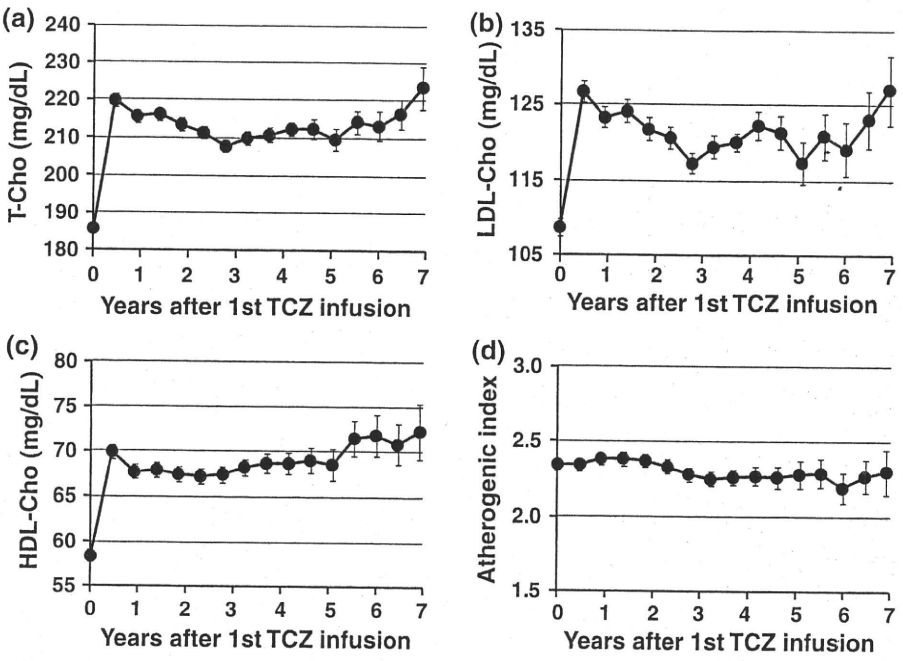

Fig. 4 Serum total, low-density lipoprotein (*LDL*) and high-density lipoprotein (*HDL*) cholesterol (*Cho*), and atherogenic index during TCZ treatment. **a** Total cholesterol, **b** LDL cholesterol, **c** HDL cholesterol, **d** atherogenic index. *T-cho* Total cholesterol. *Filled circles* and *bars*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

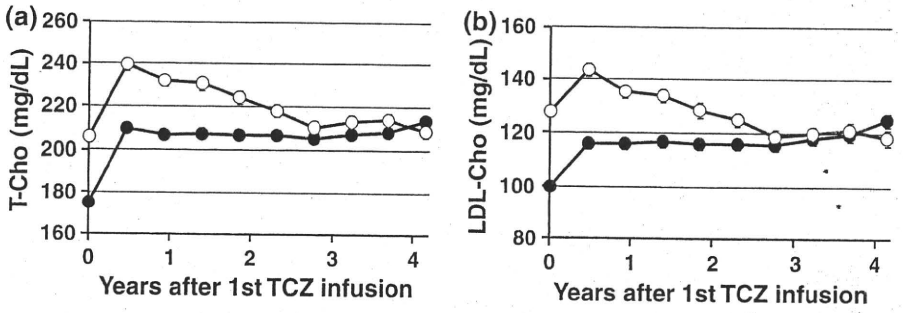

Fig. 5 Effects of statin in hypercholesterolemic patients during tocilizumab treatment. Total cholesterol (**a**) and LDL cholesterol (**b**) in patients who received statin treatment (*open circle*) and those who did not (*filled circle*). *Circles (filled and open)* and *bars* Mean ± SE

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

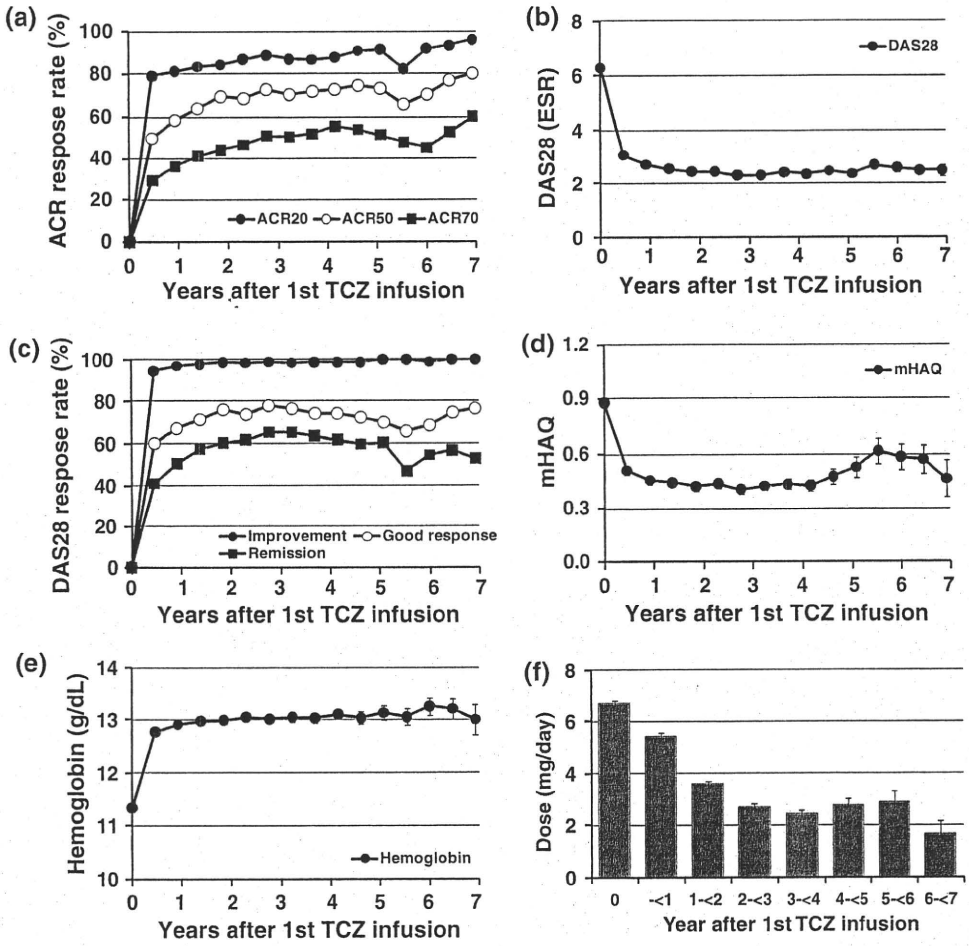

Fig. 6 Indicators of disease activity during tocilizumab treatment. **a** ACR20, -50, and -70 improvement rates [rates of 20, 50, and 70% improvement according to American College of Rheumatology (*ACR*) criteria], **b** mean of Disease Activity Score for 28 joints (*DAS28*), **c** DAS remission rate (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

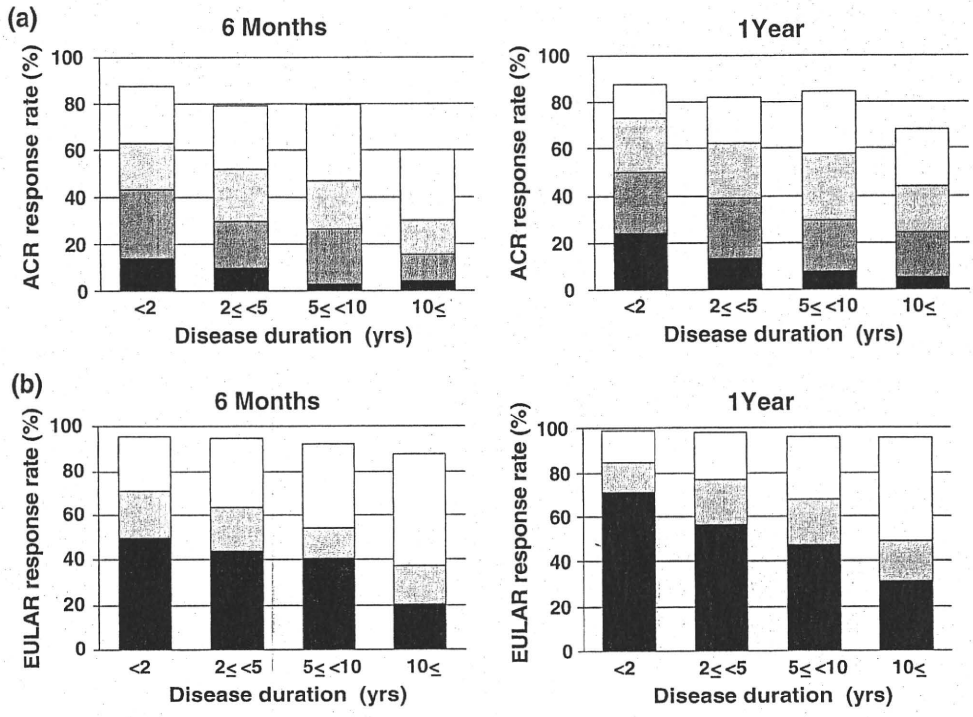

Fig. 7 Relationship between efficacy of TCZ and disease duration. **a** ACR20, -50, -70, and -90 response rates at 6 months and 1 year after first tocilizumab infusion according to disease duration. *Filled bars* ACR90 rate, *dark-shaded bars* ACR70 rate, *light-shaded bars* ACR50 rate, *open bars* ACR20 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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Interleukin-6 as a Therapeutic Target in Candidate Inflammatory Diseases

N Nishimoto[1]

Interleukin (IL)-6 is a multifunctional cytokine that regulates immune response, inflammation, and hematopoiesis. Although IL-6 plays several important physiological roles, deregulated overproduction of IL-6 causes various clinical symptoms and abnormalities in laboratory test results. Overproduction of IL-6 has been shown to underlie a number of autoimmune and inflammatory diseases, including rheumatoid arthritis (RA), systemic-onset juvenile idiopathic arthritis (soJIA), and Castleman's disease, as well as malignancies such as multiple myeloma and mesothelioma. Blocking of IL-6 signaling may be therapeutic in diseases characterized by pathological IL-6 overproduction. This review provides an overview of IL-6 as a therapeutic target in candidate inflammatory diseases.

Cytokines exert a wide range of biological effects. Because of their important role in normal physiology, the actions of cytokines are regulated by a number of exquisite molecular mechanisms, including cytokine networks. Disruption of such regulation may result in a variety of autoimmune and inflammatory disorders. Although the exact causes of autoimmune diseases such as rheumatoid arthritis (RA) and systemic-onset juvenile idiopathic arthritis (soJIA) are not fully understood, deregulated overproduction of proinflammatory cytokines such as tumor necrosis factor (TNF), interleukin (IL)-1, and IL-6, as well as the resultant disequilibrium between proinflammatory and anti-inflammatory cytokines, have been shown to underlie the pathophysiology of these diseases.

IL-6 was originally identified as a T-cell-derived factor that induces activated B cells to differentiate into antibody-producing cells.[1,2] After the complementary DNA for IL-6 was cloned in 1986, it was shown to be produced by various cell types, including T cells, B cells, monocytes, fibroblasts, endothelial cells, and synovial cells.[2] This molecule had been investigated under the names interferon β2, 26-kDa protein, hybridoma/plasmacytoma growth factor, and hepatocyte-stimulating factor, but these entities were later unified under the term "IL-6." Because IL-6 is multifunctional, *in vivo* overproduction of it causes various clinical symptoms and abnormalities in laboratory test results, which may well explain the manifestations observed in patients with various inflammatory diseases, including RA and soJIA.[2,3] This has led to the idea that blocking IL-6 action may be therapeutic in diseases in which IL-6 is pathologically overproduced. Indeed, the success in treating certain diseases with drugs that antagonize IL-6 action has provided further support for a pathological role of IL-6 in those diseases. This review discusses IL-6 as a therapeutic target in candidate inflammatory diseases.

PATHOLOGICAL ROLES OF IL-6 IN INFLAMMATORY DISEASES

IL-6 is a multifunctional cytokine with biological activities including regulation of immune response, inflammation, and hematopoiesis.[2] The pathological roles of IL-6 in inflammatory diseases that are candidates for IL-6 targeting therapy are shown in **Figure 1**. IL-6 induces T-cell proliferation through upregulation of the IL-2 receptor and contributes to cytotoxic T-cell differentiation. Recently, research has focused on T helper (Th) cells that produce IL-17, IL-17F, IL-6, and TNF but not IL-4 or interferon-γ. The pathogenic role of these Th cells in autoimmune diseases is becoming more clearly defined. These $CD4^+$ T cells are known as Th17 cells and are distinct from both Th1 cells, which produce interferon-γ and mediate cellular immunity, and Th2 cells, which produce IL-4, IL-5, and IL-13 and mediate humoral immunity and allergic response.[4] In the presence of IL-6, transforming growth factor-β induces the differentiation of Th17 cells from naive T cells, whereas exposure to transforming growth factor-β alone induces differentiation of naturally occurring $CD4^+CD25^+$Forkhead box $P3^+$ T regulatory cells, which inhibit autoimmunity and protect against tissue injury.[5] In generating Th17 and T regulatory cells, therefore, IL-6 is a key cytokine, although the pathological role of Th17 cells in human disease remains obscure.

IL-6 is responsible for multiple inflammatory manifestations.[2,3] *In vivo* treatment with IL-6 induces systemic inflammatory symptoms such as fever, generalized fatigue, and anorexia, as well as abnormalities in laboratory test results, including increases in levels of acute-phase proteins, C-reactive protein,

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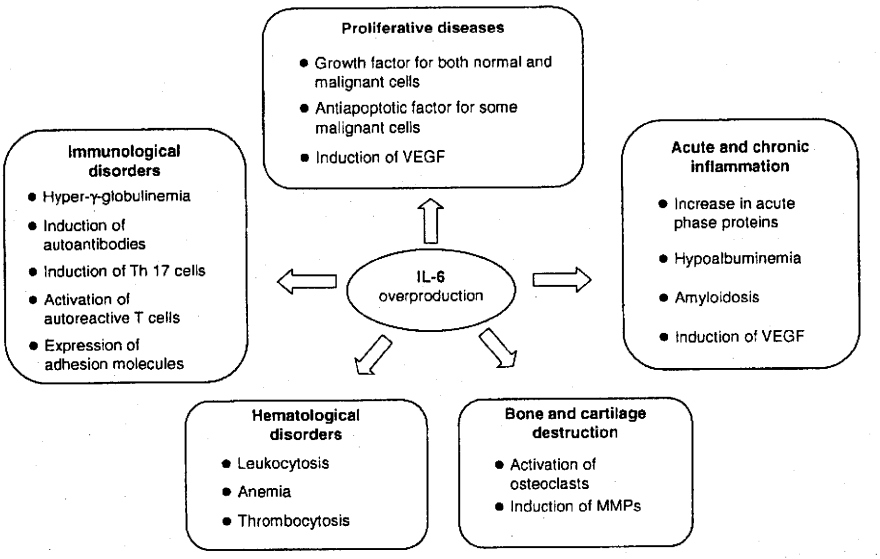

Figure 1 Pathological roles of IL-6 in the candidate inflammatory diseases for IL-6 targeting therapy Th17 cells: T helper (Th) cells that produce IL-17, IL-17F, IL-6, and tumor necrosis factor but not IL-4 or interferon-γ. IL, interleukin; MMPs, matrix metalloproteinases; VEGF, vascular endothelial growth factor.

serum amyloid A, and fibrinogen, and decreases in serum concentrations of albumin. In inflammatory organs, IL-6 induces local infiltration of immunocompetent cells via upregulation of adhesion molecules. It also induces angiogenesis by augmenting the production of vascular endothelial growth factor. This growth factor increases vascular permeability and leads to inflammatory edema. In the affected joints of RA patients, vascular endothelial growth factor–mediated angiogenesis is necessary for synovial pannus formation, and this causes destruction of the joint. In bone metabolism, IL-6, in the presence of soluble IL-6 receptor, induces osteoclast differentiation, resulting in the characteristic bone absorption and joint destruction seen in RA. This function of IL-6 also explains why osteoporosis is associated not only with chronic inflammation but also with postmenopausal status.

IL-6 is also a potent inducer of hepcidin, an iron-regulatory peptide hormone produced in the liver that negatively regulates intestinal iron absorption and macrophage-mediated iron recycling. In addition, excessive IL-6 signaling induces the production of suppressor of cytokine signaling molecules, intracellular negative feedback factors that inhibit the Janus kinase–signal transducer and activator of transcription signaling pathway. Given that transduction of the erythropoietin receptor signal requires the same pathway, the action of erythropoietin can be suppressed by suppressor of cytokine signaling. Excessive production of IL-6 therefore contributes to the hypoferremic anemia of chronic inflammation. IL-6 is a growth factor not only for malignant cells of multiple myeloma and renal cell carcinoma but also for nontumor cells, including the mesangial cells of the kidney. This suggests that IL-6 overproduction may be involved in the pathogenesis of mesangial proliferative glomerulonephritis.

These data have encouraged clinicians to focus on IL-6 antagonism as a potential therapy for inflammatory diseases that are refractory to conventional therapy with agents such as corticosteroids.

CLINICAL BENEFITS OF IL-6 INHIBITION IN RA

RA is the most common chronic arthropathy worldwide. It is characterized by persistent synovitis, progressive destruction of cartilage and bone in multiple joints, and emergence of various autoantibodies, including rheumatoid factor. Overproduction of IL-6 has been demonstrated to play a pathological role in this disease.[3] Murine antihuman IL-6 neutralizing antibody, BE-8, was the first IL-6 antagonist to be evaluated in a clinical trial, but it showed limited efficacy in RA treatment.[6] Tocilizumab, a humanized monoclonal antibody that recognizes the IL-6 binding site of human IL-6R, has been evaluated in a series of clinical trials using a variety of study designs all over the world.[3] Tocilizumab, both as monotherapy and in combination with methotrexate, has been shown to be effective in RA patients who have had insufficient response not only to conventional therapy with methotrexate or other disease-modifying antirheumatic drugs[7–15] but also to TNF inhibitors[16] (which, until the advent of tocilizumab, had been the most effective therapy). The blocking of IL-6, a molecule different from TNF, is therefore a viable strategy for treating patients whose disease is refractory to anti-TNF therapy. Tocilizumab retards the progression of structural joint damage and improves physical function.[11] It also causes a marked alleviation of anemia. These effects are critical for maintaining patients' quality of life. Because tocilizumab normalizes serum amyloid A levels, it is expected to ameliorate the amyloid A amyloidosis secondary to RA and other inflammatory diseases. Another benefit of tocilizumab is that secondary loss of efficacy is very rare, seldom occurring even in a 5-year clinical trial.[15]

With regard to the safety of tocilizumab, infections comprise the most common class of adverse events, similar to the adverse-event profile of TNF inhibitors.[3,9–16] Because IL-6 inhibition can suppress acute-phase reactions (e.g., fever, increase in C-reactive protein concentration), it can obscure the symptoms of infection and thereby delay their detection. Therefore, careful monitoring

Table 1 Antibodies targeting IL-6 for candidate inflammatory diseases

Drug (developer)	Properties	Candidate diseases	Reference(s)
Tocilizumab	Humanized mAb to IL-6 receptor	RA	7–16
		Systemic-onset JIA	18,19
		Adult-onset Still's disease	20,21
		Crohn's disease	22
		Takayasu arteritis	23
		CINCA syndrome	24
		Castleman's disease	26,27
		AA amyloidosis	32,33
		Relapsing polychondritis	34
		Polyarticular type JIA	n.a.
		Multiple myeloma	n.a.
		Pancreas tumor	n.a.
BE-8	Murine mAb to IL-6	RA	6
		Castleman's disease	25
		Multiple myeloma	28,31
		Plasma cell leukemia	35
		Lymphoma	36
		Renal cell carcinoma	37
CNTO-328	Chimeric mAb to IL-6	Multiple myeloma	29,30
		Prostate tumor	n.a.
		Castleman's disease	n.a.
		Renal cell carcinoma	n.a.
		Non-Hodgkin's lymphoma	n.a.
		Cachexia	n.a.
CNTO-136	Fully human mAb to IL-6	RA	n.a.
		Cutaneous lupus erythematosus	n.a.
		Systemic lupus erythematosus	n.a.
REGN-88	Fully human mAb to IL-6 receptor	RA	n.a.
ALD518	Humanized mAb to IL-6	RA	n.a.
		Cachexia, fatigue	n.a.

AA amyloidosis, amyloid A amyloidosis; CINCA, chronic infantile neurologic, cutaneous, articular; IL, interleukin; JIA, juvenile idiopathic arthritis; mAb, monoclonal antibody; n.a., not available; RA, rheumatoid arthritis.

must be undertaken during IL-6 inhibition treatment. An increase in serum cholesterol levels was a frequently reported event in every clinical trial. Although cardiovascular complications were not reported in association with the increased cholesterol levels, excessive levels of total cholesterol should be controlled with lipid-lowering agents. In studies to date, the safety of tocilizumab is comparable to that of TNF inhibitors and acceptable, given the benefit provided. Data from a large patient registry will further elucidate the safety profile of tocilizumab.

CLINICAL BENEFITS OF IL-6 INHIBITION IN OTHER RHEUMATIC DISEASES

Tocilizumab is also a promising therapeutic option for other rheumatic diseases, including soJIA, adult-onset Still's disease, and other immunological diseases.

soJIA is one of the most common rheumatic diseases of childhood. In addition to arthritis, patients exhibit spiking fever, evanescent skin rash, lymphadenopathy, hepatosplenomegaly, serositis, growth retardation, and developmental abnormalities.[17] Patients with soJIA may develop macrophage activation syndrome, which is sometimes fatal. soJIA is often refractory to conventional treatments such as corticosteroids and methotrexate, which are usually effective for other types of JIA; even TNF inhibitors show limited efficacy in this condition. Given the central role of IL-6 in the disease, it is a potential therapeutic target of tocilizumab. Indeed, tocilizumab has been shown to achieve a dramatic decrease in disease activity and to ameliorate growth retardation.[18,19] On the basis of the results of clinical trials, tocilizumab was approved in Japan for the treatment of soJIA in April 2008, and clinical trials are ongoing worldwide. Adult-onset Still's disease has pathological features similar to those of soJIA. Some case reports have suggested a clinical benefit of IL-6 inhibition in this disease.[20,21]

The chronic inflammatory bowel diseases Crohn's disease and ulcerative colitis are other candidate disorders for anti-IL-6 therapy. A phase II trial demonstrated significant benefits of using tocilizumab in the therapeutic management of Crohn's disease.[22]

Vasculitis is another candidate for anti-IL-6 therapy. A case of Takayasu arteritis that was refractory to conventional immunosuppressive therapy was successfully treated with tocilizumab.[23] Mutations in the *NALP3/CIAS1/PYPAF1* gene are associated with Muckle–Wells syndrome, familial cold autoinflammatory syndrome, and neonatal-onset multisystem inflammatory disease, also known as chronic infantile neurologic, cutaneous, and articular (CINCA) syndrome. Because NALP3 is involved in processing IL-1β, IL-1 blockade could be therapeutic in patients with Muckle–Wells syndrome. Tocilizumab therapy was reportedly successful in a CINCA patient whose disease was refractory to IL-1R antagonism.[24] However, the data available are too limited to allow an accurate assessment of the clinical efficacy of tocilizumab in the treatment of these diseases.

CLINICAL BENEFITS OF IL-6 INHIBITION IN CASTLEMAN'S DISEASE AND OTHER PROLIFERATIVE DISEASES

Multicentric Castleman's disease is an atypical lymphoproliferative disorder with systemic inflammatory manifestations. All the manifestations of this disease can be accounted for by IL-6 overproduction. Indeed, BE-8 as well as tocilizumab treatment markedly relieved clinical symptoms, including

lymphadenopathy, and reduced abnormalities in laboratory test results.[25–27] Glomerulonephritis and interstitial lung disease (both of which are associated with multicentric Castleman's disease) also showed improvement with tocilizumab therapy, suggesting that the drug has therapeutic efficacy in such conditions. Tocilizumab was approved in Japan as an orphan drug for Castleman's disease in April 2005.

IL-6 acts as a growth factor or antiapoptotic factor in various malignancies, including multiple myeloma, mesothelioma, and renal cell carcinoma. IL-6, produced mainly by bone marrow stromal cells, stimulates the growth of myeloma cells and protects them from apoptosis. The angiogenic characteristic of IL-6 is also favorable for tumor development. Therefore, IL-6 may be a therapeutic target in these IL-6-related neoplasm diseases. Clinical studies using neutralizing anti-IL-6 antibodies have shown the therapeutic efficacy of these antibodies in hematological malignancies, including myeloma.[28–31] From the viewpoint of inflammatory manifestations, mesothelioma and pancreas cancer may be good candidate diseases for IL-6 inhibition. Antibodies targeting IL-6 or IL-6R for candidate diseases are summarized in **Table 1**.

CONCLUSION

This review discusses anti-IL-6 therapy in a variety of candidate inflammatory diseases. Because of the diverse biological functions of IL-6, its inhibition has a wide array of therapeutic applications. Tocilizumab has been approved for RA, JIA, and Castleman's disease in Japan and for RA in the European Union, Brazil, India, and other countries. A second generation of IL-6 inhibitors, including neutralizing anti-IL-6 antibodies, are under development. So far, we have no evidence to show whether it would be a better strategy to inhibit the ligand or to inhibit the receptor.

Future studies will probably continue to establish the therapeutic efficacy of anti-IL-6 therapy in a number of refractory inflammatory diseases.

CONFLICT OF INTEREST

N.N., as a medical adviser, received a consulting fee and royalty for a soJIA patent from Chugai Pharmaceutical Co., Ltd., the company that produces tocilizumab. He also works on the scientific advisory board of Hoffmann-La Roche, which developed tocilizumab in collaboration with Chugai Pharmaceutical Co., Ltd.

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LETTER

DNA microarray analysis of rheumatoid arthritis susceptibility genes identified by genome-wide association studies

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See related review by Clarke and Vyse, http://arthritis-research.com/content/11/5/248

In a recent interesting review, Alex Clarke and Timothy Vyse described the genetics of rheumatic disease [1]. In the past several years, genome-wide association studies (GWAS) have led to the identification of six high-risk rheumatoid arthritis (RA) susceptibility genes – namely, *CD244*, *PADI4*, *SLC22A2*, *PTPN22*, *CTLA4*, and *STAT4* (summarized in [2]). *In vitro* studies using mutant alleles and cultured cells have revealed the individual up-regulation of *CD244*, *PADI4*, *SLC22A2*, and *PTPN22* [2-6]; however, studies on the expression of RA susceptibility genes in RA patients are rare. We therefore investigated the expression of the above-mentioned six RA susceptibility genes in 112 RA patients using DNA microarray analysis. This study aims to clarify whether DNA microarray analysis and GWAS produce comparable results with respect to RA susceptibility genes.

Total RNA extracted from total peripheral blood cells obtained from 112 RA patients and 45 healthy individuals was used to prepare aminoallyl RNA. As a reference, mixed RNA from 45 healthy individuals was used. The aminoallyl RNA of each individual and the reference was subjected to Cy3 and Cy5 labeling, respectively, and was hybridized with an oligonucleotide-based DNA microarray. The data obtained were analyzed by nonparametric statistical group comparison. The intensities of the no-probe spots were used as the background. The median and standard deviation of the background intensity were calculated. The genes with an intensity value that was less than the median plus 2 standard deviation of the background intensity were identified as null. The Cy3/Cy5 ratios of all spots on the DNA microarray were normalized using the global ratio median. Only gene expression data that were collected from at least 80% of samples from each group were selected for further analysis. The unpaired Mann–Whitney test was used to determine statistically significant differences in the mRNA expression levels between the RA and healthy groups. Statistical significance was set at $P < 0.05$.

The results of our DNA microarray analysis showed that the expressions of four out of the six RA susceptibility genes were significantly higher in RA patients than in healthy individuals (1.0×10^{-16} to 2.32×10^{-5}) (Table 1). As described above, the upregulation of these four genes (*CD244*, *PADI4*, *SLC22A2*, and *PTPN22*) has been previously confirmed in *in vitro* studies. We found, however, that *CTLA4* expression levels were similar between the RA and control groups, whereas *STAT4* expression was significantly downregulated in the RA group (1.38×10^{-8}). We investigated the expression of other RA susceptibility genes – namely, *TRF1/C5* [7], *CD40* [8], and *CCL21* [8] – and found that their expressions were similar in both groups. The genetic risk factors for RA were recently reported to differ between Caucasian and Asian (Korean) populations [9]. The samples used in our microarray analysis were derived from the same Asian (Japanese) cohort. The expression profiles for these three genes may therefore not be consistent with the profiles determined by GWAS.

In this study, we revealed the correlation between five out of the six high-risk RA susceptibility genes using DNA microarray analysis. Prostate cancer susceptibility genes identified by GWAS were recently reported to be consistent with those identified by microarray analysis [10]. We therefore concluded that the combination of microarray analysis and GWAS would be a more effective approach for gene identification than the analysis of individual datasets. Moreover, the simultaneous use of both methods would allow for more accurate identification of RA candidate genes.

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Table 1. Candidate genes identified from rheumatoid arthritis genome-wide association studies

Gene	GeneID	PMID	Gene expression (up or down)	Microarray *P* values[a]
CD244	605554	18794858	Up	1.0×10^{-3}
PADI4	605347	12833157	Up	$2.32 \times 10^{-}$
SLC22A2	602608	14608356	Up	$1.94 \times 10^{-}$
PTPN22	600716	15208781	Up	9.66×10^{-5}
CTLA4	123890	16380915	No change	0.767
STAT4	600558	17804842	Up	1.38×10^{-6}

[a]*P* values determined by comparison between 112 rheumatoid arthritis patients and 45 healthy individuals.

Abbreviations
GWAS, genome-wide association studies; RA, rheumatoid arthritis.

Competing interests
This study was financially supported partly by the grant from the Ministry of Health, Labor and Welfare of Japan.

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ORIGINAL ARTICLE

Assessment of the validity of the 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) as a disease activity index of rheumatoid arthritis in the efficacy evaluation of 24-week treatment with tocilizumab: subanalysis of the SATORI study

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Abstract As tocilizumab (TCZ) greatly inhibits inflammatory markers, methods of evaluating rheumatoid arthritis (RA) disease activity that include inflammatory markers may overestimate the effect of TCZ treatment. We have evaluated the impact of inflammatory markers on the efficacy of TCZ by comparing the efficacy indicated by the 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR) with that indicated by the clinical and simplified disease activity indexes (CDAI and SDAI, respectively) and the American College of Rheumatology (ACR) core set criteria in a double-blind study of TCZ—the SATORI study. The Spearman correlation coefficient between DAS28-ESR and CDAI was comparable between that at week 24 and that at baseline [correlation coefficient at baseline and week 24 was 0.823 ($p < 0.0001$) and 0.818 ($p < 0.0001$), respectively]. A large difference between the DAS28 remission rate and CDAI remission rate was observed at week 24. However, these results are comparable to those of a previous study conducted with non-TCZ-treated patients. Moreover, the same results were obtained in the comparison between the DAS28-ESR and SDAI, even though the SDAI includes an inflammatory parameter as a component. These results confirm that the DAS28-ESR has a validity comparable to that of other methods in terms of evaluating the RA treatment efficacy of TCZ, despite its strong inflammatory marker-inhibiting effects.

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Keywords Interleukin 6 · Clinical disease activity index · Simplified disease activity index · Acute phase protein · Inflammatory markers

Introduction

Tocilizumab (TCZ) is a monoclonal anti-interleukin-6 (IL-6) receptor antibody that binds to cell membrane-bound IL-6 receptors and to free soluble IL-6 receptors in the serum, thereby blocking IL-6 signalling into cells [1]. This drug was developed to treat patients with rheumatoid arthritis (RA), Castleman's disease and juvenile idiopathic arthritis, and has been approved as a treatment for these indications in Japan [2–9]. It has been reported that treatment with TCZ alone or in combination with disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), has therapeutic effects in RA patients who had an inadequate response to anti-tumour necrosis factor (TNF) therapy or non-biologic DMARDs or in those who are MTX naive or had an inadequate response to MTX [2–13].

TCZ directly inhibits the production of acute phase proteins, such as C-reactive protein (CRP) and fibrinogen from hepatocytes, by directly inhibiting the action of IL-6. Consequently, the CRP level and erythrocyte sedimentation rate (ESR) rapidly and intensively decrease with the initiation of TCZ treatment before any improvement in swollen or tender joint counts (TJCs) is observed [14], possibly resulting in a discrepancy between an improvement in inflammatory markers and an improvement in actual RA disease activity. This has led to concern among clinicians on the possibility that methods of evaluating RA disease activity that include CRP and ESR may overstate the therapeutic effect of TCZ treatment for RA compared to methods that do not.

To investigate the validity of the 28-joint Disease Activity Score using ESR (DAS28-ESR) for evaluating the efficacy of TCZ as a treatment for RA, we compared the efficacy assessment in the SATORI study (a double-blind, comparative study of TCZ conducted in Japan) [4] using the DAS28-ESR [15] with the efficacy assessments using the clinical disease activity index (CDAI) [16], simplified disease activity index (SDAI) [17] and American College of Rheumatology (ACR) response [18].

Patients and methods

Patients

This study was based on data from the SATORI study that has been previously published [4]. The inclusion and exclusion criteria for enrolment in the SATORI study were as follows. Eligible patients were between 20 and 75 years old, fulfilled the ACR (formerly, the American Rheumatism Association) 1987 revised criteria for the classification of RA and had disease duration >6 months. All candidates had been treated with MTX (8 mg/week) for at least 8 weeks prior to enrolment but showed an inadequate response to MTX at enrolment by the persistence of active disease, defined as ≥6 tender joints (of 49 evaluated), ≥6 swollen joints (of 46 evaluated) and ESR ≥ 30 mm/h or CRP ≥ 10 mg/L. Patients were excluded if, immediately prior to the initiation of TCZ treatment (start of study), they had received anti-TNF agents or leflunomide within 12 weeks, plasma exchange therapy or surgical treatment within 4 weeks, or DMARDs other than MTX or immunosuppressants within 2 weeks. Patients who had received oral corticosteroids (≤10 mg/day prednisolone) were enrolled if the dosage had not been changed within the 2 week period immediately preceding the start of TCZ treatment. Eligible patients had a white blood cell count $\geq 3.5 \times 10^9$/L, a lymphocyte count $\geq 0.5 \times 10^9$/L or a platelet count of at least the lower limit of normal as defined by the local laboratory used for all analyses. Patients were excluded if they were functional class IV according to Steinbrocker's criteria [19], had aspartate transaminase, alanine transaminase or serum creatinine ≥1.5 times the upper limit of normal, were positive for hepatitis B surface antigen and/or hepatitis C virus antibody, had pulmonary fibrosis or active pulmonary disease, had a history of serious adverse drug reaction to MTX, had concomitant pleural effusion, ascites or varicella infection or were excessive users of alcohol on a regular basis. Patients were excluded if they had a history of serious allergic reaction, or if they had significant cardiac, blood, respiratory system, neurologic, endocrine, renal, hepatic or gastrointestinal disease or an active infection requiring medication within 4 weeks before the start of treatment. Sexually active premenopausal women were required to have a negative urine pregnancy test result at the time of entry to the study and to use effective contraception throughout the study period.

Protocol

The following is a summary of the protocol of the SATORI study [4]. This trial is registered at http://www.clinicaltrials.gov (NCT00144521). The first patient was enrolled on 27 January 2004, and the last patient exited the study on 15 February 2005. Patients were randomly assigned to receive one of the following treatments for 24 weeks: (1) TCZ (8 mg/kg) once every 4 weeks plus MTX placebo (TCZ group); (2) or TCZ placebo plus MTX 8 mg/week (control group). Randomization was achieved by centralized allocation at a patient enrolment center. The dosage of TCZ used in this study was chosen based on the results of an earlier dose-finding study; the dose of MTX was the maximum dose allowed in Japan. Oral corticosteroids equivalent to <10 mg/day prednisolone were allowed, but the dose could not be increased during the study. Intra-articular injections of corticosteroid (only one joint at one treatment) and hyaluronate preparations were allowed. The use of one nonsteroidal anti-inflammatory drug (NSAID), including switching to another NSAID, was allowed. DMARDs, intravenous or intramuscular corticosteroids, plasmapheresis and surgical treatment were not allowed.

Efficacy evaluation

Efficacy was evaluated every 4 weeks by calculating the DAS28-ESR, CDAI and SDAI scores and the ACR response category. Changes in DAS28-ESR, CDAI and SDAI from baseline to week 24 were also calculated, and the DAS28-ESR and ACR response categories were compared qualitatively [20]. Remission was evaluated using the following remission criteria, and the results were compared: DAS28-ESR < 2.6; SDAI ≤ 3.3; CDAI ≤ 2.8 [21–23]. ACR20, ACR50 and ACR70 responses are defined as 20, 50 and 70% improvement, respectively, in the tender joint count (TJC) and swollen joint count (SJC), and 20, 50 and 70% improvement, respectively, in at least three of the following five parameters: (1) patient self-assessed function (health assessment questionnaire); (2) patient global assessment (PGA); (3) physician global assessment (MDGA); (4) patient pain assessment; (5) either ESR or CRP.

The following formulae were used to calculate DAS28-ESR, SDAI and CDAI, respectively: (1) DAS28-ESR = $0.56\sqrt{\text{TJC}} + 0.28\sqrt{\text{SJC}} + 0.70\ \ln(\text{ESR}) + 0.014$ PGA (mm); (2) SDAI = SJC + TJC + PGA (cm) + MDGA (cm) + CRP (mg/dL); (3) CDAI = SJC + TJC + PGA (cm) + MDGA (cm), where SJC and TJC are the respective counts for 28 joints.

Statistical analysis

Change in continuous variables (DAS28-ESR, CDAI and SDAI) is amenable to simple linear regression analysis; therefore, the latter two variables were compared by linear regression with DAS28-ESR as the independent variable. The probability of a significant association between the independent and dependent variables was defined as $p < 0.05$.

Results

Time courses of disease activity scores and their components

Fifty-three of the 61 patients enrolled in the TCZ-treatment group in the SATORI study completed the study (24 weeks), and disease activity was measured in 53 patients at various time points. Figure 1 shows the time courses of the DAS28-ESR, CDAI and SDAI values and each of the evaluation items used to calculate these indices. DAS28-ESR tended to progressively improve during the TCZ treatment, with the mean DAS28-ESR improving from 6.06 at baseline to 2.77 at week 24. The CDAI and SDAI also progressively improved during the TCZ treatment. Furthermore, each of the evaluation items, with the exception of ESR and CRP, used to calculate DAS28-ESR, CDAI and SDAI progressively improved during the TCZ treatment. Conversely, the ESR and CRP levels rapidly decreased from week 0 to week 4, following which they remained approximately constant (Fig. 1). At week 24, joint swelling in the 28 joints of the DAS28 had completely improved (i.e., SJC = 0) in 13 patients (24.5%), and joint tenderness had completely improved (i.e., TJC = 0) in 20 patients (37.7%). The sum of the SJC and TJC at week 24 was ≤1 in 13 patients (24.5%).

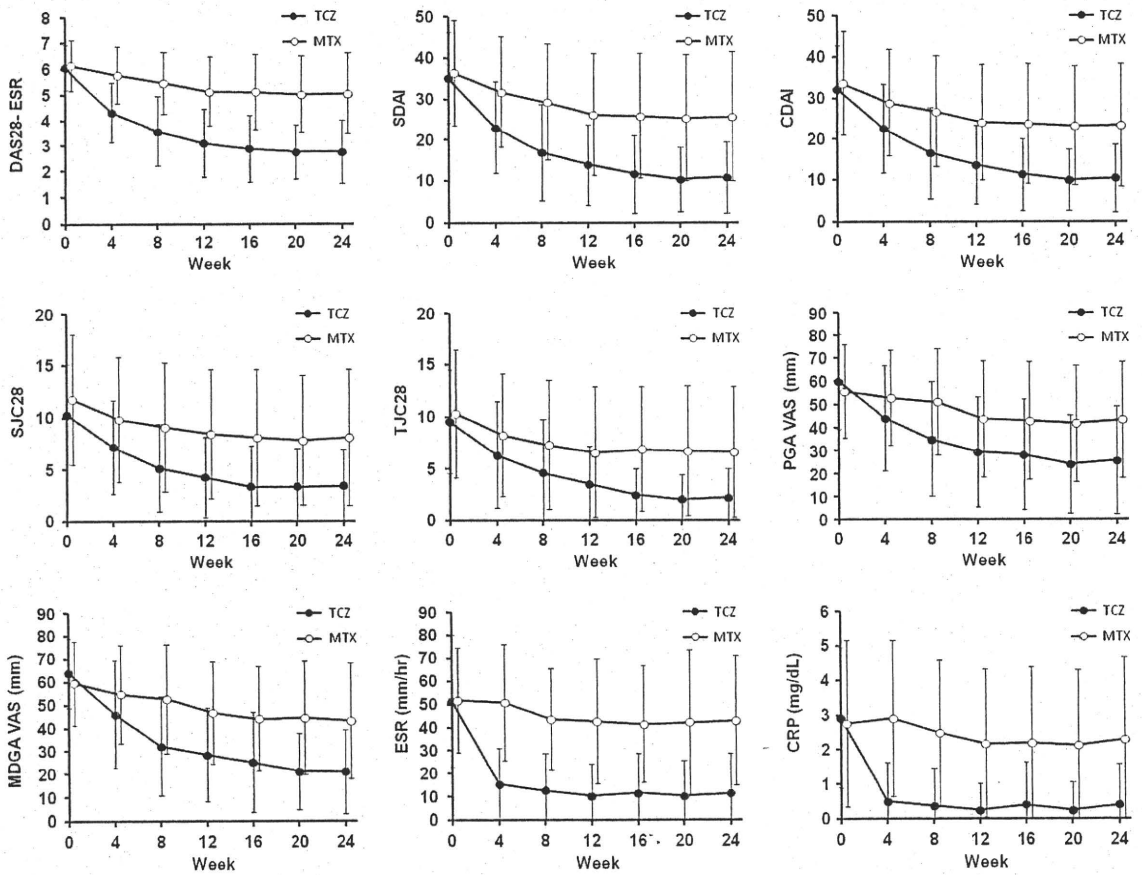

Fig. 1 Change in the indices of rheumatoid arthritis (RA) disease activity and in the variables used to calculate those indices over the 24-week study. The indices and variables shown are the 28-joint disease activity score using erythrocyte sedimentation rate (DAS28-ESR), the clinical and simplified disease activity indices (CDAI and SDAI, respectively), 28-joint swollen and tender joint counts (SJC28 and TJC28, respectively), visual analog scale (VAS) of patient and physician global assessment (PGA and MDGA, respectively), C-reactive protein (CRP) and ESR. The treatment received was either tocilizumab (TCZ) or methotrexate (MTX). Mean values and standard deviations are shown. The data of the TCZ group and control group are shown as mean values among the 53 TCZ patients and 37 MTX patients who completed the 24-week study

Correlations between DAS28-ESR and CDAI or SDAI, and between DAS28-CRP and CDAI or SDAI

Figure 2a is a scatter plot of the results for each patient in the TCZ group and shows the correlations between DAS28-ESR and CDAI at baseline and at week 24, and between the change in DAS28-ESR and change in CDAI from baseline to week 24. The Spearman coefficient of correlation between DAS28-ESR and CDAI at week 24 was 0.823 ($p < 0.0001$), which was comparable to that at

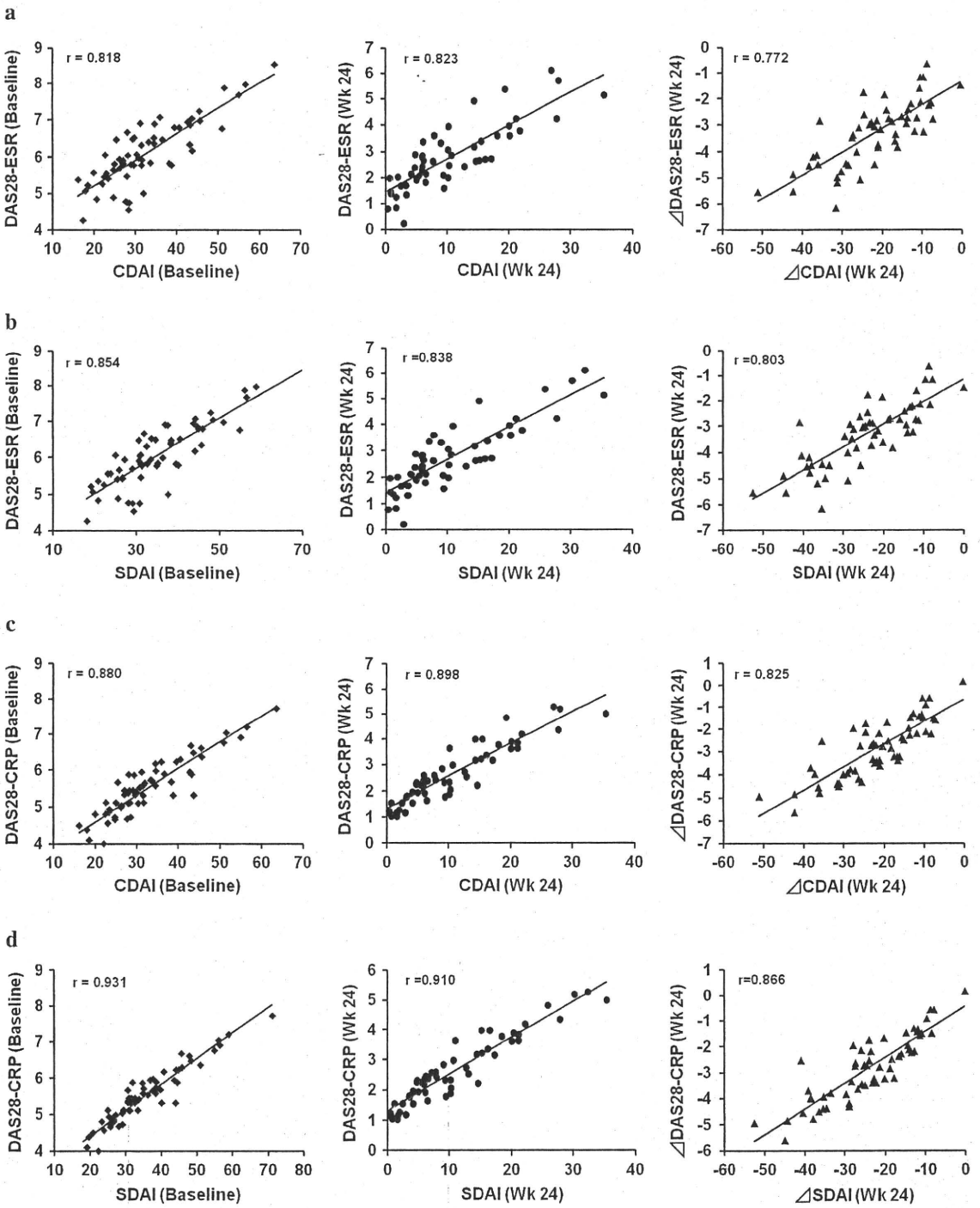

Fig. 2 Scatter plots of DAS28-ESR/DAS28-CRP versus CDAI/SDAI at baseline and at week 24, and change in DAS28-ESR/DAS28-CRP versus change in CDAI/SDAI at week 24 in the TCZ group. The results of the 61 patients at baseline and the 53 patients who completed the 24-week study in the TCZ group are shown. All regression lines indicate a highly significant correlation between DAS28-ESR/DAS28-CRP and CDAI/SDAI. **a** DAS28-ESR vs. CDAI, **b** DAS28-ESR vs. SDAI, **c** DAS28-CRP vs. CDAI, **d** DAS28-CRP vs. SDAI

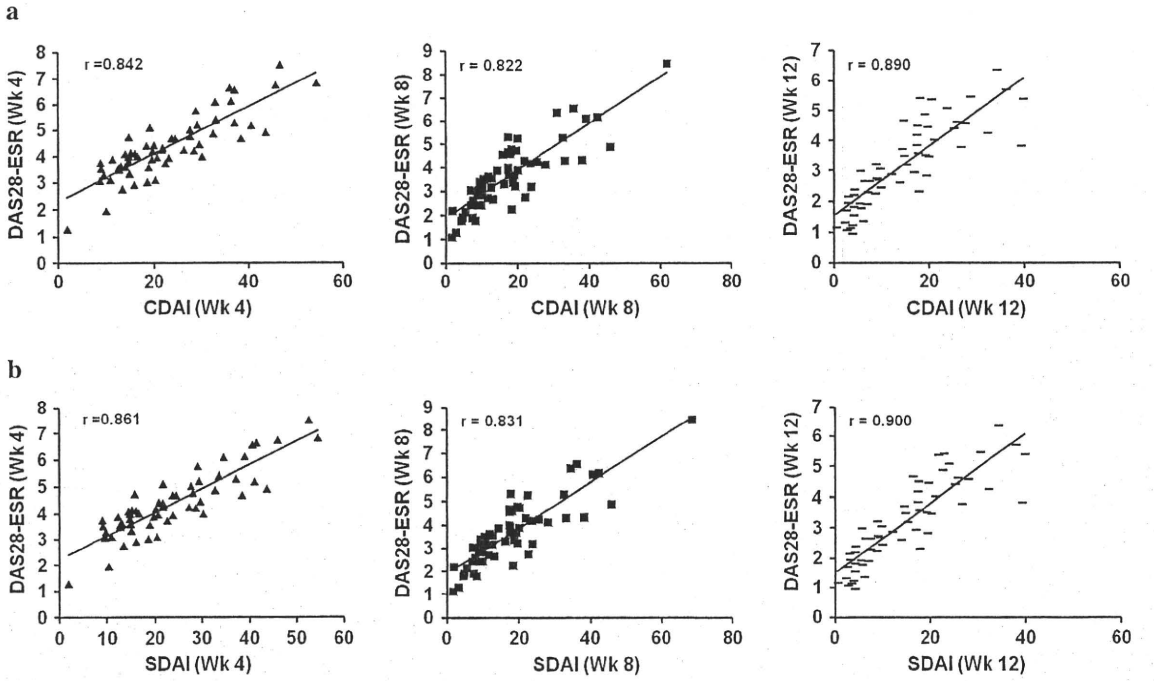

Fig. 3 Scatter plots of DAS28-ESR versus CDAI/SDAI at weeks 4, 8, and 12 in the TCZ group. The results of 58 patients at week 4, 60 patients at week 8, and 59 patients at week 12 in the TCZ group are shown. The difference in patient numbers is due to missing ESR data. All regression lines indicate a highly significant correlation between DAS28-ESR and CDAI/SDAI. **a** DAS28-ESR vs. CDAI (week 4, 8, 12), **b** DAS28-ESR vs. SDAI (week 4, 8, 12)

baseline (0.818, $p < 0.0001$). The coefficient of correlation between the change in DAS28-ESR and change in CDAI from baseline to week 24 was 0.772 ($p < 0.0001$).

The Spearman coefficient of correlation between DAS28-ESR and SDAI at week 24 was 0.838 ($p < 0.0001$), which was comparable to that at baseline (0.854, $p < 0.0001$). The coefficient of correlation between the change in DAS28-ESR and the change in SDAI from baseline to week 24 was 0.803 ($p < 0.0001$) (Fig. 2b).

Because the DAS28-CRP is also frequently used to evaluate the disease activity of RA and because the CRP level is also considerably decreased by TCZ, a similar analysis was performed between DAS28-CRP and CDAI as well as between DAS28-CRP and SDAI. As shown in the Fig. 2c and d, the results were essentially the same as those between the DAS28-ESR and CDAS or SADI, although Spearman coefficient of correlation was always higher (Fig. 2c, d).

During the initial phase of TCZ treatment, rheumatologists frequently observe a rapid decrease in inflammatory markers, such as CRP and ESR, while the arthritis shows a more gradual improvement. To determine whether or not the DAS28-ESR and the other indices may become separated in the relatively early phase of the TCZ treatment, we also examined the correlation between DAS28-ESR and CDAI/SDAI at weeks 4, 8, and 12 (Fig. 3; Table 1). The Spearman coefficient of correlation between DAS28-ESR and CDAI was almost constant during the treatment period, and there was no significant decrease in week 4 or 8. The data were essentially the same as those between DAS28-ESR and SDAI in the TCZ treatment and those in the control MTX treatment (Table 1). The same results were also obtained from DAS28-CRP and CDAI and SDAI (data not shown).

Table 1 Spearman coefficient of correlation between DAS28-ESR and CDAI or SDAI during treatment with TCZ or MTX

Indices of disease activity	Weeks after the first treatment				
	0	4	8	12	24
DAS28-ESR vs. CDAI					
TCZ	0.818	0.842	0.822	0.890	0.823
MTX	0.883	0.865	0.911	0.921	0.887
DAS28-ESR vs. SDAI					
TCZ	0.854	0.861	0.831	0.900	0.838
MTX	0.893	0.869	0.902	0.930	0.897

DAS28-ESR 28-joint disease activity score using erythrocyte sedimentation rate, *CDAI*, *SDAI*, clinical and simplified disease activity indices, respectively, *TCZ* tocilizumab, *MTX* methotrexate

Comparison between DAS28-ESR remission and CDAI or SDAI remission

Although DAS28-ESR well correlated with CDAI and SDAI, the rate of remission based on the DAS28-ESR

Table 2 Remission and clinical variables in the tocilizumab-treated group of the SATORI study at week 24

Variable	*n* (%)
DAS28-ESR < 2.6 (% of patients who participated in the full 24-week study)	25 (47.2)
SJC in 28 joints = 0 in DAS remitters (% in DAS remitters)	11 (44.0)
TJC in 28 joints = 0 in DAS remitters (% in DAS remitters)	17 (68.0)
SJC + TJC in 28 joints ≤ 1 in DAS remitters (% in DAS remitters)	12 (48.0)
CDAI < 2.8 (% of patients who participated in the full 24-week study)	8 (15.1)
SJC in 28 joints = 0 in CDAI remitters (% in CDAI remitters)	7 (87.5)
TJC in 28 joints = 0 in CDAI remitters (% in CDAI remitters)	8 (100)
SJC + TJC in 28 joints ≤ 1 in CDAI remitters (% in CDAI remitters)	7 (87.5)
SDAI < 3.3 (% of patients who participated in the full 24-week study)	9 (17.0)
SJC in 28 joints = 0 in SDAI remitters (% in SDAI remitters)	8 (88.9)
TJC in 28 joints = 0 in SDAI remitters (% in SDAI remitters)	9 (100)
SJC + TJC in 28 joints ≤ 1 in SDAI remitters (% in SDAI remitters)	8 (88.9)

SJC swollen joint count, *TJC* tender joint count

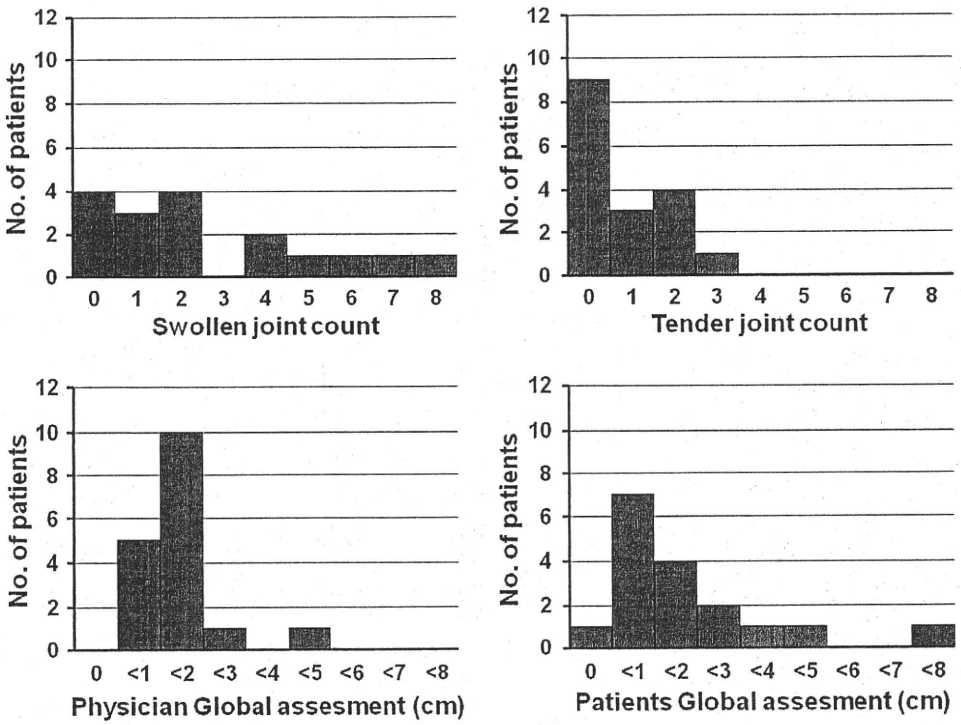

Fig. 4 Histograms of CDAI remission variables in the 17 patients who were in remission according to the DAS28 but not according to the CDAI

was quite different from that based on the CDAI and SDAI, respectively. At week 24, DAS28-ESR remission was attained in 47.2% of the patients, even though the CDAI and SDAI remission rates were only 15.1 and 17.0%, respectively (Table 2). To explore the reasons for the difference in these rates, we examined the characteristics of the patients who were in remission according to the DAS28 ("remitters") but not according to the CDAI or SDAI. Among the 17 patients who were in DAS28 remission but not CDAI remission, six patients (35.3%) had a SJC ≥ 4 and five patients (31.5%) had a high patient global score (>3 cm; Fig. 4). In contrast, CDAI remitters generally had low scores on all measurements, and joint swelling and tenderness improved in most of these patients (Table 2). The same results were obtained when the distribution of each component of SDAI was analysed in the patients who attained DAS28 remission but not SDAI remission (Fig. 5; Table 2).

In the control (TCZ placebo plus MTX 8 mg/week) group, only one patient (1.6%) achieved even DAS28-ESR remission; this patient also achieved CDAI and SDAI remission. The number was too small and, therefore, a similar analysis was not available.

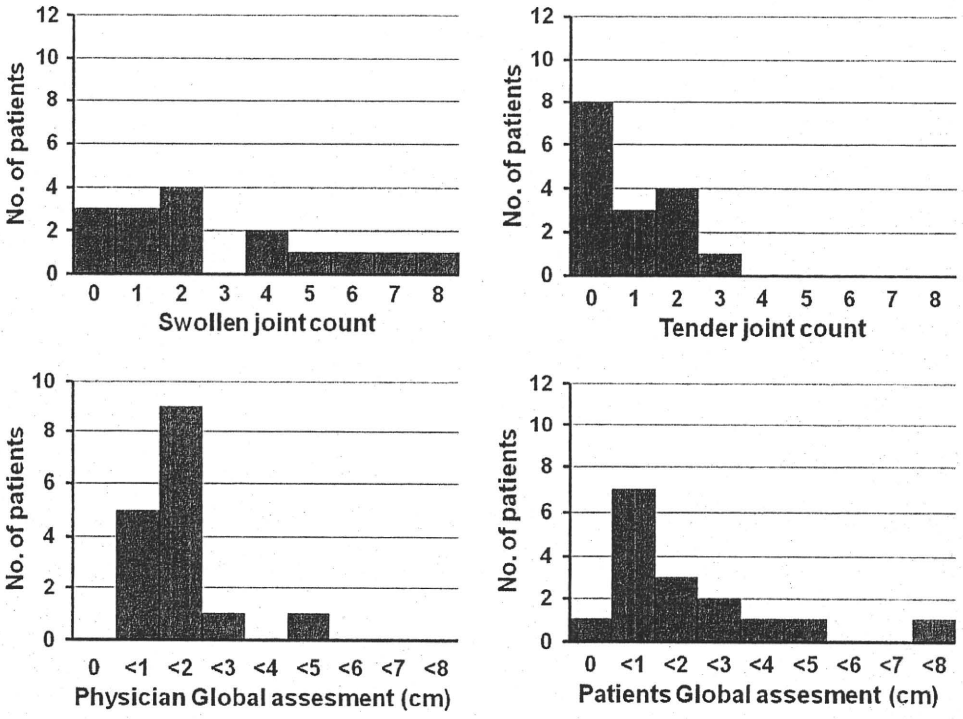

Fig. 5 Histograms of SDAI remission variables in the 16 patients who attained remission according to the DAS28 but not according to the SDAI

Correlation between ACR response category and changes in DAS28, CDAI and SDAI

Among the TCZ-treated patients who completed the 24-week study, the ACR20, ACR50 and ACR70 response rates at week 24 were 83.0 (44/53), 54.7 (29/53) and 32.1% (17/53), respectively. The CDAI and SDAI remitters (8 and 10 patients, respectively) all achieved ACR70. However, among the 25 DAS28-ESR remitters, 17 (68%) achieved ACR70, three achieved ACR50 and five achieved only ACR20. No patient achieved DAS28-ESR remission without achieving at least ACR20. Among the DAS28-ESR remitters who achieved ACR70, the maximum DAS28-ESR score was 2.43.

Discussion

To compare the validity of methods of evaluating the anti-rheumatic effects of TCZ, an IL-6 receptor inhibitor that significantly reduces the level of inflammatory markers such as ESR and CRP, we investigated the correlations between DAS28-ESR and other methods for evaluating RA disease activity, namely, CDAI, SDAI and the ACR core set response category.

We found that the Spearman coefficient of correlation between DAS28-ESR and CDAI (whose formula does not include any inflammatory markers) at week 24 was >0.8 and that this correlation coefficient was comparable to those determined at baseline and weeks 4, 8, and 12, respectively. There was no decrease in the correlation coefficient related to the rapid improvement of ESR after the introduction of TCZ treatment. The same results were obtained when we compared the Spearman coefficient of correlation between DAS28-ESR and SDAI (whose formula includes the CRP level). The coefficients of correlation between DAS28-ESR and SDAI were also always >0.8. These results suggest that the DAS28-ESR score is not markedly lowered by the sudden decrease in ESR that occurs during the first 4 weeks of treatment with TCZ.

Shaver et al. [24] examined the correlation coefficient between DAS28 and CDAI among RA patients in the setting of a community rheumatology practice. Although all of the patients enrolled in their study did not receive TCZ treatment because TCZ had not yet been launched in the USA during the study period, the correlation coefficient obtained between these two indices was quite similar to our result. These researchers also reported that there was a large difference between the remission rate based on the DAS28 and that based on the CDAI and that only about 30% of DAS remitters could attain CDAI remission. The CDAI remitter and DAS remitter rates in our study were comparable with the respective rates in their study. These results suggest that a difference between DAS remission and CDAI remission is not specific to TCZ treatment, i.e., this difference was accrued due to the distinction in the definition of remission criterion in the DAS28-ESR and CDAI. These results also suggest that DAS28-ESR is as