

Longterm Safety and Effectiveness of the Anti-interleukin 6 Receptor Monoclonal Antibody Tocilizumab in Patients with Systemic Juvenile Idiopathic Arthritis in Japan

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ABSTRACT. Objective. To assess the longterm safety and effectiveness of tocilizumab (TCZ) in systemic-onset juvenile idiopathic arthritis (sJIA).

Methods. The longterm extension phase of 2 pivotal studies (phase II with 11 patients and phase III with 56 patients) in patients with active sJIA was analyzed. Patients received open-label TCZ (8 mg/kg, every 2 weeks) without concomitant use of disease-modifying antirheumatic drugs.

Results. In total, 67 patients were enrolled. All patients received corticosteroid at baseline. Median duration of exposure to TCZ was 3.4 years. Nine patients withdrew from the study [4 because of adverse events (AE), 4 because of the development of anti-TCZ antibodies, and 1 because of inadequate response]. Rates of AE and serious AE were 803.7/100 patient-years (PY) and 34.7/100 PY, respectively. The most common serious AE were infections (13.2/100 PY). No cases of malignancy or death were reported. Two serious infusion reactions were reported in patients testing negative for anti-TCZ antibodies. One definite macrophage activation syndrome (MAS) case and 1 potential MAS case were identified. American College of Rheumatology (ACR) response rates attained early in the TCZ treatment period were maintained throughout the study: at Week 168, JIA ACR 30, 50, 70, 90, and 100 response rates were 80.3%, 80.3%, 75.4%, 60.7%, and 18.0%, respectively. In total, 22 of 67 patients (32.8%) completely discontinued corticosteroids without flare.

Conclusion. TCZ has demonstrated durability of effectiveness in the longterm treatment of children with sJIA and has shown good tolerability and a low discontinuation rate associated with AE, development of anti-TCZ antibodies, or inadequate response. (ClinicalTrials.gov NCT00144599 and NCT00144612). (J Rheumatol First Release March 15 2014; doi:10.3899/jrheum.130690)

Key Indexing Terms:

DISEASE-MODIFYING ANTIRHEUMATIC DRUG JUVENILE IDIOPATHIC ARTHRITIS
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Current treatment recommendations for systemic-onset juvenile idiopathic arthritis (sJIA) include nonsteroidal antiinflammatory drugs and corticosteroids, with initiation

of traditional disease-modifying antirheumatic drugs [DMARD; e.g., methotrexate (MTX) and/or biologics (tumor necrosis factor (TNF)- α inhibitors or interleukin 1

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including rheumatoid arthritis and Castleman disease.

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(IL-1) inhibitors] in patients with ongoing disease activity¹. However, TNF- α inhibitors reportedly have relatively poor effectiveness in the treatment of sJIA patients with active systemic features^{2,3,4,5}. Anakinra, an IL-1 receptor antagonist, has demonstrated efficacy specifically in patients with sJIA⁶; however, its use may be limited by the necessity of daily subcutaneous dosing and its poorly characterized longterm efficacy and tolerability. Canakinumab, an anti-IL-1 β monoclonal antibody, has demonstrated efficacy in patients with sJIA⁷; however, its longterm safety and effectiveness are not yet clear.

Tocilizumab (TCZ) is a humanized anti-IL-6 receptor monoclonal antibody. Translational and early clinical studies suggested a pivotal role for IL-6 as well as IL-1 in the inflammatory process of sJIA^{8,9}. Preliminary phase II trials of TCZ for the treatment of sJIA had promising results; effects of TCZ on systemic and articular components were sustained, even in patients with severe disease refractory to other treatments^{10,11}. A randomized, double-blind, placebo-controlled, withdrawal, phase III trial of TCZ for the treatment of sJIA was conducted at 8 university and children's hospitals in Japan. Results of the lead-in phase, the placebo-controlled, double-blind phase, and the first 48 weeks of an open-label extension have been published¹². Moreover, the improvement in growth observed after TCZ treatment was briefly reported¹³. A randomized, double-blind, placebo-controlled, phase III study (TENDER) was also conducted in patients from Western countries¹⁴. Based on these results, TCZ was approved for the treatment of patients with sJIA in Japan in 2008 and in Europe and the United States in 2011. We present our analysis of longterm safety and effectiveness data from Japanese clinical studies of TCZ in patients with sJIA.

MATERIALS AND METHODS

Patients. The eligibility criteria and study design for each study have already been reported^{11,12} (ClinicalTrials.gov NCT00144599 and NCT00144612). Briefly, as described¹², eligible patients had to be between 2 and 19 years of age at enrollment and had to meet the International League of Associations for Rheumatology classification criteria for JIA, including disease onset before the 16th birthday¹⁵. Inclusion also required active disease, which was defined by C-reactive protein (CRP) elevation (≥ 15 mg/l; normal range, < 3 mg/l) and inadequate response to corticosteroids (≥ 0.2 mg/kg prednisolone equivalent) for ≥ 3 months. Treatment with intraarticular corticosteroids, methylprednisolone pulse treatment, and traditional DMARD or immunosuppressive drugs (e.g., MTX, cyclosporine, or sulfasalazine) must have been discontinued before the initiation of TCZ treatment, and anti-TNF agents must have been discontinued for 12 weeks. Patients with important concurrent medical conditions were excluded from this study, as were those with leukopenia ($< 3.5 \times 10^9/l$) or thrombocytopenia ($< 100 \times 10^9/l$), cardiac disease, active infection, or macrophage activation syndrome (MAS) as defined by the preliminary diagnostic guidelines for MAS outlined in the article by Ravelli, *et al*¹⁶ during the period of prestudy hospital admission.

Our study complied with the principles of Good Clinical Practice (GCP) and the Declaration of Helsinki. Protocols and amendments were approved by the Japanese Ministry of Health, Labor, and Welfare and by the institutional review board at each center. The parent or guardian of

every child gave written informed consent, and the child gave assent when appropriate. GCP standards were maintained throughout the longterm extension (LTE) study.

Study design and outcomes. Our analysis describes 2 clinical studies of TCZ in sJIA and their LTE. The initial clinical studies examined were an open-label, dose-escalation, phase II study¹¹ and a phase III study that included an open-label, lead-in phase (6 weeks) and a randomized, double-blind, placebo-controlled, withdrawal phase (12 weeks)¹². The patient population for this analysis consisted of all patients in the 2 clinical studies and/or extension studies who received at least 1 dose of TCZ. In the LTE of both studies, patients were to receive TCZ 8 mg/kg every 2 weeks. The dosing interval was adjusted according to the disease activity measured by American College of Rheumatology (ACR) core set for JIA responses (JIA ACR) and CRP concentrations, and it could be shortened, but not to less than 1 week. JIA ACR components were assessed every 6 weeks, and CRP concentrations were assessed every 2 weeks. JIA ACR components included the following: physician and patient/parent general assessments on a 100-mm visual analog scale; functional ability [Childhood Health Assessment Questionnaire (CHAQ), Japanese version]; number of active joints defined by the presence of swelling or, if no swelling was present, restriction of motion accompanied by pain, tenderness, or both; number of joints with limitation of movement; and erythrocyte sedimentation rate (ESR)¹⁷. Oral corticosteroids were allowed if the dosage had not been changed within 4 weeks for the phase II study and within 2 weeks for the phase III study. Corticosteroid doses were maintained during the phase II and III study periods and were allowed to be tapered at the investigator's discretion during the LTE study, with no specific protocol-defined corticosteroid-tapering scheme. Laboratory assessments for safety, including assessment of anti-TCZ antibody, were performed every 2 weeks during the first 6 weeks and every 6 weeks thereafter. Serum anti-TCZ antibodies that neutralized TCZ activity (titer cutoff, > 3.91 ng/ml) and immunoglobulin E-type anti-TCZ antibodies (titer cutoff, ≥ 0.34 UA/ml) were measured by ELISA¹⁸. An independent safety committee identified all cases of potential MAS [i.e., reported event term of MAS, or disease flare with accompanying alanine aminotransferase (ALT)/aspartate aminotransferase (AST) elevations] after the end of the study. All patients who withdrew from the study were required to return for followup 2 weeks after treatment discontinuation.

Statistical analysis. Adverse events (AE) were analyzed for up to 5 years for all patients who received at least 1 dose of the study drug during the study period by using Medical Dictionary for Regulatory Activities (MedDRA version 8.0) terminology; incidence was summarized by the total number of a given AE per 100 patient-years (PY). Laboratory abnormalities were graded according to National Cancer Institute Common Terminology Criteria for Adverse Events, version 3. Serious AE were defined as AE that were fatal or life-threatening, resulting in permanent or significant disability or requiring prolonged inpatient hospitalization.

Response rates and 95% CI for patients achieving JIA ACR 30, 50, 70, 90, and 100 response at the final visit were calculated. Patients who withdrew during the 168-week study period were designated as non-responders. Patients who finished fewer than 168 weeks of treatment because the study itself had been terminated were designated as censored patients. The TCZ treatment period was defined as the time of first TCZ infusion to the time of the last infusion. Efficacy measurements in the patients after the designation period were not imputed. JIA ACR component variables were summarized at each timepoint.

RESULTS

Patients. Overall, 67 patients were enrolled in the phase II and phase III studies. In this population (Table 1), 56.7% (38/67) of the patients were female, median (minimum-maximum) age at initial study entry was 8.0 years (range 2–19), and duration of disease was 3.8 years (range

Table 1. Baseline demographics and disease characteristics.

Characteristics	Enrolled Patients, n = 67
Sex, n (%)	
Male	29 (43.3)
Female	38 (56.7)
Age, yrs	
Mean (\pm SD)/median (min–max)	8.3 (\pm 4.3)/8.0 (2–19)
Age group, n (%), yrs	
2–5	22 (32.8)
6–10	27 (40.3)
11–15	13 (19.4)
16–19	5 (7.5)
Age at disease onset, yrs*	
Mean (\pm SD)/median (min–max)	4.4 (\pm 2.8)/3.7 (0–14)
Disease duration, yrs	
Mean (\pm SD)/median (min–max)	4.4 (\pm 3.5)/3.8 (0.4–16.2)
Previous DMARD treatments, n	
Mean (\pm SD)/median (min–max)	2.3 (\pm 1.3)/2 (1–6)
Methotrexate, n (%)	56 (83.6)
Cyclosporine, n (%)	45 (67.2)
Mizoribine, n (%)	19 (28.4)
Cyclophosphamide, n (%)	9 (13.4)
PSL-equivalent corticosteroid dose at study entry, mg/kg/day, n = 67	
Mean (\pm SD)/median (min–max)	0.51 (\pm 0.35)/0.37 (0.03–1.8)
Active joints, n	
Mean (\pm SD)/median (min–max)	6.6 (\pm 8.0)/4 (0–39)
Joints with limited range of motion, n	
Mean (\pm SD)/median (min–max)	6.0 (\pm 10.5)/1 (0–47)
Physician global assessment, mm	
Mean (\pm SD)/median (min–max)	55.3 (\pm 17.4)/52.0 (18–100)
Parent/patient global assessment, mm	
Mean (\pm SD)/median (min–max)	53.1 (\pm 19.3)/52.0 (0–90)
CRP, mg/l	
Mean (\pm SD)/median (min–max)	64.2 (\pm 55.4)/44.0 (3–291)
Normal range	< 3.0
IL-6, pg/ml	
Mean (\pm SD)/median (min–max)	41.9 (\pm 39.6)/30.0 (0.4–182.0)
Normal range	< 4.0

* Disease developed before each patient's 16th birthday. DMARD: disease-modifying antirheumatic drugs; PSL: prednisolone; CRP: C-reactive protein; IL: interleukin.

0.4–16.2), yielding a median age at diagnosis of 3.7 years (range 0–14). Fifty-nine patients received DMARD before starting TCZ treatment. The median number of previous disease-modifying treatments was 2 (range 1–6). The most common DMARD was MTX, taken by 56 patients (83.6%). In accordance with the study protocol, all DMARD were discontinued before TCZ treatment. During the study period, including the LTE phase, no patients received any DMARD. Three patients (4.5%) previously received an anti-TNF agent. All 67 patients were receiving corticosteroid before starting TCZ treatment in the phase II or phase III studies. Median daily corticosteroid dose was 0.37 (range, 0.03–1.8) mg/kg prednisolone equivalent at initial study entry. During the study period, including the LTE phase, no patients received any intraarticular corticosteroid. Of the initial 67 patients, 60 were enrolled in the LTE study.

Mean duration of TCZ treatment was 3.4 years (range, 0.04–6.22), and total exposure was 228 PY. In total, 9 patients withdrew from the study, 4 (6.0%) as a result of AE [2 because of an anaphylactoid reaction and 2 because of a gastrointestinal hemorrhage (previously reported in the phase III study)], 1 (1.5%) because of an unsatisfactory response, and 4 (6.0%) in response to the development of anti-TCZ antibodies. Fifty-two patients completed the entire 168 weeks of treatment, and 6 patients completed fewer than 168 weeks of treatment because the study was terminated. Treatment weeks for these 6 patients numbered 126, 135, 136, 150, 156, and 164, respectively. All 6 patients were counted (Figure 1).

Safety. All 67 patients received at least 1 infusion of TCZ and reported at least 1 AE during the entire study period, with an overall event rate of 803.7/100 PY. No deaths were reported during the study period. Most AE (93.1%) were mild. The most commonly reported AE are summarized in Table 2. Serious AE were reported by 32 patients (47.8%; 34.7 events/100 PY); the most common serious AE were infections (13.2 events/100 PY), laboratory test abnormalities (5.3 events/100 PY), musculoskeletal and connective tissue disorders (3.9 events/100 PY), and gastrointestinal disorders (3.9 events/100 PY). All serious AE are listed in Table 3. Fifty-four percent of the reported serious AE were mild. The most common serious AE were infections, including gastroenteritis (12 events), pneumonia (7), bronchitis (2), cellulitis (2), nasopharyngitis (2), subcutaneous abscess (2), peritonsillar abscess (1), varicella (1), and infectious enteritis (1). No patient developed pulmonary hypertension. No malignant tumors were reported. One independently selected patient with possibly MAS-related AE (i.e., nonserious rash and fever with liver enzyme elevation) was identified as having definite MAS. Another patient with liver transaminase levels that increased with disease flare was identified as potentially having MAS. There was no evidence of hepatitis B virus or herpes B virus infection or reactivation in those 2 patients (who developed MAS). TCZ treatments were restarted after symptoms improved, and no further MAS-related AE were reported in those patients.

Two patients (3.0%), each of whom tested negative for anti-TCZ antibodies, experienced serious infusion reactions that developed early during TCZ treatment (by the fifth infusion). Overall, only 5 patients (7.5%; 3 in the phase III study and 2 in the LTE study) tested positive for anti-TCZ antibodies. Results in 1 patient, however, quickly turned negative, and TCZ treatment was continued with no infusion reaction and no decrease in effectiveness. The other 4 patients experienced mild to moderate infusion reactions, causing them to be withdrawn from the study without receiving any premedication such as steroids or antihistamines as a precaution, as stipulated in the study protocol. At the last observation point, disease activity had increased in

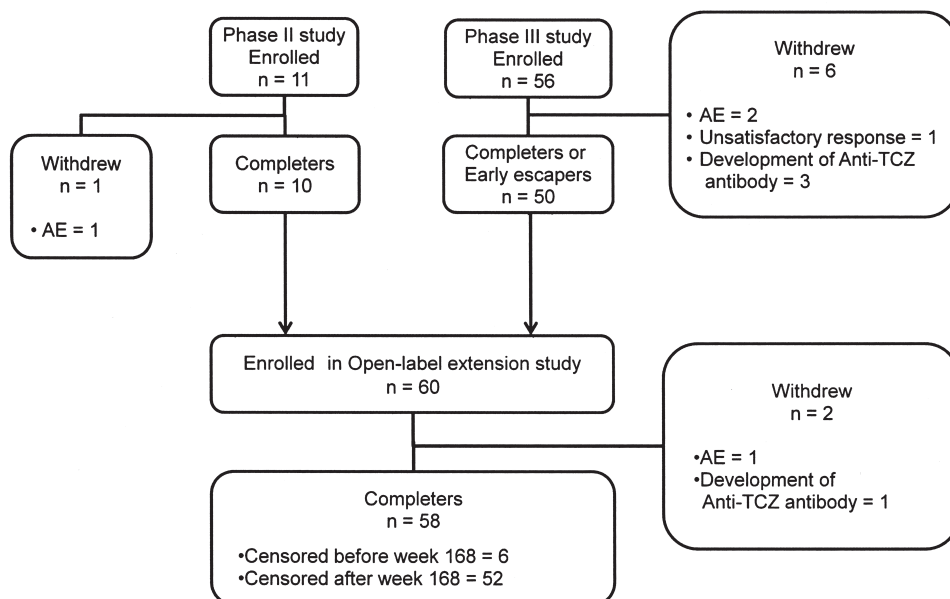


Figure 1. Patient disposition. AE: adverse event; TCZ: tocilizumab.

2 patients, and their respective JIA ACR responses were changed from 50 and 70 before anti-TCZ antibody development to 0 and 30 at the last observation point.

Grade 3 neutropenia (500 to < 1000/ml) was reported in 12 patients (17.9%), and grade 4 neutropenia (< 500/ml) was reported in 1 patient (1.5%). All decreases in neutrophil counts were transient. The patient with grade 4 neutropenia (single occurrence) had a preceding event of disease flare and had received treatment with intravenous corticosteroids and cyclosporine for the episode. This patient was the one identified as a definite MAS case by an independent safety committee after the end of study. No temporally associated serious infections were reported after the development of grade 3 or 4 neutropenia. All patients who developed neutropenia restarted TCZ treatment after they had recovered. No cases of neutropenia were reported in these patients after they restarted TCZ treatment without preventive administration of granulocyte colony stimulating factor.

Mean levels of liver enzyme remained stable over the course of the study. Grade 3 elevations [$> 5\times$ to $20\times$ upper limit of normal (ULN)] in ALT and AST levels occurred in 6 patients (9.0%) and 4 patients (6.0%), respectively. Grade 4 elevations ($> 20\times$ ULN) in these enzymes occurred in 2 patients (3.0%) and 1 patient (1.5%), respectively. Grade 3 or 4 transaminase increases appeared to be associated with other preceding events (disease flares or infections), although a causal relationship with TCZ could not be excluded. Grade 4 transaminase elevation in 1 patient improved to grade 2 during the study period. Grade 3 or grade 4 transaminase elevations in other patients improved to normal range during the study period. Mean total chole-

sterol levels also were not increased during the study, although 8 patients (11.9%) experienced grade 2 elevations in total cholesterol ($> 300\text{--}400$ mg/dl), and 1 patient (1.5%) had a grade 3 elevation ($> 400\text{--}500$ mg/dl). Because total cholesterol elevations normalized when the corticosteroid dose was tapered, lipid-lowering agents were not required in the 9 patients with grade 2 or 3 total cholesterol elevations.

Effectiveness. Response rates attained early in the TCZ treatment period were maintained throughout the LTE study period (Figure 2). At Week 168, JIA ACR 30, 50, 70, 90, and 100 response rates were 80.3% (49/61; 95% CI: 68.2–89.4%), 80.3% (49/61; 95% CI: 68.2–89.4%), 75.4% (46/61; 95% CI: 62.7–85.5%), 60.7% (37/61; 95% CI: 47.3–72.8), and 18.0% (11/61; 95% CI: 9.4–30.0), respectively. Improvements in individual JIA ACR core components [physician global assessments, patient global assessments, CHAQ (Japanese version), number of active joints, number of joints with loss of movement, and ESR] seen within the first 12 to 48 weeks of TCZ treatment were maintained across 168 weeks in the LTE (Figure 3). There was no difference in effectiveness between the biologic-naïve patients and the biologic-prior use patients.

All 67 patients were receiving oral corticosteroids at baseline (mean daily dose, 0.51 mg/kg prednisolone or equivalent). Mean daily corticosteroid doses gradually decreased during TCZ treatment (Figure 4). Twenty-two patients (32.8%) completely discontinued corticosteroids during TCZ therapy. In addition, 16 patients (23.9%) could decrease their corticosteroid dose by at least 70%, and 9 patients (13.4%) could decrease their corticosteroid dose by at least 50% during the study period without disease flare. Another indirect measure of improved disease state was

Table 2. Summary of the most common adverse events (> 5 events/100 patient-years).

System Organ Class	Condition*	Events, n	Events per 100 Patient-Years
Infections and infestations	Nasopharyngitis	305	133.8
	Upper respiratory tract infection	167	73.3
	Gastroenteritis	111	48.7
	Pharyngitis	46	20.2
	Bronchitis	37	16.2
	Influenza	25	11.0
	Otitis media	19	8.3
	Hordeolum	16	7.0
	Bronchitis, acute	13	5.7
	Gastroenteritis, viral	13	5.7
	Pneumonia	12	5.3
	Rhinitis	12	5.3
Laboratory test abnormalities	Alanine aminotransferase increased	33	14.5
	Aspartate aminotransferase increased	27	11.8
	Blood lactate dehydrogenase increased	21	9.2
	Neutrophil count decreased	18	7.9
	Lymphocyte count decreased	17	7.5
	Blood cholesterol increased	15	6.6
	Beta-N-acetyl-D-glucosaminidase increased	12	5.3
	Diarrhea	17	7.5
Gastrointestinal disorders	Vomiting	16	7.0
	Constipation	15	6.6
	Stomatitis	15	6.6
	Abdominal pain	13	5.7
	Eczema	46	20.2
Skin and subcutaneous tissue disorders	Urticaria	28	12.3
	Heat rash	14	6.1
	Rash	12	5.3
	Upper respiratory tract inflammation	59	25.9
Respiratory, thoracic, and mediastinal disorders	Rhinitis, allergic	12	5.3
	Arthropod sting	35	15.4
Injury, poisoning, and procedural complications	Contusion	14	6.1
	Headache	13	5.7
Nervous system disorders			

*Preferred term.

improvement of anemia. Mean hemoglobin concentration increased by about 2 g/dl from baseline to Week 168, reflecting improvement in anemia of chronic inflammation.

During the LTE study, the mean TCZ treatment interval was 15.2 days. The treatment interval was stable during the study period. The maximum treatment interval in this study was 81.6 weeks. Anti-TCZ antibody was not determined after TCZ treatment was restarted. The TCZ treatment interval was shortened to less than 10 days in 35 patients. During the shortened treatment intervals, the incidence rate of AE was not increased compared with the 2-week treatment period.

DISCUSSION

In this LTE study, treatment with TCZ without MTX for a mean duration of 3.4 years (177 weeks) and up to 5 years resulted in sustained clinical improvements in children with active sJIA. The effectiveness of TCZ was well maintained, with JIA ACR 50/70/90/100 responses at Week 168 of 80.3%, 75.4%, 60.7%, and 18.0%, respectively. Most

patients were able to reduce their corticosteroid doses over time when treated with TCZ. In total, 22 patients (32.8%) completely discontinued corticosteroids during TCZ therapy. In addition, 16 patients (23.9%) could decrease their corticosteroid dose by at least 70%, and 9 patients (13.4%) could decrease their corticosteroid dose by at least 50% during the study period without disease flare. Given that the previous report showed that high-dose corticosteroids inhibit growth in patients with sJIA and that growth improved in patients who decreased their corticosteroid dose^{13,19}, the corticosteroid-tapering effect of TCZ shown in our study may be beneficial for improving growth in patients with sJIA.

Patients with chronic inflammation often show mild to moderate chronic anemia that is driven largely by hepcidin, a peptide hormone induced by IL-6²⁰. IL-6 receptor inhibition by TCZ treatment resulted in marked improvement in anemia associated with active sJIA, potentially in part because of amelioration of hepcidin overproduction.

The longterm safety profile of TCZ was consistent with

Table 3. All serious adverse events.

System Organ Class	Condition*	Events, n	Events per 100 Patient-Years
Infections and infestations	Gastroenteritis	12	5.3
	Pneumonia	7	3.1
	Bronchitis	2	0.9
	Subcutaneous abscess	2	0.9
	Cellulitis	2	0.9
	Nasopharyngitis	2	0.9
	Peritonsillar abscess	1	0.4
	Varicella	1	0.4
Skeletal disorders	Infectious enteritis	1	0.4
	Juvenile arthritis	4	1.8
	Arthralgia	2	0.9
	Arthritis	1	0.9
	Aseptic necrosis bone	1	0.9
Laboratory test abnormalities	Alanine aminotransferase increased	5	2.2
	Aspartate aminotransferase increased	5	2.2
	Neutrophil count decreased	1	0.4
	Lymphocyte count decreased	1	0.4
Immune system disorders	Anaphylactoid reaction	2	0.9
Hepatobiliary disorders	Hepatic function abnormality	2	0.9
Surgical and medical procedures	Cataract operation	4	1.8
Blood and lymphatic system disorders	Lymphadenitis	1	0.4
Metabolism and nutrition disorders	Hypoglycemia	1	0.4
Eye disorders	Cataract	1	0.4
Respiratory, thoracic, and mediastinal disorders	Asthma	1	0.4
Gastrointestinal disorders	Inguinal hernia	2	0.9
	Ileus	2	0.9
	Enterocolitis	1	0.4
	Gastrointestinal hemorrhage	1	0.4
	Abdominal pain	1	0.4
	Duodenal perforation	1	0.4
	Intussusception	1	0.4
	Erythema multiforme	1	0.4
Skin and subcutaneous disorders	Rash	1	0.4
	Urticaria	1	0.4
	Chest pain	1	0.4
General disorders and administration site conditions	Pyrexia	1	0.4
	Femur fracture	1	0.4
Injury, poisoning, and procedural complications	Joint dislocation	1	0.4

* Preferred term.

that of previous findings in sJIA^{12,14} and rheumatoid arthritis (RA)²¹. Although serious AE and infections were reported more frequently in our study than in clinical trials of TCZ in adult patients with RA or in the Western sJIA study (i.e., the TENDER study¹⁴), 54% of reported serious AE (predominantly upper respiratory tract infections and gastroenteritis) were mild. Because sJIA can progress to fatal complications such as MAS, sJIA patients with mild AE in our study tended to be hospitalized for careful monitoring more frequently than adult patients enrolled in TCZ trials. In addition, the relatively higher incidence rates of mild infection are not unexpected given the vulnerable school-age patient population, which is susceptible to the endemics of seasonal infectious disease. Careful monitoring

is needed for these patients during treatment of infection, even if the symptom and/or sign of inflammation is mild. Overall, 4 patients tested positive continuously for anti-TCZ antibodies. These patients experienced mild to moderate infusion reactions, and 2 of them showed decreased effectiveness of TCZ. These patients were withdrawn from the study. Although we do not have any data for the patients who continuously received TCZ treatment and developed anti-TCZ antibody, physicians should suspect the development of anti-TCZ antibody and take appropriate steps if a sudden increase in disease activity or infusion reactions is observed during TCZ treatment.

In our study, identification of 2 selected cases revealed potential MAS cases that appeared to be associated with

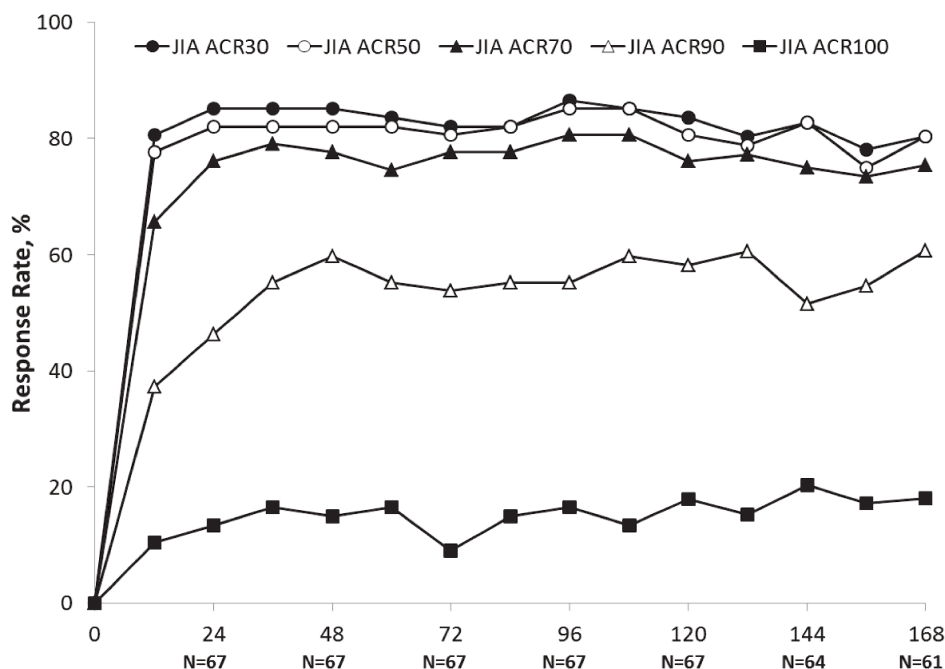


Figure 2. JIA ACR response rates (JIA ACR 30, JIA ACR 50, JIA ACR 70, JIA ACR 90, and JIA ACR 100) by treatment week in the longterm extension study. JIA ACR: American College of Rheumatology core set for juvenile idiopathic arthritis.

preceding infections and disease flares. In general, a diagnosis of MAS can be difficult given similarities to sepsis-like syndromes, virus-associated hemophagocytic syndrome, or routine sJIA flares²². In addition, the previous study reported that the clinical symptoms and laboratory findings of MAS in patients receiving TCZ therapy appeared to be milder than those in patients not receiving TCZ therapy²³. For these reasons, further research is needed to confirm the effect of TCZ and other conventional/biologic DMARD on the development of MAS.

A slight difference in the time course of lipid elevation was noted in patients with sJIA treated with TCZ compared with patients with other indications treated with TCZ because elevated lipid levels subsided without lipid-lowering agents when the corticosteroid dose was tapered.

The results of our LTE study suggest that the overall benefit/risk profile of TCZ in children with sJIA is acceptable given the severity of the disease and the observed improvements in clinical symptoms and the corticosteroid-tapering effects associated with TCZ treatment.

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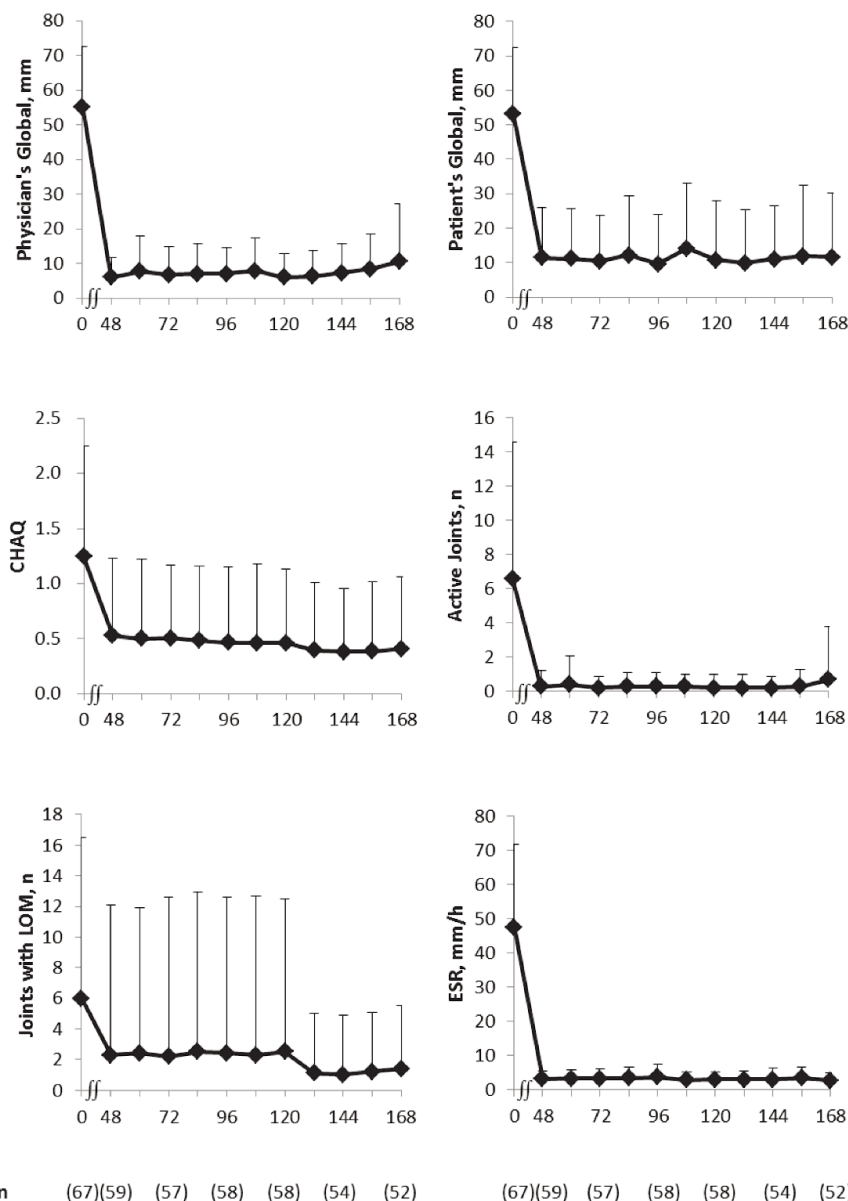


Figure 3. Mean (+SD) changes in JIA ACR core set components through Week 168 of the tocilizumab longterm extension study. CHAQ: Childhood Health Assessment Questionnaire (Japanese version); ESR: erythrocyte sedimentation rate; JIA ACR: American College of Rheumatology core set for juvenile idiopathic arthritis; LOM: loss of movement.

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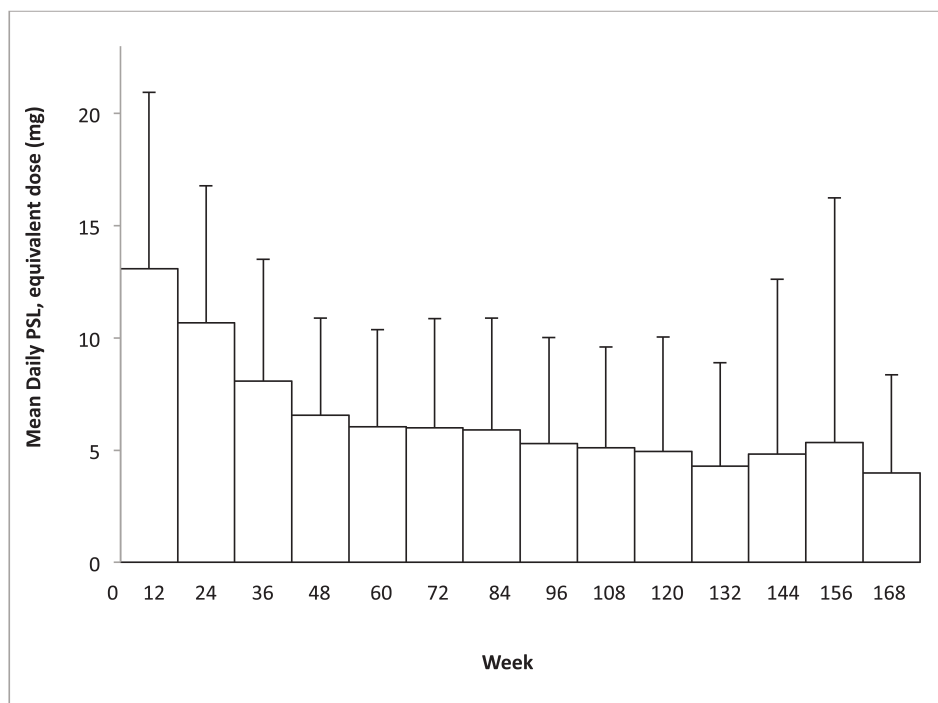


Figure 4. Change in mean (+SD) daily prednisolone (PSL) equivalent corticosteroid dose with tocilizumab treatment over 168 weeks in a longterm extension study. Percentages and numbers of patients who discontinued corticosteroids are also shown.

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