Efficacy of tocilizumab therapy in Korean patients with adult-onset Still's disease: a multicentre retrospective study of 22 cases

S.T. Song[1], J.J. Kim[1], S. Lee[1], H.A. Kim[2], E.Y. Lee[3], K.C. Shin[3], J.H. Lee[4], K.H. Lee[5], S.T. Choi[6], H.S. Cha[7], D.H. Yoo[1]

[1]Hanyang University Hospital for Rheumatic Diseases, Seoul; [2]Ajou University School of Medicine, Suwan; [3]Seoul National University College of Medicine, Seoul; [4]Ilsan Paik Hospital, Inje University, Goyang; [5]Dongguk University Ilsan Hospital, Goyang; [6]Chung-Ang University College of Medicine, Seoul; [7]Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Republic of Korea.

*Seung Taek Song, MD**
*Jin Ju Kim, MD, PhD**
Seung Lee, MD
Hyoun-Ah Kim, MD, PhD
Eun Young Lee, MD, PhD
KiChul Shin, MD, PhD
Joo Hyun Lee, MD, PhD
Kwang-Hoon Lee, MD
Sang Tae Choi, MD
Hoon-Suk Cha, MD, PhD
Dae-Hyun Yoo, MD, PhD

**These authors contributed equally to this study.*

Please address correspondence and reprint requests to:
Dae-Hyun Yoo, MD, PhD,
Department of Rheumatology,
Hanyang University Hospital for Rheumatic Diseases,
220 Wangsimni-Ro, Seongdong-Gu,
Seoul 04763, Republic of Korea.
E-mail: dhyoo@hanyang.ac.kr

Received on February 7, 2016; accepted in revised form on May 26, 2016.

Clin Exp Rheumatol 2016; 34 (Suppl. 102): S64-S71.

Key words: adult-onset Still's disease, refractory, biological agents, tocilizumab, interleukin

Competing interests: D.H. Yoo is a scientific consultant of Celltrion Inc. The other authors have declared no competing interests.

ABSTRACT

Objective. *To evaluate the efficacy of tocilizumab (TCZ), a monoclonal antibody against the interleukin (IL)-6 receptor, for refractory adult-onset Still's disease (AOSD) in the Korean population.*

Methods. *This retrospective study included 22 Korean patients with refractory AOSD who were given TCZ at one of seven university hospital-based clinics for rheumatic disease. Patients were subdivided into groups according to disease course: monocyclic, systemic polycyclic, and chronic articular. Modified Pouchot scores, including laboratory and clinical findings, were analysed at 6 months and 12 months.*

Results. *TCZ was given at 4–8 mg/kg every 4-5 weeks (8 mg/kg every 4-5 weeks in 18 patients, 6 mg/kg every 4 weeks in 2, and 4 mg/kg every 4 weeks in 2) for 7.5 months (median, IQR: 4.0-12.3). A good response (measured as a decrease of >2 in the modified Pouchot score) was achieved in 50.0% of patients (11 of 22) at 6 months and in 64.3% (9 of 14) at 12 months.*

The dose of corticosteroid dose was reduced from 11.5 mg/day (median, IQR: 10.0–21.3) immediately before TCZ therapy to 7.5 mg/day (median, IQR: 5.0–10.0, p=0.002) at 6 months and finally to 6.3 mg/day (median, IQR: 5.0–7.5, p=0.002) at 12 months. Only one patient discontinued TCZ treatment due to facial swelling accompanied by high blood pressure. In all others, adverse events subsided with delayed TCZ therapy, and TCZ therapy was continued successfully without problems.

Conclusion. *TCZ was effective for treating Korean AOSD patients who were refractory to conventional therapy or other anti-cytokine biologics, showing a corticosteroid-sparing effect and an acceptable tolerance profile.*

Introduction

Adult-onset Still's disease (AOSD) is a systemic inflammatory disorder of unknown aetiology. It is characterised by spiking fever, evanescent rash, arthritis, and leukocytosis (1, 2). Arthritis occurs in almost 90% of AOSD patients, and in around half of those patients, destructive arthritis may progress over time (3).

Treatment for AOSD includes NSAIDs, corticosteroids, and synthetic immune modulators such as methotrexate (MTX) (4). For decades, corticosteroids have been the mainstay for treating patients with AOSD in spite of their many adverse effects, such as hypertension, osteoporosis, avascular necrosis, and metabolic disturbances (5-7). However, corticosteroids are sometimes insufficient for AOSD treatment. When decreasing the dose of corticosteroids, relapse of AOSD often occurs. Thus, immune modulators have been used to prevent relapses of AOSD, which simultaneously allows for reduced corticosteroid dosage.

Recently, several studies have reported that pro-inflammatory cytokines including interleukin (IL)-1, IL-6, IL-18, tumour necrosis factor (TNF)-α, and interferon (INF)-γ, are involved in the pathogenesis of AOSD (8-10). Particularly, IL-6 seems to play an important role in systemic symptoms including fever, rash, serositis, lymphadenopathy, and hepatosplenomegaly as well as synovitis (11, 12). With advances in our understanding of the roles of cytokines in AOSD, physicians have tried to treat AOSD patients with anti-cytokine biologics, such as inhibitors of TNF, IL-1, or IL-6. Consequently, in small studies, refractory AOSD patients have been treated successfully with anti-cytokine biologics, including anti-TNFα inhibi-

tors (13) and the human IL-1 receptor antagonist (anakinra) (14-16), and the humanised monoclonal antibody against the IL-6 receptor (tocilizumab, TCZ) (17-20).

However, the effect of anti-cytokine biologics on AOSD might vary; TNF-α blockers seem to be more effective in arthritis than in systemic symptoms (21), while IL-1 inhibitors are more effective in systemic symptoms than articular symptoms (15, 22). In the case of TCZ, a few small studies showed efficacy in treating both systemic and articular disease along with corticosteroids-sparing effects (17-20). In this study, we retrospectively assessed the efficacy of TCZ therapy for refractory AOSD in the Korean population.

Patients and methods

Study population

We retrospectively assessed 22 Korean patients with refractory AOSD who were given TCZ in university hospital-based clinics for rheumatic disease. All recruited AOSD patients met the criteria proposed by Yamaguchi *et al*. (23). Refractory AOSD is the condition in which AOSD-related symptoms such as fever, rash, or arthritis persist despite treatment with corticosteroids, immune modulators, or anti-cytokine biologics other than TCZ. Because TCZ has not been approved to treat AOSD in Korea, it was used off-label. Thus, we obtained written informed consent approval at each hospital from all patients before TCZ therapy. This study was approved by the local ethics committees, in accordance with the Declaration of Helsinki.

Laboratory data

Laboratory data related to disease activity, such as complete blood cell count, erythrocyte sedimentation rate (ESR), serum C-reactive protein (CRP) and ferritin levels, and liver enzymes, was collected.

Assessment of TCZ efficacy

We stratified the TCZ-treated patients with AOSD according to disease course as follows: 1) monocyclic, defined as a single episode that faded and was followed by persistent remis-

Table I. Clinical characteristics of the 22 patients with adult-onset Still's disease treated with tocilizumab.

	Total (n=22)	Polycyclic (n=11)	Chronic articular (n=11)	*p*-value
Female, n (%)	17 (77.3)	9 (81.8)	8 (72.7)	1.000
Age (years)	36.0 (29.8-66.3)	66.0 (29.0-71.0)	32.0 (30.0-36.0)	0.047
Age at diagnosis (years)	29.5 (23.0-65.0)	65.0 (25.0-68.0)	24.0 (22.0-32.0)	0.008
Duration of disease (months)	70.5 (23.0-65.0)	38.0 (24.0-61.0)	114.0 (89.0-128.0)	<0.001
Duration from onset to starting TCZ (months)	36.5 (8.0-90.8)	13.0 (6.0-27.0)	89.0 (48.0-121.0)	0.001
Modified Pouchot score	3.0 (2.0-4.3)	3.0 (2.0-5.0)	2.0 (1.0-4.0)	0.060
Fever, n (%)	10 (45.5)	7 (63.6)	3 (27.3)	0.087
Sore throat, n (%)	4 (18.2)	3 (27.3)	1 (9.1)	0.586
Skin rash, n (%)	11 (50.0)	8 (72.7)	3 (27.3)	0.033
Itching, n (%)	8 (36.4)	7 (63.6)	1 (9.1)	0.024
Arthritis, n (%)	17 (77.3)	6 (54.5)	11 (100.0)	0.035
Tender joint count	4.0 (0.0-11.0)	0.0 (0.0-8.0)	10.0 (3.0-15.0)	0.013
Swollen joint count	4.0 (0.0-15.3)	0.0 (0.0-2.0)	15.0 (4.0-21.0)	0.001
Myalgia, n (%)	8 (36.4)	4 (36.4)	4 (36.4)	1.000
Lymphadenopathy, n (%)	2 (9.1)	2 (18.2)	0 (0.0)	0.476
Hepatomegaly or abnormal LFT, N (%)	6 (27.3)	4 (36.4)	2 (18.2)	0.635
Laboratory				
Leukocyte count (/mm^3)	11,500 (8,800-18,520)	13,880 (8,150-18,720)	11,500 (9,150-19,180)	0.725
Ferritin (ng/mL)	647 (229-1,946)	1,946 (968-2492)	475 (165-628)	0.009
ESR (mm/hour)	53.0 (40.0-95.0)	53.5 (44.8-92.8)	52.0 (37.0-107.0)	0.888
CRP (mg/dL)	3.8 (1.4-6.3)	3.2 (1.2-5.1)	5.1 (2.0-7.3)	0.379

Values are the median (IQR) unless otherwise indicated.
Basic characteristics between the patients with or without the history of biologic therapy are compared.
CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; LFT: liver function test; TCZ: tocilizumab.

Table II. History of medications in the 22 patients with adult-onset Still's disease before tocilizumab therapy.

	Total (n=22)	Polycyclic (n=11)	Chronic articular (n=11)	*p*-value
Dosage of PDS (mg), median (IQR)	12.5 (10.0-20.0)	20.0 (12.5-27.5)	10.0 (6.9-14.4)	0.047
DMARDs, median (IQR)	3.0 (2.0-3.3)	2.0 (1.0-3.0)	3.0 (2.0-4.0)	0.154
Methotrexate	20 (90.9)	9 (81.8)	11 (100.0)	0.476
Leflunomide	12 (54.5)	3 (27.3)	9 (81.8)	0.010
Azathioprine	9 (40.9)	4 (36.4)	5 (45.5)	1.000
Cyclosporine	8 (36.4)	4 (36.4)	4 (36.4)	1.000
Hydroxychloroquine	7 (31.8)	5 (45.5)	2 (18.2)	0.361
Tacrolimus	1 (4.5)	0 (0.0)	1 (9.1)	1.000
Patients with biologics, ever used	13 (59.1)	4 (36.4)	9 (81.8)	0.080
One biologics, ever used	7	3	4	
Two biologics, ever used	4	1	3	
Three biologics, ever used	2	0	2	
The total number of biologics, ever used	21	5	16	
Anti-TNF-α	18 (85.7)	4 (80.0)	14 (87.5)	0.080
Infliximab	7	3	4	1.000
Etanercept	7	1	6	0.063
Adalimumab	4	0	4	0.090
Abatacept	2 (9.1)	1 (10.0)	1 (7.1)	1.000
Anakinra	1 (4.5)	0 (0.0)	1 (7.1)	1.000

Values are the number (percentage) unless otherwise indicated.
Medication history is compared between the patients with polycyclic type and those with chronic articular type. Anti-TNF-α: anti-tumour necrosis factor- α; DMARDs: disease-modifying anti-rheumatic drugs; IQR: interquartile range; PDS: prednisolone; TCZ: tocilizumab.

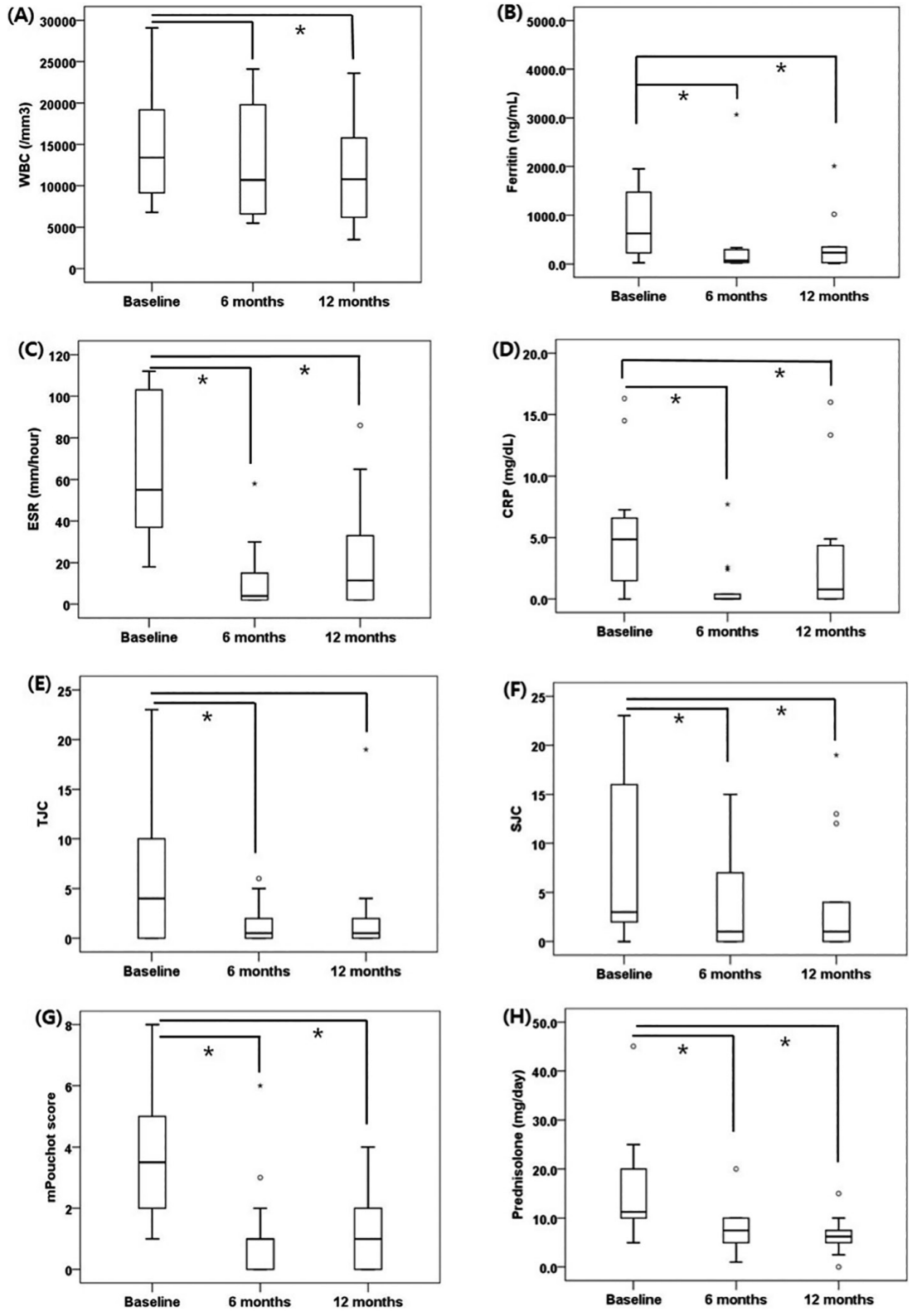

Fig. 1. Improvement of clinical and laboratory findings of patients with adult-onset Still's disease treated with tocilizumab at 12 months. (data expressed as median values compared with basal results):
A: Leukocyte count
B: Ferritin
C: ESR
D: CRP
E: TJC
F: SJC
G: mPouchot score
H: Prednisolone

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate; mPouchot: modified Pouchot; SJC: swollen joint count; TCJ: tender joint count; WBC: white blood cell. $^{*}p<0.05$. $^{**}p<0.001$.

sion; 2) systemic polycyclic, defined as complete remission followed by 1 or more exacerbations; and 3) chronic articular, defined as persistently active disease associated with polyarthritis. We compared clinical and laboratory findings between before and after (6 and 12 months) TCZ therapy. For assessment of efficacy, we used the modified Pouchot score (from 0 to 12) (24) that included spiking fever, skin rash, sore throat, arthritis, myalgia, pleuritic, pericarditis, pneumonitis, lymphadenopathy, hepatomegaly or abnormal liver function test, leukocytosis ≥15,000/mm^2, and serum ferritin >3,000 ng/mL. Active AOSD was defined by a modified Pouchot score was

Table III. Improvement of clinical and laboratory findings of patients with adult-onset Still's disease treated with tocilizumab at the 6-month assessment.

	Polycyclic (n=11)			Chronic articular (n=11)		
	Baseline	6-month	*p*-value	Baseline	6-month	*p*-value
Modified Pouchot score	3.0 (2.0-5.0)	1.0 (0.0-1.0)	0.007	2.0 (1.0-4.0)	1.0 (1.0-1.0)	0.011
Systemic symptoms, n (%)	10 (90.9)	3 (27.3)	0.016	3 (30.0)	0 (0.0)	0.250
Fever, n (%)	7 (63.6)	1 (9.1)	0.031	3 (27.3)	0 (0.0)	-
Sore throat, n (%)	3 (27.3)	1 (9.1)	0.625	1 (9.1)	0 (0.0)	-
Skin rash, n (%)	8 (72.7)	2 (18.2)	0.031	3 (27.3)	0 (0.0)	-
Itching, n (%)	7 (63.6)	2 (18.2)	0.063	1 (9.1)	0 (0.0)	-
Arthritis, n (%)	6 (54.5)	5 (45.5)	1.000	11 (100.0)	9 (81.8)	-
Tender joint count	0.0 (0.0-8.0)	0.0 (0.0-0.0)	0.046	10.0 (3.0-15.0)	2.0 (0.0-5.0)	0.010
Swollen joint count	0.0 (0.0-2.0)	0.0 (0.0-1.0)	0.058	15.0 (4.0-21.0)	6.0 (1.0-8.0)	0.007
Myalgia, n (%)	4 (36.4)	0 (0.0)	-	4 (36.4)	0 (0.0)	-
Lymphadenopathy, n (%)	2 (18.2)	0 (0.0)	-	0 (0.0)	0 (0.0)	-
Hepatomegaly or abnormal LFT, n (%)	4 (36.4)	4 (36.4)	1.000	2 (18.2)	0 (0.0)	-
Laboratory						
Leukocyte count (/mm^3)	13,880 (8,150-18,720)	6,900 (5,440-9,800)	0.169	11,500 (9,150-19,180)	8,440 (5,900-13,200)	0.037
Ferritin (ng/mL)	1,946 (968-2492)	72 (28-339)	0.036	475 (165-628)	55 (26-163)	0.018
ESR (mm/hour)	53.5 (44.8-92.8)	14.0 (2.0-37.0)	0.007	52.0 (37.0-107.0)	5.0 (2.0-11.0)	0.003
CRP (mg/dL)	3.2 (1.2-5.1)	0.0 (0.0-2.0)	0.059	5.1 (2.0-7.3)	0.0 (0.0-0.7)	0.005
Dosage of PDS (mg)	20.0 (12.5-27.5)	5.0 (3.8-8.8)	0.012	10.0 (6.9-14.4)	6.3 (2.5-10.0)	0.011

Values are the median (IQR) unless otherwise indicated.
Clinical and laboratory findings of AOSD patients who were divided into polycyclic and chronic articular groups were analysed between the baseline assessment and 6-month assessment after tocilizumab therapy by the Wilcoxon signed-rank test and McNemar test.
Anti-TNF-α: anti-tumour necrosis factor- α; CRP: C-reactive protein; DMARDs: disease-modifying anti-rheumatic drugs; ESR: erythrocyte sedimentation rate; IQR: interquartile range; LFT: liver function test; PDS: prednisolone; TCZ: Tocilizumab.

more than 2. Remission of AOSD was defined by a modified Pouchot score of 0. A good response to TCZ was defined as a decreased modified Pouchot score more than 2 score with decreased acute phase reactants compared to initial treatment of TCZ. A partial response was defined as a decrease of 1 ≤ modified Pouchot score ≤2 or at least 20% improvement in both the tender joint count and the swollen joint count. Data on adverse events were obtained from patient medical records.

Statistical analysis

Continuous data are presented as the median with interquartile range (IQR) or as the number and percentage, as appropriate. Data were analysed by Mann-Whitney test or Wilcoxon signed-rank test for continuous variables and Fisher's exact test or McNemar's test for categorical variables. *p*-values of <0.05 were considered statistically significant. Statistical analyses were performed using SPSS 18 (PASW 18, IBM).

Results

Characteristics of AOSD

Twenty-two AOSD patients (17 women and 5 men) were treated with TCZ in this study.

The clinical characteristics and comparison of the characteristics between systemic polycyclic and chronic articular patterns for all 22 AOSD patients are shown in Table I. Exactly half of patients had active AOSD (modified Pouchot score >2). Although the other half did not have active AOSD (1 ≤ modified Pouchot score ≤2), 9 patients had persistent polyarthritis, and 2 patients had intermittent fever.

At the starting point of TCZ therapy, the most frequent clinical features were articular symptoms (n=17, 77.3%), skin rash (n=11, 50.0%), fever (n=10, 45.5%), and myalgia (n=8, 36.4%). Most patients had elevated levels of ferritin (median 647 ng/mL [IQR: 229–1,946]), ESR (median 53.0 mm/hour [IQR: 40.0–95.0]), and CRP (median 3.8 mg/dL [IQR: 1.4–6.3]). In the chronic articular group, the patients were younger and had longer disease duration than those in the systemic polycyclic group (p=0.047 and p=<0.001, respectively). Systemic symptoms including skin rash and itching were significantly lower in the chronic articular group (p=0.033 and p=0.024, respectively), and both the tender joint count and swollen joint count were significantly lower in the systemic polycyclic group (p=0.013 and p=0.001, respectively). The level of ferritin was significantly lower in the chronic articular group than in the systemic polycyclic group (median 475 ng/mL [IQR: 165–628] *vs*. 1,946 ng/mL [IQR: 968–2492], p=0.009).

Before TCZ therapy, all patients were treated with corticosteroids and synthetic immune modulators, and 13 (59.1%) of them had received other anti-cytokine biologics (Table II). In the chronic articular group, anti-cytokine biologics were used more frequently, but the corticosteroid dose at the start of TCZ therapy was lower than in the systemic polycyclic group

Table IV. Adverse events occurring in patients who are treated with tocilizumab.

Adverse events	Tocilizumab n=22	Severity[1]	Causality[2]
Patients with at least one AE	4 (18.2)	-	-
Total number of AEs*	8	-	-
High blood pressure	2 (25.0)	Grade 2	Possible
Hair loss	2 (25.0)	Grade 1	Probable
Pneumonia	1 (12.5)	Grade 3	Possible
Dyslipidaemia	1 (12.5)	Grade 2	Possible
Headache	1 (12.5)	Grade 2	Possible
Puffy face	1 (12.5)	Grade 2	Probable

Values are the number (percentage) unless stated otherwise.
*Multiple occurrences of the same AE in one individual were counted only once. [1]The Common Toxicity Criteria for Adverse Events (CTCAE) version 4. [2]The WHO-UMC system for standardised case causality assessment. AE: adverse event.

(p=0.018 and p=0.047, respectively, Table II).

Effectiveness of TCZ

In this study, TCZ was given at 4–8 mg/kg every 4–5 weeks (8 mg/kg every 4–5 weeks in 18 patients, 6 mg/kg every 4 weeks in 2, and 4 mg/kg every 4 weeks in 2) for 7.5 months (median, IQR: 4.0–12.3). Nineteen patients were treated in combination with synthetic immune modulators (14 with MTX, 3 with leflunomide, and 2 with cyclosporine). Three patients were treated with TCZ as a monotherapy.

Improvement in clinical and laboratory findings following TCZ therapy for 12 months is shown in Figure 1. A good response (decrease of >2 modified Pouchot score) was achieved in 50.0% of patients (11 of 22) at 6 months and 64.3% (9 of 14) at 12 months. A partial response (decrease of 1 ≤ modified Pouchot score ≤2) was found in 31.8% of patients (7 of 22) at 6 months and in 14.3% (2 of 14) at 12 months; in four of those followed until 12 months, TCZ had been discontinued for more than 4 months, and the improvement in clinical and laboratory findings in 3 patients was maintained until 12 months. Furthermore, the dose of corticosteroids was reduced from 11.3 mg/day (median, IQR: 10.0–21.3 [mean 15.7 mg/day, SD 10.4]) immediately before TCZ therapy to 7.5 mg/day (median, IQR: 5.0–10.0 [mean 7.8 mg/day, SD 4.4], p=0.002) at 6 months and then to 6.3 mg/day (median, IQR: 5.0–7.5 [mean 6.4 mg/day, SD 3.5], p=0.002) at 12 months.

All measured parameters including the modified Pouchot score, tender and swollen joint count, ESR, serum levels of CRP and ferritin, and the dose of prednisolone were all significantly decreased in both the systemic polycyclic group and the chronic articular group (Table III). These results were similar in 13 AOSD patients who were refractory to TNF-α blockers.

Adverse events

During the follow-up period (median 12 months [IQR: 6–12]), 4 patients (18.2%) reported adverse events (n=8), such as high blood pressure, hair loss, leukopenia, healthcare-associated pneumonia, hyperlipidaemia, headache, and facial swelling, without serious adverse events (Table IV). Only one patient discontinued TCZ treatment due to facial swelling accompanied by high blood pressure. In others, the adverse events subsided with delayed-TCZ therapy and then TCZ therapy was continued successfully without further problems.

Discussion

In this multicentre retrospective study, we observed that TCZ remarkably improved clinical symptoms and laboratory markers of disease activity in patients with refractory AOSD, even in non-responders to other anti-cytokine biologics. Our findings that TCZ could effectively resolve disease activity were consistent with findings from previous case series (Table V) (18-20, 25). High levels of IL-6 are related to systemic AOSD symptoms and are correlated with increased acute-phase reactants (serum CRP and ferritin), thrombocytosis, leukocyte levels (26), and disease activity (9, 27, 28). Based on our understanding of the roles of IL-6 in AOSD, TCZ has been used in a few small studies, which determined that its safety and efficacy were consistent with its results in the treatment of RA (17-20, 29-31). Recently, the efficacy of TCZ in systemic juvenile idiopathic arthritis (JIA), the juvenile counterpart of AOSD, has been validated, and a TCZ therapy protocol has been proposed (32-36). An increasing number of reports have showed that TCZ is effective in patients with refractory AOSD (17-20). Although the dose of TCZ in the treatment of RA and systemic JIA is well established (29, 34-36), no protocols for the dose of TCZ are available for treating AOSD. As in other studies (18, 19), our patients received variable doses of TCZ (4-8 mg/kg every 4–5 weeks). Eighteen (81.8%) of our 22 patients received a TCZ dose of 8 mg/kg every 4–5 weeks, but the others received a reduced dose of 4–6 mg/kg every 4 weeks due to economic considerations.

We observed significant reductions in inflammatory markers (CRP levels and ESR) following the initiation of TCZ therapy. These results were comparable to previous studies that reported rapid improvement in clinical and laboratory findings after 3 months or 6 months of TCZ therapy (19, 25). The effect was maintained in our patients until 12 months. However, one member of our study group, a 27-year-old woman with chronic articular AOSD with systemic symptoms, was given a TCZ dose of 4 mg/kg every 4 weeks; she showed resolution of her systemic symptoms, but her polyarthritis was not improved after 12 months of treatment with TCZ. We believe that the reason for persistent poly-arthritis in this patient was the low dose of TCZ. In another case, an 82-year-old woman with systemic polycyclic AOSD was given a TCZ therapy dose of 8 mg/kg every 5 weeks and showed delayed improvement after 6 months.

We determined that articular manifestations in AOSD patients seems to be less responsive to treatment compared with systemic symptoms. Among the 13 patients with systemic symptoms at

Table V. Comparison of outcome measurements of tocilizumab treatment for refractory adult-onset Still's disease.

	Puechal *et al*. (16) (n=14)	Cipriani *et al*. (18) (n=11)	Ortiz-Sanjuan *et al*. (35) (n=34)	Present study (n=22)
Age at baseline, mean (range), year	38.4 (23–68)	46.5 (28–73)	38.7 (16–74)	45.3 (27–82)
Disease duration, mean (range), year	13.6 (3–27)	6.1 (1–12)	¶4.2 (1–9)	6.3 (2–15)
TCZ dosing	5–8 mg/kg every 2 or 4 weeks (8 mg/kg every month, n=9)	8 mg/kg every 4 weeks	8 mg/kg every 4 weeks in 22, 4 mg/kg every 4 weeks in 2, and 8 mg/kg every 2 weeks in 10	4–8 mg/kg every 4–5 weeks (8 mg/kg every 4–5 weeks, n=18)
Concomitant therapies	NR	MTX in 8	MTX in 18, and HCQ in 1	MTX in 20, LFN in 12, AZA in 9, CsA in 8, HCQ in 7, and tacrolimus in 1
Outcome	EULAR remission was 57% at 6 months	EULAR remission was 63.63% at 6 months and 81.82% at 12 months	Improvement of articular manifestation in 64.7% at 12 months	Good response was 50.0% at 6 months and 64.3% at 12 months
Corticosteroid weaning	Yes	Yes	Yes	Yes
Adverse events	High blood pressure and diabetes mellitus in 1, necrotising angiodermatitis in 1, chest pain and chills in 1, mild dyslipidaemia in 1, and increased ALT levels in 1	Infection in one and injection-site reaction in 2	Infections in 9, mild leukopenia or neutropenia in 4, elevated hepatic enzyme levels in 4, hypercholesterolemia in 1 and headache in 1	Pneumonia in 1, HBP, hair loss, dyslipidaemia, headache, and puffy face in 3

ALT: alanine aminotransferase; AOSD: adult-onset Still's disease; AZA: azathioprine; CsA: cyclosporine; HBP: high blood pressure; HCQ: hydroxychloroquine; LFN: leflunomide; MTX: methotrexate; NR: not reported; TCZ: tocilizumab. ¶Median (IQR), years.

the start of TCZ treatment, 10 (76.9%) showed improvement in these symptoms after 6 months of TCZ therapy. On the other hand, only 25.0% (4 of 16) and 30% (3 of 10) of patients with articular manifestations showed remission after 6 and 12 months of TCZ therapy, respectively. However, improvement of more than 50% of articular symptoms was observed in 62.5% (10 of 16) and 40% (4 of 10) of AOSD patients after 6 and 12 months of TCZ therapy, respectively. A previous study (18) also reported improvement in articular manifestation remission (European League Against Rheumatism [EULAR] remission [Disease Activity Score (DAS) in 28 joints of <2.6]) (37) in 36% and 57% of patients after 3 and 6 months of TCZ therapy, respectively. These results suggest that improvement of articular manifestations might be progressive and maintained over time.

We observed significant improvements in clinical and laboratory findings in both the systemic polycyclic group and the chronic articular group despite a 59.2% mean reduction in corticosteroid dose after the onset of TCZ therapy (from mean 15.7 mg/day [SD 10.4] before TCZ therapy to 7.8 mg/day [SD 4.4] at 6 months and to 6.4 mg/day [SD 3.5] at 12 months). This corticosteroids-sparing effect is very important in patients with refractory AOSD because a high cumulative dose of corticosteroids may result in serious adverse effects.

In this study, we determined that TCZ was comparatively safe. Only 1 patient, a 50-year-old woman, had to discontinue TCZ after she developed a facial swelling and a headache. Her symptoms were resolved after cessation of TCZ therapy. One patient, a 36-year-old woman, developed healthcare-associated pneumonia; she fully recovered following cessation of TCZ and treatment with antibiotics and then restarted TCZ therapy with no further adverse symptoms. Other minor adverse events, including mild leukopenia, high blood pressure, and hair loss, were transient.

The optimal dose and duration of TCZ therapy in AOSD remains unclear. To prevent adverse effects related to corticosteroids, a protocol for the introduction of steroid-sparing agents or anti-cytokine biologics and for corticosteroid tapering should be developed. Considering the efficacy and the safety of TCZ in RA (29-31) and systemic JIA (34-36), in conjunction with the results of a series of previous small studies in AOSD (17-20, 25), we feel that TCZ can be used in those who are dependent on and refractory to corticosteroids, and who have suffered adverse effects of corticosteroid treatment. If stable clinical and laboratory findings are maintained with TCZ therapy, the corticosteroids can be tapered off relatively rapidly. Once remission is maintained with low-dose corticosteroids, the dose or the interval of TCZ administration may be adjusted gradually. It should not be discontinued hastily, because this can lead to relapse. There is still no adequate evidence to suggest how physicians modify TCZ therapy when remission has been maintained for a long time.

The strength of this study is the analysis of data according to disease course. More than half of TCZ-treated patients with AOSD were refractory to other anti-cytokine biologics. We demonstrated that TCZ therapy was effective in both polycyclic and chronic articular types of AOSD as well as in AOSD pa-

tients refractory to other anti-cytokine biologics.

This study has several limitations. First, it is a small retrospective study. Thus, we could not assess the very early response for TCZ therapy. Because patient global assessments were not recorded periodically, we could not calculate DAS28 to compare the efficacy of TCZ with other studies, and the interval of TCZ administration was not strictly regulated. Second, the patients enrolled in this study were treated with different doses and treatment durations of TCZ. We speculate that this condition might result in lowering the remission rate of TCZ therapy. Lastly, we could not assess the long-term efficacy of TCZ therapy. A large-scale, prospective, multinational clinical trial is required to assess the efficacy and safety of TCZ in AOSD. Also, further studies are needed to clarify which patients are relapsed and progress to chronic articular course in a large scale of clinical study.

In conclusion, most patients experienced improvement in both clinical manifestations and laboratory data after TCZ therapy, and the improvements were sustained over time. After starting TCZ therapy, the dose of corticosteroids was able to be significantly decreased. Finally, the adverse effects of TCZ therapy found in this study were tolerable and were comparable to those reported in RA patients treated with TCZ. Taken together, our results provide the basis for establishing an appropriate therapeutic protocol for patients with refractory AOSD.

References

1. EFTHIMIOU P, PAIK PK, BIELORY L: Diagnosis and management of adult onset Still's disease. *Ann Rheum Dis* 2006; 65: 564-72.
2. BALCI MA, PAMUK ON, PAMUK GE, UZUNDERE FK, DONMEZ S: Epidemiology and outcome of adult-onset Still's disease in Northwestern Thrace region in Turkey. *Clin Exp Rheumatol* 2015.
3. CABANE J, MICHON A, ZIZA JM *et al*.: Comparison of long term evolution of adult onset and juvenile onset Still's disease, both followed up for more than 10 years. *Ann Rheum Dis* 1990; 49: 283-5.
4. AYDINTUG AO, D'CRUZ D, CERVERA R, KHAMASHTA MA, HUGHES GR: Low dose methotrexate treatment in adult Still's disease. *J Rheumatol* 1992; 19: 431-5.
5. CURTIS JR, WESTFALL AO, ALLISON J *et al*.: Population-based assessment of adverse events associated with long-term glucocorticoid use. *Arthritis Rheum* 2006; 55: 420-6.
6. HUSCHER D, THIELE K, GROMNICA-IHLE E *et al*.: Dose-related patterns of glucocorticoid-induced side effects. *Ann Rheum Dis* 2009; 68: 1119-24.
7. BOUMPAS DT, CHROUSOS GP, WILDER RL, CUPPS TR, BALOW JE: Glucocorticoid therapy for immune-mediated diseases: basic and clinical correlates. *Ann Intern Med* 1993; 119: 1198-208.
8. EFTHIMIOU P, KONTZIAS A, WARD CM, OGDEN NS: Adult-onset Still's disease: can recent advances in our understanding of its pathogenesis lead to targeted therapy? *Nat Clin Pract Rheumatol* 2007; 3: 328-35.
9. CHEN DY, LAN JL, LIN FJ, HSIEH TY: Proinflammatory cytokine profiles in sera and pathological tissues of patients with active untreated adult onset Still's disease. *J Rheumatol* 2004; 31: 2189-98.
10. CANTARINI L, RIGANTE D: Adult-onset autoinflammatory disorders: a still debated entity? *Clin Exp Rheumatol* 2015; 33: 137-40.
11. DE BENEDETTI F, MASSA M, PIGNATTI P, ALBANI S, NOVICK D, MARTINI A: Serum soluble interleukin 6 (IL-6) receptor and IL-6/soluble IL-6 receptor complex in systemic juvenile rheumatoid arthritis. *J Clin Invest* 1994; 93: 2114-9.
12. DE BENEDETTI F: Tocilizumab for systemic juvenile idiopathic arthritis. *New Engl J Med* 2013; 368: 1256-7.
13. FAUTREL B, SIBILIA J, MARIETTE X, COMBE B: Tumour necrosis factor alpha blocking agents in refractory adult Still's disease: an observational study of 20 cases. *Ann Rheum Dis* 2005; 64: 262-6.
14. NORDSTROM D, KNIGHT A, LUUKKAINEN R *et al*.: Beneficial effect of interleukin 1 inhibition with anakinra in adult-onset Still's disease. An open, randomized, multicenter study. *J Rheumatol* 2012; 39: 2008-11.
15. GIAMPIETRO C, RIDENE M, LEQUERRE T *et al*.: Anakinra in adult-onset Still's disease: long-term treatment in patients resistant to conventional therapy. *Arthritis Care Res* 2013; 65: 822-6.
16. LEQUERRE T, QUARTIER P, ROSELLINI D *et al*.: Interleukin-1 receptor antagonist (anakinra) treatment in patients with systemic-onset juvenile idiopathic arthritis or adult onset Still disease: preliminary experience in France. *Ann Rheum Dis* 2008; 67: 302-8.
17. DE BOYSSON H, FEVRIER J, NICOLLE A, AUZARY C, GEFFRAY L: Tocilizumab in the treatment of the adult-onset Still's disease: current clinical evidence. *Clin Rheumatol* 2013; 32: 141-7.
18. PUECHAL X, DEBANDT M, BERTHELOT JM *et al*.: Tocilizumab in refractory adult Still's disease. *Arthritis Care Res* 2011; 63: 155-9.
19. ELKAYAM O, JIRIES N, DRANITZKI Z *et al*.: Tocilizumab in adult-onset Still's disease: the Israeli experience. *J Rheumatol* 2014; 41: 244-7.
20. CIPRIANI P, RUSCITTI P, CARUBBI F *et al*.: Tocilizumab for the treatment of adult-onset Still's disease: results from a case series. *Clin Rheumatol* 2014; 33: 49-55.
21. GERFAUD-VALENTIN M, MAUCORT-BOULCH D, HOT A *et al*.: Adult-onset still disease: manifestations, treatment, outcome, and prognostic factors in 57 patients. *Medicine* 2014; 93: 91-9.
22. LO GULLO A, CARUSO A, PIPITONE N, MACCHIONI P, PAZZOLA G, SALVARANI C: Canakinumab in a case of adult onset still's disease: efficacy only on systemic manifestations. *Joint Bone Spine* 2014; 81: 376-7.
23. YAMAGUCHI M, OHTA A, TSUNEMATSU T *et al*.: Preliminary criteria for classification of adult Still's disease. *J Rheumatol* 1992; 19: 424-30.
24. RAU M, SCHILLER M, KRIENKE S, HEYDER P, LORENZ H, BLANK N: Clinical manifestations but not cytokine profiles differentiate adult-onset Still's disease and sepsis. *J Rheumatol* 2010; 37: 2369-76.
25. ORTIZ-SANJUAN F, BLANCO R, CALVO-RIO V *et al*.: Efficacy of tocilizumab in conventional treatment-refractory adult-onset Still's disease: multicenter retrospective open-label study of thirty-four patients. *Arthritis Rheum* (Hoboken, NJ) 2014; 66: 1659-65.
26. BAGNARI V, COLINA M, CIANCIO G, GOVONI M, TROTTA F: Adult-onset Still's disease. *Rheumatology Int* 2010; 30: 855-62.
27. HOSHINO T, OHTA A, YANG D *et al*.: Elevated serum interleukin 6, interferon-gamma, and tumor necrosis factor-alpha levels in patients with adult Still's disease. *J Rheumatol* 1998; 25: 396-8.
28. FUJII T, NOJIMA T, YASUOKA H *et al*.: Cytokine and immunogenetic profiles in Japanese patients with adult Still's disease. Association with chronic articular disease. *Rheumatology* (Oxford) 2001; 40: 1398-404.
29. KREMER JM, BLANCO R, BRZOSKO M *et al*.: Tocilizumab inhibits structural joint damage in rheumatoid arthritis patients with inadequate responses to methotrexate: results from the double-blind treatment phase of a randomized placebo-controlled trial of tocilizumab safety and prevention of structural joint damage at one year. *Arthritis Rheum* 2011; 63: 609-21.
30. STRAND V, BURMESTER GR, OGALE S, DEVENPORT J, JOHN A, EMERY P: Improvements in health-related quality of life after treatment with tocilizumab in patients with rheumatoid arthritis refractory to tumour necrosis factor inhibitors: results from the 24-week randomized controlled RADIATE study. *Rheumatology* (Oxford) 2012; 51: 1860-9.
31. MAINI RN, TAYLOR PC, SZECHINSKI J *et al*.: Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; 54: 2817-29.
32. YOKOTA S, IMAGAWA T, MORI M *et al*.: Efficacy and safety of tocilizumab in patients with systemic-onset juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled, withdrawal phase III trial. *Lancet* 2008; 371: 998-1006.
33. WOO P, WILKINSON N, PRIEUR AM *et al*.: Open label phase II trial of single, ascending doses of MRA in Caucasian children with severe systemic juvenile idiopathic arthritis: proof of principle of the efficacy of IL-6 re-

ceptor blockade in this type of arthritis and demonstration of prolonged clinical improvement. *Arthritis Res Ther* 2005; 7: R1281-8.

34. RINGOLD S, WEISS PF, BEUKELMAN T *et al*.: 2013 update of the 2011 American College of Rheumatology recommendations for the treatment of juvenile idiopathic arthritis: recommendations for the medical therapy of children with systemic juvenile idiopathic arthritis and tuberculosis screening among children receiving biologic medications. *Arthritis Rheum* 2013; 65: 2499-512.
35. DEWITT EM, KIMURA Y, BEUKELMAN T *et al*.: Consensus treatment plans for new-onset systemic juvenile idiopathic arthritis. *Arthritis Care Res* 2012; 64: 1001-10.
36. DE BENEDETTI F, BRUNNER HI, RUPERTO N *et al*.: Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *New Engl J Med* 2012; 367: 2385-95.
37. VAN GESTEL AM, PREVOO ML, VAN 'T HOF MA, VAN RIJSWIJK MH, VAN DE PUTTE LB, VAN RIEL PL: Development and validation of the European League Against Rheumatism response criteria for rheumatoid arthritis. Comparison with the preliminary American College of Rheumatology and the World Health Organization/International League Against Rheumatism Criteria. *Arthritis Rheum* 1996; 39: 34-40.