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EXTENDED REPORT

Efficacy and safety of tocilizumab in patients with polyarticular-course juvenile idiopathic arthritis: results from a phase 3, randomised, double-blind withdrawal trial

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ABSTRACT

Objective To evaluate the interleukin-6 receptor inhibitor tocilizumab for the treatment of patients with polyarticular-course juvenile idiopathic arthritis (pcJIA).

Methods This three-part, randomised, placebo-controlled, double-blind withdrawal study (NCT00988221) included patients who had active pcJIA for ≥ 6 months and inadequate responses to methotrexate. During part 1, patients received open-label tocilizumab every 4 weeks (8 or 10 mg/kg for body weight (BW) < 30 kg; 8 mg/kg for BW ≥ 30 kg). At week 16, patients with \geq JIA-American College of Rheumatology (ACR) 30 improvement entered the 24-week, double-blind part 2 after randomisation 1:1 to placebo or tocilizumab (stratified by methotrexate and steroid background therapy) for evaluation of the primary end point: JIA flare, compared with week 16. Patients flaring or completing part 2 received open-label tocilizumab.

Results In part 1, 188 patients received tocilizumab (< 30 kg: 10 mg/kg (n=35) or 8 mg/kg (n=34); ≥ 30 kg: n=119). In part 2, 163 patients received tocilizumab (n=82) or placebo (n=81). JIA flare occurred in 48.1% of patients on placebo versus 25.6% continuing tocilizumab (difference in means adjusted for stratification: -0.21 ; 95% CI -0.35 to -0.08 ; p=0.0024). At the end of part 2, 64.6% and 45.1% of patients receiving tocilizumab had JIA-ACR70 and JIA-ACR90 responses, respectively. Rates/100 patient-years (PY) of adverse events (AEs) and serious AEs (SAEs) were 480 and 12.5, respectively; infections were the most common SAE (4.9/100 PY).

Conclusions Tocilizumab treatment results in significant improvement, maintained over time, of pcJIA signs and symptoms and has a safety profile consistent with that for adults with rheumatoid arthritis.

Trial registration number: NCT00988221.

INTRODUCTION

Juvenile idiopathic arthritis (JIA) is a heterogeneous group of chronic arthritides of unknown cause with an onset before 16 years of patient age.¹ A substantial proportion of patients have polyarticular-course JIA (pcJIA) and are at risk for profound disability.^{2–3} Although these patients may respond to methotrexate (MTX) or biological agents approved for pcJIA, up to 30% continue to have active disease.^{4–5}

Interleukin-6 (IL-6) is increased in the serum and synovial fluid of patients with pcJIA; IL-6 concentrations are positively correlated with the severity of joint involvement and with C-reactive protein (CRP) levels.⁶ Tocilizumab is a humanised, monoclonal, antihuman IL-6 receptor (IL-6R) antibody that binds to membrane and soluble IL-6R, inhibiting IL-6-mediated signalling.^{7–8} Clinical trials have shown that tocilizumab is efficacious in the treatment of patients with rheumatoid arthritis (RA) and systemic JIA (sJIA).^{9–10}

The aim of this study was to evaluate the efficacy and safety of tocilizumab in patients with active pcJIA and inadequate responses to MTX.

METHODS**Study design**

This three-part study, CHERISH, was conducted by members of the Paediatric Rheumatology International Trials Organisation (PRINTO)¹¹ and the Pediatric Rheumatology Collaborative Study Group (PRCSG) at 58 centres in Australia, Canada, Europe, Latin America, Russia and the USA.

Part 1 was a 16-week, active-treatment, open-label, lead-in period in which patients whose body weight (BW) was 30 kg or more received intravenous tocilizumab 8 mg/kg (8 mg/kg for 30 kg or more group) every 4 weeks. Patients weighing less

than 30 kg were randomly assigned 1:1 to receive intravenous tocilizumab at 8 mg/kg (8 mg/kg for less than 30 kg group) or 10 mg/kg (10 mg/kg for less than 30 kg group) every 4 weeks. Based on pharmacokinetic modelling and simulation, doses of 10 mg/kg for patients weighing less than 30 kg achieved tocilizumab exposure comparable to that of 8 mg/kg for patients weighing 30 kg or more.

At week 16, patients entered the double-blind withdrawal period (part 2) provided they had experienced at least a JIA-American College of Rheumatology (ACR) 30 response (JIA-ACR30), defined as 30% or greater improvement of three or more of the six JIA core response variables (JIA-CRVs) without greater than 30% worsening in more than one of the remaining JIA-CRVs compared with baseline¹² (see 'Assessment and outcomes'). Patients who did not achieve JIA-ACR30 response in part 1 were withdrawn from the study.

In part 2, JIA-ACR30 responders were randomly assigned 1:1 to receive placebo or to continue tocilizumab as in part 1, stratified by MTX and glucocorticoid use. Patients continued in part 2 until week 40, unless they experienced JIA-flare (30% or greater worsening in three of the six JIA-CRVs without more than 30% improvement in more than one remaining JIA-CRV) compared with week 16.¹³ On completion of part 2 or after JIA-flare, patients entered part 3 of the study (64 weeks) and received open-label tocilizumab at the same dose received in part 1. Throughout, patients continued treatment until withdrawal of informed consent, loss of follow-up or study end.

Here, we report efficacy results to week 40 (end of part 2) and safety results to the last data cut (184.4 patient-years (PY) of tocilizumab exposure). The study was conducted in accordance with the Declaration of Helsinki and good clinical practice guidelines and with local requirements. Enrolment started 14 October 2009 and ended 31 January 2011. The study was reported following recommendations of the CONSORT statement.¹⁴

Patients

Eligible patients were 2 to 17 years old, received diagnoses of rheumatoid factor-positive or rheumatoid factor-negative pcJIA or extended oligoarticular JIA,¹⁵ had disease durations of at least 6 months and had inadequate responses to or were intolerant of MTX. Patients also had to have five or more active joints, defined as the presence of swollen joints (or, in the absence of swelling, joints with limitation of movement (LOM) plus pain on motion and/or tenderness with palpation), with LOM present in at least three of the active joints. Patients could have been previously treated with biological agents. Stable doses of non-steroidal anti-inflammatory drugs, low-dose glucocorticoids (no greater than 0.2 mg/kg/day prednisone; daily maximum, 10 mg) and MTX (10–20 mg/m² body surface area/week) were allowed. Additional eligibility criteria are listed in online supplementary appendix S1.

Assessment and outcomes

Clinical assessments (baseline, week 2, week 4 and every 4 weeks thereafter) included the six JIA-CRVs: number of joints with active arthritis, number of joints with LOM, physician global assessment (PGA) of disease activity (range, 0–100; 0=inactive disease), assessment of patient overall well-being (range, 0–100; 0=very poor), physical function measured by the Childhood Health Assessment Questionnaire-Disability Index (CHAQ-DI; range, 0–3; 0=no disability) and erythrocyte sedimentation rate (ESR).¹⁶ Clinically inactive disease was defined as PGA, indicating no disease activity plus absence of all

the following: joints with active arthritis, uveitis and ESR greater than 20 mm/h.¹⁷

The primary efficacy end point was the proportion of patients in whom a JIA-flare occurred¹³ during part 2 (up to and including week 40) compared with week 16. Secondary end points evaluated at week 40 included JIA-ACR30/50/70/90 responses,¹⁶ change from baseline in JIA-CRVs and clinically inactive disease.¹⁷

Statistical analysis

Sample size estimation assumed JIA-flare rates of 35% for the tocilizumab groups and 65% for the placebo group in part 2. Thus, 60 patients had to be randomly assigned to each group in part 2 to achieve more than 80% power to detect a significant difference in JIA-flare rates between groups using a two-sided significance test with $\alpha=0.05$. Based on an expected JIA-ACR30 response rate of 65% in the tocilizumab group in part 1, recruitment of 185 patients into part 1 was planned to ensure that a sufficient number of patients were available for randomisation in part 2. To control for the type 1 error rate, secondary end points were tested in a hierarchical fixed-sequence approach provided the primary end point was found to be statistically significant (see online supplementary table S1).

Primary end point analysis was conducted with the Cochran–Mantel–Haenszel (CMH) test, adjusted for stratification factors (background use of MTX and oral glucocorticoids); patients who withdrew or for whom the end point could not be determined were considered to have experienced JIA-flare. For secondary end points, the CMH test was used to determine statistical significance for differences in JIA-ACR30/50/70/90 responders at week 40 compared with baseline; patients who escaped or withdrew or for whom the end point could not be determined were considered non-responders. Continuous variables were evaluated using analysis of variance, adjusted for baseline differences between groups and stratification variables. A last-observation-carried-forward approach was used for patients who withdrew or experienced flare and who escaped to open-label tocilizumab.

Ad hoc analysis was conducted in patients continuously treated with tocilizumab up to week 40, including those who escaped from blinded to open-label tocilizumab, using an intent-to-treat (ITT) approach. Evaluations of JIA-flare (primary outcome), JIA-ACR response rates and clinically inactive disease status were performed in real time by independent masked evaluators at the coordinating centres of PRINTO and PRCSG, according to validated criteria.^{2 13 16 17}

The safety population consisted of all patients who received at least one dose of study medication. Safety data included full-exposure data for each patient. Exposure to tocilizumab varied for individual patients, depending on the period from the first dose of tocilizumab to the date of data cut or withdrawal (maximum exposure, 1.8 years). Serious infections were defined in accordance with the definition of serious adverse events (SAEs) in the International Conference on Harmonisation guidelines.¹⁸ The trial is registered with ClinicalTrials.gov, number NCT00988221.

RESULTS

Patient demographics and disposition

In part 1, 188 patients were enrolled and received at least one dose of tocilizumab (figure 1). Disease characteristics at baseline were generally similar across the three groups, with exceptions as expected according to the body weight-based dosing regimen (table 1).

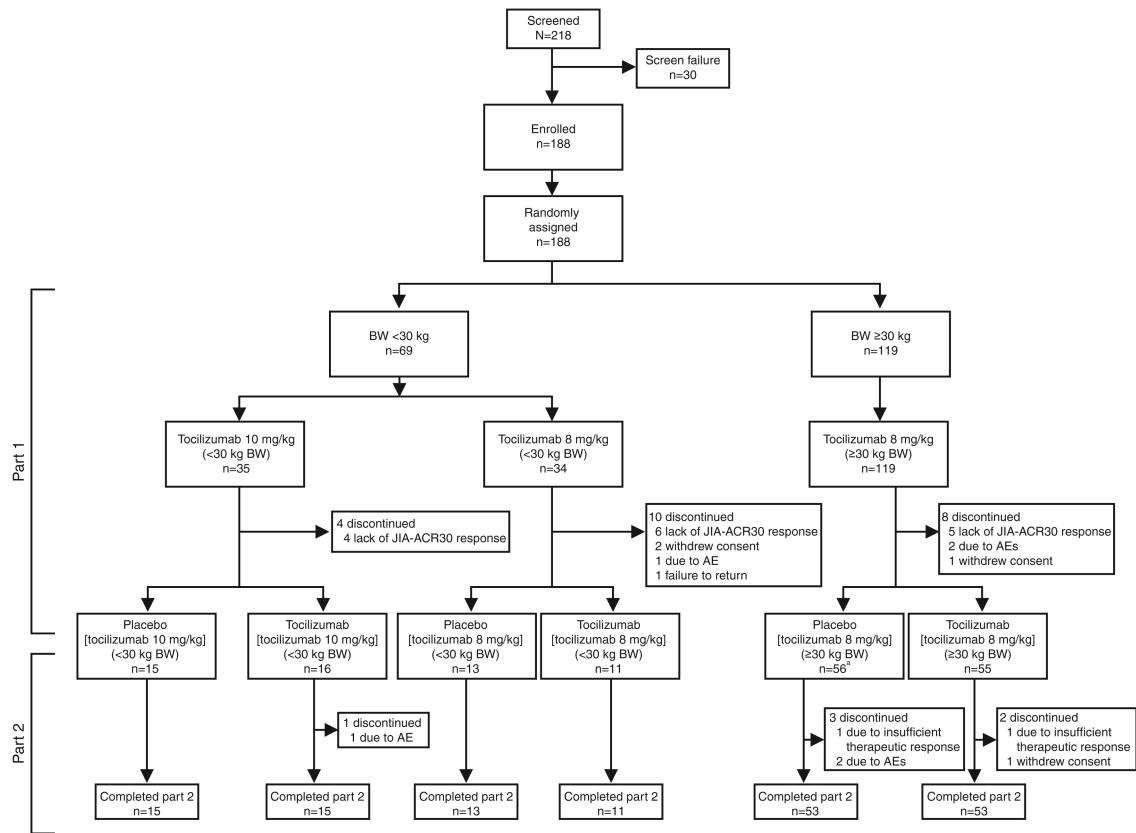


Figure 1 Summary of patient disposition. Part 1 treatment is indicated in parentheses. ^aThree patients were not included in the ITT population for part 2 because they discontinued before receiving a single dose of study drug. AE, adverse event; BW, body weight; JIA-ACR, juvenile idiopathic arthritis-American College of Rheumatology; ITT, intent-to-treat.

Table 1 Demographic and disease characteristics at baseline

	Tocilizumab 8 mg/kg <30 kg n=34	Tocilizumab 10 mg/kg <30 kg n=35	Tocilizumab 8 mg/kg ≥30 kg n=119	All Tocilizumab N=188*
Age (years)	7.6 (2.71)	6.9 (3.02)	13.1 (2.78)	11.0 (4.01)
Females, n (%)	24 (71)	30 (86)	90 (76)	144 (77)
Weight (kg)	22.4 (5.3)	20.7 (5.7)	50.0 (12.6)	39.6 (17.3)
Disease duration (years)	3.5 (2.57)	3.4 (2.39)	4.7 (4.16)	4.2 (3.67)
Rheumatoid factor positive, n (%)	2 (6)	4 (11)	48 (40)	54 (29)
Previous DMARD use, n (%)	26 (76)	21 (60)	87 (73)	134 (71)
Previous biological agent use, n (%) [†]	6 (18)	8 (23)	47 (39)	61 (32)
Joints with active arthritis, n	21.2 (13.6)	23.9 (18.3)	18.9 (13.0)	20.3 (14.3)
Joints with LOM, n	17.3 (13.3)	23.1 (19.2)	16.0 (12.7)	17.6 (14.4)
Assessment of patient overall well-being VAS	59.1 (26.2)	51.5 (26.9)	51.6 (24.1)	52.9 (25.0)
Physician global assessment of JIA activity VAS	64.7 (18.5)	64.7 (20.5)	59.4 (21.3)	61.4 (20.7)
CRP (mg/L) [‡]	26.6 (33.6)	21.8 (32.3)	22.8 (38.8)	23.3 (36.6)
CHAQ-DI score	1.8 (0.68)	1.7 (0.71)	1.2 (0.69)	1.4 (0.74)
ESR (mm/h) [§]	36.6 (23.0)	35.1 (24.1)	34.2 (26.7)	34.8 (25.5)
Concurrent MTX use, n (%)	30 (88)	29 (83)	89 (75)	148 (79)
Dose (mg/m ² /week)	13.8 (2.9)	16.5 (11.1)	11.6 (2.7)	13.0 (5.7)
Concurrent glucocorticoid use, n (%) [¶]	18 (53)	15 (43)	54 (45)	87 (46)
Dose (mg/kg/day) [¶]	0.15 (0.038)	0.15 (0.033)	0.12 (0.052)	0.13 (0.048)

Values are mean (SD) unless stated otherwise.

*Included are all patients randomly assigned to receive tocilizumab 10 mg/kg (patients weighing <30 kg), tocilizumab 8 mg/kg (patients weighing <30 kg) or tocilizumab 8 mg/kg (patients weighing ≥30 kg) in part 1.

[†]Nine per cent of patients previously received three or more biological agents. TNF inhibitors were administered to 56 patients, anakinra to 5 patients, abatacept to 5 patients and canakinumab to 1 patient.

[‡]Standard reference range was 0–10 mg/L.

[§]Standard reference range was 0–18 mm/h.

[¶]These were measured in prednisone equivalents.

CHAQ-DI, Childhood Health Assessment Questionnaire-Disability Index; CRP, C-reactive protein; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; JIA, juvenile idiopathic arthritis; LOM, limitation of movement; MTX, methotrexate; TNF, tumour necrosis factor; VAS, visual analogue scale (range, 0–100 mm).

In part 1, 15 (7.9%) of 188 patients did not achieve JIA-ACR30 response and were discontinued from the study (figure 1). Additional withdrawals in part 1 occurred because of AEs (three patients), refusal of treatment (three patients) and loss of follow-up (one patient). Of the remaining 166 patients who entered part 2, 6 were discontinued (AEs, 3 patients; insufficient therapeutic response, 2 patients; withdrawal of consent, 1 patient). Because 3 of the 166 patients entering part 2 discontinued the study before receiving a single dose of study drug, the ITT population for part 2 was 163 patients—81 randomly assigned to placebo and 82 to continued tocilizumab.

Efficacy in the open-label phase (part 1)

Part 1 was completed by 168 (89.4%) of 188 patients achieving JIA-ACR30 response (figure 2A). Higher-level JIA-ACR70 and JIA-ACR90 responses were attained by 117 (62.2%) of 188 and 49 (26.1%) of 188 patients, respectively. All six JIA-CRVs markedly improved from baseline to week 16 (figure 2B).

JIA-ACR30/50/70/90 response rates were numerically lower in the 8 mg/kg less than 30 kg group than in the other two groups (figure 2C). Consistently, tocilizumab concentrations over time and steady-state exposures were numerically lower in the 8 mg/kg less than 30 kg group than in the other two groups (see online supplementary table S2, supplementary figure S1A).

Changes in soluble IL-6R levels and inflammation markers (CRP, ESR) were also more similar between 10 mg/kg for the less than 30 kg group and 8 mg/kg for the 30 kg or more group (see online supplementary figure S1B–D).

Efficacy in the double-blind, withdrawal phase (part 2)

The primary end point at week 40 was met; there were significantly more JIA-flares in the placebo group than in patients remaining on tocilizumab (39/81 (48.1%) vs 21/82 (25.6%); adjusted difference in flare rate: -0.21 ; 95% CI -0.35 to -0.08 ; $p=0.0024$). JIA-flares were evident in the placebo group as early as 28 days after randomisation in part 2 (figure 2D). Robustness of the primary end point result was confirmed by logistic regression analysis (see online supplementary appendix S2).

In the placebo and the tocilizumab groups, JIA-ACR70 and JIA-ACR90 response rates were numerically higher in patients receiving MTX than in those not receiving MTX; rates were numerically lower in patients who previously received other biological agents than in biological-naïve patients (table 2). No differences were observed in response to tocilizumab between patients who were rheumatoid factor-positive and those who were not (data not shown).

Ad hoc analysis of patients who received tocilizumab continuously in parts 1 and 2, including those who escaped in part 2,

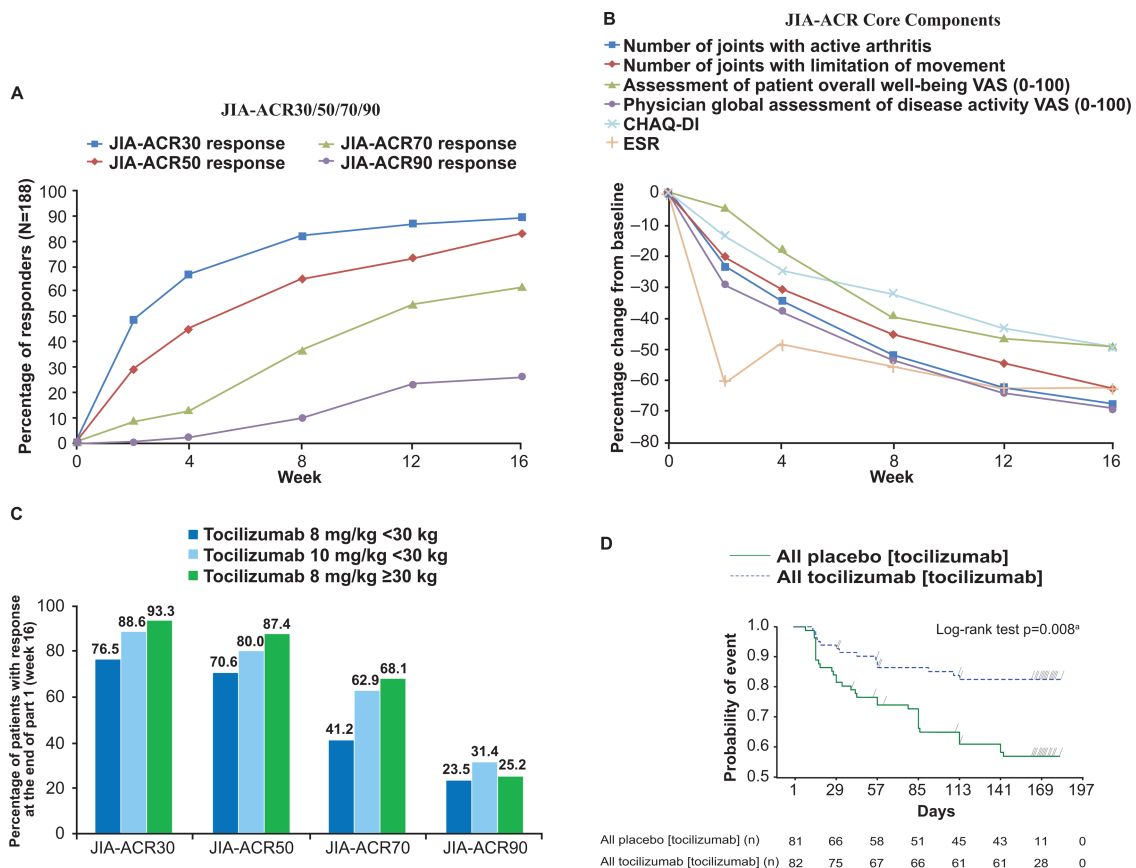


Figure 2 (A) JIA-ACR30/50/70/90 response rates by visit in part 1. (B) Line plot of JIA-ACR core components by week in part 1. (C) JIA-ACR30/50/70/90 improvement by treatment group at the end of part 1 at week 16. (D) Time to JIA-ACR30 flare after randomisation in the withdrawal phase (part 2); part 1 treatment is indicated in parentheses. For JIA-ACR responses (A, C), $n=188$. For JIA-ACR core components (B), $n=182$ – 187 for number of joints with active arthritis and number of joints with limitation of movement; $n=178$ – 184 for assessment of patient overall well-being; $n=181$ – 187 for physician global assessment of disease activity; $n=182$ – 184 for CHAQ-DI; and $n=182$ – 188 for ESR. For time to JIA-ACR30 flare (D), n =number of patients remaining in the study at each time point. ^aLog-rank test adjusted for stratification factors applied at randomisation in part 1 was a predefined, exploratory analysis. HR, 0.36; 95% CI 0.19 to 0.67. CHAQ-DI, Childhood Health Assessment Questionnaire-Disability Index; ESR, erythrocyte sedimentation rate; JIA-ACR, juvenile idiopathic arthritis-American College of Rheumatology; VAS, visual analogue scale.

Table 2 Proportion of patients in the ITT population with JIA-ACR70 and JIA-ACR90 response at week 40 by background methotrexate use, background glucocorticoid use and previous biological agent use at baseline*

Concomitant therapies and previous exposure to biological agent	Response level	Placebo n=81†		Tocilizumab n=82†	
		Yes	No	Yes	No
Background methotrexate	JIA-ACR70	30/64 (46.9)	4/17 (23.5)	45/67 (67.2)	8/15 (53.3)
	JIA-ACR90	18/64 (28.1)	1/17 (5.9)	32/67 (47.8)	5/15 (33.3)
Background glucocorticoid	JIA-ACR70	14/38 (36.8)	20/43 (46.5)	23/33 (69.7)	30/49 (61.2)
	JIA-ACR90	5/38 (13.2)	14/43 (32.6)	16/33 (48.5)	21/49 (42.9)
Previous biological agent	JIA-ACR70	2/23 (8.7)	32/58 (55.2)	13/27 (48.1)	40/55 (72.7)
	JIA-ACR90	2/23 (8.7)	17/58 (29.3)	5/27 (18.5)	32/55 (58.2)

*Patients who withdrew or escaped to open-label tocilizumab or for whom the end point could not be determined were classified as non-responders.

†Values are n of N (% of N).

ITT, intent-to-treat; JIA-ACR, juvenile idiopathic arthritis-American College of Rheumatology based on percentage changes of the JIA-CRVs.

demonstrated JIA-ACR70 and JIA-ACR90 response rates of 78.0% (64/82) and 48.8% (40/82), respectively, at week 40 compared with baseline, with improvement from baseline in all individual JIA-CRVs (table 3).

Safety

AEs and SAEs are shown in table 4 for the safety population (n=188) at the time of data cut. Overall, 159 (84.6%) patients reported at least one AE. Rates of AEs/100 PY of exposure were similar across the three groups (8 mg/kg for 30 kg or more, 501.9; 10 mg/kg for less than 30 kg, 445.6; 8 mg/kg for less than 30 kg, 471.9). A total of 16 AEs in 16 (8.5%) patients were considered severe, and seven AEs led to study discontinuation. Common AEs were pneumonia, reported in four (2.1%) patients (three in the 8 mg/kg for 30 kg or more group, one in the 10 mg/kg for less than 30 kg group), followed by bronchitis in two (1.1%) patients (both in the 10 mg/kg for less than 30 kg group) and cellulitis in two (1.1%) patients (both in the 8 mg/kg for 30 kg or more group).

No deaths were reported during the study, and no malignancies were identified. In the safety population, 17 (9.0%) patients reported 22 SAEs, with a rate of 12.5/100 PY. Also, 5 of the 22 SAEs (benign intracranial hypertension, uveitis, urinary calculus, pneumonia, cellulitis) in 5 (2.7%) patients were considered by the investigator to be related to tocilizumab.

Laboratory abnormalities included alanine aminotransferase elevations 3 × upper limit of normal (ULN) or greater in seven (3.7%) patients, aspartate aminotransferase elevations 3 × ULN or greater in one (0.5%) patient, neutropenia (less than 1000

cells/mm³) in seven (3.7%) patients and thrombocytopenia (less than 50 000 cells/mm³) in two (1%) patients. These haematological abnormalities were not associated with infection or bleeding events. Low-density lipoprotein (LDL)-cholesterol levels 110 mg/dL or greater were observed in 21 (11.4%) patients, whereas total cholesterol levels 170 mg/dL or greater occurred in 64 (34.6%) of 185 patients assessed for cholesterol. No patients were treated with lipid-lowering agents. One patient had a positive antitocilizumab antibody assay result, without anaphylactic reaction, and discontinued during part 1 for lack of efficacy.

DISCUSSION

Results of this study demonstrate that intravenous tocilizumab 10 mg/kg administered every 4 weeks in patients weighing less than 30 kg and intravenous tocilizumab 8 mg/kg administered every 4 weeks in patients weighing 30 kg or more are safe and efficacious for the management of pcJIA. Results were clinically meaningful because a high proportion (89%) of patients achieved JIA-ACR30 response by week 16; 62% of patients achieved JIA-ACR70 response, and 26% even achieved JIA-ACR90 response.

The primary end point at week 40 was met: significantly more placebo-treated than tocilizumab-treated patients experienced JIA-flare during the double-blind, 24-week withdrawal phase. Patients who received tocilizumab for 40 weeks experienced marked improvement in all JIA-CRVs from baseline.

At the end of part 1, JIA-ACR response rates in patients weighing less than 30 kg who received tocilizumab 10 mg/kg

Table 3 Improvement of all JIA-ACR core components at the end of part 2 (week 40) for the ITT population receiving tocilizumab in parts 1 and 2 (n=82)* compared with baseline

JIA-ACR core response variables†	Baseline	Week 40	Week 40 (change from baseline)‡
Joints with active arthritis (range, 0–71)	19.7 (13.95)	3.2 (8.06)	–14.5 (11.14)
Joints with a limitation of movement (range, 0–67)	16.5 (13.81)	3.9 (6.95)	–10.2 (8.97)
Assessment of patient overall well-being, VAS (range, 0–100)	45.5 (23.11)	8.8 (16.12)	–31.1 (28.52)
Physician global assessment of disease activity, VAS (range, 0–100)	57.8 (20.30)	6.2 (7.75)	–45.6 (21.47)
CHAQ-DI (range, 0–3)	1.216 (0.67)	0.333 (0.47)	–0.804 (0.65)
ESR (mm/h)	31.7 (22.88)	5.4 (6.08)	–25.2 (21.97)

*Ad hoc analysis.

†Values are mean (SD).

‡Change from baseline was calculated using last-observation-carried-forward imputation for missing values; in other columns, missing values were not imputed.

CHAQ-DI, Childhood Health Assessment Questionnaire-Disability Index; ESR, erythrocyte sedimentation rate; ITT, intent-to-treat; JIA-ACR, juvenile idiopathic arthritis-American College of Rheumatology; ULN, upper limit of normal; VAS, visual analogue scale (0–100 mm).

Table 4 Serious adverse events and adverse events occurring in at least 5% of the patients by treatment group for events

Adverse events*	Part 1†	Part 2‡		All-exposure safety group§ N=188
	Tocilizumab N=188	All tocilizumab n=82	All placebo‡ n=81	
Duration in study (years)	59.92	32.33	27.41	184.4
Patients with at least one AE	124 (66.0)	58 (70.7)	60 (74.1)	159 (84.6)
Total number of AEs¶	365	147	141	885
Rate of AEs per 100 PY**	609.2	454.7	514.4	479.8
Most frequently reported (>5%) AEs				
Nasopharyngitis	23 (12.2)	14 (17.1)	9 (11.1)	39 (20.7)
Headache	15 (8.0)	3 (3.7)	–	26 (13.8)
Upper respiratory infection	13 (6.9)	4 (4.9)	2 (2.5)	19 (10.1)
Cough	7 (3.7)	2 (2.4)	1 (1.2)	18 (9.6)
Pharyngitis	8 (4.3)	3 (3.7)	3 (3.7)	17 (9.0)
Nausea	12 (6.4)	2 (2.4)	2 (2.5)	16 (8.5)
Diarrhoea	7 (3.7)	2 (2.4)	3 (3.7)	14 (7.4)
Rhinitis	7 (3.7)	2 (2.4)	1 (1.2)	14 (7.4)
Vomiting	4 (2.1)	3 (3.7)	1 (1.2)	14 (7.4)
Abdominal pain	5 (2.7)	2 (2.4)	2 (2.5)	13 (6.9)
Oropharyngeal pain	8 (4.3)	1 (1.2)	5 (6.2)	13 (6.9)
Rash	3 (1.6)	4 (4.9)	1 (1.2)	10 (5.3)
SAEs				
Patients with at least one SAE	7 (3.7)	3 (3.7)	3 (3.7)	17 (9.0)
Rate of SAEs per 100 PY	13.4	9.3	10.9	12.5
Patients with at least one infectious SAE	4 (2.1)	1 (1.2)	–	9 (4.8)
Rates of infectious SAEs per 100 PY	6.7	3.1	–	4.9
SAEs by preferred term				
Pneumonia	1 (0.5)	1 (1.2)	–	4 (2.1)
Bronchitis	2 (1.1)	–	–	2 (1.1)
Cellulitis	1 (0.5)	–	–	2 (1.1)
Varicella	–	–	–	1 (0.5)
Neck injury	–	–	–	1 (0.5)
Synovial rupture	–	–	–	1 (0.5)
Upper limb fracture	–	1 (1.2)	–	1 (0.5)
Sclerosing cholangitis	1 (0.5)	–	–	1 (0.5)
Hypertransaminasemia	1 (0.5)	–	–	1 (0.5)
Back pain	–	–	–	1 (0.5)
Osteoporosis	–	–	–	1 (0.5)
Familial Mediterranean fever††	–	–	–	1 (0.5)
Uveitis	–	–	1 (1.2)	1 (0.5)
Constipation	1 (0.5)	–	–	1 (0.5)
Benign intracranial hypertension	1 (0.5)	–	–	1 (0.5)
Psychosomatic disease	–	1 (1.2)	–	1 (0.5)
Urinary calculus	–	–	–	1 (0.5)
Enterocolitis	–	–	1 (1.2)	–
Complicated migraine	–	–	1 (1.2)	–
AEs leading to study drug discontinuation				
Increased blood bilirubin level‡‡	–	1 (1.2)	–	1 (0.5)
Serum sickness-like reaction§§	1 (0.5)	–	–	1 (0.5)
Gastroenteritis	–	–	1 (1.2)	1 (0.5)***
Pneumonia	1 (0.5)	–	–	1 (0.5)
Sclerosing cholangitis¶¶	1 (0.5)	–	–	1 (0.5)
Benign intracranial hypertension	1 (0.5)	–	–	1 (0.5)

Values are n (%) unless stated otherwise.

*Multiple occurrences of the same AE in one individual were counted only once, except where noted.

†Sixteen-week, open-label, lead-in part 1 with all patients receiving tocilizumab.

‡Both groups received tocilizumab open-label during part 1 before entering part 2 (24-week withdrawal phase). AE data on open-label tocilizumab escape therapy were excluded.

§Summarises all AEs except those that occurred in a patient once on placebo and includes data after week 40 because safety was based on the data cut.

¶Multiple occurrences of the same AE in one individual were counted.

**Patient-year.

††Recurrence in patient with pJIA, with flare of familial Mediterranean fever.

‡‡Highest total bilirubin reading, 50 µmol/L (normal range, 3–24 µmol/L); two consecutive readings >51 mmol/L mandated withdrawal per protocol. The event resolved without sequelae.

§§Patient with serum sickness-like reaction and subcutaneous swelling on dorsum of hand, forearm and foot; the patient was discontinued from the study.

¶¶The patient had transaminitis on study entry: 139 U/L aspartate aminotransferase, 147 U/L alanine aminotransferase; highest readings: 287 U/L aspartate aminotransferase, 289 U/L alanine aminotransferase. Liver biopsy was performed on study day 134; results were compatible with sclerosing cholangitis. The event was unresolved and considered unrelated to study medication.

***Occurred 46 days after the last of five doses of placebo.

AE, adverse event; JIA, juvenile idiopathic arthritis; PY, patient-years; SAE, serious adverse event.

were similar to those in patients weighing 30 kg or more who received tocilizumab 8 mg/kg, whereas rates were lower in patients weighing less than 30 kg who received tocilizumab 8 mg/kg. This is consistent with the 8 mg/kg dose resulting in a lower tocilizumab exposure in patients weighing less than 30 kg. Higher body weight-adjusted dosing in lighter patients with pcJIA is consistent with the kind of dosing required to achieve comparable tocilizumab exposures and JIA-ACR response rates between lighter and heavier patients with pcJIA.¹⁰

Notably, the results reported here reflect the efficacy of tocilizumab when 24 (14.7%) of 163 patients received suboptimal doses of tocilizumab (ie, patients weighing less than 30 kg who received the 8 mg/kg dose). The absolute difference in flare rates among groups observed in this study may be influenced by longevity of the drug response and duration of the withdrawal phase.

Biological agent-naïve patients experienced a lower incidence of flare regardless of assignment to tocilizumab or placebo. This observation is in keeping with reports from clinical trials of other biological agents in pcJIA⁵ and is consistent with the notion that patients who received previous biological therapy represent a more treatment-resistant subgroup.¹⁹ Nevertheless, JIA-ACR70 response was observed in 48.1% of tocilizumab-treated patients whose previous treatment with a biological agent failed.

Similarly, concomitant MTX yielded fewer flare events, regardless of assignment to tocilizumab or placebo. Statistical testing was not planned to assess the significance of the impact of MTX on efficacy outcomes. However, even without background MTX, 53.3% of the patients receiving tocilizumab achieved JIA-ACR70 response by week 40.

The pattern of AEs observed in this study of patients with pcJIA is consistent with the known safety profile of tocilizumab reported in other phase 3 studies.²⁰ The frequency of neutropenia (3.7%) was similar to that reported in adults with RA (4.7%)²⁰ but lower than that reported in children with sJIA (16.9%) who receive tocilizumab in 2-weekly intervals.¹⁰ Similarly, the rate of serious infections (4.9/100 PY) was lower than that reported for children with sJIA (11.0/100 PY)¹⁰ but similar to that reported for adults with RA (4.7/100 PY).

Hypercholesterolemia occurred in adults with RA²⁰ and in children with sJIA. Levels of cholesterol exceeding the ULN for total-cholesterol or LDL-cholesterol were observed at least once in 31% of the patients who received tocilizumab.¹⁰ Total-cholesterol levels above 170 mg/dL occurred in 34.6% of children in this study with pcJIA, whereas 11.4% had LDL-cholesterol levels of 110 mg/dL or greater. Total-cholesterol and LDL-cholesterol exceeding such levels have been considered marginally elevated in children.²¹ The clinical relevance of isolated elevations in cholesterol level, as observed in this study, is unclear because of diurnal variations in lipid levels and because of differences in normative values based on age and sex.²² Of note, lipid elevations in adults with RA treated with tocilizumab do not appear to convey increased risks for cardiovascular disorders or events with appropriate management.⁹

This study allowed for the acquisition of data on the magnitude of the therapeutic effect of tocilizumab in patients with active pcJIA (part 1) and for the demonstration that this effect was indeed due to tocilizumab (part 2). Although the withdrawal design of this study was valuable in minimising placebo treatment in children with pcJIA, it had potential limitations. Patients who did not achieve JIA-ACR30 responses in the open-label, lead-in phase on tocilizumab were withdrawn, limiting information about dose responsiveness. Lead-in treatment of

placebo patients with tocilizumab limited the ability to determine safety and efficacy differences over the limited withdrawal period, especially because the biological effects of tocilizumab might have endured beyond the time taken to clear the drug.

Conclusions

Tocilizumab treatment provided sustained and clinically meaningful improvement for patients with pcJIA on monthly dosing of 8 mg/kg in patients weighing 30 kg or more and 10 mg/kg in patients weighing less than 30 kg. The safety profile of tocilizumab in this patient population was consistent with that seen in adults with RA.

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REFERENCES

- 1 Prakkien B, Albani S, Martini A. Juvenile idiopathic arthritis. *Lancet* 2011;377:2138–49.
- 2 Ruperto N, Giannini EH, Pistorio A, *et al.* Is it time to move to active comparator trials in juvenile idiopathic arthritis? a review of current study designs. *Arthritis Rheum* 2010;62:3131–9.
- 3 Ravelli A, Martini A. Juvenile idiopathic arthritis. *Lancet* 2007;369:767–78.
- 4 Lovell DJ. Update on treatment of arthritis in children: new treatments, new goals. *Bull NYU Hosp Jt Dis* 2006;64:72–6.
- 5 Otten MH, Prince FH, Anink J, *et al.* Effectiveness and safety of a second and third biological agent after failing etanercept in juvenile idiopathic arthritis: results from the Dutch National ABC Register. *Ann Rheum Dis* 2013;72:721–7.
- 6 De Benedetti F, Robbioni P, Massa M, *et al.* Serum interleukin-6 levels and joint involvement in polyarticular and pauciarticular juvenile chronic arthritis. *Clin Exp Rheumatol* 1992;10:493–8.
- 7 Mihara M, Kasutani K, Okazaki M, *et al.* Tocilizumab inhibits signal transduction mediated by both mIL-6R and sIL-6R, but not by the receptors of other members of IL-6 cytokine family. *Int Immunopharmacol* 2005;5:1731–40.
- 8 Nishimoto N, Kishimoto T. Humanized antihuman IL-6 receptor antibody, tocilizumab. *Handb Exp Pharmacol* 2008;181:151–60.
- 9 Navarro-Millan I, Singh JA, Curtis JR. Systematic review of tocilizumab for rheumatoid arthritis: a new biologic agent targeting the interleukin-6 receptor. *Clin Ther* 2012;34:788–802.e3.
- 10 De Benedetti F, Brunner HI, Ruperto N, *et al.* Randomized trial of tocilizumab in systemic juvenile idiopathic arthritis. *N Engl J Med* 2012;367:2385–95.
- 11 Ruperto N, Martini A. Networking in paediatrics: the example of the Paediatric Rheumatology International Trials Organisation (PRINTO). *Arch Dis Child* 2011;96:596–601.
- 12 Lovell DJ, Giannini EH, Reiff A, *et al.* Etanercept in children with polyarticular juvenile rheumatoid arthritis: Pediatric Rheumatology Collaborative Study Group. *N Engl J Med* 2000;342:763–9.
- 13 Brunner HI, Lovell DJ, Finck BK, *et al.* Preliminary definition of disease flare in juvenile rheumatoid arthritis. *J Rheumatol* 2002;29:1058–64.
- 14 Schulz KF, Altman DG, Moher D. CONSORT 2010 statement: updated guidelines for reporting parallel group randomised trials. *BMJ* 2010;340:c332.
- 15 Petty RE, Southwood TR, Manners P, *et al.* International League of Associations for Rheumatology classification of juvenile idiopathic arthritis: second revision, Edmonton, 2001. *J Rheumatol* 2004;31:390–2.
- 16 Giannini EH, Ruperto N, Ravelli A, *et al.* Preliminary definition of improvement in juvenile arthritis. *Arthritis Rheum* 1997;40:1202–9.
- 17 Wallace CA, Ruperto N, Giannini E, *et al.* Preliminary criteria for clinical remission for select categories of juvenile idiopathic arthritis. *J Rheumatol* 2004;31:2290–4.
- 18 European Medicines Agency. ICH Topic E 2 A: Clinical safety data management: definitions and standards for expedited reporting: step 5. http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500002749.pdf (accessed 13 Nov 2013).
- 19 Ruperto N, Lovell DJ, Quartier P, *et al.* Abatacept in children with juvenile idiopathic arthritis: a randomised, double-blind, placebo-controlled withdrawal trial. *Lancet* 2008;372:383–91.
- 20 Schiff MH, Kremer JM, Jahreis A, *et al.* Integrated safety in tocilizumab clinical trials. *Arthritis Res Ther* 2011;13:R141.
- 21 Daniels SR, Greer FR. Lipid screening and cardiovascular health in childhood. *Pediatrics* 2008;122:198–208.
- 22 Skinner AC, Steiner MJ, Chung AE, *et al.* Cholesterol curves to identify population norms by age and sex in healthy weight children. *Clin Pediatr* 2012;51:233–7.