ORIGINAL ARTICLE

Randomized Trial of Tocilizumab in Systemic Juvenile Idiopathic Arthritis

Fabrizio De Benedetti, M.D., Ph.D., Hermine I. Brunner, M.D., Nicolino Ruperto, M.D., M.P.H., Andrew Kenwright, B.Sc., Stephen Wright, M.D., Inmaculada Calvo, M.D., Ruben Cuttica, M.D., Angelo Ravelli, M.D., Rayfel Schneider, M.D., Patricia Woo, M.D., Ph.D., Carine Wouters, M.D., Ricardo Xavier, M.D., Lawrence Zemel, M.D., Eileen Baildam, M.D., Ruben Burgos-Vargas, M.D., Pavla Dolezalova, M.D., Stella M. Garay, M.D., Rosa Merino, M.D., Rik Joos, M.D., Alexei Grom, M.D., Ph.D., Nico Wulffraat, M.D., Zbigniew Zuber, M.D., Francesco Zulian, M.D., Daniel Lovell, M.D., M.P.H., and Alberto Martini, M.D., for the PRINTO and PRCSG*

ABSTRACT

BACKGROUND

Systemic juvenile idiopathic arthritis (JIA) is the most severe subtype of JIA; treatment options are limited. Interleukin-6 plays a pathogenic role in systemic JIA.

METHODS

We randomly assigned 112 children, 2 to 17 years of age, with active systemic JIA (duration of ≥6 months and inadequate responses to nonsteroidal antiinflammatory drugs and glucocorticoids) to the anti–interleukin-6 receptor antibody tocilizumab (at a dose of 8 mg per kilogram of body weight if the weight was ≥30 kg or 12 mg per kilogram if the weight was <30 kg) or placebo given intravenously every 2 weeks during the 12-week, double-blind phase. Patients meeting the predefined criteria for nonresponse were offered open-label tocilizumab. All patients could enter an open-label extension.

RESULTS

At week 12, the primary end point (an absence of fever and an improvement of 30% or more on at least three of the six variables in the American College of Rheumatology [ACR] core set for JIA, with no more than one variable worsening by more than 30%) was met in significantly more patients in the tocilizumab group than in the placebo group (64 of 75 [85%] vs. 9 of 37 [24%], P<0.001). At week 52, 80% of the patients who received tocilizumab had at least 70% improvement with no fever, including 59% who had 90% improvement; in addition, 48% of the patients had no joints with active arthritis, and 52% had discontinued oral glucocorticoids. In the double-blind phase, 159 adverse events, including 60 infections (2 serious), occurred in the tocilizumab group, as compared with 38, including 15 infections, in the placebo group. In the double-blind and extension periods combined, 39 serious adverse events (0.25 per patient-year), including 18 serious infections (0.11 per patient-year), occurred in patients who received tocilizumab. Neutropenia developed in 19 patients (17 patients with grade 3 and 2 patients with grade 4), and 21 had aminotransferase levels that were more than 2.5 times the upper limit of the normal range.

CONCLUSIONS

Tocilizumab was efficacious in severe, persistent systemic JIA. Adverse events were common and included infection, neutropenia, and increased aminotransferase levels. (Funded by Hoffmann–La Roche; ClinicalTrials.gov number, NCT00642460.)

The authors' affiliations are listed in the Appendix. Address reprint requests to Dr. De Benedetti at the IRCCS Ospedale Pediatrico Bambino Gesù, Piazza S. Onofrio 4, 00165 Rome, Italy, or at fabrizio.debenedetti@opbg.net.

*The principal investigators for the Paediatric Rheumatology International Trials Organisation (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) are listed in the Supplementary Appendix, available at NEJM.org.

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Systemic juvenile idiopathic arthritis (JIA) is characterized by chronic arthritis, systemic manifestations (spiking fever, rash, hepatosplenomegaly, lymphadenopathy, and serositis), and substantially elevated inflammatory markers.[1] It is the most severe subtype of JIA; approximately half the patients have an unremitting course of chronic polyarthritis (with or without persistent systemic features). Substantial joint damage and disability often develop in these patients.[2,3] Treatment remains challenging because of the limited efficacy of methotrexate[4] and tumor necrosis factor inhibitors[5,6] and because of the major toxicity of high-dose glucocorticoids. Efficacy of the interleukin-1 inhibitor anakinra has been reported in a subset of patients.[7-9]

In systemic JIA, the markedly increased levels of interleukin-6 in serum and synovium are related to many clinical and laboratory features.[10-15] Tocilizumab (Actemra; Hoffmann–La Roche) is a humanized, antihuman interleukin-6–receptor monoclonal antibody that blocks soluble and membrane-bound receptors. A previous study with a withdrawal design showed that tocilizumab at a dose of 8 mg per kilogram of body weight, administered every 2 weeks, improved the clinical and laboratory features of systemic JIA.[16]

This phase 3 trial was conducted to evaluate the efficacy and safety of tocilizumab in children with systemic JIA. Children were treated with a dosing regimen based on body weight and derived from modeling and simulation (see the Supplementary Appendix, available with the full text of this article at NEJM.org). We present efficacy and safety data from the randomized, double-blind, placebo-controlled phase of the trial and from the subsequent open-label extension reaching at least 1 year of treatment with tocilizumab.

Methods

Study Design

This ongoing, 5-year study was conducted at 43 centers — members of the Paediatric Rheumatology International Trials Organisation[17] (PRINTO) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) — and has two parts: a randomized, double-blind, placebo-controlled, parallel, two-group, 12-week phase and a single-group, open-label extension (up to 5 years). The institutional review board or independent ethics committee at each center approved the study. Parents or guardians provided written informed consent, and patients provided written informed assent, according to national requirements.

Patients were randomly assigned in a 2:1 ratio to receive tocilizumab (at a dose of 12 mg per kilogram if the weight was <30 kg or 8 mg per kilogram if the weight was ≥30 kg) or placebo intravenously every 2 weeks for 12 weeks in a double-blind manner. Patients were stratified according to weight (<30 kg vs. ≥30 kg), duration of disease (<4 years vs. ≥4 years), concomitant dose of oral glucocorticoid (<0.3 mg per kilogram per day of prednisone equivalent vs. ≥0.3 mg per kilogram per day), and concomitant methotrexate therapy (yes vs. no). Patients were offered open-label tocilizumab if they met the predefined criteria for nonresponse: fever (>38°C for ≥3 consecutive days), symptomatic serositis, the macrophage activation syndrome, or a JIA ACR 30 flare (≥30% worsening in three or more of the six variables of the American College of Rheumatology [ACR] core set for JIA and ≥30% improvement in no more than one variable).[18,19] At week 12, all patients receiving placebo made the transition to open-label tocilizumab. Glucocorticoid tapering was permitted (from week 6) according to predefined rules (see the Supplementary Appendix).

Study Oversight

The study was designed by four of the authors and the sponsor (Hoffmann–La Roche). Confidentiality agreements were in place between the sponsor and the investigators. The sponsor was responsible for data processing and management, statistical analysis, and reporting of the results. Data analysis was conducted by three of the authors. The first draft of the manuscript was written by the first author, with assistance from two authors employed by the sponsor and medical writers paid by the sponsor. All the authors made the decision to submit the manuscript for publication. All authors vouch for the veracity of the data, analyses, and trial protocol and vouch that the trial was conducted and reported consistently with the protocol. The protocol, including the statistical analysis plan, is available at NEJM.org.

Patients

Eligible patients were 2 to 17 years of age, had received a diagnosis of systemic JIA according to International League of Associations for Rheumatology criteria,[1] and had persistent disease

(≥6 months) and inadequate responses to nonsteroidal antiinflammatory drugs (NSAIDs) and glucocorticoids. Patients had to either have five or more active joints or have two or more active joints plus fever (>38°C for ≥5 days during the 14-day screening period).

Treatment with stable doses of NSAIDs, oral glucocorticoids (at a maximum dose of 0.5 mg of a prednisone equivalent per kilogram per day or 30 mg per day, whichever was lower, for ≥2 weeks before baseline), and methotrexate (≤20 mg per square meter of body-surface area for ≥8 weeks before baseline) was permitted. Other disease-modifying antirheumatic drugs and biologic agents were not allowed.

ASSESSMENT AND OUTCOMES

Biweekly clinical assessment included the six variables of the ACR core set for JIA: the number of joints with active arthritis, the number of joints with limited range of motion (both determined by certified joint assessors who were unaware of the study assignments), the physician's global assessment of disease activity (with scores ranging from 0 to 100 and higher scores indicating more active disease), the parent's or patient's global assessment of overall well-being (with scores ranging from 0 to 100 and higher scores indicating more active disease), physical function (as assessed with the use of the Disability Index of the Childhood Health Assessment Questionnaire [CHAQ-DI], with scores ranging from 0 to 3 and higher scores indicating more disability), and the erythrocyte sedimentation rate.[20-23] Data on fever, which was assessed by measurement of tympanic temperatures, and rash were recorded at least twice daily (morning and afternoon) in an electronic home diary.

The primary outcome was the proportion of patients who had a JIA ACR 30 response, defined as an improvement of 30% or more in three or more of the six variables of the ACR core set for JIA,[18] with no more than 1 variable worsening by more than 30%, and an absence of fever.

Fever was considered present if, in the preceding week, one or more of the twice-daily measurements was 37.5°C or higher or if measurements were missing on 4 or more days. The JIA ACR 50, JIA ACR 70, and JIA ACR 90 responses (defined as improvements of at least 50%, 70%, and 90%, respectively, in at least three of the six core criteria for JIA, with worsening of more than 30% in no more than one criterion) were also evaluated. Flare, inactive disease, and adherence to the glucocorticoid-tapering guidelines were determined by independent evaluators, who were unaware of the study assignments, at the coordinating centers of PRINTO and PRCSG, according to validated criteria.[18,19,24]

STATISTICAL ANALYSIS

Assuming JIA ACR 30 response rates of 70% for patients who received tocilizumab and 40% for those who received placebo, we calculated that a sample of 108 patients (72 patients in the tocilizumab group and 36 in the placebo group) would provide approximately 80% power to detect a significant difference at week 12 with the use of a two-sided test and an alpha level of 0.05. In total, 112 patients were enrolled. All comparisons were between tocilizumab (at doses of 8 mg per kilogram and 12 mg per kilogram) and placebo.

Demographic and baseline disease characteristics were summarized with the use of descriptive statistics. Efficacy in the double-blind phase was assessed by means of a modified intention-to-treat analysis, which included patients who received at least one dose of study medication. All analyses, including the 22 secondary outcomes, were prespecified and included adjustment for stratification factors at randomization. For dichotomous-response outcomes, the Cochran–Mantel–Haenszel test was used; patients were categorized as either having a response or not having a response, and patients who did not complete the study were classified as not having a response. Logistic regression was used in the confirmatory analyses.

For outcomes based on change from baseline, analysis of variance was used; the original plan was for this analysis to be performed only for data from patients who completed the study. However, a large number of patients in the placebo group did not complete the study. To provide an analysis among comparable groups, the last-observation-carried-forward method was used, with the most recent postbaseline assessment of the JIA ACR response included in the analysis. The results of these two analyses were similar (for an analysis of patients who completed the double-blind phase, see Table S2 in the Supplementary Appendix). For the open-label extension, baseline data were obtained at the date of the first infusion of tocilizumab for patients who made the transition from

Table 1. Baseline Demographic and Clinical Characteristics of the Patients in the Intention-to-Treat Population.*

Characteristic	Placebo (N=37)	Tocilizumab (N=75)
Female sex — no. (%)	17 (46)	39 (52)
White race — no. (%)†	32 (86)	67 (89)
Age — yr	9.1±4.4	10.0±4.6
Weight — kg	31.7±16.8	34.7±20.9
Duration of disease — yr	5.1±4.4	5.2±4.0
Prior use of DMARDs		
Mean no. of DMARDs	1.4±1.4	1.3±1.1
≥1 DMARD — no. (%)	25 (68)	55 (73)
Methotrexate	20 (54)	45 (60)
Cyclosporine	12 (32)	21 (28)
Sulfasalazine	4 (11)	6 (8)
Thalidomide	3 (8)	7 (9)
Other‡	11 (30)	16 (21)
Prior use of a biologic agent — no. (%)	29 (78)	63 (84)
Prior use of an interleukin-1 inhibitor — no. (%)	13 (35)	41 (55)
Prior use of an anti-TNF agent — no. (%)	26 (70)	55 (73)
Methotrexate		
Current use — no. (%)	26 (70)	52 (69)
Mean dose — mg/m²/wk	9.4±7.1	9.4±7.1
Oral glucocorticoid		
Current use — no. (%)	31 (84)	70 (93)
Mean dose — mg/kg/day§	0.27±0.17	0.29±0.18

* Plus–minus values are means ±SD. None of these characteristics differed significantly between the two groups (P>0.05 for all comparisons). DMARD denotes disease-modifying antirheumatic drug, and TNF tumor necrosis factor.
† Race was determined by the investigator.
‡ For full details of the other DMARDs, see Table S6 in the Supplementary Appendix.
§ For each oral glucocorticoid used, the prednisone equivalent was calculated.

placebo to tocilizumab. The efficacy and safety populations included all patients who underwent randomization and received at least one dose of study medication. Efficacy results are presented up to week 52 of treatment with tocilizumab.

Safety data include full-exposure data for each patient. The exposures of individual patients to tocilizumab varied, depending on the period from the first dose of tocilizumab to the date of data cutoff or withdrawal (maximum exposure, 2.15 years). Serious infections were defined in accordance with the definition of serious adverse events in the International Conference on Harmonisation guidelines (see the protocol and Supplementary Appendix).[25]

RESULTS

STUDY POPULATION

Of the 112 patients enrolled, 37 were randomly assigned to placebo and 75 to tocilizumab. Baseline demographic and disease characteristics were balanced between the groups (Tables 1 and 2). Patients had persistent disease (mean duration, 5 years) and polyarthritis (high counts of active joints), and approximately half had systemic features (fever or rash) at the time of enrollment.

A total of 20 patients who received placebo (54%) met the criteria for nonresponse (including 13 patients within the first 2 weeks), as well as 1 patient who received tocilizumab (1%); these patients did not complete the double-blind phase and made the transition to open-label tocilizumab. A total of 14 patients (2 patients during the double-blind phase and 12 during the open-label extension) withdrew from the study (Fig. S1 in the Supplementary Appendix).

EFFICACY IN THE DOUBLE-BLIND PHASE

At week 12, significantly more patients who received tocilizumab than those who received placebo met the primary outcome of a JIA ACR 30 response and an absence of fever (85% vs. 24%, P<0.001) (Table 2). All 22 predefined secondary end points reached statistical significance (Table S2 in the Supplementary Appendix). Significant differences in all variables in the ACR core set for JIA were observed between the tocilizumab and placebo groups (Table 2). Significantly more patients in the tocilizumab group than in the placebo group had a JIA ACR 70 response (71% vs. 8%, P<0.001) or a JIA ACR 90 response (37% vs. 5%, P<0.001). Systemic symptoms (fever and rash) and laboratory abnormalities (anemia, thrombocytosis, and hyperferritinemia) significantly improved with tocilizumab (Table 2). Using prespecified exploratory logistic-regression models, we found that the proportions of patients who met the primary outcome and the criteria for the JIA ACR 30, JIA ACR 50, JIA ACR 70, and JIA ACR 90 responses were higher in the tocilizumab group than in the placebo group (Table S3 in the Supplementary Appendix).

Mean post hoc estimated pharmacokinetic exposures in patients weighing less than 30 kg or 30 kg or more indicated similar exposure. For patients weighing less than 30 kg, the area under the curve at 2 weeks was 1345.6 μg per milliliter

Table 2. Change from Baseline in ACR Core Set of Variables and in Systemic and Laboratory Features of Juvenile Idiopathic Arthritis (JIA) during the Double-Blind Phase.*

Variable	Placebo (N=37)		Tocilizumab (N=75)		Difference (95% CI)
	Baseline	Week 12	Baseline	Week 12	
JIA ACR 30 response and no fever — no. (%)	—	9 (24)	—	64 (85)	61 (45 to 78)
ACR core set of variables†					
No. of joints with active arthritis‡	16.9	15.3	21.3	7.6	–70.4 (–92.3 to –48.5)§
No. of joints with limited range of motion¶	17.9	17.2	20.7	10.4	–86.9 (–128.9 to –44.8)§
Score for physician's global assessment of disease activity‖	61.4	53.8	69.6	22.1	–53.5 (–66.1 to –40.8)
Score for patient's global assessment of overall well-being**	56.3	54.4	60.3	21.8	–71.0 (–88.1 to –53.9)§
CHAQ-DI score††	1.7	1.5	1.7	1.0	–55.7 (–82.1 to –29.2)§
ESR — mm/hr	54.1	59.8	57.6	4.4	–128.9 (–154.3 to –103.5)§
Systemic features — no./total no. (%)‡‡					
Fever	24/37 (65)	19/24 (79)	41/75 (55)	6/41 (15)	65.3 (40.6 to 90.0)§§
Rash¶¶	18/37 (49)	16/18 (89)	22/75 (29)	8/22 (36)	52.1 (21.6 to 82.5)§§
Laboratory features — no./total no. (%)‡‡					
Elevated C-reactive protein‖‖	34/37 (92)	32/34 (94)	72/75 (96)	1/72 (1)	93.1 (78.4 to 100)§§
Anemia***	29/37 (78)	27/29 (93)	50/75 (67)	10/50 (20)	73.9 (55.5 to 92.3)§§
Thrombocytosis†††	26/37 (70)	25/26 (96)	52/75 (69)	5/52 (10)	88.3 (69.4 to 100)§§
Hyperferritinemia‡‡‡	15/37 (41)	13/15 (87)	23/75 (31)	2/23 (9)	86.7 (52.4 to 100)§§

* P<0.001 for all comparisons. ACR denotes the American College of Rheumatology, and ESR erythrocyte sedimentation rate. CI denotes confidence interval.
† All values are means.
‡ The range of possible values for number of joints with active arthritis was 0 to 71.
§ The difference is the adjusted mean difference in percentage change from baseline.
¶ The range of possible values for number of joints with limited range of motion was 0 to 67.
‖ The physician's global assessment of disease activity was based on a 100-mm visual-analogue scale, with scores ranging from 0 to 100 and higher scores indicating more active disease.
** The patient's global assessment of overall well-being was based on a 100-mm visual-analogue scale, with scores ranging from 0 to 100 and higher scores indicating more active disease. This assessment was completed by the parent or guardian, if necessary (see the Supplementary Appendix).
†† Scores on the Childhood Health Assessment Questionnaire–Disability Index (CHAQ-DI) range from 0 to 3, with higher scores indicating greater disability.
‡‡ The baseline data are the numbers and percentages of patients with an abnormality, with the number of patients in the study group as the denominator. The data for week 12 are the numbers and percentages of patients with a persistent abnormality, with the number of patients who had the abnormality at baseline as the denominator.
§§ Values are weighted percentages with adjustment for stratification factors applied at randomization.
¶¶ Rash was defined as a rash due to systemic disease activity that occurred during the 14 days preceding the time point.
‖‖ The upper limit of the normal range for C-reactive protein in this study was 0.28 mg per deciliter.
*** Anemia was defined as a hemoglobin level below the lower limit of the normal range for the patient's age and sex.
††† Thrombocytosis was defined as a platelet count above the upper limit of the normal range for the patient's age and sex.
‡‡‡ An elevated ferritin level was defined as a ferritin level above the upper limit of the normal range for the patient's age.

per day, the minimum concentration 60.5 μg per milliliter, and the maximum concentration 263.3 μg per milliliter; for those weighing 30 kg or more, the area under the curve at 2 weeks was 1337.0 μg per milliliter per day, the minimum concentration 54.5 μg per milliliter, and the maximum concentration 225.7 μg per milliliter. There were no significant differences between these two groups with respect to the primary outcome or the rate of a JIA ACR 70 or JIA ACR 90 response (data not shown).

EFFICACY IN THE OPEN-LABEL EXTENSION PHASE

In the open-label extension phase, which included 73 patients randomly assigned to receive tocilizumab who continued to receive it owing to a good

response and 37 randomly assigned to receive placebo, a progressive improvement of systemic JIA was observed; 59% of these patients had a JIA ACR 90 response and an absence of fever at week 52 (Fig. 1A). Five additional patients had a JIA ACR 90 response but were considered not to have had a response because of the presence of fever (3 of the 5 patients had insufficient temperature recordings, according to the data-handling rules). The mean (±SD) count of active joints decreased to 2.8±6.5 at week 52, and 48% of the patients had no active joints (Fig. S2A in the Supplementary Appendix). A total of 28% of the patients met the criteria for clinically inactive disease.[24] Physical function improved; at week 52, 38% of the patients had moderate or severe functional impairment (CHAQ-DI score, ≥0.75), as compared with 82% at baseline (Fig. S2B in the Supplementary Appendix). The need for oral glucocorticoids decreased; 52% of the patients discontinued glucocorticoids, and the mean prednisone-equivalent dose decreased to 0.06±0.09 mg per kilogram per day (Fig. 1B).

SAFETY

Table 3 summarizes adverse events that occurred during the double-blind phase alone and cumulatively during the double-blind phase and open-label treatment with tocilizumab. In the double-blind phase, more patients in the tocilizumab group than in the placebo group had adverse events (66 vs. 18 patients), and infection developed in more patients in the tocilizumab group than in the placebo group (41 vs. 11 patients). The rate of infection was 3.4 per patient-year with tocilizumab, 2.9 per patient-year with placebo, and 3.0 per patient-year during open-label treatment. In the double-blind phase, 4 serious adverse events (including two infections) occurred in 3 patients in the tocilizumab group, as compared with none in the placebo group. Cumulatively, 39 serious adverse events occurred, including 18 serious infections that resolved without sequelae. Opportunistic infection and tuberculosis were not reported. The rate of serious adverse events per patient-year was 0.23 during the double-blind phase and 0.25 cumulatively. Adverse events led to the discontinuation of tocilizumab in 6 patients (Table S5 in the Supplementary Appendix), including 2 in whom withdrawal was mandated by the protocol because of increased aminotransferase levels). Three episodes of the macrophage activation syndrome were reported, all of which resolved (see the Supplementary Appendix).

Three deaths occurred during tocilizumab treatment (two after the data-cutoff point at 52 weeks): a 17-year-old boy, with long-standing disease and severe growth retardation, who had a JIA ACR 90 response, died suddenly from suspected tension pneumothorax at week 50; another patient died from injuries sustained in a traffic accident at week 90; and the third died from probable streptococcal sepsis at week 104 of treatment. Death also occurred in three patients who received tocilizumab and who had withdrawn from the study. Pulmonary hypertension caused by suspected pulmonary veno-occlusive disease developed in one patient after 50 weeks of treatment; this patient withdrew from the study and died 13 months later. Another patient withdrew after 48 weeks owing to lack of efficacy and died from pulmonary hypertension 6 months later. The third patient withdrew after 50 weeks owing to lack of efficacy and died from probable macrophage activation syndrome 13 months later. The latter two patients died while receiving other biologic agents for persistently active systemic JIA.

In patients receiving tocilizumab, grade 3 neutropenia (0.5×10^9 to $<1.0\times10^9$ neutrophils per liter) developed in 17 patients, and grade 4 neutropenia ($<0.5\times10^9$ neutrophils per liter) developed in 2 (see the Supplementary Appendix). Among patients with neutropenia, seven infections (none graded by the investigators as serious) were reported, with the most recent neutrophil count showing grade 4 neutropenia (in association with a mild upper respiratory tract infection) or grade 3 neutropenia (in association with three episodes of mild nasopharyngitis in 2 patients, two episodes of mild conjunctivitis in 1 patient, and a tooth abscess of moderate intensity in 1 patient) (see the Supplementary Appendix). Increases in the alanine aminotransferase level to more than 2.5 times the upper limit of the normal range occurred in 21 patients. At least one value for total cholesterol and one value for low-density lipoprotein (LDL) cholesterol were above the upper limit of the normal range in 31% of the patients who received tocilizumab and in 14% of those who received placebo.

At baseline, testing for antitocilizumab antibodies was negative in all patients. Antitocilizumab antibodies developed in two patients; both withdrew because of adverse events (see the Supplementary Appendix).

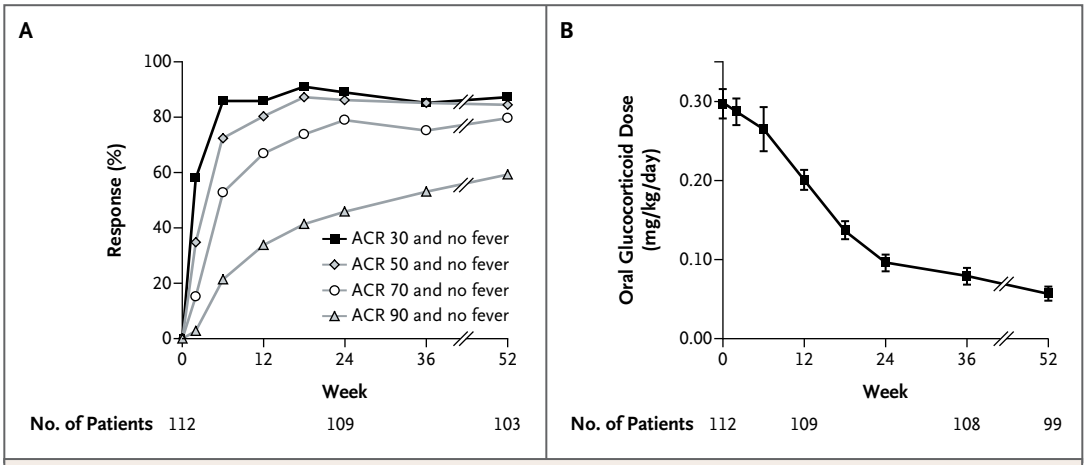

Figure 1. Clinical Improvement after 52 Weeks of Tocilizumab Treatment.

Panel A shows the American College of Rheumatology (ACR) responses for the core set of variables for juvenile idiopathic arthritis (JIA) and absence of fever. The JIA ACR 30, JIA ACR 50, JIA ACR 70, and JIA ACR 90 responses were defined as improvements of at least 30%, 50%, 70%, and 90%, respectively, in at least three of the six response variables, with worsening of more than 30% in no more than one of the six variables. In patients who were continuing treatment, the last-observation-carried-forward rule was applied to missing data on the JIA ACR response at visits. Panel B shows the mean oral glucocorticoid dose, with I bars indicating standard deviations. For each glucocorticoid used, the prednisone equivalent was calculated. Data at week 52 from three patients were not included because they had not yet reached that time point at the time of the data cutoff.

DISCUSSION

Persistently active systemic JIA represents a major therapeutic challenge. Traditional disease-modifying antirheumatic drugs and tumor necrosis factor inhibitors have limited benefit. The long-term use of glucocorticoids exposes patients to substantial toxicity with little, if any, effect on the outcome. Ample evidence points to excessive production of interleukin-6 as a key pathogenic factor in systemic JIA.[3,12] Our placebo-controlled trial showed that inhibition of interleukin-6 with tocilizumab is efficacious in patients with established disease and widespread chronic arthritis.

In the randomized, double-blind phase, JIA ACR response rates were higher among patients who received tocilizumab than among those who received placebo. The primary outcome (JIA ACR 30 response and absence of fever) occurred in 85% of the patients who received tocilizumab. Two thirds of patients who received tocilizumab had a JIA ACR 30 response at week 2, after receiving one dose. During open-label treatment, control of the systemic and laboratory features of the disease was sustained, with a progressive decrease in joint involvement and clinically relevant improvement in physical function. Almost one third of patients had clinically inactive disease at week 52. Glucocorticoid sparing, with maintenance of disease control, was also achieved: 52% of the patients discontinued oral glucocorticoids, with the remaining patients receiving doses in the range associated with minimal toxicity. The dosing regimen for tocilizumab that was based on body weight was appropriate, yielding uniform drug exposure across the wide age range in our study population.

Patients with a duration of disease shorter than 6 months were excluded; therefore, patients with monocyclic or polycyclic courses who have frequent, short-term, spontaneous remissions and good long-term outcomes were most likely not included in the study. The patients we enrolled were those with severe, persistent systemic JIA for whom no effective treatment was available, as reflected by the long duration of disease, large number of active joints, and high frequency of previous exposure to biologic agents at baseline.

In the double-blind phase, adverse events occurred in more patients who received tocilizumab than in those who received placebo. The rate of infection per patient-year was 2.9 in the placebo group and 3.4 in the tocilizumab group. The cumulative rate of infection (during the double-blind phase and open-label treatment) was 3.0 per

patient-year. Cumulatively, 39 serious adverse events (including 18 serious infections) occurred in patients who received tocilizumab. Patients treated with tocilizumab appeared to have a 25% risk of a serious adverse event and an 11% risk of a serious infection per year of treatment.

There were three cases of the macrophage activation syndrome. One of the six varicella infections triggered laboratory abnormalities that were consistent with a mild case of the macrophage activation syndrome. In the other two cases, withdrawal of tocilizumab and incomplete dosing might have contributed to the development of the macrophage activation syndrome. The rate of the macrophage activation syndrome was 1.9 cases per 100 patient-years; no definitive estimate of its rate among patients with systemic JIA is available for comparison. In an animal model, high levels of interleukin-6 caused the macrophage activation syndrome in the presence of an infectious

Table 3. Adverse Events.*

Variable	Double-Blind Phase†		Cumulative Data‡
	Placebo (N=37)	Tocilizumab (N=75)	Tocilizumab (N=112)
Exposure to tocilizumab — patient-yr	5.2	17.4	157.5
Adverse events including fever and JIA			
No. of events	49	161	1315
No. of events per patient-yr	9.4	9.3	8.4
Adverse events excluding fever and JIA			
No. of events	38	159	1266
No. of events per patient-yr	7.3	9.1	8.0
Most frequently reported events — no. of patients (%)§			
Upper respiratory tract infection	4 (11)	10 (13)	35 (31)
Pharyngitis or nasopharyngitis	3 (8)	10 (13)	37 (33)
Diarrhea	1 (3)	5 (7)	19 (17)
Headache	3 (8)	7 (9)	17 (15)
Serious adverse events			
Total — no. of events	0	4	39
Angioedema ¶	0	1	1
Urticaria	0	1	1
Varicella	0	1	4
Herpes zoster	0	0	2
Upper respiratory tract infection	0	0	4
Bronchopneumonia or pneumonia	0	0	4
Gastroenteritis or gastritis	0	0	5
Macrophage activation syndrome	0	0	3
Aminotransferase increase	0	0	2
Fracture	0	0	3
Hip dislocation‖	0	0	2
Other**	0	1	8
No. of events per patient-yr	0	0.23	0.25
Infection			
No. of events	15	60	478
No. of events per patient-yr	2.9	3.4	3.0

Table 3. (Continued.)

Variable	Double-Blind Phase†		Cumulative Data‡
	Placebo (N=37)	Tocilizumab (N=75)	Tocilizumab (N=112)
Serious infection			
No. of events	0	2	18
No. of events per patient-yr	0	0.11	0.11
Clinical laboratory abnormalities — no. of patients (%)			
Neutropenia††			
Grade 3	0	5 (7)	17 (15)‡‡
Grade 4	0	0	2 (2)
Thrombocytopenia§§			
Grade 3	0	0	1 (1)‡‡
Grade 4	0	0	0
Increase in alanine aminotransferase¶¶			
Grade 2	0	5 (7)	13 (12)
Grade 3	0	1 (1)	7 (6)
Grade 4	0	0	1 (1)‡‡

* Multiple occurrences of the same adverse event in one patient were counted.
† Data on open-label tocilizumab rescue therapy were excluded.
‡ Cumulative data included data for patients who received tocilizumab in the double-blind phase and subsequently received open-label tocilizumab and for patients who were assigned to placebo and made the transition to open-label tocilizumab.
§ Only adverse events that occurred in more than 5% of patients in either group in the double-blind phase are presented. Additional adverse events that occurred in more than 5% of patients during the open-label phase are listed in Table S7 in the Supplementary Appendix.
¶ Angioedema and urticaria occurred in the same patient.
‖ The two episodes of hip dislocation occurred in the same patient.
** Eight other serious adverse events were reported: JIA, bacterial arthritis, chronic panniculitis, dehydration, pneumothorax, testicular torsion, cardiac failure, and pulmonary veno-occlusive disease. Cardiac failure related to pulmonary veno-occlusive disease was reported in the same patient, who died 13 months after withdrawing from the study (see the description in the Supplementary Appendix).
†† Grade 3 neutropenia was defined as a neutrophil count of 0.5×10^9 to less than 1.0×10^9 per liter, and grade 4 as a neutrophil count of less than 0.5×10^9 per liter.
‡‡ One episode each of grade 3 neutropenia, grade 3 thrombocytopenia, and a grade 4 increase in the alanine aminotransferase level occurred during the macrophage activation syndrome.
§§ Grade 3 thrombocytopenia was defined as a platelet count of 25,000 to less than 50,000 per cubic millimeter, and grade 4 as a platelet count of less than 25,000 per cubic millimeter.
¶¶ A grade 2 increase in the alanine aminotransferase level was defined as a level that was more than 2.5 to 5.0 times the upper limit of the normal range, grade 3 as a level that was more than 5 to 20 times the upper limit of the normal range, and grade 4 as a level that was more than 20 times the upper limit of the normal range.

trigger.[26] One patient with a 10-year history of treatment-resistant systemic JIA had pulmonary hypertension. Occurrences of pulmonary hypertension have been reported in severe cases of systemic JIA, requiring multiple treatments. At the onset of symptoms of the lung disease, the majority of patients were treated with biologic agents (including 12 patients with interleukin-1 inhibitors, 2 with tocilizumab, and 3 with tumor necrosis factor inhibitors).[27,28]

Six of the 112 enrolled patients died, including 3 who were receiving tocilizumab during the study: 1 patient died from suspected tension pneumothorax, 1 from probable streptococcal sepsis, and 1 in a traffic accident. The other three deaths occurred 6, 12, and 13 months after withdrawal (in 2 patients who withdrew owing to lack of efficacy and in 1 who withdrew owing to pulmonary hypertension). In three retrospective cohort studies of systemic JIA, deaths oc-

curred in 2 of 80 patients,[2] in 2 of 111 patients,[29] and in 8 of 192 patients.[30] Recently, a large U.S. registry reported six deaths among 962 patients with systemic JIA.[31] However, all patients with systemic JIA, including those with monocyclic or polycyclic courses, were eligible for these studies. The mortality rate among patients with systemic JIA as severe as that in our study population is unknown.

Transient neutropenia occurred in 19 patients and resolved (tocilizumab was withheld until resolution of the neutropenia, as mandated by the protocol); seven associated infections (none serious) in 4 patients were reported. Transient increases in aminotransferase levels occurred in 21 patients. The clinical significance of serum lipid changes in children who have received anti-inflammatory treatment is unclear. A recent study[32] of lipid changes in rheumatoid arthritis showed that neutralization of interleukin-6 is associated with increases in large LDL particles rather than small LDL particles (the latter are considered proatherogenic).

In conclusion, inhibition of interleukin-6 with tocilizumab is efficacious in severe, persistent, and unresponsive systemic JIA. The benefits of this treatment must be weighed against the risks of infection, neutropenia, and abnormalities in results of liver-function tests. Longer-term safety data are warranted.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

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APPENDIX

The authors' affiliations are as follows: the Division of Rheumatology, Department of Medicine, Istituto Di Ricovero e Cura a Carattere Scientifico (IRCCS) Ospedale Pediatrico Bambino Gesù, Rome (F.D.B.), IRCCS Istituto G. Gaslini, Pediatria II, Reumatologia, Paediatric Rheumatology International Trials Organisation (PRINTO) Coordinating Center, Genoa (N.R., A.R., A.M.), Dipartimento di Pediatria, Università degli Studi di Genova, Genoa (A.R., A.M.), and the Department of Pediatrics, Unita di Reumatologia Pediatrica, Università di Padova, Padua (F.Z.) — all in Italy; the Division of Rheumatology, Department of Pediatrics, Cincinnati Children's Hospital Medical Center, Pediatric Rheumatology Collaborative Study Group (PRCSG) Coordinating Center, Cincinnati (H.I.B., A.G., D.L.); Hoffmann–La Roche, Welwyn Garden City (A.K., S.W.), the Department of Rheumatology, Great Ormond Street Hospital for Sick Children, London (P.W.), and Alder Hey Children's National Health Service Foundation Trust, Liverpool (E.B.) — all in the United Kingdom; the Pediatric Rheumatology Department, Hospital Universitario La Fe, Valencia (I.C.), and Unidad de Reumatologia Pediatrica, Hospital Universitario La Paz, Madrid (R.M.) — both in Spain; the Rheumatology Section, Hospital Gral de Niños Pedro Elizalde, Buenos Aires (R.C.), and Unidad de Reumatologia, Hospital Sor Maria Ludovica, La Plata (S.M.G.) — both in Argentina; the Department of Pediatrics, Division of Rheumatology, Hospital for Sick Children, University of Toronto, Toronto (R.S.); the Division of Pediatric Rheumatology, Department of Pediatrics, University Hospital Gasthuisberg, Leuven (C.W.), and Centrum voor Kinderreumatologie, Universitair Ziekenhuis, Ghent (R.J.) — both in Belgium; the Rheumatology Service, Hospital de Clinicas de Porto Alegre, Universidade Federal do Rio Grande do Sul, Porto Alegre, Brazil (R.X.); Pediatric Rheumatology, Connecticut Children's Medical Center, Hartford (L.Z.); Departmento de Reumatologia, Hospital General de Mexico, and the Faculty of Medicine, Universidad Nacional Autonoma de Mexico, Mexico City (R.B.-V.); the Department of Pediatrics and Adolescent Medicine, Charles University in Prague, and General University Hospital, Prague, Czech Republic (P.D.); the Department of Pediatric Immunology and Rheumatology, Wilhelmina Kinderziekenhuis, Universitair Medisch Centrum, Utrecht, the Netherlands (N.W.); and the Department of Rheumatology, Oddzial Dzieci Starszych, Wojewodzki Specjalistyczny Szpital Dzieciecy Sw Ludwika, Krakow, Poland (Z.Z.).

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