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Efficacy and Safety of Canakinumab in Patients With Systemic Juvenile Idiopathic Arthritis With and Without Fever at Baseline: Results From an Open-Label, Active-Treatment Extension Study

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Objective. To evaluate the long-term efficacy and safety of canakinumab and explore prediction of response in patients with systemic juvenile idiopathic arthritis (JIA) with or without fever at treatment initiation.

Methods. At enrollment, patients with active systemic JIA (ages 2 to <20 years) started open-label canakinumab (4 mg/kg every 4 weeks subcutaneously). Efficacy measures included the adapted JIA American College of Rheumatology (aJIA-ACR) criteria, the Juvenile Arthritis Disease Activity Score (JADAS), and clinically inactive disease and clinical remission on medication, evaluated by either the JADAS or ACR criteria.

Results. Of the 123 patients (70 with fever and 52 without fever [fever status was not reported for 1 patient]), 84 (68.3%) completed the study (median duration 1.8 years). Comparable efficacy (aJIA-ACR 50/70/90/100) was observed by day 15 in both subgroups (60.0%/48.6%/37.1%/24.3% in those with fever and 67.3%/48.1%/34.6%/19.2% in those without fever), and further increased thereafter. By month 6, clinical remission according to the JADAS or the ACR criteria was achieved in 17 (24.3%) and 26 (37.1%), respectively, of patients with fever and 9 (17.3%) and 12 (23.1%), respectively, of patients without fever. Median time to onset of clinical remission according to the JADAS or ACR criteria was 57 and 30 days, respectively, in those with fever, and 58 and 142 days, respectively, in those without fever. An aJIA-ACR 50 response by day 15 was the strongest predictor of achieving clinical remission according to the JADAS (odds ratio [OR] 13 [95% confidence interval (95% CI) 4, 42]; $P < 0.0001$) or glucocorticoid discontinuation (OR 19 [95% CI 3, 114]; $P = 0.002$). Of the 71 of 123 patients (57.7%) who received glucocorticoids at study entry, 27 (38.0%) discontinued glucocorticoids and 21 (29.6%) reached a dose of <0.2 mg/kg/day, with no difference between those with and those without fever; 13 patients (10.6%) tolerated a sustained canakinumab dose reduction to 2 mg/kg every 4 weeks. No new safety findings were observed.

Conclusion. Canakinumab provided rapid and sustained improvement of active systemic JIA irrespective of the presence of fever at treatment initiation.

INTRODUCTION

Systemic juvenile idiopathic arthritis (JIA) manifests with arthritis and systemic features such as fever, rash, hepatosplenomegaly, and lymphadenopathy. In many patients, the systemic features resolve and chronic arthritis is the persistent main clinical finding that is often difficult to treat (1,2). A major complication of systemic JIA is macrophage activation syndrome (MAS) (3–6). It has been suggested that the immunology of systemic JIA changes during the disease course, especially after the systemic features present at diagnosis have resolved (7). Poor control of disease activity can lead to long-term disability and reduced patient quality

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of life (1,8). To prevent poor disease outcomes, achievement of clinical remission, or at least a low disease activity state, with discontinuation of glucocorticoids, constitute important and realistic targets for systemic JIA treatment strategies (9–11).

Studies have shown that blockade of interleukin-1 (IL-1) and IL-6 are effective treatment strategies for systemic JIA (12–18). Canakinumab, a selective anti–IL-1β monoclonal antibody that has been tested in 3 phase II and III trials (15,19,20), demonstrated fast onset of action in systemic JIA, followed by sustained efficacy associated with glucocorticoid discontinuation in a substantial number of patients, with a well-characterized long-term safety profile. An early response to canakinumab seemed to be a predictor of long-term control of systemic JIA features (20).

However, little is known about potential differences in response to canakinumab between systemic JIA patients with and those without fever or other systemic features (rash, lymphadenopathy, or hepatosplenomegaly) at the time of treatment initiation. Herein, long-term efficacy and safety of canakinumab in a cohort of patients with and patients without fever at enrollment are reported.

PATIENTS AND METHODS

Study design. This was a prospective, long-term, open-label active treatment study of newly recruited canakinumab-naive patients with systemic JIA, with or without fever at enrollment, introduced via a Protocol Amendment of the previously published extension study in which only children with fever were enrolled (ClinicalTrials.gov identifiers: NCT00889863 and NCT00886769) (20). The aim of the study was to compare the efficacy of canakinumab for the treatment of patients with systemic JIA with fever and patients with systemic JIA without fever at the time of canakinumab initiation. The study also aimed to collect additional safety information, especially with regard to the risk of MAS, since patients with a history of MAS were allowed to participate in the trial.

Canakinumab therapy was initiated at 4 mg/kg body weight every 4 weeks. After 2 months in the study, patients were allowed to taper glucocorticoids as guided by the protocol. After 6 months of treatment, canakinumab tapering from 4 mg/kg to 2 mg/kg every 4 weeks was permitted as per physician judgment in patients who were glucocorticoid-free (Supplementary Methods, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract).

Patients. Patients (ages 2 to <20 years) with active systemic JIA were allowed to enroll in the study. Active systemic JIA was defined by the presence of ≥2 of the following criteria: 1) fever at baseline (defined as spiking, intermittent fever [body temperature >38°C] for ≥1 day during the screening period and within 1 week before the first canakinumab dose), 2) rash, 3) serositis, 4) hepatosplenomegaly, 5) lymphadenopathy, 6) arthritis in ≥2 active joints,

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and 7) C-reactive protein (CRP) level of >30 mg/liter (normal range 0–10 mg/liter). Patients with a history of MAS more than 6 months prior to baseline were allowed to participate in the trial. Treatment with stable doses of nonsteroidal antiinflammatory drugs, glucocorticoids (≤1.0 mg/kg/day of prednisone equivalent, maximum 60 mg/day for ≥3 days prior to baseline), and/or methotrexate (MTX) were permitted. Major exclusion criteria were concomitant treatment with another biologic disease-modifying antirheumatic drug (bDMARD), prior exposure to canakinumab, malignancies, and active and/or recurrent infections, including HIV and hepatitis B or C infection.

Patients were enrolled into and followed up in the study between February 8, 2012 and December 10, 2014 in 15 countries at 37 centers that were members of the Paediatric Rheumatology International Trials Organisation (PRINTO) (21) and the Pediatric Rheumatology Collaborative Study Group (PRCSG) (22). (See Appendix A for a list of additional investigators from PRINTO and PRCSG.) The institutional review board at each participating center approved the protocol. The trial was conducted in accordance with the Declaration of Helsinki, and written informed consent was obtained from all patients or their parents/guardians.

Disease activity and safety assessments. Efficacy of canakinumab was assessed by time windows on day 15, at month 3, and every 3 months thereafter by means of various composite measures: 1) adapted JIA American College of Rheumatology (aJIA-ACR) 50/70/90/100 response criteria (23,24), which include the components of the JIA core set along with the absence of fever (defined as a temperature ≤38°C in the preceding 7 days); 2) clinically inactive disease and clinical remission on medication, defined as ≥6 consecutive months of clinically inactive disease, evaluated using both the ACR criteria (25,26) and the Juvenile Arthritis Disease Activity Score in 71 joints using the CRP level (JADAS-71-CRP); and 3) disease activity measured by JADAS-71-CRP (≤1 = inactive disease, ≤3.8 = low disease activity; 3.9–10.5 = moderate disease activity, and >10.5 = high disease activity) (27–29). The degree of systemic features was reflected in the physician global evaluation of disease activity measured on a visual analog scale.

Safety and tolerability of canakinumab were evaluated in terms of adverse events (AEs), serious AEs (SAEs), and clinical and laboratory assessments from first injection until the last available observation. Serious infections, malignancies, and cases of MAS were adjudicated by independent committees (3).

Anticanakinumab antibodies were measured by means of a screening assay, followed by a confirmatory and titration assay, along with serum canakinumab concentrations (pharmacokinetics) to accurately assess immunogenicity (30,31).

Statistical analysis. The Consolidated Standards of Reporting Trials (CONSORT) (32,33) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) (34) statements were followed. One patient was excluded from the efficacy analyses since fever status was unknown at baseline. Demographic characteristics, baseline characteristics, and response to therapy were descriptively summarized for the fever subgroups using frequencies or percentages or the median (quartile 1 [Q1], quartile 3 [Q3]) as appropriate. Efficacy and safety were assessed for the subgroups of patients defined by 1) the presence or absence of fever at baseline, 2) prior use of any bDMARDs; and 3) treatment with anakinra or tocilizumab just prior to enrollment.

Safety was also assessed for the subgroup of patients who were receiving glucocorticoids at baseline. Fever subgroups were compared for prior use of bDMARDs at baseline by Wilcoxon's 2-sample test and for CRP levels by Fisher's exact test. Efficacy analyses were performed in 2 ways: 1) in the modified intent-to-treat (ITT) population based on observed data (35) and 2) with missing data imputed using last observation carried forward (LOCF).

To identify predictors of achieving remission, clinical remission according to the JADAS was modeled using the generalized mixed models framework. Predictor (or independent) variables of the first model included early response (aJIA-ACR 50 response by day 15), fever status, MTX use, prior use of bDMARDs, and glucocorticoid use at baseline. In a second model, prior use of bDMARDs was replaced by prior exposure to anakinra or tocilizumab. All models included a center-related random effect. In order to assess the predictability of the models, the area under the curve resulting from the receiver operating characteristic curve was calculated.

The median (Q1, Q3) time to start of clinical remission according to the JADAS was also determined by subgroups. The time to start of clinical remission according to the JADAS was defined as the time interval between starting canakinumab and the first visit when clinically inactive disease according to the JADAS that persisted for 6 or more consecutive months was observed. In order to check whether these results were reproducible for remission according to the ACR criteria, all analyses were duplicated for clinical remission according to the ACR criteria.

Glucocorticoid tapering was analyzed for the percentage of patients who discontinued and dosages at the end of the study (percentage of patients receiving >0.2 mg/kg/day, and percentage of patients receiving <0.2 mg/kg/day). A mixed model was used to identify predictors of glucocorticoid discontinuation; early response and baseline characteristics of fever, prior use of bDMARDs, JADAS, and CRP, and a center-related random effect, were used as independent variables. Glucocorticoid dosages were reported as prednisone equivalent dosages per body weight (mg/kg/day).

AEs were analyzed every 3 months from baseline until the end of the study as incidence and exposure-adjusted incidence (per 100 patient-years) together with the corresponding Poisson 95% confidence interval (95% CI) as per the primary system organ class and preferred term based on the Medical Dictionary for Regulatory Activities (version 17.1). AEs were analyzed for the

subgroups divided by fever status at baseline, glucocorticoid use at baseline, prior exposure to bDMARDs, and prior exposure to anakinra or tocilizumab. Safety was assessed in all study participants who received ≥1 dose of canakinumab.

One of the 124 enrolled patients was excluded from analysis due to missing informed consent. Thus, efficacy and safety results are reported for the modified ITT population of 123 patients. *P* values are nominal.

RESULTS

Baseline characteristics and disposition of the patients with fever and patients without fever. Demographic and baseline characteristics of 123 patients, including 70 with fever (56.9%) and 52 without fever (42.3%) are presented in Table 1 (fever status at baseline was not reported for 1 patient). Patients with fever were older at onset of systemic JIA and had higher CRP levels at baseline than patients without fever (median 123.7 mg/liter versus 49.7 mg/liter; $P < 0.0001$). At baseline, the patients with fever and those without fever both had high disease activity, many joints with active arthritis, and similar MTX and glucocorticoid use. There were numerical differences in prior bDMARD exposure (68.6% [48 of 70] of those with fever versus 57.7% [30 of 52] of those without fever; $P = 0.255$). Anakinra was the most frequently used prior bDMARD.

The study was completed by 84 patients (68.3%) (median exposure 1.8 years [range 0–2.8 years]), including 49 (70.0%) with fever and 35 (67.3%) without fever (Figure 1). Inadequate response to canakinumab was the main reason for study discontinuation (n = 10 in each group); more patients with fever (n = 10) discontinued due to AEs than patients without fever (n = 4).

Efficacy of canakinumab by fever status at baseline. Figure 2A shows aJIA-ACR 50/70/90/100 responses on day 15 after canakinumab initiation. In the fever group, aJIA-ACR 50 was achieved in 42 patients (60.0%), aJIA-ACR 70 was achieved in 34 patients (48.6%), aJIA-ACR 90 was achieved in 26 patients (37.1%), and aJIA-ACR 100 was achieved in 17 patients (24.3%). Similar levels of response occurred in the group without fever, with aJIA-ACR 50, 70, 90, and 100 responses achieved in 35 patients (67.3%), 25 patients (48.1%), 18 patients (34.6%), and 10 patients (19.2%), respectively. Response rates increased until month 6 after canakinumab initiation and were sustained for the initial 1.5 years of the study in both subgroups. The apparent decline

Table 1. Demographic and baseline disease characteristics of the 123 patients with systemic JIA*

Characteristic	Patients with fever (n = 70)	Patients without fever (n = 52)
Sex, no. (%) female	44 (62.9)	31 (59.6)
Race, no. (%) white	63 (90.0)	47 (90.4)
Presence of systemic signs for >6 months of disease, no. (%)	55 (78.6)	39 (75.0)
Age at systemic JIA onset, years†	6.5 (3.2, 11.5)	4.3 (2.1, 8.2)
Age at enrollment, years	10.5 (6.6, 13.4)	8.2 (4.6, 12.2)
Disease duration at enrollment, years†	1.2 (0.3, 4.0)	1.4 (0.5, 3.1)
CRP at baseline (normal ≤10 mg/liter)	123.7 (45, 223.3)	49.7 (10.5, 91.0)
Physician global assessment of disease activity, VAS	55 (40, 71)	54 (35.5, 64.5)
No. of joints with active arthritis‡	5.0 (3, 16)	6.5 (4, 12.5)
No. of joints with limited range of motion§	5.0 (2, 14)	5.0 (3, 11)
C-HAQ disability index score¶	1.6 (0.8, 2.1)	1.3 (0.6, 1.8)
Patient assessment of overall well-being, VAS#	61 (31.0, 75.0)	48 (27.0, 66.0)
JADAS-71-CRP**	24.4 (18.5, 33.3)	20.4 (16.7, 29.3)
MTX therapy, no. (%)	30 (42.9)	23 (44.2)
Glucocorticoid use, no. (%)	39 (55.7)	31 (59.6)
Any prior use of biologic DMARDs, no. (%)††	48 (68.6)	30 (57.7)
1 biologic DMARD	30 (42.9)	15 (28.8)
2 biologic DMARDs	18 (25.7)	15 (28.8)

* Fever status was not reported at baseline for 1 patient; therefore, the numbers of patients do not total 123. Except where indicated otherwise, values are the median (quartile 1, quartile 3). JIA = juvenile idiopathic arthritis; CRP = C-reactive protein; VAS = visual analog scale; C-HAQ = Childhood Health Assessment Questionnaire; JADAS-71-CRP = Juvenile Arthritis Disease Activity Score in 71 joints using the CRP level; MTX = methotrexate.
† Data were available for 55 patients with fever and 42 patients without fever.
‡ Range of possible values 0–73.
§ Range of possible values 0–69.
¶ Range: 0–30; 0 = no disability. Data were available for 69 patients with fever.
# By parent proxy report of patient self-report; data were available for 69 patients with fever.
** Data were available for 68 patients with fever.
†† Biologic disease-modifying antirheumatic drugs (DMARDs) included anakinra, tocilizumab, etanercept, abatacept, and adalimumab.

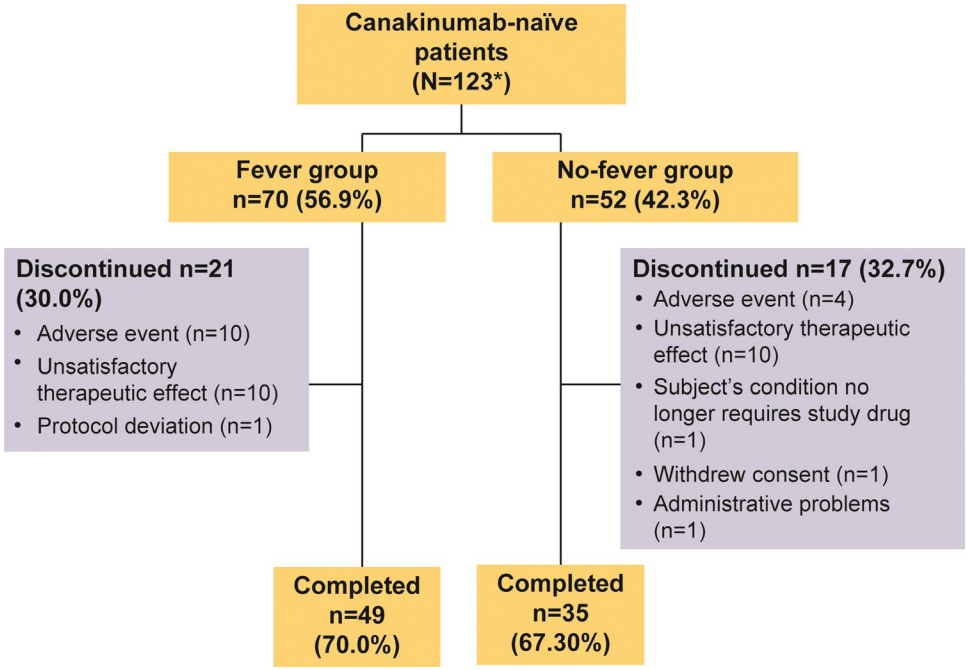


Figure 1. Disposition of the patients. * For 1 patient, fever status at baseline was not reported and not included in the efficacy and safety analysis for the fever subgroups. The patient was discontinued from the study due to loss to follow-up.

in response rates after 1.5 years was due to patients being lost to follow-up and the conservative modified ITT approach; the corresponding data for analyses using the LOCF approach are shown in Supplementary Figure 1A, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract.

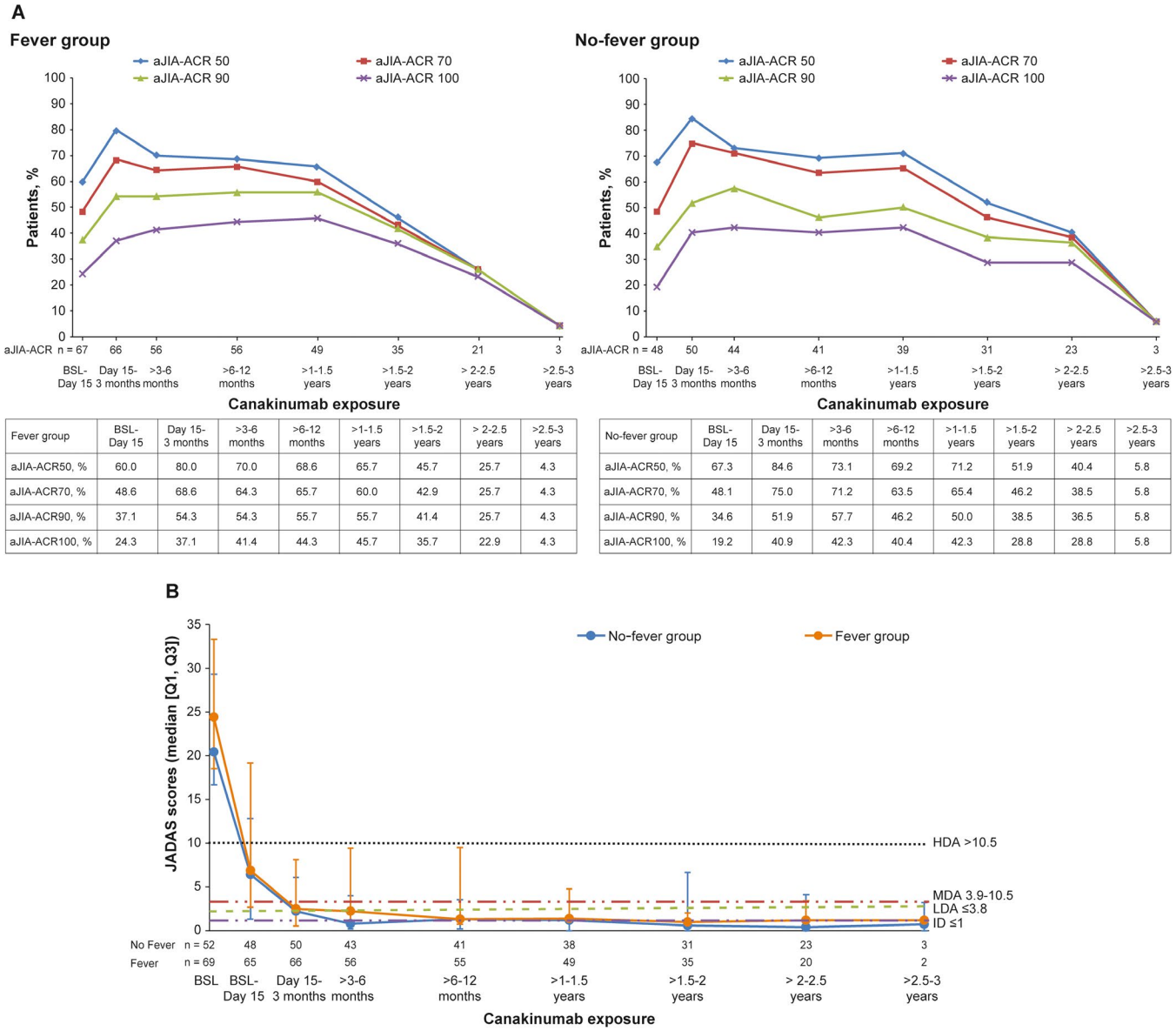
Moderate disease activity, low disease activity, and clinically inactive disease according to the JADAS-71-CRP. There was a notable decrease in JADAS-71-CRP from baseline to day 15 in both groups. The median absolute reduction in the JADAS-71-CRP was –16.6 (Q1, Q3 –23.1, –6.0) (–74.9%) in the group with fever and –11.9 (Q1, Q3 –19.2, –7.0) (–65.5 %) in the group without fever. Compared with baseline, JADAS-71-CRP at month 3 was 88.1% lower in the group with fever (median change –18.3 [Q1, Q3 –26.6, –14.5]) and 90.9% lower in the group without fever (median change –16.2 [Q1, Q3 –23.5, –12.3]). This decrease was similar at month 6 and was sustained over the course of the study thereafter. Figure 2B shows the results of the modified ITT analysis. Results of the LOCF method are shown in Supplementary Figure 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract.

Moderate disease activity according to the JADAS was achieved on day 15 and at month 3 in 45 patients (64.3%) and 51 patients (72.9%), respectively, in the group with fever and 33 patients (63.5%) and 42 patients (80.8%), respectively, in the group without fever.

Low disease activity according to the JADAS was achieved at month 3 of the study in 41 patients (58.6%) in the group with fever and 34 patients (65.4%) in the group without fever. At months 12 and 24, there were 39 patients (55.7%) and 29 patients (41.4%), respectively, in the group with fever who had low disease activity according to the JADAS, compared with 31 patients (59.6%) and 22 patients (42.3%), respectively, in the group without fever.

On day 15, clinically inactive disease according to the JADAS and clinically inactive disease according to the ACR criteria were achieved in 13 patients (18.6%) and 16 patients (22.9%), respectively, in the group with fever and 11 patients (21.2%) and 12 patients (23.1%), respectively, in the group without fever. At month 6, the number of patients with clinically inactive disease according to the JADAS and clinically inactive disease according to the ACR criteria were 27 (38.6%) and 34 (48.6%), respectively, in the group with fever, and 22 (42.3%) and 23 (44.2%), respectively, in the group without fever (see Supplementary Figure 3 for results of the modified ITT analysis and Supplementary Figure 4 for results of the LOCF method, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract).

Clinical remission and baseline predictors. The first occurrence of clinically inactive disease status that led to clinical remission according to the JADAS or clinical remission according to the ACR criteria 6 months later was achieved by 17 patients (24.3%) and 26 patients (37.1%), respectively, in the group with



Fever group	BSL-Day 15	Day 15-3 months	>3-6 months	>6-12 months	>1-1.5 years	>1.5-2 years	> 2-2.5 years	>2.5-3 years
aJIA-ACR50, %	60.0	80.0	70.0	68.6	65.7	45.7	25.7	4.3
aJIA-ACR70, %	48.6	68.6	64.3	65.7	60.0	42.9	25.7	4.3
aJIA-ACR90, %	37.1	54.3	54.3	55.7	55.7	41.4	25.7	4.3
aJIA-ACR100, %	24.3	37.1	41.4	44.3	45.7	35.7	22.9	4.3

No-fever group	BSL-Day 15	Day 15-3 months	>3-6 months	>6-12 months	>1-1.5 years	>1.5-2 years	> 2-2.5 years	>2.5-3 years
aJIA-ACR50, %	67.3	84.6	73.1	69.2	71.2	51.9	40.4	5.8
aJIA-ACR70, %	48.1	75.0	71.2	63.5	65.4	46.2	38.5	5.8
aJIA-ACR90, %	34.6	51.9	57.7	46.2	50.0	38.5	36.5	5.8
aJIA-ACR100, %	19.2	40.9	42.3	40.4	42.3	28.8	28.8	5.8

Figure 2. Treatment response to canakinumab over time in patients with fever and patients without fever at baseline (BSL) (modified intent-to-treat analysis). **A**, Adapted juvenile idiopathic arthritis American College of Rheumatology (aJIA-ACR) 50, 70, 90, and 100 response rates over time in patients with fever and patients without fever at baseline. **B**, Juvenile Arthritis Disease Activity Score in 71 joints using the C-reactive protein level (JADAS-71-CRP) scores over time in patients with fever and patients without fever at baseline. Horizontal lines represent the cutoffs for high disease activity (HDA; >10.5), moderate disease activity (MDA; 3.9–10.5), low disease activity (LDA; ≤3.8), and inactive disease (ID; ≤1). Patients with fever at baseline and patients without fever at baseline were defined as patients with fever at enrollment and patients without fever at enrollment, respectively. Only the last available assessment within the given interval is taken into account. The day 15 visit was scheduled to take place on day 15 ± 5 days. Only patients with a value at both baseline and the respective postbaseline time point are included. Q1 = quartile 1.

fever and 9 patients (17.3%) and 12 patients (23.1%), respectively, in the group without fever, within the first 6 months of canakinumab exposure. At month 12, clinical remission according to the JADAS or the ACR criteria was maintained in 16 patients (22.9%) and 26 patients (37.1%), respectively, in the group with fever and 8 patients (15.4%) and 12 patients (23.1%), respectively, in the group without fever (see Supplementary Figure 3 for results of the modified ITT analysis and Supplementary Figure 4 for results of the LOCF method). The median time to the first study visit in which clinically inactive disease subsequently led to clinical remission according to the JADAS or clinical remission according to the ACR criteria was 56.5 days and 30.0 days, respectively, in the group with fever and 57.5 days and 141.5 days, respectively, in the group without fever.

Overall, 38 patients (30.9%) and 51 patients (41.5%) reached clinical remission according to the JADAS and clinical remission

according to the ACR criteria, respectively, during the study. Patients with an early response (those who achieved an aJIA-ACR 50 response by day 15 of canakinumab treatment) were more likely to have clinical remission according to the JADAS (odds ratio [OR] 12.907 [95% CI 4.009, 41.562], $P \leq 0.001$) and clinical remission according to the ACR criteria (OR 5.728 [95% CI 2.109, 15.554], $P < 0.001$) compared with other patients (Table 2). The presence of fever at baseline and no previous use of tocilizumab were associated with an increased probability of achieving clinical remission according to the JADAS but not according to the ACR criteria. In contrast, use of MTX and no use of glucocorticoids at baseline were associated with an increased probability of achieving clinical remission according to the ACR criteria but not according to the JADAS.

An exploratory analysis comparing early and late responders based on adapted aJIA-ACR 50 response by day 15 and disease duration indicated that disease duration was not a significant predictor of clinical remission (Supplementary Table 1, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract).

Efficacy of canakinumab in bDMARD-exposed versus bDMARD-naive subgroups. Of the 123 patients, 79 (64.2%) were previously exposed to bDMARDs. Of the 42 patients exposed to anakinra, 25 (59.5%) and 13 (31.0%) previously discontinued anakinra for inefficacy and safety/tolerability reasons, respectively. Of 26 patients who had received tocilizumab, 23 (88.5%) discontinued due to inefficacy and 1 (3.8%) discontinued due to safety concerns. On day 15, adapted aJIA-ACR 50, 70, 90, and 100 responses were achieved in higher numbers of bDMARD-naive patients (34 patients [77.3%], 26 patients [59.1%], 19 patients [43.2%], and 11 patients [25.0%], respectively) than bDMARD-exposed patients (43 patients [54.4%], 33 patients [41.8%], 25 patients [31.6%], and 16 patients [20.3%], respectively). Response rates increased until month 6 and were sustained until the end of the study in both subgroups (Supplementary Figure 1B, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract). Similar trends were observed for clinically inactive disease according to the ACR criteria.

Within the initial 15 days of canakinumab therapy, JADAS-71-CRP scores decreased by –77.3% in the bDMARD-naive subgroup (median absolute change –16.5 [Q1, Q3 –21.7, –10.0]) and –65.3% in the bDMARD-exposed subgroup (median absolute change –12.3 [Q1, Q3 –22.5, –6.0]). These reductions were sustained during the study. On day 15, a similar reduction in JADAS-71-CRP scores occurred in patients with prior exposure to anakinra (–71.3%; median absolute change –14.5 [Q1, Q3 –23.0, –5.2]) compared with anakinra-naive patients (–69.6%; median absolute change –15.1 [Q1, Q3 –21.7, –7.0]). JADAS-71-CRP scores further improved, and at month 6, there was a –95.7% reduction in anakinra-exposed patients (median absolute change –21.9 [Q1, Q3 –25.3, –11.9]) versus a –94.2% reduction in anakinra-naive patients (median absolute change –18.1 [Q1, Q3 –26.6, –11.0]). On day 15, a numerically smaller reduction in JADAS-71-CRP scores occurred in patients with prior exposure to tocilizumab (–58.1%; median absolute change –12.3 [Q1, Q3 –23.8, –8.4]) compared with tocilizumab-naive patients (–70.5%; median absolute change –15.7 [Q1, Q3 –21.4, –6.0]). Improvement continued, and at month 6, JADAS-71-CRP scores were reduced –91.6% in tocilizumab-exposed patients (median absolute change –21.0 [Q1, Q3 –31.7, –15.8]) versus –95.3% in tocilizumab-naive patients (median absolute change –18.2 [Q1, Q3 –24.4, –10.2]). Reduced levels of disease activity were maintained during the study.

The median time to the start of clinical remission according to the JADAS or according to the ACR criteria was between 57 and 58 days, irrespective of bDMARD exposure.

Table 2. Baseline predictors of clinical remission with canakinumab treatment (n = 122)*

	Clinical remission according to the JADAS			Clinical remission according to the ACR criteria		
Predictor	OR (95% CI)	*P*	AUC	OR (95% CI)	*P*	AUC
Early response (aJIA-ACR 50 by day 15)†	12.907 (4.009, 41.562)	0.001	0.786	5.728 (2.109, 15.554)	0.0008	0.766
Presence of fever at baseline†	2.952 (1.189, 7.328)	0.0203	0.786	2.184 (0.910, 5.238)	0.0794	0.766
No prior biologic exposure‡	1.851 (0.746, 4.590)	0.1810	0.763	1.347 (0.537, 3.380)	0.5216	0.770
No prior tocilizumab exposure†	4.023 (1.061, 15.247)	0.0408	0.786	1.033 (0.339, 3.145)	0.9543	0.766
No prior anakinra exposure†	1.708 (0.586, 4.979)	0.3223	0.786	1.324 (0.467, 3.751)	0.5937	0.766
No MTX exposure†	1.002 (0.360, 2.793)	0.9973	0.786	0.273 (0.103, 0.732)	0.0104	0.766
No glucocorticoid exposure†	1.151 (0.439, 3.012)	0.7726	0.786	2.948 (1.116, 7.787)	0.0296	0.766

* One patient was excluded due to missing fever assessment at baseline. Odds ratios (ORs), corresponding 95% confidence intervals (95% CIs), and *P* values are from generalized mixed models with clinical remission (according to the Juvenile Arthritis Disease Activity Score [JADAS] or the American College of Rheumatology [ACR] criteria) as the outcome; predictors with an OR >1 indicate higher odds of reaching clinical remission. For the area under the curve (AUC), 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the condition), 0.7–0.8 is considered acceptable, 0.8–0.9 is considered excellent, and >0.9 is considered outstanding. aJIA-ACR = adapted juvenile idiopathic arthritis ACR criteria.
† Model with early response, fever status at baseline, prior use of methotrexate (MTX), prior exposure to anakinra, prior exposure to tocilizumab, and glucocorticoid use at baseline as covariates.
‡ Model with early response, fever status at baseline, prior use of MTX, prior use of biologic disease-modifying antirheumatic drugs, and glucocorticoid use at baseline as covariates.

There was a trend for more bDMARD-naive patients to attain clinical remission according to the JADAS (12 [27.3%]) and according to the ACR criteria (15 [34.1%]) compared with bDMARD-exposed patients (14 [17.7%] and 23 [29.1%], respectively) by month 6 of the study. Rates of clinical remission according to the JADAS and ACR criteria by subgroup were maintained at month 12 (11 [25.0%] and 16 [36.4%], respectively, for bDMARD-naive patients versus 13 [16.5%] and 22 [27.8%], respectively, for bDMARD-exposed patients) and at month 24 (14 [31.8%] and 16 [36.4%], respectively, for bDMARD-naive patients versus 9 [11.4%] and 13 [16.5%], respectively, for bDMARD-exposed patients).

Systemic manifestations beyond fever. Splenomegaly was present at baseline in 5 patients (n = 1 patient with fever and 4 patients without fever) and resolved in all cases during the study. Hepatomegaly was present at baseline in 9 patients (n = 4 with patients with fever and 5 patients without fever), and resolved in 8 patients but remained in 1 patient with fever. At baseline, 1 patient without fever had clinically significant serositis, which regressed during the study. Lymphadenopathy at baseline was observed in 9 patients (n = 3 patients with fever and 6 patients without fever) and normalized during the study.

Glucocorticoid and canakinumab tapering. Seventy-one of 123 patients (57.7%) were receiving glucocorticoids at study entry, including 39 patients with fever and 31 patients without fever. Of these patients, 15 (38.5%) with fever and 12 (38.7%) without fever discontinued glucocorticoids. The remaining patients ended the study receiving a median glucocorticoid dose of 0.24 mg/kg/day in the group with fever (Q1, Q3 0.12, 0.59) and 0.19 mg/kg/day in the group without fever (Q1, Q3 0.13, 0.5), with 11 (28.2%) with fever and 10 (32.2%) without fever receiving doses <0.2 mg/kg/day (Figure 3 and Supplementary Figure 5, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract).

Patients who achieved an early response to canakinumab were more likely to achieve glucocorticoid-free status than those who did not (OR 19.065 [95% CI 3.193, 113.84]; $P = 0.002$) (Supplementary Figure 6, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract). In addition, the lower the CRP levels at baseline the higher the likelihood for the patient to become glucocorticoid-free ($P = 0.041$).

Canakinumab tapering was attempted in 23 of 123 patients (18.7%), 18 (14.6%) of whom continued to receive a reduced dose of 2 mg/kg canakinumab every 4 weeks for 3 consecutive visits without experiencing a flare. Of these 18 patients, 13 (10.6%) continued to receive a reduced dose until the end of the study with a median duration of 0.79 years (Q1, Q3 0.46, 0.84); 3 of 5 patients who required uptitration of canakinumab to 4 mg/kg due to disease worsening regained disease control.

Safety. Overall, the median duration of canakinumab exposure was 1.8 years (range 0.8–2.1 years), corresponding to 183.69 patient-years. The exposure-adjusted incidence rate of AEs and SAEs over the duration of the study was 819 per 100 patient-years and 56 per 100 patient-years, respectively. Higher incidence rates of AEs and SAEs (1,056.85 per 100 patient-years and 95.74 per 100 patient-years, respectively) were observed during the initial 6 months of the study, and then these rates decreased to 825.49 per 100 person-years and 59.05 per 100 person-years by month 24. Rates of serious infection remained stable over time (14.73 per 100 patient-years at month 6, 14.83 per 100 person-years at month 12, and 12.28 per 100 person-years at month 24).

Safety of canakinumab in patients with fever and patients without fever at baseline. The incidence rate of AEs in both subgroups are provided in Supplementary Table 2, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract. More SAEs were observed in the group with fever than in the group without fever throughout the study. Incidence rates decreased from month 6 on in both groups (in the group with fever versus the group without fever:

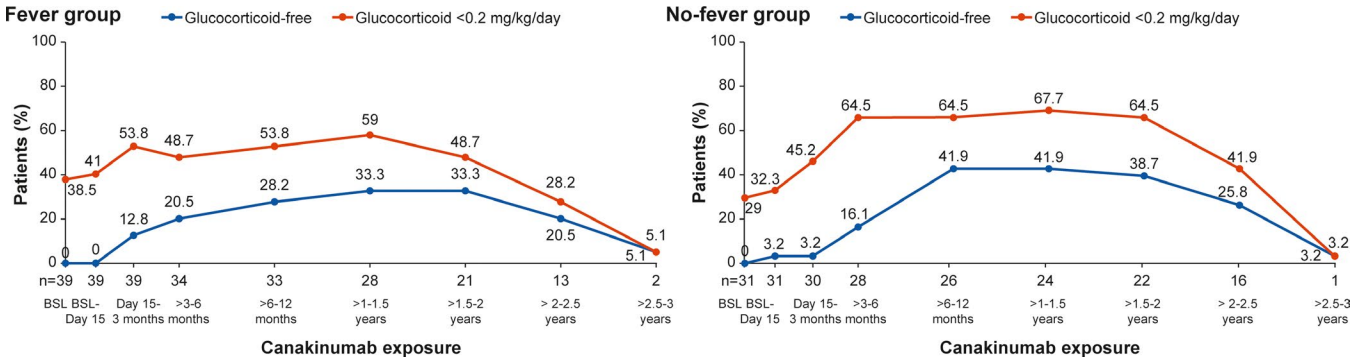


Figure 3. Glucocorticoid discontinuation and glucocorticoid tapering to <0.2 mg/kg/day in patients with fever and patients without fever at baseline (BSL) (modified intent-to-treat analysis). Only the last available assessment within the given interval is taken into account; the day 15 visit was scheduled to take place on day 15 ± 5 days.

116.15 per 100 person-years versus 69.90 per 100 person-years at month 6; 82.70 per 100 person-years versus 51.54 per 100 person-years at month 12; and 67.27 per 100 person-years versus 48.65 per 100 person-years at month 24). Rates of serious infections showed a similar pattern in both groups (Supplementary Figures 7 and 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract). The most common SAEs in both the group with fever and the group without fever were infections and infestations, musculoskeletal and connective tissue disorders, mainly indicating flares of the underlying disease, and blood and lymphatic disorders (Table 3).

Ten patients with fever had 15 events of serious infections (Table 3), 4 of which were severe (scarlet fever, herpes zoster, and 2 events of gastroenteritis), and 2 events (herpes zoster and 1 event of gastroenteritis) were considered related to study drug. Of these 15 serious infections, 2 were adjudicated as opportunistic: herpes zoster (n = 1) and rectosigmoiditis due to Epstein-Barr virus (EBV) on a background of ulcerative colitis (n = 1). Both events were severe; herpes zoster infection resolved following valacyclovir treatment, and the patient resumed canakinumab treatment until completion of the study. The patient with EBV suprainfection, although improved, discontinued the study.

In the group without fever, 3 patients had 7 events of serious infections (Table 3), 6 of which were severe (infected bites, cellulitis, lymphangitis, sepsis, lymph node abscess, and abscess neck), and 4 (cellulitis, lymphangitis, lymph node abscess, and abscess neck) were related to study drug. All events resolved.

In the safety population 3 events (infected fistula in the group without fever; salmonella sepsis and pneumonia in the group with fever) were adjudicated as uncommon, and 1 case (ulcerative colitis in association with infectious colitis due to EBV in the group with fever) was adjudicated as rare.

Safety of canakinumab considering prior bDMARD exposure and glucocorticoid use. The incidence of SAEs and serious infections at 6 months was higher in patients who were receiving glucocorticoids than in those who were not (SAEs, 110.33 per 100 patient-years versus 75.26 per 100 patient-years; serious infections, 18.91 per 100 patient-years versus 8.85 per 100 patient-years). Similarly, bDMARD-exposed patients

Table 3. Exposure-adjusted incidence rates of serious adverse events, by system organ class, in the patients with systemic JIA (n = 123)*

	No. (%)		No. of events/rate per 100 patient-years of exposure	
	Patients with fever (n = 70)	Patients without fever (n = 52)	Patients with fever (n = 70)	Patients without fever (n = 52)
Infections and infestations	10 (14.3)	3 (5.8)	15/14.8	7/8.6
Blood and lymphatic system disorders	9 (12.9)	4 (7.7)	13/12.8	8/9.8
Musculoskeletal and connective tissue disorders	10 (14.3)	7 (13.5)	13/12.8	8/9.8
General disorders and administration site conditions	4 (5.7)	2 (3.8)	6/6.0	2/2.5
Gastrointestinal disorders	2 (2.9)	3 (5.8)	3/3.0	3/3.5
Serious infections (by preferred term)				
Pneumonia	3 (4.3)	0 (0)	3/3.0	–
Gastroenteritis	2 (2.9)	0 (0)	2/2.0	–
Abscess neck	0 (0)	1 (1.9)	–	1/1.2
Bronchopneumonia	1 (1.4)	0 (0)	1/1.0	–
Cellulitis	0 (0)	1 (1.9)	-	1/1.2
Cytomegalovirus infection	1 (1.4)	0 (0)	1/1.0	–
Escherichia urinary tract infection	1 (1.4)	0 (0)	1/1.0	–
Furuncle	0 (0)	1 (1.9)	–	1/1.2
Herpes zoster	1 (1.4)	0 (0)	1/1.0	–
Infected bites	0 (0)	1 (1.9)	–	1/1.2
Influenza	1 (1.4)	0 (0)	1/1.0	–
Lymph node abscess	0 (0)	1 (1.9)	–	1/1.2
Lymphangitis	0 (0)	1 (1.9)	–	1/1.2
Otitis media acute	1 (1.4)	0 (0)	1/1.0	–
Salmonella sepsis	1 (1.4)	0 (0)	1/1.0	–
Scarlet fever	1 (1.4)	0 (0)	1/1.0	–
Sepsis	0 (0)	1 (1.9)	–	1/1.2
Staphylococcal sepsis	1 (1.4)	0 (0)	1/1.0	–
Varicella	1 (1.4)	0 (0)	1/1.0	–

* There was a total of 67,045 patient-years of exposure. A single patient may have experienced an event multiple times. Serious adverse events with a ≥5% incidence in any of the subgroups are shown. JIA = juvenile idiopathic arthritis.

(irrespective of prior biologic class) experienced more SAEs and serious infections at 6 months than bDMARD-naive patients (SAEs, 111.0 per 100 patient-years versus 69.72 per 100 patient-years; serious infections, 17.53 per 100 patient-years versus 9.96 per 100 patient-years). In all subgroups, SAEs and serious infection rates declined after month 6 (Supplementary Figures 7 and 8, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract).

One of the 5 patients (3 with fever and 2 without fever) with an adjudicated MAS event discontinued canakinumab. One patient reported 2 episodes of MAS, both in the context of systemic JIA flare. The adjudication committee noted that both episodes lacked classic laboratory features, most probably due to exposure to very high canakinumab dosing (4 mg/kg every 2 weeks) (5). There was 1 case of malignancy (anaplastic large cell lymphoma) in a patient with fever, diagnosed after 113 days of canakinumab treatment and considered unlikely to be related to canakinumab (Supplementary Results, available on the *Arthritis & Rheumatology* website at http://onlinelibrary.wiley.com/doi/10.1002/art.41436/abstract). Three patients (1 treated with MTX) had detectable anti-canakinumab antibodies with subsequent negative neutralizing antibodies.

DISCUSSION

In this 2-year, single-arm, open-label study, canakinumab therapy resulted in rapid and sustained clinical and serologic improvement accompanied by glucocorticoid discontinuation in a sizable proportion of children with active systemic JIA, irrespective of a more prominent systemic or articular phenotype at baseline. Baseline fever status had little impact on a rapid response to canakinumab, or on the ability to taper or discontinue glucocorticoids, but a trend was noted toward a higher frequency of SAEs among patients with fever at baseline.

The results of this study are consistent with those of recently published 5-year data from other patients with systemic JIA treated with canakinumab (20) and validate the notion of an early response to canakinumab as a reliable clinical predictor of sustained long-term response. As such, rapid response to canakinumab at an aJIA-ACR 50 level or higher was the most important predictor of achievement of clinical remission in a patient with systemic JIA during the study.

Our results corroborate the notion that reaching inactive disease and maintaining clinical remission of systemic JIA is possible, and hence can be considered an achievable goal of treat-to-target strategies for systemic JIA (36). In the context of treat-to-target and reduction of long-term safety effects, the ability to discontinue glucocorticoids is of particular relevance for systemic JIA. The majority of patients who needed glucocorticoid treatment at baseline were able to substantially decrease or even discontinue glucocorticoids with canakinumab therapy, highlighting the importance of canakinumab in systemic JIA therapy.

Reducing the canakinumab dose to 2 mg/kg every 4 weeks while maintaining well-controlled disease activity was only possible in a few patients who attempted tapering of canakinumab. A better understanding of how to best decrease canakinumab dosage and which patients with systemic JIA could tolerate a dose reduction is still needed. This was the primary objective of a recently completed phase IIIb/IV clinical trial (ClinicalTrials.gov identifier: NCT02296424).

The long-term use of canakinumab was well tolerated and consistent with the known safety profile of canakinumab in systemic JIA and other autoinflammatory diseases (37,38). A decline in AEs, SAEs, and serious infections was observed in this study after the first 6 months of canakinumab initiation in the overall systemic JIA population and consistently in all subgroups as identified by the presence of fever, glucocorticoid use, and prior bDMARD exposure. Glucocorticoid exposure was associated with more frequent SAEs, including serious infections, supporting the notion that early glucocorticoid tapering may be considered as one of the key imperatives in the treatment of systemic JIA.

The SAE and AE rates in this study were numerically higher than those that have been reported in other studies of systemic JIA patients treated with IL-6 and/or IL-1 inhibitors (12,14). However, such comparisons are rather difficult to make due to differences in eligibility criteria, background medications, and the severity of systemic JIA in the study population at large. Therefore, we consider differences in SAE/AE rates to be small, and hence of little or no clinical relevance.

Active systemic JIA is considered one of the risk factors for MAS (4). Despite excellent control of systemic JIA with canakinumab, MAS events occurred, even in those patients whose disease was under good control with canakinumab.

Possible limitations of this study include the small sample size and the relatively short duration, which makes the detection of rare and late safety signals unlikely. The various subgroups identified post hoc and counting of patients with systemic features other than fever in the group without fever may have introduced some interpretation bias.

In conclusion, canakinumab provided rapid and sustained high responses in systemic JIA patients with either articular or systemic phenotypes, accompanied by a significant ability to taper glucocorticoids. Sustained canakinumab tapering could be obtained in a minority of patients with well-controlled disease activity and ≥6 months after canakinumab initiation. An early response to canakinumab, consistent with the results of a previous study (20), was the strongest predictor of clinical remission, giving physicians tangible clinical elements on which to base their decision-making when treating systemic JIA.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be published. Dr. Brunner had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Brunner, Vougiouka, Martini, Lovell, Ruperto.

Acquisition of data. Brunner, Quartier, Alexeeva, Constantin, Koné-Paut, Marzan, Schneider, Wulffraat, Chasnyk, Tirosh, Kallinich, Kuemmerle-Deschner, Wouters, Lauwerys, Nikishina, Trachana, Vougiouka, Martini, Lovell, Ruperto.

Analysis and interpretation of data. Brunner, Quartier, Constantin, Koné-Paut, Schneider, Wulffraat, Kallinich, Kuemmerle-Deschner, Lauwerys, Vougiouka, Martini, Lovell, Levy, Vritzali, Ruperto.

ROLE OF THE STUDY SPONSOR

Novartis Pharma facilitated the study design together with the authors Brunner, Martini, Lovell, and Ruperto, provided writing assistance for the manuscript, and reviewed and approved the manuscript prior to submission. The authors independently collected the data, interpreted the results, and had the final decision to submit the manuscript for publication. Medical writing and editorial assistance was provided by Divya Chandrasekhar, PhD (Novartis Healthcare Pvt Ltd, Hyderabad, India, which was funded by Novartis Pharma AG, Basel, Switzerland). Publication of this article was not contingent upon approval by Novartis.

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APPENDIX A: THE PAEDIATRIC RHEUMATOLOGY INTERNATIONAL TRIALS ORGANISATION AND THE PEDIATRIC RHEUMATOLOGY COLLABORATIVE STUDY GROUP

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