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Efficacy and Safety of Canakinumab in sJIA Patients with and without Fever at Baseline: Results from an Open-label, Active Treatment Extension Study

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ABSTRACT (word limit: 250)

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

Methods: At enrollment, active sJIA patients (2–<20 years) started open-label canakinumab (4mg/kg every 4 weeks [q4w] subcutaneously). Efficacy measures included the adapted JIA American College of Rheumatology (aJIA-ACR) criteria, Juvenile Arthritis Disease Activity Score (JADAS), and clinically inactive disease (CID)/clinical remission on medication (CR), evaluated by either JADAS (CID_{JADAS}/CR_{JADAS}) or ACR criteria (CID_{ACR}/CR_{ACR}).

Results: Of the 123 patients (Fever, n=70; No-fever, n=52), 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 (Fever: 60.0%/48.6%/37.1%/24.3%; No-fever: 67.3%/48.1%/34.6%/19.2%), which further increased thereafter. By Month 6, CR_{JADAS}/CR_{ACR} was achieved by 17 (24.3%)/26 (37.1%) patients with fever and 9 (17.3%)/12 (23.1%) patients without fever. Median time to onset of CR_{JADAS}/CR_{ACR} was 57/30 days and 58/142 days in the Fever/No-fever groups, respectively. An aJIA-ACR50 response by Day 15 was the strongest predictor for achieving CR_{JADAS} (OR: 13 [4–42]; $p<0.0001$) or glucocorticoid discontinuation (OR: 19 [3–114]; $p=0.002$). Of the 71/123 (57.7%) patients 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 Fever/No-fever subgroups; 13 patients (10.6%) tolerated a sustained canakinumab dose reduction to 2 mg/kg/q4w. No new safety findings were observed.

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

INTRODUCTION

Systemic juvenile idiopathic arthritis (sJIA) 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 sJIA is macrophage activation syndrome (MAS) (3–7). It has been suggested that immunology of sJIA changes during the disease course, especially after the systemic features present at diagnosis have resolved (8). Poor control of disease activity can lead to long-term disability and reduced patient quality of life (1, 9). 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 sJIA treatment strategies (10–12).

Studies have shown that blockade of interleukin (IL)-1 and IL-6 are effective treatment strategies of sJIA (13–19). Canakinumab, a selective anti-IL-1 β monoclonal antibody, tested in 3 Phase II-III trials (16, 20, 21) demonstrated fast onset of action in sJIA, 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 sJIA features (21).

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

MATERIALS AND METHODS

Study design

This was a prospective, long-term, open-label active treatment study of newly-recruited canakinumab-naïve sJIA patients, with and without fever at enrollment, introduced via a Protocol Amendment in the extension study previously reported where only children with fever were enrolled (NCT00889863, NCT00886769) (21). The aim of the study was to compare the efficacy of canakinumab when used for the treatment of sJIA patients with or

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 as patients with history of MAS were allowed to participate in the trial.

Canakinumab therapy was commenced at 4mg/kg body weight every 4 weeks (q4w). 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 q4w was permitted as per physician judgment in patients who were glucocorticoid-free (supplementary file).

Patients

Patients (2–<20 years) with active sJIA were allowed to enroll in the study. Active sJIA was defined by the presence of ≥ 2 of the following criteria: 1) fever at baseline (defined as spiking, intermittent fever [body temperature $>38^{\circ}\text{C}$] for ≥ 1 day during the screening period and within 1 week before first canakinumab dose), 2) rash, 3) serositis, 4) hepatosplenomegaly, 5) lymphadenopathy, 6) arthritis in ≥ 2 active joints, 7) C- reactive protein (CRP) level of >30 mg/L (normal range: 0–10 mg/L). 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 anti-inflammatory 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 of canakinumab, malignancies, active and/or recurrent infections, including human immunodeficiency virus, hepatitis B or C infection.

Patients were enrolled into and followed in the study between 8th February 2012 and 10th December 2014 in 15 countries at 37 centers that were members of the Paediatric Rheumatology International Trials Organisation (PRINTO; 22) and the Pediatric Rheumatology Collaborative Study Group (PRCSG; 23). 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.

Disease activity and safety assessments

Efficacy of canakinumab was assessed by time windows at Day 15, Month 3, and 3-monthly thereafter by means of various composite measures: i) adapted JIA American College of Rheumatology (aJIA-ACR) 50/70/90/100 response criteria (24, 25), which include the components of the JIA core set along with the absence of fever (defined as temperature $\leq 38^{\circ}\text{C}$ in the preceding 7 days); ii) clinically inactive disease (CID) and clinical remission on medication (CR), defined as at least 6 consecutive months of CID were evaluated by both the ACR criteria ($\text{CID}_{\text{ACR}}/\text{CR}_{\text{ACR}}$) (26, 27) and the Juvenile Arthritis Disease Activity Score [JADAS] 71-CRP criteria ($\text{CID}_{\text{JADAS}}/\text{CR}_{\text{JADAS}}, \leq 1$); iii) disease activity was measured by means of JADAS 71-CRP levels (inactive disease, ≤ 1 ; low disease activity [LDA], ≤ 3.8 ; moderate disease activity [MDA], 3.9–10.5; high disease activity, >10.5) (28–30); 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).

Anti-canakinumab antibodies (ADA) 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 (31, 32).

Statistical analysis

The Consolidated Standards of Reporting Trials (CONSORT; 33, 34) and Strengthening the Reporting of Observational Studies in Epidemiology (STROBE; 35) statements were followed. One patient was excluded from the efficacy analyses as fever status was unknown at baseline. Demographic, baseline characteristics, and response to therapy were descriptively summarized for the fever subgroups using frequencies or percentages or medians (quartile 1 [Q1], quartile 3 [Q3]) as appropriate. Efficacy and safety were assessed

for the subgroups of patients defined by presence of i) fever at baseline, ii) prior use of any bDMARDs; and iii) treatment with anakinra or tocilizumab just prior to enrolment.

Safety was also assessed for the subgroup of patients who used glucocorticoids at baseline. Fever subgroups were compared for prior use of bDMARDs at baseline by Wilcoxon two-sample test and for CRP levels by Fisher's Exact test. Efficacy analyses were performed in two ways: (1) in the modified intent-to-treat (mITT) population based on observed data (36) and (2) with missing data imputed using last observation carried forward (LOCF).

To identify predictors of achieving remission, CR_{JADAS} was modeled using the generalized mixed models framework. Predictor (or independent) variables of the first model included early response (aJIA-ACR50 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.

Median [Q1;Q3] of the time to start of CR_{JADAS} was also determined by subgroups. Herein, time to start of CR_{JADAS} was defined as the time interval between starting canakinumab and the first visit when CID_{JADAS} that persisted for 6 or more consecutive months was observed.

In order to check whether these results were reproducible for remission as per ACR, all analyses were duplicated for CR_{ACR} .

Glucocorticoid tapering was analyzed for the percentage of patients who discontinued and amounts at end of study (median [Q1, Q3], >0.2 mg/kg/day, and <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, CRP and a center-related random effect were used as independent variables. Glucocorticoid doses were reported as prednisone equivalent doses per bodyweight (mg/kg/day).

AEs were analyzed every 3 months from baseline until the end of study as incidence and exposure-adjusted incidence (per 100 patients-years [PY]) together with the corresponding

95% Poisson confidence interval (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 by fever status at baseline, glucocorticoid use at baseline, prior exposure to bDMARDs, and prior exposure to anakinra/tocilizumab. Safety was assessed in all study participants who received at least one 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 mITT population of 123 patients. P-values listed in this manuscript are nominal.

RESULTS

Baseline characteristics and patient disposition in patients with and without fever

Demographics and baseline characteristics of 123 patients with (n=70, 56.9%) and without fever (n=52, 42.3%) are presented in **Table 1**. Patients in the Fever group were older at sJIA disease onset and had higher CRP (123.7 mg/L vs. 49.7 mg/L; $p<0.0001$) at baseline vs. the No-fever group. At baseline, the Fever and No-fever groups both had high disease activity, many active joints, and had similar MTX and glucocorticoid use. There were numerical differences in prior bDMARD exposure (Fever vs No-fever group: 68.6% [48/70] vs. 57.7% [30/52]; $p=0.255$). Anakinra was the most frequently used prior bDMARD.

The study was completed by 84 (68.3%) patients (median [min-max] exposure of 1.8 [0–2.8] years), including 49 (70.0%) in the Fever group and 35 (67.3%) in the No-fever group (**Figure 1**). Inadequate response to canakinumab was the main reason for study discontinuation (n=10 each for both groups); more patients in the Fever group (n=10) discontinued due to AEs than in the No-fever group (n=4).

Efficacy of canakinumab by fever status at baseline

Shown in **Figure 2, Panel A**, aJIA-ACR 50/70/90/100 responses (n [% of N]) at Day 15 since canakinumab initiation were achieved by 42 [60.0%]/34 [48.6%]/26 [37.1%] and 17 [24.3%] patients in the Fever group. Similar levels of response occurred in the No-fever group (aJIA-ACR 50/70/90/100: 35 [67.3%]/25 [48.1%]/18 [34.6%]/10 [19.2%]). Response rates increased until Month 6 post-canakinumab initiation and were sustained for the initial

1.5 years of the study in both subgroups. The apparent decline in response rates after 1.5 years was due to patients' loss to follow-up and the conservative mITT approach; the corresponding information on analyses using the LOCF approach is reported in the supplement (**Supplementary Figure S1A**).

JADAS71-CRP: Moderate Disease Activity, Low Disease Activity and Clinical Inactive Disease

There was a notable decrease in JADAS71-CRP from baseline to Day 15. The median absolute reduction of the JADAS71-CRP was -16.6 (Q1, -23.1 ; Q3, -6.0 ; -74.9%) in the Fever group and -11.9 (Q1, -19.2 ; Q3, -7.0 ; -65.5%) in the No-fever group. Compared with baseline, JADAS71-CRP was 88.1% lower (median change: -18.3 Q1, -26.6 ; Q3, -14.5) in the Fever group and 90.9% lower (median change: -16.2 Q1, -23.5 ; Q3, -12.3) in the No-fever group at Month 3. This decrease was similar at Month 6 and sustained over the course of the study thereafter (**Figure 2, Panel B** [mITT]; **Supplementary Figure S2** [LOCF]).

MDA_{JADAS} status at Day 15/Month 3 was achieved by 45 (64.3%)/51 (72.9%) patients in the Fever group and 33 (63.5%)/42 (80.8%) patients in the No-fever group.

LDA_{JADAS} status at Month 3 of the study occurred in 41 (58.6%) patients in the Fever group and 34 (65.4%) in the No-fever group. At Months 12/ 24, there were 39 (55.7%)/29 (41.4%) patients in the Fever group in LDA_{JADAS} status as compared with 31 (59.6%)/22 (42.3%) patients in the No-fever group.

At Day 15, CID_{JADAS}/CID_{ACR} was achieved by 13 (18.6%)/16 (22.9%) patients in the Fever group and 11 (21.2%)/12 (23.1%) patients in the No-fever group. At Month 6, the number of patients with CID_{JADAS}/CID_{ACR} were 27 (38.6%)/34 (48.6%) and 22 (42.3%)/23 (44.2%) in the Fever group vs the No-fever group (**Supplementary Figures S3** [mITT], **S4** [LOCF]).

Clinical Remission and baseline predictors

First occurrence of CID status that 6 months later led to CR_{JADAS}/CR_{ACR} was achieved by 17 (24.3%)/26 (37.1%) patients in the Fever group and 9 (17.3%)/12 (23.1%) patients in the No-fever group, within the first 6 months of canakinumab exposure. At Month 12,

CR_{JADAS}/CR_{ACR} was maintained in 16 (22.9%)/26 (37.1%) and 8 (15.4%)/12 (23.1%) patients in the Fever and No-fever groups, respectively (**Supplementary Figures S3** [mITT], **S4** [LOCF]). The median time to the first study visit in which CID subsequently led to CR_{JADAS}/CR_{ACR} was 56.5/30.0 days in the Fever group and 57.5/141.5 days in the No-fever group.

Overall, 38 (30.9%)/51 (41.5%) patients were able to reach CR_{JADAS}/CR_{ACR}, respectively, during the study. Patients with an early response (aJIA-ACR50 by Day 15 of canakinumab) were more likely to have CR_{JADAS} (odds ratio [OR]: 12.907 [CI 4.009–41.562], $p < 0.0001$) and CR_{ACR} (OR: 5.728 [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 increased probability to have CR_{JADAS}, but not CR_{ACR}. In contrast, the use of MTX and no usage of glucocorticoids at baseline were associated with increased probability of CR_{ACR}, but not CR_{JADAS}.

An exploratory analysis comparing early and late responders based on aJIA-ACR 50 by Day 15 responses and disease duration status indicated that disease duration was not a statistically significant predictor of CR (**Supplementary Table S1**).

Efficacy of canakinumab in bDMARD-exposed versus bDMARD-naïve subgroups

Of the 123 patients, 79 (64.2%) were previously exposed to bDMARDs. Of the 42 patients exposed to anakinra, 25/42 (59.5%) and 13/42 (31.0%) previously discontinued anakinra for inefficacy and safety/tolerability reasons, respectively. A total of 23/26 (88.5%) and 1/26 (3.8%) patients discontinued tocilizumab due to inefficacy and safety, respectively. At Day 15, aJIA-ACR50/70/90/100 responses (n [%N]) were numerically higher among bDMARD-naïve patients (34 [77.3%]/26 [59.1%]/19 [43.2%]/11 [25.0%]) than bDMARD-exposed patients (43 [54.4%]/33 [41.8%]/25 [31.6%]/16 [20.3%]). Response rates increased until Month 6 and were sustained until the end of the study in both subgroups (**Supplementary Figure S1B**). Similar trends were observed for CID_{ACR}.

Within the initial 15 days of canakinumab therapy, JADAS71-CRP scores decreased by 77.3% (median [Q1, Q3] of absolute change: –16.5 [–21.7, –10.0]) in bDMARD-naïve subgroup and –65.3% (median [Q1, Q3] of absolute change: –12.3 [–22.5, –6.0]) in

bDMARD-exposed subgroup. These reductions were sustained during the study. At Day 15, a similar reduction in JADAS71-CRP scores occurred in patients with prior exposure to anakinra (–71.3%, median [Q1, Q3] of absolute change: –14.5 [–23.0, –5.2]) compared with anakinra-naïve patients (–69.6% (median [Q1, Q3] of absolute change: –15.1 [–21.7, –7.0])). JADAS71-CRP scores further improved and at Month 6, there was –95.7% reduction (median [Q1, Q3] of absolute change: –21.9 [–25.3, –11.9]) in anakinra-exposed patients vs. –94.2% reduction (median [Q1, Q3] of absolute change: –18.1 [–26.6, –11.0]) in naïve patients. At Day 15, a numerically smaller reduction in JADAS71-CRP scores occurred in patients with prior exposure to tocilizumab (–58.1%, median [Q1, Q3] of absolute change: –12.3 [–23.8, –8.4]) compared with tocilizumab-naïve patients (–70.5% (median [Q1, Q3] of absolute change: –15.7 [–21.4, –6.0])). Improvement continued and at Month 6, JADAS71-CRP scores had a –91.6% reduction (median [Q1, Q3] of absolute change: –21.0 [–31.7, –15.8]) in tocilizumab-exposed patients vs. –95.3% reduction (median [Q1, Q3] of absolute change: –18.2 [–24.4, –10.2]) in naïve patients. Reduced levels of disease activity were maintained during the study.

The median time to the start of CR_{JADAS}/CR_{ACR} was between 57 to 58 days irrespective of bDMARD exposure.

There was a trend of more bDMARD-naïve patients (12 [27.3%]/15 [34.1%]) to attain CR_{JADAS}/CR_{ACR} as compared with bDMARD-exposed patients (14 [17.7%]/23 [29.1%]) by Month 6 of the study. CR_{JADAS}/CR_{ACR} rates by subgroup were maintained (bDMARD-naïve vs. bDMARD-exposed patients: 11 [25.0%]/16 [36.4%] vs. 13 [16.5%]/22 [27.8%]) at Month 12 and Month 24 (14 [31.8%]/16 [36.4%] vs. 9 [11.4%]/13 [16.5%]).

Systemic manifestations beyond fever

Splenomegaly present at baseline in 5 patients (Fever group, n=1; No-fever group, n=4) resolved during the study. Hepatomegaly at baseline in the 9 patients (Fever group, n=4; No-fever group, n=5) resolved in 8 patients but remained in 1 patient in the Fever group. At baseline, 1 patient in the No-fever group had clinically significant serositis, which regressed during the study. Lymphadenopathy at baseline observed in 9 patients (Fever group, n=3; No-fever group, n=6) normalized during the study.

Glucocorticoid and canakinumab tapering

Of the 71/123 (57.7%) patients who were on glucocorticoids at study entry, 15/39 (38.5%) patients in the Fever group and 12/31 (38.7%) in the No-fever group discontinued glucocorticoids. The remaining patients ended the study receiving a median glucocorticoid dose of 0.24 mg/kg/day (Q1,Q3: 0.12–0.59) in the Fever group and 0.19 mg/kg/day (Q1,Q3: 0.13–0.5) in the No-fever group, with 11/39 (28.2%) and 10/31 (32.2%) patients receiving doses below 0.2 mg/kg/day, respectively (**Figure 3, Supplementary Figure S5**).

Patients who achieved an early response to canakinumab were more likely to achieve glucocorticoid-free status (OR=19.065 [3.193–113.84]; p=0.002, **Supplementary Figure S6**) than those who did not. 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 23/123 patients (18.7%), 18 of whom (14.6%) remained on a reduced dose of 2mg/kg/q4w canakinumab for 3 consecutive visits without flaring. Of these 18 patients, 13 (10.6%) remained on a reduced dose until end of 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 4mg/kg due to disease worsening regained disease control.

Safety

Overall, median duration of canakinumab exposure was 1.8 (0.8–2.1) years, corresponding to 183.69 PY. The exposure-adjusted incidence rate of AEs and SAEs over the duration of the study was 819/100 PY and 56/100 PY, respectively. Higher incidence rates of AEs and SAEs (1056.85/100 PY and 95.74/100 PY) were observed during the initial 6 months of the study, and then these rates decreased to 825.49/100 PY and 59.05/100 PY by Month 24.

Rates for serious infection remained stable over time (Month 6: 14.73/100; Month 12: 14.83/100 PY; Month 24: 12.28/100 PY).

Safety of canakinumab in patients with and without fever at baseline

The incidence rate of AEs in both subgroups are provided in **Supplementary Table S2**. More SAEs were observed in the Fever group vs No-fever group throughout the study.

Incidence rates decreased from Month 6 onwards in both groups (Fever vs. No-fever group; Month 6: 116.15/100 PY vs. 69.90/100 PY; Month 12: 82.70/100 PY vs. 51.54/100 PY; Month 24: 67.27/100 PY vs. 48.65/100 PY). Rates of serious infections showed a similar pattern in both groups (**Supplementary Figure S7, S8**). The most common SAEs in the Fever and No-fever groups were infections and infestations followed by musculoskeletal and connective tissue disorders, mainly indicating flares of the underlying disease, and blood and lymphatic disorders (**Table 3**).

Ten patients in the Fever-group 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 EBV on background of ulcerative colitis (n=1). Both events were severe; herpes zoster infection resolved following valacyclovir, and the patient resumed canakinumab until completion of the study. The patient with EBV suprainfection, although improved, discontinued the study.

In the No-fever group 3 patients had 7 events of serious infections (**Table 3**), 6 of which were severe (infected bites, cellulitis, lymphangitis, sepsis, lymph node abscess, abscess neck) and 4 (cellulitis, lymphangitis, lymph node abscess, abscess neck) were related to study drug. All events resolved.

In the safety population 3 events (No-fever group: infected fistula; Fever-group: salmonella sepsis, pneumonia) were adjudicated as uncommon and 1 case (Fever-group: ulcerative colitis in association with infectious colitis due to EBV) was adjudicated as rare.

Safety of canakinumab considering prior bDMARD exposure and glucocorticoid use

The incidence of SAEs and serious infections was higher in patients with glucocorticoid use vs glucocorticoid-free patients (6 months: SAEs: 110.33/100 PY vs. 75.26/100 PY and serious infections: 18.91/100 PY vs. 8.85/100 PY). Similarly, bDMARD-exposed (irrespective of prior biologic class) vs bDMARD-naïve patients had more SAEs (6 months: 111.0/100 PY vs. 69.72/100 PY) and serious infections (17.53/100 PY vs. 9.96/100 PY). In all subgroups, SAEs and serious infection rates declined after Month 6 (**Supplementary Figure S7, S8**).

One of the 5 patients (Fever group: 3; No-fever group: 2) with an adjudicated MAS event discontinued canakinumab. One patient reported 2 episodes of MAS, both in the context of sJIA flare. The adjudication committee noted that both episodes lacked classic laboratory features most probably due to exposure to very high canakinumab dosing (4mg/kg every 2 weeks) (5). There was 1 case of malignancy (anaplastic large cell lymphoma) in the Fever group, diagnosed after 113 days of canakinumab and considered unlikely related to canakinumab (supplementary file). Three patients (1 treated with MTX) had detectable ADAs with subsequent negative neutralizing antibodies.

DISCUSSION

In this 2-year, single arm, open-label study, canakinumab therapy resulted in rapid and sustained clinical and serological improvement accompanied by glucocorticoid discontinuation in a sizable proportion of children with active sJIA, 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 towards 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 of other sJIA patients treated with canakinumab (21) and validate the notion of early response to canakinumab as a reliable clinical predictor of sustained long-term response. As such, rapid response to canakinumab at an aJIA-ACR50 level or higher was the most important predictor for an sJIA patient to achieve CR during the study.

Our results corroborate that reaching inactive disease and maintaining CR of sJIA is possible, hence can be considered an achievable goal of treat-to-target strategies for sJIA (37). In the context of treat-to-target and reduction of long-term safety effects, the ability to discontinue glucocorticoids is of particular relevance for sJIA. The majority of patients requiring glucocorticoid treatment at baseline were able to substantially decrease or even discontinue glucocorticoids with canakinumab therapy, highlighting the importance of canakinumab in sJIA therapy.

Reducing the canakinumab dose to 2mg/kg q4w 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 sJIA patient could tolerate a dose-reduction is still needed. This was the primary objective of a recently completed Phase IIIb/IV clinical trial (NCT02296424).

The long-term use of canakinumab was well tolerated and consistent with the known safety profile of canakinumab in sJIA and other autoinflammatory diseases (38, 39). A decline in AEs, SAEs, and serious infections was observed in this study after the first 6 months of canakinumab initiation in the overall sJIA 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 that early glucocorticoid tapering may be considered as one of the key imperatives in the treatment of sJIA.

The SAE and AE rates in this study were numerically higher than what has been reported in other studies of sJIA patients treated with IL-6 and/or IL-1 inhibitors (13,15). However, such comparisons are rather difficult to make due to differences in eligibility criteria, background medications, and the severity of sJIA in the study population at large. Therefore, we consider differences in SAE/AE rates to be small, hence of little or no clinical relevance.

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

Possible limitations of this study include the small sample size and the relatively short duration making the detection of rare and late safety signals unlikely. The various subgroups identified *post-hoc* and counting of patients with other systemic features than fever in the No-fever group may have introduced some interpretation bias.

In conclusion, canakinumab provided rapid and sustained high responses in sJIA 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 at least 6 months after canakinumab initiation. An

early response to canakinumab in keeping with results from the previous study (21) was the strongest predictor of CR, giving physicians tangible clinical elements on which to base their decision-making when treating sJIA.

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Figure legends

Figure 1. Patient disposition

*For 1 patient, fever at baseline was not reported and not included in the efficacy and safety analysis for the fever subgroups. The missing patient discontinued the study due to lost to follow-up

N, total number of patients in the study; n, number of patients in the fever subgroups

Figure 2. Treatment response to canakinumab over time in patients with and without fever at baseline (mITT)

Panel A: aJIA-ACR response rates over time in patients with and without fever at baseline (mITT).

Panel B: JADAS71-CRP scores over time in patients with and without fever at baseline (mITT). Horizontal lines in panel B represent the cut-offs for JADAS HDA >10.5, MDA 3.9 – 10.5, LDA ≤3.8 and inactive disease ≤1.

Patients with and without fever at baseline are defined as patients with and without fever at enrollment. Only the last available assessment within the given interval is taken into account. The visit at Day 15 was scheduled to take place at Day 15+/- 5 days. Only patients with a value at both baseline and the respective post-baseline time point are included

aJIA-ACR, adapted juvenile idiopathic arthritis by American College of Rheumatology criteria; BSL, baseline; HDA, high disease activity; ID, inactive disease; JADAS, Juvenile Arthritis Disease Activity Score; LDA, low disease activity; MDA, moderate disease activity, mITT, modified intent-to-treat; n, number of patients available for assessments in the subgroups

Figure 3. Glucocorticoid tapering and discontinuation in patients with and without fever at baseline (mITT)

Only the last available assessment within the given interval is taken into account; the visit at Day 15 was scheduled to take place at Day 15 +/- 5 days

BSL, baseline; mITT, modified intent-to-treat; n, number of patients available for assessments in the subgroups

Table 1. Demographics and baseline disease characteristics of patients

Characteristics n (%) or median (1st–3rd quartiles)	sJIA patients, N=123*	
	Fever group N=70[†]	No-fever group N=52[†]
Female	44 (62.9)	31 (59.6)
Caucasian race	63 (90.0)	47 (90.4)
Presence of systemic signs for >6 months of disease	55 (78.6)	39 (75.0)
Age at sJIA 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/L)	123.7 (45–223.3)	49.7 (10.5–91.0)
Physician global assessment of disease activity (VAS in mm)	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)
CHAQ Disability Index score ^{††}	1.6 (0.8–2.1)	1.3 (0.6–1.8)
Patient's assessment of overall wellbeing (VAS in mm) [#]	61 (31.0–75.0)	48 (27.0–66.0)
JADAS71-CRP ^{**}	24.4 (18.5–33.3)	20.4 (16.7–29.3)
MTX therapy	30 (42.9)	23 (44.2)
Glucocorticoids	39 (55.7)	31 (59.6)
Any prior use of biologic DMARDs [‡]	48 (68.6)	30 (57.7)
1 biologic DMARD	30 (42.9)	15 (28.8)
2 biologic DMARDs	18 (25.7)	15 (28.8)

*The fever question used to define these subgroups was not reported at baseline for one patient. Therefore, the numbers do not add up to 123

[†]n is indicated in the rows only if the total number is different from the heading column

[#]By parent proxy report of patient self-report; data was available only in 69 patients in the Fever group and 52 in the No-fever group

^{***}The range of possible values for number of joints with active arthritis was 0–73

[‡]The range of possible values for number of joints with limited range of motion was 0–69

^{††}Range: 0–30 = no disability; data available only for 69 patients in the Fever group

[^]Information was available only in 55 patients in the Fever group and 42 patients in the No-fever group

^{**}Data available only for 68 patients in the Fever group

[‡]Biologic DMARDs included anakinra, tocilizumab, etanercept, abatacept and adalimumab

CHAQ, Child Health Assessment Questionnaire; CRP, C–reactive protein; DMARD, disease modifying antirheumatic drug; JADAS, Juvenile Arthritis Disease Activity Score; MTX, methotrexate; SD, standard deviation; sJIA, systemic juvenile idiopathic arthritis; VAS, visual analog scale

Table 2. Baseline predictors of clinical remission with canakinumab treatment[†]

Predictor	CR _{JADAS}	AUC	CR _{ACR}	AUC
aJIA-ACR50 by 15 days*	12.907 (4.009–41.562) <i>P-value = 0.001</i>	0.786	5.728 (2.109–15.554) <i>P-value = 0.0008</i>	0.766
Presence of fever at baseline*	2.952 (1.189–7.328) <i>P-value = 0.0203</i>	0.786	2.184 (0.910–5.238) <i>P-value = 0.0794</i>	0.766
No prior biologic exposure [^]	1.851 (0.746–4.590) <i>P-value = 0.1810</i>	0.763	1.347 (0.537–3.380) <i>P-value = 0.5216</i>	0.770
No prior tocilizumab exposure*	4.023 (1.061–15.247) <i>P-value = 0.0408</i>	0.786	1.033 (0.339–3.145) <i>P-value = 0.9543</i>	0.766
No prior anakinra exposure*	1.708 (0.586–4.979) <i>P-value = 0.3223</i>	0.786	1.324 (0.467–3.751) <i>P-value = 0.5937</i>	0.766
No MTX exposure*	1.002 (0.360–2.793) <i>P-value = 0.9973</i>	0.786	0.273 (0.103–0.732) <i>P-value = 0.0104</i>	0.766
No glucocorticoid exposure*	1.151 (0.439 – 3.012) <i>P-value = 0.7726</i>	0.786	2.948 (1.116 – 7.787) <i>P-value = 0.0296</i>	0.766

n=122, one patient was excluded due to the missing fever assessment at baseline

[†]Values (odd-ratios), corresponding 95% confidence intervals and *P*-values are from generalized mixed model with clinical remission (CR_{JADAS}, CR_{ACR}) as outcome; predictors with an OR >1 have higher odds of reaching CR

An AUC (area under curve) of 0.5 suggests no discrimination (i.e., ability to diagnose patients with and without the condition), 0.7 to 0.8 is considered acceptable, 0.8 to 0.9 is considered excellent, and more than 0.9 is considered outstanding

*Model with early response, fever status at baseline, prior use of MTX, prior exposure to anakinra, prior exposure to tocilizumab and glucocorticoid use at baseline as covariate

[^]Model with early response, fever status at baseline, prior use of MTX, prior use of biologics DMARDs and glucocorticoid use at baseline as covariate

CR_{JADAS}, clinical remission defined based on Juvenile Arthritis Disease Activity Scores; CR_{ACR}, clinical remission defined as per Criteria of the American College of Rheumatology; DMARD, disease-modifying anti-rheumatic drug; MTX, methotrexate; n, number of patients in the model analysis

Table 3. Exposure-adjusted incidence rates of serious adverse events, by system organ class

	sJIA patients, N=123, 67045 PY exposure			
	m (%)		Number of events/rate per 100 patient-years of exposure	
	Fever group (n=70)	No-fever-group (n=52)	Fever group (n=70)	No-fever-group (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
<i>Serious Infections (by preferred term)</i>				
Pneumonia	3 (4.3)	0	3/3.0	-
Gastroenteritis	2 (2.9)	0	2/2.0	-
Abscess neck	0	1 (1.9)	-	1/1.2
Bronchopneumonia	1 (1.4)	0	1/1.0	-
Cellulitis	0	1 (1.9)	-	1/1.2
Cytomegalovirus infection	1 (1.4)	0	1/1.0	-

	sJIA patients, N=123, 67045 PY exposure			
	m (%)		Number of events/rate per 100 patient-years of exposure	
	Fever group (n=70)	No-fever- group (n=52)	Fever group (n=70)	No-fever- group (n=52)
Escherichia urinary tract infection	1 (1.4)	0	1/1.0	-
Furuncle	0	1 (1.9)	-	1/1.2
Herpes zoster	1 (1.4)	0	1/1.0	-
Infected bites	0	1 (1.9)	-	1/1.2
Influenza	1 (1.4)	0	1/1.0	-
Lymph node abscess	0	1 (1.9)	-	1/1.2
Lymphangitis	0	1 (1.9)	-	1/1.2
Otitis media acute	1 (1.4)	0	1/1.0	-
Salmonella sepsis	1 (1.4)	0	1/1.0	-
Scarlet fever	1 (1.4)	0	1/1.0	-
Sepsis	0	1 (1.9)	-	1/1.2
Staphylococcal sepsis	1 (1.4)	0	1/1.0	-
Varicella	1 (1.4)	0	1/1.0	-

A single patient may experience an event multiple times; column m (%) shows the number (%) of patients with adverse events; the second column shows the number of events/rate per 100 patient-years of exposure

SAEs with a $\geq 5\%$ incidence in any of the subgroups are presented

AE, adverse event; BL, baseline; N, total number of patients in the cohort; n, number of patients in subgroup; m, number of patients with adverse events; SAE, serious adverse event; sJIA, systemic juvenile idiopathic arthritis

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