Safety and efficacy of canakinumab in Japanese patients with phenotypes of cryopyrin-associated periodic syndrome as established in the first open-label, phase-3 pivotal study (24-week results)

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Abstract

Objectives

Cryopyrin-associated periodic syndrome (CAPS), a rare hereditary auto-inflammatory disease, is associated with mutations in the NLRP3 gene resulting in elevated interleukin-1β (IL-1 β) release. CAPS generally occurs in early childhood with most patients presenting with periodic fever, skin rash, osteoarthropathy, aseptic meningitis, sensorineural hearing loss and optic neuritis. Canakinumab, a fully human anti-IL-1β monoclonal antibody which binds selectively to IL-1β, has demonstrated good efficacy with CAPS. This is the first study to evaluate the safety and efficacy of canakinumab in Japanese patients with CAPS.

Methods

In this open-label study, 19 Japanese CAPS patients aged ≥2 years received canakinumab either 150 mg s.c. or 2 mg/kg for patients with a body weight ≤ 40 kg every 8 weeks for 24 weeks. The primary objective was to assess the proportion of patients who were free of relapse at week 24.

Results

A complete response was achieved in 18 (94.7%) patients with some requiring a dose and/or a frequency adjustment to attain full clinical response. The majority of patients (14/18; 77.8%) were in remission, i.e. free of relapse at week 24. Auto-inflammatory disease activity as assessed by physician's global assessment declined from baseline to end of the study (score of absent in 10.5% at baseline versus *31.6% at end of the study). Two patients had serious adverse events (SAEs), which resolved with standard treatment. One patient reported a mild injection-site reaction. No malignancies or deaths were reported during the study.*

Conclusion

Canakinumab 150 mg s.c. every 8 weeks was well-tolerated, highly efficacious and offered a convenient dosing regimen for treating Japanese patients with CAPS.

Key words

canakinumab, cryopyrin-associated periodic syndrome, interleukin-1β, auto inflammatory syndromes

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Introduction

Cryopyrin-associated periodic syndrome (CAPS) represents a group of rare inherited auto-inflammatory diseases and encompasses phenotypes of varying severity. An increase in severity is evident between phenotypes: familial cold auto-inflammatory syndrome (FCAS) is the mildest, while Muckle-Wells syndrome (MWS) is predominantly of intermediate severity, and neonatal-onset multisystem inflammatory disease (NOMID)/chronic infantile neurological cutaneous and articular syndrome (CINCA) is the most severe phenotype of CAPS. All phenotypes are characterised by urticaria-like rash, fever, variant degree of central nervous system and tissue inflammation, arthropathy, risk of development of amyloidosis (1) and other constitutional symptoms. CAPS is associated with mutations of the *NLRP3* gene encoding cryopyrin (2-6), an important component of inflammasome. Inflammasone activates caspase-1, leading to enhanced production of the cytokine interleukin-1beta (IL-1β) and subsequent inflammation (7, 8). The pathogenic role of IL-1β in CAPS has been demonstrated by the achievement of complete response after treatment with IL-1β inhibitors (9-13). Positive therapeutic effects of the IL-1 receptor antagonist and anakinra have been hampered by the need for frequent injections (14-17) associated with severe pain, which impairs the quality of life of patients, especially the paediatric population. Canakinumab (ACZ885, Ilaris®, Novartis Pharma), a fully human anti-IL-1β monoclonal antibody (18), has shown prolonged selective IL-1β inhibition (19, 20) and has demonstrated rapid (within hours), complete and sustained response in CAPS patients of mainly Caucasian origin without any consistent pattern of side effects (21). Canakinumab is approved by the US Food and Drug Administration (FDA) for FCAS and MWS (22) only and by EMA for treatment of all three phenotypes of CAPS (23).

At present, there are no approved therapies for CAPS in Japan. The present study was therefore conducted to evaluate safety and efficacy of canakinumab in Japanese paediatric and adult patients with CAPS. Herein we report the study data up to 24 weeks.

Materials and methods

Study design, patients and study definitions

This was an open-label, safety and efficacy study of canakinumab administered for 24 weeks (6 months) in Japanese patients diagnosed with FCAS, MWS or NOMID. Molecular diagnosis showed that 17 (89.5%) patients were positive for *NLRP3* mutations and two (10.5%) patients (one each with MWS and NOMID) were negative for the mutation. The study included an extension phase to provide canakinumab treatment to study patients until canakinumab is marketed in Japan. Two NOMID patients aged 2 and 3 years previously treated with anti-IL-1 agents (anakinra) were enrolled.

Patients received canakinumab 150 mg s.c. or 2 mg/kg for those patients with body weight ≤40 kg for every 8 weeks. In case of residual symptoms, stepwise increase of the dose up to 600 mg s.c. or 8 mg/kg s.c. (≤40 kg) and/or increased dosing frequency were allowed.

After a 6-hour washout period for those patients previously treated with anakinra, 19 patients were included. Ten had received anakinra prior to study initiation, of which five patients had reported a complete response, while the remaining had achieved partial response to anakinra. Patients requiring oral steroids, NSAIDs and/or disease-modifying anti-rheumatic drugs (DMARDs) were enrolled if they were on a stable dose (oral steroids: <20 mg/day or ≤0.4 mg/kg prednisone or prednisone equivalent, whichever applies) for at least 4 weeks prior to the screening visit. Steroid therapy was tapered after the first canakinumab treatment cycle (8 weeks between doses), at the discretion of the investigator. TNF-α inhibitors and IL-6 receptor blockers were not allowed during the study. Women of child bearing potential had to use an accepted form of contraception during the study and for at least 3 months after the last dose. Patients receiving live vaccine within 3 months before recruitment were excluded.

Complete response assessed at day 15 and day 29 was defined by (i) physician's global assessment of no or minimal auto-inflammatory disease (on a 5-point Likert scale ranging from absent, minimal, mild, moderate to severe) and assessment of no or minimal skin disease, and (ii) serological remission defined as serum CRP <1 mg/dL, and/or SAA <10 μg/mL. Patients who did not achieve (or maintain) complete response following canakinumab injection in any treatment period could receive a dose escalation (supporting Fig. 1). The possible step-wise up-titration regimens were: 300 mg s.c. (or 4 mg/kg for patients with a body weight ≤40 kg), 450 mg s.c. (or 6 mg/kg for patients with a body weight ≤40 kg), and 600 mg s.c. (or 8 mg/kg for patients with a body weight ≤40 kg).

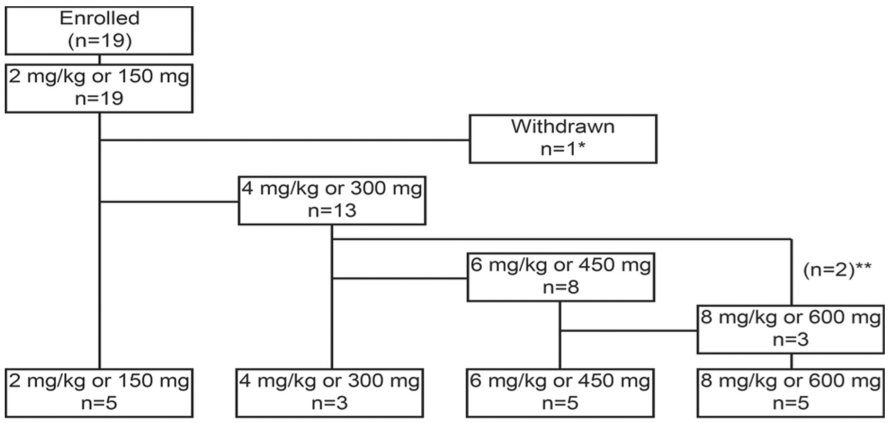
The primary efficacy endpoint was defined as the proportion of patients who did not experience a relapse at week 24. Relapse was defined as clinical relapse (physician's global assessment of both auto-inflammatory disease activity and assessment of skin disease, mild or greater) and serological relapse (serum CRP >3 mg/dL, and/or SAA >30 μg/mL).

Clinical improvement of the central nervous system (CNS) was assessed in NOMID patients only (defined as a mean weekly headache score [from the daily diary] <0.5 and a normal white cell count [≤15 cells/mm^3] in cerebrospinal fluid). Other key secondary endpoints included safety and tolerability of canakinumab, assessed by the occurrence of adverse events (AEs), serious AEs (SAEs) and immunogenicity.

This study was approved by the Independent Ethics Committee for each centre and performed in accordance to the ethical principles of the Declaration of Helsinki. All patients, parents or legal guardians (for patients aged <20 years) provided written informed consent.

Statistical analyses

Safety and full analysis set (efficacy analysis) included all patients who received at least one dose of study treatment. Only 19 patients were enrolled due to the low prevalence of CAPS, hence the estimation of statistical power was not applicable. Descriptive statistics were used to summarise demographics, baseline characteristics, efficacy and safety. Missing values were not imputed.



*One patient withdrew from this study by cancellation of the consent.

**Two patients needed two up titrations till Day 15 due to incomplete response to the first administration of canakinumab. Patients with incomplete response from the standard dosing regimen (2 mg/kg or 150 mg) received step-wise up-titration regimen. Patients who did not achieve complete response or had a relapse before the next planned administration received a dose up-titration.

Fig. 1. Patient disposition and dosing.

Results

Patients, demographic and baseline characteristics

A total of 19 CAPS patients (12 [63.2%] male/7 [36.8%] female) with a diagnosis of MWS (n=7; 36.8%) or NOMID (n=12; 63.2%) were enrolled in this study, of which 18 (94.7%) completed the 24-week study phase. One patient withdrew consent (Fig. 1). At study entry, there were 11 patients (57.9%) aged <16 years and eight patients (42.1%) aged 16 years or older. Median age was 14 years (range 2–48). Of 19 patients, five (26.3%) weighed >40 kg at baseline. Other key demographic and baseline characteristics are summarised in Table I.

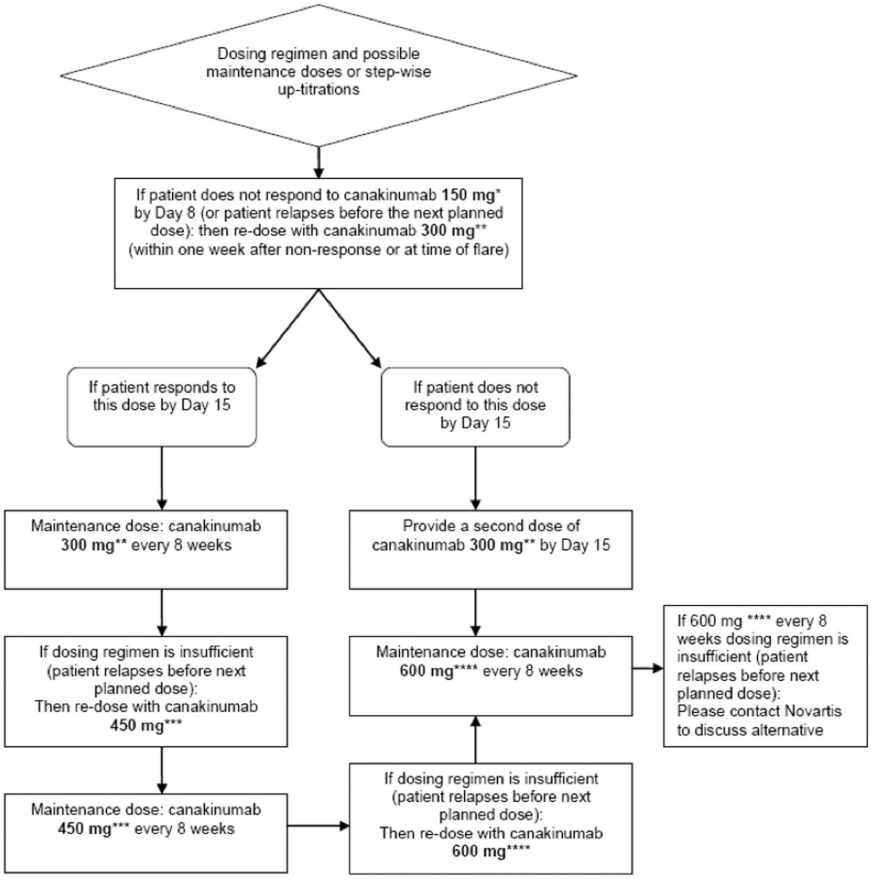
Treatment with canakinumab

At time of the 24-week analysis, the median treatment duration was 168 days (range 59–197 days) and patients received an average of 4.1 injections over 24 weeks of the study; 13 (68%) patients (MWS; n=4 and NOMID, n=9) received an up-titration of their dose, primarily due to absence of a complete response and in one patient the dose frequency was increased to every 6 weeks starting from day 49. In one NOMID patient aged 16 years, the

Table I. Baseline demographics and disease characteristics (safety population).

Characteristics	Canakinumab (n=19)
Sex, n (%)	
Male	12 (63.2)
Female	7 (36.8)
Age (years)	
Mean (SD)	14.8 (11.4)
Median (range)	14.0 (2–48)
≥2– <12 years, n (%)	8.0 (42.1)
≥12– <16 years, n (%)	3 (15.8)
≥16 years, n (%)	8 (42.1)
Weight (kg), n (%)	
≤40	14 (73.7)
>40	5 (26.3)
BMI (kg/m^2)	
Mean (SD)	17.6 (2.2)
Median (range)	17.2 (13.5–21.5)
Diagnosis, n (%)	
FCAS	0
MWS	7 (36.8)
NOMID	12 (63.2)
Molecular diagnosis of NLRP3 mutation, n (%)	19 (100.0)
Positive	17 (89.5%)
Negative	2 (10.5%)
Previous use of anakinra, n (%)	10 (52.6)
C-reactive protein (mg/dL) (normal value: <1mg/dL)	
Mean (SD)	4.52 (4.3)
Median (range)	3.3 (0.1–13.2)
Serum Amyloid A (μg/mL) (normal value: <10μg/mL)	
Mean (SD)	324.2 (364)
Median (range)	236 (2.6–1380)

BMI: body mass index; FCAS: familial cold autoinflammatory syndrome; MWS: Muckle-Wells syndrome; NOMID: neonatal-onset multisystem inflammatory disease; NLRP3: NOD-like receptor family, pyrin domain containing3; SD: standard deviation.



* canakinumab 150 mg s.c. for patients whose body weight is > 40 kg (or 2 mg/kg for patients with a body weight ≤ 40 kg)
** canakinumab 300 mg s.c. (or 4 mg/kg for patients with a body weight ≤ 40 kg)
*** canakinumab 450 mg s.c. (or 6 mg/kg for patients with a body weight ≤ 40 kg)
**** canakinumab 600 mg s.c. (or 8 mg/kg for patients with a body weight ≤ 40 kg)
There is currently no long-term safety information for doses greater than 600 mg s.c. available.
The above outlined decision tree may be applied to those patients who either did not achieve a complete response by Day 8 or Day 15 or to those patients who relapse prior to their next scheduled dose.

Supporting Fig. 1. Alternative dosing regimen for CAPS patients who do not experience sufficient symptomatic relief.

canakinumab dose was escalated to the highest dose of 600 mg. Four patients (8–25 years) with baseline body weight ≤40kg received a dose escalation to 8 mg/kg.

Proportionally higher mean last doses of canakinumab were required in patients ≤40 kg (n=12) *versus* >40 kg (n=6) at 6 mg/kg and 250 mg, respectively; in patients weighing >40 kg, the canakinumab dose administered was 350 and 150 mg for NOMID and MWS, respectively.

Efficacy

Relapse assessment. Overall, protocol-defined complete response was achieved in 18 (94.7%) patients. One patient achieved a complete response by day 148. This patient achieved clinical remission by day 29, but the inflammatory markers remained elevated until day 148. One non-responder patient achieved clinical remission, but the patient's CRP and SAA levels remained above normal during the study; however there was a significant decrease by week 24 compared to baseline. Some patients required either a dose escalation and/or a frequency adjustment to attain full clinical response (supporting Fig. 1); 15 (78.9%) patients achieved a complete response within 15 days, 2 patients were up-titrated within 29 days, and 1 patient by day 148. At week 24, the majority of patients (n=14/18 [77.8%]) were in remission, *i.e*. free of relapse (Table II).

Table II. Relapse at week 24 in MWS and NOMID patients (full analysis set).

Characteristics	Canakinumab n=19 n (%)
Number of complete responders by week 24	
Total	18 (94.7)
Day 15*	15 (78.9)
Day 29*	2 (10.5)
Day 148*	1 (5.3)
Relapse at week 24	4 (22.2)
No relapse at week 24	14 (77.8)
MWS patients	6 (85.7)
NOMID patients	8 (72.7)
No clinical/serological relapse at week 24	12 (66.7)
Discontinue prematurely prior to week 24	1 (5.6)

*Patients requiring either a dose and/or a frequency adjustment to attain full clinical response.
MWS: Muckle-Wells syndrome; NOMID: neonatal-onset multisystem inflammatory disease.

Of 12 NOMID patients, 11 achieved complete response by week 24 and nine achieved a complete response by day 15; one achieved complete response with dose adjustment by day 29 and one by day 148. Three (27.3%) out of the 11 complete responders (all NOMID patients) had a relapse at week 24. All patients with MWS (n=7) achieved complete response by week 24, though one patient had a relapse at week 24. All except one patient achieved complete response with canakinumab. All prior responders to anakinra also achieved a complete response with canakinumab.

Auto-inflammatory disease activity

The severity of auto-inflammatory disease activity as assessed by physician's global assessment declined from baseline to the end of the treatment period. This decrease in disease activity was apparent in all the individual symptom components including assessments of skin disease, headache/migraine, conjunctivitis and fatigue/malaise (Fig. 2).

Inflammatory markers

Canakinumab treatment induced a rapid decline in CRP levels within 15 days (Fig. 3a). Overall, mean CRP levels decreased by 2.94±2.99 mg/dL (38% decrease) from baseline to end of the study, day 169 (4.52 mg/dL *vs*. 1.19

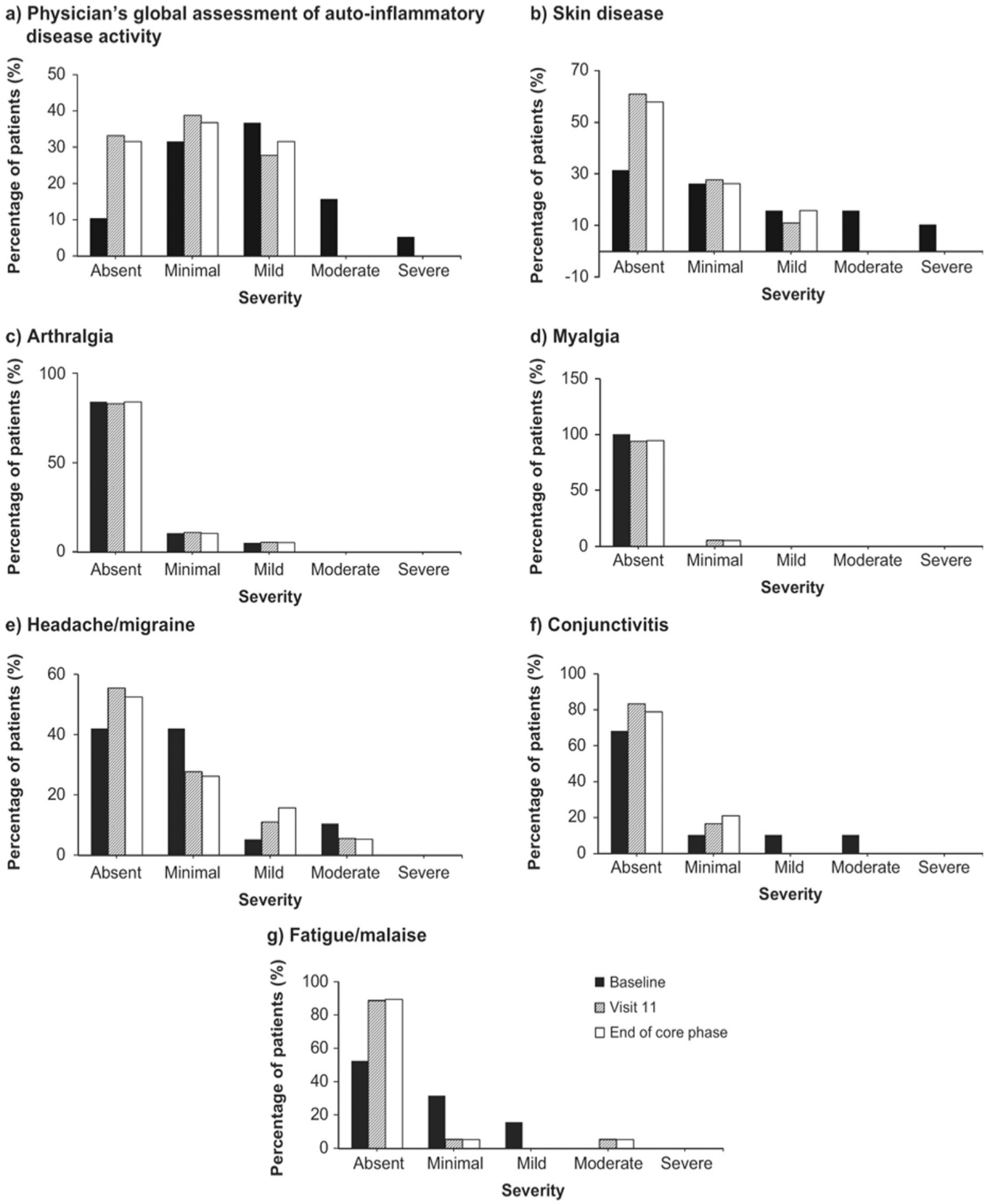


Fig. 2. Summary of assessment of auto-inflammatory disease activity (full analysis set).

mg/dL). A similar trend was observed for mean serum SAA level, which decreased from baseline to end of the study (324.19 μg/mL *vs*. 54.71 μg/mL) (Fig. 3b). On day 57, there was an increase in CRP and SAA levels, however this was driven by measurements from three patients whose mean values were near normal at other time points.

Immunogencity

Of the 19 patients, three were detected with anti-canakinumab binding antibodies during one of the post-dose assessments. However, no anti-canakinumab antibodies were detected afterwards.

Specific assessments in NOMID patients

A protocol-defined CNS remission was achieved in 33.3% (n=4/12) of the NO-

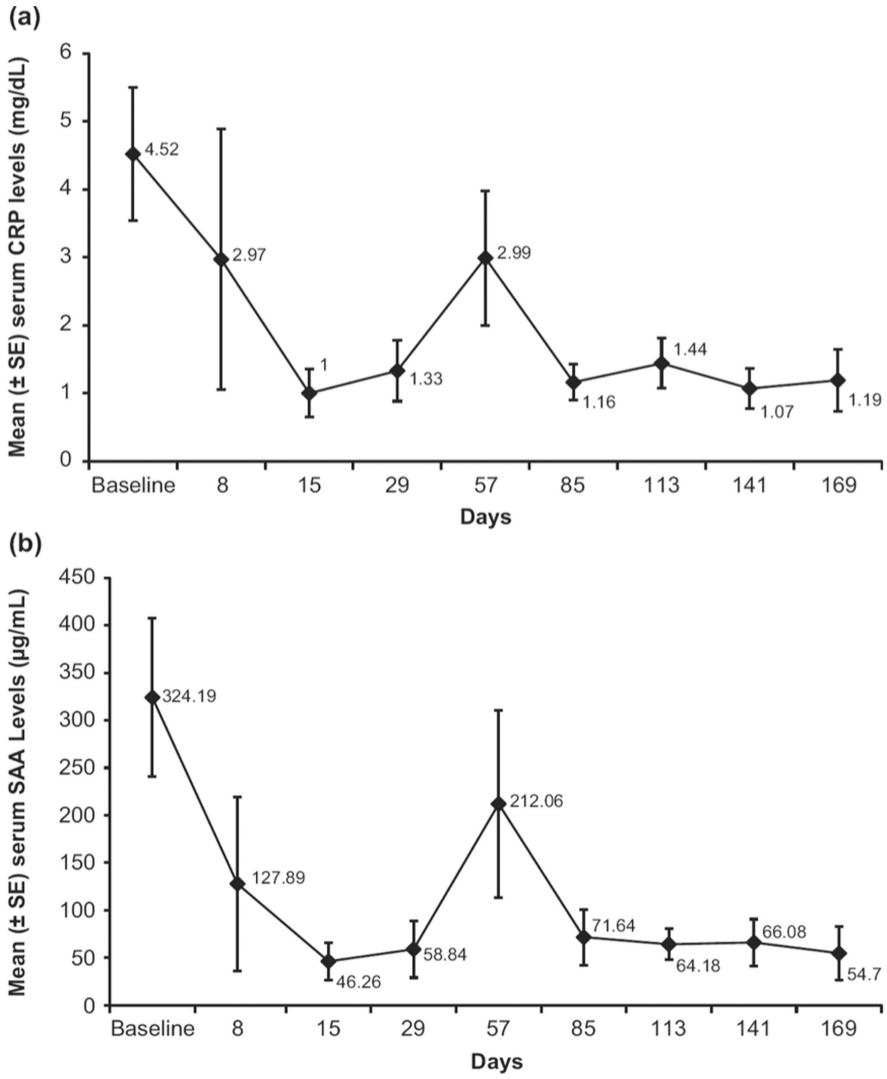


Fig. 3. **(a)** Serum CRP level across time points (full analysis set); **(b)** Serum SAA levels across time points.

MID patients by day 8 and in 41.7% (n=5/12) at the end of study; 9/12 patients had CNS remission at week 24 (with just the headache score). Lumbar puncture was only performed in 7/12 patients, of which five were in CNS remission based on the headache score and normal white cell count. A CNS relapse was reported in two (16.7%) patients on day 57 and in one patient (9.1%) on day 113. Of the three patients with a protocol-defined CNS relapse, one was uptitrated from 4mg/kg to 6mg/kg due to a concomitant clinical and serological relapse. In the other two patients, no uptitration was performed for CNS relapse. In these three patients, there was no association between the CNS relapse and clinical flare. The results of key cerebrospinal fluid assessments in NOMID patients were available in only 6 patients, who had both baseline and week 24 values. In these patients (n=6), mononuclear cells (lymphocytes, macrophages, monocytes) remained unchanged or elevated slightly from baseline to week 24 (normal values: adult ≤5 WBC/mm^3, newborns ≤20 WBC/mm^3). Absolute neutrophils which markedly reduced in two NOMID patients remained largely unchanged in the other three patients, even though it was elevated in one patient at week 24 compared with baseline. None of these patients reported headache, but they were noted to have elevated CRP and/or SAA levels. In addition to elevated SAA levels, one patient had physician's global assessment of autoinflammatory disease activity above minimal and had a relapse at week 24.

Table III. Most frequently occurring (>10%) adverse events regardless of study drug relationship (safety population).

Primary system organ class/ preferred term	Canakinumab n=19 n (%)
Total patients with AEs	18 (94.7)
Gastrointestinal disorders	7 (36.8)
Abdominal pain upper	2 (10.5)
Diarrhoea	2 (10.5)
Stomatitis	2 (10.5)
General disorders and administration site conditions	3 (15.8)
Infections and infestations	16 (84.2)
Nasopharyngitis	7 (36.8)
Gastroenteritis	6 (31.6)
Upper respiratory tract infection	3 (15.8)
Nervous system disorders	2 (10.5)
Respiratory, thoracic and mediastinal disorders	5 (26.3)
Rhinorrhoea	3 (15.8)
Cough	2 (10.5)
Skin and subcutaneous tissue disorders	6 (31.6)
Acne	2 (10.5)
Dry skin	2 (10.5)
Urticaria	2 (10.5)
Vascular disorders	2 (10.5)
Hypertension	2 (10.5)

A patient with multiple occurrences of an AE is counted only once in the AE category. A patient with multiple adverse events within a primary system organ class is counted only once in the total row. AE: adverse event.

Safety

Overall, 18 (94.7%) patients experienced at least one AE. The most commonly reported AEs (≥15% of patients) were nasopharyngitis (n=7, 36.8%), gastroenteritis (n=6, 31.6%), upper respiratory tract infection (n=3, 15.8%), and rhinorrhea (n=3, 15.8%). Twelve (63.2%) patients reported AEs, which were suspected to be study drug-related (Table III). The majority of AEs were mild (n=13, 68.4%) or moderate (n=3, 15.8%) in severity. Severe AEs of diffuse vasculitis and pneumonia were each reported in one (5.3%) patient. All but one MWS patient experienced at least one AE. Nasopharyngitis was reported in a higher proportion of NOMID patients (n=6, 50%) compared to MWS patients (n=1, 14.3%). All other AEs in NOMID and MWS patients occurred at similar frequencies or in less than three patients in each group. Two patients had serious AEs, which were suspected to be treat-

ment-related (Parvovirus infection and Epstein-Barr virus infection [n=1] and pneumonia [n=1]), but resolved with standard treatment. Of the 19 patients, only one reported a mild injection-site reaction. No deaths were reported during the study. Higher canakinumab s.c. doses (>150mg or 2mg/kg q8wks) did not appear to be associated with a differential safety profile.

Discussion

The present study confirms the clinical and serological efficacy of canakinumab in a Japanese population of paediatric and adult CAPS patients presenting with the most severe NOMID and MWS-phenotypes. Eighteen (94.7%) out of 19 patients enrolled in this study have achieved a complete response with some patients requiring either a dose and/or a frequency adjustment to attain full clinical response. For most patients (78.9%), irrespective of CAPS phenotype, a complete response was achieved with the standard subcutaneous canakinumab dose (13), *i.e.* 150 mg (>40 kg body weight) or 2 mg/kg (≤40 kg body weight) every 8 weeks.

All clinical symptoms frequently observed in CAPS patients such as inflammation of skin, eyes, bones, joints and meninges accompanied by recurrent fever, severe fatigue, myalgia and headache, showed an improvement during canakinumab treatment. Improvement in clinical outcomes with canakinumab therapy such as autoinflammatory disease activity, and reduction in the levels of acute phase proteins such as CRP and SAA confirms the pivotal role of IL-1β and its inhibition in CAPS.

The sustained effects of canakinumab on patient's clinical symptoms have been associated with its mean terminal half-life of 26 days and a possibly disease-modifying effect through autocrine down-regulation of IL-1β production (19). The canakinumab administration schedule of one injection every 8 weeks and the low incidence of injection-site reactions, as previously observed in other phase II and III canakinumab CAPS studies (21, 25, 26), may be beneficial, especially to paediatric patients.

In the present study, individualised uptitration in patients with an incomplete response proved to be a safe and an efficacious approach for the majority of patients achieving a complete response within one month. Patients with incomplete response, as shown by changes in clinical symptoms (headache, fever or rash according to CAPS) and raised inflammatory marker levels (elevated CRP >3 mg/dL, and/or SAA >30 μg/mL), had initially received canakunimab titrated up to 8 mg/kg. The dosage interval was shortened by up to four weeks if patients failed to achieve a complete response. There was no clear correlation between the genotype, phenotype, and treatment response. The mean dose requirement for patients ≤40 kg was found to be proportionally higher (6 mg/kg) than for those with a body weight >40 kg (250 mg). In the group of patients with a body weight >40kg, the NOMID patient subgroup required a higher mean dose compared to the MWS patient subgroup, in line with the level of severity of the disease.

At baseline, 12 NOMID patients presented with CNS symptoms that included headache and pleocytosis and 9 showed improvement in these symptoms by week 24. Patients showed no significant changes, either worsening or improvement, based on audiogram and neurological or ophthalmic assessments. Two patients showed normalisation in auditory acuity and one patient showed normalisation in visual acuity. There were no organic changes observed on magnetic resonance imaging (MRI). This may be attributed to the fact that the observation period was relatively short and approximately 53% of patients were pre-treated with anakinra at the time of the study entry.

In the present study, no patients discontinued due to unsatisfactory therapeutic effect, suggesting that an effective individual canakinumab dosing regimen was determined. The safety profile was comparable to that observed in previous canakinumab studies (21, 24), with no new or unexpected safety findings. Consistently with previous studies and other biologics, infections were the most frequent AEs and the patients responded well to standard therapy. There were no deaths, discontinuations nor dose adjustments/or interruptions due to AEs. In 3 out of 19 patients, anti-canakinumab binding antibodies were detected in one of the post-dose visits, however these patients showed no evidence of immunogenicity related AEs or impaired efficacy. The overall safety profile observed in previous canakinumab studies in CAPS was confirmed in this Japanese population including the paediatric and NOMID sub-populations.

The present study has limitations, including the small size of the patient population, the non-controlled design and the relatively short-term observation period, each of which were addressed in previous studies. Additionally, the small sample size and short follow-up period did not allow detailed assessment of side effects related to anti-IL-1 therapy such as malignant disease and autoimmunity. Long-term observation with a large population is needed to address these issues (27).

Conclusion

Canakinumab 150 mg s.c. dosed every 8 weeks proved to be efficacious and provided a convenient dosing regimen for treating Japanese patients with CAPS. Higher canakinumab doses in younger patients and in adult patients with more severe CAPS disease were efficacious in achieving a complete response and were well tolerated without any evidence of increased AEs. While these results for the treatment of CAPS with canakinumab for up to 197 days are encouraging, the long-term safety of canakinumab in CAPS patients will be further evaluated in this ongoing study.

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