Long-term safety and efficacy of canakinumab in cryopyrin-associated periodic syndrome: results from an open-label, phase III pivotal study in Japanese patients

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ABSTRACT

Objective. *To assess the long-term safety and efficacy of canakinumab in Japanese patients with cryopyrin-associated periodic syndrome (CAPS).*

Methods. *In this open-label phase 3 study, Japanese patients aged ≥2 years with CAPS received canakinumab 2–8 mg/kg subcutaneously every 8 weeks. The duration of the core treatment phase was 24 weeks followed by 22 months extension phase. The primary objective was the proportion of patients free of clinical and serologic relapse at week 24.*

Results. *The study enrolled 19 Japanese patients (median age, 14 years; range, 2–48 years) with CAPS [MWS, 7 (36.8%); NOMID, 12 (63.2%)] for a median of 109 weeks. Fifteen patients (79%) achieved a complete response by day 15, 18 (94.7%) by week 24 and all by week 48. At the end of the study, 18 (95%) were free from relapse and 11 (57.9%) were assessed as having no disease activity by the PGA. Thirteen (68%) patients (MWS, 4; NOMID, 9) had their canakinumab dose increased during the trial. All patients experienced at least one adverse event (AE), the most common being infections (100%) and 5 (26.3%) reported serious AEs. No deaths were reported and the only patient who discontinued the study early withdrew consent.*

Conclusion. *Regular canakinumab treatment every 8 weeks at dose levels from 2–8 mg/kg, based on the clinical need, represents a successful strategy to induce rapid and complete response while maintain long-term disease control in Japanese patients with CAPS. The safety profile of canakinumab was consistent with that observed from previous studies.*

Introduction

Cryopyrin-associated periodic syndrome (CAPS), a group of rare genetic, life-long, auto-inflammatory diseases, comprises a spectrum of disease activity from the mildest form familial cold auto-inflammatory syndrome (FCAS) through Muckle–Wells Syndrome (MWS), to the most severe form, neonatal-onset multisystem inflammatory disease/chronic infantile neurologic cutaneous articular syndrome (NOMID/CINCA) (1-3).

The characteristic features of CAPS are recurrent episodes of urticarial rash, fever and joint inflammation. FCAS symptoms usually arise after cold exposure (1). MWS is frequently associated with late-onset complications such as sensorineural deafness and amyloidosis (2). NOMID has a neonatal onset and is characterised by early-onset complications in the central nervous system (CNS), bones and eyes (4).

CAPS results from mutations in the cryopyrin-encoding gene, *NLRP3* (5-9). Cryopyrin is a vital part of the inflammasome complex, which in turn activates caspase-1, inducing excessive production of the cytokine interleukin-1 beta (IL-1β) by activation of pro-IL-1β (10). This results in systemic inflammation in the form of fever, leucocytosis, thrombocytosis and the production of cytokines such as IL-6, inducing the synthesis of serum amyloid A (SAA) and C-reactive protein (CRP) (11). The role of IL-1β in the pathogenesis of CAPS has been confirmed in previous studies of patients with CAPS who achieved complete response after receiving treatment with IL-1β inhibitors (12-17).

Canakinumab, a selective, human anti-IL-1β monoclonal antibody (18), provides prolonged IL-1β inhibition (19, 20). It is approved for the treatment of patients with FCAS and MWS in the United States (21) and for patients with all three phenotypes in Europe (22) and Japan (23).

In a previous phase 3 CAPS study, canakinumab [150 mg subcutaneously (s.c.) every 8 weeks (q8wk)] demonstrated rapid, complete and sustained efficacy without any consistent pattern of side effects (24). In the present study, the long-term safety and efficacy of canakinumab dosed from 2 mg/kg (150 mg maximum) to 8 mg/kg (600 mg maximum) was assessed in Japanese CAPS patients. Here, we report the full analysis results from the study, including results of special safety assessments such as audiological, ophthalmological and neurological testing.

Methods

Study design

This was an open-label, phase 3, single-treatment arm safety and efficacy study of canakinumab in Japanese CAPS patients, conducted at 3 centres from October 2009 to February 2012. The study had a 24-week core phase followed by an extension phase that lasted 22 months.

Dose regimens

The standard dose was 150 mg or 2 mg/kg in patients with body weight ≤40 kg s.c. q8wk. Patients who could not achieve or maintain complete response were permitted stepwise uptitration to a maximum dose of 600 mg (or 8 mg/kg if ≤40 kg) q8wk. (25) The dose interval could be reduced if the patient could not maintain an adequate response at the maximum dose given q8wk.

Patients

The enrolled patients were male or female, over 2 years of age with a clinical diagnosis of FCAS, MWS or NOMID, and were either treatment-naïve or had received prior treatment. Patients with prior anakinra exposure had a washout period of ≥6 hours. Patients could continue methotrexate, concomitant NSAID and/or oral steroid if they were on a stable dose (oral steroids ≤0.4 mg/kg/day prednisone equivalent) for at least 4 weeks before the screening visit.

Efficacy assessments

The primary efficacy endpoint was the proportion of patients who did not experience a relapse at Week 24. Relapse was defined as both clinical [physician's global assessment (PGA) of auto-inflammatory disease activity or assessment of skin disease ≥ minimal] and serological relapse (CRP >30 mg/L and/or SAA >30 mg/L) in a patient who had achieved complete response (clinical and serological remission). Clinical remission was defined as PGA of auto-inflammatory disease and assessment of skin disease ≤minimal. Serological remission was defined as CRP <10 mg/L and/or SAA <10 mg/L. The secondary efficacy assessments included the PGA of autoinflammatory disease activity, levels of CRP and SAA, and assessment of CNS remission [mean weekly headache score (from daily diary) <0.5 and a white blood cell count (WBC ≤15 cells/mm^3) in the cerebrospinal fluid (CSF) when a lumbar puncture was performed] and CNS relapse (mean weekly headache score ≥0.8 after CNS remission) in patients with NOMID. Lumbar puncture was performed at the investigator's discretion based on the presence of CNS signs and symptoms. Physicians assessed PGA, urticaria, arthralgia, myalgia, headache/migraine, conjunctivitis, fatigue or malaise and other symptoms by using a 5-point scale (absent, minimal, mild, moderate or severe).

Table I. Baseline demographics and disease characteristics.

Characteristics	Canakinumab (n=19)
Sex, n (%)	
Male	12 (63.2)
Female	7 (36.8)
Age (years)	
Median (range), n (%)	
≥2– <12	8 (42.1)
≥12– <16	3 (15.8)
≥16	8 (42.1)
Weight (kg), n (%)	
≤40	14 (73.7)
>40	5 (26.3)
BMI (kg/m^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 (%)	17 (89.5)
Previous use of anakinra, n (%)	10 (52.6)
C-reactive protein (mg/L); (normal value: <10 mg/L)	
Median (range)	33.0 (1.0-132)
Serum Amyloid A (mg/L); (normal value: <10 mg/L)	
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 containing 3; SD: standard deviation.

Safety assessments

Safety was assessed by reported AEs and serious AEs (SAEs), as well as special assessments including audiogram and ophthalmological assessments. Also, visual fields testing and retinal photography were performed; stereo images of the papilla evaluated papilloedema severity in all patients) and brain and inner ear magnetic resonance imaging (MRI) was done. Neurological findings were assessed by a neurology consultant focusing on signs of chronic meningitis, chronic headaches, and fever and vomiting; headache, fever and vomiting were rated on a scale 0–4 (by severity) by the patient or parent. Audiogram, ophthalmological and neurological assessments were performed every 6 months from screening until study end with MRI done at screening, 6 months, and then yearly (assessments within 6 months of baseline counted as baseline testing).

The study was conducted as per the ethical principles of the Declaration of Helsinki and Good Clinical Practice guidelines and was approved by an independent ethics committee in each hospital. All patients ≥20 years of age and parents or legal guardians of patients <20 years of age provided written informed consent.

Statistical methods

The full analysis set and safety set included all patients who received at least one dose of canakinumab during the study. Given the small sample size, the data are presented in a descriptive manner only without missing value imputation. AE coding was done using the Medical Dictionary for Regulatory Activities.

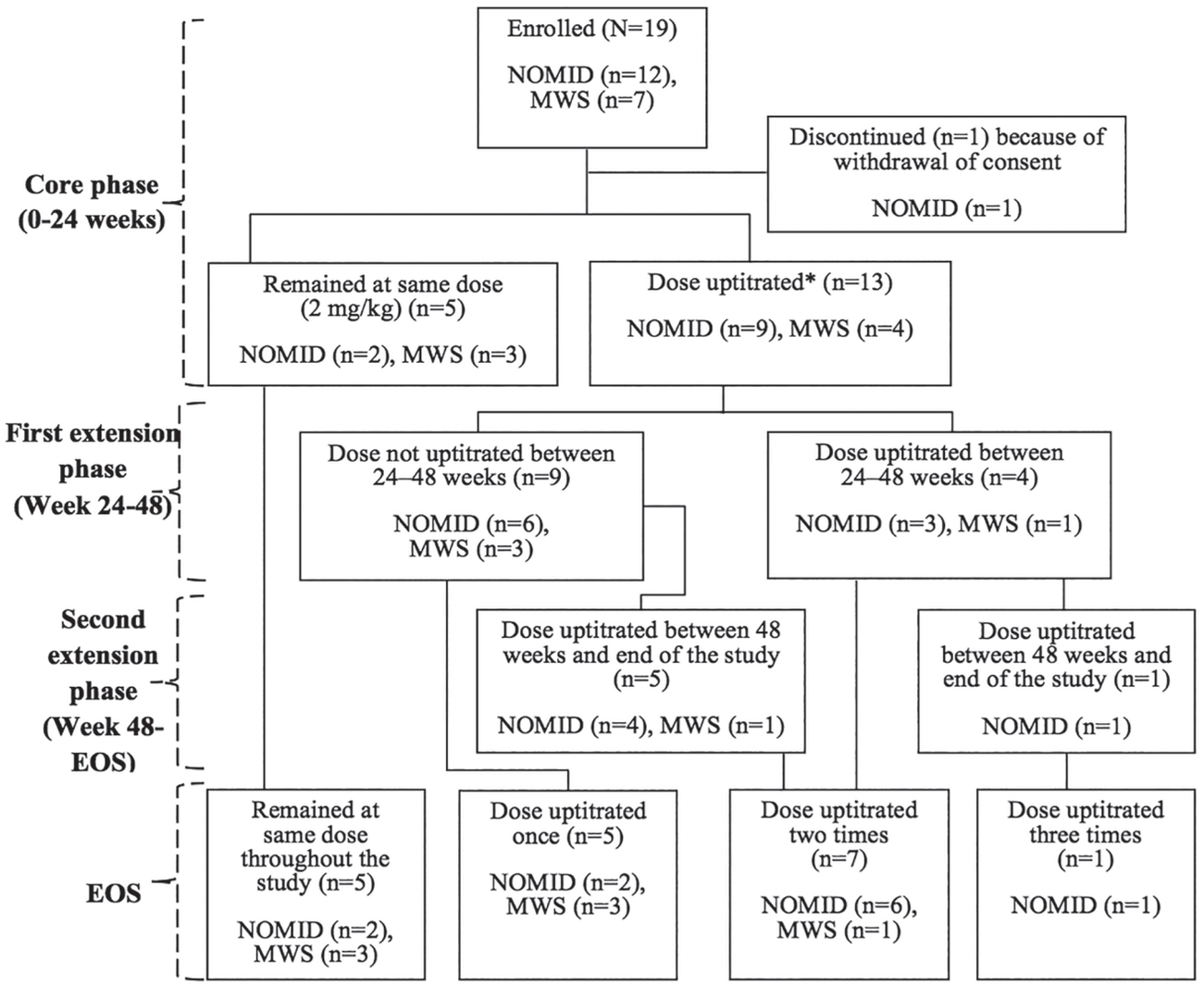


Fig. 1. Patient disposition.
*Dose uptitrated from 2 mg/kg or 150 mg to a maximum dose of 600 mg or 8 mg/kg for patients with body weight ≤40 kg every 8 weeks. EOS, end of study; MWS: Muckle–Wells Syndrome; NOMID: neonatal-onset multisystem inflammatory disease.

Results

Patients, demographic and baseline characteristics

A total of 19 Japanese CAPS patients (12 with NOMID, 7 with MWS) were enrolled with a median age of 14 years (range, 2–48 years) (Table I) (25), of whom 18 (94.7%) completed the study (Fig. 1). One patient discontinued the study early after withdrawing consent.

Treatment with canakinumab

The overall median duration of exposure was 763 days (range, 59–817 days). In 13 (68.4%) patients (4 MWS, 9 NOMID), canakinumab dose was adjusted, and for 5 (38.5%) NOMID patients, dosing interval was also shortened (Fig. 1). Eight (42.1%) patients were uptitrated to 8 mg/kg (or 600 mg) q8wk; dosing frequency was shortened for 4 of these patients to maintain response. Three of the 4 patients had their dose reduced to 6 mg/kg with the q6wk interval change, whereas one maintained the prior dose of 600 mg but the dosing interval was reduced to q6wk. The last patient with a reduced dosing interval received 6 mg/kg q6wk from Day 49 onwards without first receiving 8 mg/kg q8wk. Two of the youngest NOMID patients required dose uptitration, and the increased dose was well tolerated. All 19 patients had concomitant medications usage (Table II).

Efficacy

Relapse assessment

All 19 patients achieved complete response by the end of the study; 13 (68%) by Day 15 and 18 (94.7%) by Week 24 (Table III), with the 19th by day 316.

The percentage of patients with relapse decreased over time and is detailed by study phase in Table III. Of the 18 patients who achieved a complete response by Week 24, 14 (77.8%) remained relapse-free during that period. Of the 4 patients with relapse, 3 had NOMID and 1 had MWS. Between Week 48 and the end of the study, only 1 patient (5.3%) had a relapse.

Auto-inflammatory disease activity

The PGA of auto-inflammatory disease activity assessment showed that the percentage of patients with absence of

Table II. Most commonly taken concomitant medications during the study.

ATC class Preferred term	Canakinumab n=19 n (%)
Corticosteroids	
Glucocorticoids	16 (84.2)
Corticosteroids-plain	15 (78.9)
Corticosteroids for local oral treatment	14 (73.7)
Corticosteroids acting locally	13 (68.4)
Corticosteroids-weak (group I)	12 (63.2)
Cephalosporins and related substances	13 (68.4)
Anilides	11 (57.9)
Other antihistamines for systemic use	11 (57.9)
Other antiallergics	11 (57.9)
Macrolides	11 (57.9)
Propionic acid derivatives	10 (52.6)
Antiinflammatory preparations and non-steroids for topical use	10 (52.6)
Heparin group	10 (52.6)

Table III. Relapse assessment.

n (%)	At Week 24 (n=19)	At Week 48 (n=19)	At end of study (n=19)
Complete response	18 (94.7)	19 (100)	19 (100)
Relapse following achievement of complete response (clinical and serological)	4 (22.2)	3 (15.8)	1 (5.3)
Clinical relapse	6 (33.3)	4 (21.1)	1 (5.3)
Serological relapse	6 (33.3)	8 (42.1)	5 (26.3)

Complete response, PGA of auto-inflammatory disease activity and assessment of skin disease ≤minimal and CRP <10 mg/L and/or SAA <10 mg/L; clinical relapse, PGA of auto-inflammatory disease activity or assessment of skin disease ≥minimal; serological relapse, CRP >30 mg/L and/or SAA >30 mg/L.
CRP: C-reactive protein; PGA: physician's global assessment of auto-inflammatory disease activity; SAA: serum amyloid A.

disease activity increased from 10.5% at baseline to 57.9% at study end (Fig. 2A). At the end of the study, no patient had moderate or severe disease activity. Similar improvements were evident in the individual component symptom scores of disease activity (Fig. 2B-G).

Inflammatory markers

The CRP and SAA levels declined steadily throughout the study (Fig. 3A and B). At Day 8, there was a 70% reduction from median baseline CRP, which reduced further to a 72.7% reduction at Week 24, and an 86% reduction at study end. Similarly, by Week 24, the median baseline SAA levels (236 mg/L) had reduced to 15.7 mg/L (76.9%), and at study end, the levels had reduced to a median of 14.3 mg/L, a 92.8% reduction from baseline.

Specific assessments in NOMID patients

• *CNS relapse and remission*

Of the 12 NOMID patients, 9 (75.0%) had CNS remission at Week 24 and 7 (58.3%) at Week 48 and at study end. Three patients had a CNS relapse during the core phase and 9 during the extension phase; however, no patient had a CNS relapse from Day 701 to study end.

• *CSF findings*

CSF collection was performed in 12 patients (3 MWS, 9 NOMID), 11 at baseline, 7 during Week 1, 8 at Week 24, 7 at Week 48, 5 at Week 72, and 2 at Week 100.

At baseline, 7 patients who had discontinued anakinra within 48 hours had a median CSF protein of 180 mg/L and a median CSF total WBC of 15 cells/mm^3. The median CSF protein and total WBC counts for the remaining 4 anakinra-naïve patients were 490 mg/L and 192 cells/mm^3, respectively.

At Week 24, the median CSF protein (270 mg/L) and median total WBC count (79 cells/mm^3) were lower for patients with previous anakinra use than in anakinra-naïve patients (median CSF protein 360 mg/L; median total WBC count 140 cells/mm^3) .

Canakinumab was not detected in the CSF at Day 2 in any of the 6 patients who had CSF pharmacokinetic (PK) measurement. At the beginning of Week 24 until Week 100, canakinumab was detected with concentrations ranging between 0.0521 and 0.379 mg/L in 8 out of 13 patients who had a CSF PK measurement.

Safety

AEs, SAEs, other significant AEs and deaths

All patients experienced at least one AE during the study, with the most common being upper respiratory tract infections in 14 (73.7%) patients (Table IV). The frequency and pattern of AEs did not show a meaningful change with time (Table IV). SAEs were reported in five patients: one 4 year-old female with MWS had multiple infections over the study (Epstein–Barr virus and suspected parvovirus later with mumps meningitis and then herpes zoster; on concomitant methotrexate and prednisolone); pneumonia (n=1); sinoatrial block and headache (n=1); asthma (n=1); and appendicitis (n=1). There were no permanent discontinuations because of AEs/SAEs. In one patient, the dose was delayed 5 days because of parotitis. Severe diffuse vasculitis was reported in one NOMID patient from Day 4 onwards, however, the investigator did not suspect it to be canakinumab-related. Mild injection-site reaction was reported in one NOMID patient (at Day 143), which resolved without intervention. The frequency and pattern of AEs reported in patients whose dose was increased or whose dosing interval decreased was similar to those without any dose adjustment. No deaths were reported during the study.

Special safety assessments

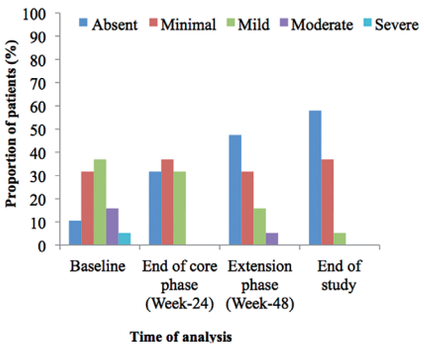
Audiological assessment

Of the 19 enrolled patients, 16 (84.2%) had an abnormal, clinically significant assessment at baseline. By the end of the study, three patients (15.8%) had their audiogram shift to normal. At the end of the core phase (Week 24), two patients had shifted to normal and an additional two shifted to normal assessment at study end; however, one of the patients with a change to normal by Week 24 returned to abnormal at Day 504. The 3 with a normal baseline tests remained normal.

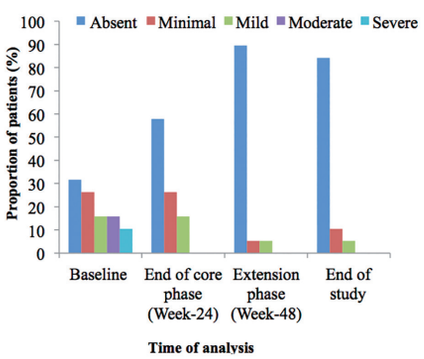
Ophthalmological assessment

Of the 19 patients, 9 (47.4%) at baseline had an abnormal clinically significant ophthalmological assessment and 2 (10.5%) had an insignificant test. At study end, one patient each with ab-

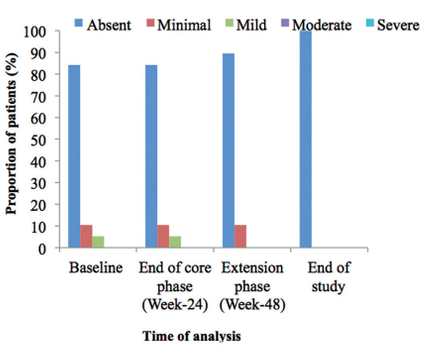
A. Physician's global assessment of auto-inflammatory disease activity.



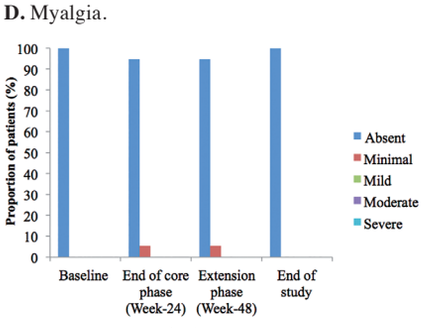
B. Skin disease (urticarial skin rash).



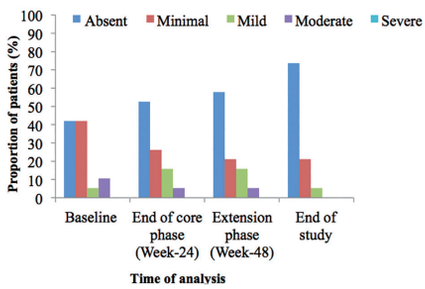
C. Arthralgia.



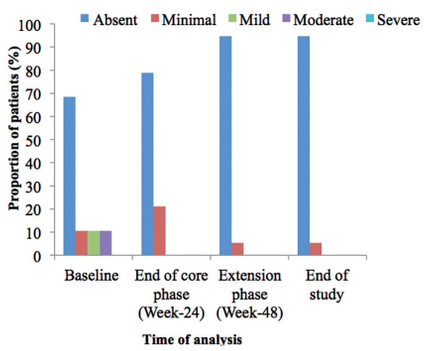
D. Myalgia.



E. Headache/migraine



F. Conjunctivitis



G. Fatigue/malaise

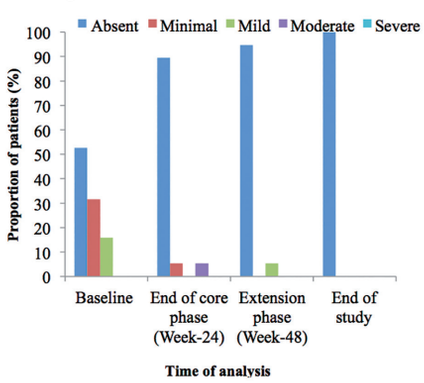


Fig. 2. Summary of assessment of autoinflammatory disease activity* (full analysis set).
*Assessed using 5-point scale: absent, minimal, mild, moderate, severe.

normal clinically significant and clinically insignificant assessment shifted to normal. There was no change from the baseline assessment for rest of the patients.

Neurological assessment

At baseline, five of the 19 (26.3%) patients had an abnormal neurological assessment that was clinically significant and one patient had an insignificant abnormal assessment. At study end, 2 patients with a clinically significant abnormal baseline test had normalised and 1 with baseline normal test developed a clinically significant abnormal test. The neurological assessment for the remaining 16 patients did not change from their baseline assessment.

MRI assessment of the brain

Of the 19 patients, baseline MRI assessments for 11 were normal, 4 (21.1%) showed a clinically significant abnormality (mild brain atrophy and sulci enlargement) and another 4 (21.1%) showed a clinically insignificant abnormality. At the last MRI assessment during the study, no further change was observed in patients. Follow-up MRI scans were performed after study end on 3 of the 4 patients with clinically insignificant baseline tests, with 1 normalising and 2 remaining unchanged.

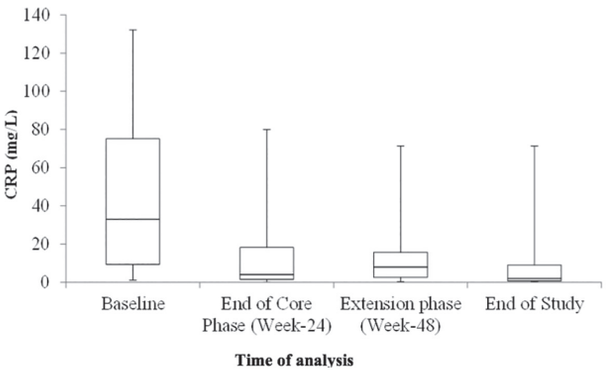
MRI assessment of the inner ear (patients with NOMID)

Of the 12 patients with NOMID, 2 (16.7%) had abnormal clinically significant MRI inner ear scans. The MRI scan for one patient showed mild spotty enhancement on the left basal portion of the cochlear nerve, and for the other, it showed deformity of the external semicircular duct and internal acoustic meatus. Follow-up scans were assessed as normal.

Discussion

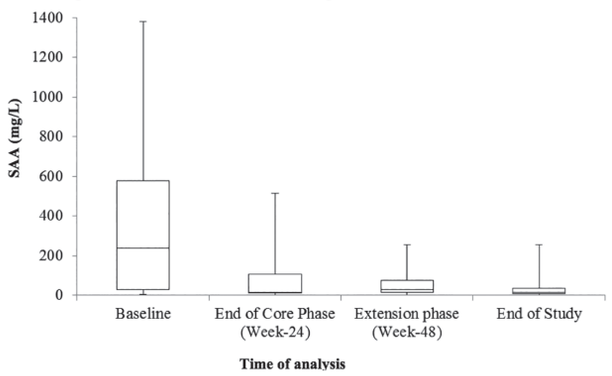
This was the first study assessing the long-term safety and efficacy of canakinumab treatment in Japanese CAPS patients, including special safety parameters related to long-term disease complications and allowing canakinumab dose adjustments up to 8 mg/kg (or 600 mg maximum) based on the clinical need. This strategy was successful as evidenced by complete response observed in 68% of patients by Day 15, which increased to 94.7% at Week 24, with 77.8% of patients being free of relapse. The remaining patient, who had not shown complete response within 24 weeks, achieved complete response by Week 48. Hence, by the end of the study, all enrolled patients had achieved complete response.

A. Change in CRP levels across time points.



Box plot denote median, Q1 and Q3 CRP values.

B. Change in SAA levels across time points.



Box plot denote median, Q1 and Q3 SSA values.

Fig. 3. Assessment of inflammatory markers.

Maintained long-term efficacy was demonstrated with very few relapses observed in only 5.3% patients (clinical relapse, 5.3%; serological relapse, 26.3%) by the end of the study.

During the study, most of the patients (68.4%) required dose adjustments, more commonly required in patients with NOMID (75%) compared with patients with the less severe MWS (57%) phenotype. This suggests that an efficacious canakinumab dose and concentration of canakinumab, based on individual patient response, is required for successful control of clinical signs and symptoms of different CAPS phenotypes. As demonstrated by Caorsi *et al*., 2013 (26), canakinumab dose levels were driven by phenotype severity as the majority of dose adjustments occurred in patients with NOMID. The intensified dose regimens were found to be efficacious and without any additional side effects related to an increased dose.

Almost all patients (94.7%) completed the entire study duration (core plus extension phase) successfully. The total median exposure of 768 days was also noteworthy. These two observations together demonstrate that canakinumab was well-tolerated in CAPS patients for both standard and higher doses administered q8wks or more frequently. There was no discontinuation because of unsatisfactory therapeutic effect.

As no canakinumab exposure was detected in the CSF as early as two days after initiation of canakinumab treatment but reached levels up to 0.346 mg/L at later assessments, it was speculated that penetration of canakinumab into the CSF may take longer exposure time to reach a steady state.

CAPS is known to be associated with aseptic meningitis. No patient demonstrated full resolution of their aseptic meningitis in the study with canakinumab dosed up to 8 mg/kg. Similar to systemic inflammation, it is believed that chronic meningitis in patients with CAPS is also caused by excessive production of IL-1β. However, further studies are needed to determine if this is due to CSF penetration of plasma IL-1β that occurs because of disruption of blood–brain barrier, which was caused by inflammation or activation of microglia as a result of a *NLRP3* mutation. In this study, canakinumab did penetrate into the CSF, but it remains unclear whether there is a linear correlation between canakinumab dose and CSF concentration which may result in resolution of the subclinical aseptic meningitis. Further studies using higher canakinumab doses as well as initiating therapy as early as possible to prevent the consequences of long-term CSF inflammation might be helpful.

The results of the special safety assessments suggested a possibility that canakinumab may modify mid to long-term disease outcome. It has been also reported that long-term treatment with IL-1 inhibitor stabilised the progression of hearing loss in patients with severe CAPS (30). Patients who had normal audiological, ophthalmological and neurological assessments at baseline did not show any abnormalities develop during the trial while receiving canakinumab. In patients with abnormal assessments at baseline, a shift to normal was observed in 18.2% of patients in ophthalmological assessment and 10.3% of patients in neurological assessment by the end of the study. Moreover, audiological assessments shifted to normal in 15.7% of patients (29). Canakinumab had no effect on the underlying disease-related long-term changes that were detected on the MRI assessment of the brain at baseline. However, the MRI assessments of the inner ear were normal for the two patients who had abnormal findings at baseline during follow-up scan at the end of the study. These findings demonstrate efficacy of canakinumab in treating sensorineural deafness, improving visual acuity and reversing short-term auditory complications of CAPS, which can be assessed by audiogram, routine neurological examination and MRI of inner ear. Although the trial had a small sample size and did not have a matched placebo control, the totality of these assessments demonstrates that canakinumab may

Table IV. Adverse events* (>10% during any study period) regardless of study drug by preferred term.

Preferred term	At the end of 24 weeks n=19	At the end of 48 weeks n=19	End of study n=19
Abdominal pain upper	2 (10.5)	2 (10.5)	2 (10.5)
Acne	2 (10.5)	2 (10.5)	2 (10.5)
Aphthous stomatitis	-	-	2 (10.5)
Allergic cough	-	2 (10.5)	2 (10.5)
Asthma	-	1 (5.3)	2 (10.5)
Bronchitis	-	1 (5.3)	3 (15.8)
Conjunctivitis	1 (5.3)	1 (5.3)	2 (10.5)
Allergic conjunctivitis	-	1 (5.3)	3 (15.8)
Constipation	1 (5.3)	2 (10.5)	2 (10.5)
Cough	2 (10.5)	3 (15.8)	3 (15.8)
Deafness neurosensory	-	-	2 (10.5)
Diarrhoea	2 (10.5)	2 (10.5)	4 (21.1)
Dental caries	-	1 (5.3)	3 (15.8)
Dry skin	2 (10.5)	2 (10.5)	2 (10.5)
Eczema	1 (5.3)	1 (5.3)	3 (15.8)
Gastroenteritis	6 (31.6)	6 (31.6)	7 (36.8)
Headache	-	1 (5.3)	2 (10.5)
Heat rash	1 (5.3)	2 (10.5)	2 (10.5)
Hordeolum	-	1 (5.3)	2 (10.5)
Hypertension	2 (10.5)	2 (10.5)	2 (10.5)
Impetigo	-	-	2 (10.5)
Influenza	-	-	2 (10.5)
Nasopharyngitis	7 (36.8)	8 (42.1)	10 (52.6)
Oropharyngeal pain	1 (5.3)	2 (10.5)	2 (10.5)
Otitis media	1 (5.3)	2 (10.5)	4 (21.1)
Acute otitis media	-	-	2 (10.5)
Pneumonia	1 (5.3)	2 (10.5)	2 (10.5)
Allergic rhinitis	-	1 (5.3)	2 (10.5)
Rhinorrhoea	3 (15.8)	3 (15.8)	3 (15.8)
Seasonal allergy	-	-	3 (15.8)
Sinusitis	1 (5.3)	2 (10.5)	5 (26.3)
Stomatitis	2 (10.5)	2 (10.5)	5 (26.3)
Upper respiratory tract infection	3 (15.8)	6 (31.6)	14 (73.7)
Urticaria	2 (10.5)	3 (15.8)	3 (15.8)
Vomiting	-	-	2 (10.5)

*Adverse events for each study period are from the beginning until the end of that study period.

prevent neurological progression and/or reversal of some neurological manifestations of MWS and NOMID.

The safety findings were consistent with results from previous studies of canakinumab in CAPS and other indications such as systemic juvenile idiopathic arthritis (24, 27, 28), with infections as the most common type of AE. No new safety signals were observed in patients. In the present study with canakinumab, only 5.2% patients showed a mild injection-site reaction, which resolved without any intervention. This compares favourably with the 20% injection-site reaction rate reported for the daily injection regimen of anakinra (30).

The response of Japanese patients with CAPS to canakinumab is in line with results from the phase III study conducted in white patients (24), in which 97% of patients achieved complete remission with canakinumab and infections were the most common AEs (65.7%) encountered. The data from this trial support that the efficacy and safety profile of canakinumab is independent of the ethnic background of the patient.

The strength of this study is the long duration for which the efficacy and safety of canakinumab in CAPS could be demonstrated. However, the study had limitations with regard to its small sample size (a consequence of the exceedingly low CAPS prevalence) and the open-label study design. Moreover, no patient with FCAS was enrolled, and hence it is difficult to reach a conclusion from this study on canakinumab treatment of FCAS.

Conclusions

Canakinumab treatment demonstrated early, complete and sustained efficacy over a long period in Japanese patients with CAPS, including patients from 2-4 years of age. Allowing stepwise canakinumab dose uptitration to 8 mg/kg (or 600 mg for patients >40 kg) to achieve and maintain remission is a successful strategy, especially in those with severe disease phenotypes. The required dose and frequency of canakinumab was dependent on the severity of the phenotype of the disease and appeared to be less determined by age. Canakinumab dosed up to 8 mg/kg used for a long period of time showed a safety profile consistent with that observed from previous studies.

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