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Two-year results from an open-label, multicentre, phase III study evaluating the safety and efficacy of canakinumab in patients with cryopyrin-associated periodic syndrome across different severity phenotypes

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ABSTRACT

Objective Longer-term effects of prolonged selective interleukin-1β blockade with canakinumab were evaluated in the largest cohort of cryopyrin-associated periodic syndrome (CAPS) patients studied to date.

Methods Adult and paediatric CAPS patients (n=166, including canakinumab-naive and pretreated patients from previous studies) received canakinumab subcutaneously 150 mg or 2 mg/kg (≤40 kg) every 8 weeks for up to 2 years. Response and relapse was assessed using scores for disease activity, skin rash and C-reactive protein (CRP) and/or serum amyloid A (SAA) levels.

Results Complete response was achieved in 85 of 109 canakinumab-naive patients (78%; 79/85 patients within 8 days, and five patients between days 10 and 21). Of 141 patients with an available relapse assessment, 90% did not relapse, their CRP/SAA levels normalised (<10 mg/l) by day 8, and remained in the normal range thereafter. Median treatment duration was 414 days (29–687 days). Upward adjustments of dose or frequency were needed in 24.1% patients; mostly children and those with severe CAPS. Predominant adverse events (AE) were infections (65.7%) of mostly mild-to-moderate severity. Serious AE reported in 18 patients (10.8%) were mainly infections and were responsive to standard treatment. The majority of patients (92%) reported having no injection-site reactions and only 8% patients reported mild-to-moderate reactions. Patients receiving vaccination (15%) showed normal immune response.

Conclusions Subcutaneous canakinumab 150 mg every 8 weeks was well tolerated and provided substantial disease control in children and adults across all CAPS phenotypes. Higher canakinumab doses in younger patients and more severe CAPS disease were efficacious in achieving complete responses without evidence of increased AE.

Trial registration number: NCT00685373 (clinicaltrials.gov)

The cryopyrin-associated periodic syndrome (CAPS) encompasses a spectrum of varying severity; the least severe being familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS) of intermediate severity; and neonatal-onset multisystem inflammatory disease/chronic infantile neurological cutaneous and articular syndrome (NOMID/CINCA), the most severe phenotype. All phenotypes are characterised by recurrent episodes of systemic inflammation marked by fever, tissue inflammation, particularly of the joints and skin, and other constitutional symptoms. However, these can be differentiated on the basis of specific clinical features—particularly NOMID/CINCA patients have severe arthropathy and early central nervous system inflammation with chronic aseptic meningitis, cognitive deficits and progressive hearing and vision loss.[1–3] These autoinflammatory diseases are generally associated with mutations in the *NLRP3* gene encoding the cryopyrin protein, an important component of the inflammasome that activates caspase-1 resulting in inflammation driven by excessive production of the cytokine interleukin-1β (IL-1β).[4]

Anti-IL-1 therapies, such as anakinra (IL-1 receptor antagonist) and rilonacept (soluble IL-1 decoy receptor), have shown positive therapeutic effects but the need for frequent injections and reactions at the injection site pose limitations.[5 6] Canakinumab (ACZ885, Ilaris; Novartis Pharma AG, Basel, Switzerland), a fully human monoclonal antibody, provides selective and prolonged IL-1β blockade and has demonstrated a rapid (within hours), complete and sustained response in most CAPS patients without any consistent pattern of side effects.[7–10] Canakinumab is approved by the US Food and Drug Administration for FCAS and MWS and by the European Medicines Agency for treatment of all the three phenotypes of CAPS.[11 12]

This study, the largest conducted to date, evaluates the longer-term effects of canakinumab in paediatric and adult patients across all CAPS phenotypes. The response to treatment with canakinumab was assessed in canakinumab-naive patients at day 8; disease activity and immunogenicity of canakinumab were also determined during the study.

Patients with NOMID/CINCA are a challenge for the clinician, as it is hoped that optimal dosing of anti-IL-1 therapy and careful interdisciplinary follow-up may prevent the development of permanent organ damage. The present study also assessed dose and/or frequency adjustments, the effect of canakinumab on tissue damage from inflammation of the central nervous system with a focus on NOMID/CINCA patients.

METHODS

Study design, patients and study definitions

This was an open-label, phase III study conducted at 33 centres. Adult and paediatric CAPS patients aged 3 years and older (canakinumab-naive and roll-over pretreated with canakinumab from a previous study) received canakinumab subcutaneously 150 mg or weight-based 2 mg/kg (body weight ≤40 kg) every 8 weeks for up to 2 years. In the case of residual symptoms, patients were maintained on a more intense dosing regimen (increased dose of up to 600 mg subcutaneously or 8 mg/kg subcutaneously (≤40 kg) and/or increased dosing frequency).

Patients previously treated with other anti-IL-1 agents were included after a washout period of at least 1 day for anakinra and at least 8 weeks for other anti-IL-1 agents. Molecular testing of the *NLRP3* mutation was performed in all cases, either before enrollment or during the study. Women of childbearing potential used an accepted contraceptive method throughout the study and for at least 3 months after the last dose. Patients with hypersensitivity to canakinumab components, those who received live vaccination within 3 months before recruitment and those with infections including tuberculosis were excluded. The study was approved by the independent ethics committee for each centre and performed in accordance with the ethical principles of the Declaration of Helsinki. All patients or their parents/guardians provided written informed consent.

Assessment of complete response and relapse utilised a previously reported definition[7] and included ratings for disease activity, skin rash and C-reactive protein (CRP) and/or serum amyloid A (SAA) protein.

Statistical analyses

Analyses included all patients who received at least one dose of study treatment. Descriptive statistics were used to summarise demographics, baseline characteristics, efficacy and safety. Missing values were not imputed.

RESULTS

Patients, demographic and baseline characteristics

One hundred and sixty-six patients (109 canakinumab-naive and 57 roll-over patients) with diagnoses of FCAS (n=30), MWS (n=103), or NOMID/CINCA (n=32), were treated. One patient did not have CAPS, was enrolled in a protocol deviation and discontinued the study on day 29 post-dose. One hundred fifty-one patients (91%) completed the study. Reasons for discontinuation were adverse events (AE, n=3), withdrawal of consent (n=5), unsatisfactory therapeutic effect (n=3), loss to follow-up (n=2) and disease condition unsuitable for treatment as judged by investigator (n=1).

There were 119 adults aged 18 years and over and 47 children aged 3 years and over to less than 18 years. *NLRP3* mutation was confirmed in 156 patients (94%), while genetic analysis was negative or indeterminate in 10 patients (6%). The major mutations identified were R260W (n=49), T348M (n=17), A439V (n=12), E311K (n=13) and L355P (n=17). The patient who was enrolled in protocol deviation reported *NLRP3* polymorphism, T219T. The patient demographics and clinical characteristics are given in (table 1).

Clinical response to canakinumab

Of the 109 canakinumab-naive patients, 85 (78%) achieved complete response (79 within day 8, and five patients between days 10 and 21, one child's response could not be analysed due to a missing CRP/SAA assessment). Another 23 patients who did not achieve the protocol-defined complete response demonstrated variable symptomatic improvements (either a decline in CRP/SAA levels or an improvement in disease activity or skin rashes). Relapse data were available for 141 patients: 127 (90%) had no relapse with 8-weekly dosing of canakinumab, and 14 (10%) demonstrated clinical relapse on at least one occasion. In the 109 canakinumab-naive patients the baseline median CRP and SAA levels (19.60 (0.4–257.6) and 35.60 (0–2010.0) mg/l) normalised after the initiation of canakinumab (day 8, 2.45 (0.2–147.9) and 4.90 (0–636.0) mg/l, respectively). In the paediatric subgroup of canakinumab-naive patients, CRP and SAA values also decreased rapidly from baseline (14.80 (0.5–195.7) and 40.55 (0–709.0) mg/l to 2.45 (0.3–123.6) and 7.35 (0–636.0) mg/l, respectively). Baseline CRP and SAA levels were normal in 58 roll-over patients. For the entire cohort, CRP and SAA levels remained within the normal range at all measurements up to 2 years (figure 1A, B). At baseline, 56% (93/165 patients) of the patients had mild-to-moderate or severe disease, while at week 8 the majority of patients (79%) showed absent/minimal disease, and 21% of the patients had mild-to-moderate disease symptoms of arthralgia, myalgia, headache/migraine, conjunctivitis or fatigue/malaise. Similarly, at baseline 39% (65/166 patients) of the patients had either mild-to-moderate or severe skin rash, and at week 8 almost all patients (95%, 155/163 patients) showed minimal or no rash. Disease severity and skin rash for paediatric (assessed at week 8) and canakinumab-naive patients (assessed at day 8 and week 8) were similar to those of the entire cohort (table 2) and improvements were maintained throughout the study.

Neurological involvement

Changes from baseline in clinically significant abnormality of neurological, audiogram and ophthalmological assessment at study end are presented here for the entire cohort and for those with NOMID/CINCA.

Twenty patients (four NOMID/CINCA) in the entire cohort had abnormal findings determined by a neurologist at baseline (bilateral hearing loss related to central neurofibromatosis,* hypocusis of right side (NOMID/CINCA, 21-year-old woman), bilateral hearing insufficiency (NOMID/CINCA, 18-year-old woman), polyneuropathy, bilateral carpal tunnel syndrome, language delay, limited ability of reading and writing (NOMID/CINCA, 15-year-old girl),* mild cerebella findings with diminished tendon reflexes in lower extremities,* distal atrophy in hands,‡ weakness in left leg,‡ chronic headache (n=9, including one NOMID/CINCA patient, 24-year-old woman),# hearing loss (n=2). Repeat neurological assessments during 2 years of canakinumab treatment showed normalisation in nine patients (*,# n=6 including one NOMID/CINCA patient) while two showed improvement.‡ One patient with normal baseline assessment developed bilateral carpal tunnel syndrome at the end of 2 years of treatment.

At baseline, 63 patients showed abnormal audiograms, which, following canakinumab treatment, normalised in nine, improved in 13 and remained unchanged for 29 patients; while follow-up was not available for 12 patients. In four NOMID/CINCA patients (aged 3–24 years) the abnormal audiogram remained unchanged during 2 years of treatment.

Abnormal ophthalmological findings, seen in 22 patients, normalised in one patient, improved in six patients and remained unchanged in 15 patients. The resolution of macular oedema was observed for one eye of a NOMID/CINCA patient and

Table 1 Patient demographics and clinical characteristics

Variable	Paediatric n=47	FCAS n=30	MWS n=103	NOMID* n=32	Overall n=166
Baseline age, years, n (%)					
<18	47 (100)	5 (16.7)	23 (22.3)	18 (56.3)	47(28.3)
≥18	–	25 (83.3)	80 (77.7)	14 (43.7)	119 (71.7)
Sex, n (%)					
Female	30 (63.8)	18 (60.0)	58 (56.3)	21 (65.6)	97 (58.4)
Male	17 (36.2)	12 (40.0)	45 (43.7)	11 (34.4)	69 (41.6)
Age, years					
Mean (SD)	10.2 (4.12)	34.8 (20.94)	34.3 (17.59)	17.2 (10.80)	30.9 (18.43)
Cohort, n (%)					
Patients from phase II study	5 (10.6)	1 (3.3)	21 (20.4)	2 (6.3)	24 (14.5)
Patients from phase III study	4 (8.5)	0	29 (28.2)	4 (12.5)	33 (19.9)
Canakinumab-naive patients	38 (80.9)	29 (96.7)	53 (51.5)	26 (81.3)	109 (65.7)
Race, n (%)					
Caucasian	47 (100)	30 (100)	99 (96.1)	31 (96.9)	161 (97.0)
Others	0	0	4 (3.9)	1 (3.1)	5 (3.0)
Molecular diagnosis of *NLRP3* mutation, n (%)					
Positive	41 (87.2)	30 (100)	100 (97.1)	26 (81.3)	156 (94.0)
Negative†	6 (12.8)	0	3 (2.9)	6 (18.8)	10 (6.0)
Physician's global assessment of disease activity, n (%)					
Absent	6 (12.8)	4 (13.3)	24 (23.3)	5 (15.6)	34 (20.5)
Minimal	10 (21.3)	6 (20.0)	24 (23.3)	8 (25.0)	38 (22.9)
Mild	17 (36.2)	6 (20.0)	32 (31.1)	9 (28.1)	47 (28.3)
Moderate	12 (25.5)	12 (40.0)	19 (18.4)	9 (28.1)	40 (24.1)
Severe	2 (4.3)	2 (6.7)	3 (2.9)	1 (3.1)	6 (3.6)
Missing	0	0	1 (1.0)	0	1 (0.6)
Assessment of skin disease, n (%)					
Absent	16 (34.0)	7 (23.3)	59 (57.3)	11 (34.4)	78 (47.0)
Minimal	7 (14.9)	4 (13.3)	15 (14.6)	4 (12.5)	23 (13.9)
Mild	9 (19.1)	7 (23.3)	14 (13.6)	4 (12.5)	25 (15.1)
Moderate	12 (25.5)	9 (30.0)	14 (13.6)	8 (25.0)	31 (18.7)
Severe	3 (6.4)	3 (10.0)	1 (1.0)	5 (15.6)	9 (5.4)

*Including 18 patients with MWS/NOMID overlap.
†Patients with either a negative or indeterminate NLRP3 mutation are classified as negative for a molecular diagnosis of NLRP3 mutation.
FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease.

clinical improvement in blepheratis was recorded in another NOMID/CINCA patient.

Amyloidosis

Four patients had confirmed renal AA amyloidosis. Of these, three patients had achieved significant improvement in renal function (remission of nephrotic syndrome and stable creatinine clearance) before study entry after 17–23 months of complete response to anakinra and this improvement was maintained on canakinumab treatment. One patient with renal AA amyloidosis did not respond clinically to canakinumab, and renal dysfunction progressed.

Dose or dosing frequency adjustments

The median duration of treatment was 414 days (29–687 days) for the entire cohort and 290 days (29–625 days) for paediatric patients. Overall, the median number of subcutaneous injections administered was eight (one to 23). Higher doses were required in paediatric (≤40 kg) compared with adult patients and NOMID/CINCA versus other phenotypes to control disease (table 3).

For the entire cohort, the dose or dose frequency was adjusted in 40 (24.1%) patients to control disease activity (based on investigator assessment). In 36 patients (21.7%) the dose was escalated; in the majority of patients the initial dose was doubled but in five adult (four MWS, one NOMID/CINCA) the dose was increased to 600 mg and four paediatric (two MWS, two NOMID) patients were given 8 mg/kg (≤40 kg) at least once. The dose frequency was adjusted in 19 (11.4%) patients (reduced in 17, increased in two patients on at least one instance). A higher proportion of paediatric and NOMID/CINCA patients required an adjustment of dose or dosing frequency compared with adults or other phenotypes (table 4). One MWS paediatric patient (roll-over; E311K mutation) on a single occasion at day 148 and another MWS paediatric patient (V198M mutation) every 4 weeks from day 20 onwards to more than 440 days were treated by the investigator with an alternative dosing regimen of 10 mg/kg intravenously.

AE and tolerability

Canakinumab was generally well tolerated. No deaths were reported and most AE were transient and mild to moderate in severity. AE were not found to cluster around any specific type. Overall, 90.4% of patients experienced at least one AE (table 5).

Infections were more frequent in paediatric than adult patients (74.5% vs 62.2%; elderly ≥65 years reporting 50% of these events). The spectrum of AE after subcutaneous 600 mg

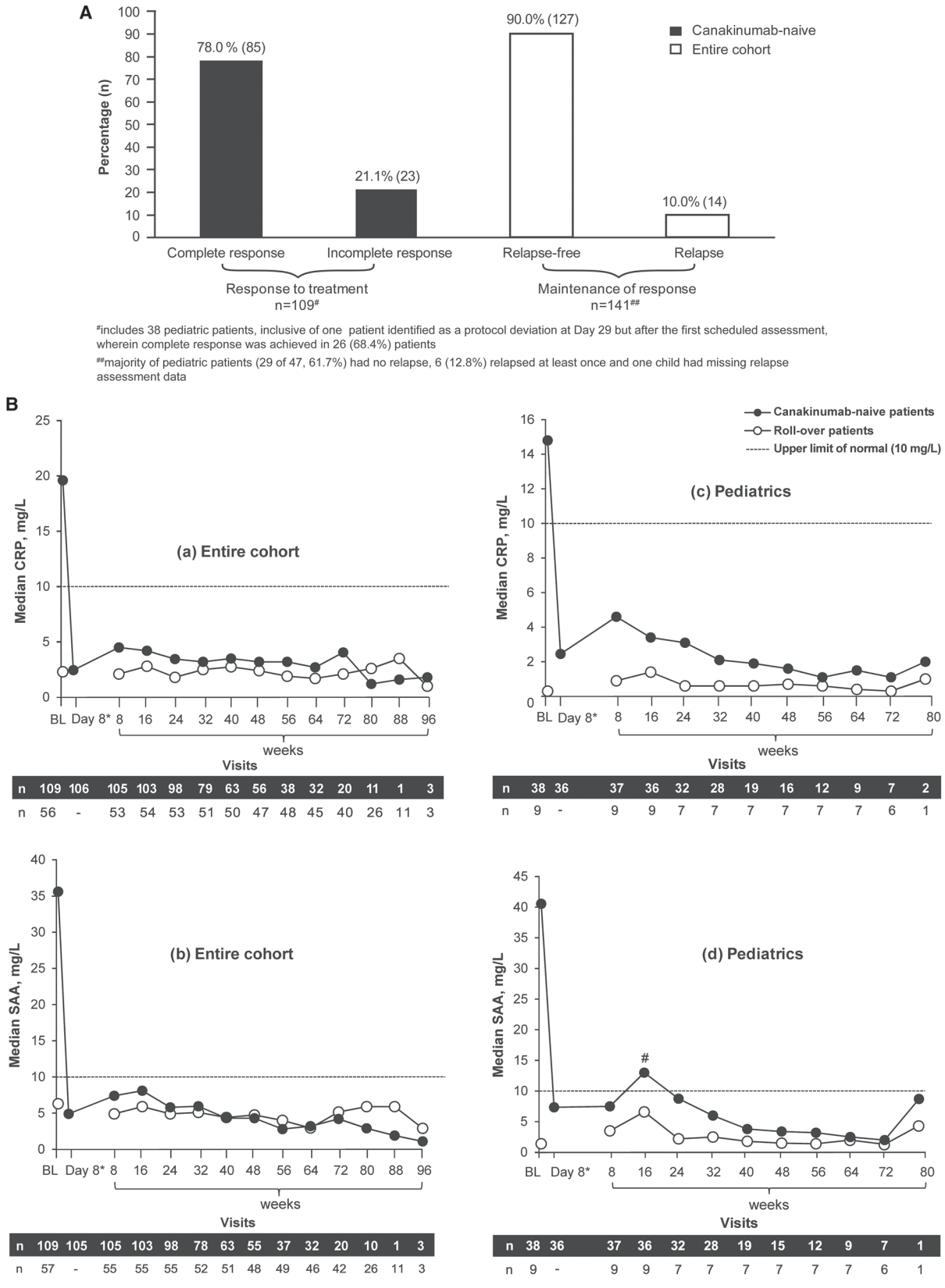

Figure 1 Clinical response to canakinumab. (A) Sustained remission with canakinumab; (B) Median C-reactive protein (CRP) and serum amyloid A (SAA) levels in entire cohort (a and b) and paediatric (c and d) according to previous treatment with canakinumab, ie, canakinumab-naive or roll-over patients.

Table 2 Physician assessment

	Overall		Naive		Paediatric patients		Naive paediatric patients	
	Baseline n=166*	Week 8 n=163	Baseline n=108†	Day 8 N=109	Baseline n=47	Week 8 n=47‡	Baseline n=38	Day 8 n=38
Disease activity, n (%)								
Absent	34 (20.6)	76 (46.6)	14 (13.0)	55 (50.5)	6 (12.8)	26 (56.5)	3 (7.9)	20 (52.6)
Minimal	38 (23.0)	53 (32.5)	22 (20.4)	39 (35.8)	10 (21.3)	10 (21.7)	9 (23.7)	12 (31.6)
Mild	47 (28.5)	28 (17.2)	32 (29.6)	12 (11.0)	17 (36.2)	9 (19.6)	13 (34.2)	5 (13.2)
Moderate	40 (24.2)	6 (3.7)	35 (32.4)	2 (1.8)	12 (25.5)	1 (2.2)	12 (31.6)	1 (2.6)
Severe	6 (3.6)	0	5 (4.6)	1 (0.9)	2 (4.3)	0	1 (2.6)	0
Rash, n (%)								
Absent	78 (47.0)	127 (77.9)	30 (27.5)	89 (81.7)	16 (34.0)	38 (82.6)	8 (21.1)	34 (89.5)
Minimal	23 (13.9)	28 (17.2)	18 (16.5)	14 (12.8)	7 (14.9)	5 (10.9)	6 (15.8)	2 (5.3)
Mild	25 (15.1)	7 (4.3)	21 (19.3)	5 (4.6)	9 (19.1)	2 (4.3)	9 (23.7)	2 (5.3)
Moderate	31 (18.7)	0	31 (28.4)	1 (0.9)	12 (25.5)	0	12 (31.6)	0
Severe	9 (5.4)	1 (0.6)	9 (8.3)	0	3 (6.4)	1 (2.2)	3 (7.9)	0

Physician's assessed disease activity and skin rash at baseline, day 8 and thereafter every 8 weeks. These improvements were maintained until 2 years (or earlier in the case of premature discontinuation).
By phenotype in canakinumab-naive patients 97% of FCAS patients, 85% of MWS patients and 77% of NOMID patients were rated as having absent/minimal disease at day 8. Improvement in the skin disease was the same across the phenotypes.
For disease activity *165; rash †109 and ‡46.
FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease.

Table 3 Dose by phenotype and weight groups

	Weight groups	
Phenotype (>40 kg/≤40 kg)	>40 kg Mean dose, mg	≤40 kg* Mean dose, mg/kg
FCAS (27/3)	188.9	2.7
MWS (90/13)	199.8	5.5
NOMID/CINCA (19/13)	228.9	5.8

Values are n (%).
*On average dosed on mg/kg basis.
CINCA, chronic infantile neurological cutaneous and articular syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease.

(>40 kg) or 8 mg/kg (≤40 kg) doses were not different from those observed with the standard canakinumab dose. The patient continuing on 10 mg/kg intravenous dose also did not experience any noteworthy AE or haematological or biochemistry abnormalities.

Serious adverse events (SAE) were more frequent in paediatric patients than in the entire cohort (12.8% vs 10.8%) and affected predominantly the upper respiratory tract (bronchitis and influenza stain H1N1 (n=1, NOMID), tonsillitis (n=2, MWS), pneumonia (n=1, MWS) not suspected to be treatment related). Intra-abdominal abscess following appendicitis was considered possibly treatment related in a paediatric MWS patient. In adults, tonsillitis (n=1, NOMID), pneumonia (n=1, MWS) and cellulitis (n=1, MWS) were not related to treatment and three other SAE, ie, worsening of headache (n=1, MWS) and spontaneous abortion in the patient's wife (n=1, MWS) were considered possibly related to treatment. Details of infection SAE are presented in table 5. The available microbiological data, although limited, suggested the presence of commonly seen streptococcus in one child with tonsillitis. None of the SAE including infections were fatal or led to the discontinuation of treatment. All infection SAE responded to standard of care with no further episode of serious infections on treatment. No case of tuberculosis was reported.

Fourteen patients required dose adjustment or interruption due to mild to moderate AE (except two severe events of worsened asthenia and polyarthritis). Two mild events of an increase in CRP levels and increased erythrocyte sedimentation rate leading to dose adjustment or interruption were suspected to be treatment related.

There were three discontinuations—due to the AE of severe nephrotic syndrome/proteinuria (not related to treatment), serum sickness syndrome (increased hive-like rash, joint pain and significant joint swelling, and myalgia), and mild worsening of pre-existing multiple sclerosis-like lesions on MRI (suspected to be possibly related to treatment); however, the lesions showed no progression on follow-up MRI and the patient was re-enrolled and completed the study. Serum sickness-like-reaction was reported on day 169. All observed Pharmacokinetic/Pharmacodynamic parameters (PK/PD) and immunogenicity levels were similar to those of other patients participating in the study. Therefore, there was no evidence suggesting that the event of serum sickness was caused by canakinumab IL-1β complexes or antibodies against canakinumab. The symptoms improved with loratidine and prednisone within a week, but full resolution took a couple of months.

There were no reported injection-site reactions in the majority (92%) of patients and 8% reported mild-to-moderate reactions on at least one occasion.

Other safety evaluations

Vertigo was reported as medical history in 5.4% patients and as an AE in three adults and one child; all of MWS phenotype (days of reporting AE in individual patient—day 1, day 26, day 6 for adults, and day 382 for child patient) and in one adult the event recurred on day 24 (one and the same patient had a vertigo event on Day 6 and on Day 24). Biochemistry evaluations at the end of the study showed no clinically significant changes from baseline. Abnormally low baseline haemoglobin levels in 12 patients normalised on-treatment in nine patients, high platelet count in 21 patients at baseline normalised in 16 patients, and high white blood cells count at baseline normalised in 25 of 31 patients.

Patients receiving a vaccination (n=25, 15.0%) including antigen against influenza (n=15, 9.0%), pneumococcus infection (n=5, 3.0%) and MMR live-attenuated virus (n=1, 0.6%) during the study did not show any associated AE. No abnormal immune responses or pathogen-related infections were reported in these patients.

Antinuclear antibodies (ANA) were assayed at baseline and at the end of the study. Negative ANA at baseline changed to

Table 4 Increase in dose or dosing frequency by age-group and phenotype

Adjustments	Total n=166	Adult n=119	Paediatric n=47	FCAS n=30	MWS n=103	NOMID/CINCA n=32
Dose or frequency adjustments	40 (24.1)	23 (19.3)	17 (36.2)	5 (16.6)	20 (19.4)	15 (46.9)
Dose adjustments	36 (21.7)	20 (16.8)	16 (34.0)	5 (16.6)	17 (16.5)	14 (43.8)
Frequency adjustments	19† (11.4)	8 (6.7)	11 (23.4)	0	11 (10.7)	8 (25.0)

†Reduced in 17, increased in two patients on at least one instance.
CINCA, chronic infantile neurological cutaneous and articular syndrome; FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease.

positive in five patients at the end of 2 years. Five patients with a positive ANA result at baseline followed one negative result before a positive test result at the last available assessment. There was no sign of any correlation between ANA results and clinical autoimmune disease. No anti-canakinumab antibodies were detected.

DISCUSSION

This is the largest study of anti-IL-1 therapy in CAPS patients conducted to date. The study allowed us to obtain safety as well as clinical and laboratory data after up to 2 years of treatment (mean treatment duration of 414 days) with canakinumab in paediatric and adult patients with different phenotypes of CAPS including the severest phenotype NOMID/CINCA.

Regular canakinumab treatment was associated with a rapid onset, substantial and sustained treatment effect; canakinumab provided complete response within 8 days in the majority of treatment-naive patients and was associated with a considerable improvement in symptoms and suppression of systemic inflammation with normalised ranges of SAA and CRP. The improvement was persistent and patients remained relapse free with regular canakinumab. Although mild-to-moderate symptoms were observed in 21% of the patients, the symptom scoring might have been confounded by AE (unrelated to canakinumab) or medical history with similar symptoms.

Complete response across all three CAPS phenotypes was achieved with canakinumab standard doses,[9] ie, 150 mg (>40 kg body weight) or 2 mg/kg (≤40 kg body weight) every 8 weeks in the majority of patients. In 36 (21.7%) patients higher doses were required up to 600 mg or 8 mg/kg (in patients weighing ≤40 kg). Paediatric and NOMID/CINCA patients required more dose or frequency adjustments to control their disease activity. One paediatric MWS patient on an increased canakinumab dose, a non-responder to previous anakinra treatment, was a carrier of a V198M mutation, which is related to a heterogeneous CAPS phenotype with variable response to increasing doses of anti-IL-1 medication.[1 13]

Unrecognised and previously untreated neurological symptoms often respond dramatically to anti-IL-1 medications such as anakinra.[14] Similar improvements were recently reported in one case after treatment with canakinumab,[15] and were confirmed in the present study. We also observed a pattern of normalisation or stabilisation in audiograms with canakinumab. In the present study there was no deterioration of ophthalmological abnormalities. Similarly, in three patients with AA amyloidosis (very effectively pretreated with anakinra), renal function remained stable. One patient with renal AA amyloidosis did not respond clinically to canakinumab and renal dysfunction progressed. Previous studies have shown stabilisation of amyloid-related proteinuria with anti-IL-1 medication in selected cases with early diagnosis.[16–21] Taken together, these findings indicate

Table 5 AE greater than 5% by preferred term and SAE

	Canakinumab		
	n (%)	No of events	Event rate by patient-year
No of patients	166		
At least one AE	150 (90.4)	1019	5.93
Abdominal pain	13 (7.8)	14	0.08
Diarrhoea	18 (10.8)	21	0.12
Nausea	11 (6.6)		
Vomiting	16 (9.6)	18	0.10
Bronchitis	18 (10.8)	19	0.11
Rhinitis	27 (16.3)	29	0.17
Upper respiratory tract infection	17 (10.2)	22	0.13
Arthralgia	24 (14.5)	29	0.17
Back pain	12 (7.2)	19	0.11
Pain in extremity	9 (5.4)	9	0.05
Headache	34 (20.5)	59	0.34
Cough	16 (9.6)	23	0.13
Oropharyngeal pain	14 (8.4)	16	0.93
SAE/severity	**Relationship with study drug**	**No of events**	**Event rate by patient-year**
At least one SAE, n (%)	18 (10.8)		
Adults			
Forearm fracture left side/ moderate	Not suspected	1	0.006
Tonsillitis*/severe	Not suspected	1	0.006
Pneumonia* /mild	Not suspected	1	0.006
Carpal tunnel syndrome / severe	Not suspected	1	0.006
Dental cyst/asymptomatic	Not suspected	1	0.006
Spontaneous abortion in the patient's wife/severe	Suspected	1	0.006
Cellulitis*/severe	Not suspected	1	0.006
Elective abortion/severe	Not suspected	1	0.006
Pregnancy/severe	Not suspected	2	0.012
Worsening of headache/ moderate	Not suspected	1	0.006
Worsening of synovial cyst in the lumbar spine/ moderate	Not suspected	1	0.006
Children			
Chronic tonsillitis*/mild	Not suspected	1	0.006
Intra-abdominal abscess following appendicitis/ severe	Suspected	1	0.006
Tonsillitis*/severe	Suspected	2	0.012
Bronchitis/H1N1/severe infection*	Not suspected	1	0.006
Pneumonia*	Not suspected	1	0.006

Patients with tonsillitis had a history of predisposing factors at baseline—adenoidectomy (adult); Varicella infection and feet oedema (child). Paediatric patients with pneumonia or H1N1 infection had underlying respiratory disease. Adult patients experiencing serious cellulitis had risk factors for infection at baseline—glandular fever, mouth ulcers and conjunctivitis.
Infections* = 8 (4.8).
AE, adverse event; SAE, serious adverse event.

that treatment may effectively reverse some complications of CAPS, but in advanced cases the pre-existing inflammatory damage is irreversible even with complete control of CAPS disease activity.

The safety data in general confirmed the earlier reassuring data,[7] with only five SAE occurring, no evidence of immunogenicity, and only occasional mild injection site reactions. The AE did not cluster around a specific phenotype or age group; except for more infections reported in children. This is not surprising as IL-1 blockade in children may interfere with non-specific innate immunity towards infections.[22] Of interest, three adults and one child with MWS developed vertigo on at least one occasion. Vertigo has previously been reported in two children with MWS treated with canakinumab;[7 23–25] however, the mechanism of this apparently self-limiting AE is not yet clear. An alternative treatment regimen of 10 mg/kg intravenous canakinumab was well tolerated with no noteworthy incidence of AE/haematological/biochemistry abnormalities. The detection of ANA was infrequent and correlation with either clinical effectiveness or safety is unclear. Vaccination response to influenza, pneumococcus infection and MMR live attenuated virus was not verified by the measurement of antibody titre; however, no patient experienced an infection of the vaccinated antigen. A single dose of 300 mg subcutaneous canakinumab is reported not to affect the induction and persistence of antibody responses in vaccinated healthy subjects.[26]

To date there have been no studies in larger patient cohorts of all CAPS phenotypes evaluating longer-term effects of anti-IL-1 medications. Series reported with rilonacept,[6 27] anakinra[5 14 16 17 28–30] and canakinumab[7] in small numbers of CAPS patients demonstrated the efficacy of anti-IL-1 medications in this previously difficult to treat disease. Results to date although encouraging are inadequate to define clearly the longer-term risk/benefit ratio in particular disease phenotypes or in children in particular. This study included sufficient numbers of children and different CAPS phenotypes to analyse their responses to longer-term canakinumab separately. While overall efficacy and safety results are in line with previously published data,[7 23–25] the data indicate that children are relatively under-dosed compared with adults, and patients with more severe disease may require more canakinumab, perhaps consistent with increased IL-1β generation driving more severe symptoms. Laboratory findings in the present study need further confirmation from data of larger roll-over cohorts and of patients with a longer washout period for anakinra.

In conclusion, the administration of canakinumab subcutaneously 150 mg every 8 weeks was associated with near complete suppression of inflammatory disease in children and adults across all CAPS phenotypes. Young age and more severe CAPS disease appear to be associated with a higher dose requirement. Higher doses were well tolerated with no evidence of increased predisposition to serious infections. The extremely low discontinuation rates suggest that canakinumab is well tolerated by both adults and children. Data from this study support earlier evidence of the beneficial effects of IL-1β blockade on short-term CAPS symptoms, and the results presented here suggest that some neurological damage may be at least partly reversible. CAPS is a life-long disease and long-term surveillance of treated patients will be required to monitor for evolving disease complications, prevention of irreversible neurosensory damage developing in the first place and treatment-related AE. A registry for all CAPS patients treated with canakinumab has now been set up to investigate the safety of long-term treatment.

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