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Original article

Long-term safety profile of anakinra in patients with severe cryopyrin-associated periodic syndromes

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Abstract

Objective. Anakinra is approved for the treatment of RA and cryopyrin-associated periodic syndromes (CAPS). While the anakinra safety profile is well established in RA, the long-term safety profile in severe CAPS is less well documented and will therefore be discussed in this report.

Methods. A prospective, open-label, single centre, clinical cohort study was conducted at the National Institutes of Health in the USA, from 2003 to 2010, investigating the efficacy and safety of anakinra treatment for up to 5 years in 43 patients with CAPS. Safety was evaluated using adverse event (AE) reports, laboratory assessments, vital signs and diary reports.

Results. In total, 1233 AEs were reported during the study, with a yearly rate of 7.7 AEs per patient. The event rate decreased over time, and dose escalation during the study did not affect AE frequency. Anakinra had similar safety profiles in adults and children. The most frequently reported AEs were typical CAPS disease symptoms such as headache and arthralgia. Injection site reactions occurred mainly during the first month of anakinra treatment. In total, 14 patients experienced 24 serious AEs (SAEs), all of which resolved during the study period. The most common types of SAEs were infections such as pneumonia and gastroenteritis. There were no permanent discontinuations of treatment due to AEs.

Conclusion. In this study anakinra treatment of patients with severe CAPS for up to 5 years was safe and well tolerated both in paediatric and adult patients, with most AEs emerging during the first months after treatment initiation.

Trial registration: ClincialTrials.gov, clinicaltrials.gov, NCT00069329

Key words: adverse event (AE), anakinra, clinical trial, cryopyrin-associated periodic syndromes (CAPS), neonatal-onset multisystem inflammatory disease (NOMID), safety, injection site reactions (ISR), infections, headache

CLINICAL SCIENCE

Rheumatology key messages

- Long-term anakinra use is well tolerated both in children and adults with cryopyrin-associated periodic syndromes.
- Most adverse events appear during the first months of cryopyrin-associated periodic syndromes treatment with anakinra.
- Continued anakinra treatment during infections prevented cryopyrin-associated periodic syndromes flares without complicating the course of infections.

Introduction

Cryopyrin-associated periodic syndromes (CAPS) include a spectrum of rare inherited autoinflammatory syndromes spanning three clinical phenotypes with increasing severity: familial cold autoinflammatory syndrome, Muckle–Wells syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID), also known as

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chronic infantile neurological cutaneous articular syndrome. CAPS is an ultrarare disease occurring in ~1:1 000 000 [1]. Inflammatory episodes of fever, urticarial rash, joint pain and elevations in acute-phase reactants are present in all CAPS patients regardless of the overall clinical phenotype. The milder form, familial cold autoinflammatory syndrome, is characterized by life-long, cold-induced inflammatory episodes of fever, neutrophilic urticaria, malaise and arthralgia. The disease manifestations remit in between flares. MWS has a similar presentation, but the episodes are usually not triggered by cold, and systemic inflammation is typically present at all times. The disease is of intermediate severity and typically associated with more intense and enduring flares and morbidity, including progressive hearing loss in up to 75% of MWS patients and kidney failure secondary to amyloidosis in ~25% in the European cohort of patients [2]. The development of amyloidosis is rare in patients growing up in the USA [3]. Persistent fatigue with significant impact on quality of life is commonly found.

The most severe form, NOMID, is characterized by a neonatal or early infancy onset and involves continuous multiple organ inflammation. Clinical features include fevers and neutrophilic urticaria, conjunctivitis, headache due to aseptic meningitis and increased intracranial pressure, joint pain, craniofacial dysmorphia with prominent foreheads in patients with increased intracranial pressure, and extuberant bone lesions. In addition, these patients have sensorineural progressive hearing loss, visual impairment due to chronic papilloedema and cognitive impairment. Approximately 20% of patients with NOMID syndrome do not survive into adulthood if untreated [4, 5].

CAPS is caused by heterozygous gain-of-function mutations in *NLRP3*, the gene encoding cryopyrin. *NLRP3* mutations result in constitutive activation of caspase 1, the enzyme cleaving the precursor of IL-1β into the active form [6]. Signalling via the IL-1 receptor type I is crucial for the pathogenesis of CAPS and was first demonstrated by the induction of clinical response in CAPS patients treated with the recombinant IL-1 receptor antagonist (IL-1Ra) anakinra [7] and later confirmed in several studies blocking IL-1β [1, 2, 4].

IL-1 is a potent mediator of inflammation and anakinra was developed to replicate the body's endogenous pathway to block IL-1 receptor signalling. Anakinra was initially approved by the Food and Drug Administration for the treatment of RA, for which it has been used for >10 years across the USA, European Union, Canada and Australia. Since 2012 anakinra is also approved for the treatment of NOMID in the USA and for all types of CAPS in the European Union (2013) and Australia (2014). Recently, anakinra has also been used in patients with various autoinflammatory diseases and conditions with evidence of IL-1 involvement [8, 9]. The safety profile of anakinra is well documented in adult patients with RA [10–14] for whom the most frequently reported adverse events (AEs) are injection site reactions (ISRs), typically reported within the first 4 weeks of therapy, usually lasting 14–28 days [15]. The development of ISRs in patients who have not previously experienced ISRs is uncommon after the first month of therapy. A higher rate of serious infections in anakinra-treated RA patients compared with placebo (1.8% *vs* 0.7%) was also observed. As a result, anakinra treatment has been stopped during infections in clinical practice, with a consequent risk for flares of the underlying disease. Most patients continue anakinra treatment after the infection has resolved.

Here we present the anakinra safety profile documented from an open-label clinical study of severe CAPS patients, predominantly children, with anakinra exposures up to 5 years. The safety profiles over time across different age groups are presented, with focus on the most commonly observed AEs, headache, infections and ISRs.

Methods

This was a prospective, open-label clinical cohort study with the aim to determine the efficacy and safety of anakinra in controlling inflammatory manifestations in adult and paediatric patients with severe CAPS. The study was conducted at the National Institutes of Health Clinical Centre, Bethesda, USA and is open ended, with a primary publication from 2006 (n = 18) [4] and a secondary publication from 2012 (n = 26) [9], which has now been followed up with this extended analysis on the safety profile (n = 43). This study was conducted in accordance with the Declaration of Helsinki, and the protocol was approved by the National Institute of Arthritis and Musculoskeletal and Skin Diseases Institutional Review Board. Written informed consent was obtained from all patients or their legal guardians.

Up to the cut-off date of the study data analysis (16 August 2010), 43 patients, representing a large proportion of the total North American severe CAPS population, were included and treated for up to 5 years. The starting dose of anakinra was initially 0.5 to <1.5 mg/kg/day but higher starting doses (1.5–2.5 mg/kg/day) were allowed later during the study. Maintenance doses were individually adjusted depending on the clinical response during the course of the treatment to achieve remission of laboratory and organ specific signs of inflammation. The maximum approved anakinra dose allowed in the study protocol was 10 mg/kg/day, irrespective of age.

Safety was evaluated using AE reports, laboratory assessments and vital signs. Data were collected from the local care provider or from information obtained by the National Institutes of Health staff during scheduled visits. The patients also filled out a daily diary, mainly for the purpose of recording symptoms of CAPS. However, data capturing of CAPS symptoms in the daily diaries were typically not reported as AEs, unless specifically brought up during the scheduled visits.

All patients who received at least one dose of anakinra were included in the safety population used for the present analysis. All AEs were classified according to the Medical Dictionary for Regulatory Activities coding system. Frequencies of AEs are presented as number and percentage of patients affected and by yearly AE reporting rates. The rates are calculated as number of

events divided by patient years of exposure to anakinra treatment. Further analysis of AEs was conducted by classifying the events by the age at the time of event onset (<2, 2–11, 12–17 and ⩾18 years).

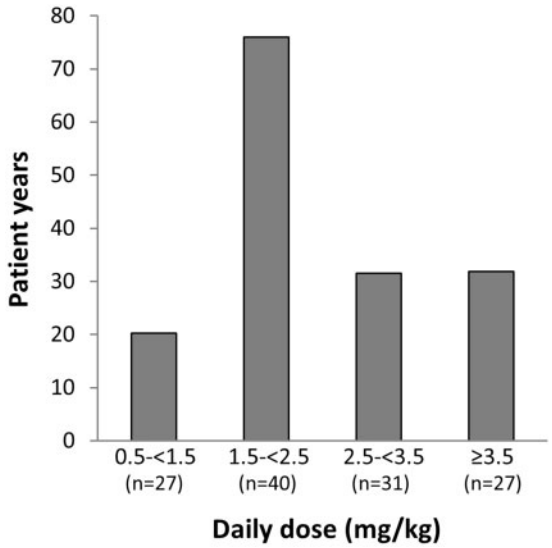
Results

Demographic data and anakinra exposure

In total, 43 patients diagnosed with severe CAPS, 36 with NOMID and 7 with characteristics overlapping between MWS and NOMID were included in the study. Of the 43 patients, 36 (84%) were paediatric (<18 years), with a majority (31 patients, 72%) being <12 years of age. Seven adult patients were also included. The youngest patient was 8 months old at anakinra treatment initiation while the oldest patient was 46 years old. Overall, 58% of the patients were female and 84% were white.

Anakinra was administered as daily s.c. injections. Patients were followed in this study for up to 5 years, with a median exposure of 4.9 and a total exposure of 159.8 patient years. The starting dose was initially 0.5 to <1.5 mg/kg/day but was adjusted to 1.5–2.5 mg/kg/day during the course of the study. Out of 43 patients, 26 (60%) had a starting dose of 0.5 to <1.5 mg/kg/day and 17 patients (40%) started on 1.5–2.5 mg/kg/day. Depending on the clinical response, individual dose adjustments were performed throughout the study and the median maintenance dose after 5 years of treatment was 3.1 mg/kg/day (range; 2.0–5.0 mg/kg/day). The most common dose in the study was 1.5–2.5 mg/kg/day with a total exposure of 76 patient years (Fig. 1). The highest dose given was 8 mg/kg/day and was administered temporarily to one patient only. A total of eight patients received doses of >4.5 mg/kg/day at some time during the study.

Fig. 1 Exposure per dose level in the study population



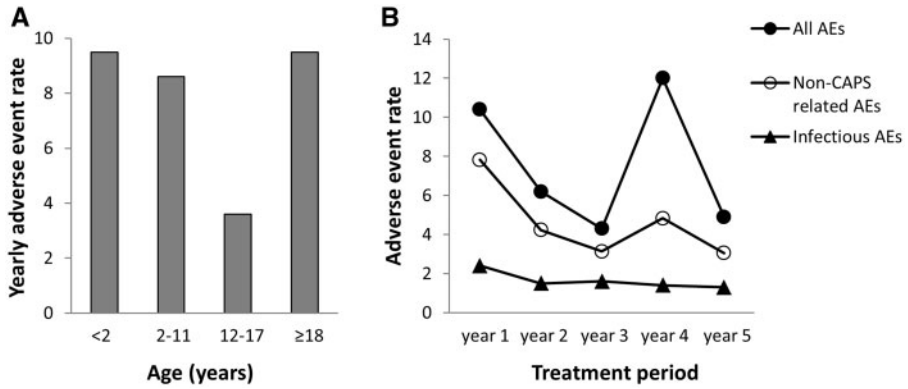
Exposure per dose level (daily s.c. dose).

Adverse events

The number of AEs reported during the 5-year study period was 1233, giving an overall reporting rate of 7.7 events per patient year. Overall, the reporting rates for individual event types classified by preferred term were low with no rate exceeding 0.8 events per patient year. The reporting rates in infants (<2 years), children (2–11 years) and adults (⩾18 years) were similar: 9.5, 8.6 and 9.5, respectively (Fig. 2A). A lower yearly AE reporting rate, 3.6, was observed in the age group 12–17 years. Of note is that this group only included five patients.

The yearly AE rate decreased during the first 3 years (Fig. 2B). The peak at year 4 is explained by an altered reporting procedure where all general CAPS disease symptoms recorded in patient diaries were reported also as AEs during 1 year. The yearly rate of infections and

Fig. 2 Adverse event rates by age group and over time



(**A**) Yearly event rate by age at onset for the safety population (n = 43) in infants (<2 years), children (2–11 years), adolescents (12–17 years) and adults (⩾18 years). (**B**) Adverse event rate over time during the study period. In the line representing non-CAPS related AEs the following AEs were excluded: ocular hyperaemia pyrexia, fatigue, malaise, arthralgia, headache, dizziness, rash and urticaria.

Table 1 Number of adverse events

Type of Adverse Event	No. of patients (%) (n = 43)	No. of events	Severity, n (%)		
			Mild	Moderate	Severe
Adverse events (all)	41 (95.3)	1233	1060 (86.0)	159 (12.9)	14 (1.1)
Adverse events in ⩾ 5 patients					
Headache	21 (48.8)	115	99 (86.1)	16 (13.9)	—
Arthralgia	18 (41.9)	133[a]	121 (91.0)	11 (8.3)	—
Pyrexia	17 (39.5)	51	43 (84.3)	8 (15.7)	—
Upper respiratory tract infection	17 (39.5)	48	39 (81.3)	8 (16.7)	1 (2.1)
Nasopharyngitis	15 (34.9)	40	39 (97.5)	1 (2.5)	—
Rash	14 (32.6)	51	44 (86.3)	7 (13.7)	—
Ocular hyperaemia	12 (27.9)	35[a]	33 (94.3)	1 (2.9)	—
Sinusitis	12 (27.9)	28	23 (82.1)	5 (17.9)	—
Ear infection	11 (25.6)	23	20 (87.0)	3 (13.0)	—
Otitis media	11 (25.6)	20	14 (70.0)	6 (30.0)	—
Fatigue	10 (23.3)	27	25 (92.6)	1 (3.7)	1 (3.7)
Diarrhoea	10 (23.3)	16	15 (93.8)	1 (6.3)	—
Oropharyngeal pain	9 (20.9)	27	22 (81.5)	4 (14.8)	1 (3.7)
Pain in extremity	9 (20.9)	27	26 (96.3)	1 (3.7)	—
Cough	9 (20.9)	19	18 (94.7)	1 (5.3)	—
Injection site reaction	8 (18.6)	12	8 (66.7)	4 (33.3)	—
Neck pain	8 (18.6)	11	10 (90.9)	1 (9.1)	—
Vomiting	7 (16.3)	25	21 (84.0)	4 (16.0)	—
Back pain	7 (16.3)	22	18 (81.8)	4 (18.2)	—
Gastroenteritis	7 (16.3)	8[a]	4 (50.0)	3 (37.5)	—
Nasal congestion	6 (14.0)	14	14 (100)	—	—
Nausea	6 (14.0)	14	12 (85.7)	2 (14.3)	—
Abdominal pain	6 (14.0)	11	11 (100.0)	—	—
Sleep disorder	6 (14.0)	10	9 (90.0)	1 (10.0)	—
Urinary tract infection	6 (14.0)	10	8 (80.0)	1 (10.0)	1 (10.0)
Gastrointestinal viral infection	6 (14.0)	8	8 (100.0)	—	—
Viral infection	6 (14.0)	8	6 (75.0)	2 (25.0)	—
Condition aggravated	5 (11.6)	7	5 (71.4)	2 (28.6)	—
Fall	5 (11.6)	6	5 (83.3)	1 (16.7)	—
Pneumonia	5 (11.6)	6	2 (33.3)	4 (66.7)	—
Post lumbar puncture syndrome	5 (11.6)	5	2 (40.0)	2 (40.0)	1 (20.0)

Adverse events are expressed according to MedDRA preferred term nomenclature. [a]For one of the reported events the classification of severity is missing.

infestations was slightly higher during the first year compared with the remaining study period where the average was more than two infections per patient per year (Fig. 2B). The frequency of infections does not increase during year 4. When omitting typical CAPS symptoms from the analysis of AEs during the fourth year of the study (ocular hyperaemia, pyrexia, fatigue, malaise, arthralgia, headache, dizziness, rash and urticaria) the overall AE reporting rates show a general decrease over the study period without the marked peak at year 4. Just like the reporting rate for non-serious AEs, the reporting rate for SAEs declined during the study: 11 serious AEs were recorded during the first 6 months, another nine during the following 6 months while the remaining four occurred later in the study.

The most frequently reported AEs in the study, year 4 included, were headache (115 events in 21 patients) and arthralgia (133 events in 18 patients) (Table 1), both symptoms representing typical CAPS disease manifestations. Headache was reported slightly less frequently at higher anakinra doses (⩾3.5 mg/kg/day; rate 0.6 events per patient year) compared with lower doses (<3.5 mg/kg/day; rate 0.8 per patient year).

Among all AEs, 86% were classified as mild, 13% as moderate and 1% as severe. Six of the 14 severe AEs were infections. None of the AEs led to discontinuation of the study drug; however, in one patient who developed a wound infection, cellulitis and chest pain, the drug was temporarily stopped. All other patients continued on anakinra, also during infections. Five patients experienced 11 AEs that led to dose adjustments. All adjustments were dose increases due to disease flares during the AEs. At four of these occasions, the flares were induced by infections.

Serious adverse events

During the study, 14 patients experienced 24 serious AEs (SAEs); all but three occurred during the first 12 months of anakinra treatment (Table 2). There were no deaths and all

TABLE 2 Complete listing of serious adverse events

Patient no. (n = 43)	Age at AE onset/ sex	Serious adverse event(s)	Time from anakinra start to AE onset	Intensity	Action taken with study drug
2000	7/M	Post lumbar puncture syndrome	Same day	Mild	No action
2000	7/M	Cardiac catheterization	14 days	Mild	No action
2001	19/M	Cellulitis Wound infection Chest pain	6 days	Severe	Temporarily stopped
2007	4/M	Post lumbar puncture syndrome	2 days	Moderate	No action
2007	5/M	Uveitis	8 months	Moderate	No action
2009	5/F	Gastroenteritis	8 months	Moderate	No action
2009	8/F	Macrophage activation syndrome Postoperative wound infection	51 months	Severe	No action
2011	28/F	Post lumbar puncture syndrome	12 months	Severe	No action
2015	12/F	Condition aggravated	6 months	Moderate	No action
2020	2/F	Meningitis enteroviral	12 months	Moderate	Dose increased
2021	1.5/M	Arthritis bacterial	8 months	Severe	No action
2021	1.5/M	Lymphadenitis bacterial	10 months	Severe	No action
2021	1.2 / M	Pneumonia Otitis media	7 months	Moderate	No action
2024	5/M	Gastroenteritis	26 months	Not known	No action
2030	2/F	Traumatic lumbar puncture	6 months	Severe	No action
2031	2/F	Convulsion	18 months	Mild	No action
2035	1.2/F	Pneumonia Sinusitis	6 months	Moderate	Dose increased
2038	7/F	Post lumbar puncture syndrome	5 months	Mild	No action
2042	1.3/F	Pneumonia	7 months	Moderate	No action

AE: adverse event.

events resolved during the study period. Infections were the most common types of SAEs: 13 events in seven patients of which seven events occurred in three patients <2 years of age. The most common infections were pneumonia and gastroenteritis, occurring in three and two patients, respectively. Five SAEs were post-spinal headaches related to lumbar punctures that were performed as part of the study procedure. There was one event of macrophage activation syndrome during the study. The event occurred in connection with a postoperative infection in a patient who had two previous episodes of macrophage activation syndrome before the start of anakinra treatment. The patient was treated with prednisolone and ciclosporin, and the anakinra dose was maintained at 2 mg/kg/day. The event resolved without sequelae. This patient lacked any germline or somatic mutations in NLRP3 in DNA generated from whole blood, but fulfilled the clinical criteria of NOMID and had an excellent response to anakinra therapy.

Injection site reactions

The most common side effects of anakinra treatment in RA studies are ISRs such as redness, itching, rash and pain [10–12]. In this study 10 patients experienced 17 ISR events, including one vaccination site reaction (Table 3). As expected, the majority of events, 11 (65%), occurred during the first month and 13 (76%) were reported during the first 6 months. No ISRs were reported after 2 years. The ISRs resolved in all patients over a period of 1–74 days and in the majority of cases (71%) they resolved already within 1 week. With the exception of one event of injection site erythema in a patient 12–17 years, ISRs were only reported in patients 2–11 years and ⩾18 years of age. There was no difference in reporting rates of ISRs between males and females. Most events were mild (76%); there were no severe or serious ISRs and there were no temporary or permanent discontinuations due to ISRs.

All ISRs reported during the first 6 months of anakinra treatment occurred in the 26 patients who were enrolled early in the study and consequently received a starting dose of 0.5 to <1.5 mg/kg/day.

Infections

In the study 37 patients (86%) reported 273 infections, corresponding to a reporting rate of 1.7 infections/patient year (Table 4). Upper respiratory tract infections and nasopharyngitis were the most common ones. Among the infections, 13 were reported as SAEs in seven patients, and the most common were pneumonia (three patients) and gastroenteritis (two patients).

The overall frequency of infections remained stable over time, with the exception of a higher yearly reporting rate during the first year of treatment (2.4), compared with the following years (1.3–1.6) (Fig. 2B). The yearly AE reporting

Table 3 Number of treatment-emergent injection site reactions during the study

Reported event	Number of events				
	Month 0–6	Month 6–12	Year 2	Year 3–5	Total
Injection site reaction	11	—	1	—	12
Injection site erythema	1	—	1	—	2
Application site rash	—	—	1	—	1
Injection site eczema	1	—	—	—	1
Vaccination site reaction	—	1	—	—	1
Total	13	1	3	—	17

Table 4 Infections and infestations occurring in more than one patient (n = 43)

Infections and infestations (>1)	No. of patients (%)	No. of events
Upper respiratory tract infection	17 (39.5)	48
Nasopharyngitis	15 (34.9)	40
Sinusitis	12 (27.9)	28
Ear infection	11 (25.6)	23
Otitis media	11 (25.6)	20
Gastroenteritis	7 (16.3)	8
Gastrointestinal viral infection	6 (14.0)	8
Urinary tract infection	6 (14.0)	10
Viral infection	6 (14.0)	8
Pneumonia	5 (11.6)	6
Bronchitis	4 (9.3)	6
Gastrointestinal infection	3 (7.0)	3
Hordeolum	3 (7.0)	3
Otitis externa	3 (7.0)	3
Pharyngitis	3 (7.0)	4
Cellulitis	2 (4.7)	2
Cystitis	2 (4.7)	6
Device related infection	2 (4.7)	3
Otitis media acute	2 (4.7)	2
Pharyngitis streptococcal	2 (4.7)	6
Total infectious events	37 (86.0)	273

rate for infections was higher in patients <2 years (rate 3.4) and 2–11 years (rate 2.2), compared with other age groups. Of the 273 infections in total, 230 (84%) were mild, 36 (13%) were moderate and 7 (3%) were severe.

Anakinra treatment was not stopped during infections, except in one patient who developed serious cellulitis and a wound infection early in the study. This patient developed a severe disease flare after stopping anakinra and was therefore re-started on anakinra after 8 days (Table 2). In two serious infections and two non-serious infections (one otitis media and one gastrointestinal viral infection with fever) the dose of anakinra was increased due to disease flares in connection with the infections (Table 2).

Discussion

Here we present safety data for up to 5 years of anakinra treatment in 43 patients with severe CAPS, focusing on reports relating to headaches, ISRs and infections. The overall AE reporting rate was low, with no AEs reported with a frequency higher than 0.8 events/year. The vast majority of AEs (86%) were mild. The reporting rates were similar across age groups, except for patients 12–17 years old who had a lower reporting frequency. This could be explained by the low number of patients (n = 5) in this group. Most of the AEs were reported in the first year of the study and declined to ~5 events/patient year and this rate was maintained throughout the study, with the exception of year 4. The higher reporting frequency in year 4 can be explained by temporarily altered AE reporting routines during this period, when all notes in patient diaries, normally only used for evaluation of treatment efficacy and for decisions on dose adjustments, served as a source for AE recordings. Consequently, when excluding the daily symptoms of CAPS, the overall AE reporting rate for year 4 was similar to those seen in years 3 and 5. Similar to the reporting rate for non-SAEs, the reporting rate for SAEs declined during the study.

No clinically relevant new or unexpected AEs occurred during the study, and the safety profile was comparable to that seen in studies on patients with RA. The most frequently reported AEs were headache and arthralgia. Headache is also a symptom of severe CAPS, and all patients had headaches prior to the initiation of anakinra treatment [4]. Headaches improved dramatically during anakinra treatment and the frequency remained low throughout the study, compared with baseline [9]. However, despite the markedly reduced frequency following the initiation of anakinra treatment, headaches, mostly mild, remained the most commonly reported AE. Headaches were often managed by increasing the anakinra dose. Since also arthralgia, another common feature of severe CAPS but not a known side effect of anakinra, was reported with approximately the same frequency as headache, it is likely that the events of headache should be seen as continued disease activity in this patient population with severe CAPS rather than a side effect of anakinra.

The reporting rate of ISRs, usually the most common adverse drug reaction seen with anakinra, was lower in this study than in previous studies in RA. In fact, it was at the same level as that of RA patients receiving placebo [10–12, 16]. The reason for this difference remains

unclear, but in the context of chronic inflammation there are extensive homeostatic tissue responses that alter cytokine and cytokine receptor levels, which lead to epigenetic changes and increase the milieu for the differentiation of regulatory macrophages [17]. These tissue responses to chronic IL-1 overproduction may reduce the ability to mount local reactions to anakinra injections. As anakinra suppresses the action of IL-1 stimulation on the IL-1 receptor, the chronic tissue responses normalize on treatment. Another potential contributing factor to the low number of reported ISRs could be that patients with severe CAPS experience extensive symptom relief upon start of adequate treatment and therefore tend to be less prone to report mild ISRs.

The majority of ISRs were mild and there were no discontinuations, either temporary or permanent, due to ISRs. Just like in RA patients [15], ISRs occurred early in the study, the majority during the first month. All ISRs occurred in patients who received a lower starting dose, 0.5–1.5 mg/kg/day, that is, in patients who were recruited early in the study. This could be related to patients recruited later in the study being better informed about ISRs and measures to decrease the manifestations of them (i.e. icing the injection site, use of local application of low-potency, over the counter corticosteroid-containing creams or lotions).

Infections were the most common type of AEs, both serious and non-serious infections. Most infections were mild and non-serious, with upper respiratory tract infections and nasopharyngitis being the most common. As expected, infections were most common in the younger age groups [18]. There was no indication of increasing frequency of infections over time. On the contrary, infections were most prevalent during the first year of treatment, possibly related to the effect of increasing age during the study period. Similarly, serious infections occurred more frequently during the first year of anakinra treatment. For RA, the label states that administration of anakinra should be discontinued if a patient develops a serious infection. In this study of severe CAPS, anakinra was continued during the course of infections in 272 out of a total of 273 events. In one case anakinra was temporarily stopped during an infection, after which the patient developed a severe CAPS flare and was re-started on anakinra after 8 days, without complications and with resolution of the infection. In two serious infections and two non-serious infections, the dose of anakinra was increased due to disease flares that occurred in connection with the infections. All infections during anakinra treatment were carefully monitored. Anakinra was maintained with the same dose. In patients who experienced a concomitant CAPS flare with their infection, anakinra was temporarily increased without impact on the resolution of the infection. Although the clinical threshold for starting an antibiotic was low, the organisms isolated and the treatments used did not suggest opportunistic infections and the resolution of the infections on anakinra was as expected and not associated with complications. Observations that patients with CAPS can develop disease flares in the context of triggering infections, and that abrupt drug withdrawal results in disease flares that can be severe [4], illustrate that withholding anakinra during an infection can increase the risk of severe disease flares, suggesting that in CAPS patients continued anakinra treatment should be considered during infections, with careful monitoring of the resolution of the infections.

In summary, the data presented here show that anakinra is well tolerated during long-term treatment of both children and adults with severe CAPS. Moreover, continued treatment during infections, both serious and non-serious, prevented disease flares and did not complicate the course or outcome of the infections.

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