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REVIEW

Critical appraisal of canakinumab in the treatment of adults and children with cryopyrin-associated periodic syndrome (CAPS)

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Abstract: The cryopyrin-associated syndromes (CAPS) include three autosomal-dominant syndromes, that are caused by a mutation in the *NLRP3* gene on chromosome 1, encoding the cryopyrin protein. These syndromes, familial cold autoinflammatory syndrome, Muckle-Wells syndrome and neonatal-onset multisystem inflammatory disease, are characterized by urticaria-like rash, fever, central nervous system inflammation, an arthropathy and a risk of the development of amyloidosis in a respectively escalating degree of severity between the various syndromes. Recently the role of cryopyrin in the regulation of interleukin (IL)-1 production and activation was described and anti IL-1 therapies were found to be very effective in treating these syndromes. There are several types of anti IL-1 medications based on different mechanisms of antagonizing IL-1. This paper focuses on the efficacy and safety of canakinumab, a long-acting humanized anti IL-1 antibody, in treating these syndromes.

Keywords: canakinumab, cryopyrin-associated periodic syndromes, biologics, treatment, autoinflammatory diseases

Introduction to cryopyrin-associated periodic syndrome and prevalence

The cryopyrin-associated periodic syndromes (CAPS) include three autosomal-dominant syndromes, that are caused by a mutation in the *NLRP3* (in past also called *CIAS1/NALP3*) gene on chromosome 1, encoding the cryopyrin protein (Table 1a). The three syndromes, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells syndrome (MWS) and neonatal-onset multisystem inflammatory disease (NOMID), are characterized by urticaria-like rash, fever, central nervous system inflammation, arthropathy and the risk of later development of amyloidosis(Table 1b, 1c). These syndromes are considered variants of the same disease process that vary by severity of symptoms, systems involved and outcome.[1] All respond dramatically to anti-interleukin (IL)-1 therapy.

The prevalence of CAPS in the United States (US) is estimated at about $1/10^6$, although there are no formal studies and it is probable there is underdiagnosis of CAPS, especially the MWS variant.

Familial cold autoinflammatory syndrome

FCAS (previously called familial cold urticaria), the mildest of the CAPS, was first described in 1940 and the genetic mutation discovered in 2001.[2,3] Most FCAS patients are located in the US and there are probably several hundred patients with this disorder. It has been hypothesized that most patients originate from the same family. Almost all

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patients have a genetic mutation in the *NLRP3* gene. FCAS often starts at birth and is apparent in 95% of the patients by 6 months.

Clinical manifestations[4]

Typically, the attack starts 2 to 3 hours after generalized (not direct contact) cold exposure. Patients develop an urticaria-like rash that starts on the extremities and spreads to the trunk, low-grade fever, arthralgia, conjunctivitis, nausea, extreme thirst, sweating and headaches. The peak of the attack occurs at 6 to 8 hours and lasts up to 24 hours. The frequency of attacks is variable but can be very frequent and debilitating. The rash is not true urticaria (mast cells), rather there is a perivascular polymorphonuclear cellular infiltrate in the dermis. Amyloidosis is a rare complication of FCAS (2% to 4%).

Muckle-Wells syndrome

MWS, the intermediate severity CAPS, was described in 1962 and the genetic mutation was found together with that of FCAS.[3,5] MWS starts later in life than FCAS and can appear at any age. Most cases are in Europe. Genetic mutations in the *NLRP3* gene are found in 65% to 75% of patients.

Clinical manifestations[6]

Attacks are usually not triggered by cold exposure. A typical attack includes fever, rash, more persistent than in FCAS, arthralgia, arthritis, myalgia, headaches, conjunctivitis, episcleritis and uveitis. Attacks last up to 3 days. Often starting in adolescence, 50% to 70% of patients develop sensorineural hearing loss. Amyloidosis develops in 25% of the patients.

Neonatal-onset multisystem inflammatory disease

NOMID, termed in Europe chronic infantile neurologic, cutaneous, articular syndrome (CINCA), is the most severe of the CAPS. First described in 1981, the association with the *NLRP3* gene was found in 2002.[7,8] However, only about 50% to 60% of patients have mutations in this gene.[9]

Clinical manifestations[1,7,9]

The onset of NOMID is at or within several weeks of birth; 33% to 50% of affected infants are born prematurely. Patients present with urticaria-like rash and fever, often occurring daily. They also have symptoms related to chronic aseptic meningitis such as headaches, irritability and vomiting.

Table 1a Genetic characteristics of the cryopyrin-associated periodic syndromes

Disease	Inheritance	Chromosome	Gene defect	Protein product	Common mutations
FCAS	Dominant	1q44	CIAS1/NALP3/NLRP3	Cryopyrin	V198M, C259W, R260W
MWS	Dominant	1q44	CIAS1/NALP3/NLRP3	Cryopyrin	R260W, L, L264V, D303N
NOMID	Dominant Sporadic	1q44	CIAS1/NALP3/NLRP3	Cryopyrin	C148Q, R168Q, L264F, H, RD303H, V351M, L

Genetic mutations are found in only 50% to 70% of patients with MWS and NOMID.

Table 1b Characteristic of the cryopyrin-associated periodic syndromes

Disease	Onset age	Typical ethnicity	Common triggers	Episode duration	Interval between episodes
FCAS	First year of life	United States	Cold	<24 hours	Variable
MWS	Any age	Western Europe	Any	1–3 days	Variable
NOMID	Birth, infancy	Any	None	Continuous	None

Table 1c System involvement of the cryopyrin-associated periodic syndromes

Disease	Skin	Musculoskeletal	Eyes	Neurologic
FCAS	Urticaria-like	Arthralgia	Conjunctivitis	Headaches
MWS	Urticaria-like	Arthralgia	Conjunctivitis, episcleritis, uveitis	Hearing loss, headaches
NOMID	Urticaria-like	Epiphyseal overgrowth with deformities, cartilage overgrowth, arthritis	Conjunctivitis, uveitis, papillitis	Chronic meningitis, hearing loss, mental retardation increased intracranial pressure, headaches

Abbreviations: FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disorder.

Late neurologic complications include hydrocephalus, developmental delay, mental retardation and hearing loss. Eye findings include conjunctivitis, uveitis and papillitis of the optic nerve, and may lead to visual loss. By about 2 years, 50% of patients develop a severe arthropathy, consistently mainly of cartilage growth abnormalities leading to severe pain, metaphyseal and epiphyseal bony overgrowth, ossification irregularities, deformities and disabilities. There is little synovial inflammation in NOMID. Patients have typical morphological changes of short stature, frontal bossing, macrocephaly, saddle nose, short, thick extremities with clubbing of fingers and wrinkled skin. About 20% die by age 20 years and others develop amyloidosis.

Etiology and pathogenesis of CAPS

The three autosomal-dominant syndromes that constitute CAPS are caused by single base mutations on the *NLRP3* gene located on the long arm of chromosome 1 encoding the protein cryopyrin.[1,3,8] Some mutations are specific to one of the syndromes and some overlap among all three syndromes (Table 1a).[1,9] Often, especially in patients with NOMID, no mutations are found, thus it is clear that other factors influence the development and severity of CAPS.[9]

The cryopyrin protein contains an N-terminal pyrin domain and has an important role in regulation of the assembly of the inflammasome, a group of proteins that when assembled activate caspase-1 that cleaves pro IL-1β to active IL-1β.[10] The mutated cryopyrin protein probably increases the rate of the inflammasome assembly independently of the usual stimuli needed in wild type protein.[10,11] Thus the result is a gain of function mutation. Cryopyrin is present mainly in neutrophil cells and chondrocytes explaining the target organs of these diseases.

Management

Non-steroidal anti-inflammatory drugs (NSAIDs) and anti-histamine therapies are not effective for FCAS and MWS. Corticosteroids may alleviate symptoms but are needed frequently and may cause significant adverse effects. Anti-IL-1 agents are very effective in alleviating symptoms and decreasing inflammation.[6,12–18] In recent controlled trials, rilonacept a fusion protein soluble IL-1 receptor, and canakinumab, a humanized IL-1 antibody, have been shown to be effective in treating FCAS and MWS.[19,20] In about one-third of cases of MWS the hearing loss may be partially reversible.[21–23]

In NOMID, NSAIDs, antihistamines, corticosteroids, colchicine, methotrexate and other immunosuppressive medications are marginally effective and do not change the disease course. One case report showed that etanercept, a tumor necrosis factor soluble receptor, was effective, mainly for the joints.[24]

Recent studies have shown the dramatic effect of anakinra, a recombinant IL-1 receptor antagonist in treating the rash, fever and meningitis of NOMID with normalization of the acute phase reactants allowing a reduction in the corticosteroid dose.[25–28] However, existing joint damage and mental retardation was not reversible and many patients continue to have increased intracranial pressure despite therapy. It appears that early recognition and treatment is crucial in preventing long-term damage and disability.

Canakinumab in CAPS – mode of action

Canakinumab (ACZ885, Ilaris®; Novartis Pharma) is a recombinant, long-acting humanized anti-IL-1β monoclonal antibody, which selectively blocks IL-1β. Canakinumab also appears to have intracellular effects in addition to its' primary effect as a neutralizing antibody to IL-1. Lachmann et al demonstrated that the production of IL-1β, which is markedly increased in CAPS patients (31 ng/day mean production examined in 7 patients), was reduced to production levels of healthy controls after the administration of canakinumab (6 ng/day).[29] Thus canakinumab also acts as a negative feedback on the production of IL-1β by the inflammasome.[30]

Pharmacology/pharmacokinetics

Canakinumab binds to serum IL-1β and neutralizes its activity by blocking its interaction with IL-1 receptors with peak serum concentration occurring approximately 7 days after subcutaneous administration of a single, 150 mg dose. The range of observed half-life was 21.5 to 33 days[31,32] with a mean of 26 days.[30,31] The absolute bioavailability was 70% and the expected accumulation ratio was 1.3-fold following 6 months of subcutaneous dosing of 150 mg administered every 8 weeks. Clearance of canakinumab varied according to body weight and was estimated to be 0.174 L/day in a CAPS patient weighing 70 kg. There was no indication of accelerated clearance or time-dependent change in the pharmacokinetic properties of canakinumab following repeated administration. In pediatric CAPS patients, the peak concentrations of canakinumab occurred between 2 to 7 days following a single subcutaneous administration of 2 mg/kg (max 150 mg) of canakinumab. The half-life ranged from 22.9 to 25.7 days, similar to the pharmacokinetic properties

observed in adults. No gender- or age-related pharmacokinetic differences were observed after correction for body weight.[31]

Efficacy/comparative studies

To date there are no published comparative studies, comparing canakinumab, anakinra or rilonacept in the treatment of CAPS. Lachmann et al published a pivotal, phase III double-blind, placebo-controlled, randomized withdrawal study of canakinumab in patients with CAPS.[20] Patients who had previously received treatment with anakinra or rilonacept, were eligible to participate after a minimal "washout" period when treatment was discontinued (different for each anti IL-1 medication based on half-life) and their disease had relapsed. 49% of the patients were treated with anakinra before entering the study, but there was no data on the efficacy or adverse effects of anakinra in these patients. Patients treated with canakinumab in previous preliminary trials were also allowed to participate when their disease flared.[32,33] The study was designed as a three-part study. Overall 35 patients were enrolled, aged 4 to 75 years, weighing between 15–100 kg. It is important to note that the authors did not present details on the proportion of patients with each subtype of CAPS. In the first part, patients received 150 mg or 2 mg/kg (for patients ≤40 kg) of open label canakinumab by a single, subcutaneous injection. Those with a complete response to treatment by day 15 who did not flare by the end of 8 weeks entered part 2 and were randomly assigned to receive either 150 mg of canakinumab or placebo every 8 weeks for up to 24 weeks. After the completion of part 2 or at the time of relapse, whichever occurred first, patients proceeded to part 3 and received at least 2 more open-label doses of canakinumab.

The primary study outcome measure was the proportion of patients in part 2 with a relapse (Table 2) of CAPS during canakinumab treatment, as compared with placebo. Secondary outcome measures included the proportion of patients with a complete response in part 1, the value of inflammatory markers (C-reactive protein, serum amyloid A), global assessments by physicians and patients and safety data. In the open-label first part, the symptoms of CAPS started to diminish in all patients within 24 hours and 97% of the patients had a complete response by day 15. One patient did not maintain complete response and two other patients refused randomization and were excluded from part 2. Thirty-one patients were randomized. During the second part of the study, all 15 patients in the canakinumab group remained in remission. In contrast, 13 of the 16 patients (81%) in the placebo group had a disease flare ($P < 0.001$), within a median of 100 days. The inflammatory markers remained within the normal range in the canakinumab group, but increased in the placebo group. At the final assessment at the end of part 3, a total of 30 of the 31 (97%) patients who had entered this part of the study had no or minimal disease activity, according to the physician's assessment, and the remaining patient had mild disease activity. Rash was absent in 29 of the 31 patients (94%) and was minimal in the other 2 patients. Either no or minimal symptoms were reported by 26 of the 31 patients (84%), mild symptoms were reported by 1 patient, moderate symptoms by 2 patients, and severe symptoms by 1 patient, who also had fibromyalgia; data were missing for 1 patient.

A later multi-center open-label cohort study enrolled a total of 98 patients, including 18 pediatric patients.[34] Fifty-four patients were included from various studies of Lachmann et al[20,32,33] and 44 were canakinumab-naïve patients. The patients received 150 mg or 2 mg/kg (for patients ≤40kg) of canakinumab every 8 weeks by subcutaneous injection. The primary outcome measure was to assess the long-term safety but secondary outcomes included assessment of response for canakinumab naïve patients, the maintenance of response for patients already receiving canakinumab and the percentage of patients requiring dose adjustment. The complete response for canakinumab-naïve patients was defined as in Table 2. A complete response was observed in 41 of the 44 canakinumab-naïve patients (93.2%). Relapse data were available

Table 2 Descriptions of response in pivotal and other canakinumab studies in cryopyrin-associated periodic syndromes (CAPS)

	Disease activity assessments[a]	Rash	Laboratory activity markers[b]
Complete response	no or minimal disease activity	no or minimal	within normal range
Relapse	greater than minimal	more than minimal	above normal range

[a]Disease activity assessments were performed monthly by physicians who assessed the global disease activity and each of the following symptoms: urticarial rash, arthralgia, myalgia, headache, conjunctivitis, fatigue or malaise, and other symptoms related or unrelated to CAPS, The assessments were performed with the use of a 5-point scale. [b]The values for serum C-reactive protein and serum amyloid A that was within the normal range (<10mg/L for both measures) or defined as relapse when the value for either was greater than 30 mg/L.

for 86% of the patients; 90.6% of these had no relapse, and 5.9% had experienced at least 1 relapse. At least 1 dose adjustment was required by 16.3% of the patients (the dose adjustment was not described in the abstract).

In the pediatric subgroup of this study (n = 18; range 5 to 17 years; 8 adolescents [≥12 years]; all were ≥15 kg), 11 were naïve to canakinumab and 7 were rolled over from Lachmann's et al study.[35] Complete response was achieved in 9 (81.8%) canakinumab-naïve patients by day 8. The majority of canakinumab-treated pediatric patients were relapse free (11 out of 18). Three MWS patients experienced 1 relapse, 3 had missing relapse assessments and 1 MWS/NOMID overlap patient did not achieve complete response and the dose was uptitrated. Seven children (36.8%) received at least 1 protocol-defined dose adjustment (first dose doubled) or at least 1 frequency adjustment. In other studies of canakinumab the median effect of one 150 mg dose of canakinumab was 127 days.[29]

As a result of the pivotal study results canakinumab was approved by the United States Food and Drug Administration in June 2009 for the treatment of FACS and MWS in adults and children 4 years of age and older (www.accessdata.fda.gov/drugsatfda_docs/label/2009/125319s000lbl.pdf), and in October 2009 by the European Medicines Agency for use in all subtypes of CAPS (www.ema.europa.eu/humandocs/Humans/EPAR/ilaris/ilaris.htm).

However there are still important questions of efficacy not answered by these studies, particularly for MWS and NOMID associated with long-term damage. These include the prevention of amyloidosis, the prevention of arthropathy in NOMID, the prevention of neurologic damage, especially hearing loss in MWS and NOMID as well as ocular and other central nervous system (CNS) damage related to NOMID. Another unanswered question is whether existing damage can be reversed including amyloidosis,[36] hearing loss, CNS function (mental retardation, for example) and the arthropathy associated with NOMID. Initial studies in anakinra indicate only limited ability to reverse existing damage.[37]

An important issue in answering these questions is whether there is adequate penetration of canakinumab to the CNS via the blood – brain barrier and whether current CNS levels are sufficient to treat these manifestations. As we noted, in Lachmann's studies it was not clear how many patients had classic NOMID and whether current doses and frequency of administration of canakinumab would be sufficient for these patients.

Canakinumab effect on issues related to general health, fatigue, function and quality of life of CAPS patients

Lachmann et al examined issues of general health, fatigue and function among the patients in the controlled phase III, 48 week study.[38] Baseline scores for general mental and physical health measured by use of the Short-Form (SF)-36® and fatigue measured by use of the Functional Assessment of Chronic Illness Therapy (FACIT)-Fatigue® questionnaires were significantly lower than those expected in the general population. Following the first canakinumab dose, SF-36 and FACIT-Fatigue® scores improved to the levels expected in the general population (time to improvement not described). An improvement in functional disability was observed as shown by Health Assessment Questionnaire (HAQ) disability scores. Health-Related Quality of Life (HRQoL) scores at 48 weeks were comparable to those observed following the first injection, and to the general population, suggesting the sustained effect of therapy of canakinumab on primarily patient driven outcomes.

Thus, canakinumab for treatment of CAPS has shown a rapid and sustained significant impact on important physician- and patient-derived outcomes.

Safety and tolerability

Lachmann et al reported no deaths or life-threatening adverse effects (AE) in the pivotal study.[20] Two patients had serious AEs in the open-label part 3, one a urinary tract infection requiring hospitalization and the other was an episode of vertigo accompanied by acute closed-angle glaucoma. Both patients discontinued therapy. Overall 29 (83%) of the patients had AEs with 12 (34%) developing infectious AEs. There was a significant difference between canakinumab and placebo only in the rate of suspected infections ($P = 0.03$). While numbers are small, vertigo was seen solely in canakinumab-treated patients with MWS who often have cochlear involvement as part of their disease. Table 3 describes the AEs seen most frequently in this cohort.

In various publications and abstracts safety data has been reported on 102 adult and pediatric patients with CAPS exposed to canakinumab.[20,29,32–35] These included 20 patients with FCAS, 72 MWS, 10 MWS/NOMID overlap. Sixty-two patients were treated for at least 6 months, 56 for at least 1 year and 4 for at least 3 years. A total of 9 serious AEs were reported. Among these were infections in 3 patients and vertigo in 2. One of the infections included

Table 3 Adverse events seen in more than 10% of patients using canakinumab for cryopyrin-associated periodic syndromes: controlled study[20] (N = 35)

Adverse event	N (%)
Nasopharyngitis	12 (34)
Diarrhea	7 (20)
Influenza	6 (17)
Rhinitis	6 (17)
Nausea	4 (14)
Headache	5 (14)
Pharyngitis	5 (14)
Weight gain	4 (11)
Musculoskeletal pain	4 (11)
Vertigo[a]	4 (11)

[a]Exclusive to patients with Muckle-Wells syndrome.

an intra-abdominal abscess following appendectomy. As in the controlled study, the most common AEs were nasopharyngitis and gastrointestinal disturbance. Other common AEs included influenza and headache (actual numbers of each AE unavailable from published data). There was no change in the AE profile among the longer treated patients. One patient discontinued treatment due to a potential infection. There were no cases of malignancy or opportunistic, including mycobacterium, infections reported. Also there were no cases of autoantibody formation to canakinumab or autoimmune/demyelinating AEs reported. No significant differences in safety were noted between the adult and pediatric patients.[34,35]

Injection site and allergic reactions appear to be minimal. In parts 1 and 2 of the controlled study 31 patients reported having no injection-site reactions; 4 patients reported a mild reaction. In part 2, a total of 13 of the 15 patients (87%) receiving canakinumab and 15 of the 16 patients (94%) receiving placebo reported no injection-site reactions. None were severe or led to discontinuation of treatment.

There are no data on safety in pregnancy in humans, although in extremely high doses given to marmoset monkeys and mice, delays in fetal skeletal development were found. No evidence of fetal malformations or embryonic toxicity was found in animal studies.

Several safety issues are in need of further investigation. Longer-term follow-up of greater numbers of patients is necessary. The lack of patients with classic NOMID is also noted. While in most cases of CAPS canakinumab is used as monotherapy, the safety of canakinumab combined with other immunosuppressant medications, used often for NOMID (at least prior to the use of anti-IL-1 therapies), may present additional safety hazards. The lack of head-to-head studies preclude direct comparison of different anti-IL-1 therapies but the safety profile of all appears similar, with perhaps more cases of vertigo and significantly fewer injection-site reactions with canakinumab.

Patient satisfaction/acceptability

In general patient satisfaction was remarkable with only 1 early withdrawal in the controlled study due to lack of efficacy. In the placebo withdrawal part of the controlled study four patients in the canakinumab group reported having severe symptoms associated with other disorders: 2 patients in 1 household had acute gastroenteritis, a third patient had painful fibromyalgia, and a fourth had migraine headaches. The effect on HRQoL was previously reported as well as the minimal injection-site reactions. Patients with MWS, especially those with hearing loss, need to be aware of the potential development of vertigo with treatment.

Conclusions, place in therapy

The efficacy of canakinumab in the treatment of CAPS provides proof of concept that IL-1β is an important factor in the pathogenesis of this disorder. Canakinumab given at 150 mg per dose induced a complete response after the administration of a single dose in almost all the patients as well as inflammatory markers, and the effect appears to be sustained for up to at least 2 months between injections and continues to be effective with very little patient drop-out for longer periods. Some patients need higher doses (up to 300 mg) to induce a complete response. HRQoL and general mental and physical health and fatigue scores improved to the levels expected in the general population. The effect of canakinumab was similar in adults and children. To date, no deaths or life-threatening AEs have ocurred in CAPS patients treated with canakinumab and only mild AEs and symptoms were noted, none of which affected continuation of treatment. Still, there is a potentially higher risk for systemic infections and perhaps vertigo, especially in patients with MWS, which require special attention. The ability to administer canakinumab every 2 months with implications for compliance and minimal injection-site reactions is also attractive.

Other anti IL-1 medications (anakinra and rilonacept) also have demonstrated efficacy in CAPS.[18,19,28] However, the prolonged duration of action of canakinumab and low incidence of injection-site reactions may confer certain advantages for canakinumab, since both anakinra and rilonacept are frequently associated with injection-site reactions, and both require more frequent administration (daily for anakinra and weekly for rilonacept).[18,19,28] However,

unlike anakinra, there is still a relative lack of data on the effect of canakinumab in NOMID, especially on CNS manifestations and whether adjustments in doses and frequency are needed. A potential downside of canakinumab that has not been demonstrated in studies performed to date include the prolonged and profound neutralization of IL-1 and possible effects on infections or the response of the innate immune systems to infections. This issue necessitates further safety monitoring in long-term follow-up studies and post-marketing registries.

In conclusion, the dramatic role of canakinumab in the treatment of CAPS has been well demonstrated, particularly in patients with FCAS and MWS.

Disclosures

The authors declare no conflicts of interest.

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