Cryopyrinopathies: update on pathogenesis and treatment

Bénédicte Neven*, Anne-Marie Prieur and Pierre Quartier dit Maire

SUMMARY

Cryopyrinopathies are a group of rare autoinflammatory diseases that includes familial cold autoinflammatory syndrome, Muckle–Wells syndrome and chronic infantile neurologic cutaneous articular syndrome (also termed neonatal-onset multisystemic inflammatory disease). These syndromes were initially considered to be distinct disease entities despite some clinical similarities; however, mutations of the same gene have since been found in all three cryopyrinopathies. These diseases, therefore, are not separate but represent a continuum of subphenotypes. The gene in question, *CIAS1* (now renamed *NLRP3*) encodes NALP3 (also known as cryopyrin). NALP3 is an important mediator of inflammation and interleukin 1β processing. New therapies based on biologic agents that specifically target interleukin 1β are currently being developed. These new agents have provided very encouraging results for patients with these long-lasting inflammatory conditions—which used to be considered refractory to treatment. The development of therapeutic options for these cryopyrinopathies illustrates effective translation of basic science to clinical practice and the convergence of human genetics and targeted therapies.

KEYWORDS autoinflammatory syndromes, chronic infantile neurologic articular syndrome, familial cold autoinflammatory syndrome, interleukin 1β, Muckle–Wells syndrome

REVIEW CRITERIA

We searched PubMed using the following search terms alone or in combination: "familial cold autoinflammatory syndrome", "familial cold urticaria", "Muckle–Wells syndrome", "CINCA", "NOMID", "CIAS1", "NALP3", "cryopyrin" and "autoinflammatory syndromes". This research was complemented by the authors' databases of relevant literature. Therapeutic recommendations were based on the authors' clinical experience.

CME

B Neven is a Consultant in Pediatric Immunology and Rheumatology at the Hôpital Necker-Enfants-Malades, Paris, and Postdoctoral Research Fellow at INSERM Unit 768, Development Normal et Pathologique du Système Immunitaire, Université Descartes, Paris, France. A-M Prieur and P Quartier dit Maire are Pediatricians at the National Reference Center for Juvenile Arthritis, Department of Pediatric Immunohematology and Rheumatology at the Hôpital Necker-Enfants-Malades, Paris, France.

Correspondence
*Hôpital Necker, Service d'Immunologie Pédiatrique, 149 rue de Sèvres, 75015 Paris, France
benedicte.neven@nck.aphp.fr

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Learning objectives

Upon completion of this activity, participants should be able to:

1 Describe clinical features of Muckle–Wells syndrome (MWS).
2 Distinguish between familial cold autoinflammatory syndrome (FCAS) and the other 2 autoinflammatory syndromes.
3 Identify the most severe clinical features of chronic infantile neurological, cutaneous, and articular syndrome/neonatal-onset multisystemic inflammatory disease (CINCA/NOMID).
4 Identify the most common medication currently used for the autoinflammatory syndromes.

Competing interests

The authors, the Associate Publisher R Ashton and the CME questions author D Lie declared no competing interests.

INTRODUCTION

Cryopyrinopathies are autoinflammatory diseases characterized by recurrent bouts of systemic inflammation that involve several tissues, including joints and skin. Unlike autoimmune diseases, autoinflammatory syndromes are not associated with antigen-specific T-cell responses or high titers of autoantibodies, but are related to disorders of the innate immune system.[1] The full list of autoinflammatory syndromes can be seen in Box 1. Most of the genes associated with the syndromes listed in Box 1 encode proteins that are important mediators of apoptosis, inflammation and cytokine processing. This Review focuses on cryopyrinopathies: familial cold autoinflammatory syndrome (FCAS), Muckle–Wells syndrome (MWS), and chronic infantile neurological

Box 1 The autoinflammatory syndromes.

- Familial Mediterranean fever (the archetype of this group)
- Hyperimmunoglobulin D with periodic fever syndrome
- Pyogenic sterile arthritis, pyoderma gangrenosum and acne syndrome
- TNF (tumor necrosis factor) receptor-associated periodic syndrome
- Familial cold autoinflammatory syndrome
- Muckle–Wells syndrome
- Chronic infantile neurological cutaneous articular syndrome (also known as neonatal-onset multisystemic inflammatory disease)
- Blau syndrome
- Hereditary periodic fever syndrome (related to mutations in the *NLRP12* gene [nucleotide-binding oligomerization domain and leucine-rich-repeat family, pyrin domain containing 12])[64]

cutaneous articular syndrome (CINCA; also known as neonatal-onset multisystemic inflammatory disease, abbreviated to NOMID). These three autoinflammatory syndromes are closely related, both genetically and in terms of clinical symptoms. Clinical characteristics, mechanisms of disease, and new treatment options for these syndromes are discussed in this Review.

CLINICAL MANIFESTATIONS

FCAS, MWS and CINCA (NOMID) were originally described as distinct clinical entities despite the fact that their symptoms overlap; patients often present with fever, pseudourticarial skin rash, and joint involvement of varying severity associated with neutrophil-mediated inflammation and an intense acute-phase response. In reality, these three syndromes exist on a continuum of severity; FCAS is the mildest condition, CINCA (NOMID) the most severe, and MWS has an intermediate-severity phenotype.

Clinical characteristics of FCAS, MWS and CINCA (NOMID) are given in Table 1 and detailed below. The skin rash—a key symptom of all three diseases—is usually the first notable manifestation and develops shortly after birth or in early infancy. This rash exhibits the same clinical and histological characteristics regardless of syndrome: it is migratory, maculopapular, urticaria-like and usually nonpruritic (Figure 1A). A few patients report a burning sensation. The intensity of the skin rash can vary from patient to patient and with disease activity. The rash shows dermal perivascular infiltration with polymorphonuclear cells, a histological finding that contrasts with the typical lymphocytic and eosinophilic infiltration seen in classical urticaria (Figure 1B). For this reason, the rash associated with FCAS, MWS and CINCA (NOMID) is commonly called pseudourticaria.

Familial cold autoinflammatory syndrome

FCAS, also known as familial cold urticaria, was first described in 1940 by Kile and Rusk.[2] This autosomal-dominant syndrome is characterized by recurrent, short, self-limited episodes of low-grade fever, rash and arthralgia that are precipitated by exposure to cold temperatures.[3–5] Other commonly reported symptoms include conjunctivitis, muscle pain, profuse sweating, drowsiness, headaches, nausea and extreme thirst. Symptoms usually begin 1–2 h after generalized exposure to cold temperatures or to a considerable drop in temperature, and the duration of attacks is usually short (<24 h). In most patients with FCAS, the severity of the crisis correlates with the intensity of the cold trigger. Predictably, attacks are more frequent in winter, on damp and windy days, and following exposure to air conditioning. Patients frequently report a pattern of feeling well in the morning after a warm night, but symptoms develop after a cold trigger and worsen as the day progresses. Early onset of the disease, at birth or within the first 6 months of life, is common. Although late-onset renal amyloidosis was reported in several members of one family affected by FCAS, deafness and amyloidosis are not usually observed in FCAS, in contradistinction to MWS and CINCA (NOMID).[3–5] Leukocytosis and increased plasma levels of acute-phase reactants are observed during episodes of inflammation.

Muckle–Wells syndrome

MWS was first described in 1962 by Muckle and Wells,[6] in members of one family who presented with urticaria, deafness and renal amyloidosis. The disease is characterized by recurrent episodes of fever and rash associated with joint and eye manifestations, although fever is not always present. Precipitating factors cannot usually be identified, and triggering by cold is rarely observed. The course of the disease varies between individuals, from the typical recurrent attacks of inflammation to near-permanent symptoms. As

Table 1 Clinical characteristics of cryopyrinopathies.

Feature	FCAS	MWS	CINCA (NOMID)
Severity	Low	Medium	High
Trigger	Cold exposure	None	None
Frequency of fever and/or rash	Usually daily symptoms with circadian rhythm	Variable: rare to daily symptoms with circadian rhythm	Variable: usually rare fever and daily rash
Joint involvement	Arthralgia	Arthralgia, arthritis	Arthralgia, arthritis, overgrowth arthropathy
Neurological involvement	None	None	Chronic aseptic meningitis (headache, possible mental delay)
Eye involvement	Conjunctivitis	Conjunctivitis, uveitis	Uveitis, papillary edema, possible optic neuritis
Deafness	No	Frequent (60–70%)	Frequent (>60%)
Amyloidosis	No	Frequent (~25%)	Frequent (~25%)
Inheritance	Autosomal-dominant	Autosomal-dominant (typical) or *de novo* (rare)	*De novo* (typical) or autosomal-dominant (rare)

Abbreviations: CINCA (NOMID), chronic infantile neurological cutaneous articular syndrome (neonatal-onset multisystemic inflammatory disease); FCAS, familial cold autoinflammatory syndrome; MWS, Muckle–Wells syndrome.

with FCAS, patients with MWS often describe a pattern of worsening symptoms in the evening. Joint manifestations can be mild (i.e. short episodes of arthralgia), but recurrent episodes of joint swelling that predominantly affect the large joints have been observed[7] and joint destruction has been reported in one family.[8] As in FCAS, conjunctivitis is also frequently present. Episcleritis and iridocyclitis have been reported in several cases.[9] Neurological involvement in MWS is usually not described, although headache and papilledema have been reported in some cases.[9,10] Perceptive deafness is common (occurring in approximately 70% of cases) and usually begins in childhood or early adulthood; the mechanism that leads to this sensorial involvement is not completely understood. Amyloidosis, caused by chronic inflammation, is the most serious complication of MWS and develops in adulthood in approximately 25% of cases; it manifests as proteinuria, followed by impaired renal function. Leukocytosis and increased plasma levels of acute-phase reactants are observed during episodes of inflammation, or near-permanently in severely affected individuals.

Chronic infantile neurological cutaneous articular syndrome

CINCA (NOMID) is associated with the most severe phenotype in this spectrum of diseases. This syndrome was first described by Prieur in the early 1980s[11,12] as a chronic inflammatory disease with rash, articular involvement and chronic, aseptic meningitis. First symptoms of CINCA (NOMID) occur at birth or in early infancy. Fever can be intermittent, very mild, or in some cases absent. The rash varies in intensity from patient to patient and with disease activity. Bone and joint inflammation also vary in severity: in approximately two-thirds of patients, joint manifestations are limited to arthralgia and transient swelling without effusion, and occur during flare-ups. In one-third of patients, however, severe and disabling arthropathy occurs as a result of overgrowth of the patella and the epiphyses of long bones (Figure 2). This arthropathy can cause gross deformity of the joints, with pain and a limited range of motion. Knees, ankles, wrists and elbows are the joints most commonly affected bilaterally, but small joints can also be involved. Radiological manifestations of the arthropathy associated with CINCA (NOMID) are distinctive; the most characteristic changes occur in the metaphysis and epiphysis, with overgrowth and irregular ossification.[13] In very young children, bowing, shortening and widening of the long bones with a periosteal reaction can be observed. Abnormalities of the central nervous system (CNS) are present in almost all patients and are caused by a chronic, aseptic meningitis in which polymorphonuclear cells infiltrate the cerebrospinal fluid (CSF). Features of the disease phenotype

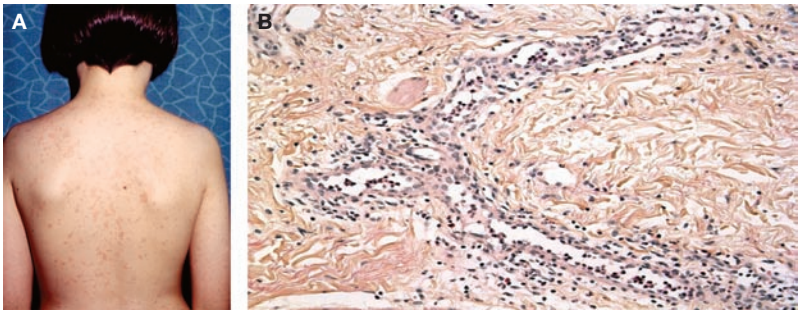

Figure 1 Skin rash in a patient with cryopyrinopathy. (**A**) The characteristic maculopapular skin rash of cryopyrinopathies. (**B**) The histologic features of this skin rash usually include dermal perivascular infiltration with polymorphonuclear cells.

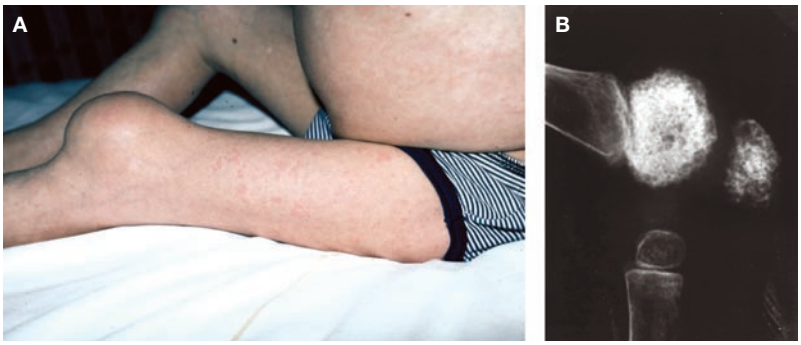

Figure 2 Overgrowth arthropathy in a patient with CINCA (NOMID). (**A**) Patellar overgrowth, which is characteristically observed in some patients who have CINCA (NOMID) with articular overgrowth. (**B**) Radiological image of a knee in a child with CINCA (NOMID) and articular overgrowth. Irregular ossification of the long-bone epiphyses, metaphysis and patella are evident. Abbreviations: CINCA (NOMID), chronic infantile neurological cutaneous articular syndrome (neonatal-onset multisystemic inflammatory diseases).

related to CNS involvement vary in severity. Chronic headaches, vomiting and papilledema (seen on fundoscopy) are frequently observed consequences of chronic increased intracranial pressure. Spastic diplegia and epilepsy occasionally develop. Cognitive impairment occurs in severely affected patients. CSF examination shows variable hypercellularity of polymorphonuclear cells and/or hyperproteinorachia, and the CSF evinces an increased open pressure. CT findings can be normal or show mild ventricular dilatation and enlarged subdural fluid spaces, suggestive of mild cerebral atrophy. Leptomeningeal enhancement can be observed on MRI after gadolinium injection. Ocular disease consists of anterior uveitis in approximately 50% of patients with CINCA (NOMID) and posterior uveitis in another 20%.[14] Optic atrophy can also develop. Ocular manifestations can progress to blindness, and 25% of patients have a major ocular disability in adulthood. Perceptive deafness is frequent and usually develops in late childhood or subsequently. Patients frequently have macrocrania, frontal bossing and saddle nose. Amyloid A amyloidosis develops with increasing age in some patients. Severe disabilities are frequent, and premature death is possible in severely affected patients. Prematurity and dysmaturity occur in one-third of patients. Umbilical-cord anomalies have been observed in a few cases.[15–17] Leukocytosis and increased plasma levels of acute-phase reactants are both permanent symptoms in most cases.

Common overlapping symptoms

Careful examination of patients with cryopyrinopathies usually reveals an extensive overlap of clinical symptoms.[10,18–20] Patients with MWS might report symptoms that are consistent with FCAS, such as cold susceptibility (i.e. an increased frequency of attacks in winter), or symptoms consistent with mild CNS involvement, such as frequent headaches or asymptomatic papilledema, as seen in patients with CINCA (NOMID). Similarly, these signs can become increasingly obvious in patients as they age. Families with cryopyrinopathies can show mild phenotypic variability between affected individuals;[20] however, the most severe manifestations of CINCA (NOMID)—overgrowth arthropathy or severe neurological involvement—have never been reported in families whose affected members have relatively mild cryopyrinopathies.

GENETIC FACTORS AND MECHANISMS OF DISEASE

Molecular basis of cryopyrinopathies

FCAS, MWS and CINCA (NOMID) are all caused by dominantly inherited or *de novo* mutations in *CIAS1* (now known as *NLRP3* [nucleotide-binding oligomerization domain, leucine-rich-repeat family, pyrin domain containing 3]). The official name for the protein encoded by this gene is NALP3 (NACHT, leucine-rich repeat and pyrin domains containing protein 3), but it has had several other names, including cryopyrin and PYPAF1 (pyrin-domain-containing Apaf1-like protein 1).[21,22] NALP3 belongs to the large family of NLR (nucleotide-binding domain and leucine-rich-repeat containing) proteins with 22 members in humans.[23] These proteins have key roles in innate immunity;[24] they are thought to be the intracellular equivalent of Toll-like receptors and activate various signaling cascades

in response to metabolic stressors or microbial molecules that gain access to the cell.[25] Among the large family of NLR proteins, the NALPs are the largest subgroup with 14 members. All, including NALP3, have an amino-terminal pyrin domain, a central NACHT domain with a nucleotide-binding site and a carboxy-terminal leucine-rich repeat.[26]

Function of NALP3

NALP3 interacts with other intracellular proteins to form a large complex called the inflammasome (Figure 3).[27] This complex is critically important in innate immunity, as it detects intracellular pathogens and other danger signals. Mechanisms of activation and regulation of the NALP3 inflammasome have been gradually elucidated. At rest, NALP3 is maintained in an inactive state in the cell cytoplasm. As shown by various *in vitro* and gene-knockout animal studies, NALP3 can be activated by a range of 'pathogen-associated molecular patterns',[28–30] which include bacterial muramyl dipeptide, bacterial RNA or viral RNA, and by 'danger-associated molecular patterns'[31–35] such as ATP, decreased intracellular potassium concentration, imidazoquinoline, monosodium urate crystals (which provoke inflammation and lead to gout), various skin irritants and ultraviolet B radiation. After activation via the leucine-rich-repeat domain, NALP3 interacts with ASC (apoptosis-associated speck-like protein containing a caspase recruitment domain) and CARD8 (caspase recruitment domain containing protein 8; also known as CARDINAL).[27,36] When associated with the inflammasome, ASC can interact with procaspase 1 to mediate its conversion to caspase 1. Caspase 1, in turn, activates the interleukin (IL) precursors pro-IL-1β and pro-IL-18 to become proinflammatory IL-1β and IL-18, respectively.

CIAS1 mutations

The mechanism by which *CIAS1* mutations cause inflammatory diseases is still not completely understood, but *in vitro* studies suggest that these mutations have a gain-of-function effect, probably through the loss of a regulatory step associated with NALP3 activation.[37,38] The induction of inflammatory disease flares by exposure to cold in patients with FCAS also remains intriguing. New agents that target the IL-1 pathway have been proposed as potential treatments for patients with cryopyrinopathies as a result of these findings.

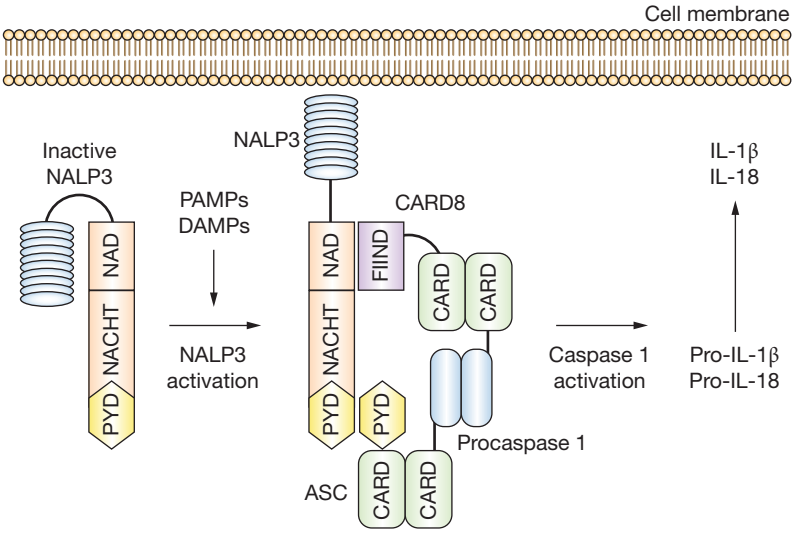

Figure 3 The NALP3 inflammasome. At rest, NALP3 is inactive in the cytoplasm. After being activated via its leucine-rich repeat by various PAMPs (such as muramyl dipeptides, bacterial or viral RNA) or DAMPs (such as uric acid crystals, ATP, low intracellular concentrations of potassium, skin irritants, ultraviolet B radiation), NALP3 is unfolded and interacts with ASC (by homotypic interaction between their pyrin domains) and CARD8. ASC then interacts with procaspase 1 through a homotypic interaction between their caspase recruitment domains, to mediate activation of caspase 1. Caspase 1 activates pro-IL-1β and pro-IL-18 become active IL-1β and IL-18, respectively. Abbreviations: ASC, apoptosis-associated speck-like protein containing a caspase recruitment domain; CARD8, caspase recruitment domain family, member 8; DAMP, danger-associated molecular pattern; FIIND, function to find domain; IL, interleukin; NACHT, an acronym derived from Nucleotide-binding oligomerization domain, leucine-rich-repeat family; Apoptosis inhibitory protein; Class II, major histocompatibility complex transactivator; Het-E incompatibility locus protein from *Podospora anserina*; Telomerase-associated protein 1; NAD, NACHT-associated domain; NALP3, NACHT, leucine-rich repeat, and pyrin domains containing protein 3; PAMP, pathogen-associated molecular pattern; PYD, pyrin domain.

To date, approximately 60 disease-associated mutations in *CIAS1* have been reported, almost all located in the region encoding the NACHT domain and its flanking structures (i.e. in exon three). In the past 5 years, four mutations have been identified in exons four and six within the region that encodes the leucine-rich repeat.[31,39,40] Of the identified mutations, all but one are missense mutations.[41] Some degree of genotype–phenotype correlation has been observed in the cryopyrinopathies; mutations found in patients with mild forms of cryopyrinopathy have not been identified in severely affected patients and vice versa. Additional genetic or environmental factors might also modulate the phenotypic expression of disease.[18,42] Few patients with FCAS and MWS, but approximately 40% of patients with

CINCA (NOMID), do not carry any known *CIAS1* mutations, which suggests that the cryopyrinopathies are genetically heterogeneous. Saito *et al*. have described three patients with CINCA (NOMID) who had somatic mosaicism; these patients carried a mutation in exon three of *CIAS1* that occurred with different frequencies in whole blood and leukocytes.[43,44] This mechanism could account for some, but not all, patients classified as *CIAS1*-mutation negative.

MANAGEMENT

Cryopyrinopathies have a major influence on patients' quality of life; they cause considerable morbidity and even death in severe cases. Until recently, the therapeutic options for patients with these disorders have been very limited. NSAIDs and corticosteroids induce very mild improvement. There have been anecdotal case reports of beneficial effects for tumor necrosis factor blockers and thalidomide.[45] Thanks to substantial advances in our understanding of the genetic basis and mechanisms of disease for these disorders, new therapeutic strategies that target the IL-1 pathway are currently being developed. Anakinra, a recombinant, nonglycosylated homolog of the human IL-1 receptor antagonist, competitively inhibits binding of IL-1α and IL-1β to the IL-1 receptor. The safety and tolerability of this drug has been established in patients with arthritis, and it has been extensively used to treat patients with rheumatoid arthritis.[46,47]

Treatment of familial cold autoinflammatory syndrome and Muckle–Wells syndrome with anakinra

Anakinra was first used to treat two adult patients with a MWS phenotype; the drug was given daily by subcutaneous injection at a dose of 100 mg. The efficacy of this treatment was remarkable: all inflammatory symptoms (rash, fever and arthralgia) ceased a few hours after the first injection, and serum amyloid A protein levels normalized in a few days.[48] Hoffman *et al*. confirmed the striking efficacy of anakinra in prevention of acute inflammation in patients with FCAS,[49,50] and a number of studies confirmed the benefits of this treatment in patients with MWS, including improved hearing in selected cases.[51–53] Anakinra very efficiently normalizes leukocytosis as well as levels of biologic inflammatory markers such as C-reactive protein and serum amyloid A protein. Some reports have also shown progressive improvement in amyloid-related proteinuria and nephritic syndrome if anakinra treatment is initiated before irreversible renal damage occurs.[48,54,55] These benefits of IL-1 receptor antagonism in patients with FCAS and MWS are long-lasting (to date, the longest duration of continuous treatment reported in the literature is 3.5 years).[54] In adult patients, anakinra is usually initially prescribed at a dose of 100 mg per day, but maintenance doses can be reduced to 0.3–0.5 mg/kg daily in mild cases.[54]

Anakinra in treatment of chronic infantile neurological cutaneous articular syndrome

The very encouraging results for anakinra in FCAS and MWS provided hope that this treatment would benefit severely affected patients with CINCA (NOMID), who might have serious, long-term disabilities that result from a broad range of symptoms that can include CNS involvement. Isolated case reports suggested anakinra was efficacious in this patient setting.[10,19,56,57] Goldbach-Mansky *et al*.[58] conducted an elegant, single-center study of 18 patients with CINCA (NOMID), mostly children, who had active disease. This study assessed the effects of anakinra on a broad range of symptoms. At baseline, all patients presented with CNS involvement and 11 had bony overgrowth. The starting dose of anakinra was 1 mg/kg per day, administered by subcutaneous injection, but was increased to 2 mg/kg per day in patients who had an incomplete response. All patients showed an immediate clinical improvement and rapid normalization of inflammatory biological markers. After 6 months, hearing had improved in one-third of the patients. Headache frequency, intracranial pressure and CSF protein levels decreased significantly compared with their baseline values, and cochlear and leptomeningeal enhancement (visible on patients' initial cerebral MRI scans) also improved in some individuals. Of note, in this study, 40% of the patients had no *CIAS1* mutations; however, in terms of clinical manifestations of CINCA (NOMID) and response to anakinra, there were no differences between patients with or without *CIAS1* mutations. Data on the long-term benefits of anakinra in patients with CINCA (NOMID) are still lacking. In our experience, the dose of anakinra required to control severe CINCA (NOMID), particularly if neurological involvement is severe, is higher than that recommended for patients with FCAS and MWS; we have successfully treated patients (median age at baseline 8.5 years, range 0.25–20 years) with up to 3 mg/kg per day of anakinra. Anakinra

is well tolerated even at these high doses; we have not yet observed any adverse effects, apart from minor local pain and erythema at the injection site that tended to diminish gradually in most patients (B Neven *et al*., unpublished data).

New treatment perspectives

Interleukin 1 inhibition

Currently, a number of IL-1 inhibitors are in various stages of development. These include 'cytokine traps' and monoclonal antibodies to IL-1β. The IL-1 trap (Rilonacept®; Regeneron Pharmaceuticals, Inc., Tarrytown, NY) is a long-acting IL-1 blocker that comprises the extracellular domain of the human type 1 IL-1 receptor coupled to a human IgG_1 antibody. The safety and efficacy of weekly subcutaneous injections of Rilonacept® (160 mg/week) were recently evaluated in 47 adult patients with FCAS and MWS.[59] After 1 year, Hoffman *et al*. confirmed that this treatment was effective (in terms of improved clinical symptoms and biological inflammatory markers); the most frequent adverse events reported were injection-site reactions (48%) and infections (most of which were upper respiratory tract infections). Overall, two patients died: a 70-year-old woman who had acute *Streptococcus pneumoniae* meningitis and a 37-year-old patient who had coronary atherosclerosis. Rilonacept® has now been approved by the FDA for treatment of patients with MWS and FCAS who are older than 11 years. ACZ885 (Novartis International AG, Basel, Switzerland) is a new human IgG_1 monoclonal antibody directed against IL-1β that has a long half-life. ACZ885 is currently under investigation as a treatment for patients with cryopyrinopathies.[60,61]

Caspase 1 inhibition

Caspase 1 is another potential target of therapies for cryopyrinopathies. VX-765 (Vertex Pharmaceuticals, Cambridge, MA) is an orally active caspase 1 inhibitor that was able to block IL-1β secretion *in vitro* when peripheral blood mononuclear cells isolated from patients with FCAS were stimulated with lipopolysaccharide.[62] A limited, open-label study of this drug has been conducted in six patients with MWS; these patients showed partial clinical and biological improvement with VX-765 treatment.[63]

Practical considerations

Despite the promising results of anti-IL-1 agents in the treatment of patients with cryopyrinopathies, it is important to note that blockade of IL-1, especially with high-affinity, long-acting molecules, raises a potential risk of serious infections. This risk is particularly high in young children, in whom the immature immune response is less effective against polysaccharide-encapsulated bacteria. Moreover, safety data on these long-acting anti-IL-1 molecules are still lacking. Vaccination against *S. pneumoniae* should be updated before starting any anti-IL-1 therapy, especially in pediatric patients, and antibiotic prophylaxis should be considered in very young children treated with a high dose of anakinra. Cholesterol and triglyceride levels should also be monitored, especially in adults with other risk factors of coronaropathies.

CONCLUSIONS

The development of successful therapeutic options for cryopyrinopathies illustrates the effective translation of basic science to clinical practice. Study of the disease mechanisms of FCAS, MWS and CINCA (NOMID) has revealed that these diseases represent a continuum of subphenotypes with a common molecular origin, and has elucidated the fundamental role of IL-1β in the innate immune response and in disease pathogenesis.

Dramatic clinical improvements are seen in patients with cryopyrinopathies who are treated by blockade of IL-1β with anakinra, a homolog of the human IL-1 receptor antagonist. Treatment of patients with CINCA (NOMID) is more complex than that for patients with milder forms of cryopyrinopathy because patients with CINCA (NOMID) have a broader range of symptoms; in severely affected patients, neurological involvement might be difficult to abrogate completely and increased doses of anakinra are often necessary. Therapy should be initiated as early as possible following diagnosis, before the onset of irreversible damage caused by chronic inflammation. Similar magnitudes of response to anakinra have been seen in patients regardless of whether they carry *CIAS1* mutations, which indicates that the underlying disease mechanisms are similar in both groups of patients. New generations of IL-1β blockers, with longer half-lives and higher affinity for the IL-1 receptor than anakinra has, are currently under investigation and might offer therapeutic benefits to patients in the near future; however, safety data on new anti IL-1β therapies are still lacking and the potential risk of infections is an important consideration. The efficacy of these new drugs in patients who have CINCA (NOMID) and neurological involvement is unknown.

Importantly, the NALP3 inflammasome is involved in the pathogenesis of other inflammatory disorders such as gout or pseudogout. Understanding the pathophysiology of rare conditions can, therefore, identify potential new therapeutic options for treatment of patients with these relatively common diseases.

KEY POINTS

- The autoinflammatory conditions FCAS, MWS and CINCA (NOMID) are autosomal-dominant or sporadic syndromes that represent a continuum of subphenotypes (FCAS is the mildest condition, CINCA/NOMID the most severe)
- FCAS, MWS and CINCA (NOMID) are caused by mutations of the same gene, *CIAS1* (now termed *NLRP3*), which encodes NALP3, also known as cryopyrin, an important mediator of inflammation and interleukin 1β processing
- Promising new therapies based on biologic agents that target interleukin 1β, are currently under investigation for the treatment of patients with these cryopyrinopathies
- Treatment of CINCA (NOMID) is more complex than that of other cryopyrinopathies because patients with CINCA (NOMID) have severe disease and the broadest range of symptoms
- The potential risk of serious infections during treatment with interleukin 1 antagonists has to be considered, especially in the pediatric population; this risk may be exacerbated by use of high-affinity, long-acting molecules
- The development of therapeutic options for these cryopyrinopathies illustrates the effective translation of basic science to clinical practice and the convergence of human genetics and targeted therapy

References

1 Stojanov S and Kastner DL (2005) Familial autoinflammatory diseases: genetics, pathogenesis and treatment. *Curr Opin Rheumatol* **17:** 586–599
2 Kile RL and Rusk HA (1940) A case of cold urticaria with an unusual familial history. *JAMA* **114:** 1067–1068
3 Hoffman HM *et al*. (2001) Familial cold autoinflammatory syndrome: phenotype and genotype of an autosomal dominant periodic fever. *J Allergy Clin Immunol* **108:** 615–620
4 Hoffman HM *et al*. (2003) Fine structure mapping of *CIAS1*: identification of an ancestral haplotype and a common FCAS mutation, L353P. *Hum Genet* **112:** 209–216
5 Johnstone RF *et al*. (2003) A large kindred with familial cold autoinflammatory syndrome. *Ann Allergy Asthma Immunol* **90:** 233–237
6 Muckle TJ *et al*. (1962) Urticaria, deafness and amyloidosis: a new heredo-familial syndrome. *Q J Med* **122:** 235–248
7 Watts RA *et al*. (1994) The arthropathy of the Muckle–Wells syndrome. *Br J Rheumatol* **33:** 1184–1187
8 Lequerre T *et al*. (2007) A cryopyrin-associated periodic syndrome with joint destruction. *Rheumatology (Oxford)* **46:** 709–714
9 Prost A *et al*. (1976) Intermittent rheumatism revealing a familial syndrome. Arthritis—urticarian eruptions—deafness: Muckle–Wells syndrome without kidney amylosis [French]. *Rev Rhum Mal Osteoartic* **43:** 201–208
10 Hawkins PN *et al*. (2004) Spectrum of clinical features in Muckle–Wells syndrome and response to anakinra. *Arthritis Rheum* **50:** 607–612
11 Prieur AM and Griscelli C (1980) Chronic meningo-cutaneo-articular syndrome in children [French]. *Rev Rhum Mal Osteoartic* **47:** 645–649
12 Prieur AM and Griscelli C (1981) Arthropathy with rash, chronic meningitis, eye lesions, and mental retardation. *J Pediatr* **99:** 79–83
13 Hill SC *et al*. (2007) Arthropathy of neonatal onset multisystem inflammatory disease (NOMID/CINCA). *Pediatr Radiol* **37:** 145–152
14 Dollfus H *et al*. (2000) Chronic infantile neurological cutaneous and articular/neonatal onset multisystem inflammatory disease syndrome: ocular manifestations in a recently recognized chronic inflammatory disease of childhood. *Arch Ophthalmol* **118:** 1386–1392
15 Prieur AM *et al*. (1987) A chronic, infantile, neurological, cutaneous and articular (CINCA) syndrome. A specific entity analysed in 30 patients. *Scand J Rheumatol Suppl* **66:** 57–68
16 Torbiak RP *et al*. (1989) NOMID—a neonatal syndrome of multisystem inflammation. *Skeletal Radiol* **18:** 359–364
17 Prieur AM (2001) A recently recognised chronic inflammatory disease of early onset characterised by the triad of rash, central nervous system involvement and arthropathy. *Clin Exp Rheumatol* **19:** 103–106
18 Neven B *et al*. (2004) Molecular basis of the spectral expression of *CIAS1* mutations associated with phagocytic cell-mediated autoinflammatory disorders CINCA/NOMID, MWS, and FCU. *Blood* **103:** 2809–2815
19 Granel B *et al*. (2005) Dramatic improvement with anakinra in a case of chronic infantile neurological cutaneous and articular (CINCA) syndrome. *Rheumatology (Oxford)* **44:** 689–690
20 Hentgen V *et al*. (2005) Intrafamilial variable phenotypic expression of a *CIAS1* mutation: from Muckle–Wells to chronic infantile neurological cutaneous and articular syndrome. *J Rheumatol* **32:** 747–751
21 Hoffman HM *et al*. (2001) Mutation of a new gene encoding a putative pyrin-like protein causes familial cold autoinflammatory syndrome and Muckle–Wells syndrome. *Nat Genet* **29:** 301–305
22 Feldmann J *et al*. (2002) Chronic infantile neurological cutaneous and articular syndrome is caused by mutations in *CIAS1*, a gene highly expressed in polymorphonuclear cells and chondrocytes. *Am J Hum Genet* **71:** 198–203
23 Ting JP *et al*. (2006) CATERPILLERs, pyrin and hereditary immunological disorders. *Nat Rev Immunol* **6:** 183–195
24 Fritz JH and Girardin SE (2005) How Toll-like receptors and Nod-like receptors contribute to innate immunity in mammals. *J Endotoxin Res* **11:** 390–394
25 Fritz JH (2006) Nod-like proteins in immunity, inflammation and disease. *Nat Immunol* **7:** 1250–1257
26 Manji GA *et al*. (2002) PYPAF1, a PYRIN-containing Apaf1-like protein that assembles with ASC and regulates activation of NFκB. *J Biol Chem* **277:** 11570–11575
27 Martinon F (2002) The inflammasome: a molecular platform triggering activation of inflammatory caspases and processing of proIL-β. *Mol Cell* **10:** 417–426

28 Martinon F *et al*. (2004) Identification of bacterial muramyl dipeptide as activator of the NALP3/cryopyrin inflammasome. *Curr Biol* **14:** 1929–1934
29 Kanneganti TD *et al*. (2006) Bacterial RNA and small antiviral compounds activate caspase-1 through cryopyrin/NALP3. *Nature* **440:** 233–236
30 Kanneganti TD *et al*. (2006) Critical role for cryopyrin/NALP3 in activation of caspase-1 in response to viral infection and double-stranded RNA. *J Biol Chem* **281:** 36560–36568
31 Jesus AA *et al*. (2007) Phenotype–genotype analysis of cryopyrin-associated periodic syndromes (CAPS): description of a rare non-exon 3 and a novel *CIAS1* missense mutation. *J Clin Immunol* **28:** 134–138
32 Mariathasan S *et al*. (2006) Cryopyrin activates the inflammasome in response to toxins and ATP. *Nature* **440:** 228–232
33 Martinon F *et al*. (2006) Gout-associated uric acid crystals activate the NALP3 inflammasome. *Nature* **440:** 237–241
34 Feldmeyer L *et al*. (2007) The inflammasome mediates UVB-induced activation and secretion of interleukin-1β by keratinocytes. *Curr Biol* **17:** 1140–1145
35 Petrilli V *et al*. (2007) Activation of the NALP3 inflammasome is triggered by low intracellular potassium concentration. *Cell Death Differ* **14:** 1583–1589
36 Yu JW *et al*. (2006) Cryopyrin and pyrin activate caspase-1, but not NFκB, via ASC oligomerization. *Cell Death Differ* **13:** 236–249
37 Dowds TA *et al*. (2004). Cryopyrin-induced interleukin 1β secretion in monocytic cells: enhanced activity of disease-associated mutants and requirement for ASC. *J Biol Chem* **279:** 21924–21928
38 Agostini L *et al*. (2004) NALP3 forms an IL-1β-processing inflammasome with increased activity in Muckle–Wells autoinflammatory disorder. *Immunity* **20:** 319–325
39 Frenkel J *et al*. (2004). Variant chronic infantile neurologic, cutaneous, articular syndrome due to a mutation within the leucine-rich repeat domain of *CIAS1*. *Arthritis Rheum* **50:** 2719–2720
40 Matsubayashi T *et al*. (2006) Anakinra therapy for CINCA syndrome with a novel mutation in exon 4 of the *CIAS1* gene. *Acta Paediatr* **95:** 246–249
41 Jeru I *et al*. (2006) PYPAF1 nonsense mutation in a patient with an unusual autoinflammatory syndrome: role of PYPAF1 in inflammation. *Arthritis Rheum* **54:** 508–514
42 Aksentijevich I *et al*. (2007) The clinical continuum of cryopyrinopathies: novel *CIAS1* mutations in North American patients and a new cryopyrin model. *Arthritis Rheum* **56:** 1273–1285
43 Saito M *et al*. (2005) Somatic mosaicism of *CIAS1* in a patient with chronic infantile neurologic, cutaneous, articular syndrome. *Arthritis Rheum* **52:** 3579–3585
44 Saito M *et al*. (2007) Disease-associated *CIAS1* mutations induce monocyte death, revealing low-level mosaicism in mutation-negative cryopyrin-associated periodic syndrome patients. *Blood* **111:** 2132–2141
45 Kallinich T (2005) The clinical course of a child with CINCA/NOMID syndrome improved during and after treatment with thalidomide. *Scand J Rheumatol* **34:** 246–249
46 Fleischmann RM *et al*. (2003) Anakinra, a recombinant human interleukin-1 receptor antagonist (r-metHuIL-1RA), in patients with rheumatoid arthritis: a large, international, multicenter, placebo-controlled trial. *Arthritis Rheum* **48:** 927–934
47 Schiff MH *et al*. (2004) The safety of anakinra in high-risk patients with active rheumatoid arthritis: six-month observations of patients with comorbid conditions. *Arthritis Rheum* **50:** 1752–1760
48 Hawkins PN *et al*. (2003) Interleukin-1-receptor antagonist in the Muckle–Wells syndrome. *N Engl J Med* **348:** 2583–2584
49 Hoffman HM *et al*. (2004) Prevention of cold-associated acute inflammation in familial cold autoinflammatory syndrome by interleukin-1 receptor antagonist. *Lancet* **364:** 1779–1785
50 O'Connell SM *et al*. (2007) Response to IL-1-receptor antagonist in a child with familial cold autoinflammatory syndrome. *Pediatr Dermatol* **24:** 85–89
51 Rynne M *et al*. (2006) Hearing improvement in a patient with variant Muckle–Wells syndrome in response to interleukin 1 receptor antagonism. *Ann Rheum Dis* **65:** 533–534
52 Mirault T *et al*. (2006) Recovery from deafness in a patient with Muckle–Wells syndrome treated with anakinra. *Arthritis Rheum* **54:** 1697–1700
53 Dalgic B *et al*. (2007) A variant Muckle–Wells syndrome with a novel mutation in *CIAS1* gene responding to anakinra. *Pediatr Nephrol* **22:** 1391–1394
54 Leslie KS *et al*. (2006) Phenotype, genotype, and sustained response to anakinra in 22 patients with autoinflammatory disease associated with CIAS-1/NALP3 mutations. *Arch Dermatol* **142:** 1591–1597
55 Thornton BD *et al*. (2007) Successful treatment of renal amyloidosis due to familial cold autoinflammatory syndrome using an interleukin 1 receptor antagonist. *Am J Kidney Dis* **49:** 477–481
56 Frenkel J *et al*. (2004) Anakinra in mutation-negative NOMID/CINCA syndrome: comment on the articles by Hawkins *et al.* and Hoffman and Patel. *Arthritis Rheum* **50:** 3738–3739
57 Lovell DJ *et al*. (2005) Interleukin-1 blockade by anakinra improves clinical symptoms in patients with neonatal-onset multisystem inflammatory disease. *Arthritis Rheum* **52:** 1283–1286
58 Goldbach-Mansky R *et al*. (2006) Neonatal-onset multisystem inflammatory disease responsive to interleukin-1β inhibition. *N Engl J Med* **355:** 581–592
59 Hoffman H *et al*. (2008) Rilonacept in patients with cryopyrin-associated periodic syndromes (CAPS): the durability of symptoms over 48 weeks. Presented at the Fifth International Congress on FMF and Systemic Autoinflammatory Diseases: 2008 April 4–8, Rome, Italy
60 Kuemmerle-Deschner JB *et al*. (2008) Long-lasting response to ACZ885 (a new human IgG1 anti IL-1beta monoclonal antibody) in patients with Muckle-Wells syndrome (MWS). Presented at the Fifth International Congress on FMF and Systemic Autoinflammatory Diseases: 2008 April 4–8, Rome, Italy
61 Lachmann H *et al*. Treatment of cryopyrin associated periodic syndrome with a fully human anti IL-1beta monoclonal antiboby (ACZ885): results from a subcutaneous administration study. Presented at the Fifth International Congress on FMF and Systemic Autoinflammatory Diseases: 2008 April 4–8, Rome, Italy
62 Stack JH *et al*. (2005) IL-converting enzyme/caspase-1 inhibitor VX-765 blocks the hypersensitive response to an inflammatory stimulus in monocytes from familial cold autoinflammatory syndrome patients. *J Immunol* **175:** 2630–2634
63 Lachmann H *et al*. (2005) An orally active ICE/Caspase-1 inhibitor, VX-765, reduces inflammatory biomarkers and symptoms in patients with Muckle–Wells symptoms. Presented at the Fourth International Congress on the Systemic Autoinflammatory Diseases, "FMF and Beyond": 2005 November 6–10, Bethesda, MD, USA
64 Jeru I *et al*. (2008) Mutations in NALP12 cause hereditary periodic fever syndromes. *Proc Natl Acad Sci USA* **105:** 1614–1619

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