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IL-1 Blockade in Autoinflammatory Syndromes[1]

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Abstract

Monogenic autoinflammatory syndromes present with excessive systemic inflammation including fever, rashes, arthritis, and organ-specific inflammation and are caused by defects in single genes encoding proteins that regulate innate inflammatory pathways. Pathogenic variants in two interleukin-1 (IL-1)–regulating genes, *NLRP3* and *IL1RN*, cause two severe and early-onset autoinflammatory syndromes, CAPS (cryopyrin associated periodic syndromes) and DIRA (deficiency of IL-1 receptor antagonist). The discovery of the mutations that cause CAPS and DIRA led to clinical and basic research that uncovered the key role of IL-1 in an extended spectrum of immune dysregulatory conditions. *NLRP3* encodes cryopyrin, an intracellular "molecular sensor" that forms a multimolecular platform, the NLRP3 inflammasome, which links "danger recognition" to the activation of the proinflammatory cytokine IL-1β. The success and safety profile of drugs targeting IL-1 in the treatment of CAPS and DIRA have encouraged their wider use in other autoinflammatory syndromes including the classic hereditary periodic fever syndromes (familial Mediterranean fever, TNF receptor–associated periodic syndrome, and hyperimmunoglobulinemia D with periodic fever syndrome) and additional immune dysregulatory conditions that are not genetically well defined, including Still's, Behcet's, and Schnitzler diseases. The fact that the accumulation of metabolic substrates such as monosodium urate, ceramide, cholesterol, and glucose can trigger the NLRP3 inflammasome connects metabolic stress to IL-1β-mediated inflammation and provides a rationale for therapeutically targeting IL-1 in prevalent diseases such as gout, diabetes mellitus, and coronary artery disease.

Keywords

anakinra; rilonacept; canakinumab; interleukin-1; hereditary periodic fever syndromes

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THE DISCOVERY OF MONOGENIC AUTOINFLAMMATORY DISEASES AND THE LINK TO IL-1

Concepts of Autoinflammatory Diseases and Autoimmune Diseases

The concept of autoinflammation was introduced in 1999 to distinguish two monogenic hereditary periodic fever syndromes, FMF and TRAPS, from classic autoimmune diseases, such as systemic lupus erythematosus (SLE) and other rheumatic diseases (1). Familial Mediterranean fever (FMF) is caused by autosomal recessive mutations in *MEFV* (2, 3); the TNF receptor-associated periodic syndrome (TRAPS) is caused by autosomal dominant mutations in the tumor necrosis factor (TNF) receptor type I gene, *TNFRSF1A* (1). Whereas the autoimmune diseases are attributed to adaptive immunity dysregulation, the autoinflammatory diseases are thought to be caused by defects in innate immunity proteins and thus marked by the absence of pathogenic autoantibodies or autoreactive T cells (1) (**Figure 1**). During the past decade, the ongoing discovery of monogenic defects in innate immune pathways led to a validation and refinement of the concept of autoinflammation. However, several novel conditions present with pathology suggesting both autoinflammatory and autoimmune disease manifestations, demonstrating that the innate and adaptive immune systems integrate to coordinate immune responses and should be considered as two extremes of a continuum (4). Thus, monogenic autoinflammatory diseases can be more accurately defined as immune dysregulatory conditions marked by excessive inflammation, mediated predominantly by cells and molecules of the innate immune system and with a significant host predisposition (5).

Autoinflammatory Diseases Caused by Mutated Proteins in the IL-1 Pathways

A growing number of monogenic autoinflammatory diseases are known to be caused by dysregulation in cytokine pathways other than interleukin (IL)-1 (reviewed in 6, 7), but this review focuses on autoinflammatory disorders with clinical and mechanistic evidence of IL-1-mediated pathology. Mutations in genes encoding proteins in the IL-1 pathways cause CAPS (cryopyrin-associated periodic syndromes) and DIRA (deficiency of IL-1 receptor antagonist).

CAPS—In 2001, Hoffman et al. reported that gain-of-function mutations in a then-novel gene, *CIAS1*/*NLRP3* (8), cause two clinically characterized autosomal dominant syndromes: the familial cold autoinflammatory syndrome (FCAS) (9) and Muckle-Wells syndrome (MWS) (10). Both present at or around birth and persist throughout life. Patients have flares of neutrophilic urticaria (**Figure 2*a***); fever; conjunctivitis; arthralgia/arthritis induced by cold exposure; and, in MWS, usually constant systemic inflammation with intermittent disease exacerbations. In MWS, progressive sensorineural hearing loss develops in the second to third decade of life (11) (**Table 1**). The finding that de novo mutations in the same gene also cause neonatal-onset multisystem inflammatory disease (NOMID), a sporadically occurring disorder also known as chronic infantile neurological cutaneous and articular syndrome (CINCA) (12, 13), forged the concept that these three disorders form a disease-severity spectrum. This spectrum of disorders, now referred to as cryopyrin-associated periodic syndromes (CAPS), has FCAS on the milder end and NOMID on the severe end. In

addition to the symptoms described for FCAS and MWS, NOMID patients present with severe sensorineural hearing loss (**Figure 2*m*** and ***n***) starting in their first decade of life, papilledema (**Figure 2*k***), inflammation of the central nervous sytem (CNS) including aseptic meningitis (**Figure 2*g***), and bony overgrowth (**Figure 2*c*** and ***d***) (**Table 1**). CAPS can also be caused by somatic mosaicism in *NLRP3* (14).

DIRA—Another rare monogenic condition that pointed to the prominent role of IL-1 in systemic inflammation is caused by autosomal recessive loss-of-function mutations in the IL-1 receptor antagonist gene, *IL1RN*, an endogenously occurring antagonist of IL-1 signaling. Affected children present within the first weeks of life with symptoms of systemic inflammation (elevation of acute phase reactants and low-grade fever), pustular rashes (**Figure 2*b***), joint swelling, oral mucosal lesions, and severe bone pain when being picked up. The clinical presentation resembles that of neonatal sepsis and osteomyelitis. Radiographic characteristics of the bony lesions include periosteal elevation along multiple long bones, heterotopic ossifications around the proximal femur, widening of ribs and clavicles (**Figure 2*e*** and ***f***), and multifocal osteolytic lesions involving long bones or ribs and vertebral bodies, and can lead to spinal cord compression. CNS vasculitis is a rare manifestation (**Figure 2*i*** and ***j***) (**Table 1**). Failure to recognize the disease and treat it with the recombinant IL-1 receptor antagonist anakinra can lead to the development of a severe inflammatory response syndrome and death from multiorgan failure (15, 16).

ACTIVATION AND REGULATION OF THE INNATE IMMUNE CYTOKINE IL-1

IL-1α and IL-1β are proinflammatory cytokines that activate cells by binding and signaling through the IL-1 receptor type I (IL-1RI). They are the most powerful endogenous fever-inducing molecules (pyrogens) known. A third member of that family, the IL-1 receptor antagonist (IL-1Ra) (17), regulates IL-1 signaling at the receptor level by competing with IL-1α and IL-1β for IL-1RI binding, thus preventing the formation of a receptor signaling complex and terminating IL-1α- and IL-1β-mediated signaling (**Figure 3*a***).

IL-1α is constitutively expressed as a precursor in cells forming biological barriers, such as epithelial cells, keratinocytes, and mucosal and endothelial cells, as well as other organ cells. IL-1α does not require processing for activation and is released from damaged or dying cells. In contrast, IL-1β must be proteolytically cleaved into its active form (**Figure 3**). Active IL-1β is primarily generated in a subset of blood monocytes, dendritic cells, and tissue macrophages, where its activation and release are tightly regulated, although studies systematically assessing other cells capable of producing IL-1β are limited (**Figure 3**) (18).

The NLRP3 Inflammasome: a Sensor of “Danger” and Regulator of IL-1β Production

NLRP3/*CIAS1*, the gene mutated in CAPS, encodes the first “intracellular” pattern recognition receptor (PRR) that was identified in humans (22). Its product, the protein cryopyrin, is one of 23 members of a group of cytoplasmic nucleotide-binding oligomerization domain (NOD)-like receptors (NLRs) (19). Many PRRs, including Toll-like receptors (TLRs), and C-type lectin receptors (CLRs), are expressed on the cell surface or in the endosome of immune and tissue cells, and initiate signaling cascades that result in proinflammatory gene expression (20), the RIG-like receptors (RLRs) and the NLRP3

inflammasome are located in the cytoplasm and are activated by intracellular signals, although they coordinate responses with extracellular receptors (**Figure 3**) (17).

Cryopyrin recruits the adapter proteins ASC/PYCARD and CARD8/CARDINAL/TUCAN, as well as procaspase-1, to form a caspase-1/IL-1β-activating platform, the NLRP3 inflammasome. Upon stimulation, the NLRP3 inflammasome activates the proteolytic enzyme caspase-1, which cleaves inactive pro-IL-1β and pro-IL-18 into their active forms (**Figure 3**) (21, 22). Inflammasome activation requires at least two signals: a priming step, through for example a TLR, that leads to the transcription and translation of pro-IL-1β, and a second signal that leads to inflammasome and caspase-1 activation. A growing number of chemically and structurally diverse exogenous and host-derived endogenous molecules have been shown to initiate NLRP3 inflammasome-dependent IL-1β activation. Many of those exogenous triggers provide the first signal and interact with respective PRRs. Such triggers include whole pathogens (*Staphylococcus aureus* and *Listeria monocytogenes*, *Candida albicans* and *Saccharomyces cerevisiae*), pathogen-associated molecular patterns (PAMPs), such as lipopolysaccharide (LPS), (viral) nucleic acids, muramyl dipeptide, and bacterial toxins. Stimuli that provide the second signal include large, insoluble, inorganic, crystallinic structures in the environment, such as asbestos and silica, which are phagocytized by macrophages and lead to lysosomal rupture, a critical step in inflammasome activation. It is likely that the second signal for inflammasome activation can also come from endogenous triggers released during cellular injury or death (i.e., extracellular ATP and hyaluronan) or indicators of metabolic stress (i.e., glucose, monosodium urate, calcium pyrophosphate dehydrate crystals, amyloid-β fibrils, ceramide, cholesterol crystals, and pancreatic amyloid peptide). However, these chemically diverse triggers cannot possibly bind directly to the inflammasome. A search for common pathways (**Figure 3*a***) is under way.

Models of inflammasome activation have recently been reviewed (23, 24). Potential common pathways may involve the production of mitochondrial reactive oxygen species (ROS); ion fluxes, such as K^+ efflux from the cell and Ca^{2+} release from the endoplasmic reticulum; and protein kinase activation. How these signals converge to activate the inflammasome remains unclear. Two molecules have recently been shown to bind directly to the NLRP3 inflammasome: oxidized mitochondrial (oximito) DNA, which is released by dysfunctional mitochondria, and cyclic AMP (cAMP). Both are attractive candidates for a converging mechanism. Binding of oxi-mito DNA activates the inflammasome, whereas cAMP binding is inhibitory (25).

NLRP3 mutations in CAPS patients lead to constitutive overactivation of the inflammasome (26). Indeed, IL-1β production has been estimated from quantifying IL-1β bound to canakinumab complexes after administration of canakinumab, a monoclonal antibody that targets IL-1β (**Figure 3*b***). In healthy controls, IL-1β concentrations recovered from the drug complexes were ~6 ng/dl, whereas patients with FCAS/MWS had a fivefold increase (27, 28). In NOMID/CINCA patients, IL-1β concentrations are even higher (our personal observations). Monocytes with CAPS-associated *NLRP3* mutations have a higher baseline redox state than healthy controls and only require a single trigger, LPS, to rapidly release IL-1β. In contrast, control cells require a second signal, such as ATP, for a fast release of IL-1β (29). In addition, the mutations affect binding of the negative regulator cAMP to the

NACHT domain of mutant NLRP3 (30), suggesting a decrease in negative regulation, which leaves mutant NLRP3 more amenable to activation.

The "physiologic" triggers of inflammasome activation that induce disease flares in CAPS are not well characterized. Cold exposure triggers disease flares in FCAS patients and not in MWS and NOMID patients, but the molecular mechanisms leading to cold-induced flares are not known (31). Infections and physical and mental stress can cause and exacerbate disease flares, suggesting exogenous (signal 1) and endogenous triggers (signal 2) may exacerbate disease.

Clinical Consequences of the Loss of IL-1 Receptor Antagonist Function in DIRA

Whereas CAPS reflects the clinical consequences of the overproduction and secretion of active IL-1β, DIRA reflects the effects of an inability to block and terminate IL-1 signaling. In DIRA, the genetic mutations lead to nonexpression of the IL-1 receptor antagonist, either due to large homozygous genomic deletions as seen in a founder genetic mutation in Puerto Rico (15, 16), or due to homozygous nonsense mutations (15). Other mutations lead to the expression of a nonfunctional protein (32). The clinical impact of uninhibited IL-1 signaling in humans is more severe than had been expected based on knockout animal models (**Figure 2**). Patients present in the neonatal period with systemic inflammation, manifested by elevations of acute phase reactants, as well as bone and skin inflammation. One third of children are born small for gestational age, with evidence of an intrauterine onset. Infants can also develop a life-threatening systemic inflammatory response syndrome due to uncontrolled escalating inflammation. Skin pathergy can be induced by mechanical injury to the skin and can lead to the development of pustular lesions (**Figure 2*b***). IL-1 receptor antagonist, which is expressed in high concentrations in the epidermis, is absent or dysfunctional in DIRA, and IL-1α released during mechanical irritation might initiate and perpetuate skin inflammation. Patients also have a high risk of developing blood clots at areas of line placement. Other rare disease manifestations include CNS vasculitis (**Figure 2*i, j***).

TARGETING IL-1 IN AUTOINFLAMMATORY DISEASES

Three drugs that target IL-1 are approved by the US Food and Drug Administration (FDA) for the treatment of CAPS. The short-acting recombinant IL-1 receptor antagonist named anakinra (Kineret®, distributed by SOBI) was approved for the treatment of patients with NOMID in 2012, and the two long-acting IL-1-blocking agents, rilonacept (Arcalyst®, Regeneron) (IL-1 Trap) and canakinumab (Ilaris®, Novartis) were developed under the FDA orphan drug program and approved for the treatment of CAPS in 2008 and 2009, respectively. Anakinra, which blocks IL-1α and -β binding to the IL-1 receptor, is administered as a daily subcutaneous injection. Rilonacept, a recombinant soluble IL-1 receptor, consists of the extracellular residues of the two IL-1 receptor subunits, IL-1R1 and IL-1RAcP, that were switched in tandem and complexed to the Fc portion of IgG1. Rilonacept binds IL-1α and IL-1β as well and is administered as a weekly subcutaneous injection. Canakinumab, a fully humanized anti-IL-1β monoclonal antibody that selectively binds soluble IL-1β, is administered every 4–8 weeks by subcutaneous injection (**Figure 3*b***).

The success of IL-1 blockade in CAPS and DIRA, coupled with the good safety profile of IL-1 inhibiting agents, led to wider use of these agents in a range of monogenic autoinflammatory conditions and also in a number of genetically undifferentiated fever syndromes (**Figure 4**). The role of IL-1 is also studied in a group of metabolic conditions, including gout/pseudogout and others presenting with chronic low-grade inflammation, such as metabolic syndrome, type 1 and type 2 diabetes mellitus, stroke, and myocardial infarction (**Figure 4**) (33).

Clinical Studies in Patients with Monogenic Autoinflammatory Diseases

The outcomes assessed in studies in CAPS and DIRA were (*a*) to improve the disease symptoms, including rashes, fevers, and joint pain, and/or to reduce the attack frequency and duration in patients with the periodic fever syndromes, and (*b*) to reduce/normalize the systemic inflammatory response markers in the blood [C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), and in some instances serum amyloid A (SAA)]. Recent studies have also addressed whether IL-1 blocking treatment of CAPS and DIRA can (*c*) prevent inflammation-related progression of organ damage. **Supplemental Table 1** profiles the randomized controlled studies, open-label studies, and case studies in these disorders (follow the **Supplemental Material link** from the Annual Reviews home page at **http://www.annualreviews.org**).

Clinical studies in patients with CAPS and DIRA—Clinical studies have established the pivotal role of IL-1 in inflammatory disease manifestations and IL-1–mediated organ damage. Initial clinical studies assessing the efficacy of the IL-1-blocking agent anakinra and later studies with the long-acting IL-1-blocking agents conducted mainly in FCAS and MWS patients uniformly show significant improvement in the clinical symptoms of CAPS, including rash, headaches, fevers, and joint pain, and also marked improvement in inflammatory markers, with resolution of clinical symptoms and normalization of acute-phase reactants (i.e., remission) in 64–97% of patients with severe disease (**Supplemental Table 1**).

Two randomized double-blind placebo-controlled studies on IL-1 blockade in CAPS have been performed. Rilonacept was superior to placebo in improving the primary (composite symptom score) and secondary (flare days, single-symptom scores, and global assessments of disease activity) endpoints in a 24-week study enrolling 47 patients with MWS or FCAS phenotypes (34). Canakinumab induced complete response in the open-label phase of a 48-week study that included 35 patients with MWS (n = 31) and NOMID (n = 4) phenotypes. In the randomized phase, 81% of the patients in the placebo group relapsed, whereas all patients in the drug group remained in remission (35). The efficacy of the short-acting IL-1 inhibitor, anakinra, has been assessed since 2004 in several open-label studies that included 4 to 61 patients with the three disease phenotypes followed for up to five years **(Supplemental Table 1)**.

Early studies in patients with NOMID also showed that drug treatment can reverse organ inflammation including aseptic meningitis, papilledema, and cochlear inflammation (the cause of progressive hearing loss) (36). These observations allow us to separate

inflammatory disease manifestations and inflammation-induced organ damage, as outlined in **Table 1** and **Figure 2*d,h,l,n***. Aggressive individual dose escalations were needed to achieve suppression of inflammation at the organ level. The doses of IL-1-blocking therapy that are needed to suppress systemic and organ inflammation in CAPS patients depend on disease severity and the extent of organ involvement. For anakinra, doses up to 10 mg/kg per day (37, 38) have been used, and dosing adjustments up to 8 mg/kg every 4–6 weeks have also been suggested for patients with more severe CAPS on canakinumab (39). Longer-term outcome studies with 5–10-year follow-up suggest sustained responses to IL-1-blocking therapy (37, 38). With optimal treatment adjustments, the progression of hearing loss and vision loss can be halted in most patients assessed in studies for up to five years (38), but longer-term follow-up data are needed on all three agents (**Table 1**). The efficacy of IL-1 blockade in CAPS stresses the importance of early diagnosis and treatment.

The role of IL-1 in the monogenic "classic" hereditary fever syndromes—The "classic" hereditary fever syndromes are familial Mediterranean fever (FMF), TNF receptor–associated periodic syndrome (TRAPS), and hyperimmunoglobulinemia D with periodic fever syndrome (HIDS). IL-1-blocking agents have been studied in order to reduce the frequency and duration of FMF, TRAPS, and HIDS attacks and to reduce systemic inflammation in patients with refractory hereditary fever syndromes. Positive clinical responses in all three disorders suggest a contribution of IL-1-mediated pathology to the clinical phenotype, although other, less well-understood inflammatory pathways in addition to IL-1 are likely operative.

FMF is caused by autosomal recessive mutations in *MEFV* and is characterized by recurrent one- to three-day attacks of fever, serositis presenting as abdominal or pleuritic chest pain, and arthritis. Autosomal dominant forms of FMF are also seen (2, 3, 40). FMF is the most prevalent autoinflammatory disease worldwide with more than 100,000 affected individuals. The most dreaded complication is systemic amyloidosis leading to renal failure (41). Although the mainstay of treatment for FMF is daily oral prophylactic colchicine, IL-1 blocking treatments have been administered to patients unresponsive or intolerant to therapeutic doses of colchicine (42). A randomized placebo-controlled trial has recently suggested that the long-acting IL-1 inhibitor rilonacept can reduce the number and severity of inflammatory disease flares (43). Earlier case reports have described improvement of FMF using IL-1 blockade with anakinra and canakinumab (**Supplemental Table 1**).

A number of studies have investigated a mechanism for IL-1 activation by mutant pyrin. In vitro studies with wildtype and mutant pyrin suggest that wildtype pyrin-ASC interaction may inhibit the assembly of the NLRP3 inflammasome by competing for the adaptor protein ASC (apoptosis-associated speck-like protein containing CARD), which is necessary for complex assembly (22, 26, 44). Mice expressing a truncated mutant pyrin are more sensitive to endotoxin shock, and macrophages from pyrin knockout mice produce increased amounts of IL-1β when stimulated in culture. These findings suggest an inhibitory effect of wildtype but not mutant pyrin on inflammasome activation. Wildtype pyrin may directly bind to caspase-1 and inhibit caspase-1 activation and IL-1β production (45, 46). In a mouse model transgenic for the human mutant pyrin, pyrin and ASC may themselves form their own "inflammasome complex" and thus activate caspase-1 and IL-1β (47). Different

experimental conditions may account for the differences observed. Whether the mechanisms described above can be operational in patients with FMF will need to be clarified in future studies.

TRAPS is an autosomal dominant, multisystem autoinflammatory disorder caused by mutations in *TNFRSF1A*, the gene encoding the 55-kDa TNF receptor (3). TRAPS attacks resemble those in FMF, including the presence of abdominal pain, pleurisy, joint pain, and increased acute phase reactants. However, TRAPS attacks can last up to several weeks, and the rash is migratory, with areas of erythema and swelling overlying areas of myalgia. Conjunctivitis and periorbital edema can be present (48, 49). TRAPS attacks do not respond to colchicine but relatively promptly to corticosteroids. Corticosteroids as well as TNF-inhibiting drugs, i.e., etanercept, can be used to attenuate intermittent attacks and to reduce the frequency, severity, and duration of attacks (50). More recently, anti-IL-1 therapy with either the recombinant IL-1Ra anakinra or the longer-acting agent canakinumab has been used empirically with satisfactory responses (**Supplemental Table 1**). Patients with a high risk for the development of amyloidosis may benefit from earlier and more aggressive IL-1-blocking therapy (51).

Recent mechanistic studies shed light on a link between mutant TNF receptor (TNFR1) and IL-1-mediated clinical disease. Mutant TNFR1 molecules are not transported to the cell surface but are trapped in the endoplasmic reticulum (ER) of the cells, where they accumulate to levels tenfold higher than wildtype levels (52, 53). Cells from patients with TRAPS mutations spontaneously produce mitochondrial reactive oxygen species (ROS). This leads to activation of c-Jun amino-terminal kinase (JNK) and p38, which are mitogen-activated protein (MAP) kinases, as well as production of proinflammatory cytokines including IL-1, TNF, IL-6 and likely others (53, 54).

HIDS is an autosomal recessive disorder caused by loss-of-function mutations in the gene encoding mevalonate kinase, *MVK*, an enzyme of the cholesterol pathway. Patients present with three-to-seven-day episodes of fever, significant lymphadenopathy, vomiting, diarrhea, a variable maculopapular rash, and splenomegaly. Blood monocytes from these patients secrete more IL-1β than cells from unaffected individuals (55). It is still unclear how mutations in mevalonate kinase result in increased production of IL-1β. However, in patients with insufficient responses to nonsteroidal anti-inflammatory drugs (NSAIDs) and/or intolerance to corticosteroids, IL-1-blocking agents have been used. Open-label case reports with the anti-IL-1 drugs (anakinra and canakinumab) report complete and partial remissions in 85% and 10% of the patients, respectively (**Supplemental Table 1**).

Other monogenic autoinflammatory diseases with variable responses to IL-1-blocking therapy—Majeed syndrome is caused by autosomal recessive mutations in *LPIN2* (56) and has clinical similarities with DIRA. It presents with systemic inflammation, pustular skin lesions, aseptic osteomyelitis, and dysery-thropoietic anemia. Recent case reports show a rapid and complete response to IL-1-blocking therapy (**Supplemental Table 1**) and suggest a major role of IL-1 in the disease pathogenesis, but pathways that link *LPIN2* to the IL-1-mediated pathology are still speculative.

Pyogenic arthritis, pyoderma gangrenosum and acne (PAPA) syndrome is an autosomal dominant, autoinflammatory disorder caused by mutations in *PSTPIP1*. It presents with a classic clinical triad of severe scarring cystic acne, recurrent destructive pyogenic arthritis, and difficult-to-control pyoderma gangrenosum. PAPA syndrome is exceedingly rare and treatment can be very challenging. Intra-articular as well as parenteral corticosteroids are useful in the management of the articular and cutaneous manifestations, and prolonged courses of high doses are often required to control the disease, leading to significant side effects and medication-associated morbidity (57–62). TNF inhibitors (58, 59, 63–66), alone or in combination with IL-1-blocking agents (**Supplemental Table 1**), improve disease control, but in most instances high doses of corticosteroids are used concomitantly (59, 60, 64). Responses to IL-1 (**Supplemental Table 1**) and TNF inhibitors are incomplete, suggesting the contribution of additional inflammatory pathways to the disease pathogenesis (64).

Pediatric granulomatous arthritis (PGA), also called Blau syndrome, is caused by autosomal dominant gain-of-function mutations in the NACHT domain (exon 4) of another intracellular NOD-like receptor (NLR), the intracellular sensor of danger, *NOD2*/*CARD15* (67, 68). Patients present with a triad of granulomatous polyarthritis, panuveitis, and granulomatous exanthema. NSAIDs, systemic corticosteroids (69), and immunosuppressants, as well as biologics targeting TNF and IL-1 (**Supplemental Table 1**), result in clinical benefit, especially in patients with refractory uveitis (70). However, the inflammatory pathways that lead to the disease are still incompletely understood.

FCAS2, a mild periodic fever syndrome with variable, nonspecific findings of fever, rashes, and joint pain, is caused by mutations in *NLRP1*2, another member of the NLR family. In two cases with more severe disease, anakinra has been tried with only partial responses (**Supplemental Table 1**).

Inhibition of IL-1 in Diseases with Autoinflammatory Phenotypes and Unknown Genetics

Some chronic multisystem inflammatory diseases are poorly responsive to immunosuppressive therapies and are only partially responsive to high doses of corticosteroids and TNF-blocking therapies. Recently, IL-1-blocking agents have suggested a role for IL-1 in some of these conditions and led to their grouping as disorders with autoinflammatory phenotype and loosely defined IL-1-mediated pathology.

Schnitzler syndrome is a rare acquired systemic inflammatory disease with clinical similarities to FCAS and MWS syndrome. It presents with fever flares, chronic neutrophilic urticaria, and a monoclonal Ig gammopathy that can progress into Waldenstroöm macroglobulinemia, or lymphoplasmacytic lymphoma. Multiple case reports and small series indicate its rapid and sustained responsiveness to monotherapy with IL-1-blocking agents (**Supplemental Table 1**).

Behcçet’s disease is a multisystem inflammatory disorder that presents with recurrent oral and genital ulcers, skin pathergy, ocular inflammation, intermittent rashes, gastrointestinal ulceration, neurologic disease, fevers, and arthritis without autoantibody production. A case report and a small case series of seven patients evaluated the response of two recombinant

anti-IL-1β antibodies (canakinumab and gevokizumab) on uveitis, with rapid and durable responses in some patients with resistant uveitis. Gevokizumab has not been approved by the FDA yet **(Supplemental Table 1)**.

Periodic fever, aphthous stomatitis, pharyngitis and adenitis (PFAPA) is a childhood disease that presents with recurrent attacks of periodic high fever at intervals of about 3–5 weeks, as well as with aphthous ulcers, pharyngitis and/or adenitis. In between episodes, the children are asymptomatic, and throat cultures and search for infectious etiologies are negative. The disease lasts throughout childhood, but attacks become less frequent after puberty. Treatment varies and includes on-demand NSAIDS and oral corticosteroids. Tonsillectomy may reduce the frequency of attacks, and recently on-demand IL-1-inhibiting drugs (anakinra) have been used with complete response (**Supplemental Table 1**).

Adult-onset Still's disease (AOSD) and systemic-onset juvenile idiopathic arthritis (SoJIA) are likely the same entity or closely related. These debilitating diseases present with a triad of persistent high spiking fevers, joint pain, and a distinctive salmon-colored rash during high fevers. Patients have neutrophilia, high CRP, elevated serum ferritin levels, and elevated liver enzymes. Some patients respond initially to NSAIDs and corticosteroid therapy but develop therapy resistance. Anti-TNF drugs and methotrexate are usually ineffective. Blood monocytes from these patients secrete more IL-1β than do monocytes from healthy controls (71). To date, no genetic cause has been identified for this disease, but treatment with IL-1β blockers is highly effective, allowing lowering of corticosteroid doses and improving growth. Recently, the long-acting IL-1 inhibitor canakinumab was approved for the treatment of patients with SoJIA. In a multicenter randomized placebo-controlled study, 84% of canakinumab-treated patients achieved at least a 30% reduction in joint swelling and count (ACR30) compared to only 10% in the placebo group (**Supplemental Table 1**) (72). Long-term efficacy and safety have been studied in 24 SoJIA patients treated with rilonacept, which led to a sustained clinical response over two years in >50% of the patients (73). Additionally, a double-blind placebo-controlled study of anakinra enrolling 24 patients showed a higher frequency of responders to the drug in comparison with placebo in the randomized phase (4 weeks), and by the end of the open-label phase (12 months), 43% of the patients were considered responders (74). In adult-onset Still's disease, one randomized study enrolling 22 patients has demonstrated that more patients on anakinra than on a disease-modifying antirheumatic drug (DMARD) achieved disease remission (75) (**Supplemental Table 1**).

Synovitis, acne, pustulosis, hyperostosis and osteitis (SAPHO) syndrome and chronic recurrent multifocal osteomyelitis (CRMO) are autoinflammatory disorders that affect the bone and might pathogenically be related conditions. Whereas SAPHO syndrome usually presents in older adolescents or adults (76–80), classic CRMO presents in school-aged children with multifocal, sterile, osteolytic bone lesions, with or without fever. Associated inflammatory disorders include palmoplantar pustulosis, psoriasis, and Crohn disease (81, 82). The predilection for bone involvement in adults favors bones of the anterior chest and other bones of the axial skeleton (83), whereas in children, the vertebrae and metaphyses of the long bones are more commonly involved (84, 85). Two case series showed partial clinical and laboratory response to anakinra in six out of the total of seven patients with

SAPHO (**Supplemental Table 1**). The only case report on IL-1 blockade in CRMO showed a partial and nonsustained response to anakinra in one pediatric patient (**Supplemental Table 1**).

Clinical Studies in Other Diseases with Proposed IL-1-Mediated Pathology

Except for gout, the diseases discussed in this section do not present with the acute clinical features of systemic autoinflammatory disease. They present with metabolically driven low-grade chronic inflammation, also referred to as metainflammation, which is believed to contribute to disease severity and outcome (86). Tissue-activated macrophages are thought to contribute to chronic inflammation in obesity, insulin resistance, type 2 diabetes, and atherosclerosis (87). The finding that metabolites that accumulate in the respective disorders, including monosodium urate crystals, fatty acids, glucose, ceramide, and cholesterol can act as metabolic triggers that activate the IL-1-activating NLRP3 inflammasome in tissue macrophages led to studies targeting IL-1 in these disorders.

The clinical impact of blocking IL-1 is best established in acute gout. Four randomized double-blind placebo-controlled studies showed sustained responses to treatment with either canakinumab or rilonacept compared to placebo or to triamcinolone acetonide. Canakinumab led to significant relief of pain, decreased the inflammatory markers, and reduced the risk of new flares in patients with acute gouty arthritis (n = 456) (88). A decrease in the occurrence of flares during initiation of uric acid–lowering therapy (ULT) in comparison with colchicine was also observed (n = 432) (89). Additionally, the monoclonal anti-IL-1 antibody has been shown to reduce the occurrence of acute flares in patients with refractory gouty arthritis (n = 143) (90). Rilonacept has also been evaluated in a study including 241 patients that showed a significant reduction of the number of gout flares during initiation of ULT (91) (**Supplemental Table 1**).

Clinical data with IL-1 blockade in diabetes mellitus (DM) type 2 and metabolic syndrome are less clear. In 2007, a double-blind placebo-controlled randomized study including 70 patients with DM type 2 showed that anakinra significantly reduced glycated hemoglobin (HbA1c) levels, increased C-peptide secretion, and reduced the ratio of proinsulin to insulin (PI/I) and the levels of serum IL-6 in comparison with placebo. Two years later, the same group evaluated the 70 patients 39 weeks after anakinra withdrawal and concluded that PI/I ratio, CRP levels, and IL-6 levels, but not C-peptide secretion, remained improved (92). More recently, efficacy of canakinumab was evaluated in a study that included 556 patients with DM type 2. Compared with placebo, canakinumab induced a nonsignificant improvement in HbA1c, glucose, and insulin levels. However, the levels of CRP, IL-6, and fibrinogen significantly decreased upon treatment in comparison with placebo (93) (**Supplemental Table 1**). In DM type 1, two randomized double-blind placebo-controlled studies have shown that neither anakinra (n = 51) nor canakinumab (n = 66) induced response as a single immunomodulatory drug in patients with recent-onset disease (94) (**Supplemental Table 1**). In one study in nondiabetic patients with metabolic syndrome, anakinra did not improve insulin resistance (95) (**Supplemental Table 1**).

Two randomized studies assessing IL-1 blockade with anakinra in patients with cortical strokes and following myocardial infarction (MI) address the hypothesis that IL-1 released

from necrotic and dying cells may increase collateral tissue damage and outcome. In both studies, anakinra significantly decreased CRP levels and led to a lower rate of heart failure in the MI patients and better survival at three months poststroke, cautiously suggesting potential benefit (96, 97) (**Supplemental Table 1**). In addition, preliminary data in multiple myeloma suggest possible benefit, although no benefit was seen in decreasing graft-versus-host disease in patients undergoing allogeneic stem cell transplantation (98) (**Supplemental Table 1**).

CONCLUDING REMARKS

The discovery of the role of IL-1 in patients with rare monogenic autoinflammatory syndromes underscores the value of studying rare diseases to better understand genetically more complex common disorders. The availability of therapeutic agents that block IL-1 has allowed us to probe for IL-1-mediated pathology in a broader spectrum of diseases and group these diseases based on treatment responses. The mechanistic understanding of pathways that regulate IL-1 biology and of factors that influence IL-1 activation and secretion may allow for the development of novel therapeutic strategies that target NLRP3 inflammasome activation more directly and may increase the therapeutic options for patients with autoinflammatory diseases in the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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SUMMARY POINTS

1. The discovery of monogenic defects in genes regulating IL-1 activation and signaling led to clinical and basic investigations revealing a key role of the proinflammatory cytokine IL-1 in human disease. *NLRP3*/*CIAS1* is mutated in patients with cryopyrin-associated periodic syndromes (CAPS), encodes an intracellular sensor of “molecular danger,” and assembles a molecular platform, the NLRP3 inflammasome, that links the pathogenesis of CAPS and other autoinflammatory diseases to dysregulated stress recognition and oversecretion of IL-1β.
2. The successful treatment of patients with CAPS, DIRA, and a number of other autoinflammatory syndromes with IL-1-blocking agents provided proof of concept for the pivotal role of IL-1 in the pathogenesis of several autoinflammatory diseases.
3. Early treatment can prevent IL-1-mediated organ damage in patients with autoinflammatory syndromes, thus stressing the importance of early diagnosis and treatment.
4. The discovery that metabolic stimuli, including monosodium urate, ceramide, lipids, cholesterol, and amyloid fibrils, can stimulate the NLRP3 inflammasome has revealed links between metabolic diseases and immune activation and led to the exploration of the role of IL-1 in common immune-linked metabolic diseases such as gout, pseudogout, atherosclerosis, and diabetes.

FUTURE ISSUES

1. IL-1 plays a key role in many autoinflammatory diseases.
2. In IL-1 responsive autoinflammatory diseases, existing data focus on inflammasome activation and IL-1β release from monocytes, but careful assessment of IL-1 regulation in organ-specific cells is necessary to better understand the organ-specific disease manifestations that are often characteristic of a specific disorder.
3. Although involvement of IL-1 in immune-linked metabolic diseases has been proposed, future studies are needed to clinically define the role of IL-1 blockade as single or supplementary therapy in these conditions.
4. In a growing number of autoinflammatory conditions, IL-1 is contributing only partially or not at all to the disease phenotype. This indicates the need to better understand additional cytokine pathways that lead to inflammatory phenotypes, which will require novel therapeutic approaches.

RELATED RESOURCE

A Web database archiving genetic variants in the currently recognized monogenic "autoinflammatory diseases" can be used to interrogate disease-related variants (**http://fmf.igh.cnrs.fr/ISSAID/infevers/**).

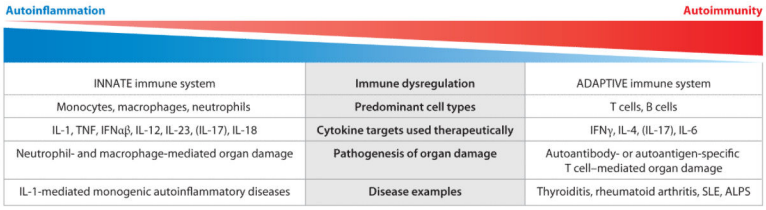

Figure 1.

Comparison and intersection between autoinflammation and autoimmunity concepts. SLE, systemic lupus erythematosus; ALPS, autoimmune lymphoproliferative syndrome.

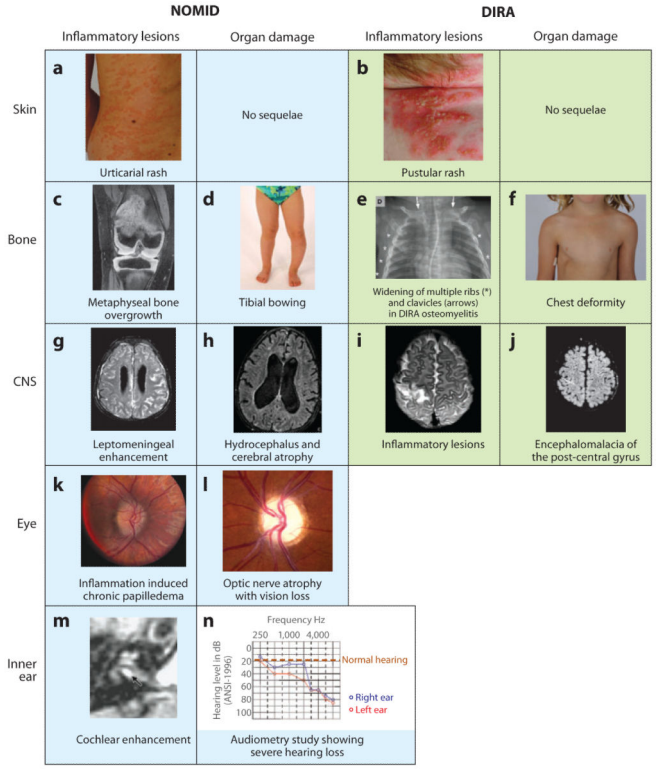

Figure 2.

Inflammatory clinical manifestations and organ damage in the IL-1-mediated diseases; in neonatal-onset multisystem inflammatory disease (NOMID), which is the severe form of cryopyrin-associated periodic syndromes (CAPS); and deficiency of interleukin-1 receptor antagonist (DIRA).

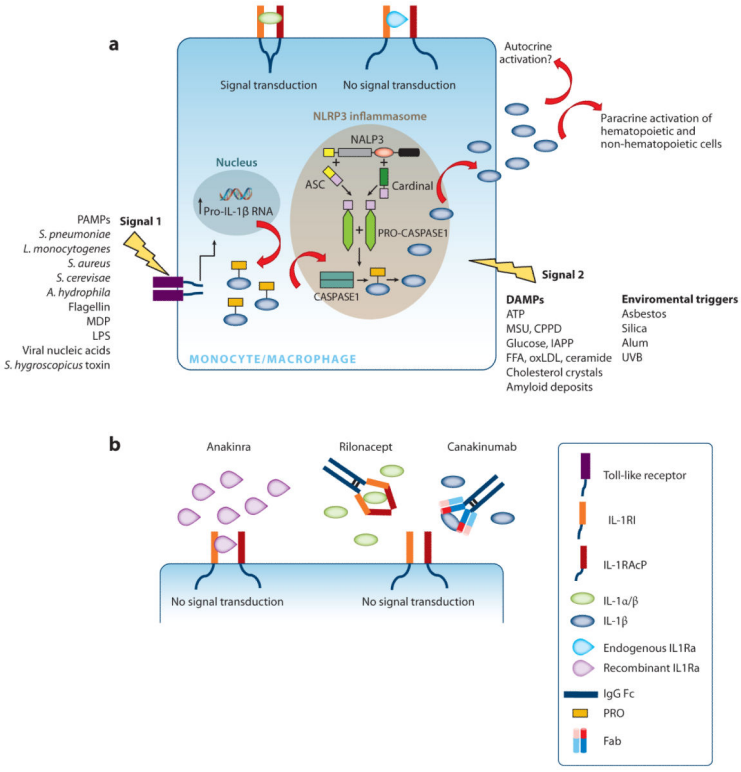

Figure 3.

(*a*) Mechanism of IL-1 secretion and signaling. (*b*) Mechanism of IL-1 inhibition with the three currently approved treatments for CAPS. See text for explanation. CPPD, calcium pyrophosphate dehydrate crystals; DAMPs, danger-associated molecular patterns; FFA, free fatty acids; IAPP, islet amyloid polypeptide; LPS, lipopolysaccharide; MDP, muramyl dipeptide; MSU, monosodium urate; oxLDL, oxidized low-density lipoprotein; PAMPs, pathogen associated molecular patterns.

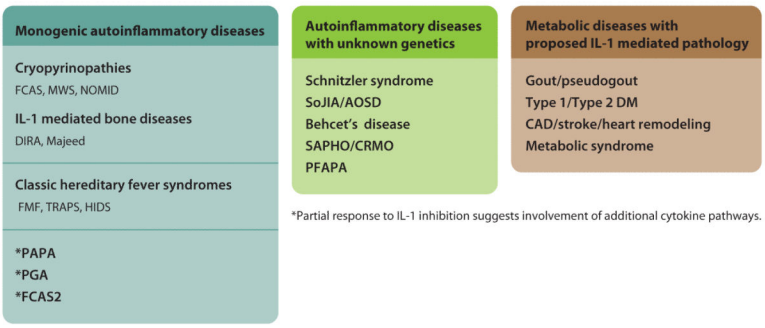

Figure 4.

Diseases with established or proposed IL-1-mediated pathology. FCAS, familial cold autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; DIRA, deficiency of interleukin-1 receptor antagonist; FMF, familial Mediterranean fever; TRAPS, TNF receptor-associated periodic syndrome; HIDS, hyperimmunoglobulinemia D with periodic fever syndrome; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne syndrome; PGA, pediatric granulomatous arthritis; SoJIA, systemic-onset juvenile idiopathic arthritis; AOSD, adult-onset Still's disease; SAPHO, synovitis, acne, pustulosis, hyperostosis, and osteitis syndrome; CRMO, chronic recurrent multifocal osteomyelitis; PFAPA, periodic fever, aphthous stomatitis, pharyngitis, and adenitis syndrome; DM, diabetes mellitus; CAD, coronary artery disease.

Table 1

Demographic, genetic, and acute clinical features and chronic inflammatory damage of the monogenic autoinflammatory diseases

		Cryopyrinopathies				Hereditary periodic fever syndromes		
		CAPS-FCAS	CAPS-MWS	CAPS-NOMID	DIRA	FMF	TRAPS	HIDS
Inheritance		AD[a]	AD	AD, mostly sporadic	AR	AR[b]	AD	AR
Ethnic distribution		Primarily European	Northern European	Any ethnicity	Newfoundland, Puerto Rican, Brazilian, Dutch, Palestinian	Jewish, Arab, Armenian, Turkish, Italian	Broad ethnic distribution; original families of Irish/Scottish descent	Dutch, Northern European
Gene (chromosome)		*NLRP3* (1q44)	*NLRP3* (1q44)	*NLRP3* (1q44)	*IL1RN* (2q14.2)	*MEFV* (16p13.3)	*TNFRSF1A* (12p13)	*MVK* (12q24)
Protein		Cryopyrin (NLRP3)	Cryopyrin (NLRP3)	Cryopyrin (NLRP3)	IL1RA	Pyrin	55-kDa TNF receptor	Mevalonate kinase
Pathogenesis		IL-1β mediated	IL-1β mediated	IL-1 β mediated	IL-1 mediated	Predominantly IL-1 mediated + unknown pathway	Partially IL-1 mediated + TNF + ROS	Partially IL-1 mediated + unknown pathway
Typical attack length		30 min–72 h	1–2 days or continuous with flares	Continuous with exacerbations	Variable	1–3 days	>7 days	3–7 days
Skin	Acute inflammation	Cold-induced neutrophilic urticaria	Neutrophilic urticaria	Neutrophilic urticaria	Pustular dermatitis	ELE	Migratory erythema often accompanying myalgia, ELE	Maculopapular or purpuric exanthema, aphthous oral ulcers
CNS	Acute inflammation	Headache	Headache, intermittent aseptic meningitis with flares	Headache, chronic aseptic meningitis	Rare CNS vasculitis	Aseptic meningitis (rare)	Headache, aseptic meningitis (rare)	Uncommon
	Chronic damage	None	None	Cognitive impairment	Rare encephalo-malacia	None	None	None
Eye	Acute inflammation	Conjunctivitis	Conjunctivitis, episcleritis, optic disk edema/ papilledema	Conjunctivitis, uveitis, optic disk edema/ papilledema	Rare conjunctivitis	Uncommon	Periorbital edema, conjunctivitis, uveitis	Uncommon
	Chronic damage	None	Corneal opacification	Chronic papilledema, progressive	None	None	None	None

		Cryopyrinopathies			DIRA	Hereditary periodic fever syndromes		
		CAPS-FCAS	CAPS-MWS	CAPS-NOMID		FMF	TRAPS	HIDS
				amaurosis, corneal opacification				
Inner ear	Acute inflammation	None	Cochlear edema	Cochlear edema	None	None	None	None
	Chronic damage	None	Progressive sensorineural hearing loss	Progressive sensorineural hearing loss	None	None	None	None
Musculoskeletal	Acute inflammation	Myalgia, arthralgia	Myalgia, arthralgia, oligoarticular arthritis	Myalgia, arthralgia, and arthritis	Recurrent multifocal aseptic osteomyelitis, periostitis	Exercise-induced myalgia, protracted febrile myalgia (rare), large-joint episodic arthritis	Migratory myalgia, arthralgia, nonerosive arthritis	Arthralgia, nonerosive acute polyarthritis; myalgia is uncommon
	Chronic damage	None	None	Chronic arthritis, epiphyseal bony overgrowth, contractures	Vertebral destruction, odontoid destruction with neck instability	Chronic arthritis of hip, sacroiliitis, arthrosis, erosive joint damage	None	None
Serosal	Acute inflammation	Absent	Pericarditis (rare), peritonitis (rare) and pleuritis (rare)	Pericarditis (rare), peritonitis (rare) and pleuritis (rare)	Uncommon	Peritonitis, pleuritis, pericarditis, tunica vaginalis involvement	Peritonitis, pleuritis, pericarditis, tunica vaginalis involvement	Peritonitis is uncommon; pleuritis is rare
	Chronic damage	None	Peritoneal adhesions	None	None	Peritoneal adhesions	Peritoneal adhesions	Peritoneal adhesions
Systemic inflammation	Acute inflammation	Fever and increased acute phase reactants[c]	Fever, increased acute phase reactants, occasional lymphadenopathy	Fever, increased acute phase reactants, occasional lymphadenopathy, hepatosplenomegaly	Occasional fever in few patients, increased acute phase reactants	Fever and increased acute phase reactants	Fever, increased acute phase reactants and occasional lymphadenopathy	Fever, increased acute phase reactants, extremely frequent cervical lymphadenopathy and frequent hepatosplenomegaly
	Chronic damage[d]	Amyloidosis is uncommon (~2%)	Amyloidosis is observed in up to 25% of cases in	Amyloidosis is observed in untreated patients who	Amyloidosis risk is unknown	Amyloidosis risk varies according to genotype and	Amyloidosis is observed in ~14% of cases	Amyloidosis is rare

		Cryopyrinopathies				Hereditary periodic fever syndromes		
		CAPS-FCAS	CAPS-MWS	CAPS-NOMID	DIRA	FMF	TRAPS	HIDS
			Europe	achieve adulthood		environment		
Treatment		Anti-IL1 agents (anakinra, canakinumab, rilonacept)	Anti-IL1 agents (anakinra, canakinumab, rilonacept)	Anti-IL1 agents (anakinra, canakinumab)	Anti-IL1 agents (anakinra)	Daily oral colchicine, anti-IL1 agents (anakinra, rilonacept, canakinumab)	Etanercept, anti-IL1 agents (anakinra)	NSAIDs, CS, simvastatin, anti-IL1 agents (anakinra, canakinumab)

Abbreviations: AD, autosomal dominant; AR, autosomal recessive; CAPS, cryopyrin-associated periodic syndrome; CNS, central nervous system; CS, corticosteroids; DIRA, deficiency of interleukin 1 receptor antagonist; ELE, erysipelas-like erythema; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyperimmunoglobulinemia D syndrome with periodic fever; IL, interleukin; MWS, Muckle-Wells syndrome; NOMID, neonatal-onset multisystem inflammatory disease; NSAIDs, nonsteroidal anti-inflammatory drugs; ROS, reactive oxygen species; TNF, tumor necrosis factor; TRAPS, TNF receptor–associated periodic syndrome.

[a] Mostly familial; sporadic cases are known.

[b] FMF can also occur as an autosomal dominant disease.

[c] Acute phase reactants: C-reactive protein, erythrocyte sedimentation rate, and serum amyloid A protein.

[d] In all diseases, chronic anemia, growth retardation, and osteopenia can occur as long-term complications in the severe and untreated cases.