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Autoinflammation: From monogenic syndromes to common skin diseases

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Abstract

Autoinflammation is characterized by aberrant regulation of the innate immune system and often manifests as periodic fevers and systemic inflammation involving multiple organs, including the skin. Mutations leading to abnormal behavior or activity of the interleukin 1 beta (IL-1ß)-processing inflammasome complex have been found in several rare autoinflammatory syndromes, for which anticytokine therapy such as IL-1 or tumor necrosis factor-alfa inhibition may be effective. It is becoming clear that features of autoinflammation also affect common dermatoses, some of which were previously thought to be solely autoimmune in origin (eg, vitiligo, systemic lupus erythematosus). Recognizing the pathogenetic role of autoinflammation can open up new avenues for the targeted treatment of complex, inflammatory dermatoses.

Keywords

anakinra; autoinflammation; common dermatoses; inflammasomes; interleukin-1 beta; periodic fevers

The discovery of monogenic origins for seemingly unprovoked inflammatory episodes in patients with periodic fever syndromes has led to a new disease pathogenesis model known as autoinflammation. This concept is distinct from autoimmunity, in which lymphocyte-mediated immune responses are directed against specific self-antigens. Autoinflammation, by contrast, is characterized by aberrant regulation of the innate immune system. As a more complete understanding of autoinflammation emerges, it is also becoming clear that these pathways may play an important role in common dermatologic disease, leading to the possibility of new therapeutic approaches for these conditions.

A family of genes known as the nucleotide-binding domain leucine-rich repeat-containing (*NLR*) genes are integral to autoinflammation.[1] Thus far 22 human *NLR* genes have been identified.[2] Most *NLR*s include a caspase-recruiting domain (*CARD*) or a pyrin domain at

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the N-terminal, a central nucleotide-binding domain (*NACHT*), and a C-terminal leucine-rich repeat domain (Fig 1). Each *NLR* encodes a NLR protein (NLRP), which interacts with the apoptosis-associated speck-like protein and the precursor form of caspase-1 to form a multiprotein structure known as an inflammasome. Upon formation of the inflammasome, caspase-1 becomes activated and hydrolyzes the interleukin (IL)-1 family precursors into their active cytokine counterparts.[3] Caspase-1 can also mediate secretion of IL-1 alpha (IL-1α) and fibroblast growth factor 2.[4]

NLR mutations may lead to inappropriate activation of or failure to inhibit inflammasomes,[5] resulting in abnormal secretion of inflammatory cytokines (primarily IL-1ß, IL-6, and IL-18). Although incompletely understood, active IL-1ß appears to prime the production of its precursor pro-IL-1ß, thereby perpetuating autoinflammatory responses that further damage affected tissues.[6,7] Alternative pathways of autoinflammation have also been suggested, including inflammasome activation by mitochondria-derived reactive oxygen species in response to exogenous pathogens or endogenous danger signals.[8]

Both infectious and noninfectious stimuli are capable of triggering innate immune responses through membrane-bound pattern recognition receptors (PRRs) such as Toll-like receptors (TLRs) or cytosolic PRRs such as the aforementioned NLRPs.[9] Binding of TLRs to pathogen- or danger-associated molecular patterns activates expression of inflammatory cytokines via nuclear gene transcription factors (Fig 1). Independent of the role of TLRs, NLRPs in the cytosol function as innate sensors of intracellular pathogen- and danger-associated molecular patterns. Their direct binding is responsible for the formation of inflammasomes, activation and secretion of inflammatory cytokines, and the subsequent cascade of extracellular downstream effects of inflammation (Fig 1). See Tables I and II for a summary of autoinflammatory syndromes and their therapies.

MONOGENIC AUTOINFLAMMATORY SYNDROMES

Cryopyrin-associated periodic syndrome

Cryopyrin-associated period syndrome (CAPS) is a rare childhood-onset disorder that presents with a wide spectrum of severity. In fact, CAPS encompasses 3 distinct phenotypes, listed in the order of increasing severity: familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disorder. As the name suggests, episodes of familial cold autoinflammatory syndrome may follow exposure to low ambient temperatures.[10,11] The hallmarks of CAPS episodes are evanescent, nonpruritic, urticaria-like papules and confluent geographic plaques on the trunk and extremities, periodic fevers, and distal arthralgia (Fig 2).[10,12,13] Skin histology reveals a sparse interstitial, perivascular, or perieccrine neutrophilic infiltrate.

Less common features of CAPS are ocular involvement, including conjunctivitis, episcleritis, and uveitis, and neurologic manifestations, which encompass headaches, sensorineural hearing loss, and chronic meningitis.[14,15] Secondary amyloid A amyloidosis most frequently affects the kidney and can lead to nephrotic syndrome. One case series reported 6 cases of reactive amyloidosis out of 22 patients.[14] Leukocytosis and elevation of C-reactive protein (CRP) and serum protein amyloid A are almost always present, whereas

the erythrocyte sedimentation rate (ESR) is variably elevated.[16] IL-1ß expression is up-regulated in tissues of patients with CAPS.[7,14,17] There are no known susceptibility markers in patients with CAPS for the development of amyloidosis.

Mutations in the *NLRP3* gene [also referred to as the *CIAS1* (cold-induced autoinflammatory syndrome 1) or *NALP3* (nacht domain-, leucine-rich repeat-, and PYD-containing protein 3) gene], which codes for the cryopyrin NLRP, are dominantly inherited; however, de novo *NLRP3* mutations have been reported.[18-20] Targeted inhibition of IL-1ß has revolutionized the treatment of patients with CAPS. Treatment with anakinra, a recombinant-DNA analog of the human IL-1 receptor antagonist (RA), typically leads to rapid clearance of skin lesions and improvement of amyloidosis-induced nephrotic syndrome.[21-25] Rilonacept, a "cytokine trap" antibody with high affinity for anti-IL-1, is also effective,[26-28] and canakinumab, a fully human monoclonal antibody against IL-1ß, demonstrated a 97% complete response rate in a recent clinical trial.[29]

Pyogenic arthritis, pyoderma gangrenosum, and acne syndrome

Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA) syndrome is a dominantly inherited disorder characterized by pyoderma gangrenosum (PG), acne vulgaris, and pyogenic arthritis primarily involving the appendicular skeleton.[30] PG and arthritis typically present in early childhood, whereas acne often begins during puberty. PG lesions are characterized as single or multiple deep, "beefy red" ulcers with bluish, undermined borders (Fig 3). Common locations are the legs and face and occasionally the intertriginous regions. Skin ulcers in PAPA syndrome are indistinguishable from PG lesions secondary to other causes.

Mutations in *PSTPIP1* (proline-serine-threonine phosphatase interacting protein 1), also known as *CD2BP1*, cause increased binding of the protein pyrin to the pyrin domain of NLRP, leading to inflammasome formation.[31] Laboratory findings include elevated IL-1ß, tumor necrosis factor (TNF)-alfa, CRP, and ESR, as well as hypogammaglobulinemia.[32-34] Acne and PG typically respond to infliximab and etanercept, respectively, whereas response to anakinra is variable.[35-38] Control of inflammation can sometimes be achieved with prednisone (15-60 mg/d).[39]

Blau syndrome

Blau syndrome is an autosomal dominant disorder presenting in childhood with cutaneous granulomata, symmetric polyarthritis (with or without camptodactyly), and ocular manifestations, including uveitis, iritis, vitritis, and closed-angle glaucoma.[40-43] Skin examination reveals nonpruritic, generalized, densely populated erythematous papules.[44,45] Recalcitrant, tender leg ulcers with granulating bases and poorly demarcated flat borders have been described (in contrast to the well-defined undermined borders of PG ulcers).[46] Histopathology reveals noncaseating granulomata.[44,45,47] Granulomatous infiltration of the lungs, kidneys, liver, and of the arterial and nervous systems may also occur.[48-52]

Missense mutations in the *CARD15* (caspase-recruiting domain 15) gene, also known as *NOD2* (nucleotide-binding oligomerization domain) gene, are responsible for Blau syndrome.[42,53] CARD15 serves as an activator of the nuclear factor kappa B pathway in

monocytes, leading to expression of inflammatory cytokines that in turn contribute to the development of granulomata in affected tissues.[54,55] Increased IgA, IgG, ESR, and angiotensin-converting enzyme levels have been documented.[41] Response to targeted anti-IL-1 therapy is inconsistent, and serum IL-1ß levels do not necessarily correlate with disease severity.[56,57] Infliximab and thalidomide have been used with moderate success,[58,59] whereas treatment with prednisone (2 mg/kg/d) may be necessary to control ocular inflammation.[40,43] Surgical intervention is an option for advanced glaucoma.[43]

TNF receptor—associated periodic syndrome

TNF receptor—associated periodic syndrome (TRAPS) is a dominantly inherited disorder that presents with prolonged periodic fevers (typically 7-21 days), erysipelas-like macules and patches overlying focal myalgia, abdominal pain, conjunctivitis, unilateral periorbital edema, and occasional lymphadenopathy.[60,61] Most patients develop skin manifestations during early childhood: warm, blanchable, erythematous macules and patches with a tendency to migrate from the trunk to distal extremities. Other morphologies include widespread reticulate erythema or annular edematous plaques.[61,62]

Mutations in the *TNFRSF1A* (tumor necrosis factor receptor superfamily, member 1A) gene coding for a TNF receptor are associated with reduced concentrations of the cytosolic, soluble form of the receptor.[63] This may be a result of “defective shedding” of the receptor from it position on the cell surface. However, some patients with TRAPS manifest normal levels of the membrane-bound TNF receptor.[64] Plasma levels of ESR, CRP, haptoglobin, fibrinogen, and ferritin may be elevated during inflammatory attacks. Histology of skin specimens reveals perivascular and interstitial infiltrate of lymphocytes and monocytes—distinct from the neutrophilic infiltrate observed in CAPS.[61]

With regard to treatment, the respective use of anakinra and tocilizumab, a humanized monoclonal anti-IL-6 receptor antibody, has produced moderate success.[65,66] Anecdotal reports of the efficacy of etanercept can be found, including improvement of amyloidosis-induced nephrotic syndrome.[67,68] However, 2 studies involving 7 and 15 patients, respectively, did not show resolution of symptoms or normalization of laboratory parameters with etanercept.[69,70] An in vitro study of cellular response to infliximab demonstrated no therapeutic benefits for patients with TRAPS. In this study, infliximab treatment paradoxically led to increased levels of IL-6, IL-8, and IL-12.[71]

Hyper-IgD syndrome

Hyper-IgD syndrome (HIDS), or mevalonate kinase deficiency, is an autosomal recessive disorder characterized by periodic fevers, arthralgia, gastrointestinal disturbances, lymphadenopathy, and splenomegaly.[72-74] Skin findings range from intermittent, painful, ill-defined erythematous macules and papules to edematous, erythematous plaques with prominent borders and occasionally central clearing (Fig 4). Common areas of involvement are the trunk and extremities but can extend to the face, neck, and buttocks. Amyloidosis can be present in severe cases.[73] Immunohistology of lesional skin reveals perivascular deposition of IgD and C3 complexes.[75]

Mutations in the *MVK* (mevalonate kinase) gene, which codes for the enzyme mevalonate kinase, disrupt cholesterol synthesis, resulting in decreased serum cholesterol levels and an episodic increase in urinary mevalonic acid.[76] Speculation about the pathogenetic role of inflammasomes has not been successful.[77,78] The characteristic feature of HIDS is elevation of serum IgD,[73,79] whereas IgA elevation is variable.[80] Ex vivo expression of TNF-alfa and IL-1ß is up-regulated during primary attacks.[81] Simvastatin dosed at 20 or 80 mg/d is efficacious for patients with HIDS, via inhibition of mevalonic acid production.[82-86] HIDS might respond to anakinra (20-100 mg/d)[86-89] or canakinumab.[74] Therapeutic trials with etanercept and adalimumab have yielded mixed results, and colchicine is generally ineffective.[82-85]

Familial Mediterranean fever syndrome

Familial Mediterranean fever (FMF) syndrome is an early-onset, autosomal recessive disorder presenting with periodic fevers, an erysipelas-like rash, synovitis, and serositis in patients of Mediterranean descent. Other reported features include Henoch-Schönlein purpura, polyarteritis nodosa, and protracted febrile myalgia.[90-100] The classic erysipeloid rash of FMF appears as tender, erythematous plaques with sharply demarcated, advancing borders localized to bilateral legs. Histopathology typically reveals dermal edema and a sparse perivascular infiltrate composed of lymphocytes, neutrophils, and histiocytes. Amyloidosis is a rare complication of FMF.[90,101]

FMF is caused by mutations in the *MEFV* (*MEditerrean FeVer*) gene, which encodes pyrin, a key protein involved in inflammasome activation.[102-104] Patients with homozygous *MEFV* mutations from Armenia, Turkey, and Arabian countries are at high risk of developing amyloidosis and should be placed on long-term prophylactic colchicine.[105] Intravenous or oral colchicine has been shown to reduce the severity of acute inflammatory episodes.[106] IL-1 inhibition represents an alternative option for the treatment of FMF.[107-111] Etanercept and sulfasalazine, respectively, may prove to be helpful, whereas thalidomide administration has yielded conflicting results.[106,112-116]

Deficiency of IL-1-RA syndrome

In 2009, Aksentijevich et al[117] described a novel autoinflammatory syndrome characterized by neonatal-onset, generalized pustulosis, periostitis, and osteomyelitis with negative bone-tissue culture findings (Fig 5). Abnormal radiographic skeletal features were commonly observed, whereas nail changes and hepatosplenomegaly were intermittent findings. Therapy with disease-modifying antirheumatic drugs and prednisone at 2 mg/kg/d did not diminish symptoms or normalize levels of acute-phase reactants.[117] Two of the 9 reported children died of multiorgan failure secondary to severe inflammation, and another died from complications of pulmonary hemosiderosis.

The new entity was named “deficiency of the interleukin-1 receptor antagonist” (DIRA) based on the discovery of homozygous mutations in the *IL1RN* (interleukin 1 receptor antagonist) gene, which encodes a circulating antagonist to IL-1ß signaling.[117] Monocytes of patients with DIRA secrete a truncated, nonfunctional version of the anti-IL-1ß

antagonist, leading to hyperresponsiveness of inflammatory cells to IL-1ß stimulation. Not surprisingly, therapeutic response to anakinra was rapid.[117]

Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature syndrome

Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature (CANDLE) syndrome, first described by Torrelo et al[118] in 2010, is characterized by generalized annular erythematous/violaceous plaques, edematous eyelids, progressive facial lipodystrophy, arthralgia, early-onset periodic fevers, and delayed physical development (Fig 6).[119] Homozygous and heterozygous mutations in the *PSMB8* (proteasome subunit ß type 8) gene have been identified.[120] Impaired proteasome function means that damaged proteins serving as signals of cellular stress are not adequately degraded, leading to chronic inflammation.[120] ESR and hepatic transaminase levels are consistently elevated in patients with CANDLE syndrome. Skin histology typically shows mature neutrophils and perivascular/interstitial infiltrates rich in myeloid cells.[118] Lipodystrophy may be a result of chronic inflammation involving adipose tissue.[121,122] Patients generally respond poorly to anakinra, intravenous immunoglobulin, infliximab, etanercept, cyclosporine, and prednisone.[118,119] Partial response to methotrexate has been reported.[118]

OTHER AUTOINFLAMMATORY SYNDROMES

Synovitis, acne, pustulosis, hyperostosis, osteitis syndrome

Synovitis, acne, pustulosis, hyperostosis, osteitis (SAPHO) syndrome is characterized by severe acne, palmoplantar pustulosis or palmoplantar pustular psoriasis, chronic inflammation of sternoclavicular and sternocostal synchondroses, osteosclerosis and hypertrophic osteitis of the vertebrae and femurs, as well as synovitis involving the elbows, knees, metacarpophalangeal, and proximal interphalangeal joints.[123-128] Sterile pustules measuring 2 to 4 mm in diameter are localized to the palms and soles, sometimes studding scaly erythematous plaques. Inflamed comedones and pustules of acne vulgaris can be found on the face and upper aspect of the trunk. Acne conglobata, acne fulminans, and acne inversa appear as suppurating cysts, nodules, abscesses, and sinus tracts.[123,129] Dermatologic and rheumatologic manifestations are not temporally related.[130]

Both *Staphylococcus aureus* and *Propionibacterium acnes* have been implicated in triggering the inflammatory attacks of SAPHO syndrome. *P acnes* has been cultured from bone specimens, a sternal osteosclerotic lesion, and intervertebral material from affected individuals.[131] This has led to the hypothesis that the inflammation may be a result of multiple failed attempts to clear the bacterium.[131] Serum levels of ESR and CRP are elevated. Successful treatment with anakinra has been reported.[132,133] TNF-alfa blockade with infliximab, etanercept, or adalimumab can be helpful for some patients.[134] Several case reports have documented response of skin manifestations to colchicine (1-1.5 mg/d), prednisone (5 mg/d), etretinate (20-50 mg/d), dapsone, and tonsillectomy.[134-142]

Schnitzler syndrome

Schnitzler syndrome is a rare disorder characterized by recurrent fevers, urticaria, arthritis, hyperostosis, osteosclerosis, and IgM gammopathy.[143-145] Skin findings consist of asymptomatic erythematous, edematous plaques with prominent borders, primarily found on the trunk and lower extremities. Lymphadenopathy, hepatomegaly, polyclonal lymphoplasmacytic infiltration of the bone marrow, and rarely, severe anemia and life-threatening thrombophilia have been reported.[146,147] Impaired renal function and Waldenstrom macroglobulinemia may occur as late sequelae.[148-153]

No genetic basis for Schnitzler syndrome has been found. Laboratory investigations reveal elevation of IL-1ß, IL-6, IL-18, ESR, and CRP levels.[154-156] Histology of lesional skin demonstrates a perivascular infiltrate consisting of lymphocytes, histiocytes, and neutrophils.[145] Immunofluorescence staining shows IgM deposits in the papillary dermis or at the basement membrane.[145] Daily administration of anakinra has provided long-term control.[157-160] Psoralen combined with ultraviolet A therapy and IL-6 blockade with tocilizumab may be effective, respectively.[161,162] Other treatments that have been used with variable success include TNF-alfa inhibition, thalidomide, colchicine, systemic steroids, and interferon alfa-2b.[163-171]

Systemic-onset juvenile idiopathic arthritis

Systemic-onset juvenile idiopathic arthritis (SOJIA) is a childhood-onset, relapsing inflammatory disorder with spiking fevers, an evanescent morbilliform rash occurring daily, and polyarticular arthritis.[172,173] Skin examination reveals diffuse erythematous macules and papules closely distributed on the trunk, the upper extremities, and less frequently, on the face.[173-176] Histology of lesional skin shows a perivascular and interstitial infiltrate composed of (in order of decreasing frequency) neutrophils, monocytes, lymphocytes, and eosinophils.[177] Neutrophils can also be visualized in perieccrine tissues and at the dermoepidermal junction.[177]

Elevated IL-6 levels, which have been found to parallel febrile episodes, suggest a possible role for IL-6 blockade therapy.[172] No genetic mutations have been found in patients with SOJIA. Anakinra and canakinumab may reduce the severity of inflammatory attacks.[178-180]

AUTOINFLAMMATION IN COMMON SKIN DISEASES

Evidence of abnormal innate immunity can be found in common dermatoses, including atopic dermatitis, contact dermatitis, psoriasis, PG, neutrophilic dermatoses, acne, alopecia areata, vitiligo, and systemic lupus erythematosus (SLE). The pathogenesis of atopic dermatitis involves complex interactions among environmental triggers (eg, *S. aureus*), disruption of the epidermal barrier, IgE dysregulation, and genetic factors, including single nucleotide polymorphisms (SNPs) and de novo mutations in the *NOD1*, *NLR*, and *CARD15* genes.[181-183] Exactly which *NLR* polymorphisms predispose patients to atopic dermatitis is a topic deserving further investigation, as *NLRP1* and *NLRP3* SNPs have been not found to be associated with atopic dermatitis.[184] Interestingly, the house dust mite allergen *Dermatophagoides pteronyssinus* has been shown to stimulate secretion of IL-1ß and IL-18

from human keratinocytes.[185] Contact sensitizers can also activate the IL-1ß-processing inflammasomes in the hypersensitive reaction of contact dermatitis.[186]

Abnormal interactions between antigen-presenting cells and T-helper lymphocytes (helper T cells type 1 and type 17) in psoriasis lead to excessive keratinocyte proliferation and elevated serum levels of TNF-alfa, interferon-α, and IL-8.[187] Recent discovery of other pathways and cytokines relevant to psoriatic inflammation has led to emerging targeted therapies (eg, IL-23, IL-17, JAK kinase signaling). A role of innate immunity in psoriasis has been suggested by increased expression of PRRs (eg, TLR-2, TLR-4, dectin-1) in patients with psoriasis compared with nonpsoriatic control subjects.[188,189] For instance, expression of TLR-2 is positively correlated with levels of danger-associated molecular patterns and the aforementioned inflammatory cytokines, respectively.[189]

Decreased IL-1ß expression and increased IL-1-RA activity can be demonstrated in active psoriatic skin.[190,191] The opposite situation has also been reported, where IL-1β expression is increased and IL-1-RA expression is decreased in lesional epidermis of patients with psoriasis.[192,193] The use of anakinra (100 mg/d) in 9 patients with psoriatic arthritis led to improvement of psoriasis in 2 patients, new plaques in 1 patient, and worsening of plaques in 4 patients.[194]

Recently, a new autoinflammatory pathway has been described for patients with an early-onset heritable form of generalized pustular psoriasis. A whole-genome scan was conducted on 9 Tunisian families, revealing homozygous missense mutations in the *IL36RN* gene in affected patients.[195] *IL36RN* encodes the IL-36-RA, which counters inflammation in an analogous manner to IL-1-RA in DIRA syndrome. Serum IL-1ß, IL-1α, IL-6, and IL-8 are elevated.[195,196] Successful therapy with anakinra has been reported for pustular psoriasis and its variant, acrodermatitis continua of Hallopeau.[196,197] These reports, along with the pustulosis characteristic of DIRA, suggest a role for innate immunity and autoinflammation in a subset of patients with pustular skin disease and a possible new avenue of treatment, particularly for patients with concurrent systemic inflammatory symptoms.

PG might in part be mediated by autoinflammation. Mutations in *PSTPIP1* are characteristic of PAPA syndrome[198,199] but have also been described in patients with PG who lack other features of PAPA syndrome.[200] Both Crohn's disease and Blau syndrome are associated with mutations that compromise function of the antibacterial factor CARD15.[201,202] Interestingly, PG is a well-recognized manifestation of Crohn's disease but to our knowledge has not been associated with Blau syndrome. One of the authors (K. S. L.) has observed 1 case of PG in a patient with CAPS. Reported response of PG to anakinra in 1 patient, who tested negative for *PSTPIP1* mutations, warrants further investigation of the role of IL-1 inhibition.[203]

Although no genetic mutations have been directly linked to Sweet syndrome, it has been found in patients with CAPS and Crohn's disease, and neutrophilic infiltrates are characteristic of many monogenic autoinflammatory diseases.[14,204,205] Anakinra has been used anecdotally in patients with neutrophilic dermatoses, but its role for these conditions remains to be determined.[206,207]

The pathogenesis of acne involves microbial triggers, aberrant keratinocyte adhesion, hormonal imbalance, and genetic factors. Predisposition to severe acne vulgaris has been linked with *TLR-2, TNF-2*, and *IL1RN* polymorphisms.[208,209] For both acne vulgaris and acne rosacea, expression of the PRR TLR-2 has been found to be up-regulated in response to microbial stimulation.[210] PRRs are crucial gateways to innate immunity, and alteration of their activity is likely to have an impact on the normal inflammatory response in the epidermis.

Granulomatous lesions of acne rosacea have been documented in a patient with a known mutation predisposing to Crohn's disease and Blau syndrome.[211] The overlap of acne conglobata, hidradenitis suppurativa, and PG also suggests a common pathway involving innate immunity, which is further implicated by the favorable response of these disorders to IL-1 inhibition.[203,212,213]

Known *MEFV* and *TNFRSF1A* mutations responsible for FMF and TRAPS, respectively, have been found in patients with Behçet disease.[214-217] Associations between patchy alopecia areata and *IL1RN*SNPs[218,219] as well as between vitiligo and *NALP1* SNPs[220] have also been reported. One report documented improvement of vitiligo after administration of infliximab.[221] However, an open-label, pilot study (N = 4) using etanercept at 50 mg weekly for 12 weeks and 25 mg weekly for an additional 4 weeks showed no repigmentation of vitiligo lesions.[222]

The past 2 decades of research have highlighted the important role of *IL-1-RA* polymorphisms in SLE.[223-226] Affected individuals with high levels of IL-1-RA tend to be at a lower risk of developing lupus nephritis compared with those possessing normal IL-1-RA levels.[227] In addition, certain *NALP1* SNPs have been associated with susceptibility to the dermatitis, arthritis, and nephritis of SLE.[228] The response of musculoskeletal and joint symptoms to anakinra, albeit transient, warrants further investigation into the potential of IL-1 blockade therapy.[229]

Our understanding of the innate immune system has expanded significantly in the last decade through the study of the rare monogenic autoinflammatory syndromes. It is also becoming clear that features of autoinflammation may affect several common dermatoses, including those previously thought to be solely autoimmune in origin (eg, SLE, vitiligo). It may be more helpful to view these syndromes and diseases as part of a spectrum of self-directed tissue injury mediated by adaptive and innate pathways. Recognition of aberrant activity of inflammasomes and other key mediators of the innate immune system opens up the possibility for new, targeted therapies for many complex and recalcitrant inflammatory dermatoses.

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Abbreviations used:

CAPS	cryopyrin-associated periodic syndrome
CARD	caspase-recruiting domain
CRP	C-reactive protein
DIRA	deficiency of the interleukin-1 receptor antagonist
ESR	erythrocyte sedimentation rate
FMF	familial Mediterranean fever
HIDS	hyper-IgD syndrome
IL	interleukin
NLR	nucleotide-binding domain leucine-rich repeat-containing
NLRP	nucleotide-binding domain leucine-rich repeat-containing protein
PAPA	pyogenic arthritis, pyoderma gangrenosum, and acne
PG	pyoderma gangrenosum
PRR	pattern recognition receptor
RA	receptor antagonist
SLE	systemic lupus erythematosus
SNPs	single nucleotide polymorphisms
TLR	Toll-like receptor
TNF	tumor necrosis factor
TRAPS	tumor necrosis factor receptor—associated periodic syndrome

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CAPSULE SUMMARY

- Autoinflammation is characterized by aberrant regulation of the innate immune system.
- Pathways mediating innate immunity, many of which are related to the interleukin-1ß-processing inflammasome, are common targets in monogenic autoinflammatory syndromes.
- Several common dermatoses have been found to be affected by features of autoinflammatory disease, leading to the possibility of new, targeted therapies.

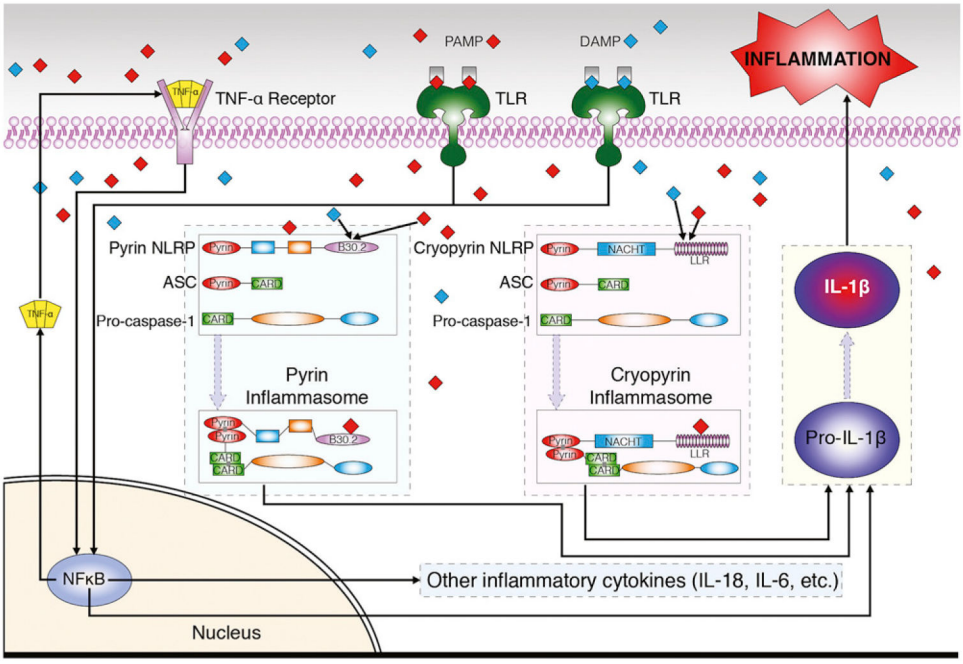

Fig 1.

Autoinflammatory syndromes. Illustration of commonly targeted pathways. *ASC*, Apoptosis-associated speck-like protein; *DAMP*, danger-associated molecular pattern; *IL*, interleukin; *NFκB*, nuclear factor kappa B; *NLRP*, nucleotide-binding domain leucine-rich repeat-containing protein; *PAMP*, pathogen-associated molecular pattern; *TLR*, Toll-like receptor, *TNF-α*, tumor necrosis factor alpha.

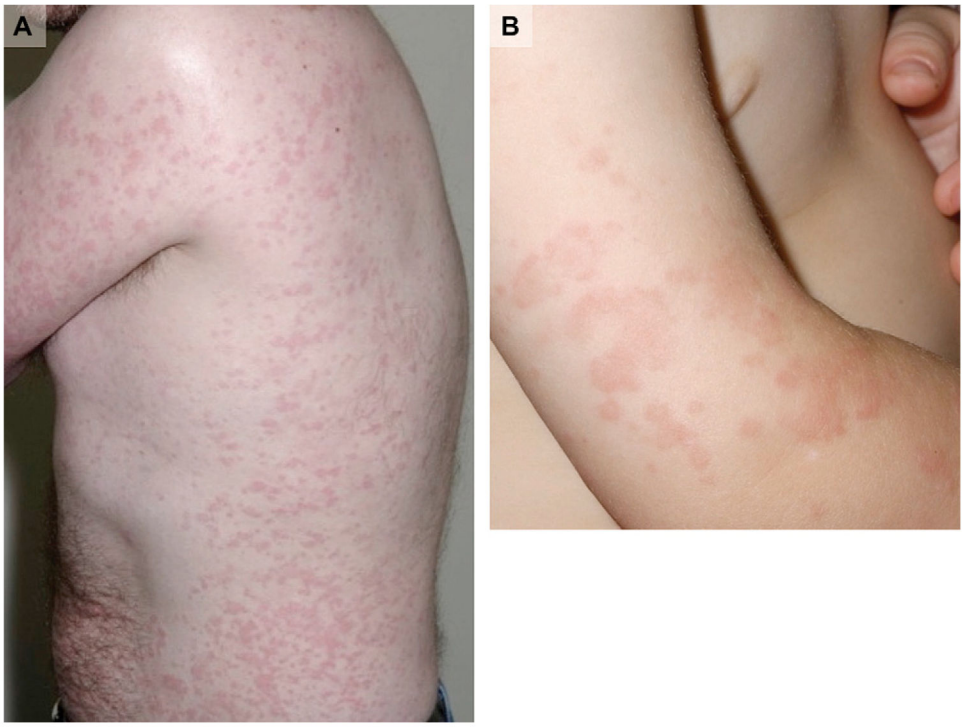

Fig 2.

Cryopyrin-associated periodic syndrome. **A**, Familial cold autoinflammatory syndrome, urticaria-like eruption in adult. **B**, Muckle-Wells syndrome, urticaria-like dermatitis in child.

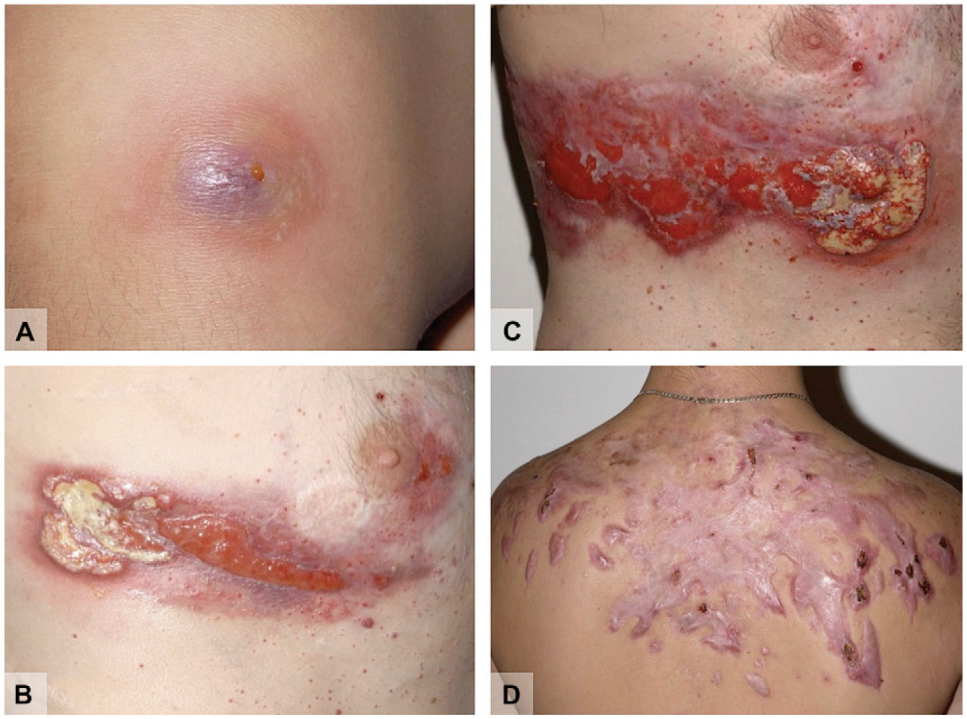

Fig 3.

Pyogenic arthritis, pyoderma gangrenosum (PG), and acne (PAPA) syndrome. **A**, PG in its early stage. **B**, Developing PG. **C**, Progression and scarring of the same PG. **D**, Extensive hypertrophic scarring at sites of severe acne involvement.

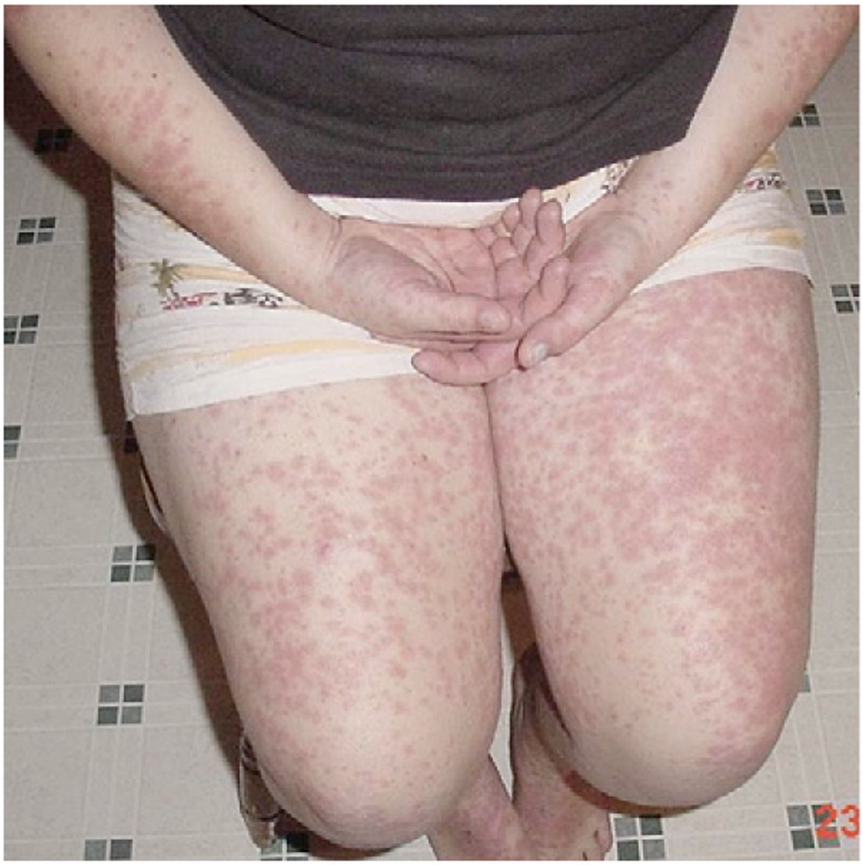

Fig 4.

Hyper-IgD syndrome. Discrete, confluent pink papules and plaques. (Used with permission of Karyl S. Barron, MD, Deputy Director, Division of Intramural Research, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Department of Health and Human Services.)

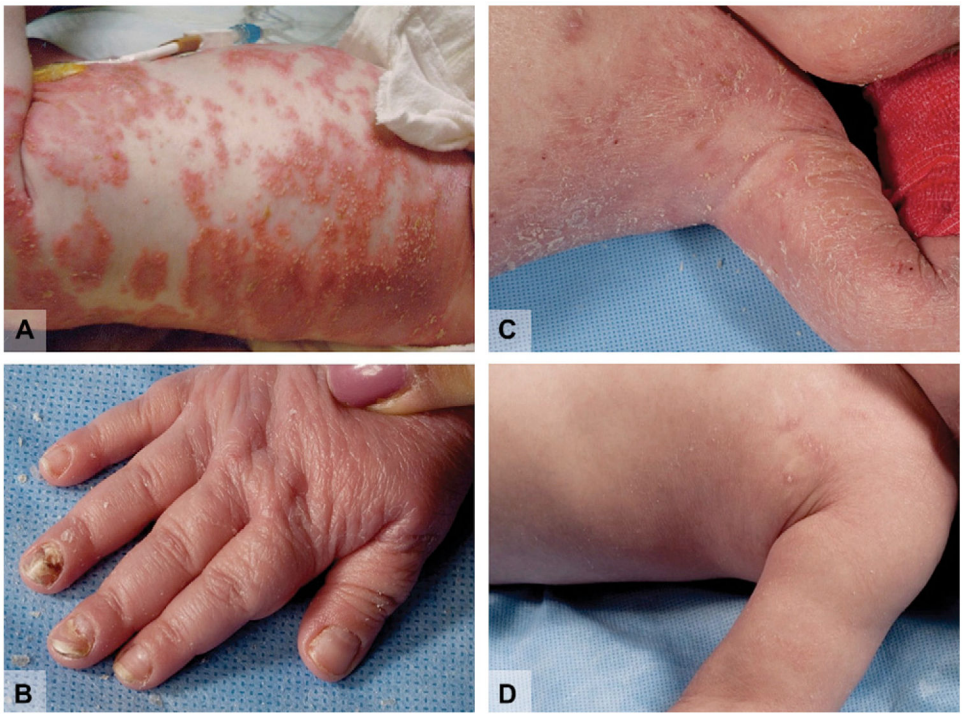

Fig 5.

Deficiency of interleukin (IL)-1 receptor antagonist (DIRA) syndrome. **A**, Generalized pustulosis. **B**, Nail dystrophy. **C**, Patient with DIRA before IL-1 blockade therapy. **D**, Same child after 5-day course of subcutaneous anakinra 100 mg/d.

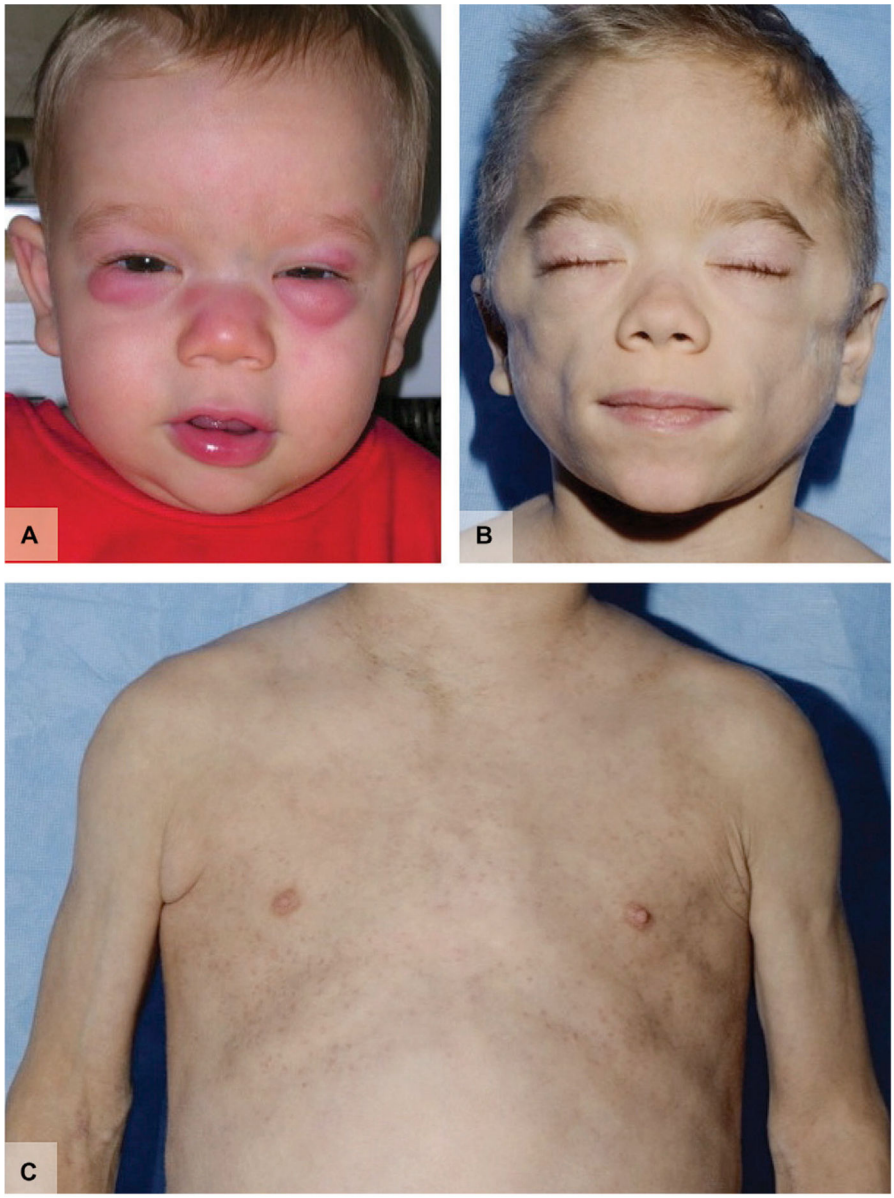

Fig 6.

Chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature (CANDLE) syndrome. **A**, Violaceous, edematous eyelids. **B**, Facial lipodystrophy of same patient several years later. **C**, Lipoatrophy of the torso.

Table I.

Clinical features, molecular basis, histologic and laboratory findings of autoinflammatory syndromes

Disease	Skin and nail findings	Systemic manifestations	Length of fevers	Histology	*Gene*/protein	Laboratory findings
CAPS (AD)	Urticaria-like eruptions	Fevers, distal arthralgia, neurologic symptoms, eye disease, amyloidosis	Daily	Perivascular, interstitial, or perieccrine neutrophilic infiltrate	*NLRP3/CIAS1* Cryopyrin	Leukocyte count (↑), CRP, ESR, and SAA (↑), creatinine (↑), IL-1ß (↑)
PAPA syndrome (AD)	Pyoderma gangrenosum, acne	Pyogenic arthritis	Variable	–	*PSTPIP1* PSTPIP1	CRP and ESR (↑), gammaglobulin (↓); IL-1ß and TNF-alfa (↑); joint culture (often –)
Blau syndrome (AD)	Densely populated, erythematous papular eruptions	Fevers, polyarthritis (±camptodactyly), eye disorders;granulomatous kidney, liver, lung, and CNS disease	Variable	Noncaseating granulomata	*CARD15* CARD15	ESR (↑), ACE (↑), IgA and IgG (↑); IL-1ß (↑)
TRAPS (AD)	Erysipelas-like macules and patches overlying myalgia	Fevers, focal myalgia, abdominal pain, conjunctivitis, periorbital edema, LAD	7-21 d	Perivascular and interstitial lymphocytic infiltrate	*TNFRSF1A* TNF receptor	CRP and ESR (↑), haptoglobin, fibrinogen, and ferritin (↑)
HIDS (AR)	Intermittent erythematous macules or morbilliform papular eruptions	Fevers, arthralgia, severe abdominal pain, LAD, splenomegaly, amyloidosis	1-2 d	Perivascular IgD and C3 complex deposits	*MVK* Mevalonate kinase	IgD and IgA (↑), IL-1ß and TNF-alfa (↑);urine mevalonic acid (↑)
FMF syndrome (AR)	Acral erysipelas-like erythema and purpuric lesions	Periodic fevers, synovitis, serositis, HSP, polyarteritis nodosa, protracted febrile myalgia, amyloidosis	1-3 d	Perivascular lymphocytes, neutrophils, and histiocytes	*MEFV* Pyrin	CRP and ESR (↑), SAA (↑), creatinine (↑); IL-1ß and TNF-alfa (↑)
DIRA syndrome (likely AR)	Generalized pustulosis, nail changes (±)	Periostitis, osteomyelitis, hepatosplenomegaly, radiographic skeletal abnormalities	Variable	Neutrophilic infiltrate with hyperkeratosis, follicular pustules	*IL1RN* IL-1 antagonist	IL-1ß (↑);bone-tissue culture (often –)
CANDLE syndrome (likely AR)	Annular violaceous plaques	Fevers, edematous eyelids, progressive facial lipodystrophy, arthralgia, and delayed physical development	Daily	Perivascular and interstitial neutrophilic infiltrate	*PSMB8* PSMB8	ESR and hepatic transaminases (↑)
SAPHO syndrome	Palmoplantar pustulosis (±psoriasis), severe acne	Chronic synchondrosis inflammation, osteosclerosis, hypertrophic osteitis, and synovitis	Variable	–	–	CRP and ESR (↑); IL-1ß and TNF-alfa (↑); skin culture for *Staphylococcus aureus* and *Propionibacterium acnes* (often +)
Schnitzler syndrome	Nonpruritic urticarial plaques	Fevers, arthritis, hyperostosis, osteosclerosis, IgM gammopathy	–	Perivascular lymphocytes, histiocytes, and neutrophils	–	CRP and ESR (↑); IL-1ß, IL-6, and IL-18 (↑)
SOJIA	Morbilliform erythematous macules and papules	Spiking fevers, polyarticular arthritis	Daily	Perivascular and interstitial neutrophils and lymphocytes	–	IL-1ß, IL-6, and IL-18 (↑)

ACE, Angiotensin-converting enzyme; *AD*, autosomal dominant; *AR*, autosomal recessive; *CANDLE*, chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature; *CAPS*, cryopyrin-associated periodic syndrome; *CARD*, caspase-recruiting domain; *CARD15*, caspase-recruiting domain 15; *CIAS1*, cold-induced autoinflammatory syndrome 1; *CNS*, central nervous system; *CRP*, C-reactive protein; *DIRA*, deficiency of interleukin-1 receptor antagonist; *ESR*, erythrocyte sedimentation rate; *FMF*, familial Mediterranean fever; *HIDS*, hyper-IgD syndrome; *HSP*, Henoch-Schönlein purpura; *IL*, interleukin; *IL1RN*, interleukin 1 receptor antagonist; *LAD*, lymphadenopathy; *MEFV*, mediterrean fever; *MVK*, mevalonate kinase; *NLRP*, nucleotide-binding domain leucine-rich repeat-containing protein; *NLRP3*, nucleotide-binding domain leucine-rich repeat-containing protein 3; *PAPA*, pyogenic arthritis, pyoderma gangrenosum, and acne; *PSMB8*, proteasome subunit ß type 8;

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PSTPIP1, proline-serine-threonine phosphatase interacting protein 1; *SAA*, serum amyloid A; *SAPHO*, synovitis, acne, pustulosis, hyperostosis, and osteitis; *SOJIA*, systemic-onset juvenile idiopathic arthritis; *TNF*, tumor necrosis factor; *TNFRSF1A*, tumor necrosis factor receptor superfamily, member 1A; *TRAPS*, tumor necrosis factor receptor—associated periodic syndrome.

Table II.

Reported therapies for treatment of autoinflammatory disease

Treatment (route)	Anakinra, canakinumab, and rilonacept (all SC)	Infliximab (IV), etanercept and adalimumab (SC)	Prednisone (PO)	Colchicine (PO/IV)	Thalidomide (PO)	Simvastatin (PO)	Tocilizumab (IV)	Other
Mechanism	IL-1 inhibition	TNF inhibition	Decreases inflammation	Inhibits leukocyte migration	Down-regulates leukocyte migration	HMG-CoA reductase inhibitor	IL-6 receptor antagonist	
Adverse effects	Injection-site rxn, infections, URI, HA, nausea diarrhea, neutropenia	Injection-site rxn, infusion rxn (infliximab), infection, URI, abdominal pain, nausea, HA	Adrenal suppression, psychosis, insomnia, vertigo, acne, osteoporosis, myopathy	Diarrhea, nausea, vomiting	Rash, HA, polyneuropathy	(↑)CPK, (↑) transaminases, constipation, URI, flatulence	URI, HA, gastritis, HTN, (↑)ALT, (↑)lipids, (↓)neutrophils and platelets	
CAPS	-Anakinra 1-10 mg/kg/d up to 100 mg/d -Canakinumab 150 mg/8 wk -Rilonacept 300-320 mg loading, then 100-320 mg/wk							
PAPA syndrome	Anakinra 100 mg/d	-Infliximab 4 mg/kg ×4 doses -Etanercept 25 mg BIW	2 mg/kg/d up to 60 mg/d					-IVIG 400 mg/kg -Isotretinoin PO 0.3-0.5 mg/kg/d
Blau syndrome		-Infliximab 10 mg/kg/8 wk -Combined infliximab 5 mg/kg/6 wk, prednisolone 5 mg/d, and methotrexate 15.7 mg/wk	-0.1 mg/kg up to 60 mg/d -0.5-2.5 mg/kg/2 d		2 mg/kg/d up to 75 mg/d			-Azithromycin PO 10 mg/kg TIW -Eye surgery for advanced glaucoma
TRAPS	Anakinra 1.5 mg/kg/d	Etanercept 0.4 mg/kg up to 25 mg BIW	60 mg/d				8 mg/kg/mo	
HIDS	-Anakinra 1-2 mg/kg/d -Canakinumab	Etanercept 0.8 mg/kg/wk				20-80 mg/d		
FMF syndrome	-Anakinra 100 mg/1-2 d -Canakinumab 2 mg/kg/8 wk	Etanercept 0.8 mg/kg up to 25 mg BIW		-PO 1-20 mg/d -IV 1 mg/wk				Sulfasalazine PO 50 mg/kg/d
DIRA syndrome	Anakinra 1-3 mg/kg/d							
CANDLE syndrome								Methotrexate IV 10 mg/m^2/wk and PO 0.3 mg/kg/wk
SAPHO syndrome	Anakinra 100 mg/d		5 mg/d	1-1.5 mg/d				Etretinate PO 20-50 mg/d

Treatment (route)	Anakinra, canakinumab, and rilonacept (all SC)	Infliximab (IV), etanercept and adalimumab (SC)	Prednisone (PO)	Colchicine (PO/IV)	Thalidomide (PO)	Simvastatin (PO)	Tocilizumab (IV)	Other
Schnitzler syndrome	-Anakinra 100 mg/d -Combined anakinra 100 mg/d and methotrexate 5 mg/wk	Adalimumab 40 mg/2 wk	Combined prednisone 2 mg/d and anakinra 100 mg/d		100 mg/d		8 mg/kg/mo	-PUVA TIW -Rituximab 1 g/2 wk -Interferon alfa-2b 3 MIU TIW
SOJIA syndrome	-Anakinra 1-2 mg/kg/d up to 100 mg/d -Canakinumab 4 mg/kg/4 wk							

ALT, Alanine aminotransferase; *BIW*, biweekly; *CANDLE*, chronic atypical neutrophilic dermatitis with lipodystrophy and elevated temperature; *CAPS*, cryopyrin-associated periodic syndrome; *CPK*, creatine phosphokinase; *DIRA*, deficiency of interleukin-1 receptor antagonist; *FMF*, familial Mediterranean fever; *HA*, headache; *HIDS*, hyper-IgD syndrome; *HMG-CoA*, 3-hydroxy-3-methylglutaryl coenzyme A; *HTN*, hypertension; *IL*, interleukin; *IV*, intravenous; *IVIG*, intravenous immunoglobulin; *MIU*, million units; *PAPA*, pyogenic arthritis, pyoderma gangrenosum, and acne; *PO*, per os (by mouth); *PUVA*, psoralen plus ultraviolet A; *rxn*, reaction; *SAPHO*, synovitis, acne, pustulosis, hyperostosis, and osteitis; *SC*, subcutaneous; *SOJIA*, systemic-onset juvenile idiopathic arthritis; *TIW*, 3 times a week; *TNF*, tumor necrosis factor; *TRAPS*, tumor necrosis factor receptor—associated periodic syndrome; *URI*, upper respiratory tract infection.

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