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Targeting cytokines to treat autoinflammatory diseases

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ABSTRACT

Autoinflammatory diseases are rare group of conditions manifested by recurrent fevers, systemic inflammation, and dysfunctions of the innate immune system. These conditions are characterized by overproduction or lack of inhibition of various cytokines, and the advent of biologic drugs that block specific cytokines involved in these conditions has revolutionized their treatment. In this review, I will discuss the most common autoinflammatory conditions of adulthood including familial Mediterranean fever (FMF), cryopyrin-associated periodic syndrome (CAPS), mevalonate kinase deficiency/hyperimmunoglobulinemia D Syndrome (MKD/HIDS), TNF receptor-associated autoinflammatory syndrome (TRAPS), and systemic juvenile idiopathic arthritis/adult-onset Still's disease (SJIA/AOSD). I will discuss how IL-1, IL-6, IL-18, and TNF play pathogenic roles in these conditions and will review the evidence behind cytokine blockade for these diseases. Throughout the paper, I will reflect on gaps in knowledge of autoinflammatory diseases and will highlight the latest advances and newest drugs in development.

1. Introduction

Autoinflammatory diseases are a group of rare conditions manifested by recurrent fevers and systemic inflammation. Unlike autoimmune conditions, which are characterized by dysfunctions of the humoral immune system that results in loss of tolerance and development of autoantibodies, autoinflammatory diseases arise from errors in the innate immune system and lack high-titer antibodies or antigen-specific T cells.

The concept of autoinflammation was first described in 1999 after the discovery of the gene that causes TNF receptor-associated autoinflammatory syndrome (TRAPS) [1]. Since then, dozens of new diseases have been identified that result from innate immune system dysfunction leading to autoinflammation [2]. At the same time, conditions that have been known for over 100 years, such as Still's disease [3] and familial Mediterranean fever [4] are now categorized under the autoinflammatory umbrella. An understanding of the pathophysiology of these rare illnesses has provided insights into the inner workings of the immune system and inflammation, and are now implicated in much more common disorders including gout, type 2 diabetes, multiple sclerosis, and coronary artery disease [5].

Traditionally, the term “autoinflammatory disease” referred to a group of monogenic periodic fever syndromes that present with recurring episodes of fever and stereotypical symptoms. However, as our understanding of the molecular pathways of these conditions has advanced, the group of autoinflammatory diseases has evolved to include diseases in which the innate immune system plays the primary pathogenic role, even when fever is absent.

In this review, I will address the most common autoinflammatory diseases of adulthood (Table 1) and the central cytokines involved in their pathogenesis, and will discuss how cytokine blockade has revolutionized their treatment (Table 2).

2. The cytokines

2.1. Interleukin-1

The interleukin-1 (IL-1) family is composed of several cytokines, many of which are involved in autoinflammatory diseases including IL-1α, IL-1β, IL-1 receptor antagonist (IL-1Ra), IL-18, IL-36, and IL-36 receptor antagonist. These cytokines are critical to the function of the immune system, especially in protecting the host against infections. Interleukin-1 cytokines are tightly regulated at various levels, including at production, maturation, receptor binding, post-receptor signaling,

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Table 1
Autoinflammatory diseases, their phenotypes, mechanism of disease, and cytokine blockers used in their treatment. FCAS: familial cold autoinflammatory syndrome, MWS: Muckle-Wells syndrome, NOMID: neonatal onset multisystem inflammatory disease.

Disease	Gene/protein	Phenotype	Mechanism	Treatment options with cytokine blockade
Familial Mediterranean fever (FMF)	*MEFV*/pyrin	Fever and serositis lasting 1–3 days.	Mutations in pyrin prevents its phosphorylation, leading to constitutive activation of the inflammasome	Anakinra, canakinumab, rilonacept
Cryopyrin-associated periodic syndrome (CAPS)	*NLRP3*/NLRP3	FCAS: Fever, urticarial-like rash, arthralgias triggered by cold exposure. MWS: FCAS symptoms but may be more chronic, complicated by amyloid, hearing loss. NOMID: neonatal presentation with persistent rash, fevers, aseptic meningitis, developmental delays, frontal bossing, arthropathy	Gain-of-function mutations in *NLRP3* cause excessive release of IL-1β and systemic inflammation	Anakinra, rilonacept, canakinumab
Mevalonate kinase deficiency (MKD) / Hyperimmunoglobulinemia D Syndrome (HIDS)	*MVK*/mevalonate kinase	Recurrent fevers typically lasting 4 days manifested by lymphadenopathy, abdominal pain, diarrhea, arthralgias, vomiting, oral ulcers	Defects in *MVK* lead to low levels of geranylgeranyl pyrophosphate, RhoA inactivation, leading to activation of the pyrin inflammasome	Anakinra, canakinumab, etanercept
TNF receptor-associated autoinflammatory syndrome (TRAPS)	*TNFRSF1A*/TNFR1	Recurrent fevers lasting 1-2 weeks associated with limb pain, abdominal pain, rash, eye manifestations	Mutations affect receptor folding and trafficking, leading to intracellular accumulation and stress	Etanercept, anakinra, canakinumab, tocilizumab
Systemic juvenile idiopathic arthritis (SJIA) / Adult-onset Still's disease (AOSD)	Polygenic	Spiking fevers, arthritis, evanescent rash, hepatosplenomegaly, lymphadenopathy, leukocytosis	Activation of neutrophils and macrophages, as well as Th17 cells	Anakinra, canakinumab, tocilizumab, tadekinig alpha

and through the presence of naturally-occurring inhibitors [6]. Genetic mutations that result in overproduction of IL-1 or absence of receptor antagonists lead to autoinflammatory disorders.

Pro-IL-1α is an active molecule that is constitutively present in most cells and works as a transcription factor due to the presence of a nuclear localization sequence. During necrosis, pro-IL-1α is released to the extracellular space and binds to and activates the interleukin-1 receptor type I (IL-1R1) without the need for further processing [7]. Thus, pro-IL-1α works as an alarmin, a molecule that serves as an early warning signal to activate the innate and adaptive immune systems [8]. Binding of pro-IL-1α to IL-1R1 leads to the production of IL-1β and a more sustained immune response.

IL-1β is the most potent endogenous pyrogen: it enhances leukocyte migration, activates the hypothalamus-pituitary-adrenal axis, aand prolongs the lifespan and stimulates effector function of neutrophils and macrophages [9]. IL-1β release requires two signals: the first, usually provided by exogenous triggers, leads to transcription of pro-IL-1b, an inert pro-peptide [10]. The second signal is triggered by an intracellular sensor that activates the inflammasome to cleave of pro-IL-1b into its active form by caspase-1. Unlike IL-1α, IL-1β is not present in healthy cells.

Inactive pro-IL1b accumulates in the cytoplasm until it is processed by the inflammasome [11]. Activation of the inflammasome is the rate-limiting step of processing and secreting the inactive pro-IL1b into the active molecule. Inflammasomes are groups of large, intracellular protein complexes that have sensor proteins (e.g., NLRP3), effector proteins (e.g., caspase-1), and an adaptor protein (e.g., Apoptosis-associated speck-like protein containing a caspase recruitment domain, or ASC) [11]. Danger-associated molecular patterns (DAMPs) or pathogen-associated molecular patterns (PAMPs) lead to activation of the inflammasome. The NLRP3 inflammasome, for instance, is activated by a variety of signals including ATP, toxins, crystals, nucleic acids, fungal, bacterial, viral pathogens, and cholesterol, all of which induce similar downstream events [12]. NLRP3 senses these molecules and causes ASC to form prion-like filaments, which interact with pro-caspase-1 to produce its own prion-like filaments that induce autoproteolytic maturation of pro-caspase-1 into caspase-1. This leads to cleavage of pro-IL-1b and pro-IL-18 into IL-1β and IL-18, and to their secretion outside the cell.

IL-1α, IL-1β, and IL-1Ra bind to IL-1R1, which is present on the cell surface of all nucleated cells. When IL-1α or IL-1β binds, a structural change occurs which allows the binding of IL-1 receptor type 3 (IL-1R3, previously known as IL-1R accessory protein) to IL-1R1, approximating their Toll/interleukin-1 receptor (TIR) domains. This allows MyD88 to bind to the TIR, triggering a kinase cascade that produces inflammatory signals and activates NFkB [13]. In contrast, when IL-1Ra binds to the IL-1R1 receptor, it does not induce a conformational change, and thus signal transduction does not occur [6].

Interestingly, the intracellular TIR domain of the IL-1R1 is homologous to the intracellular domains of Toll-like receptors (TLRs), and thus activation of TLRs and IL-1R1 lead to similar intracellular responses, including induction of cyclooxygenase type 2, expression of adhesion molecules, synthesis of nitric oxide, augment antigen recognition, activate lymphocyte function, and production of cytokines and chemokines [13].

2.2. IL-1 inhibitors

2.2.1. Anakinra

In 1987, an inhibitor was isolated from the urine of febrile patients which prevented binding of IL-1 to its receptor [14]. The inhibitor was purified and found to be a pure IL-1 receptor antagonist (IL-1Ra) [15]. It blocks both IL-1α and IL-1β from binding to the IL1-R1, and it is coded by the gene IL1RN.

Recombinant human IL-1Ra (rhIL-1Ra, now called anakinra) was first used in the treatment of sepsis syndrome and septic shock, as it was

Table 2
Cytokine inhibitors, their structures, mechanisms of action, methods of administration, and uses for various diseases. RA: rheumatoid arthritis, NOMID: neonatal onset multisystem inflammatory disease, CAPS: cryopyrin-associated periodic syndrome, SJIA/AOSD: systemic juvenile idiopathic arthritis/adult onset Still's disease, FMF: Familial Mediterranean fever, TRAPS: TNF receptor-associated autoinflammatory syndrome, MKD/HIDS: Mevalonate kinase deficiency / Hyperimmunoglobulinemia D Syndrome, EU: European Union, AS: ankylosing spondylitis, CD: Crohn disease, PP: plaque psoriasis, PsA: psoriatic arthritis, UC: ulcerative colitis, GCA: giant cell arteritis, NLRC4-MAS: NLRC4-Related Macrophage Activation Syndrome, XIAP: X-linked inhibitor of apoptosis, HLH: hemophagocytic lymphohistiocytosis.

Drug	Structure	How it works	Administration	FDA-approved uses	Use in autoinflammatory diseases
IL-1 inhibitors					
Anakinra	Recombinant human IL-1 receptor antagonist	Blocks IL-1α and IL-1β from binding to the IL-R1 receptor	Daily subcutaneous injection	RA, NOMID In EU: CAPS, SJIA/AOSD	CAPS, FMF, MKD/HIDS, TRAPS, SJIA/AOSD
Canakinumab	Human monoclonal IL-1β antibody	Binds to IL-1β and blocks its binding to IL-1R1 receptor	Subcutaneous injections every 4–8 weeks	CAPS, colchicine-resistant FMF, HIDS/MKD, TRAPS, SJIA. In EU also for: AOSD, gouty arthritis	CAPS, FMF, MKD/HIDS, TRAPS, SJIA/AOSD
Rilonacept	Human IgG1 FC antibody (IL-1 Trap), composed of a fusion of the Fc of IgG1 and the extracellular domains of IL-1R1 and IL-1R3 receptors	Soluble decoy receptor that binds to IL-1α, IL-1β, and IL-1Ra, preventing their interaction with cell surface receptors	Weekly subcutaneous injections	CAPS	CAPS, FMF
IL-6 inhibitors					
Tocilizumab and sarilumab	Humanized monoclonal antibodies against IL-6 receptor	Bind to the soluble and membrane-bound IL-6 receptors, preventing active IL-6 from binding	Tocilizumab: subcutaneous injection every 1–2 weeks or IV infusion every 4 weeks. Sarilumab: subcutaneous injection every 2 weeks.	Tocilizumab: RA, GCA, JIA, SJIA, cytokine release syndrome from CAR T-cell treatment. Sarilumab: RA	SJIA, TRAPS
Tofacitinib	Selective inhibitor of JAK1 and JAK3	Binds to the ATP binding site in JAK, inhibiting its phosphorylation and activation, leading to downregulation of IL-6	Oral tablet once or twice daily	RA, PsA, UC	Interferonopathies
IL-18 inhibitors					
Tadekinig alfa	Recombinant human IL-18BP	Binds to IL-18 and inhibits its function	Subcutaneous injection three times per week	None. It has Breakthrough Therapy Designation for treatment of NLRC4-MAS and XIAP deficiency, and orphan designation for the treatment of HLH. In EU, it has orphan designation for the treatment of HLH	NLRC4-MAS, XIAP deficiency, HLH, AOSD
TNF Inhibitors					
Etanercept	Fusion protein combining two soluble TNFR2 with the Fc portion of IgG1	Binds to TNF-α and TNF-b, preventing their binding to their receptors	Subcutaneous injections weekly	AS, PsA, RA, PP	MKD/HIDS, TRAPS
Infliximab	Chimeric anti-TNF-α antibody with mouse origin Fv and human FC	Bind to and neutralize cell-bound and soluble TNFa	Intravenous infusions every 4–8 weeks	AS, CD, PP, PsA, RA, UC	None
Adalimumab Golimumab	Fully human monoclonal antibodies against TNF-α	Bind to and neutralize cell-bound and soluble TNFa	Adalimumab: subcutaneous injections every 2 weeks. Golimumab: IV infusions every 8 weeks or monthly subcutaneous injections	ADA: AS, CD, hidradenitis suppurativa, PP, PsA, RA, UC, uveitis. GOL: AS, PsA, RA, UC	None
Certolizumab pegol	Recombinant, humanized antibody Fab' fragment against TNF-α conjugated to polyethylene glycol	Binds to and neutralizes TNF-α. Lacking the Fc region, It does not induce complement activation or form immune complexes and does not cross the placenta.	Subcutaneous injections every 2–4 weeks.	AS, CD, PP, PsA, RA	None

shown that IL-1 was a mediator of the pathogenesis of these syndromes. A randomized, double-blind, placebo-controlled trial of the use of rhIL-1RA did not show a survival benefit as compared to placebo [16]. However, a recent re-analysis of the original data found that anakinra improved survival in a subset of patients with features of the macrophage activation syndrome (defined as the presence of hepatobiliary dysfunction and disseminated intravascular coagulation) [17].

Anakinra was then tested in patients with rheumatoid arthritis since IL-1 was the first cytokine detected in synovial fluid of patients with RA [18]. The study found that anakinra was effective and safe in the treatment of RA [19], and it led to the FDA approval of anakinra for the treatment of moderately to severely active rheumatoid arthritis.

Anakinra was first attempted to treat autoinflammatory diseases after it was found that patients with NOMID had markedly elevated levels of IL-1β in Western analysis of their monocyte lysates [20]. Treatment with anakinra led to marked improvement in clinical and laboratory manifestations of the disease. Since then, anakinra has been used successfully in many autoinflammatory disorders with overproduction of IL-1, and it is sometimes used in patients with undefined inflammatory syndromes to test whether autoinflammation may play a role in the pathogenesis of their disease [21].

Anakinra is FDA-approved for the treatment of RA and the NOMID form of CAPS in children older than 8 months. In the EU, anakinra is approved for RA, all forms of CAPS (FCAS, Muckle-Wells, and CINCA/NOMID) and SJIA/AOSD in children and adults. It is administered via daily subcutaneous injections.

2.2.2. Canakinumab

Canakinumab is a human monoclonal antihuman IL-1β antibody of the immunoglobin G1/k isotype. It binds to human IL-1β and blocks its binding to IL-1 receptors [22]. It does not block IL-1α. In the US, Canakinumab is FDA approved for the treatment of CAPS, FMF, HIDS/MKD, TRAPS, and SJIA. In Europe, it is also approved for the treatment of adults with AOSD and gouty arthritis in patients for who cannot tolerate or do not respond to NSAIDs, colchicine, and steroids. Because of its long half-life, it is typically administered every 4–8 weeks as a subcutaneous injection.

2.2.3. Rilonacept

Rilonacept is a human IgG1 Fc antibody (IL-1 Trap) that is composed of a fusion of the constant region of IgG1 (IgG1 Fc) and the extracellular domains of IL-1R1 and IL-1R3 [23]. Thus, it works as a soluble decoy receptor that binds to IL-1α, IL-1β, and IL-1Ra and prevents the interaction of these cytokines with cell surface receptors. Rilonacept is approved in the US for treatment of CAPS in children (ages 12 or older) and adults. It is usually administered as weekly subcutaneous injections.

2.2.4. Others

Other IL-1 blockers that are in clinical trials but not yet FDA approved include gevokizumab, a monoclonal antibody against IL-1β, similar to canakinumab, as well as belnacasan (VX-765), a caspase-1 inhibitor.

2.3. Interleukin-18

IL-18 is part of the interleukin-1 family. Like IL-1β, IL-18 is produced as a pro-peptide that needs to be cleaved by caspase-1 after activation of the inflammasome. Unlike IL-1β, which is not found in healthy cells, the IL-18 precursor is present and constitutively expressed in monocytes and epithelial cells of healthy subjects [13]. IL-18 binds to the interleukin-1 receptor type 5 (IL-1R5) with low affinity. However, in cells that expressed the co-receptor interleukin-1 receptor type 7 (IL-1R7), a high-affinity complex is formed, which is then able to approximate TIR domains and follow a cascade similar to that of IL-1.

Interestingly, in the presence of IL-12 or IL-15, which increase the expression of IL-1R7, IL-18 plays a role in the Th1 paradigm and induces interferon-gamma [13]. In the absence of IL-12 and IL-15, IL-18 participates in responses similar to that of IL-1 including increasing cell adhesion molecules and nitric oxide synthesis. However, unlike 1 L-1, TNF, or IL-6, IL-18 does not induce fever.

IL-18 is negatively regulated by IL-18 binding protein (IL-18BP) which neutralizes IL-18 and prevents binding to its receptor. Interferon-gamma increases gene expression and synthesis of IL-18BP, thus serving as a negative feedback loop [13].

2.3.1. Interleukin-18 inhibitors

Tadekinig alfa is a recombinant human IL-18BP. It received Breakthrough Therapy Designation from the FDA for treatment of monogenic IL-18 associated autoinflammatory conditions such as NLRC4 and XIAP deficiency, as well as orphan designation status for the treatment of hemophagocytic lymphohistiocytosis (HLH). In the European Union, it has received orphan designation for the treatment of HLH. A current clinical trial is exploring the use of tadekinig alfa in patients with NLRC4 mutations and XIAP deficiency (ClinicalTrials.gov Identifier: NCT03113760). It is administered via subcutaneous injections three times per week.

2.4. Interleukin-6

Interleukin-6 is an interesting molecule in that it has both inflammatory and anti-inflammatory properties which are exhibited depending on the context in which it IL-6 secreted. IL-6 binds to the membrane-bound IL-6 receptor (mIL-6R), which leads to association with a second protein, gp130, a 130 kDa transmembrane protein that dimerizes and initiates signaling [24]. The IL-6 receptor is expressed in only a few cells, including hepatocytes, megakaryocytes, and some leukocytes and epithelial cells [25]. Unlike the mIL-6R, gp130 is ubiquitously expressed in most cells.

gp130 activates cytoplasmic Janus-activated tyrosine kinases (JAKs), which drive activation of STAT1 and STAT3 and produce downstream signaling through the Ras/mitogen-activated protein kinase cascade (MAPK) pathways [25]. This is termed the “classic” signaling of IL-6. In the liver, this IL-6 pathway drives the acute phase response including expression of CRP, serum amyloid A, fibrinogen, haptoglobin, and hepcidin.

Despite the limited cell types that express the IL-6R, IL-6 has pleiotropic effects across many different organs. How IL-6 exerts influence in cells that do not express its receptor was a puzzle until it was found that IL-6 also binds to a soluble IL-6R (sIL-6R), and that this IL-6/sIL-6R complex can associate with membrane-bound gp130 (found in most cells) to induce dimerization and intracellular signaling [24]. This type of signaling is referred to as “*trans*-signaling.”

sIL-6R is shed from the cell surface through proteolysis with ADAM-17 as well as through alternative mRNA splicing of IL-6R [25]. The IL-6/sIL-6R complex then signals through *trans*-signaling and propagates the inflammatory response by encouraging leukocyte activation and survival as well as affecting tissue permeability.

Classic signaling, in contrast, is thought to be anti-inflammatory and promotes immune homeostasis, including maintenance of the epithelial barrier, hematopoiesis, and glucose and lipid metabolism [25].

In the blood, soluble gp130 (sgp130) works to neutralize the IL-6/sIL-6R and thus acts as a buffer in the blood, limiting *trans*-signaling [24].

2.4.1. IL-6 inhibitors

Currently, two FDA-approved drugs block IL-6: tocilizumab and sarilumab are humanized monoclonal antibodies against IL-6R. They bind to the IL-6 binding site of both sIL-6R and mIL-6R and thus block both classical and *trans*-signaling pathways. Tocilizumab is FDA-approved for the treatment of rheumatoid arthritis, giant cell arteritis, JIA, and SJIA, as well as for the cytokine release syndrome induced by

chimeric antigen receptor (CAR) T-cell. It is typically administered as a subcutaneous injection every 1–2 weeks, or as an intravenous infusion every 4 weeks. Sarilumab was recently approved for the treatment of RA and is administered via subcutaneous injection every 2 weeks.

In clinical trials there are other drugs that block IL-6 in various ways, including an engineered sgp130FC fusion protein (FE999301), antibodies against IL-6 (olokizumab, sirilumab, clazakizumab), a neutralizing sIL-6R nanobody, and an avimer (avidity multimer) that comprises small protein domains with binding regions for IL-6 [25].

Tofacitinib is a potent, selective inhibitor that preferentially inhibits JAK1 and JAK3 and affects downstream intracellular signaling of various cytokines, including that of IL-6 [26], thus it is sometimes considered an IL-6 blocker. It is FDA-approved for psoriatic arthritis, rheumatoid arthritis, and ulcerative colitis and is administered as an oral pill once or twice daily. Tofacitinib also blocks intracellular signaling of interferon and has been effective in the treatment of interferonopathies [27], a group of autoinflammatory diseases with excess interferon production.

2.5. Tumor necrosis factor

Tumor necrosis factor (TNF) and their receptors regulate cellular activation and apoptosis. TNF was first discovered by Coley in 1894 when he induced necrosis of human tumors by injecting patients with bacterial filtrates [28]. In 1975, Carswell described this human factor as TNF.

TNF-α is an inflammatory cytokine that promotes cellular activation and migration of leukocytes to inflammatory sites. The gene for TNF-α is located on chromosome 6, and its transcription is induced by NF-κB. Two forms of TNF-α exist, a membrane-bound and a soluble homotrimeric form. TNF-α-converting enzyme (TACE), a metalloproteinase, cleaves the membrane-bound protein to release the soluble molecule. Membrane-bound TNFa (mTNF-α) can bind to and stimulate TNF receptors on other cells and may produce slightly different effects than the soluble form of TNF [29]. TNF-α is mainly produced by monocytes and macrophages. TNF-b is a closely related molecule, also known as lymphotoxin-a, is primarily produced by T-cells and only exists in the soluble form.

Two TNF receptors, found on nearly all cell types, serve as the targets of TNF. TNFR1 is constitutively expressed on all cell types (except erythrocytes), whereas TNFR2 is induced and expressed in more substantial amounts on hematopoietic and endothelial cells. TNF receptors have extracellular domains that can be cleaved and released as a soluble receptor which binds to soluble or membrane-bound TNF and acts as a naturally-occurring inhibitor.

Binding of TNF to TNFR1 and TNFR2 is similar, but the binding to TNFR1 is almost irreversible whereas the binding of TNFR2 is more dynamic.

The effects of TNF binding to its receptor is broad and increases expression of adhesion molecules, synthesis of other cytokines (IL-1 and IL-6) and chemokines (RANTES, MIP-1), activates leukocytes, inhibits regulatory T cells, induces the production of MMP that degrades tissue, upregulates RANK ligand expression, induces apoptosis, as well as has various antiviral and antitumor effects.

The recognition of TNF as a significant mediator of inflammation initially led to the development of TNF inhibitors to treat sepsis [30]. At the same time, knowing that the synovium of patients with rheumatoid arthritis patients produces several different cytokines, TNF was thought to be the master regulator of inflammation in RA, as its blockade appeared to downregulate other inflammatory molecules (IL-1, IL-6, GM-CSF) in the synovial fluid [31]. It also leads to decreases in serum level of acute phase reactants including C-reactive protein, serum amyloid A, fibrinogen [32]. Levels of anti-inflammatory molecules, including IL-1 receptor antagonist and soluble TNF receptors, were also reduced.

Testing of TNF inhibition in patients with rheumatoid arthritis was found to have multiple benefits, including reduced leukocyte recruitment into the joint, decreased expression of pro-inflammatory cytokines, reduced angiogenesis, increased activity of regulatory T cells, normalization of T cell hyporesponsiveness, and prevention of joint erosion [33].

2.5.1. TNF inhibitors

Various drugs to block TNF activity have been developed. While they share many biological, clinical, and adverse effects, there are notable differences between them. Five TNF inhibitors have been developed and approved by the FDA to treat a variety of inflammatory conditions. Etanercept is a fusion protein that combines two soluble TNFR2 with the Fc portion of IgG1. Etanercept binds to both TNF-α and TNF-b.

In contrast, infliximab, adalimumab, and golimumab are monoclonal IgG1 antibodies. Infliximab is a chimeric anti-TNF-α antibody with a variable region (Fv) of mouse origin and a human constant region (Fc). Adalimumab and golimumab are fully human monoclonal antibodies against TNF-α. These three antibodies are equally able to neutralize soluble and cell-bound TNF.

Certolizumab pegol is a recombinant, humanized antibody Fab' fragment against TNF-alpha, conjugated to polyethylene glycol. The attachment of a PEG moiety increases its half-life. Because it does not have an Fc region, it does not fix complement or mediate cell-dependent cytotoxicity, unlike the other TNF antagonists. In contrast to the other TNF monoclonal antibodies, certolizumab is univalent and does not cross-link mTNF-α or soluble TNF; thus it does not form immune complexes. The lack of Fc also prevents it from crossing the placenta, a potential advantage for pregnant women with autoimmune conditions.

As the patent for these drugs is expiring, many biosimilars have emerged with properties largely identical to their originator drugs.

3. The diseases

3.1. Familial Mediterranean Fever (FMF)

Familial Mediterranean fever (FMF) is the most common genetic autoinflammatory disease worldwide. It is caused by mutations in *MEFV*, the gene that codes for a sensor protein called pyrin. FMF typically presents with recurrent episodes of fever and serositis (usually manifested by peritonitis), lasting 1–3 days, associated with significant elevation of inflammatory markers during flares. In between flares, patients are well. Untreated, FMF may lead to amyloidosis, renal failure, and death. It is most common in people of Turkish, Armenian, Arab, and Sephardic Jewish descent [34].

Wildtype pyrin is an intracellular sensor for bacterial toxins, such as those from *Clostridium difficile* [35]. FMF-causing mutations in pyrin prevent its phosphorylation, thus leading to constitutive activation of the inflammasome [2]. Although initially considered an autosomal recessive disease, FMF is now believed to be caused by gain-of-function mutations in *MEFV* with gene-dosage effect, so that patients with only one mutation in *MEFV* may still be symptomatic [2].

Since the discovery of the efficacy of colchicine in most patients with FMF in 1972 [37], and the demonstration that it prevents amyloidosis [38] and that it is safe in children [39], colchicine has become the standard of care for patients with this syndrome. The European League Against Rheumatism (EULAR) recommends the use of colchicine as soon as the diagnosis of FMF is made [36]. For patients who continue to have frequent flares despite maximally tolerated doses of colchicine (those who are "colchicine-resistant"), or those who continue to have elevation in inflammatory markers, especially serum amyloid A (SAA) protein between flares, the addition of IL-1 inhibitors should be considered. These patients are still encouraged to use colchicine to prevent amyloidosis, as long-term data on the efficacy of IL-1 inhibition to avert amyloidosis is unknown.

Several published studies have described the efficacy of IL-1 inhibition in patients with FMF. A systemic review of over 100 patients

with colchicine-resistant FMF treated with IL-1 inhibitors found complete response (without a single attack during treatment) in 76.5% of patients treated with anakinra and in 67.5% of patients with canakinumab [40]. In another large retrospective review of 172 Turkish patients with colchicine-resistant FMF, complete remission was achieved in 40% and 65% in patients treated with anakinra and canakinumab, respectively, and attack frequency and inflammatory markers were significantly reduced [41].

A small ($n = 14$) randomized trial of rilonacept in colchicine-resistant or colchicine-intolerant FMF showed it significantly reduced the frequency of FMF attacks as compared to placebo (0.77 attacks per month on rilonacept vs. 2 on placebo) [42]. However, rilonacept was not effective in all patients, especially in those with more rare *MEFV* mutations, and it did not decrease the duration of attacks once they occurred.

One small ($n = 25$) randomized trial demonstrated that anakinra was effective in reducing the frequency of attacks of most patients (1.7 per month with anakinra vs. 3.5 per month in placebo) [43].

A recent randomized study of 63 patients with colchicine-resistant FMF revealed the efficacy of canakinumab in controlling and preventing flares, as compared to placebo, (with 61% of patients having no flares for 16 weeks, as compared to 6% in placebo) [44]. Canakinumab is the only FDA-approved cytokine blocker for the treatment of colchicine-resistant FMF in the United States.

3.2. Cryopyrin-associated periodic syndrome (CAPS)

Cryopyrin-associated periodic syndrome (CAPS) is a group of related diseases caused by mutations in *NLRP3*. While previously considered three separate conditions, familial cold autoinflammatory syndrome (FCAS), Muckle-Wells Syndrome (MWS), and neonatal-onset multisystem inflammatory disease (NOMID, also called chronic infantile neurologic cutaneous articular (CINCA) syndrome), they are now grouped under the umbrella of CAPS, as the distinction between each of these conditions is not always clear.

Patients with FCAS, the mildest form of the disease, generally have recurrent episodes of fever, urticarial-like rash, arthralgia, and conjunctivitis, triggered after cold exposure [45]. Patients with MWS may have a more chronic course, with episodes not always triggered by cold exposure, and they may develop AA amyloid and sensorineural hearing loss. NOMID patients present shortly after birth with an urticaria-like rash, intermittent fevers, chronic inflammation, aseptic meningitis, developmental delays, hearing loss, as well as frontal bossing, saddle-nose, and arthropathy and joint contractures of large joints [46].

Anakinra was first reported to be dramatically effective in 2 patients with MWS [47] and then in patients with FCAS when faced with an experimental cold challenge [48]. Anakinra was also shown to be very useful in patients with NOMID in the resolution of rash, improvement of inflammatory markers and in neurological signs and symptoms [49]. Not surprisingly, anakinra has been shown to have good CNS penetration in non-human primates [50]. Anakinra is the first and only FDA-approved medication for the treatment of NOMID/CINCA in the US; it is also approved for all forms of CAPS in Europe.

A placebo-controlled trial of the use of rilonacept for patients with FCAS and MWS showed it to be significantly effective in improving signs and symptoms of CAPS, including the reduction of inflammatory markers [23]. This study led to the FDA-approval of rilonacept for the treatment of FCAS and MWS (but not NOMID) in the US.

Canakinumab has been studied in many patients with CAPS. A trial of patients with FCAS and MWS showed that 97% had a complete response to canakinumab including normalization of inflammatory markers [51], and this led to the FDA-approval of canakinumab for the treatment of FCAS and MWS in the US. A 24-month study of canakinumab in children with NOMID demonstrated improvement in symptoms and inflammatory markers, but most continued to have evidence of CNS inflammation, including the presence of inflammatory cells and elevated levels of IL-6 [52]. Unlike anakinra, the CNS penetration of canakinumab is unknown, and most trials have required a significant escalation in doses to achieve adequate responses.

Patients with clinical evidence of CAPS but no observed mutations in *NLRP3* have also been shown to respond favorably to treatment with IL-1 inhibition.

EULAR ecommendations for the treatment of patients with CAPS suggest the use of IL-1 inhibition for the whole spectrum of CAPS at any age, starting as soon as possible in patients with active disease [53].

3.3. Mevalonate kinase deficiency (MKD)/Hyperimmunoglobulinemia D Syndrome (HIDS)

Mevalonate kinase deficiency (MKD), also known as Hyperimmunoglobulinemia D Syndrome (HIDS) is a recurrent fever syndrome that results from mutations in mevalonate kinase, encoded by the *MVK* gene [54] [55]. It causes a syndrome of recurrent fevers, typically starting at around 6 months of age, lasting 3–7 days, manifested by lymphadenopathy, abdominal pain, diarrhea, arthralgias, vomiting, and oral ulcers [56].

Mevalonate kinase is responsible for cholesterol biosynthesis, as well as for the synthesis of products involved in RNA, hemoglobin and other proteins [57]. It is hypothesized that defects in mevalonate kinase activity lead to low levels of geranylgeranyl pyrophosphate, RhoA inactivation, and diminished P13K activation, thus leading to activation of the pyrin inflammasome [2]. Patients with complete absence of enzymatic activity of mevalonate kinase have a more severe phenotype including recurring fevers and severe developmental delays in a syndrome called mevalonic aciduria that is generally fatal in childhood [58].

Cytokine blockade in patients with MKD has been attempted with anakinra both as continuous treatment and on-demand therapy during attacks. Use of anakinra during attacks led to a reduction in fever duration, the height of fever, levels of CRP, and decreases the episode severity [59]. It was most effective if used within 24 h of an attack. However, continuous anakinra use did not reduce the frequency of attacks.

Another group investigated continuous anakinra or canakinumab for patients with MKD. They found these drugs induced complete remission in a third of patients, while the rest experienced partial remission with decreasing frequency and severity of flares, as well as improvement in levels of acute phase reactants [60].

Etanercept has also been reported to be effective in 65% of patients in one large database of 17 patients, although only one had complete response [61].

A randomized trial of canakinumab in 72 patients with MKD showed 35% with complete response (resolution of current flare and absence of flares for 16 weeks), which increased to 57% with higher doses of canakinumab [44]. Even in patients that did not have a complete response in this study, they still experienced decreased frequency and intensity of flares, as well as improvement in the inflammatory markers.

EULAR recommendations for the treatment of patients with MKD include use NSAIDs or glucocorticoids during attacks, use of IL-1 blockade during attacks, or consideration of IL-1 blockade or etanercept for maintenance therapy [53].

3.4. TNF receptor-associated autoinflammatory syndrome (TRAPS)

TNF receptor-associated autoinflammatory syndrome (TRAPS) is caused by heterozygous mutations in the tumor necrosis factor receptor superfamily member 1A (*TNFRSF1A*) gene, which encodes the TNF receptor type I (TNFR1) [1]. It was first described in 1982 as “familial Hibernian fever” in an Irish family with several members affected [62]. Since then, patients from various ethnicities have been found to harbor the mutation [63]. Most patients present with episodes recurrent fevers

lasting days to weeks, manifested by limb pain, abdominal pain, rash, and eye manifestations (periorbital edema, periorbital pain, and conjunctivitis). Ten percent of patients in one large registry were found to develop AA amyloidosis.

How mutations in *TNFRSF1A* lead to disease is still unclear. Mutations most commonly affect the extracellular domain of the TNF receptor, and it is thought that they affect receptor folding and trafficking, which allow the mutated receptor to accumulate intracellularly, causing intracellular stress, and leading to overproduction of inflammatory cytokines [64]. Interestingly, the mutated TNF receptors require its wildtype counterpart to produce disease, and it seems that it causes inflammation in both TNF-dependent and TNF-independent manners.

A trial of the use of etanercept in 15 patients with TRAPS showed that it was effective in decreasing symptoms, increasing symptom-free days, and in reducing levels of acute-phase reactants between flares [65]. However, most patients still reported symptoms related to TRAPS, even at high doses of the drug, and most patients in the study discontinued etanercept after a few years due to perceived lack of efficacy. In the Eurofever registry, etanercept was beneficial in most patients that used the medication, although only one-third experienced a complete response [61].

The effect of other TNF inhibitors was not as beneficial. Infliximab was not effective in most patients and may have even triggered flares in some patients [66] [67].

Anakinra was also attempted in patients with severe TRAPS that required almost continuous treatment with steroids [68]. Anakinra was effective in controlling symptoms, normalizing levels of acute-phase reactants, and preventing flares. The Eurofever registry found that anakinra showed a complete response in 26 of 33 patients (79%) and partial response in 5 others [61].

Canakinumab was also attempted in 20 patients with TRAPS with excellent effect; a complete or almost complete response was achieved by 19 of 20 patients, including improvement in symptoms, decreases in CRP and serum amyloid A levels, as well as improved health-related quality of life measures [69]. A recent randomized placebo-controlled trial showed that at week 16, 45% of patients assigned to canakinumab had complete response (defined as resolution of baseline flare and absence of flares for 16 weeks), as compared to 8% in placebo; this increased to 73% if the dose of canakinumab was increased [44]. Patients that did not have complete response to canakinumab still benefited from this drug by having decreased frequency of flares.

IL-6 was noted to be significantly elevated in TNFR1-mutant cells and in the serum of TNFR-1 mutant mice and in patients with TRAPS [64]. One patient with TRAPS who failed etanercept and anakinra was started on tocilizumab and showed resolution of his acute flare and had no more flares during the six months of treatment, as well as improvement in acute phase reactants [70]. A second patient with TRAPS also received tocilizumab and had a good long-term response for over 3 years to tocilizumab including clinical and laboratory markers [71].

EULAR guidelines recommend the use of NSAIDs or glucocorticoids during attacks; IL-1 blockade was recommended for most patients, while etanercept was thought to be beneficial for some, but its effect was thought to decline over time [53].

3.5. Systemic juvenile idiopathic arthritis (SJIA) and Adult-onset Still's disease (AOSD)

Systemic juvenile idiopathic arthritis (SJIA) and adult-onset Still's disease (AOSD) are now considered to be the same condition, differing only on their age of onset. They both exhibit similar clinical and laboratory features including daily spiking fevers, joint involvement, evanescent rash, leukocytosis, activation of the innate immune system (neutrophils an macrophages), and elevation of inflammatory cytokines including IL-1, IL-6, and IL-18. Results from gene expression analyses also demonstrate indistinguishable results across both conditions [72]. Unlike the monogenic autoinflammatory syndromes, no single gene has been found to cause SJIA/AOSD; instead, it is thought that environmental triggers (infections), genetic factors, immune mechanisms, and pathogenic antigens may lead to the expression of the disease [73].

About a third of patients with AOSD have a monocyclic course, with a single episode followed by good health, 44% have a polycyclic course, with complete remission between flares, while 26% have chronic disease usually associated with polyarthritis [74].

SJIA was first noted to be different from other types of juvenile idiopathic arthritis (JIA) because levels of IL-1β in patients with SJIA were significantly elevated as compared to other forms of JIA, and SJIA patients did not respond to treatments with TNF inhibitors. In 2005, a trial of anakinra in children with SJIA showed complete remission in 7 out of 9 patients, and partial remission in the other two [75]. A retrospective study of 46 patients with SJIA showed that anakinra monotherapy, or in combination with corticosteroids or DMARDs, was effective in controlling the systemic symptoms and prevention of refractory arthritis in 90% of patients [76]. A prospective cohort study of anakinra use as first-line therapy in 20 patients with SJIA revealed excellent response including control of the systemic symptoms, normalization of the inflammatory markers and arthritis in 80% of patients within 30 days, and > 80% achieved disease remission, either on or off medications, after 3 years [77]. These results are significantly improved as compared to historical cohorts before the use of biologics [78], suggesting that aggressive, early treatment with cytokine blockade may change the course of the disease.

A current randomized clinical trial is evaluating the efficacy of anakinra in children and adults with SJIA/AOSD (ClinicalTrials.gov Identifier: NCT03265132).

Two randomized, double-blind, placebo-controlled studies of the use of canakinumab for patients with SJIA showed that a single injection of the drug resulted in inactive disease in 33% of patients after two weeks [79]. After two years of continuous treatment with canakinumab, 62% of patients had inactive disease, and 82% had shown a good response to the drug. Canakinumab was also shown to be helpful in tapering or discontinuing glucocorticoids.

Interleukin-6 was also shown to be significantly elevated in peripheral blood and synovial fluid in patients with SJIA; peripheral blood mononuclear cells from patients also have increased unstimulated production of IL-6 [80]. A randomized trial of the use of tocilizumab in patients with active SJIA showed at least 30% improvement in symptoms (ACR30) and absence of fever in 85% of patients after 12 weeks, as compared to 24% in placebo. After one year, 80% of patients on tocilizumab showed at least 70% improvement (ACR70) and lack of fever.

A recent large international genetic study of 770 patients with SJIA showed that single nucleotide polymorphisms (SNPs) in the promoter region of the IL1RN gene are associated with the development of SJIA [81]. Patients who had SNPs that placed them at increased risk of SJIA had a lower IL1RN expression, whereas those with higher IL1RN expression were at lowest risk. Furthermore, researchers showed that patients who were non-responders to anakinra were those that had the highest expression of IL1RN (they already had elevated levels of IL-1Ra and thus did not respond to recombinant IL-1Ra). Therefore, their findings suggest that genetic analysis may be used to guide treatment in the future.

Although IL-1 blockade is effective in treating diseases that are prone to develop macrophage activation syndrome (MAS), such as SJIA, treatment with these drugs is not protective against the development of MAS [82] [79], suggesting that other cytokines may be involved. IL-18 has been found to be elevated in the sera, synovium, lymph nodes, and liver of patients with AOSD [73]. IL-18 levels also correlate with measures of disease activity and are associated with other biomarkers of disease [83]. In patients with SJIA with incomplete response to anakinra, IL-18 levels were elevated [77], suggesing that this cytokine may also be involved in the pathogenesis of at least some patients with SJIA.

IL-18 is regulated by IL-18 binding protein (IL-18BP) which neutralizes IL-18 and prevents binding to its receptor. One open-label study of the safety and efficacy of tadekinig alfa, a recombinant human IL-18BP, showed clinical and laboratory response in 50% of patients 3 weeks after starting the drug, demonstrating another potential option for patients with AOSD [84].

4. Conclusions

It does not always happen that the discovery of a new group of illnesses coincides with the development of their treatment. However, over the last 20 years, the discovery of autoinflammatory diseases has gone hand-in-hand with the advent of biologic drugs that block cytokines involved in these conditions. Although biologics were not initially developed for the purpose of treating these rare syndromes, autoinflammatory diseases have become the primary indication for many of these medications. Biologics have revolutionized the treatment of patients with autoinflammatory disorders—while some autoinflammatory diseases were previously lethal in childhood, treatment with cytokine blockers now allows children with these conditions to grow up and lead mostly normal lives.

The understanding of the pathophysiology of autoinflammatory diseases, especially the role of the inflammasome, has shed light on basic inflammatory mechanisms that are involved in a variety of much more common diseases, including coronary artery disease, type 2 diabetes, gout, and Alzheimer's. The study of autoinflammation has even led to novel approaches for treating diseases that affect millions of people worldwide [85].

Although we have learned a lot about these rare syndromes since their discovery, much work remains. Large numbers of patients with autoinflammatory syndromes do not have genetic mutations in genes known to cause autoinflammatory diseases [86]. The role of the environment (infections, the microbiome, and physical and emotional stress) in the expression of disease is also poorly understood. Although several drugs are available for patients with autoinflammatory conditions, we do not yet know which drug will most benefit a particular patient. Fortunately, animal models of autoinflammatory diseases [87], advances in genetics [88], and big data [89] have the potential to provide us with much-needed answers in the future.

Disclosures

The author has nothing to disclose.

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