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Chapter 12

Immunotherapeutic Biologic Agents to Treat Autoinflammatory Diseases

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Additional information is available at the end of the chapter

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Abstract

In recent years, innovative treatment for patients with autoimmune and autoinflammatory diseases has advanced in concert with our increased understanding of molecular and clinical immunology. Deeper understanding of autoimmunity has allowed for the development of cutting-edge biologic drugs for patients with relatively common autoimmune diseases. During this same period, knowledge regarding the molecular bases of autoinflammatory genetic diseases has also greatly expanded. Biologic immunotherapeutic agents developed for autoimmune diseases that primarily target cytokines that are also dysregulated in the uncommon autoinflammatory diseases are the focus of this article. In the following pages, selected genetic autoinflammatory diseases and key immunotherapeutic treatment approaches are addressed. The current understanding of these diseases and mechanisms by which therapeutic agents may benefit patients are reviewed. Indications, risks, and additional considerations for the use of these agents in treatment of autoinflammatory disorders are addressed as well.

Keywords: biologic agents, autoinflammatory diseases, cytokines, inflammasome, IL-1, TNF, IL-6, interferon

1. Introduction

Over the past 20 years, scientific work that uncovered the genetic basis of autoinflammatory diseases (AutoIDx) has expanded knowledge about pathways of the innate system. Important discoveries have linked autoinflammation to defects in the innate immune system and autoimmunity largely to changes in adaptive immune function. Immunotherapeutic agents which target cells, cytokines, and mediators of immunologic responses are part of our current "toolbox" to treat autoimmune diseases. These pharmacological agents also target and treat the excess downstream inflammatory mediators produced by genetic mutations in the innate immune

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system that cause the syndromes identified as AutoIDx. This review addresses key immunotherapeutic biologic approaches for treating selected AutoIDx. Current therapeutic approaches, as well as risks and additional considerations in the use of these agents, are addressed.

2. Innate and adaptive immunity

The innate and adaptive immune systems normally work together in integrated fashion utilizing antigen-specific and antigen-independent mechanisms. The host's first line of defense is the innate system which recognizes nonspecific immunologic signals and then directs further innate system activities in concert with the adaptive immune system. In this way, the extent and complexity of the overall immunologic response is enhanced. Genetic defects in the function and control of the innate immune system cause the AutoIDx. These disorders produce unprovoked, often self-limited episodic inflammation that is not associated with antigen-specific T cell reactions or with autoantibody production. AutoIDx have no association with specific Major histocompatibility complex (MHC) alleles, unlike autoimmune diseases. Research and newer genetic techniques as exemplified by next-generation sequencing have uncovered the etiologies of multiple AutoIDx, although mutations underlying some AutoIDx remain unknown. Each discovery has furthered our understanding of pathways and therapeutic targets in the innate immune system [1].

The innate immune system is composed of effector cells, such as activated macrophages, as well as receptors, cytokines, and downstream response proteins. Surface pattern recognition receptors including Toll-like receptors (TLRs) and pathogen-associated molecular patterns (PAMPS) can activate inflammasome assembly through effects on NF-κB production and subsequent immunological signaling (Signal 1 activation). Molecules such as crystals in gout, heat-shock proteins, damaged tissue (such as with burns), as well as other PAMPS and damage-associated molecular patterns (DAMPS) (Signal 2 activation) can also provoke this response. Following Signal 1 and 2 triggers, intracellular pattern recognition proteins, including nucleotide-binding oligomerization domain-like receptors (NOD-like receptors, NLRs such as NOD-like receptor P3 (NLRP3), and NOD-like receptor C4 (NLRC4)) and cytoplasmic DNA receptors [2], are then activated. Cytoplasmic NLRs oligomerize in response to these initial signals, forming inflammasomes that are multimeric scaffolded structures that further activate cytokines [3, 4]. Inflammasomes specific to different NLR structures perpetuate cascading downstream signals. NLRP3 specifically is associated with apoptosis-associated speck-like protein containing (ASC) a caspase recruitment domain (CARD) and procaspase-1. Inflammasome NLRP3 is key as it leads to production of the central cytokine, interleukin (IL)-1, via the caspase-1 activation cascade. This is followed by conversion of IL-1β and IL-18 from inactive to enzymatically active proteins (see **Figure 1**) [5, 6]. Loss-of-function or gain-of-function gene mutations that code regulatory proteins which control inflammasome scaffold formation and subsequent cytokine activity are among the causes of AutoIDx.

Unlike AutoIDx, relatively more common autoimmune disorders, including systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA), are largely caused by defective tolerance,

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but the innate immune system plays a key role as well. Some autoimmune diseases, especially early-onset Crohn's disease (CrD) and sarcoidosis, are caused by innate system dysregulation occurring in concert with adaptive immune dysfunction [7]. Autoimmune diseases today are regularly treated with pharmaceutical biologic agents that target relevant inflammatory pathways. These therapies have changed the lives of the many people affected by such diseases. AutoIDx affect fewer individuals, but these populations nonetheless have benefitted from current-day immunologic therapeutic discoveries which are the focus of this review (for detailed reviews of the adaptive and innate immune systems and autoimmunity, see Refs. [8–12]).

3. Autoinflammatory diseases

The AutoIDx were identified through translational research efforts starting with uncovering the genetic cause of familial Mediterranean fever (FMF) [13] followed by identification of genes for cryopyrin-associated periodic syndromes (CAPS). AutoIDx may present with typical monthly episodes, or may be more unpredictable, with exacerbations no more than 2–3 times per year. Typical spells can be set off by seemingly innocuous triggers such as vaccination or cool environmental temperature [14]. Each disease has well-characterized features, usually including fevers, hence the former term "periodic fever syndromes" (see **Tables 1** and **2**). Below, representative conditions for which biologic therapies have been used are addressed in some detail.

3.1. Cryopyrin-associated periodic syndromes

CAPS are monogenetic dominant disorders due to the defective cold-induced autoinflammatory syndrome 1 (CIAS1) or NLRP3 gene which alters the protein cryopyrin. CAPS exhibit a range of severity based on variable penetrance of the mutations: familial cold autoinflammatory syndrome (FCAS) is the mildest, Muckle-Wells syndrome (MWS) has moderate features, and neonatal-onset multisystem inflammatory disease (NOMID, also termed chronic infantile neurological, cutaneous, articular syndrome CINCA) is the most severe and potentially life-threatening disease. Features are usually present in newborns with rash and fever; additionally, in MWS and NOMID, arthritis develops. In FCAS a cold environment precipitates exacerbations of symptoms. NOMID may cause severe arthritis with destructive bony overgrowth, as well as chronic meningitis and developmental delays. NOMID and MWS may lead to hearing loss; amyloidosis and renal failure develop in 25% of untreated individuals [1, 14].

In CAPS, gain-of-function dominant mutations occur in NLRP3, a member of the NLR protein family. Somatic mosaicism may also be associated with typical symptoms. In NOMID sporadic mutations are frequent, with up to 40% having no identifiable mutation [1]. In CAPS, spontaneous activation of cell surface TLRs and cytoplasmic sensors occurs followed by antigen unprovoked assembly of the inflammasome complex. Caspase-1 is then activated and converts both pro-IL-1ß and pro-IL-18 to operational cytokines [3, 5]. Excess activity of the assembled multimolecular inflammasome results in unregulated production of IL-1ß, causing CAPS. Overproduction of IL-1β causes further downstream excess inflammatory responses. If left untreated CAPS can lead to increased serum amyloid A (SAA) protein accumulation, amyloidosis, and renal failure [1, 14].

Disease (acronym)	Gene; heritance	Affected protein Functional changes
IL-1β activation disorders of the inflammasome		
Cryopyrin-associated periodic syndrome • Familial cold autoinflammatory syndrome (FCAS) • Muckle-Wells syndrome (MWS) • Neonatal-onset multisystem inflammatory disease (NOMID)	NLRP3, CIAS1 (1q44); AD	Cryopyrin NALP3/PYPAF1 Inflammasome activation Excess IL-1β production
Deficiency of the interleukin-1 receptor antagonist (DIRA)	IL-1RN (2q14.2); AR	Lack of IL-1Ra Unopposed IL-1 signaling
NOD-like receptor C4-MAS	NLRC4; AD	IL-1β and IL-18 produced Macrophage activation
Familial Mediterranean fever (FMF)	MEFV (16p13.3); AR (AD)	Defective pyrin (marenostrin) Increased IL-1 activation
Hypergammaglobulinemia D syndrome (HIDS)	MVK (12p24); AR	Defective mevalonate kinase IL-1β dysregulation
Pyogenic arthritis, pyoderma gangrenosum, and acne (PAPA)	PSTPIP1 (15q24-25.1); AD	PSTPIP1 dysfunction Cytoskeletal changes stimulates inflammasome
TNF disorders of the innate immune system		
TNF receptor-associated periodic syndrome (TRAPS)	TNFRSF1A (12p13); AD	Mutant TNF receptor activates Inflammation via Il-1
Deficiency of adenosine deaminase (DADA)	CERC1; AR	Lack of activity of ADA2 Stimulate TNF dysregulation
Interferon activation disorders		
STING-associated vasculopathy of infancy (SAVI)	TMEM173; AD	STING activation Increased IFN-β transcription
Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE)	PSMB8; AR	Proteasome dysfunction Induced IFN response genes

AD, autosomal dominant; ADA, adenosine deaminase; AR, autosomal recessive; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy/elevated temperature; CAPS, cryopyrin-associated periodic syndromes; CNS, central nervous system; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of the IL-1 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; IFN, interferon; IL-1, interleukin-1; ILD, interstitial lung disease; JAK, Janus kinase; MAB, monoclonal antibody; MAS, macrophage activation syndrome; MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; NLRC4, NOD-like receptor C4; NOMID, neonatal-onset multisystem inflammatory disease; NR, not reported; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; SAVI, STING-associated vasculopathy with onset in infancy; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome

Table 1. Classification of selected autoinflammatory disease (adapted from Refs. [15–17]).

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	Ethnicity	Duration of episodes	Clinical features	Amyloid
FMF	Arab, Turkish, Jewish, Armenian	1–3 days	Erysipeloid rash, serositis, peritonitis, episodic inflammatory arthritis	Variable; significant risk
TRAPS	No specific group	>7–10 days	Rash, myalgia, serositis, arthritis, conjunctivitis, periorbital edema	10%
HIDS	Dutch, French, other Europeans	3–7 days	Maculopapular rash, abdominal pain, diarrhea, polyarthritis, ulcers, adenopathy	Rare
CAPS: FCAS	Mainly European	Often <24 h	Cold triggered urticarial-like rash; nausea; arthralgia	Uncommon
CAPS: MWS	Northern European	2–3 days	Urticarial-like rash, arthritis, conjunctivitis, hearing loss	Up to 25%
CAPS: NOMID	No specific group	Continuous with flares	Urticarial-like rash, chronic arthritis and overgrowth, uveitis, meningitis, developmental delay	Up to 25%
PAPA	NR	Early joints; later skin lesions	Fever, sterile arthritis, skin ulcerations, pyoderma gangrenosum, severe cystic acne	NR
DIRA	Lebanon, Brazil, Turkey, and others	Continuous from onset	Fever, pustular neutrophilic dermatitis, aseptic osteitis	NR
SAVI	NR	Continuous from onset	Fever, ischemic skin, digital necrosis, arthritis, myositis, ILD	NR

AD, autosomal dominant; ADA, adenosine deaminase; AR, autosomal recessive; CANDLE, chronic atypical neutrophilic dermatosis with lipodystrophy/elevated temperature; CAPS, cryopyrin-associated periodic syndromes; CNS, central nervous system; DADA2, deficiency of adenosine deaminase 2; DIRA, deficiency of the IL-1 receptor antagonist; FCAS, familial cold autoinflammatory syndrome; FMF, familial Mediterranean fever; HIDS, hyper-IgD syndrome; IFN, interferon; IL-1, interleukin-1; ILD, interstitial lung disease; JAK, Janus kinase; MAB, monoclonal antibody; MAS, macrophage activation syndrome; MKD, mevalonate kinase deficiency; MWS, Muckle-Wells syndrome; NLRC4, NOD-like receptor C4; NOMID, neonatal-onset multisystem inflammatory disease; NR, not reported; PAPA, pyogenic arthritis, pyoderma gangrenosum, and acne; SAVI, STING-associated vasculopathy with onset in infancy; TNF, tumor necrosis factor; TRAPS, TNF receptor-associated periodic syndrome

Table 2. Features of selected autoinflammatory diseases (adapted from Refs. [15, 17]).

3.2. Deficiency of the IL-1 receptor antagonist (DIRA)

The naturally occurring protein, "IL-1 receptor antagonist," attenuates downstream activation of IL-1 produced by normal function of the inflammasome. Loss-of-function gene mutations cause DIRA due to dysfunctional IL-1 receptor binding to this defective protein which normally would prevent dampening of IL-1 activity [3]. DIRA differs from CAPS possibly due to uninterrupted

overactivity of both IL-1β and IL-1α in DIRA. Presentation during the newborn period is typical with fever, skin pustulosis, with neutrophilic infiltrates, and a characteristic pattern of osteitis of ribs, clavicles, vertebrae, and hips. If the excess cytokine levels are untreated in DIRA patients, there is significant morbidity and mortality due to uncontrolled IL-1 effects [16].

3.3. NLRC4-related macrophage activation syndrome (MAS)

Inflammasome dysregulation from a mutation in NOD-like receptor C4 (NLRC4) causes NLRC4-MAS. Analysis shows spontaneous inflammasome operability and activation of capsace-1 causing deregulated release of IL-1β as well as production of extremely high levels of IL-18. Fever, colitis, arthralgias, and life-threatening MAS, similar to systemic juvenile idiopathic arthritis (JIA), develop in these children [4, 18]. In MAS, presentation includes coagulopathy, pancytopenia, and hyperferritinemia, with significant morbidity and mortality. Extremely high levels of IL-18 are characteristic of this disorder but not CAPS. Anti-IL-1 therapies are currently on the market, but there are no available anti-IL-18 blockers, a limitation in optimally treating this disorder.

3.4. TNF receptor-associated periodic syndrome

TNF receptor-associated periodic syndrome (TRAPS) is due to dominant mutations in the TNFRSF1A gene [14, 19]. Irregular 2–4 week cycles occur 2–6 times a year [20, 21]. Symptoms include fever, rash, periorbital swelling, arthritis, and conjunctivitis. Serositis, similar to FMF, is reported, but in contrast, renal failure due to amyloidosis is uncommon.

Pathogenesis appears to be due to varying mutational effects on the activation of NF-κB (Signal 1) and caspace which each cause increased cytokine release. NF-κB dysregulation promotes inflammation by inducing cytokine production and also by leading to inflammatory cell apoptosis [16]. Unchecked IL-1β release in TRAPS patients is due in part to effects of exaggerated production of mitochondrial reactive oxygen species (Signal 2) as well as increased caspace-1 activity. In addition, impaired mutant TNF receptor shedding occurs. Mutant 55 kDa TNF receptor 1a surface-based receptors appear to have several defects: abnormal protein-folding responses, binding TNF less effectively causing defective TNF-associated apoptosis, prolongation of immune responses to non-mutated receptor-bound TNF, and uncontrolled downstream signaling [22]. Abnormal p55 receptors shed in TRAPS are unable to serve as naturally occurring decoys for circulating TNF [20]. These mechanisms suggest benefit of anti-TNF as well as anti-IL-1 approaches [3, 20–25].

3.5. Familial Mediterranean fever

FMF is due to recessive Mediterranean fever gene (MEFV) mutations and is the most common AutoIDx. It is characterized by self-limited episodes of fever, serositis, arthritis, and renal failure due to amyloidosis. It is theorized that pyrin has a role in IL-1 activation by suppressing pro-caspase-1 activation possibly through competition for ASC. Defective pyrin does not bind normally to ASC, weakening its negative regulator function in NLRP3 inflammasome activation [16]. Mutations hence cause uncontrolled activation of capsace-1 via the IL-1 inflammasome [23, 26]. A unique pyrin-related inflammasome also leads to activation of IL-1 and seems to be important in FMF as well [1].

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Colchicine has been a standard FMF treatment since the 1970s. Its mechanism is due to inhibition of both cytoplasmic microtubules and inflammasome activity [27]. Pyrin also binds microtubules; this pyrin-like action of colchicine in FMF may explain its efficacy in part [16]. About 10% of FMF patients fail colchicine therapy. Given the high morbidity in FMF, alternative biologic therapies addressing cytokine dysregulation are used in such cases.

3.6. Interferonopathies

A group of AutoIDx related to uncontrolled type I interferon (IFN) activity has been recently described including stimulator of IFN genes (STING) associated with vasculopathy of infancy" (SAVI)" [1, 2, 28]. Early-onset livedo reticularis, ulcerative skin lesions, pulmonary symptoms, and Raynaud's disease with vasculopathy are described. SAVI is due to mutations in STING transmembrane proteins increasing IFN levels [28]. The abnormal STING induces IFN regulatory factor that translocates to nuclei and promotes transcription of IFN [2]. The overproduction of type I IFN binds to receptors [IFN associated receptor IFNAR-1 or IFNAR-2], leading to unchecked protein kinase signaling and increased IFN-induced cytokine release. Targeting this pathway may be effective for SAVI and other interferon-driven inflammatory diseases, such as SLE, a more common primarily autoimmune disorder [1].

4. Immunotherapeutic agents

Early immunologic intervention has evolved from the use of vaccines in the late 1800s to administration of intravenous immunoglobulin in the 1980s to current-day immunotherapeutics. Advances such as production of monoclonal antibodies (MABs) by creation of hybridomas and molecular cloning have paralleled our growing understanding of immunology. Innovative work identifying receptors and signaling pathways to identify new therapeutic targets for autoimmunity paralleled the discovery of the genetic AutoIDx. Widespread production and utilization of immunotherapeutics are directly attributable to these efforts [11, 29–31].

Food and Drug Administration (FDA)-approved medications are regularly tested for applicability for additional disease processes. Therapies marketed for relatively common autoimmune diseases, such as RA, are studied as potential treatment of AutoIDx "orphan diseases." The following is a review of selected immunotherapeutic medications used to treat AutoIDx based on scientific evidence and immunologic pathways (see **Table 3**; see **Figure 1**). Side effects, toxicities, and additional considerations with the use of these therapeutic agents are also addressed.

4.1. Anti-IL-1 therapy

The central mediator for multiple AutoIDx, IL-1, was one of the first identified cytokines. It was termed the "endogenous pyrogen" since fever is one of its main consequences. Inactive IL-1β is cleaved to its active form by the IL-1 inflammasome complex. Its naturally occurring receptor antagonist, IL-1Ra, was engineered into an immunotherapeutic, anakinra, and

Generic name	Brand name	Approved indications	Type	Mechanism of action
Adalimumab	Humira	RA, Ps, AS, PsA, uveitis, CrD, JIA	Human MAB	Inhibits TNF-α
Anakinra	Kineret	RA, CAPS	Recombinant protein	IL-1 receptor antagonist
Canakinumab	Ilaris	CAPS, JIA	Human MAB	Inhibits IL-1β
Certolizumab	Cimzia	RA, AS, PsA, CrD	Humanized FAB	Inhibits TNF-α
Etanercept	Enbrel	RA, JIA, Ps, PsA, AS	Fusion receptor	Soluble TNF-α receptor antagonist
Golimumab	Simponi	RA, Ps, AS, PsA, CrD, UC	Human MAB	Inhibits TNF-α
Infliximab	Remicade	RA, AS, PsA, UC, CrD	Chimeric MAB	Inhibits TNF-α
IFN-β 1a	Rebif	MS	Cytokine inhibitor	Targets type 1 IFN
IFN-β 1b	Betaseron	MS	Cytokine inhibitor	Targets type 1 IFN
Rilonacept	Arcalyst	CAPS	Fusion receptor	Targets IL-1R1/IL-R accessory receptor
Tocilizumab	Actemra	RA, JIA, sJIA	Humanized MAB	Inhibits IL-6 receptor
Tofacitinib	Xeljanz	RA	Small molecule; JAK inhibitor	Specifically blocks JAK-STAT pathway

AS, ankylosing spondylitis; CAPS, cryopyrin associated periodic syndromes; CrD, Crohn's disease; FAB, antibody fragment; IFN, interferon; JAK, Janus kinase; MAB, monoclonal antibody; MS, multiple sclerosis; JIA, juvenile idiopathic arthritis; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis; sJIA, systemic JIA; SLE, systemic lupus erythematosus; TNF, tumor necrosis factor; UC, ulcerative colitis

Table 3. Selected immunotherapeutic agents for autoinflammatory diseases (adapted from Refs. [11, 17]).

approved by the FDA in 2001 for treatment of RA. This agent is a competitive inhibitor of IL-1α and IL-1β receptor binding because the drug itself adheres to the receptor but does not produce downstream signaling. While its benefit in RA has never been dramatic, anti-IL-1 therapy is key in management of CAPS as well as other AutoIDx. Three anti-IL-1 agents are FDA approved and used in CAPS. Approved in 2009, canakinumab is a MAB to IL-1β with a long half-life that enables dosing every 1–2 months. Rilonacept is a fusion protein made from IL-1R accessory protein linked to the Fc portion of an IgG1 molecule which inhibits IL-1β and downstream signaling. It also acts as a soluble decoy for IL-1α, also preventing this cytokine from binding with the receptor. These agents control FCAS and MWS and are partly beneficial in NOMID [32–37].

Dysregulation of IL-1 as a key mediator is important in other disorders including systemic JIA and adult-onset Still's disease (AOSD) [38–40]. These diseases are also thought to be part of the spectrum of AutoIDx and respond well, sometimes dramatically, to anti-IL-1 agents. Given the presence of MAS and similarity to systemic JIA, NLRC4-MAS has been treated and responds, at least in part, to anti-IL-1 therapy [1, 3, 41]. The predominance of high IL-18 levels, which are not diminished with this approach, may explain the partial response to anti-IL-1 treatment.

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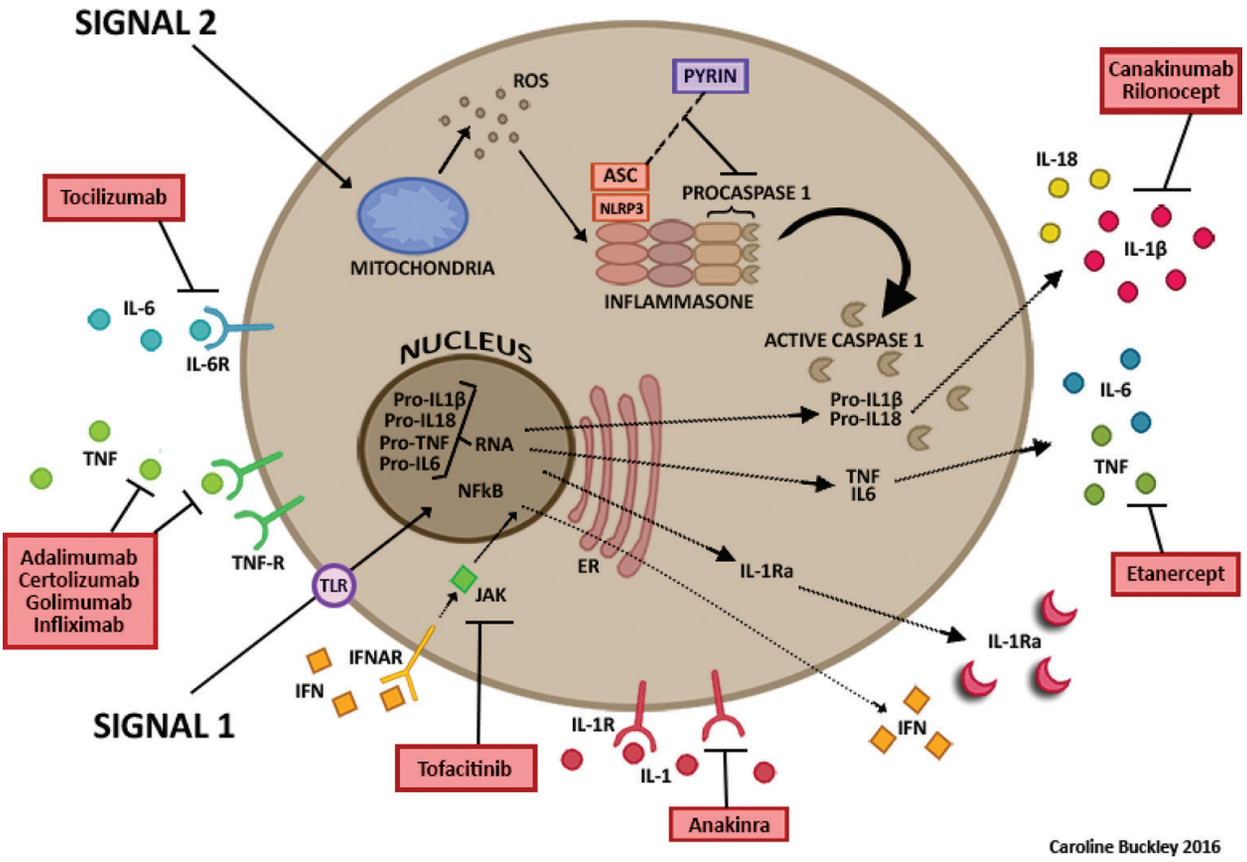


Figure 1. Targeted sites for therapeutic agents used in autoinflammatory diseases. Signal 1 inflammasome activation: surface pattern recognition receptors such as Toll-like receptors (TLR) and pathogen-associated molecular patterns stimulate production of molecules such as NF-κB and activate inflammasome assembly through downstream immunologic processes. Signal 2 inflammasome activation: molecules such as crystals in gout, heat-shock proteins, or damaged tissue (such as burns) as well as other pathogen-associated molecular patterns and damage-associated molecular patterns activate inflammasome assembly through production of reactive oxygen species (ROS) as well as downstream immunologic processes. ASC, apoptosis-associated speck protein; ER, endoplasmic reticulum; IFNAR, interferon-associated receptor; IFN, interferon; IL-1, interleukin-1; IL-1 R, IL-1 receptor; IL-1Ra, IL-1 receptor antagonist; IL-6, interleukin 6; IL-6R, IL-6 receptor; IL-18, interleukin-18; JAK, Janus kinase; NLRP3, NOD-like receptor P3; ROS, reactive oxygen species; TLR, Toll-like receptor; TNF, tumor necrosis factor; TNF-R, TNF receptor.

Unfortunately, no anti-IL-18 agents are currently marketed although efforts to develop such agents are underway. In DIRA, excessive IL-1β and IL-1α are both released. Based on pathogenesis of this disorder, and the understanding that some available agents inhibit both IL-1β and IL-1α actions, anti-IL-1 agents have been successfully used in DIRA [16].

In several other AutoIDx, pathogenesis involves activation of the IL-1 inflammasome by Signal 2 mechanisms including elevated reactive oxygen species, PAMPS and DAMPs. In TRAPS, caspace-1 is activated in vitro even while treated with anti-TNF therapy [23]. Hence, anti-IL-1 treatment may be ideal for treating these patients [42]. In FMF, defective pyrin fails to suppress inflammasome behavior, and pro-IL-1 is increasingly activated. Reports detail response to anti-IL-1 therapy in FMF [6, 14, 43]. All these observations confirm response to anti-IL-1 therapy by a spectrum of AutoIDx [3, 21, 25, 43, 44].

4.2. Anti-TNF therapy

TNF is part of a superfamily of cytokines that induce necrosis of cancer cells, leading to the term "tumor necrosis factor." TNF-α is present on the surface of cells as a transmembrane protein, and its cleavage leads to release of soluble TNF-α. Two receptors regulate this cytokine's function – TNF receptor TNFR1 55 kd and TNFR2 75 kd. The 55 kd receptor is membrane bound, and upon stimulation by TNF-α, cells release other cytokines such as IL-2 and IFN. Extracellular TNFR2 75 kd receptors deactivate soluble TNF, blunting its action. The anti-TNF agent, etanercept, an injectable biologic approved for the treatment of RA in 1998 and JIA in 1999, is an engineered fusion protein comprised of two naturally occurring soluble human 75-kd TNF receptors linked to an Fc portion of an IgG1. Etanercept mimics the natural receptor by binding extracellular TNF, limiting activation of the inflammatory response. In CrD, pathogenesis involves innate immune system activation through membrane-bound TNF. Especially in early-onset disease, NOD gene mutations and dysfunctional NF-κB activation are also pathogenic [7]. In CrD, etanercept has been found to be less effective likely due to the predominance of membrane-bound TNF in this disorder rather than soluble TNF that is inhibited by this agent [45]. Differences in receptor localization, binding, and downstream signaling explain therapeutic differences between anti-TNF agents. Infliximab is a chimeric MAB, whereas golimumab and adalimumab are humanized MABs; all three have inhibitory effects at both TNF locations. Certolizumab is an antibody fragment (FAB) that attaches to membrane-bound as well as membrane-soluble TNF. All four are more effective in CrD than is etanercept.

In TRAPS, as etanercept is a soluble p75 kd receptor, it binds extracellular, soluble TNF unbound by dysfunctional p55 mutant receptors. Some TNFR1 mutations effect cysteine residues increasing risk of amyloidosis. Successful use of etanercept minimizes this complication [20, 46]. Etanercept may be beneficial in TRAPS patients but has a variable effect; other biologic agents, especially IL-1 blockers, may be more beneficial [47]. Anti-TNF MABs such as infliximab may cause paradoxical increased inflammation due to varying effects on both TNF receptors. Infliximab is therefore not used in etanercept failures [23, 48, 49].

Anti-TNF therapy has a role in FMF in colchicine failures [27, 50]. Etanercept and MAB anti-TNF therapies have been reported to be of some benefit in these patients. Good clinical and biological responses suggest these agents are options for more resistant FMF cases to prevent amyloidosis.

4.3. Anti-IL-6 therapy

By binding to its cell surface receptor and subsequent activation of DAMPS, TLRs, and intracellular protein kinase signaling, IL-6 has been shown to be an important cytokine in the inflammatory cascade. Complex interactions exist between IL-1 and Il-6 regulatory pathways. IL-6 also stimulates the adaptive immune system through B cell immunoglobulin production, elevated inflammatory markers (C-reactive protein), and promotion of Th17 cell maturation. Tocilizumab is a humanized MAB that blocks IL-6 signaling by adhering to membrane-bound IL-6 and its soluble receptors. This agent blocks downstream activation of adhesion molecules, osteoclasts, and maturation of both T and B cells [51]. As IL-6 is a key cytokine in RA, AOSD and systemic JIA (now thought to be part of the AutoIDx family), and inhibition of its function by tocilizumab has clinical benefit, this cytokine antagonist was approved by the FDA [52].

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Tocilizumab is not as effective in CAPS as anti-IL-1 inhibitors, with lack of response in NOMID possibly due to the extremely high IL-1 levels in this disease that requires more direct blockade of IL-1 that cannot be achieved through anti-IL-6 approaches. In TRAPS and FMF, several case reports detail clinical response to tocilizumab following inadequate response to etanercept; however, cytokine levels did not change appreciably [27, 49, 53, 54]. The benefit of anti-IL-6 therapy in other AutoIDx remains to be determined.

4.4. Interferons

Induced IFNs bind to IFN-α receptors on plasmadendritic cells. These cells upregulate many IFN-induced genes and are termed the "IFN signature" [55]. These gene products have inhibiting and/or activating effects on downstream immunologic activity. As a therapeutic agent, IFN-α has been used in hepatitis C and relapsing and remitting multiple sclerosis, an autoimmune neurologic disease. IFN-α therapy in colchicine-resistant FMF was reportedly beneficial but not confirmed in subsequent studies [27]. The IFN signature correlates with disease activity in autoimmune diseases and identifies response subsets. The IFN signature may also be important in the pathogenesis of subsets of AutoIDx, as well [56]. Treatments that inhibit IFN signaling pathways continue to be sought for the more common autoimmune diseases [11, 57, 58] which should then result in additional agents for study in AutoIDx.

4.5. Cytokine signaling

Strategies that employ cytokine receptor blockers or that provide decoys for soluble cytokines have been reviewed above. Alternatively, reducing effects of cytokines can be achieved through interference with post-receptor intracellular downstream signaling pathways. As suggested above, targeting IFN pathways may be a successful approach for some AutoIDx. Recently, AutoIDx related to IFN dysregulation, the interferonopathies, have been identified. Normally, IFN binding to receptors exerts downstream effects through intracellular pathways via protein kinases. JAK-STAT signaling transmits extracellular information to nuclei influencing DNA transcription and increasing IFN and cytokine production. Tofacitinib is the first JAK inhibitor recently approved for treatment of RA. The AutoIDx SAVI is due to a mutation affecting STING membrane receptors leading to excessive IFN production. Overstimulation of downstream immunologic activity due to abnormally high levels of IFN-IFNAR binding can lead to increased signaling that can be blocked by tofacitinib JAK-inhibition. In this way, overabundant downstream IFN effects are limited. Studies show 60% improvement in inflammation in vitro. Clinical trials in patients with this rare disorder are underway [2, 28].

5. Considerations in the use of immunotherapeutics

Some patients with AutoIDx have severe illnesses, and treatment is necessary to alleviate morbidity and prevent mortality. However, concerns regarding potential toxicity of immunotherapeutics must be addressed. Risks are present with all agents: infection, induction of carcinogenesis, autoantibody formation, and development of demyelination. Additionally, infusion or injection site reactions, as well as generally transient side effects, such as increased

liver function tests, decreased blood cell counts, and abnormalities in lipid profiles, have been attributed to these agents. Dose adjustments, premedication administration, and addressing concomitant risk factors often minimize side effects. Depending on concerns due to the patient's underlying disease, toxicity fears may or may not take precedence in medication selection.

5.1. Infections

Immunotherapeutic agents all produce some degree of immunosuppression in addition to their disease controlling effects. Development of opportunistic infections with viruses, fungi, atypical bacteria, and prion associated complications (such as progressive multifocal leukoencephalopathy) are potential concerns. FDA warnings advise against prescribing these drugs for patients with active infections including hepatitis C or B [51, 59]. Continued vigilance by patients and assessment by health care providers for any possible infectious complication is necessary when using immunotherapeutic agents.

Given concerns about risk of reactivation of tuberculosis (MTB), all patients are screened for MTB prior to starting biologic therapies [60, 61]. MTB confinement in granulomas requires normal CD8+ T cells and TNF activity; infliximab and biologics that effect receptor-bound TNF inhibit this function [62]. Little data exists regarding MTB risk for agents other than anti-TNF drugs [61]; however, screening for MTB is requested for most patients prior to starting biologic therapy.

5.2. Neoplastic disease

Patients with RA, psoriatic arthritis, and CrD are at risk of developing disease-related malignancies over their lives. The concern has been raised that biologic agents increase this risk. Large epidemiologic studies have not substantiated this concern for the most part. The rate of lymphoma in RA patients treated with biologic agents is similar to those who have never been treated. Those with prior cancer diagnoses are not at increased risk of recurrence [63, 64]. In 2008, a report from the FDA raised concerns about biologic agents and neoplastic disease in pediatric CrD and JIA patients. The pediatric rheumatology community worldwide has questioned this interpretation of JIA data [65]. Continued surveillance and monitoring of malignancies is crucial post-marketing for all biologic agents as the medical community, and patients remain vigilant regarding this important issue.

5.3. Demyelination

Studies using early anti-TNF-α agents in multiple sclerosis patients detected worsening disease, and trials were halted. The development of demyelinating toxicity in RA patients also has been reported. The mechanism of this side effect may be related to blocking effects on TNF receptor2 75 kd which is required for oligodendrocyte growth. Current anti-TNF therapies block TNFR2 75 kd as well as TNFR1 55 kd; the latter of which is linked more tightly to other autoimmune diseases as well as to TRAPS. Given that some anti-TNF blockers inhibit both receptors, improved control of inflammation may be met with worsening demyelination – an unacceptable trade-off. Future agents that selectively block TNFR1 55 kd might alleviate this

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concern [11]. Current approaches include close monitoring all patients treated with anti-TNF agents for any concerning neurologic signs.

5.4. Human anti-chimeric antibody and autoantibody formation

In theory, more human-like MABs might be less immunogenic and less susceptible to human anti-chimeric antibody (HACA) formation [51, 66]. HACAs are thought to be responsible for side effects, interference with laboratory testing, as well as potential decrease in efficacy of these therapies. Decreased response to treatment due to HACAs has been of specific concern following the use of certain agents, such as infliximab in CrD and RA [67, 68]. Patients who developed anti-infliximab HACAs are also more likely to have infusion reactions and possibly reduced therapeutic benefit. Awareness of the risk of HACA formation and its consequences is crucial information for prescribing clinicians [69, 70].

Autoantibody formation in patients receiving immunotherapeutic agents is well described [70]. Development of antinuclear antibodies (ANAs) is reported in patients in biologic trials. HACAs may produce false-positive autoantibody results due to interference in laboratory tests [70]. Autoimmune syndromes have been triggered by the use of immunotherapeutic in patients with RA and, in theory, also may develop in similarly treated patients with AutoIDx [51, 71]. One must be aware of the potential for these agents to cause false-positive autoantibodies or to trigger onset of autoimmunity. These concerns must be recognized by patients and be part of surveillance by practitioners caring for individuals on biologics.

5.5. Selection of immunotherapeutics

Immunotherapeutic agents currently available are often administered parenterally. Intravenous and self-injected formulations of these agents are typically prescribed for patients. Infusion medications tend to be even more expensive due to nursing and infusion center costs in addition to the price of the drug itself, making treatment cost prohibitive for some patients. Studies also show that patient preferences regarding medication choices (oral versus injection versus infusion therapy) often do not coincide with providers' intuition about patient choices. Access to medical care, attentive nursing, insurance coverage and cost are key factors for patients' choice of therapy [72]. "Biosimilar" generic-type biologic agents are soon coming to the US market with estimated savings of 20–35% off name-brand charges. These agents will be economically advantageous to insurers and patients, assuming these "similar" medications are truly as effective as name-brand biologic agents [73]. These less expensive immunotherapeutics could potentially be accessed by more patients, improving disease control for a greater number of afflicted individuals.

6. Future directions/outlook

Safe and effective treatment options are the goals of biologic drug development and utilization. In the future, scientific advances in precision medicine and next-generation sequencing will enable precise identification of disease phenotypes/genotypes to predict response to and

toxicity from biologic agents for autoimmune diseases [74, 75]. This advance will increase our ability to tailor immunotherapeutic selection for those with AutoIDx to target recognized consequences of genetic mutations. As knowledge about autoinflammation continues to expand, new and more directed therapies will be trialed and utilized to treat these rare disorders. In this era of the "triple aim" in patient care, attention to patient experience, improving population health, and minimizing complications of disease and treatment, including cost, one can predict that the outlook for this population with rare genetic inflammatory diseases will be much brighter with greater opportunities for them to be treated with disease-specific and targeted therapies. Increasingly, these therapies have changed the lives of patients with AutoIDx in recent years and will be able to make even more of a difference in the future.

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