Review article

Biologics and JAK inhibitors for the treatment of monogenic systemic autoinflammatory diseases in children

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Systemic autoinflammatory diseases (SAIDs) are caused by aberrant activation of 1 or more inflammatory pathways in an antigen-independent manner. Monogenic forms of SAIDs typically manifest during childhood, and early treatment is essential to minimize morbidity and mortality. On the basis of the mechanism of disease and the dominant cytokine(s) that propagates inflammation, monogenic SAIDs can be grouped into major categories including inflammasomopathies/disorders of IL-1, interferonopathies, and disorders of nuclear factor-κB and/or aberrant TNF activity. This classification scheme has direct therapeutic relevance given the availability of biologic agents and small-molecule inhibitors that specifically target these pathways. Here, we review the experience of using biologics that target IL-1 and TNF as well as using Janus kinase inhibitors for the treatment of monogenic SAIDs in pediatric patients. We provide an evidence-based guide for the use of these medications and discuss their mechanism of action, safety profile, and strategies for therapeutic monitoring. (J Allergy Clin Immunol 2023;151:607-18.)

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Systemic autoinflammatory diseases (SAIDs) are a heterogeneous group of conditions characterized by aberrant activation of the inflammatory cascades in an antigen-independent manner.[1,2] Dysregulation of the innate immune system leading to excess production of proinflammatory cytokines is a hallmark of SAIDs. From a simplistic view, this central mechanism distinguishes autoinflammation from autoimmunity caused by dysfunction of the adaptive immune system that results in a loss of tolerance to self-antigens, although manifestations of autoimmunity can be seen in some SAIDs.[3-5]

Advances in immunology and molecular genetics have drastically accelerated the discovery of SAIDs in the past 2 decades. Since the initial description of familial Mediterranean fever (FMF) in 1997, more than 50 monogenic SAIDs have been described.[6] These diseases typically arise from loss-of-function variants of regulatory proteins that normally restrain the inflammatory response or from gain-of-function variants of innate immune sensors and their downstream messengers. These immune pathways are tightly regulated during steady state, because somatic mutations affecting only a small fraction of cells are sufficient to trigger autoinflammation with multiorgan manifestations.[7]

Regardless of the underlying mechanism, a typical feature of SAIDs is early age of disease onset, although adult-onset cases are also being increasingly recognized. The accrual of damage over time creates significant challenges for the long-term health of affected individuals and early treatment is essential to improve outcome. In this review, we evaluate the evidence for use of biologics and Janus kinase inhibitors (Jakinibs) for the treatment of SAIDs in pediatric patients and discuss their mechanism of action, safety profile, and strategies for therapeutic monitoring.

GENERAL PRINCIPLES FOR THE TREATMENT OF SAIDs

To maintain the therapeutic focus of this review, we do not discuss the pathophysiology of each disease in detail because several excellent review articles on the mechanistic underpinnings of SAIDs are available[2,8-10] Table E1 (in the Online Repository available at www.jacionline.org) provides a brief description of the SAIDs mentioned in this review. SAIDs can be stratified into several categories on the basis of the dominant immune

Abbreviations used

AGS: Aicardi-Goutières syndrome
CAPS: Cryopyrin-associated periodic syndrome
DADA2: Deficiency of adenosine deaminase 2
DIRA: Deficiency of IL-1 receptor antagonist
DMARD: Disease-modifying antirheumatic drug
FMF: Familial Mediterranean fever
HA20: Haploinsufficiency of the NF-κB regulator A20
HIDS: Hyper-IgD syndrome
HOIL-1: Haem-oxidized iron regulatory protein 2 ubiquitin ligase 1
IFN-I: Type I interferons
JAK: Janus kinase
Jakinib: Janus kinase inhibitor
JIA: Juvenile idiopathic arthritis
LoE: Level of evidence
MAS: Macrophage activation syndrome
MKD: Mevalonate kinase deficiency
NF-κB: Nuclear factor-κB
NLRC4: Nucleotide-binding and oligomerization domain–like receptor subfamily C
NLRP3: NOD-like receptor family pyrin domain–containing 3
NOD: Nucleotide-binding and oligomerization domain
NOMID: Neonatal-onset multisystem inflammatory disease
OTULIN: OTU deubiquitinase with linear linkage specificity
SAID: Systemic autoinflammatory disease
STAT: Signal transducer and activator of transcription
TNFi: TNF inhibitors
TRAPS: TNF receptor–associated periodic syndrome

pathway responsible for the inflammatory response.[1,11] Classification of SAIDs by inflammasomopathies/disorders of IL-1, interferonopathies, and disorders of nuclear factor-κB (NF-κB) and/or aberrant TNF activity is not only helpful in considering the pathogenic mechanisms but also has direct therapeutic implications given the availability of biologic agents and small-molecule inhibitors that specifically target these pathways.

SAIDs are complex diseases and each possesses its own broad spectrum of clinical manifestations. Penetrance and disease severity are highly variable, even among family members who share the same pathogenic variant(s). Inflammatory pathways do not operate in silo and cytokine cross talk can achieve synergistic or antagonistic effects. Therefore, even for conditions with a well-defined mechanism, the collective experience in the field is essential to establish the best treatment approach. In most instances, empiric treatment of patients with SAIDs is trialed long before the identification of causal genes. Some SAIDs are effectively managed by glucocorticoids on an episodic basis, whereas others respond well to nonbiologic disease-modifying antirheumatic drugs (DMARDs). Colchicine, for example, remains the first-line treatment for patients with FMF and may also be highly effective for cases of undefined SAIDs.[12-15] However, the intense and chronic inflammation associated with SAIDs is often refractory to treatment with these traditional anti-inflammatory agents, including glucocorticoids. Persistent inflammation can lead to additional complications such as amyloidosis. Prolonged use of glucocorticoids in children causes stunted growth and a plethora of detrimental consequences.

The use of biologics and Jakinibs has revolutionized the treatment of many chronic inflammatory diseases in children, including juvenile idiopathic arthritis (JIA) and inflammatory bowel disease.[16,17] These agents are increasingly used to treat SAIDs on the basis of the mechanistic understanding of these conditions. The experience of treating patients with SAIDs often starts with the off-label use of available medications, because clinical trials for children with rare diseases are inherently difficult given the small number of patients and their phenotypic heterogeneity. Multicenter and international collaborations have aided the development of clinical trials, and in some cases, the remarkable efficacy of targeted therapy has led to rapid approval of SAIDs as new indications by regulatory agencies.

LITERATURE REVIEW ON TREATMENT STRATEGIES FOR SAIDs

In the following sections, we review the use of biologics for the treatment of inflammasomopathies/disorders of IL-1 production and disorders of NF-κB and/or aberrant TNF activity as well as the use of Jakinibs for the treatment of interferonopathies (Fig 1). The details of systemic literature review are provided in Table E2 (in the Online Repository available at www.jacionline.org). We evaluate the level of evidence (LoE) for the use of available agents for SAIDs using guidelines established by the Oxford Centre for Evidence-Based Medicine in 2011.[18] LoE is determined on the basis of the availability of systematic reviews of randomized trials (level 1), randomized trials (level 2), nonrandomized controlled cohort/follow-up studies (level 3), case series/case-control studies (level 4), and mechanism-based reasoning (level 5). Consistency among studies is indicated by grades A to D: grade A, consistent level 1 studies; grade B, consistent level 2 or level 3 studies or extrapolations from level 1 studies; grade C, level 4 studies or extrapolations from level 2 or level 3 studies; and grade D, level 5 evidence or inconsistent or inconclusive studies of any level.[18] The literature for each agent was reviewed by at least 2 members of the study team, and LoE was assigned after discussion with all members of the team. Evidence level 5D was assigned for ultrarare diseases with 3 or fewer cases available because of the paucity of evidence.

For each class of medications, we provide a table that summarizes the available evidence, current approval status by the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA), the number of studies/patients reviewed, and the pediatric dosage approved by the FDA/EMA (if available) or the typical dose range used in the studies. A similar approach was recently used in a review of select inflammasomopathies and periodic fever, aphthous ulcers, pharyngitis, and adenitis syndrome.[19] The evidence ratings reflect our analyses of available data from published studies but do not represent expert consensus statements recommending the use of these medications. For each class of medications reviewed, a companion extended table that provides details of studies included in our literature review is provided in Tables E3 to E5 (in the Online Repository available at www.jacionline.org). We recognize that the literature is skewed toward reporting positive outcomes, and readers should evaluate the source articles for details of the cases, dosing strategies, and treatment outcomes.

Nonmonogenic autoinflammatory syndromes, undefined SAIDs, and monogenic diseases with less-defined mechanisms

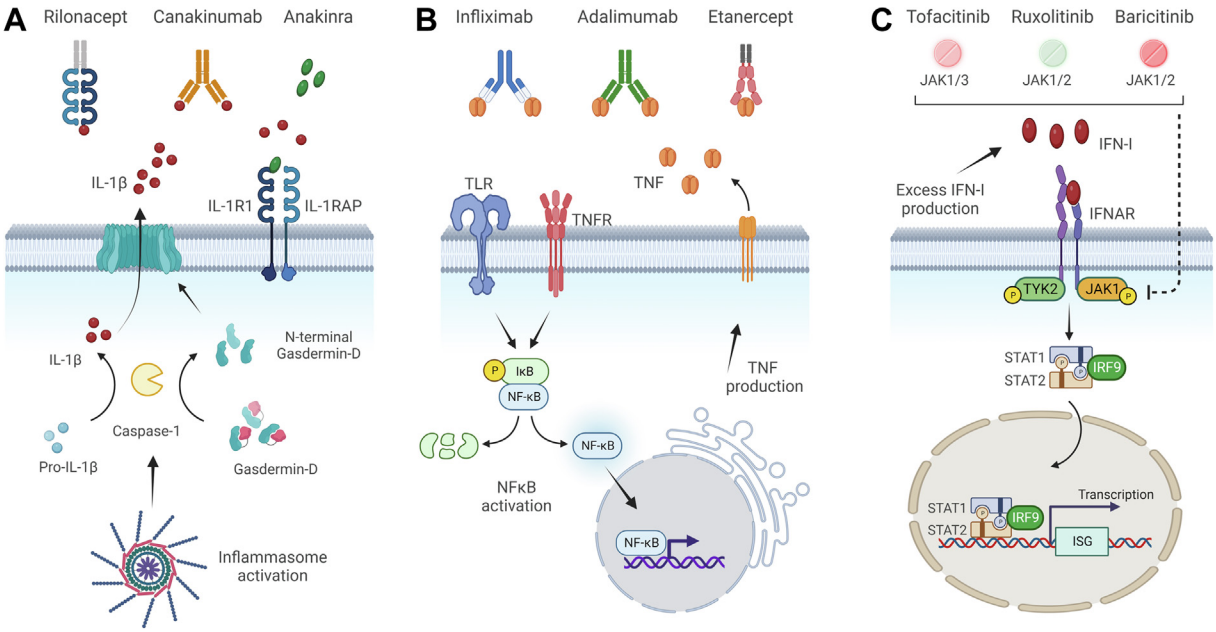

FIG 1. Therapeutic targets and available agents for the treatment of systemic autoinflammatory diseases. **A,** In inflammasomopathies, aberrant activation of the inflammasomes triggers the activation of caspase 1, which proteolytically generates active IL-1β and N-terminal gasdermin D. IL-1β is released through membrane pores formed by N-terminal gasdermin D and binds to IL-1 receptor to propagate the inflammatory response. IL-1 inhibitors include anakinra (recombinant IL-1RA), canakinumab (monoclonal anti–IL-1β), and rilonacept (dimeric fusion protein consisting of IL-1R1 and IL-1RAP conjugated to the Fc portion of human IgG1). **B,** Disorders of NF-κB result in increased production of TNF among other proinflammatory mediators. Membrane-bound TNF is cleaved to form soluble TNF, which binds to TNFR to regulate cell death and promote NF-κB activation. TNFi include infliximab (chimeric human/mouse mAb), adalimumab (humanized mAb), and etanercept (dimer of soluble TNFR2 fused to the Fc portion of IgG1). Many innate immune sensors such as TLRs also induce inflammation via NF-κB activation. **C,** Interferonopathies result from excess production of IFN-I, which binds to IFNAR to mediate JAK-STAT signaling. Inhibition of JAK by tofacitinib, ruxolitinib, and baricitinib is an approach increasingly used for the treatment of interferonopathies. *IFNAR*, IFN α/β receptor; *IL-1R1*, IL-1 receptor 1; *IL-1RA*, IL-1 receptor antagonist; *IL-1RAP*, IL-1 receptor accessory protein; *IRF9*, IFN regulatory factor 9; *ISG*, interferon-stimulated gene; *TLR*, Toll-like receptor; *TNFR*, TNF receptor; *TYK2*, tyrosine protein kinase 2.

and inconsistent treatment experience are not discussed in detail in this review. For detailed discussions and expert consensus on the diagnostic evaluation and management of SAIDs, we strongly recommend the 2021 European Alliance of Associations for Rheumatology/American College of Rheumatology points-to-consider articles for IL-1–mediated autoinflammatory diseases and interferonopathies.[20,21]

Treatment of inflammasomopathies/disorders of IL-1

Inflammasomes are supramolecular complexes that form in the cytoplasm in response to specific danger signals.[22] The structural composition and mechanistic details of several inflammasomes have been elucidated; these pathways converge to activate caspase 1, which then cleaves pro–IL-1β, pro–IL-18, and gasdermin D, leading to the release of active IL-1β and IL-18 through membrane pores in a process known as pyroptosis.[23] Aberrant activation of the inflammasomes and excess production of IL-1β connect the pathology of SAIDs collectively known as inflammasomopathies.[8]

The pathogenic role of IL-1 as demonstrated by the clinical efficacy of IL-1 inhibition is well documented for diseases that implicate dysregulation of the pyrin inflammasome (ie, FMF and hyper-IgD syndrome [HIDS]) or the cryopyrin/NOD-like receptor family pyrin domain–containing 3 (NLRP3) inflammasome (ie, cryopyrin-associated periodic syndrome [CAPS] and Majeed syndrome).[24-28] CAPS is caused by gain-of-function variants of NLRP3 and represents a spectrum of SAIDs of increasing severity, including familial cold autoinflammatory syndrome, Muckle-Wells syndrome, and neonatal-onset multisystem inflammatory disease (NOMID).[29-31]

Excess IL-1 signaling alone is sufficient to cause the development of severe multisystem inflammation, as illustrated by patients with deficiency of IL-1 receptor antagonist (DIRA).[32,33] The link to inflammasome/IL-1 activation may be less direct for some conditions grouped under this category. TNF receptor–associated periodic syndrome (TRAPS) caused by mutations of a TNF receptor subunit is intuitively a disease of TNF dysregulation but data from mechanistic studies and clinical trials increasingly favor a central role of IL-1β.[4,24,34,35] In the case of the recently described neonatal onset of pancytopenia,

TABLE I. Use of IL-1 inhibitors in inflammasomopathies/disorders of IL-1

Agent	Disease	LoE	FDA	EMA	No. of studies (no. of patients)	Pediatric dosing
Anakinra	crFMF	2C	—	√	9 (>100)	Start: 1-2 mg/kg/d; maximum 100 mg/d.
	MKD/HIDS	3C	—	—	7 (86)	Titrate to 3-4 mg/kg/d if necessary;
	TRAPS	3C	—	—	5 (>100)	maximum 200 mg/d.
	FCAS/MWS	3C	—	√	5 (>100)	
	NOMID/CINCA*	3C	√	√	4 (61)	
	DIRA*	3C	√	—	10 (17)	
	PAPA	4C	—	—	7 (14)	
	Majeed syndrome	4C	—	—	4 (7)	
	NOCARH	4C	—	—	2 (7)	
Canakinumab	crFMF	2B	√	√	9 (>200)	≤40 kg: 2 mg/kg every 4 wk;
	MKD/HIDS	2B	√	√	7 (>100)	Titrate to 4 mg/kg every 4 wk if necessary.
	TRAPS	2B	√	√	4 (61)	>40 kg: 150-300 mg every 4 wk.
	FACS/MWS†	2B	√	√	10 (>200)	
	NOMID/CINCA‡	2B	—	√	9 (>100)	
	PAPA	4C	—	—	4 (4)	
	Majeed syndrome	5D	—	—	2 (3)	
Rilonacept	crFMF	2C	—	—	1 (14)	2.2 mg/kg weekly.
	FACS/MWS	2B	√	—	3 (>100)	Start: 4.4 mg/kg weekly, maintenance
	DIRA	3C	√	—	1 (6)	2.2 mg/kg weekly; maximum 320 mg weekly.

CINCA, Chronic infantile neurological cutaneous articular syndrome; *crFMF*, colchicine-resistant familial Mediterranean fever; *FCAS/MWS*, familial cold autoinflammatory syndrome/Muckle-Wells syndrome; *NOCARH*, neonatal onset of pancytopenia, autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis; *PAPA*, pyogenic arthritis, pyoderma gangrenosum, and acne.
*Maximum 8 mg/kg/d.
†Dose every 8 wk.
‡2-8 mg/kg every 4-8 wk; maximum 600 mg/d.

autoinflammation, rash, and episodes of hemophagocytic lymphohistiocytosis, pathogenic variants of cell division cycle 42 misdirect the translated protein to the Golgi apparatus and cause pyrin activation.[36,37]

Currently, there are 3 available biologic agents that target IL-1: anakinra, rilonacept, and canakinumab (Fig 1, *A*). Anakinra is a recombinant form of the endogenous IL-1 receptor antagonist that attenuates IL-1α and IL-1β signaling by competitive binding to the IL-1 receptor complex. Canakinumab is a human mAb that neutralizes IL-1β, whereas rilonacept is a soluble receptor that traps IL-1α and IL-1β. Additional drug candidates that target the inflammasomes and IL-1 have been recently reviewed.[8] IL-1β is the key driver of pathology in most inflammasomopathies and it is effectively neutralized by all 3 IL-1 antagonists, although studies that directly compare the relative efficacy of these agents for a given indication are lacking. Anakinra is approved for the treatment of NOMID by the FDA and for all forms of CAPS by the EMA. Canakinumab first received approval for CAPS, and its indications subsequently expanded to include colchicine-resistant FMF, TRAPS, and mevalonate kinase deficiency (MKD) in the United States and Europe on the basis of the results from the Canakinumab Pivotal Umbrella Study in Three Hereditary Periodic Fevers trial.[24] Rilonacept is FDA-approved for the treatment of CAPS (familial cold autoinflammatory syndrome and Muckle-Wells syndrome), but its availability is currently limited to the United States.[38] Table I presents the evidence for the use of IL-1 antagonist in patients with inflammasomopathies/disorders of IL-1. Details of individual studies included in our literature review are provided in Table E3 (in the Online Repository available at www.jacionline.org).

The IL-1 antagonists are given as subcutaneous injections but their pharmacokinetics and frequency of administration are highly variable. Anakinra is given daily, rilonacept is dosed weekly, and canakinumab is administered every 4 to 8 weeks.[39] For a trial of IL-1 blockade when the diagnosis is uncertain, clinicians often prefer anakinra because of its short half-life and rapid onset of action. However, daily injections are challenging in young children and the dosing schedule of canakinumab may be better tolerated. In circumstances in which IL-1α may also contribute to the inflammatory response (ie, DIRA), the dual specificity for IL-1α and IL-1β makes anakinra and rilonacept preferred over canakinumab. For SAIDs with central nervous system involvement (ie, CAPS), there is no direct *in vivo* comparison of IL-1 antagonists to evaluate their ability to penetrate the blood-brain barrier. *In vitro* modeling of the blood-brain barrier suggests that anakinra is transported more efficiently than canakinumab.[40] Although both anakinra and canakinumab are clinically effective for NOMID, anakinra treatment was associated with a greater reduction of IL-6, C-X-C motif chemokine ligand 10 (CXCL-10), IL-18, and white blood cell levels in the cerebrospinal fluid compared with that associated with canakinumab treatment in a small study of 8 patients.[41]

The levels of IL-1α and IL-1β in the peripheral blood are generally low and cannot be used reliably to track disease activity in patients with inflammasomopathies/disorders of IL-1. Serum levels of IL-1β in patients with CAPS are captured only after the administration of canakinumab and formation of IL-1β–antibody complexes.[42] Clinically, rapid improvement of disease manifestation is often seen after the administration of IL-1 antagonists, in parallel with reductions in neutrophil count and inflammatory markers such as C-reactive protein, erythrocyte sedimentation rate, serum amyloid A, and S100 proteins.[20,42] Disease activity and damage can also be monitored using the

validated Autoinflammatory Diseases Activity Index and the Autoinflammatory Disease Damage Index to aid in adjustment of therapy.[43] American College of Rheumatology (ACR)/European Alliance of Associations for Rheumatology (EULAR) guidance is available for disease-specific monitoring of CAPS, TRAPS, MKD, and DIRA.

IL-1 antagonists are generally well tolerated with comparable safety profiles. Injection-site reactions characterized by localized erythema and painful induration are common during the initial weeks of therapy, especially with anakinra and rilonacept.[39] The cause of site reactions remains unclear but these findings are transient and resolve spontaneously in most cases, sometimes requiring topical therapies and/or antihistamines. Despite the multiple roles of IL-1 in innate and adaptive immunity, the infection risk associated with IL-1 blockade appears to be modest. Early studies on anakinra did not reveal significantly increased risk for serious infections in adults with rheumatoid arthritis or patients with bacterial sepsis (even at much higher doses compared with the treatment of SAIDs).[44,45] In the Canakinumab Anti-inflammatory Thrombosis Outcomes Study, increased mortality related to infections was associated with canakinumab treatment but death was more likely in individuals with older age and diabetes.[46] Heightened risk for opportunistic infections such as tuberculosis was not noted in these trials. Although long-term data are limited in the pediatric population, infections related to the use of IL-1 antagonists are uncommon and the favorable safety profile has broadened the use of these medications for systemic JIA, Kawasaki disease, macrophage activation syndrome (MAS), and multisystem inflammatory syndrome in children associated with coronavirus disease 2019.[47-50] Concerns for increased malignancy risk are also minimal for IL-1 antagonists. In fact, inflammation mediated by IL-1 may promote oncogenesis, and canakinumab treatment was associated with a substantial reduction of lung cancer risk in the Canakinumab Anti-inflammatory Thrombosis Outcomes Study.[51]

Treatment of disorders of NF-κB and/or aberrant TNF activity

NF-κB is a family of essential transcription factors that mediate proinflammatory and antiapoptotic effects of multiple danger-sensing pathways. Detailed reviews of NF-κB biology are available.[52,53] Inducers of NF-κB signaling include Toll-like receptors, nucleotide-binding and oligomerization domain (NOD)-like receptors, and the inflammatory cytokines TNF and IL-1. Activation and nuclear translocation of NF-κB result in the production of TNF, IL-6, and other cytokines/chemokines to propagate the inflammatory response. To prevent excess inflammation, NF-κB activation is tightly controlled by inhibitory proteins that are in turn intricately regulated by a system of ubiquitination and proteasomal degradation.[53,54] Reflecting the complexity of NF-κB signaling and its large network of regulatory pathways, the pathologic mechanisms for disorders of NF-κB and/or aberrant TNF activity are not straightforward.

NOD2 is a cytoplasmic sensor that activates NF-κB on detection of muramyl dipeptide derived from bacterial cell wall.[55,56] *NOD2* mutations are responsible for Blau syndrome, an autosomal-dominant disease characterized by arthritis, uveitis, and granulomatous dermatitis.[57] Excess activation of NF-κB due to gain-of-function *NOD2* variants is thought to be the basis of chronic inflammation, and TNF inhibitors (TNFi) can be highly effective for Blau syndrome.[58,59] In contrast, a recent study argues that NOD2 may have an inhibitory role, and the inability to cross-regulate inflammatory triggers due to loss-of-function mutations is responsible for the aberrant NF-κB activation in Blau syndrome.[60]

A20 and OTU deubiquitinase with linear linkage specificity (OTULIN) are deubiquitinases that negatively regulate NF-κB signaling by modulating proteasomal degradation of upstream mediators. These known functions can explain the increased NF-κB activation and TNF production in patients with haploinsufficiency of the NF-κB regulator A20 (HA20) and deficiency of OTULIN (otulipenia/OTULIN-related autoinflammatory syndrome).[61-64] OTULIN also antagonizes the function of linear ubiquitin assembly complex (comprising haem-oxidized iron regulatory protein 2 ubiquitin ligase 1 [HOIL-1], HOIL-1–interacting protein, and SHANK associated RH domain interactor [SHARPIN]). Interestingly, pathogenic mutations in HOIL-1 and HOIL-1–interacting protein that lead to decreased NF-κB activity also cause SAIDs that are at least partially responsive to TNF inhibition.[65,66] Increased cell death induced by TNF signaling may be the trigger of spontaneous inflammation in these conditions. A similar mechanism of enhanced cell death may explain the autoinflammatory features of RELA haploinsufficiency and TANK-binding kinase 1 deficiency in the setting of reduced NF-κB function.[67,68] Although it may seem counterintuitive that excess as well as insufficient activation of NF-κB can lead to autoinflammation, this enigma is in part explained by differential utilization of NF-κB among different cell types, setting up scenarios in which some cells are hyperresponsive while others are paradoxically hyporesponsive to the same inflammatory stimulus.[69]

In some instances such as in the deficiency of adenosine deaminase 2 (DADA2), the pathogenic mechanism remains unclear and the classification as a disorder of aberrant TNF activity largely reflects the experience of treating patients with TNFi.[70] Activation of macrophages by neutrophil extracellular traps is a potential source of TNF in DADA2.[71] However, data for the effectiveness of TNF inhibition in DADA2 are largely restricted to the vasculitic/inflammatory phenotype. Severe hematologic and immunologic derangements in DADA2 are typically refractory to TNFi and require allogeneic hemopoietic stem cell transplant.[72,73]

TNFi are often used for the treatment of JIA and inflammatory bowel disease in children. Interestingly, musculoskeletal and intestinal inflammation are common manifestations of SAIDs caused by aberrant NF-κB and/or TNF activity. TNFi used for the treatment of SAIDs include etanercept (recombinant soluble TNF receptor 2 and IgG1 Fc fusion protein), infliximab (chimeric human/mouse mAb), and adalimumab (humanized mAb) (Fig 1, *B*). Currently, SAIDs are not among the approved indications of TNFi. Table II provides a summary of evidence for the use of TNFi in SAIDs. Details of individual studies from our literature review are provided in Table E4 (in the Online Repository available at www.jacionline.org).

Beyond its role as a mediator of inflammation, NF-κB is critically involved in adaptive immunity as a downstream effector of B-cell receptor and T-cell receptor signaling cascades.[53,74] A noncanonical pathway of NF-κB signaling is further required for lymphoid tissue development.[74] The multiple essential

TABLE II. Use of TNFi in disorders of NF-κB and/or aberrant TNF activity

Agent	Disease	LoE	FDA	EMA	No. of studies (no. of patients)	Pediatric dosing
Etanercept	DADA2	3C	—	—	10 (49)	0.8 mg/kg weekly or 0.4 mg/kg twice weekly.
	HA20	4C	—	—	9 (18)	Maximum: 50 mg/wk.
	Blau syndrome	4C	—	—	7 (8)	
	LUBAC	5D	—	—	2 (3)	
	ORAS	5D	—	—	2 (2)	
Infliximab	DADA2	3C	—	—	8 (15)	Loading: 5-6 mg/kg on weeks 0, 2, and 6.
	HA20	4C	—	—	9 (18)	Maintenance: every 4-8 wk. Titrate dose up to 10 mg/kg or increase treatment frequency if necessary.
	Blau syndrome	4C	—	—	14 (29)	
	ORAS	5D	—	—	2 (2)	
	TBK1 deficiency	5D	—	—	1 (2)	
	RELA haploinsufficiency	5D	—	—	1 (1)	
Adalimumab	DADA2	3C	—	—	8 (42)	10-40 mg every 2 wk;* increase dose or frequency if necessary.
	Blau syndrome	4C	—	—	15 (16)	
	HA20	4C	—	—	5 (8)	

LUBAC, Linear ubiquitin assembly complex; *ORAS*, OTU deubiquitinase with linear linkage specificity–related autoinflammatory syndrome; *TBK1*, TANK-binding kinase 1.
*Dosages were variable among studies. Recommended doses for JIA and pediatric ulcerative colitis are provided here for reference. JIA: 10 to <15 kg: 10 mg every 2 wk; 15 to <30 kg: 20 mg every 2 wk; ≥30 kg: 40 mg every 2 wk. Pediatric ulcerative colitis: 20-40 kg: 20 mg weekly or 40 mg every 2 wk; >40 kg: 40 mg weekly or 80 mg every 2 wk.

immune functions of NF-κB likely explain the frequent presence of immunodeficiency in disorders of NF-κB signaling. As with any immunosuppressive treatment, the risks and benefits of TNFi in patients with underlying immunodeficiency should be considered on a case-by-case basis.

Disease manifestations and levels of acute-phase reactants should be followed to determine disease activity and treatment response for disorders of NF-κB and/or aberrant TNF activity. Standardized assays to measure TNF levels are not routinely available for clinical use, and TNF levels in the peripheral blood may increase after treatment because of drug-cytokine complexes.[75] Transcriptomic signatures of NF-κB and TNF signaling have been developed and may be helpful in assessing immune activation and treatment response on a research basis.[76,77]

The development of neutralizing antibodies to TNFi poses a serious concern for the long-term efficacy of these medications.[78] Antidrug antibodies are rare for etanercept but can occur in 15% to 30% of patients treated with infliximab or adalimumab. In situations wherein a disease flare may lead to significant complications, such as stroke or brain hemorrhage in patients with DADA2, periodic monitoring of antidrug antibodies should be considered. Concurrent use of DMARDs such as methotrexate has been shown to restrain the development of antidrug antibodies, but evidence of this approach in SAIDs has not been demonstrated.[79]

The safety profile of TNFi in children is generally favorable on the basis of studies on JIA.[80] Mild injection-site reactions to etanercept and adalimumab can occur in approximately one-third of cases, whereas infliximab treatment is associated with infusion reactions in 10% to 20% of patients. Two meta-analyses concurred that serious infections and opportunistic infections are not significantly increased in patients with JIA treated with TNFi compared with other treatment groups.[81,82] However, patients with SAIDs that implicate NF-κB dysregulation may have considerably higher risks at baseline because of their intrinsic immunodeficiency. Rare adverse effects of TNFi include psoriasis, autoimmunity, demyelinating disease, and nonmelanoma skin cancer.[83] The incidence of these findings in the pediatric population is unknown. Natural history studies and clinical trials are needed to determine the prevalence of these findings in patients with SAIDs and the potential associations with immunosuppressive therapy.

Treatment of interferonopathies

Interferonopathies are a group of monogenic SAIDs with pathology primarily mediated by increased production of type I interferons (IFN-I) and/or dysregulated IFN-I signaling.[3,9] Discussion of IFN-I is typically confined to IFN-α and IFN-β, but the cytokine family also includes IFN-ε, IFN-κ, and IFN-ω. IFN-I are best known for their role in orchestrating the body's immune response to viruses.[84] Recognition of exogenous and endogenous nucleic acids by one of several innate sensing pathways culminates in the production of IFN-I, which then binds to the IFN-α/β receptor complex to activate Janus kinase 1 (JAK1) and tyrosine protein kinase 2. JAK activation recruits and phosphorylates signal transducer and activator of transcription 1 and 2 (STAT1 and STAT2), which together form a heterodimer that complexes with IFN regulatory factor 9 and translocates into the nucleus to initiate the transcription of target genes.

The elaborate mechanisms involved in nucleic acid sensing and IFN-I production are important for antiviral defense but also license the development of SAIDs when these pathways are dysregulated.[3] Indeed, interferonopathies have been linked to gain-of-function variants of nucleic acid sensors (ie, stimulator of interferon genes, retinoic acid–inducible gene I, and melanoma differentiation–associated gene 5) and IFN-I signaling mediators (ie, JAK1, STAT1, and STAT2) as well as to loss-of-function variants of nucleases (ie, 3-prime repair exonuclease 1, ribonuclease H2A/B/C, and deoxyribonuclease 1/2/1L3), nucleic acid modifiers (ie, adenosine deaminase acting on RNA 1, and sterile α motif and histidine-aspartate domain–containing protein 1), and negative regulators of IFN-I signaling (ie, ubiquitin-specific protease 18, interferon-stimulated gene product 15, and suppressor of cytokine signaling 1). Interferonopathies can also develop in the

TABLE III. Use of Jakinibs in the treatment of interferonopathies

Agent	Disease	LoE	FDA	EMA	No. of studies (no. of patients)	Pediatric dosing*
Tofacitinib	SAVI	4C	—	—	5 (8)	10 to <20 kg: 3.2 mg twice daily.
	AGS	4C	—	—	4 (5)	20 to <40 kg: 4 mg twice daily.
	CANDLE/PRAAS	5D	—	—	3 (3)	≥40 kg: 5 mg twice daily.†
	SOCS1 haploinsufficiency	5D	—	—	1 (1)	
Baricitinib	AGS	3C	—	—	4 (40)	Start 4-8 mg total daily dose (divided in 2-3 doses) depending on weight and eGFR; detailed dosing table and strategies for dose escalation are described.‡
	CANDLE/PRAAS	3C	—	—	2 (11)	
	SAVI	4C	—	—	3 (7)	
	STAT1-GOF	4C	—	—	3 (5)	
	COPA	5D	—	—	2 (2)	
	SOCS1 haploinsufficiency	5D	—	—	1 (1)	
	C1 deficiency	5D	—	—	1 (2)	
	Deoxyribonuclease 2 deficiency	5D	—	—	1 (1)	
Ruxolitinib	STAT1 GOF	3C	—	—	12 (31)	Start 0.3-0.4 mg/kg total daily dose (divided in 2 doses).§ Maximum 1.1-2.0 mg/kg total daily dose (divided in 2 doses).§
	SAVI	4C	—	—	7 (29)	
	AGS	4C	—	—	7 (8)	
	CANDLE/PRAAS	5D	—	—	1 (1)	
	USP18 deficiency	5D	—	—	1 (1)	
	Deoxyribonuclease 2 deficiency	5D	—	—	1 (1)	

CANDLE/PRAAS, Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature/proteasome-associated autoinflammatory syndromes; *COPA*, COPI Coat Complex Subunit Alpha; *eGFR*, estimated glomerular filtration rate; *GOF*, gain of function; *SAVI*, stimulator of interferon gene–associated vasculopathy with onset in infancy; *SOCS1*, suppressor of cytokine stimulation 1; *USP18*, ubiquitin-specific protease 18.

*Dosing strategies for Jakinibs in children vary widely among studies. Most publications describe weight-based dosing, whereas some describe dosing based on body surface area.

†The recommended dosage of tofacitinib for treatment of JIA is provided.[88]

‡The dosing algorithm for baricitinib on the basis of age and eGFR described by Kim et al is referenced.[89]

§The range of initial dosing and maximum dosing for ruxolitinib is derived from large case series.[90,91]

setting of proteosome dysfunction, although the precise mechanism for IFN-I production remains to be confirmed.[2] The pathophysiology of interferonopathies has been extensively reviewed elsewhere.[3,9,85]

The manifestations of interferonopathies are often distinct from those associated with inflammasomopathies and disorders of NF-κB/excess TNF production. Progressive neurologic decline, encephalopathy, brain calcification, cutaneous vasculopathy, interstitial lung disease, and systemic autoimmunity are among the hallmarks of interferonopathies.[1] The presence of autoantibodies and organ-specific manifestations of autoimmunity (ie, glomerulonephritis, thyroiditis, and vasculitis) highlight the role of IFN-I in adaptive immunity and illustrate that the concepts of autoinflammation and autoimmunity are not mutually exclusive.

JAKs mediate IFN-I signaling directly downstream of IFN-α/β receptor, and small-molecule Jakinibs are increasingly used for the treatment of interferonopathies.[86] There are 4 members of the JAK family in humans: JAK1, JAK2, JAK3, and tyrosine protein kinase 2. The available first-generation Jakinibs including tofacitinib, baricitinib, and ruxolitinib all display selectivity toward multiple JAKs (Fig 1, *C*).[87] Baricitinib and ruxolitinib primarily target JAK1 and JAK2, whereas tofacitinib possesses greater selectivity to JAK1 and JAK3. The requirement of JAK1 in the IFN-I signaling cascade provides a rationale for the therapeutic use of these agents in patients with interferonopathies. Table III[88-91] presents the evidence for the use of first-generation Jakinibs in SAIDs, and details of individual studies are provided in Table E5 (in the Online Repository available at www.jacionline.org).

Jakinibs are approved for the treatment of polyarticular JIA (tofacitinib) in children and chronic graft-versus-host disease (ruxolitinib) in adolescents.[88,92] Their safety and efficacy in patients with interferonopathies have been demonstrated by many studies, although randomized clinical trials are lacking. In an open-label single-center study of 35 patients with Aicardi-Goutières syndrome (AGS), baricitinib treatment was associated with improved skin manifestations and neurologic function as measured by developmental milestones, even in patients with long-standing disease.[93] These findings argue against the notion that treatment is effective only to alleviate active inflammation. This study and other case series collectively demonstrate the beneficial effects of Jakinibs on quality-of-life measures and emphasize the importance of early treatment.[90,94,95] At this time, there is insufficient evidence to compare the relative efficacy of different Jakinibs, and therefore selection of these agents is typically based on availability and experience of the providers.

Unlike the inflammatory profile of SAIDs that implicate excess production of IL-1 or TNF, conventional markers of inflammation such as acute-phase reactants, neutrophilia, and thrombocytosis are less reflective of the systemic inflammation associated with interferonopathies. The diagnostic evaluation and disease monitoring of interferonopathies often rely on quantification of gene expression induced by IFN-I,[96,97] an approach used to assess IFN-I upregulation in patients with autoimmune diseases such as systemic lupus erythematosus. Evaluation of this interferon signature is typically performed on a research basis by quantitative PCR or more advanced transcriptomic techniques (ie, NanoString nCounter assay, microarray, and RNA sequencing). However, the correlation between interferon levels and disease activity may vary among the different conditions. ACR/EULAR guidance is available for disease-specific monitoring and management of AGS, stimulator of interferon genes–associated

vasculopathy of infancy, and proteasome-associated autoinflammatory syndromes/chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature.[20]

JAKs regulate the signaling of more than 40 cytokines and growth factors; thus, broad inhibition of these pathways by first-generation Jakinibs can potentially cause a wide spectrum of unwanted consequences. In practice, the safety profile of Jakinibs is largely comparable with that of other biologics.[98] Common adverse effects of Jakinibs include transient elevation of transaminases, increased high-density and low-density cholesterol levels, and increased infection risk. In trials for rheumatoid arthritis in adults, the risk of infections associated with Jakinibs treatment was comparable with that associated with other biologics except for an increased incidence of herpes zoster infection seen with all first-generation Jakinibs.[99,100] Long-term monitoring of tofacitinib treatment in adults with rheumatoid arthritis (aged ≥50 years with ≥1 additional cardiovascular risk factor) revealed that compared with TNFi, tofacitinib treatment is associated with higher risk of major cardiovascular events (hazard ratio, 1.33; 95% CI, 0.91-1.94) and malignancy (hazard ratio, 1.48; 95% CI, 1.04-2.09).[101]

It remains to be seen whether the cardiovascular and malignancy risks associated with Jakinibs are applicable to pediatric patients or healthy adults without the underlying risk factors. Although there is a paucity of safety data in the pediatric population, BK viremia associated with the use of Jakinibs has been reported in several patients with interferonopathies, and therefore routine screening is recommended to prevent nephropathy.[20,93,94,102] In the largest trial to date for the use of Jakinibs in children with JIA, the rates of serious adverse events and serious infection associated with tofacitinib exposure were 4% (incidence rate, 7.3/100 patient-years) and 2% (incidence rate, 2.4/100 patient-years), respectively, over 44 weeks.[88] Two mild cases of herpes zoster were documented, and transient elevation of transaminase levels occurred in approximately 15% of patients. Importantly, in the placebo-controlled phase of the study, there was no significant difference in the rate of adverse events between tofacitinib and placebo groups.[88] However, the impact of prolonged JAK inhibition on growth and development is unknown. This is an important question to address in the pediatric population given the role of JAK2 in growth hormone signaling. Long-term surveillance studies in children are necessary to fully understand the risk profile associated with Jakinibs.

Abrupt discontinuation of Jakinibs may lead to an acute cytokine storm syndrome because of the rebound of multiple cytokines. Experience with this phenomenon comes from patients with myelofibrosis treated with ruxolitinib. Common manifestations of the described ruxolitinib discontinuation syndrome include disease relapse, cytopenia, and worsening splenomegaly. Life-threatening complications including coagulopathy, acute respiratory distress syndrome, and septic-like shock have been described in a few cases.[103] Therefore, a gradual reduction of dosage is recommended for tapering or discontinuation of Jakinibs.

A newer generation of Jakinibs that specifically target JAK1 (upadacitinib and filgotinib) are clinically available for the treatment of rheumatoid arthritis in adults.[104] Selective disruption of IFN-I signaling without having an impact on other immune pathways can also be accomplished by neutralizing IFN-I or blocking their binding to IFN-α/β receptor. Anifrolumab, an mAb that targets IFN-α/β receptor, was recently approved for the treatment of systemic lupus erythematosus.[105] These newer agents with improved selectivity maybe advantageous compared with the existing Jakinibs for the treatment of interferonopathies. In addition, an open-label pilot study of nucleoside analog reverse-transcriptase inhibitors (abacavir, lamivudine, and zidovudine combined) in patients with AGS demonstrated a reduction of IFN-I levels.[106] This study illustrates that nucleic acids from endogenous retroviral elements may be targeted to reduce IFN-I production in some forms of interferonopathies.

THE USE OF OTHER BIOLOGICS IN SAIDs

Increased levels of IL-6 and its surrogate marker C-reactive protein are often seen in patients with SAIDs. Tocilizumab is an mAb that inhibits IL-6 signaling by binding to the soluble IL-6 receptor. The production of IL-6 occurs downstream of IL-1 signaling and NF-κB activation, but the contribution of IL-6 to the pathophysiology of SAIDs is less unclear. Tocilizumab is used as the primary therapy in the recently described cleavage-resistant receptor-interactive protein kinase 1–induced autoinflammatory syndrome.[107,108] There are also case reports and case series on the use of tocilizumab in FMF, TRAPS, and HIDS, often in patients who are refractory to other treatment options.[8]

Our earlier discussion of inflammasomopathies focused on the biology of IL-1. The activation of caspase 1 by inflammasomes also permits activation and release of IL-18, and strikingly high levels of IL-18 are associated with dysregulation of the NOD-like receptor subfamily C (NLRC4) inflammasome. Patients with gain-of-function NLRC4 variants experience early-onset colitis and MAS.[109,110] IL-18 licenses the production of IFN-γ, which plays a central role in the development of hemophagocytic lymphohistiocytosis and MAS. Inhibition of IL-18 by tadekinig alfa (recombinant human IL-18 binding protein) has demonstrated beneficial effects in cases of NLRC4-MAS and a clinical trial is ongoing (NCT03113760).[111,112] Elevated levels of IL-18 are also described in other inflammasomopathies treated with IL-1 antagonists, but the clinical significance remains to be elucidated.[113] The distinction of IL-1–opathies and IL-18–opathies has been recently proposed.[10]

Biologics targeting IL-17 and IL-12/IL-23 have been recently approved for the treatment of psoriasis and psoriatic arthritis in children. To our knowledge, these agents have not been used to treat SAIDs.

CHALLENGES IN THE TREATMENT OF SAIDs

Treatment of monogenic SAIDs remains challenging because of the rarity of these conditions and the limited understanding of their pathophysiology. The 3 groups of SAIDs reviewed in the earlier sections are categorized largely on the basis of the mechanism of inflammation related to the underlying monogenic defects. In practice, monogenic disorders comprise only a fraction of SAIDs and many patients with features of systemic autoinflammation possess genetic variants that are not considered pathogenic/likely pathogenic, or have no detectable defects at all in genes associated with SAIDs. Some of these patients may have known nonmonogenic autoinflammatory syndromes such as systemic JIA (Still disease) and periodic fever, aphthous ulcers, pharyngitis, and adenitis syndrome, for which treatment algorithms are available. The remainder comprise a highly heterogeneous group under the diagnosis of undefined SAIDs. Although there is no standardized

treatment for patients with undefined SAIDs, a treat-to-target approach of trialing nonsteroidal anti-inflammatory drugs, colchicine, DMARDs, corticosteroids, and biologics while weighing the risks and benefits of each treatment is used. As shown by a large study from the EuroFever Registry, many patients with undefined SAIDs respond well to nonsteroidal anti-inflammatory drugs, corticosteroids, colchicine, and anakinra.[114]

Even for SAIDs with well-characterized monogenic defects, the trichotomous grouping is an oversimplification given the extensive interactions between immune pathways and our incomplete understanding of these diseases. Lessons from clinical experience often raise more questions. For instance, HA20 is mechanistically a disorder of NF-κB dysregulation and patients are typically treated with colchicine, DMARDs, and/or TNFi.[115] Curiously, an elevated expression of IFN-I–inducible genes (classically seen in interferonopathies) was observed in patients refractory to TNFi, and JAK inhibition using baricitinib effectively treated the residual inflammation in these cases.[116] In light of these findings, should the interferon signature be examined in every patient with HA20? An IFN-I signature is similarly described in DADA2 and otulipenia.[117,118] Should we consider Jakinibs for these conditions on the basis of the IFN signature alone? Moreover, aberrant activation of nucleic acid–sensing pathways that drive the development of interferonopathies also mechanistically elicits NF-κB activation and TNF production. The overlap between these pathways has practical implications given the antagonistic effects of inhibiting TNF and IFN-I pathways.[119] Furthermore, some inflammasomopathies are associated with elevated production of TNF in addition to IL-1, and beneficial effects of TNF blockade have been reported in observational studies. The same is true for the use of IL-1 inhibitors for disorders of NF-κB activation and TNF production. Do these pathways operate synergistically in the context of autoinflammation or act in parallel to drive different organ-specific manifestations? In patients who display only partial response to an agent, should the addition of another biologic (from a different class) or Jakinib be considered and do the potential benefits outweigh the added risks of immunosuppression? These questions are among the many complex issues related to the treatment of SAIDs. The combination of clinical experience, mechanistic studies, and molecular profiling of each disease is necessary to piece together these puzzles and optimize the treatment approach for each disease and each patient.

THE EVOLVING PRACTICE OF TREATING SAIDs

The availability of biologics and Jakinibs has profoundly changed how we manage SAIDs in children. However, the rarity of SAIDs and the lack of randomized controlled trials in the pediatric population will continue to be limitations for developing evidence-based treatment approaches. The bias in reporting positive findings also has an impact on our estimation of therapeutic efficacy and adverse effects. Moving forward, unbiased reporting of cases regardless of outcome and combining experience through multicenter collaborations are critical to improve the quality of evidence needed to determine the optimal agent and optimal dosing for each disease. A precise and personalized approach is necessary for the treatment of SAIDs given the degree of clinical heterogeneity even among patients with the same genotype.

Lastly, our practice of treating SAIDs will undoubtedly evolve with the rapid advances in understanding the mechanisms of autoinflammation. New forms of SAIDs as well as new treatment options will continue to appear. Deciphering the mechanistic underpinnings of each condition will define more specific druggable targets, which may eventually replace the current approach of blocking selective cytokines and their signaling pathways.

CONCLUSIONS

Tremendous progress has been made in identifying SAIDs and understanding the biology of these complex disorders since the term “autoinflammation” was coined more than 2 decades ago. Advances in immunology and genetics have elucidated several central pathways that propagate the inflammatory response in SAIDs. Leveraging the experience of treating patients with inflammatory disorders, clinicians have found success in treating patients with SAIDs using available medications. Precise targeting of pathologic mechanisms using biologics and Jakinibs has made these potentially fatal diseases manageable for many patients. With generally favorable safety profiles, these agents have become indispensable for the treatment of SAIDs. Most importantly, more clinical trials are being conducted on SAIDs and these studies will bring clarity on the best practice of treating these intriguing conditions.

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