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STAT1 and STAT3 gain of function: clinically heterogenous immune regulatory disorders

Peter Olbrich[a,b] *and Alexandra F. Freeman*[c]

Purpose of review
The identification of STAT1 gain-of-function (GOF) in 2011 and STAT3 GOF in 2014 has advanced our understanding of the host immunity along the JAK/STAT pathway and allowed targeted treatment approaches. We review the clinical features and pathogenesis of STAT1 and STAT3 GOF and how this has shaped new approaches to therapy.

Recent findings
STAT1 GOF, initially described in patients with chronic mucocutaneous candidiasis (CMC) and autoimmune thyroid disease, is now recognized to cause early-onset multisystem autoimmunity and a range of infections. STAT3 GOF comprises mostly lymphoproliferation and autoimmunity but also with varying severity, including some with life threatening organ dysfunction. Treatment has evolved along with the understanding of the pathogenesis, with patients now receiving JAK inhibition to block upstream of the STAT defect with good response in autoimmunity and CMC in STAT1 GOF. Blockade of IL-6 signaling has also been used in STAT3 GOF. Hematopoietic cell transplantation had initial poor outcomes, but outcomes are now improving with focus on the control of inflammation pretransplant.

Summary
Understanding the pathogenesis of STAT1 and STAT3 GOF has allowed great recent advancements in therapy, but many questions remain as to the best approach to therapy for each patient's clinical presentation as well as the durability of these therapies.

Keywords
immune regulatory disorders, jak inhibitors, sTAT1 gain of function, sTAT3 gain of function

INTRODUCTION

The seven members of the signal transducer and activator of transcription (STAT) family are critical mediators of cytokine and growth factor signaling, playing vital roles in immunity, cell proliferation, differentiation, and survival. Over the last two decades, there have been great gains in our understanding of host immunity amongst the STAT proteins, largely through identification and clinical phenotyping of multiple inborn errors of immunity (IEI) [1▪▪,2▪▪]. The types of genetic defects have been remarkable with several of the genes having multiple types of variants: gain of function (GOF), biallelic loss of function (LOF), dominant negative, haplo-insufficiency, and somatic GOF. STAT1 and STAT3 stand out in the field of IEI as the molecular and clinical effects of GOF and LOF mutations have been widely studied. Whereas the clinical phenotype of patients with STAT1 and STAT3 LOF or dominant negative variants is fairly consistent, those with GOF variants show very heterogenous clinical manifestations including variable infection susceptibility, immune dysregulation, malignancy, and vasculopathies [3]. Understanding the distinct and overlapping features of these syndromes provides insight into their pathogenesis and informs therapeutic approaches.

In this review, we will discuss recent advances in the clinical manifestations, genetics, immunology, and treatment of STAT1 and STAT3 GOF disease,

[a]Sección de Infectología, Reumatología e Inmunología Pediátrica, UGC de Pediatría, Hospital Universitario Virgen del Rocío, Instituto de Biomedicina de Sevilla/Universidad de Sevilla/Consejo Superior de Investigaciones Científicas, Red de Investigación Translacional en Infectología Pediátrica, [b]Departamento de Farmacología, Pediatría, y Radiología, Facultad de Medicina, Universidad de Sevilla, Seville, Spain and [c]Laboratory of Clinical Immunology and Microbiology, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

Correspondence to Alexandra F. Freeman, NIH Building 10 Room 12C103, 9000 Rockville Pike Bethesda, MD 20892, USA.
Tel: +1 301 594 9045; e-mail: Freemaal@mail.nih.gov

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KEY POINTS

- Initially described in patients with predominantly mucocutaneous candidiasis and autoimmune thyroid disease, STAT1 GOF is now recognized to cause a wide range of infection susceptibility, autoimmunity and inflammatory disease.
- With recent clinical phenotyping in about 200 patients with STAT3 GOF, the clinical heterogeneity is apparent, with varying degrees of autoimmunity, inflammatory disease, lymphoproliferation and infection susceptibility.
- There has been great progress in recent years in therapies for both STAT1 GOF and STAT3 GOF with the use of JAK inhibition, as well as IL-6 blocking agents for STAT3 GOF.
- Although initial outcomes for hematopoietic cell transplantation (HCT) were poor in STAT1 GOF, recent gains in understanding the inflammatory pathogenesis and treatment are improving HCT outcomes.

emphasizing the current understanding as well as areas for future research.

STAT1 GAIN OF FUNCTION

Clinical features.

STAT1 GOF was described in 2011 in a cohort of patients with chronic mucocutaneous candidiasis (CMC), some of whom also had autoimmunity, primarily as thyroid disease (Table 1) [4,5]. Since that time, the broad clinical phenotype of STAT1 has become apparent, with clinical heterogeneity even within families sharing the same variant [6,7].

Infections

CMC is the most common manifestation, affecting over 95% of patients [6,7] (Fig. 1). Most CMC starts in eary infancy, and the infecting Candida can develop significant antifungal resistance due to prolonged therapy. While less frequent, other fungal infections include *Pneumocystis jirovecii* pneumonia, disseminated filamentous molds, *Cryptococcus*, *Histoplasmosis*, and *Coccidioides*. Bacterial infections, particularly recurrent pneumonias, affect approximately half of patients and may lead to bronchiectasis (Fig. 1). Bacterial infections (mainly *Staphylococcus aureus*) of the skin and soft tissues are common. Although mycobacterial diseases are more characteristic for patients with STAT1 LOF, BCGitis or nontuberculous mycobacteria adenitis has been reported. Recurrent and severe viral infections affect about one-third of patients. Recurrent herpes simplex virus (HSV) infections are the most frequent, but fatal cases of JC virus-induced progressive multifocal leukoencephalopathy have been documented [8]. During the COVID, pandemic heterozygous disease courses were reported ranging from mild to fatal disease including respiratory failure and HLH [9,10▪,11].

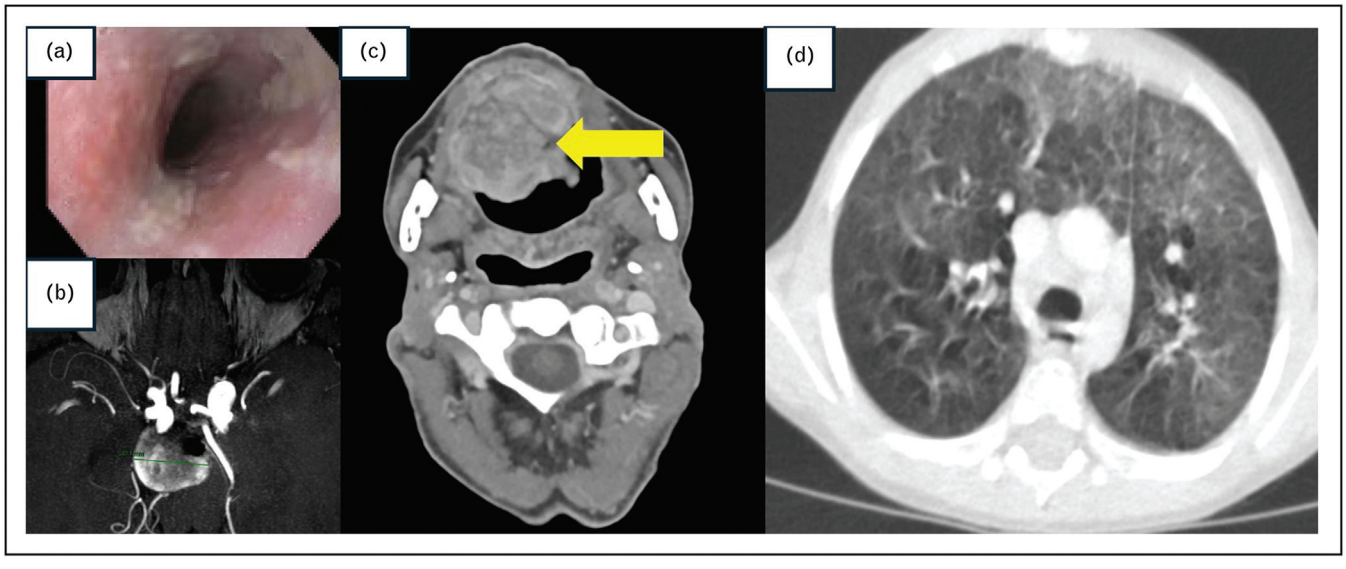

FIGURE 1. STAT1 GOF has varied clinical features. CMC is common, and can manifest with *Candida esophagitis* (a) such as in this 32 year old. Cerebral aneurysm develop in about 6% of patients, typically in childhood or early adulthood, as seen in this 6 year old (b). There is an increased risk of cancer, likely related to the CMC and chronic inflammation, such as in this 52 year old with lifelong CMC and an invasive squamous cell carcinoma of the tongue (arrow) (c). Recurrent infections may result in significant lung disease in early life, such as in this 16-year-old girl with widespread cylindrical bronchiectasis, small airway disease with air trapping leading to a mosaic pattern (d).

Table 1. Summary of clinical features and management of patients with STAT1 GOF and STAT3 GOF

	STAT1 GOF	STAT3 GOF
Main infectious manifestations	CMC (majority) Sinopulmonary (about 1/2) Mucocutaneous Viral (about 1/3) Opportunists (NTM,PJP, JC PML): infrequent	Bacterial (about 3/4) with sinopulmonary; viral (about 1/2). Fungal and opportunists infrequent
Autoimmunity/autoinflammatory	Endocrine (thyroid, IDM) (most common); dermatologic, enteropathy and hepatitis, cytopenias	Interstitial lung disease, Cytopenias, enteropathy, liver, endocrine, dermatologic, vasculitis
Other clinical findings	Aneurysm (infrequent) Malignancy (SCC)	Lymphoproliferation (about 3/4) Dermatitis (eczema) Short stature (about 1/2) Liver NRH Malignancy
Common laboratory findings	Variable; Auto-antibodies; Subset with progressive lymphopenia and hypogamm; High serum CXCL9; Low Th17 cells	Variable; lymphopenia, hypogamm, Increased DNTs (majority in those with lymphoproliferation) Low Treg (about 1/3)
Antimicrobial prophylaxis	Consider antifungals[a] Consider antibiotics for those with recurrent LRTI Consider PJP prophylaxis Consider antiviral for those with recurrent HSV/VZV, or those on Jakinib	Consider antibacterials (e.g., azithromycin) for those with recurrent LRTI/bronchiectasis. Consider antiviral for those on Jakinib
Immune modulation	Jakinibs for autoimmunity and/or CMC	Jakinibs and/or IL-6 blockade
Hematopoietic cell transplantation	Poor initial outcomes but improving with immune modulation (jakinib or emapalumab) pre-HSCT	Poor outcomes in initial reports complicated by end organ disease

CMC, chronic mucocutaneous candidiasis; DNT, double negative T cells; HSCT, hematopoietic stem cell transplantation; IDM, immune-mediated diabetes; LRTI, lower respiratory tract infections; NRH, nodular regenerative hyperplasia; NTM, nontuberculous mycobacteria; PJP, *Pneumocystis jiroveci* pneumonia; PML, progressive multifocal leukoencephalopathy; SCC, squamous cell cancer.
[a]Those in Coccidioides endemic region should be on an antifungal due to risk of disseminated disease.

Autoimmunity and inflammation

Autoimmune and inflammatory manifestations occur in about two-third of patients with STAT1GOF [6,7]. These manifestations range from easily managed autoimmune thyroiditis (most common) to more severe IPEX-like presentations, including early-onset enteropathy, insulin-dependent diabetes mellitus (IDDM), autoimmune hepatitis, cytopenias, and others [12]. Oral or genital aphthous ulcers are common and can have a significant impact on quality of life.

Aneurysms, typically cerebral, occur in about 6% of patients, with diagnosis usually in the first three decades of life [12,13▪] (Fig. 1). While some cases are linked to varicella-zoster virus, others remain unclear. There is also an increased risk of cancer, mainly squamous cell carcinoma of the skin and gastrointestinal tract, possibly related to chronic inflammation from Candida infections (Fig. 1) [6,7]. As expected, patients with autoimmune disease, aneurysms, malignancies, or severe infections often have a shortened life expectancy [6].

Laboratory findings are variable in STAT1 GOF. Lymphocyte numbers and immunoglobulins are often quite normal initially, which may result in diagnostic delays. However, abnormalities can emerge including progressive lymphopenia [14]. There appears to be increased B cell apoptosis and B cell numbers can drop significantly in some patients. Specific antibodies are variable and recent work suggests that most patients may benefit from immune globulin replacement therapy [15▪▪].

Genetics and pathogenesis

Under steady-state conditions, STAT1 remains inactive in the cytoplasm but becomes phosphorylated upon stimulation by interferons (type I, II, and III) and interleukin-27. Upon binding of its ligands, Janus kinase (JAK) phosphorylates the tyrosine 701 residue of STAT1, leading to the formation of homodimers, known as IFN-γ activated factor (GAF), or heterotrimers with STAT2 and IRF9, forming IFN-stimulated gene factor 3 (ISGF3) [16]. These

complexes translocate to the nucleus, binding to specific DNA sequences of IFN-inducible genes. After gene transcription, STAT1 is dephosphorylated and returns to the cytoplasm.

STAT1 GOF pathogenic variants have been described across the coiled-coil domain (CCD), DNA binding domain (DBD), linker domain, and SH2 domain [6,7]. Variants are largely missense. In a recent review, a total of 120 variants with over 400 STAT1 GOF cases were reported with the majority (87.6%) in the CCD or DBD domains [17▪▪]. The variants A267 V, R274Q, R274W, and T385 M, are considered hotspot variants, accounting for about 40% of cases [18]. There is a suggestion that some of the DBD variants may have a worse prognosis [19▪▪]. In particular, patients with the variant T385 M had higher rates of bronchiectasis as well as multiorgan autoimmunity [12].

Hyperphosporylation with increased pSTAT1 levels after stimulation with IFNα or IFNγ is the hallmark of the disease. The molecular basis of the hyperphosporylation and the subsequent downstream effects remains unclear. Currently, two main hypotheses have been proposed: impaired STAT1 dephosphorylation and increased STAT1 protein levels [4,17▪▪,18]. Liu *et al.* [4] first demonstrated that STAT1 GOF variants in U3C cells showed sustained phosphorylation despite kinase inhibition with staurosporin, suggesting impaired dephosphorylation. Conversely, the results of several studies have found raised total STAT1 protein levels in patients with STAT1 to be associated with high levels of pSTAT1 after stimulation, despite rapid STAT1 dephosphorylation and normal degradation [20].

IL-17 is considered a key cytokine in mucosal defense against Candida, and most STAT1 GOF patients exhibit reduced Th17 cells in peripheral blood [4]. However, some have normal Th17 levels, suggesting that other mechanisms may contribute to CMC. A prevailing hypothesis is that STAT1 GOF may have an exaggerated interferon-mediated response, leading to mucosal inflammation and fungal susceptibility, similar to autoimmune polyendocrinopathy–candidiasis–ectodermal dystrophy (APECED) [21]. This is supported by the significant improvement in CMC with JAK inhibitors, even though Th17 cell numbers are not always restored [22▪▪].

Therapy

Prior to the identification of STAT1 GOF with improved understanding of the pathogenesis of this syndrome, therapy revolved around supportive care. Antimicrobial prophylaxis included antifungals for CMC, antivirals for recurrent herpes or zoster infections, and antibiotics and/or immunoglobulin replacement therapy (IgRT) for recurrent bacterial infections [4,6]. Some with severe disease received hematopoietic cell transplantation (HCT) [23]. However, in recent years, therapeutic strategies have advanced significantly. JAK inhibitors (jakinibs), originally developed for hematologic and autoimmune diseases, have emerged as a targeted therapy for patients with hyperactivation of the JAK-STAT pathway [22▪▪,24,25]. JAK inhibition upstream of STAT1 allows reduction of STAT1 signaling.

A study of 45 patients with STAT1 GOF (67% <18 years) assessed the safety and efficacy of Jakinibs for patients with JAK/STAT-GOF IEI [22▪▪]. Reasons for starting Jakinibs included multisystem immune dysregulation (38%), infection with immune dysregulation (38%), and isolated CMC (24%). Within 1–6 months, most patients showed complete response (CR) or partial response (PR). Autoimmune conditions, including early-onset diabetes, responded well, including diabetes reversing [26]. Interstitial lung disease (ILD, CR: 10%, PR: 80%) and inflammatory bowel disease (CR: 60%, PR: 40%) also improved. Ruxolitinib, a JAK1/2 inhibitor, was the most commonly used Jakinib. Doses varied from 4.5 to 40 mg/m^2/day (median, 15 mg/m^2/day). Although jakinibs were initially aimed at managing autoimmunity, CMC often responded (CR: 42%, PR: 55%), suggesting IFNγ-driven inflammation. Consequently, antifungal prophylaxis has been discontinued during jakinib treatment in some patients, with the caveat that jakinibs should not replace prophylaxis for systemic fungal infections, such as *Coccidioides* in endemic regions. Importantly, systemic infections should be treated prior to Jakinib initiation, as there have been reports of worsening systemic fungal disease [27]. Jakinibs were generally well tolerated, with mild viral infections (23%) and unintentional weight gain being the most common side effects [22▪▪]. Despite the progress, questions remain about timing, patient and Jakinib selection, and long-term efficacy and safety. Guidelines for the use of Jakinibs in patients with JAK/STAT GOF IEI are currently under development. At present, a common treatment approach involves the combined use of a Jakinib along with IgRT and antimicrobial prophylaxis, such as cotrimoxazole, an antifungal and/or an antiviral based on the patient's history.

Historically, HCT for STAT1 GOF had poor outcomes, with high rates of graft rejection and 60% mortality, likely due to HCT being performed prior to the genetic diagnosis and in patients with significant end-organ damage [23]. However, improved control of IFNγ-driven inflammation has led to better results. Pretransplant strategies, including CXCL9 monitoring and and employing

jakinib or anti-IFNγ mAbs (e.g. emapalumab) to reduce immune activation, have increased survival rates [28▪▪]. Recent data from a cohort of patients ($n = 11$) receiving Jakinibs before HSCT showed a 91% overall survival rate [22▪▪].

STAT3 GAIN OF FUNCTION

Clinical features

STAT3 GOF disease was described in 2014 in patients with primarily autoimmunity and lymphoproliferation (Table 1) [29,30]. Since then, around 200 cases have expanded the known clinical spectrum [31▪▪]. Similar to STAT1 GOF, there is great clinical heterogeneity, even within families, unlike the more uniform clinical manifestations of those with STAT3 dominant-negative Hyper IgE syndrome.

In the study by Leiding *et al.* [31▪▪] of 191 global patients with STAT3 GOF, lymphoproliferation, including lymphadenopathy and/or splenomegaly, was the most common feature, affecting about 75% of patients. Autoimmunity frequently manifests as cytopenias, enteropathy, hepatitis, endocrinopathies, arthritis, and vasculitis. Growth failure occurs in just over half of patients, occurring from gastrointestinal disease and/or endocrinopathy.

Significant lung and liver disease has led to some patients requiring transplants. The pulmonary disease is largely ILD, occurring in about half of patients; bronchiectasis is also seen, likely from ILD and/or recurrent infections (Fig. 2) [31▪▪,32]. Liver disease not only includes autoimmune hepatitis but also progressive nodular regenerative hyperplasia (NRH) with portal hypertension (Fig. 2). Dermatologic disease ranges from eczema to psoriasis and alopecia. Infections occur in about 75% of patients, with bacterial sinopulmonary infections the most common whilst viral, fungal and opportunistic infections are rare. As many of the infections occurred under immune suppression for autoimmunity, it is challenging to estimate the true infection susceptibility of STAT3 GOF. Vascular and neurologic disease are still being delineated but there are reports of CNS vasculitis, Moya-Moya malformation, increased intracranial pressure, and stroke [31▪▪]. Ophthamologic manifestations included ocular myasthenia gravis, papilledemia and uveitis [33]. Malignancy was seen in 6% of patients, mostly lymphoma and LGL, but the true number may increase as patients age, especially because somatic STAT3 variants are associated with hematologic malignancy and many solid tumor cancers have increased STAT3 signaling [31▪▪,34].

Clinical presentation usually occurs in early childhood. Prognosis varies widely: some patients experience multiorgan failure and mortality in late childhood or early adulthood, while others have minimal symptoms into adulthood [31▪▪]. Non-HSCT related causes of death include respiratory failure, renal failure, severe enteropathy, and multiorgan failure.

The laboratory findings have been variable. Similar to autoimmune lymphoproliferative disease, many have elevated double negative T cells (DNTs) [31▪▪]. Lymphopenia and hypogammaglobulinemia are commonly reported, but have been often assessed in the setting of immune suppression

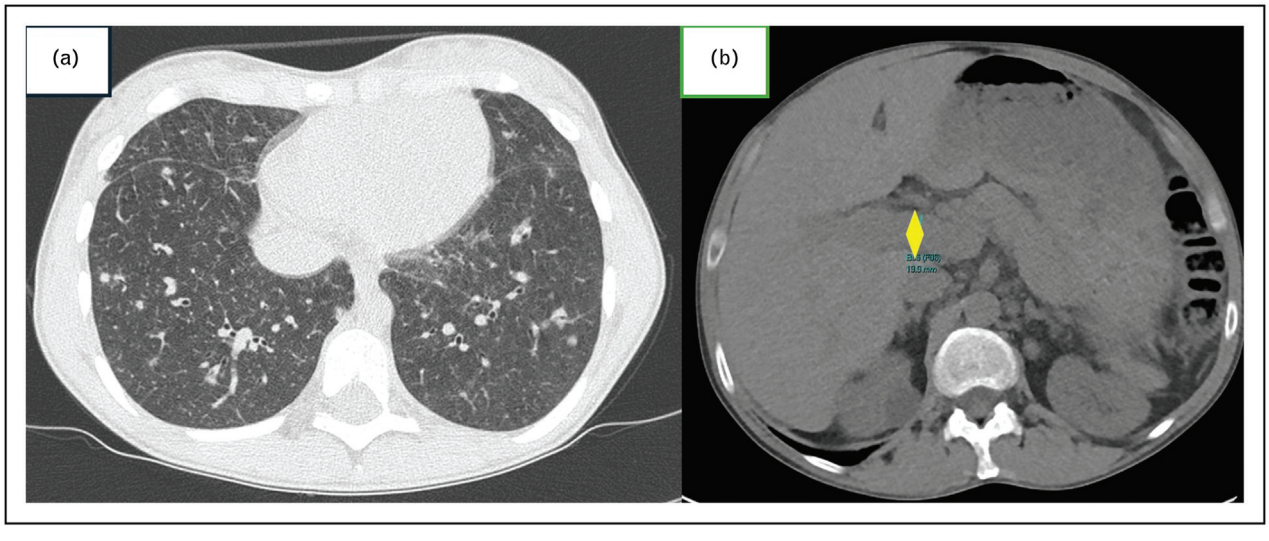

FIGURE 2. STAT3 GOF is associated with significant lung and liver disease. (a) Interstitial lung disease in a 13 year old with STAT3 GOF disease. (b) Dilated portal vein (Yellow diamond) in a 37-year-old man with liver nodular regenerative hyperplasia (NRH). Splenectomy was performed due to refractory immune mediated thrombocytopenia.

potentially affecting the results. Bacterial infections do appear more common in those with hypogammaglobulinemia, and viral infections have been more common in those with lymphopenia.

Genetics and pathogenesis

Compared to STAT3 dominant-negative HIES, where mutations are largely in the DBD and SH2 domains, the variants in STAT3 GOF span all the STAT3 domains, with the majority being in the DBD and CCD [29,30,31▪▪,35]. Almost all variants are missense changes, and there are not clear genotype/phenotype correlations. How the variants lead to increased STAT3 activity remains an area of investigation [35]. Using luciferase transcriptional activity assays, the variants leading to clinical STAT3 GOF disease show increased STAT3 transcriptional activity [30,37]. However, compared to STAT1 GOF in which patient peripheral blood mononuclear cells (PBMCs) show increased STAT1 phosphorylation, this is rarely observed in STAT3 GOF [30,38]. At least for some DBD STAT3 GOF variants, there is indication that there is delayed de-phosphorylation, but this may not be true for non-DBD variants [30,37].

STAT3 is widely expressed across tissues and is crucial for signaling various cytokines, including IL-6, IL-10, IL-21, IL-23, and IL-27 [2▪▪]. Inflammatory symptoms may arise from increased IL-6 signaling, and IL-6 blockade shows clinical benefit [24,35,39▪]. While patients with STAT3 dominant-negative HIES lack Th17 cell differentiation, one might expect elevated Th17 cells in STAT3 GOF due to their association with autoimmunity. However, STAT3 GOF patients do not consistently exhibit increased Th17 cell levels [31▪▪]. Diminished T regulatory cells might contribute to the development of autoimmunity but have been low in only about one third of patients [31▪▪,40▪]. Upregulation of *Suppression of Cytokine 3,* due to the increased STAT3 activity, likely suppresses also other STAT proteins, such as STAT5, which likely explains the common finding of short stature in both STAT5 deficiency and STAT3 GOF [30].

Therapy

To control the autoimmune and inflammatory manifestations, many patients are treated with multiple immune suppression [31▪▪,35,36▪▪]. IgRT is been often prescribed to prevent infections given the frequent hypogammaglobulinemia. In recent years, however, with the knowledge of the STAT3 variants causing disease, therapies are more focused. Jakinibs have been used, similar to STAT1 GOF, to block JAK signaling proximal to STAT3 [22▪▪,31▪▪,35,36▪▪,38,41▪,42]. Which Jakinib would be most effective is still not clear, and reports have included mostly use of ruxolitinib and tofacitinib. In a retrospective multicenter European study, 90% of patients reported feeling better overall on jakinib therapy, with the greatest CR (over 75%) in manifestations being to cytopenias and inflammatory bowel disease [22▪▪]. Lymphadenopathy had a better response than splenomegaly, which may in part be due to splenomegaly also resulting from liver NRH. The majority of patients with ILD also showed some improvement [22▪▪,42]. IL-6 is the main pro-inflammatory cytokine that signals through STAT3 and therefore therapies targeting IL-6 signaling, such as tocilizumab, have also been used to treat autoimmunity, either alone or with jakinibs [31▪▪,39▪]. Experience has varied whether IL-6 blocking therapy has been initiated before, after, or rarely at the same time of jakinib therapy. On jakinibs, with or without anti-IL-6 therapy, other systemic immune suppressants, such as corticosteroids, have been weaned [31▪▪]. Antimicrobial prophylaxis on jakinibs has varied. Jakinib can increase the risk of viral reactivation, such as zoster, and viral prophylaxis may be provided; this appears to be a more common practice in the USA than in Europe [22▪▪,24,31▪▪]. Some have started PJP prophylaxis with initiation of jakinib, and IgRT is continued in those with antibody defects. Prospective treatment studies will help to answer some of the outlying questions.

HCT outcomes have been historically poor, with an overall survival around 60%, but, similar to the initial reports in STAT1 GOF, this is hampered by significant end-organ disease in many of the patients at the time of transplant [22▪▪,31▪▪]. HCT earlier in the course may have a higher success rate and prevent some of the significant autoimmune and infection complications. However, STAT3 is expressed widely through different tissue types, and similar to STAT3 dominant negative, transplant would not be expected to be a complete cure.

CONCLUSION

Recent years have seen significant advances in identifying, describing, and treating primary immune regulatory diseases, including STAT1 and STAT3 GOF. Understanding the clinical features is driving our understanding of host immunity, which is then guiding more precise therapies. The use of jakinibs has greatly improved the inflammatory and autoimmune disease seen in STAT1 and STAT3 GOF, and changed our thinking of the pathogenesis of CMC with the paradoxical response to immune suppression. HCT outcomes are improving as we

understand the necessity of controlling the inflammation prior to transplant. However, many questions remain. New jakinibs are emerging, and which are best for these diseases remains to be answered, as well as the best indications to consider therapy, long and shorterm safety, and the durability of the response. Finally the poorly understood clinical heterogeneity makes decisions about therapies such as HCT difficult. Despite these challenges, the enormous progress made over the past decades offers exciting prospects for future developments in this area.

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Conflicts of interest

There are no conflicts of interest.

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- ■■ of outstanding interest

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