Monogenic early-onset lymphoproliferation and autoimmunity: Natural history of STAT3 gain-of-function syndrome

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Background: In 2014, germline signal transducer and activator of transcription *(STAT)* 3 gain-of-function (GOF) mutations were first described to cause a novel multisystem disease of early-onset lymphoproliferation and autoimmunity.

Objective: This pivotal cohort study defines the scope, natural history, treatment, and overall survival of a large global cohort of patients with pathogenic *STAT3* GOF variants.

Methods: We identified 191 patients from 33 countries with 72 unique mutations. Inclusion criteria included symptoms of immune dysregulation and a biochemically confirmed germline heterozygous GOF variant in *STAT3*.

Results: Overall survival was 88%, median age at onset of symptoms was 2.3 years, and median age at diagnosis was 12 years. Immune dysregulatory features were present in all patients: lymphoproliferation was the most common manifestation (73%); increased frequencies of double-negative (CD4−CD8−) T cells were found in 83% of patients tested. Autoimmune cytopenias were the second most common clinical manifestation (67%), followed by growth delay, enteropathy, skin disease, pulmonary disease, endocrinopathy, arthritis, autoimmune hepatitis, neurologic disease, vasculopathy, renal disease, and malignancy. Infections were reported in 72% of the cohort. A cellular and humoral immunodeficiency was observed in 37% and 51% of patients, respectively. Clinical symptoms dramatically improved in patients treated with JAK inhibitors, while a variety of other immunomodulatory treatment modalities were less efficacious. Thus far, 23 patients have undergone bone marrow transplantation, with a 62% survival rate.
Conclusion: : STAT3 GOF patients present with a wide array of immune-mediated disease including lymphoproliferation, autoimmune cytopenias, and multisystem autoimmunity. Patient care tends to be siloed, without a clear treatment strategy. Thus, early identification and prompt treatment implementation are lifesaving for STAT3 GOF syndrome. (J Allergy Clin Immunol 2022;■■■:■■■-■■■.)

Key words: *STAT3, gain of function, lymphoproliferation, cytopenia, autoimmunity, immune dysregulation, immunodeficiency, precision medicine*

Abbreviations used

AD-HIES:	Autosomal dominant hyper-IgE syndrome
CI:	Confidence interval
DN:	Dominant negative
DNT:	Double-negative T cell
GOF:	Gain of function
HCT:	Hematopoietic cell transplantation
ILD:	Interstitial lung disease
JAK:	Janus kinase
Jakinib:	JAK inhibitor
LGL:	Large granular cell
OS:	Overall survival
PD-1:	Programmed cell death 1
PD-L1:	Programmed death ligand 1
STAT:	Signal transducer and activator of transcription

Investigations of early-onset lymphoproliferation and multisystem autoimmunity have identified monogenic variants leading to disruption of the immune response, several of which feature significant immune dysregulation. The involvement of several and variable organ systems leads to presentation to different subspecialty clinics, causing a clinical quandary in establishing a unifying diagnosis. A streamlined approach to diagnosis and molecular characterization of these patients has the potential to lead to precision therapies. One example is signal transducer and activator of transcription (STAT) 3 gain-of-function (GOF) syndrome, which was recently recognized as an autosomal dominant primary immune regulatory disorder.[1,2] Importantly, understanding mechanisms of disease pathogenesis has led to the use of gene/pathway-guided therapies that specifically target these mechanistic causes, resulting in improved outcomes.[1,3-7]

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STAT3 is 1 of 7 members of the STAT protein family and is a critical regulator of cellular survival, proliferation, differentiation, and effector function. STAT3 is activated downstream of many cytokines including the IL-6 and IL-10 families of cytokines, as well as IL-21, IL-23, and IL-27. Binding of cytokines to their respective specific surface receptors leads to activation of Janus activating kinases (JAK), followed by JAK-mediated STAT3 phosphorylation and translocation of phosphorylated STAT3 into the nucleus, and phosphorylated STAT3 binding to specific DNA sequences resulting in transcriptional changes. Before the discovery of STAT3 GOF syndrome, heterozygous dominant negative (DN) variants in *STAT3* were an established cause of autosomal dominant hyper-IgE syndrome (AD-HIES) or Job syndrome (OMIM 147060). Somatic *STAT3* GOF variants are closely associated with large granular lymphocytic (LGL) leukemia,[8] lymphoma,[9] and solid tumors, including hepatocellular adenoma.[10] Patients with germline *STAT3* GOF variants experience heterogenous multisystem disease that can include early-onset autoimmunity, lymphoproliferation, susceptibility to infection, and growth failure.[11-13] Over the last 7 years, case reports have described the clinical features of at least 50 patients with STAT3 GOF.[3,4,11-34] The immune phenotype of STAT3 GOF patients is variable, yet hypogammaglobulinemia and lymphopenia are common features along with elevated double-negative ($CD4^-CD8^-$) $TCRab^+$ T-cell (DNT) populations and reduced Treg cells. Treatment of clinical symptoms of STAT3 GOF is challenging, often requiring multiple immunosuppressive medications. Recently, success with targeted therapy using JAK inhibitors and/or anti–IL-6R blockade has been reported.[3,27]

The clinical phenotype of STAT3 GOF is diverse, with varied presentation to different specialists. Therefore, is critical to define the scope, natural history, treatment, and overall survival (OS) of a large cohort of STAT3 GOF patients. We describe an international cohort of individuals with STAT3 GOF syndrome to aid with improved recognition of common and rare presentations, report novel variants, and enhance clinical management.

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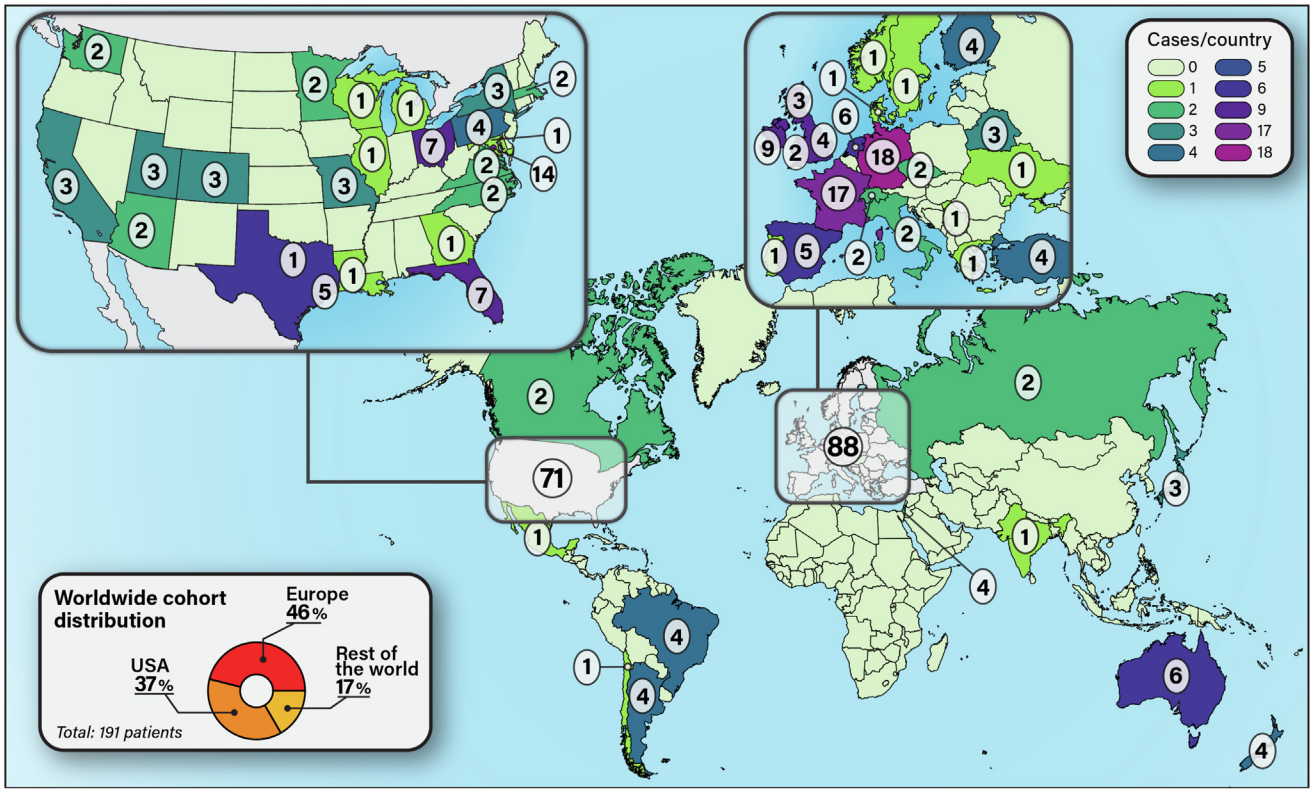

FIG 1. Country of origin for each STAT3 GOF patient. Thirty-seven percent of patients were from the United States, 46% from Europe, and 17% from the rest of the world.

METHODS

Patients

Patient data were solicited through academic organizations and when specific centers reached out to the principal investigators for functional validation of novel *STAT3* variants identified in individual patients. Inclusion criteria included symptoms of immune dysregulation and a germline heterozygous variant in *STAT3*. All variants were confirmed to be GOF at baseline using a previously reported standardized luciferase assay.[13] Deidentified data were collected on each patient using a detailed questionnaire completed by investigators at each institution (see Table E1 in this article's Online Repository at www.jacionline.org). All studies involving human subjects were performed in accordance with site-specific institutional review board–approved protocols, as well as guidelines in the 1964 Declaration of Helsinki and its later amendments, with written informed consent obtained from the patients.

Statistical analysis

Data were collected and organized by Microsoft Excel (Microsoft, Redmond, Wash), and statistical analysis was performed by SPSS v26 (IBM, Armonk, NY). Association between categorical variables was investigated by chi-square or Fisher exact test with continuity correction. The OS from first clinical manifestation was plotted using the Kaplan-Meier method, and log rank statistics were used to investigate differences among median OS based on explanatory variables. Analyses with $P < .05$ were considered statistically significant. Exploratory data analysis was conducted without multiple comparisons adjustment to the *P* value.

RESULTS

Patients

We identified 191 patients with *STAT3* GOF variants from 33 different countries (Fig 1). The cohort consisted of 115 novel and 76 previously published patients (Fig 2). There was a male predominance, with a male-to-female ratio of 1.25. Median age at onset of disease symptoms was 2.3 years. The median age at diagnosis was 12 years. The first reports of STAT3 GOF were published in 2014-15;[11-13] therefore, this cohort contains both originally described patients and those diagnosed after the initial discovery of STAT3 GOF syndrome. To keep the data consistent, we did not include unaffected healthy carriers of *STAT3* GOF variants in the analysis, although some have been reported,[13,19] because many patients were diagnosed using proband-only gene panels, and family variant segregation was not always performed.

STAT3 variants

We identified 72 unique *STAT3* variants, spanning all domains of the STAT3 protein, in the 191 patients in this cohort (Fig 2; see Table E2 in the Online Repository at www.jacionline.org). All variants, except a single amino acid deletion (Glu616del), are missense mutations. Sixty-eight of the 72 unique variants are absent from population databases such as gnomAD (see Table E3 in the Online Repository).[35] Germline *STAT3* GOF variants are predominately located in the DNA binding (n = 33, 46%) and coiled-coil (n = 19, 26%) domains. Only 3 *STAT3* GOF variants were found in the transactivation domain, but interestingly, these variants accounted for nearly a third of patients (30%, 58 patients), with 2 variants being the most commonly identified: Pro715Leu (24 patients, 13%) and Thr716Met (31 patients, 16%). The third most common variant was Arg152Trp in the coiled-coil domain (15 patients, 8%). Variants in the amino-terminal domain were

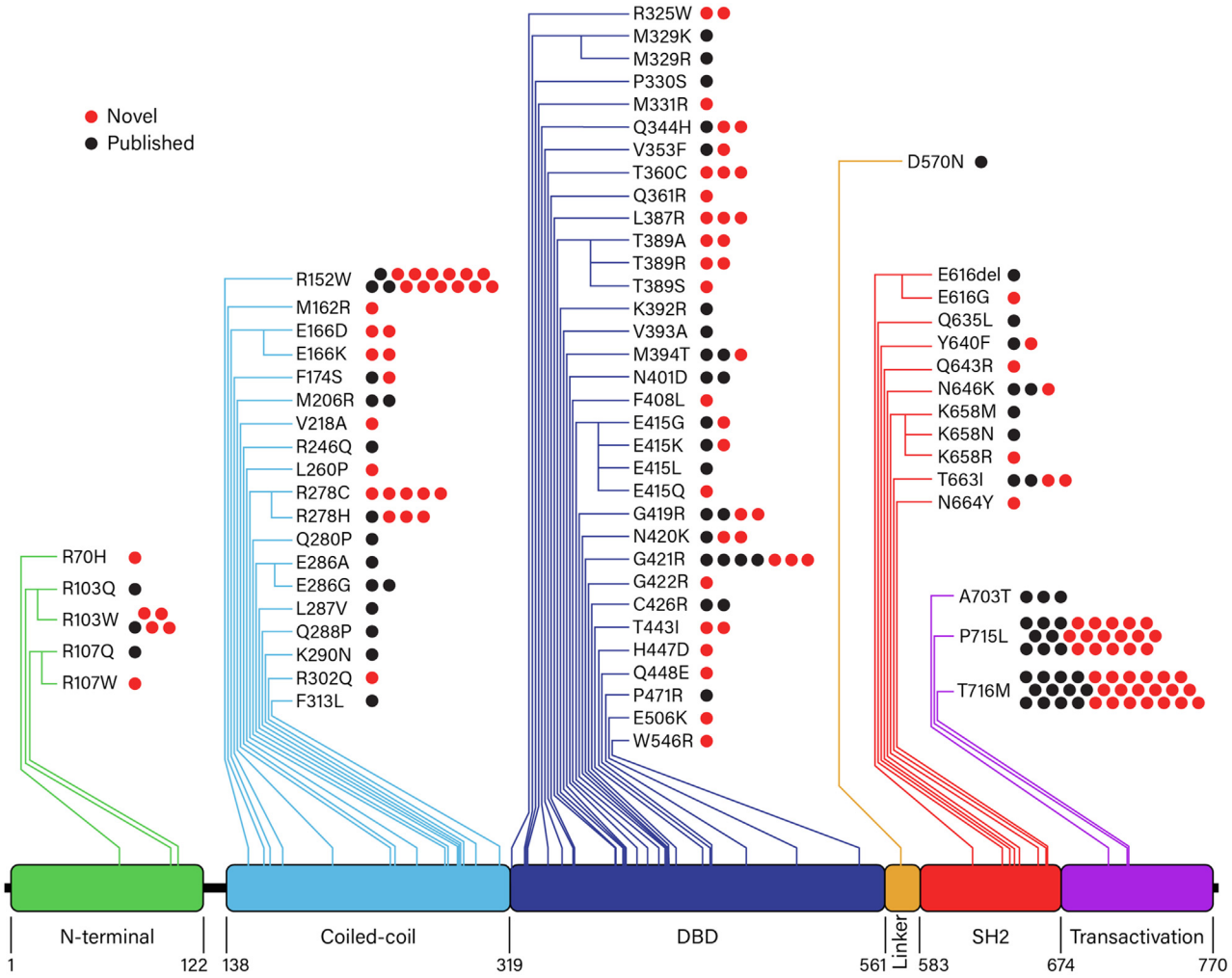

FIG 2. *STAT3* GOF mutations. Seventy-two unique *STAT3* variants spanned all domains of the STAT3 molecule. *Red dots* indicate novel patients; *black dots,* previously published patients. *A,* Alanine (Ala); *C,* cysteine (Cys); *D,* aspartic acid (Asp); *E,* glutamic acid (Glu); *F,* phenylalanine (Phe); *G,* glycine (Gly); *H,* histidine (His); *I,* isoleucine (Ile); *K,* lysine (Lys); *L,* leucine (Leu); *M,* methionine (Met); *N,* asparagine (Asn); *P,* prolie (Pro); *Q,* glutamine (Gln); *R,* arginine (Arg); *S,* serine (Ser); *T,* threonine (Thr); *V,* valine (Val); *W,* tryptophan (Trp); *Y,* tyrosine (Tyr).

the least common, with 5 different variants being identified in only 9 patients (5%). GOF variants in the SH2 domain were rare, with 11 unique SH2 domain variants in 17 patients (9%).[36] Somatic GOF variants primarily localized in the SH2 domain of *STAT3* have previously been reported to cause LGL leukemia. Interestingly, 6 of the 9 germline SH2 variants described here correspond to somatic variants identified in patients with LGL leukemia (in addition to the Phe174Ser variant in the C-C domain).[8,37,38]

Clinical manifestations

We organized clinical manifestations in the following disease categories: lymphoproliferative disease, autoimmune cytopenias, growth delay, enteropathy, skin disease, pulmonary disease, endocrinopathy, arthritis, hepatitis, neurologic disease, vasculopathy/vasculitis, renal disease, and malignancy (Fig 3; see, in the Online Repository at www.jacionline.org, Figs E1-E3 and Table E4). Only 3 patients had 1 disease category involved: respectively, 2 lineage autoimmune cytopenias, autoimmune hemolytic anemia, and growth failure. Fourteen percent of patients had 2 disease categories that most commonly included lymphoproliferation and autoimmune cytopenias. Most patients had 5 or more disease categories affected. Discrete facial features have not been previously described in patients with *STAT3* GOF variants as they have been with *STAT3* DN variants. However, patients with STAT3 GOF syndrome have characteristic round facies with cupped ears, a prominent forehead, a thin upper lip, and a smooth philtrum. These features were present irrespective of age, sex, or race (Fig 4, *A*).

Seventy-three percent of patients had evidence of lymphoproliferation most commonly manifesting as diffuse lymphadenopathy (75.5%) and/or splenomegaly (72%). Biopsies of lymph nodes often revealed follicular hyperplasia. Malignancy occurred in 12 patients;[4,12,13] all are alive (Fig E1, *B*).

Autoimmune cytopenias were the second most common clinical manifestation. Most patients had 2 or 3 cell lineages affected. Coomb-positive anemia, anti-platelet antibodies, or anti-granulocyte antibodies were present in 41% of those tested.

Pulmonary disease typically diagnosed as interstitial lung disease (ILD) occurred in 43% of patients (Fig 4, *B* and *C*). Of

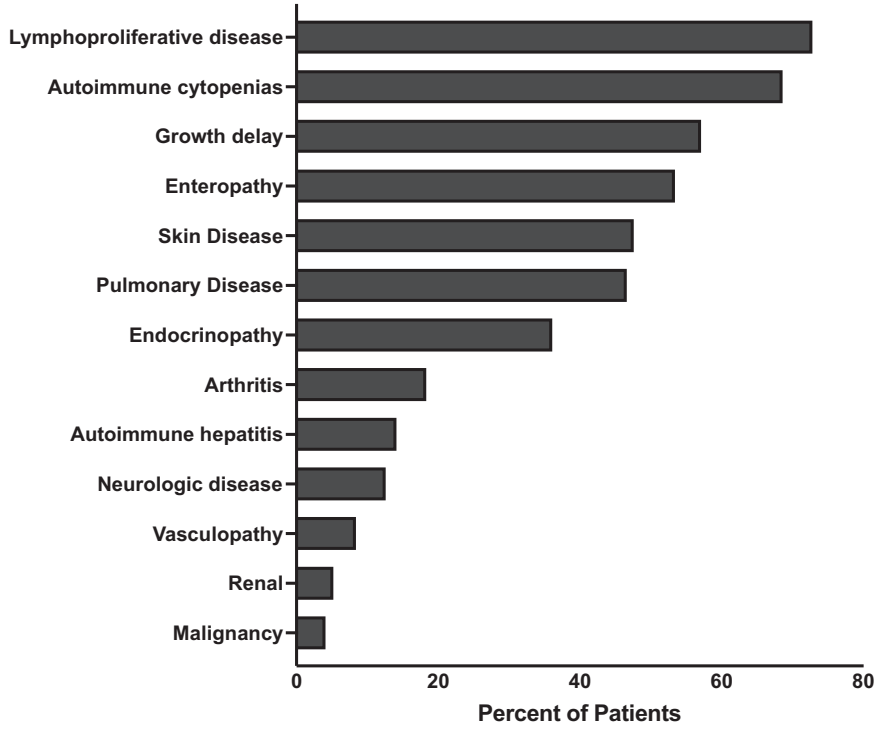

FIG 3. Clinical manifestations of STAT3 GOF patients. Percentage is shown of each clinical manifestation within the cohort of 191 patients.

patients with ILD, 26% had bronchiectasis. Patients with B-cell lymphopenia (30%, $P = .003$) and hypogammaglobulinemia (22.6%, $P = .061$), excluding those who received B-cell–depleting agents, were more likely to have bronchiectasis. In 13 patients, pulmonary disease led to fibrosis and restrictive lung disease. Two patients underwent lung transplantation for ILD; 1 patient is alive.

Growth failure remained a frequent feature of STAT3 GOF syndrome, affecting 57% of patients. Further complicating growth failure, more than half of the patients with growth failure had concurrent enteropathy (54.5%, $P < .001$). The majority of gastrointestinal manifestations began in the first 2 years of life. Fifty-three percent of patients had enteropathy most commonly diagnosed as celiac disease. Symptoms included chronic diarrhea, failure to thrive, achalasia, pseudo-obstruction, and features of colitis with 8 patients requiring total parenteral nutrition. When performed, the most common constellation of findings in the upper gastrointestinal tract was villous atrophy with small bowel thickening, and lymphocytic infiltration (Fig 4, *D* and *E*).

Autoimmune hepatitis occurred in 14% of patients. Regarding other liver-related disease, 3 patients developed portal hypertension and 1 developed hepatopulmonary syndrome. Two patients received liver transplants. Within several months, 1 patient had return of hepatitis and liver synthetic dysfunction and died of multiorgan failure resulting from sepsis.[3]

In line with significant risk of autoimmunity, patients also developed autoimmune endocrinopathies most commonly hypothyroidism, growth hormone deficiency, and early-onset diabetes (Fig E1, *D*). Other autoimmune manifestations of STAT3 GOF syndrome included arthritis, skin disease, vasculitis, and renal disease. Eighteen percent of patients developed arthritis that was characterized as polyarticular.

Dermatologic complications are a common feature of disease. Interestingly, this is also the case for AD-HIES, in which a distinctive eczematoid dermatitis emerges, typically presenting at birth.[39] Forty-eight percent of patients had skin lesions, with eczema (60%), psoriasis (12%), and alopecia (10%) being the most common findings.

In this cohort, the first cases of systemic vasculopathy are reported (7%). These vascular lesions included central nervous system vasculitis and strokes, pulmonary vasculitis, vascular malformations, Moyamoya malformation in 2 patients, and systemic vasculitis. Renal manifestations were immune mediated, and 10 patients developed chronic renal disease. Several other systemic autoimmune conditions were reported (Fig E1, *H*).

Neurologic and specifically brain abnormalities or central nervous system insults have not previously been highlighted in STAT3 GOF syndrome but now include subcortical and cortical enhancing lesions in the perisylvian regions, anterior temporal lobes, and pons (Fig 4, *F* and *G*). One patient developed bilateral facial muscle weakness resulting from myositis and muscle atrophy. Approximately 13% had neurologic complaints, and clinical symptoms were variable (Fig E1, *I*).

Immunologic abnormalities

Blood lymphocyte subsets were measured in 171 patients (see Fig E4 and Tables E5 and E6 in the Online Repository at www.jacionline.org). This analysis includes new and previously reported data.[3,11-13,15,16,18-20,23,26-28,31,34,40] $CD4^+$ T, B, and NK cell lymphopenia were common. Lymphopenia and reduced functional responses to mitogens were more likely to occur in patients

FIG 4. Clinical images of STAT3 GOF patients. **(A)** Characteristic facial appearance includes round face, prominent forehead, cupped ears, and smooth philtrum. **(B)** Interstitial infiltrate demonstrates nodules in right upper lung, bronchiectasis, and airspace disease (patient 57). **(C)** Same patient as *(B)* after treatment with tofacitinib for 5 years showing resolution of ground-glass opacities and pulmonary nodules. **(D)** Rectosigmoid biopsy sample reveals mild eosinophilia in the lamina propria and chronic changes in the form of Paneth cell metaplasia (patient 61). **(E)** Lung biopsy of right lower lobe reveals nodular and linear septal inflammation, predominantly by lymphocytes and histiocytes, without interstitial fibrosis (patient 61) (hematoxylin and eosin, original magnification 100 ×). **(F)** Chronic ischemic lesion is in the white matter of the middle frontal gyrus and right semioval center, and extensive leukoencephalopathy is evident of probable microvascular origin (patient 152). **(G)** Subcortical and cortical enhancing lesions are in the presylvian regions, anterior temporal lobes, and pons (patient 110).

concurrently or previously treated with chronic or pulse steroids. Approximately half of patients had humoral deficiency.[41]

As a marker of systemic autoimmunity,[42,43] Treg cells ($CD4^+CD25^+FOXP3^+$) and IL-17–producing ($CD4^+IL17^+$) T cells were quantified in 69 and 41 patients, respectively. Treg cell percentages were low in 39% and IL-17–producing T cells were elevated in 27% of those tested.[44]

The severe lymphoproliferation in STAT3 GOF syndrome has been described as a mimic of autoimmune lymphoproliferative disease involving defective Fas-induced apoptosis.[13] Therefore, we collected data from patients who had increased proportions of DNTs ($CD4-CD8-TCRab^+$), a cellular characteristic of autoimmune lymphoproliferative disease, or sensitivity to Fas-induced apoptosis, or both. Eighty-nine patients with lymphoproliferation had DNTs assessed, and of those, 82% had increased DNTs[45] ($P = .001$). Of the patients with lymphoproliferation and elevated DNTs, Fas-induced apoptosis was abnormal in 4 patients (although Fas apoptosis was only performed in 27 patients). This assessment supports the notion that the presence of increased numbers of DNTs[46,47] is more suggestive of lymphoproliferation driven by STAT3 GOF rather than expansion due to impaired Fas-mediated immune regulation.

Infections

Mild to severe infections occurred in 72% of patients (see Tables E7 and E8 in the Online Repository at www.jacionline.org). Bacterial infections were most common (80%), followed by viral (61%), fungal (25%), opportunistic (7%), and mycobacterial (6%) infections. Patients with hypogammaglobulinemia were most likely to develop bacterial infections (73.6%, $P = .006$). Those with $CD8^+$ (60.5%, $P = .033$) and/or $CD4^+$ T-cell lymphopenia (56.5%, $P = .018$) were more likely to develop viral infections, and those with $CD3^+$ (21.9%, $P = .007$) and/or $CD4^+$ T-cell lymphopenia (21.7%, $P = .002$) were more likely to develop fungal infections.

Treatment

Given the severity of immune-mediated disease, various forms of treatment were used to control the clinical manifestations of patients with *STAT3* GOF variants (Fig 5; see Table E4 and Table E9 in the Online Repository at www.jacionline.org). Therapies included immunomodulation, hormone replacement (insulin, growth, and thyroid hormone), and antimicrobial treatments. Overall, 77% of patients received at least 1 systemic immune-

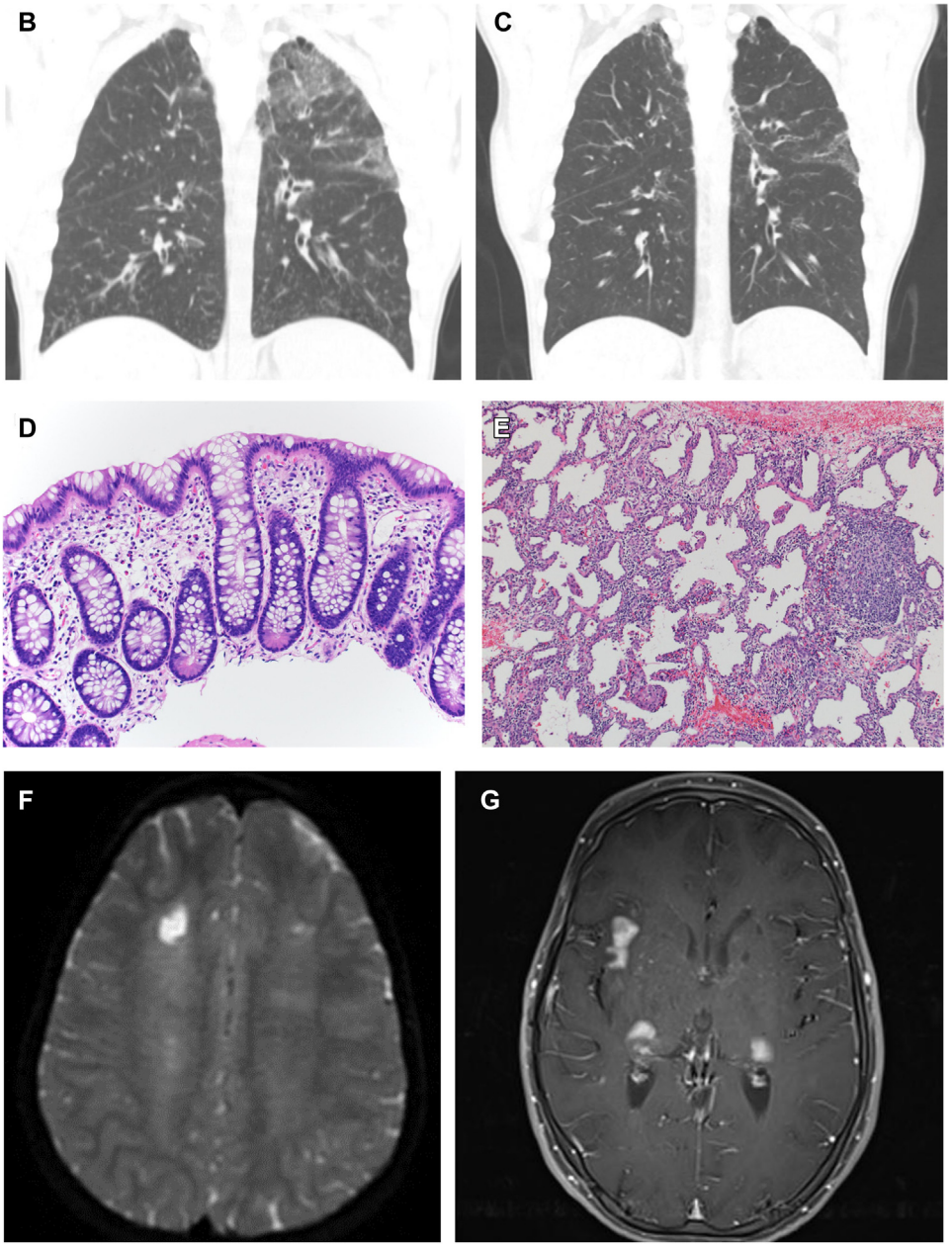

FIG 4. (Continued).

suppressing medication and 67% received immunoglobulin supplementation. Indications for immunoglobulin therapy included hypogammaglobulinemia, antimicrobial prophylaxis, and treatment for autoimmune cytopenias. Twenty-two percent of patients received hormone replacement and 43% received antimicrobial prophylaxis.

Most patients required 5 or more treatment modalities to treat disease manifestations (Fig 5, *B*). In >30% of cases, corticosteroids were provided as initial treatment that escalated to corticosteroid-sparing agents and finally precision therapy with tocilizumab and/or JAK inhibitor therapy (jakinibs) (21%). The most commonly used immune modulators were chronic systemic corticosteroids and topical corticosteroids. The disease of most patients was refractory to corticosteroid treatment, requiring second- and third-line agents to control immune dysregulation. These additional therapeutic agents included rituximab, mycophenolate mofetil, sirolimus, tacrolimus, and alemtuzumab. The disease of more than half of patients with autoimmune cytopenias failed to respond to treatment with intravenous immunoglobulin and chronic corticosteroids. Rituximab was provided to 26% of patients with autoimmune cytopenias, most in combination with mycophenolate mofetil or sirolimus. Of these patients, 79% experienced a partial response, but half required additional therapies. Splenectomy was performed in 6 patients, leading to resolution of cytopenias and/or lymphoproliferation.

Thirty-six patients received jakinibs as salvage therapy (age 3.5-48 years; median 13 years), which successfully controlled cytopenias. Tocilizumab and/or jakinibs were used to treat refractory ILD in 8 patients[3,27] and led to sufficient improvement in symptoms to permit withdrawal of supplemental oxygen in 7.

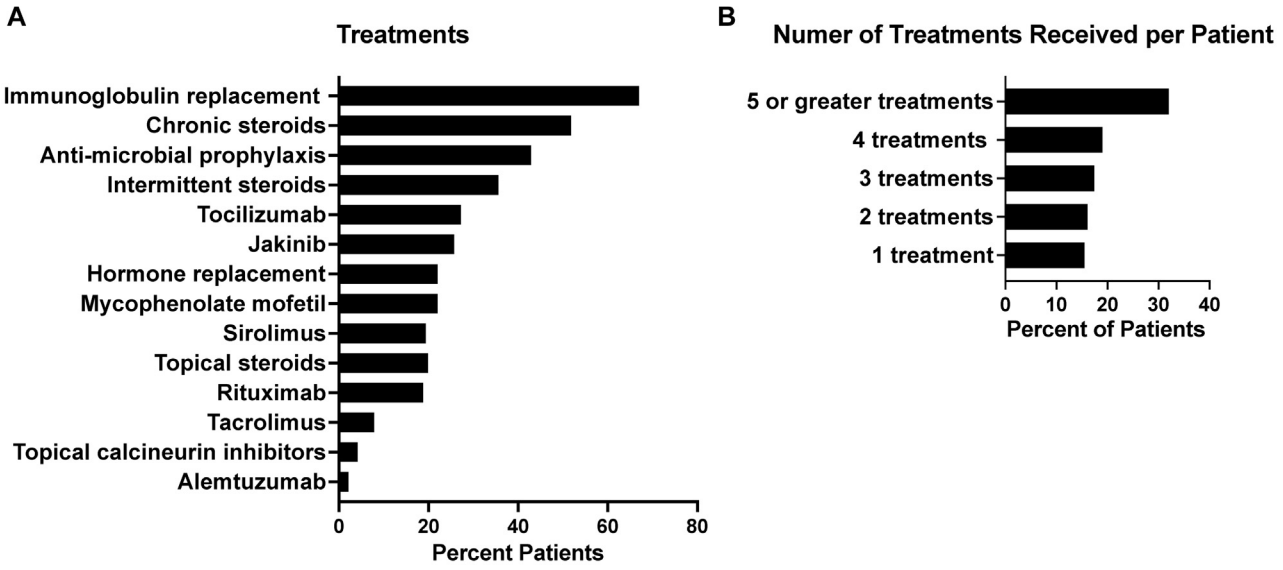

FIG 5. Treatment provided to STAT3 GOF patients. Data were available from 164 patients. **(A)** Percentage of each treatment provided to patients. **(B)** Percentage of patients receiving 1, 2, 3, 4, or 5 or more treatments.

Arthritis was the primary indication for tocilizumab and/or jakinib therapy in 6 patients; 66% had improvement of arthritis. Tocilizumab led to disease improvement in 1 patient with optic neuritis. Ruxolitinib was initiated and led to clinical improvement for 1 patient with a cerebral vascular lesion (Fig 4, *F*) in whom therapy with corticosteroids had failed, whereas another only minimally improved with pulse corticosteroids and high-dose intravenous immunoglobulin (Fig 4, *G*). Disease manifestations including diabetes mellitus,[48] pulmonary fibrosis, and pulmonary hypertension did not reverse substantially with receipt of precision therapy with tocilizumab and/or jakinibs.

Receipt of intravenous chronic steroids (57%, $P < .001$), pulse steroids (54%, $P = .035$), and tacrolimus (73%, $P = .018$) was associated with development of viral infections. Additionally, all 4 patients who received alemtuzumab developed viral infections ($P = .023$). Of the steroid-sparing agents, patients receiving mycophenolate mofetil were more likely to develop fungal infections (31%, $P = .006$). Unwanted adverse effects of tocilizumab and/or jakinibs were rare. Two patients developed significantly elevated liver transaminases after tocilizumab, and 1 patient with trilineage cytopenias had worsened bleeding episodes with jakinib therapy, leading to its discontinuation. There was no association of infection, including viral infections, in patients receiving tocilizumab and/or jakinibs.

Twenty-three patients underwent hematopoietic cell transplantation (HCT) to treat treatment-refractory life-threatening disease manifestations (unpublished data).[3,11-13,18,19,26,28,31] Indications for HCT were severe enteropathy, cytopenias, lymphoproliferative disease, and hemophagocytic lymphohistiocytosis. OS was 62%.

Domain–phenotype correlations

We sought to determine if there were any specific correlations between the domain in which the protein change occurred in each patient and corresponding clinical phenotype and survival. Although no major gene domain–phenotype correlation could be gleaned from these data, we observed the following: 56% of patients with SH2 domain variants ($P = .008$) had endocrinopathy as opposed to 44% in the coiled-coil (CCD), 43% in the DNA binding domain (DBD), 24% in the transactivation domain (TAD), and none in the N-terminal domain. Cytopenias and lymphoproliferative disease were the most common features in variants across all domains. Cytopenias occurred in 89% of patients with variants in the N-terminal domain ($P = .025$), 79% in the TAD, 76% in the CCD, 63% in the SH2 domain, and 55% in the DBD. Lymphoproliferative disease occurred in 91% of patients with variants in the coiled-coil domain and 100% with variants in the N-terminal domain ($P = .001$).

Survival

With a median age at presentation of 2.3 years, overall cumulative survival of the cohort was 88% (Fig 6, *A*). However, there were specific parameters that significantly affected survival. Twenty-three patients died, 10 of whom received HCT. Mean age at death for non-HCT patients was 23 years (4 months to 52 years). Causes of death of the 13 non-HCT patients included renal failure, progressive respiratory failure, severe enteropathy, and multiorgan failure. One patient died of progressive myositis leading to respiratory failure, and one died of complications after lung transplantation. Survival was affected by time from first clinical presentation to genetic diagnosis, but not age at presentation and disease burden (see Fig E5, *A-D,* in the Online Repository at www.jacionline.org), when assessed by the number of treatments received. Since the original reports of STAT3 GOF were published in 2014-15, a delay in definitive diagnosis was present for many subjects in the cohort whose symptoms manifested before the disease's discovery. Therefore, we sought to understand how such a delay may affect survival. When the time from presentation to diagnosis was 3 to 12 years, OS was negatively correlated (15.68 years, 95% confidence interval [CI] 14.45 to 16.91, $P < .001$). When diagnosis was delayed beyond 12 years from onset, survival was less affected, likely because patients had a milder phenotype. Providing 5 or more treatments was

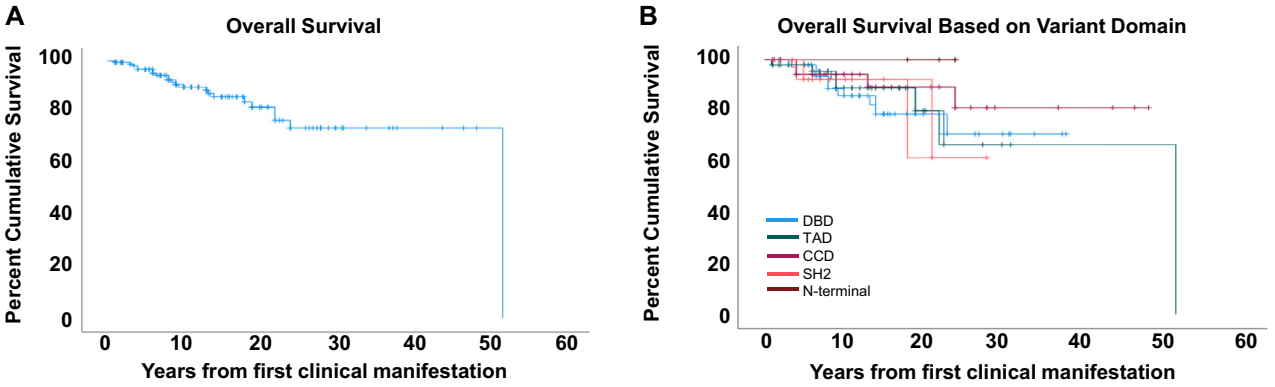

FIG 6. Survival curves of STAT3 GOF patients. **(A)** OS of STAT3 GOF patients. **(B)** OS of STAT3 GOF patients based on variant domain. *Purple,* CCD; *blue,* DBD; *brown,* N-terminal domain; *red,* SH2; *green,* TAD; $P = .0677$.

negatively associated with survival ($P < .001$) and was a better indicator of disease burden than number of disease manifestations involved.

We further analyzed whether the presence of specific disease manifestations affected survival (Fig E6, *A-N*). Although pulmonary disease was not the most common manifestation of STAT3 GOF syndrome, progressive respiratory disease leading to oxygen dependence was highly associated with death (13.25 years, 95% CI 7.85 to 18.65, $P = .002$) (Fig 7, *A*). Enteropathy (median OS not reached, $P = .034$) (Fig 7, *B;* see also Fig E6, *D,* in the Online Repository at www.jacionline.org), autoimmune hepatitis (24.0 years, 95% CI 12.62 to 35.38, $P = .004$) (Fig 7, *C,* Fig E6, *F*), growth failure (median OS not reached, $P = .026$) (Fig E6, *C*), and dependence on total parenteral nutrition (median OS not reached, $P = .024$) (Fig 7, *D,* and Fig E6, *E*) were associated with early death. Although the association of ILD with survival was not statistically different (median OS not reached, $P = .799$) (Fig E6, *H*), oxygen dependency highly correlated with worse survival (13.25 years, 95% CI 7.85 to 18.65, $P = .002$) (Fig 7, *A*; see also Fig E6, *I*), suggesting that severity of lung disease is a poor prognostic indicator. Finally, the location of the *STAT3* variant by protein domain did not correlate with OS (Fig 6, *B*).

DISCUSSION

To our knowledge, this international cohort of 191 patients is the largest series of patients with germline *STAT3* GOF variants reported to date. With this large data set we, were able to establish the spectrum of systemic autoimmunity that is often diagnosed as classic autoimmune conditions, determine the frequency of major disease manifestations, uncover unrecognized clinical symptoms, identify biomarkers for disease such as immunologic parameters, and develop recommendations regarding best treatments under a unifying diagnosis and mechanism of disease.

STAT3 GOF syndrome is a severe progressive disease with early onset affecting several organ systems. Interestingly, genotype did not predict survival; nor was it revealing as a prognostic indicator of disease manifestations. Establishing a diagnosis of STAT3 GOF is complicated by the heterogeneity of presenting symptoms, resulting in patients presenting across myriad medical specialties, which in turn results in siloed care. As reported in the initial descriptions of STAT3 GOF[11-13] and herein, nonmalignant lymphoproliferation, early-onset autoimmune cytopenias, enteropathy, and growth delay are the most common features of disease. The presence of more than one of these symptoms in a patient, especially if severe, chronic, or difficult to control, should prompt evaluation for STAT3 GOF. Diagnosis can be achieved by genetic sequencing of *STAT3.* In addition, it is important to note that the constellation of features most common in STAT3 GOF syndrome (lymphoproliferation, autoimmune cytopenias, enteropathy, ILD, growth failure) are not unique to STAT3 GOF but rather are shared by many primary immune regulatory disorders caused by other gene defects (eg, FOXP3, CTLA4, LRBA, PIK3CD). These features should prompt an evaluation for primary immune regulatory disorders including STAT3 GOF, and this is best achieved by an unbiased genetic approach—either a targeted panel or by whole exome sequencing or whole genome sequencing to assess for structural variants.

Currently, functional assessment for GOF of a novel variant is only available on a research basis. The immune phenotype of patients with this disease is variable, as were perturbations in T_H17 and Treg cell quantities historically shown to influence autoimmunity,[49-51] and thus did not aid in diagnosis. There were not sufficient numbers of subjects with Treg and T_H17 cells quantified to show a consistency in the expected phenotype in Treg and T_H17 subsets—that is, a reduction in Treg cells and an elevation in T_H17 cells.[13] However, many patients who had αβ DN T cells measured had elevated levels, suggesting that patients without an apoptotic defect and elevated αβ DN T cells should be assessed for STAT3 GOF syndrome.

In AD-HIES (*STAT3* DN) and somatic *STAT3* GOF variants, there is an increased risk of lymphoma,[52] possibly related to upregulation of programmed death ligand 1 (PD-L1),[53] and LGL leukemia,[8] respectively. Because severe lymphoproliferation, as seen in this cohort, typically raises concern for malignant transformation, the low incidence of malignancy in this cohort compared to what has been observed in AD-HIES is interesting. Reduced STAT1 expression has been previously described to cause poor upregulation of programmed cell death 1 (PD-1)/PD-L1. Because STAT1 expression is low in STAT3 GOF,[13,53] poor PD-1/PD-L1 expression in STAT3 GOF could explain both the prevalence of autoimmunity and protection from malignancy.

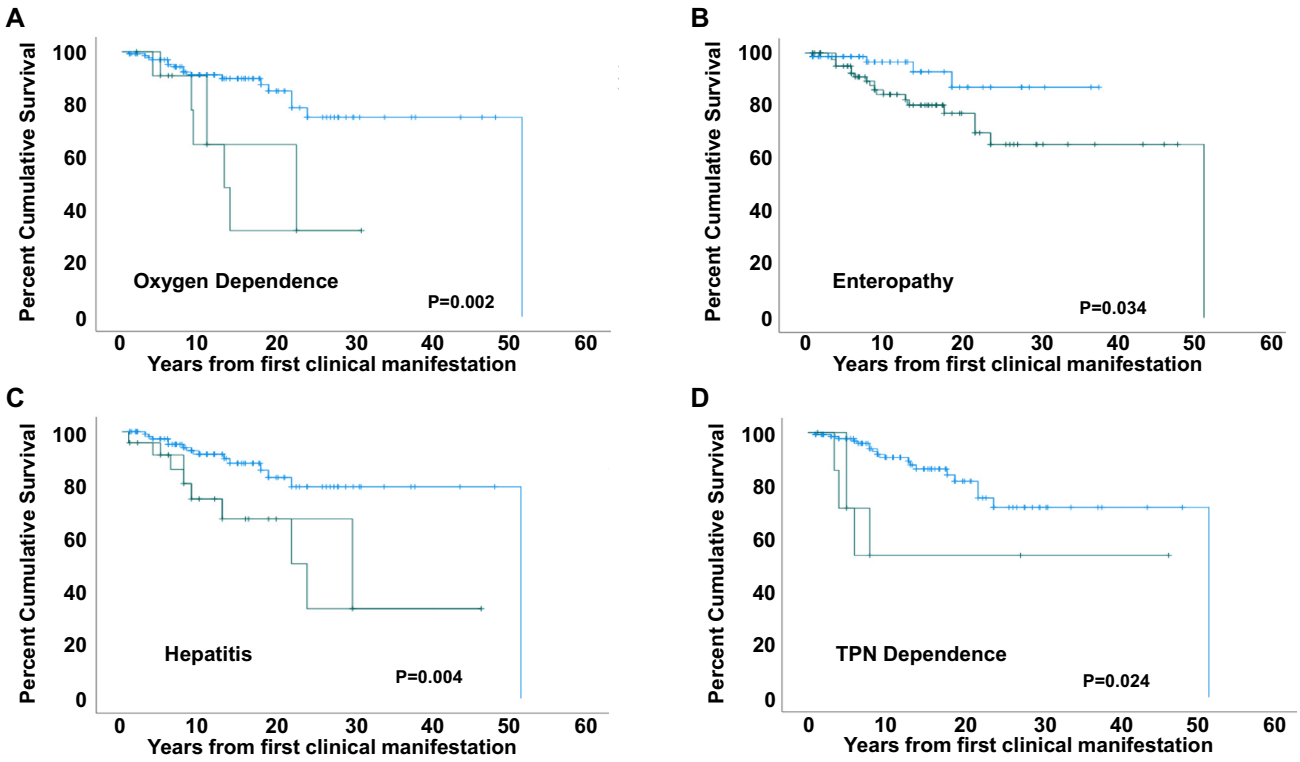

FIG 7. Survival according to clinical manifestations. Survival is significantly affected by oxygen dependance **(A)**, enteropathy **(B)**, autoimmune hepatitis **(C)**, and total parenteral nutrition (TPN) dependance **(D)**. *Green,* present; *blue,* not present.

Growth failure was observed in more than half of patients, raising concern for defects in growth hormone signaling, which requires STAT5b.[54] STAT3 regulates STAT5b, and this has been postulated as one of the important mechanisms by which these patients experience growth delay.[26]

Analysis of this large cohort revealed several new features of STAT3 GOF syndrome, including discrete facies, neurologic insults, renal disease, and vasculopathy. STAT3 plays an important role in endothelial and vascular smooth muscle cell differentiation, migration, and proliferation.[55] Enhanced STAT3 activity has been implicated in cardiovascular disease as well as vasculitic diseases including microscopic polyangiitis, other vasculitis, and glomerulonephritis.[56-59] Additionally, STAT3 hyperactivation leads to reduced pulmonary artery endothelial nitric oxide synthase, low levels of which highly correlate with development of pulmonary hypertension.[60] Indeed, treatment with jakinibs has led to clinical improvement in patients with giant cell arteritis and is a therapeutic target being explored for the treatment of cardiovascular diseases.[55,58]

The heterogeneity of symptoms in STAT3 GOF syndrome patients led to a variety of treatments. Standard immunosuppressants were often ineffective in controlling autoimmune symptoms, and most patients required more than 5 agents. Although systemic corticosteroids remain the standard first line of treatment, both corticosteroids and corticosteroid-sparing immunosuppression led to increased bacterial, viral, and fungal infections. Treatments targeting IL-6 and the JAK-STAT pathway have shown promising clinical efficacy in a small number of previously published patients with STAT3 GOF[3,27] and in this cohort. Although it is not clear whether JAK inhibition alone is sufficient, using jakinibs as the backbone of therapy is the currently preferred approach, with addition of an IL-6 blocking agent to achieve synergistic control not achieved with JAK inhibition alone. Most patients continued targeted therapy even with remission of clinical symptoms. In addition, jakinibs may be used as a bridge to HCT in severe disease. HCT was the treatment of choice for patients with severe, progressive disease, but it remains unclear whether early intervention with this definitive therapy is the optimal choice. For now, HCT remains a treatment option for patients at risk of severe disease progression.

Given the wide spectrum of autoimmune disease manifestations, high morbidity, premature death, and availability of precision therapy, recognition and diagnosis of STAT3 GOF syndrome is essential and relevant to the broader medical community. In an effort to halt disease progression, a diagnosis should prompt consideration for precision therapy (JAK-STAT inhibition, IL-6 blockade). Jakinibs and/or tocilizumab are approved by the US Food and Drug Administration for treating autoimmune diseases[61-63] and have been effective at reversing disease-related sequelae in STAT GOF disorders.[3,64,65] The long-term efficacy of these agents in treating and preventing disease-related sequelae requires further investigation. Early identification and treatment implementation are lifesaving, so it is essential that this disorder is considered in patients with lymphoproliferation and severe and/or multisystem autoimmune disease.

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Key messages

- **Identification of STAT3 GOF syndrome may improve outcomes in patients with multisystem immune-mediated disease by aiding in the selection of appropriate therapy.**
- **Over 70% of individuals with STAT3 GOF had lymphoproliferation and autoimmune cytopenias; initiation of targeted therapy led to improved patient outcomes.**

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