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Background: Inborn errors of immunity (IEI) with dysregulated JAK/STAT signaling present with variable manifestations of immune dysregulation and infections. Hematopoietic stem cell transplantation (HSCT) is potentially curative, but initially reported outcomes were poor. JAK inhibitors (JAKi) offer a targeted treatment option that may be an alternative or bridge to HSCT. However, data on their current use, treatment efficacy and adverse events are limited.

Objective: We evaluated the current off-label JAKi treatment experience for JAK/STAT inborn errors of immunity (IEI) among European Society for Immunodeficiencies (ESID)/ European Society for Blood and Marrow Transplantation (EBMT) Inborn Errors Working Party (IEWP) centers.

Methods: We conducted a multicenter retrospective study on patients with a genetic disorder of hyperactive JAK/STAT signaling who received JAKi treatment for at least 3 months.

Results: Sixty-nine patients (72% children) were evaluated (45 *STAT1* gain of function [GOF], 21 STAT3-GOF, 1 STAT5B-GOF, 1 suppressor of cytokine signaling 1 [aka *SOCS1*] loss of function, 1 JAK1-GOF). Ruxolitinib was the predominantly prescribed JAKi (80%). Overall, treatment resulted in improvement (partial or complete remission) of clinical symptoms in 87% of STAT1-GOF and in 90% of STAT3-GOF patients. We documented highly heterogeneous dosing and monitoring regimens. The response rate and time to response varied across different diseases and manifestations. Adverse events including infection and weight gain were frequent (38% of patients) but were mild (grade I-II) and transient in most patients. At last follow-up, 52 (74%) of 69 patients were still receiving JAKi treatment, and 11 patients eventually underwent HSCT after receipt of previous JAKi bridging therapy, with 91% overall survival.

Conclusions: Our study suggests that JAKi may be highly effective to treat symptomatic JAK/STAT IEI patients. Prospective studies to define optimal JAKi dosing for the variable clinical presentations and age ranges should be pursued. (J Allergy Clin Immunol 2024;153:275-86.)

Key words: *JAK/STAT signaling, gain of function, immune dysregulation, primary immunodeficiency, inborn error of immunity, JAK inhibitor, autoimmunity, ruxolitinib, baricitinib, chronic mucocutaneous candidiasis*

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Abbreviations used

AE: Adverse event
CMC: Chronic mucocutaneous candidiasis
EBMT: European Society for Blood and Marrow Transplantation
EBV: Epstein-Barr virus
ESID: European Society for Immunodeficiencies
GOF: Gain of function
HSCT: Hematopoietic stem cell transplantation
IEI: Inborn errors of immunity
IEWP: Inborn Errors Working Party
JAK: Janus kinase
JAKi: JAK inhibitor
PCJ: *Pneumocystis jirovecii*
PK: Pharmacokinetic
SOCS1: Suppressor of cytokine signaling 1
STAT: Signal transducer and activator of transcription

Severe manifestations of immune dysregulation are key clinical features of various inborn errors of immunity (IEI),[1] and the impairment or hyperactivation of key immune signaling pathways has been identified as a central emerging pathophysiologic principle. The Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathways are such key immune signaling pathway.[2-4] The most common JAK/STAT gain-of-function (GOF) IEI have been reported in patients with GOF variants in *STAT1* or *STAT3* and typically present with a variable spectrum of severe immune dysregulation (eg, lymphoproliferation, autoimmunity) and infectious complications.[3,5] In addition, patients with STAT1-GOF harbor a specific susceptibility for chronic mucocutaneous candidiasis (CMC) as a result of impaired differentiation of IL-17–producing T-helper cells.[6] STAT3-GOF patients typically present with multiple manifestations of immune dysregulation and are particularly prone to developing severe lymphoproliferation and autoimmune cytopenia.[7,8]

Treatment of these conditions requires careful balance between immunosuppression and susceptibility to infections. Specific treatment recommendations for JAK/STAT-GOF IEI are not available, and the use of immunosuppressant and antimicrobial agents usually follows symptom-based regimens (eg, corticosteroids in patients with autoimmune cytopenia and TNF-α blocking agents in patients with inflammatory bowel disease. Hematopoietic stem cell transplantation (HSCT) is a potentially curative treatment for these disorders, but previous reports documented high rates of graft rejection and poor survival.[7,9]

Advances in the understanding of the JAK/STAT signaling pathways have led to the development of orally available small molecules, which can therapeutically inhibit the JAK-associated intracellular signal transduction, the so-called JAK inhibitors (JAKi).[2] Indeed, the initially reported off-label experience in JAK/STAT-GOF IEI is encouraging.[10,11] However, the efficacy of JAKi treatment for the various clinical manifestations remains unclear, and questions on choice of drug, dosing, side effects, infectious disease reactivation, long-term benefits, and peri-HSCT application remain unsolved.

In our study, we retrospectively evaluated the JAKi treatment experience in 69 patients with genetically confirmed JAK/STAT-GOF IEI, reflecting the current treatment practice among 32 European Society for Immunodeficiencies (ESID)/European Society for Blood and Marrow Transplantation (EBMT) Inborn Errors Working Party (IEWP) centers. We provide information on treatment management, clinical response, and adverse events (AEs). Moreover, we present detailed treatment observations

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from 11 patients undergoing HSCT with previous JAKi bridging therapy.

METHODS

Data source

This international, multicenter retrospective analysis was performed after approval from the ESID/EBMT-IEWP study committee. Inclusion of patients required consent for the ESID registry (protocol 493/14 of the Ethical Committee Freiburg). Further specific eligibility criteria included a confirmed genetic diagnosis of a JAK/STAT-GOF IEI, and past or ongoing JAKi treatment for at least 3 months. A pseudonymized study-specific case report form was completed by the study centers. Data collection was performed from November 2021 to November 2022. Data of 26 of 69 patients of our study have been previously reported in single case studies or smaller case series.[6,8,12-26] For our study, all of these patients have been reevaluated using the study case report form. The assessment allowed for an extended, systematic, and harmonized comparison including data of 43 previously unreported patients. Table E1 (in this article's Online Repository available at www.jacionline.org) lists previously published cases.

Treatment response evaluation

Investigators at each institution were asked to retrospectively evaluate treatment responses. Possible categories (clinical assessment of the local physician) were (1) complete response, (2) partial response (disease manifestation markedly improved but still present), and (3) no response or not present. To evaluate the treatment influence on the activity status, patients' general well-being was subjectively assessed by physician judgment and objectively with the Karnofsky/Lansky score.

Statistical analysis

Statistical analysis was performed by GraphPad Prism 9.5.1 (GraphPad Software, La Jolla, Calif) and Microsoft Excel for Mac 16.691.1 (Microsoft, Redmond, Wash). Normal distribution was evaluated by the Shapiro-Wilk test. Paired but not normally distributed data were tested by the Wilcoxon matched pairs signed rank test. $P < .05$ was considered statistically significant. Clinical observations that occurred only in single or a small subset of patients ($n < 7$) were evaluated descriptively and are detailed in Table E2 in the Online Repository available at www.jacionline.org.

RESULTS

Clinical phenotype and genotype of study participants

Sixty-nine patients from 32 centers were included in our cohort (Table I). The underlying genetic diagnoses, in order of frequency, were STAT1-GOF ($n = 45$), followed by STAT3-GOF disease ($n = 21$), while 3 patients had other JAK/STAT IEI (suppressor of cytokine signaling 1 *[SOCS1],* JAK1-GOF, STAT5B-GOF). The median age at last follow-up was 13.0 years (range, 1-46 years), and the majority of patients with STAT1-GOF (67%) or STAT3-GOF disease (81%) were children and adolescents (<18 years).

The mutations of the STAT1-GOF patients were predominantly localized within the coiled-coil domain (23/45, 51%) and DNA-binding domain (19/45, 42%), and 1 STAT1-GOF patient each had mutations within the N-terminal domain (2%), SH2 domain (2%), and transactivation domain (2%) (see Fig E1, *A,* in the Online Repository available at www.jacionline.org). Among the STAT3-GOF patients, mutations were predominantly localized within the DNA-binding domain (10/21, 48%); few patients had mutation within the transactivation domain (4/21, 19%), coiled-coil domain (3/21, 14%), SH2 domain (3/21, 14%) or N-terminal domain (1/21, 5%) (Fig E1, *B*).

For STAT1-GOF patients, the indication to initiate JAKi treatment was multisystemic immune dysregulation (17/45, 38%), a combination of infection (including CMC) and immune dysregulation (17/45, 38%), or isolated CMC (11/45, 24%) (Table I). In STAT3-GOF patients, the reason to initiate JAKi treatment was exclusively multisystemic immune dysregulation (Table I).

The median treatment observation time was 17.0 months (range, 3-57 months), and the majority of both STAT1-GOF (69%) and STAT3-GOF (86%) patients were receiving continuous JAKi treatment at last follow-up.

Disease manifestation and response to treatment

The predominant disease manifestations in STAT1-GOF patients were aphthous mucocutaneus lesions (73%), CMC (69%), bronchiectasis (47%), inflammatory bowel disease (33%), and interstitial lung disease (22%). STAT3-GOF patients presented predominantly with lymphoproliferation (lymphadenopathy 55%, splenomegaly 43%), cytopenia (38%), inflammatory bowel disease (33%), and interstitial lung disease (38%) (Fig 1, *A*). Improvement of the patients' general well-being after initiation of JAKi treatment was reported in the majority of STAT1-GOF (87%) and STAT3-GOF (90%) patients (Fig 1, *B*). We also documented significant improvement in Karnofsky/Lansky score (see Fig E2 in the Online Repository available at www.jacionline.org).

The majority of STAT1 and STAT3-GOF patients showed either a complete or partial response of their predominant disease manifestations (Fig 1, *B*). All disease-associated symptoms were generally responsive to JAKi treatment. Figs E3 and E4, available in the Online Repository available at www.jacionline.org, illustrate the individually variable treatment responses for STAT1-GOF (Fig E3) and STAT3-GOF patients (Fig E4), including response rates for rare disease manifestation, which were only observed in individual patients. In most patients, improvement of symptoms was observed within 1 to 6 months after initiation of JAKi treatment (Figs E3 and E4, Table E2). We did not observe a correlation between the patients' genotype and JAKi treatment responses (data not shown). Because of the retrospective nature of data collection and the lack of systematic drug-level and pharmacokinetic (PK) assessments, our study did not allow for dose–treatment response evaluations. We observed positive treatment responses across all dosing schemes.

The JAKi treatment responses in the single patients with other JAK/STAT-GOF IEI are displayed in Fig E5 in the Online Repository available at www.jacionline.org.

TABLE I. Characteristics of study cohort

Characteristic	Total	STAT1-GOF	STAT3-GOF	Other
No. of subjects	69	45 (65%)	21 (30%)	3 (4%)
Age (years) at last follow-up, median (range)	13 (1-46)	14 (2-46)	11 (1-32)	9 (5-12)
Adult patients	28% (19/69)	33% (15/45)	19% (4/21)	0 (0/3)
Pediatric patients	72% (50/69)	67% (30/45)	81% (17/21)	100% (3/3)
Pediatric patients aged ≤10 years	38% (26/69)	31% (14/45)	48% (10/21)	67% (2/3)
Pediatric patients aged ≤5 years	13% (9/69)	4% (2/45)	29% (6/21)	33% (1/3)
Sex, M/F	36/33	22/23	13/8	1/2
Indication for JAKi treatment				
Multisystemic immunodysregulation		38% (17/45)	100% (21/21)	
CMC		24% (11/45)	0	
Infections (including CMC) and immune dysregulation		38% (17/45)	0	

JAKi dosing practice

Ruxolitinib (57/71, 80%, treatment observations) was the predominantly prescribed JAKi within our cohort, followed by tofacitinib (8/71, 11%) and baricitinib (6/71, 8%) (Fig 2, *A*). In 1 patient (P41, Fig E3), treatment was changed from ruxolitinib to baricitinib as a result of AEs such as mucositis, acne, and fatigue, which all resolved under baricitinib. In another patient (P24, Fig E3), treatment was changed from baricitinib to ruxolitinib because of insufficient clinical treatment response (aphthous mucocutaneus lesions and CMC), which resolved under ruxolitinib.

Variable dosing regimens for ruxolitinib were used. The individual dosing ranged from 4.5 to 40 mg/m^2/d (median, 15 mg/m^2/d) in patients with STAT1-GOF and 7.5 to 60 mg/m^2/d (median, 25 mg/m^2/d) in patients with STAT3-GOF (Fig 2, *B*). Most patients received ruxolitinib in 2 doses per day (82%), with only a few patients receiving it 3 times per day (9%) or as a single dose (9%) (Fig 2, *C*). The majority of patients (n = 39, 57%) directly began therapy with the initial target dose. In the other patients (n = 29, 42%), dosing followed a ramp-up scheme, which was primarily clinically guided (n = 23). Only in a minority of patients (n = 6) was the dose escalation guided by additional (experimental) investigations such as phosphorylation of STAT1 or PK data (see Fig E6, *A,* in the Online Repository available at www.jacionline.org). A commonly used clinical ramp-up scheme for ruxolitinib was to initiate treatment with a starting dose of 15 mg/m^2/d, followed by a dose escalation of up to 30 mg/m^2/d over 2 to 4 weeks, depending on the individual patient's treatment response and tolerance.

We documented highly variable treatment monitoring policies among the individual institutions. Generally, most centers followed patients closely after initiation of JAKi treatment (usually every 1-2 weeks for the first 3 months) and less frequently thereafter (every 1-52 weeks, median every 10 weeks). In addition to physical examination, treatment monitoring usually included a differential blood count to assess for hematologic alterations and a clinical chemistry assessment (ie, kidney, liver function tests, lipid profiles). Some centers performed additional immunologic monitoring (eg, immunoglobulin levels, lymphocyte subpopulations, STAT phosphorylation assays). Surveillance of infections was primarily carried out in case of clinical symptoms (46%). Routine PCR monitoring for viral reactivation in blood was performed in 48% of patients (Fig 2, *D*). These included testing for Epstein-Barr virus (EBV) and cytomegalovirus; other PCR evaluations were performed only in a small subset of patients (eg, herpes simplex virus, varicella zoster virus, human herpesvirus 6, BK virus, adenovirus, JC virus, *Enterovirus*). Non-PCR infection surveillance only (eg, galactomannan, microbial examination of respiratory specimens, and cultures for bacterial/fungi) was performed in 3% of patients.

JAKi dose modifications over the course of treatment were performed in 31 (45%) of 69 patients, and the decisions were primarily based on clinical judgment (21/31, 68%), either because of insufficient clinical response (14/31, 45%) or because of AEs (7/31, 23%) (Fig 2, *E*). Only in a minority of patients were dose modifications based on either assessment of PK data (5/31, 16%) or molecular evaluations (eg, STAT1 phosphorylation) (5/31, 16%). These analyses were performed locally on a research basis; the most commonly used PK protocol has been previously reported.[27] For this protocol, the PK profile was obtained using results of the limited sampling strategy and population PK modeling adapted from Chen et al[28] in order to estimated ruxolitinib area under the curve of concentrations versus time between 2 administrations (area under the curve). Because the optimal therapeutic range of ruxolitinib's area under the curve for JAK/STAT-GOF IEI is currently unknown, the analyses focused primarily on an adequate between-dose exposure and was guided by clinical response assessment. In 3 of 4 STAT1-GOF patients, PK analyses were performed because of concomitant azole treatment (fluconazole = 2 [P16, P30]; itraconazole = 1 [P11]). In 2 patients (fluconazole = 1 [P30] and itraconazole = 1 [P11]), baricitinib was primarily used to avoid metabolic interactions with the concomitant antifungal treatment. In 1 patient (P16), who received concomitant fluconazole treatment, the ruxolitinib dose was reduced by 50% after PK analyses.

Overall, JAKi treatment was discontinued in 18 of 69 patients, in 11 patients (58%) because the patients proceeded to HSCT. Among these, JAKi was abruptly stopped at the start of conditioning in 8 of 11 patients (P8, P18, P21, P26, P37, P45, P61, P65), gradually decreased over the time of conditioning in 1 of 11 patients (P11), and continued until day +4 after stem cell infusion in 1 of 11 patients (P42). For 1 HSCT patient, data were not available (P31). In the non-HSCT patients the JAKi was stopped abruptly in 4 of 7 patients (P12, P27, P41, P50), following a gradual decrease over 2 weeks in 1 of 7 patients (P39), or in the background of another immunosuppressive treatment in 1 of 7 patients (P67). For 1 patient, data were unavailable (P16). The reason for withdrawing JAKi was insufficient treatment response in 3 patients (P39, P50, P67) or presence of an AE (infection susceptibility, cytopenia, neurologic symptoms, weight gain in P12, P16, P41); Fig 2, *F;* Figs E3-E5). In 1 patient (P27), JAKi was withdrawn after remission of CMC (Fig 2, *F,* and Fig E3). In all 7 patients, including the 4 of 7 patients with abrupt stop, no signs

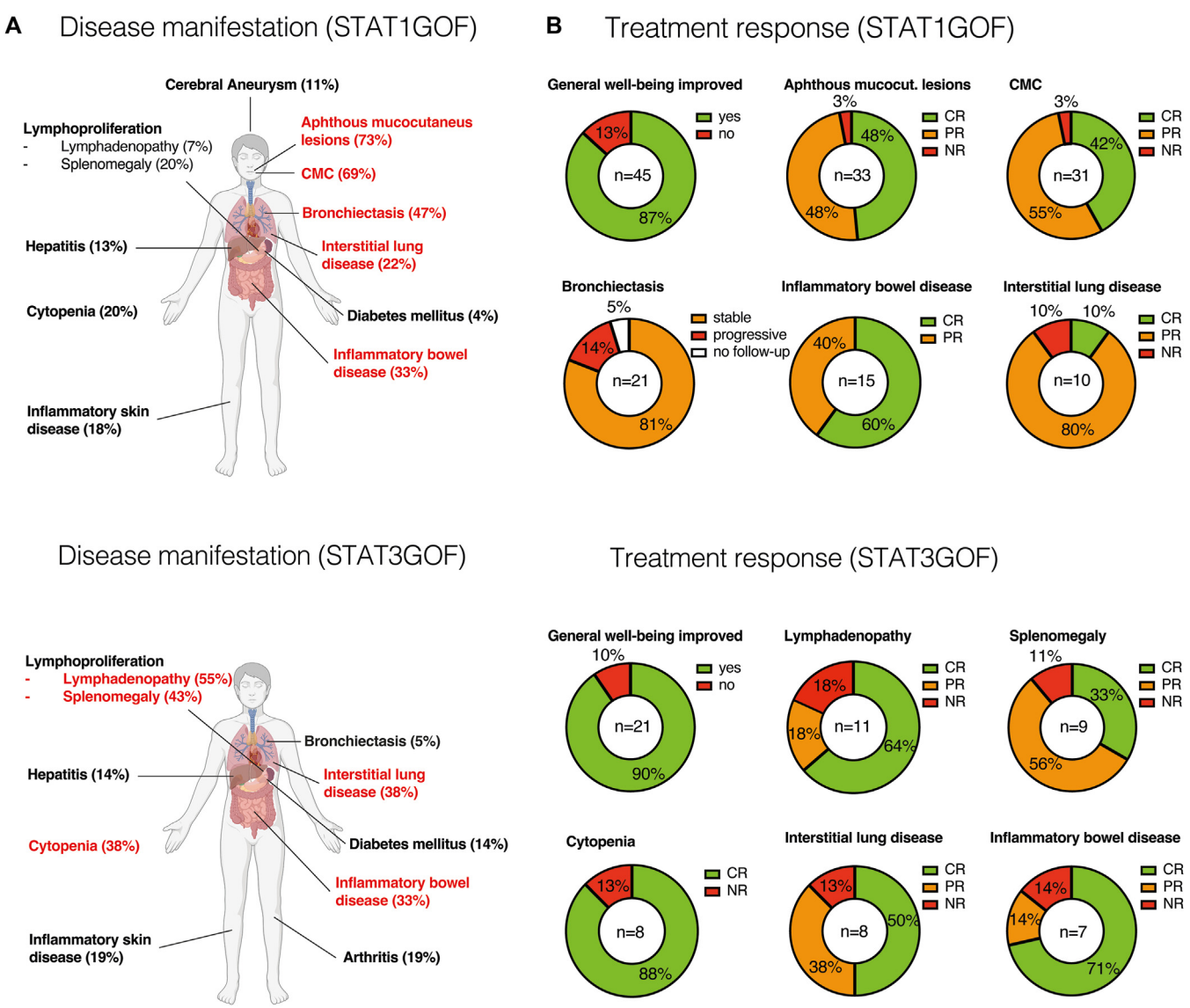

FIG 1. Disease manifestation **(A)** in STAT1-GOF *(top)* and STAT3-GOF *(bottom)* patients. *Red labeling* indicates predominantly reported disease manifestation. **(B)** JAKi treatment responses for most commonly reported disease manifestation on STAT1-GOF *(top)* and STAT3-GOF *(bottom)* patients. Complete response *(CR, green),* partial response *(PR, orange),* no response *(NR, red).* Graphic of disease manifestation was created with BioRender.com.

of a withdrawal syndrome were observed. Fig E6, *B,* provides an overview of the withdrawal procedures.

AEs observed during JAKi treatment

Our study questionnaire evaluated for both the absence and presence of JAKi-related AEs. In 43 (62%) of 69 responses, the evaluating physician did not observe an AE, which was obviously associated with the JAKi treatment. Overall, JAKi-related AEs were reported in 26 (38%) of 69 patients. The most common events were infections (n = 16, 23%) and unintentional weight gain (n = 9, 13%) (Fig 3).

Infections were mainly mild viral (eg, parainfluenza) or bacterial infections (eg, *Moraxella catarrhalis*) (n = 7). In 2 patients (P2 and P25), transient and asymptomatic viral reactivation of EBV was documented, which all resolved without treatment; and 1 patient experienced an acyclovir-responsive shingles flare (P49) (see Table E3 in the Online Repository available at www.jacionline.org). One patient (P20) presented with (clinically suspected) mycobacterial skin infection. Two other patients (P22 and P34) were reported with a newly diagnosed bacterial pneumonia (associated with *Streptococcus pneumoniae* and *Pseudomonas aeruginosa,* respectively, and both in the absence of bronchiectasis), and 1 patient (P41) experienced recurrent sepsis-like episodes, without identification of a specific pathogen. One patient (P12), without previous *Pneumocystis jirovecii* (PCJ) prophylaxis, developed chronic bronchitis; bronchoalveolar lavage analysis yielded a positive real-time quantitative PCR result for PCJ (18,800 copies/mL). Clinical symptoms resolved after a 14-day course of cotrimoxazole. Nasal and pulmonary mucormycosis

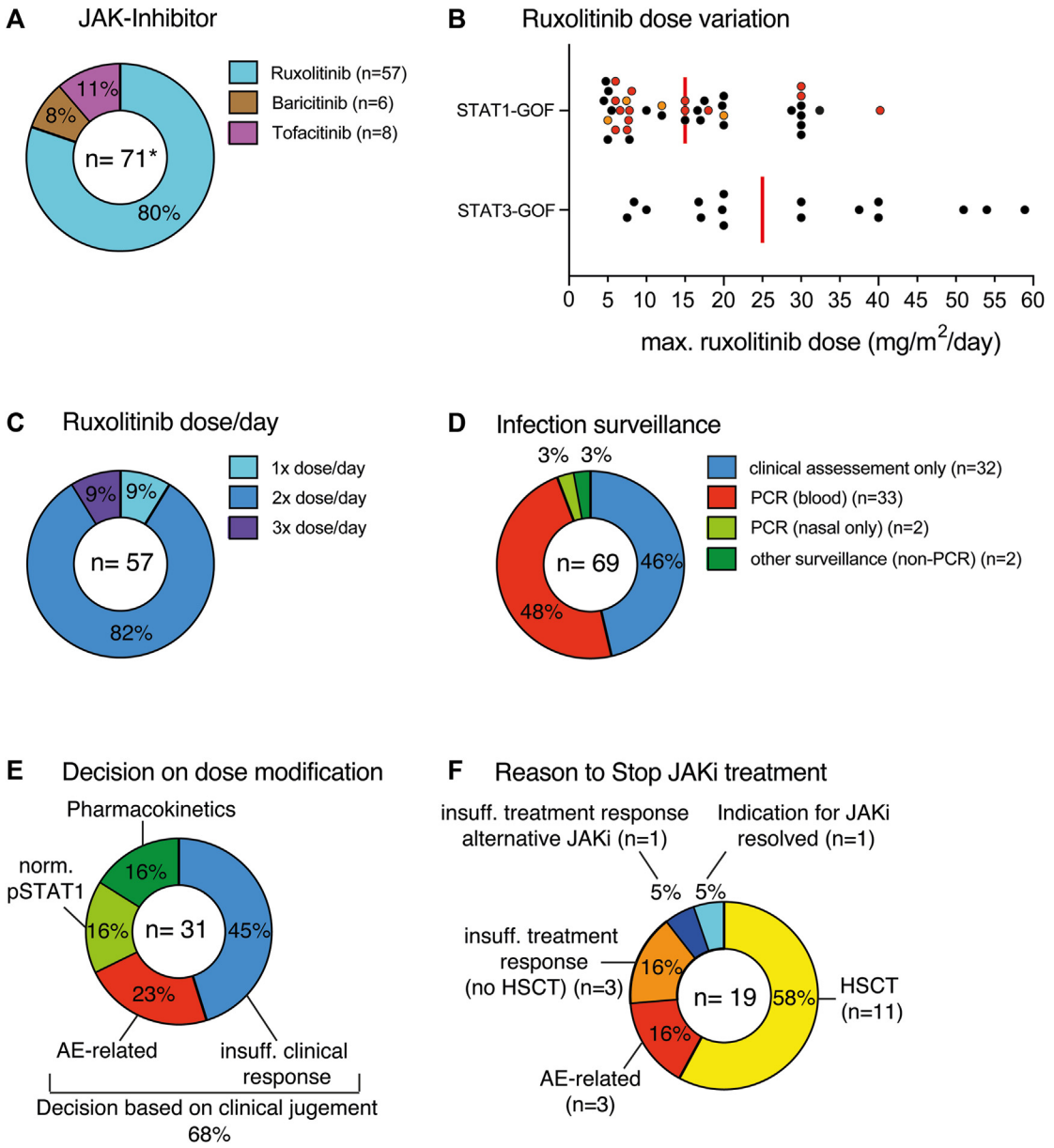

FIG 2. Percentages of different JAKi **(A)**. *Treatment observation (2 patients received ruxolitinib and baricitinib). Maximal ruxolitinib dose (mg/m^2/d) for STAT1-GOF *(top)* and STAT3-GOF patient *(bottom). Red dots* indicate concomitant fluconazole treatment; *orange dots,* concomitant azole treatment other than fluconazole (posaconazole, voriconazole, itraconazole) **(B)**. Percentage of ruxolitinib dose per day **(C)**. Infection surveillance **(D)**. Decision on dose modification **(E)** and reason to stop JAKi treatment.

was documented in 1 patient (P11), who received combined immunosuppressive treatment with baricitinib and infliximab. Antifungal treatment resulted in control of the infection, which eventually resolved after HSCT. Overall, no patient died from infection while receiving JAKi treatment. Furthermore, we observed no obvious correlation between the concomitant receipt of systemic corticosteroids and the occurrence or severity of reported infections (Table E3).

The JAKi dosing practice during episodes of infections differed considerably among individual centers. In most, JAKi treatment was continued without dose modifications during mild infectious episodes (eg, upper respiratory infections) or pneumonias. In 7 patients, JAKi was paused during ongoing infection, as follows: 1 patient with severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infection (P7), 1 patient with asymptomatic EBV reactivation (P2), 1 patient with suspected mycobacterial skin infection (P20), 1 patient with mucormycosis (P11), 1 patient with PCJ-associated bronchitis (P12), 1 patient with sepsis-like episodes (P41) and 1 patient with positive fungal sputum culture (P9). In this latter patient,

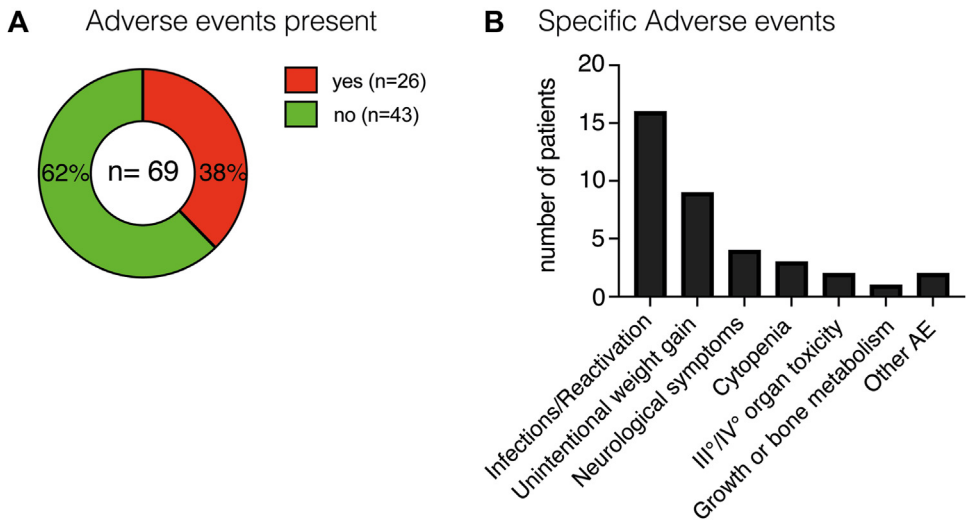

FIG 3. AEs present **(A)**. Specific AEs, black bar represent number of patients **(B)**.

JAKi treatment was reintroduced after the finding was specified as likely nonpathogenic *Penicillium* spp.

Unintentional weight gain was identified as the second most commonly reported AE (n = 9, 13%). The majority of patients were adolescents or young adults (7/9), and both male (5/9) and female (4/9) patients were affected (Fig 3; see Table E4 in the Online Repository available at www.jacionline.org). In 2 of these patients (P53 and P66), the JAKi dose was reduced, in both cases without benefit (Table E4).

Intermittent neurologic symptoms (headache, vertigo, forgetfulness) were reported in 4 patients (P12, P34, P43, P56) and were primarily observed (3/4) within the first 4 weeks after JAKi treatment initiation (see Table E5 in the Online Repository available at www.jacionline.org). In 1 patient (P12), concentration disruption and unintentional weight gain led to the termination of JAKi treatment.

In 3 patients (P11, P16, P50), a novel onset of cytopenia was observed during JAKi treatment. Whether these were JAKi-related AEs or clinical symptoms of the underlying disease remained unclear (see Table E6 in the Online Repository available at www.jacionline.org). In 2 of these patients (P16, P50) cytopenia led to the termination of JAKi treatment, which afterward resolved in 1 patient (P50) but persisted in the other (P16).

Growth- or bone metabolism–related AEs were only evaluated in patients with more than 12 months of JAKi treatment. In 1 STAT1-GOF patient (P20), osteoporosis was reported, but it was already present before JAKi initiation, so it was therefore considered a disease-related symptom (see Table E7 in the Online Repository available at www.jacionline.org).

Further individually reported AEs included elevations of creatinine or transaminases, myalgia, and mucositis (see Tables E8 and E9 in the Online Repository available at www.jacionline.org).

Two patients (P16, P65), previously treated with a JAKi, died, one (P16) after a gastrointestinal hemorrhage 8 months after JAKi withdrawal and the other (P65) of post-HSCT–onset encephalitis. In both cases, an association with the previous JAKi treatment seemed unlikely.

Concomitant treatment and effects while receiving JAKi treatment

Concomitant treatments, including antimicrobial prophylaxis and immunosuppressants, were common in our cohort (Fig 4). Systemic antifungal prophylaxis was predominantly prescribed in patients with STAT1-GOF (84% of STAT1-GOF vs 5% of STAT3-GOF). Antiviral agents (20% of STAT1-GOF vs 5% of STAT3-GOF), PCJ prophylaxis (51% of STAT1-GOF vs 29% of STAT3-GOF), and IgG-replacement therapies (53% of STAT1-GOF vs 62% of STAT3-GOF) were similarly common in STAT1-GOF and STAT3-GOF patients.

With the exception of antiviral prophylaxis in patients with STAT3-GOF (increasingly provided after initiation of JAKi treatment), we observed no significant differences in the prescription routine of prophylactic agents before and after the initiation of JAKi treatment. Despite the common improvement of CMC receiving JAKi treatment (Fig 1, *B,* and Table E2), most centers continued a systemic antifungal prophylactic regimen (84% before JAKi vs 60% while receiving JAKi treatment), likely reflecting varying local policies or general prophylactic measures under immunosuppressive treatment (Fig 4, *A*). The majority were treated with fluconazole 40% (18/45), whereas 16% (7/45) were treated using other azoles such as posaconazole (n = 3), voriconazole (n = 2), or itraconazole (n = 2) (Fig E6, *C*). Two patients received another systemic antifungal treatment (caspofungin = 1, intravenous liposomal amphotericin = 1). The JAKi was provided in a reduced dose in 5 of 18 patients receiving fluconazole and in 2 of 3 patients receiving posaconazole. There was no difference in the CMC treatment response of patients with and without continued antifungal prophylaxis (data not shown).

Fifty-one percent (23/45) of STAT1-GOF patients and 81% (17/21) of STAT3-GOF patients received systemic corticosteroids or other additional immunosuppressants (Fig 4, *B*) before initiation of JAKi treatment. After start of JAKi treatment, systemic corticosteroids or other concomitant immunosuppressants could be stopped in 65% (15/23) of STAT1-GOF and 82% (14/17) of STAT3-GOF patients (Fig 4, *B*).

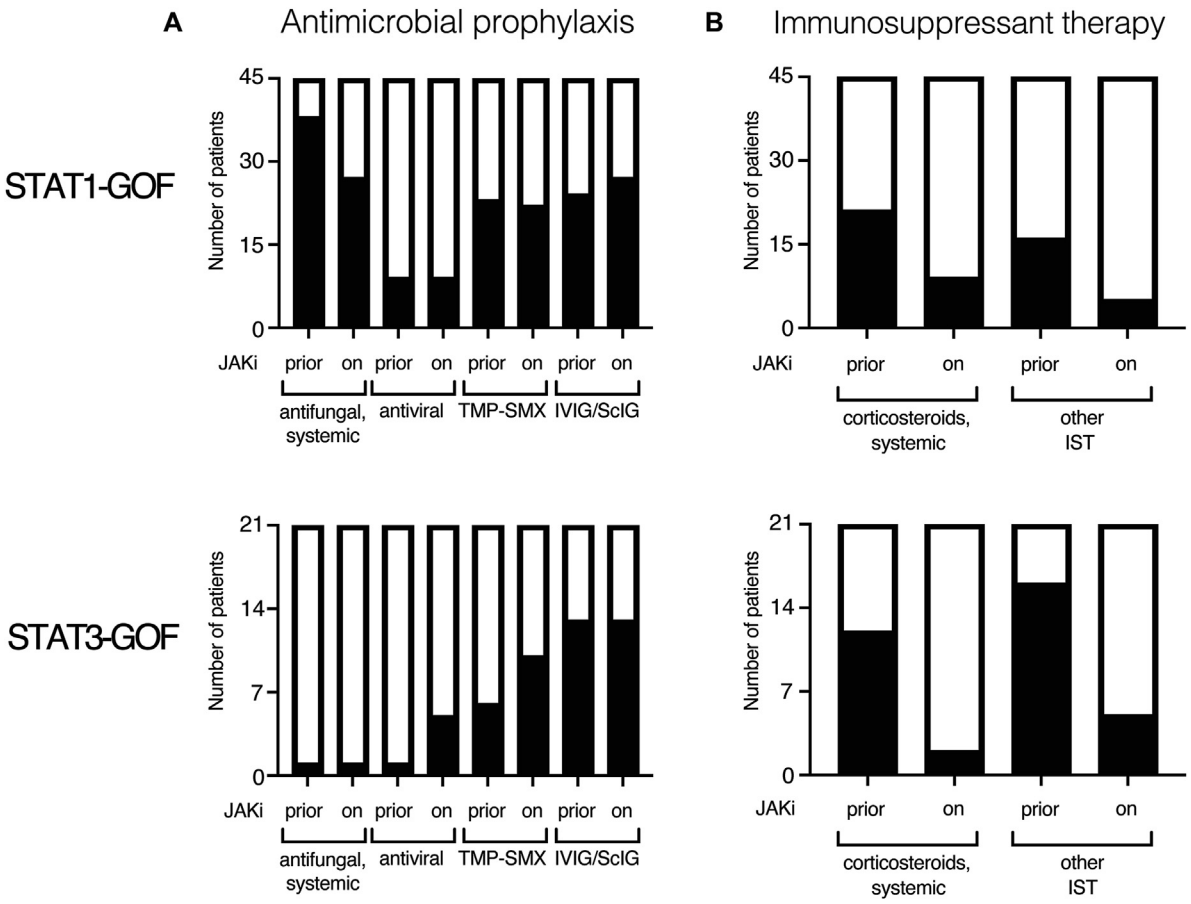

FIG 4. Concomitant treatment provided to STAT1-GOF (n = 45, *top*) and STAT3-GOF (n = 21, *bottom*) patients. *Black bars* represent number of patients receiving antimicrobial prophylaxis such as systemic antifungal, antiviral, TMP-SMX, and immunoglobulin (IVIG, ScIG) treatment **(A)**. Systemic antifungal treatment comprised fluconazole = 18, posaconazole = 3, voriconazole = 2, caspofungin = 1, intravenous liposomal amphotericin = 1. *Black bar* represents number of patients receiving IST **(B)**. Other immunosuppressant therapies (IST) were provided for STAT1-GOF (MMF = 5, rituximab = 3, hydroxychloroquine = 2, colchicine = 2, sirolimus = 2, azathioprine = 2, infliximab = 2, tocilizumab = 1, mesalazine = 1, cyclosporin = 1, tacrolimus = 1, vedolizumab = 1, adalimumab = 1, cyclophosphamide = 1) or STAT3-GOF (sirolimus = 8, tocilizumab = 7, MMF = 4, rituximab = 3, cyclosporin = 2, cyclophosphamide = 1, eculizumab = 1). *IST,* Immunosuppressant therapy; *IVIG,* intravenous immunoglobulin; *MMF,* mycophenolate mofetil; *ScIG,* subcutaneous immunoglobulin; *TMP-SMX,* cotrimoxazole.

Treatment observations in patients undergoing HSCT

Eleven patients of our study cohort underwent HSCT (9 patients with STAT1-GOF, 2 patients with STAT3-GOF); an overview is provided in Table E10 in the Online Repository available at www.jacionline.org. The clinical indications for HSCT were multisystemic immune dysregulation (n = 4), infection susceptibility (n = 2), and their combination (n = 5). The age at HSCT ranged from 1 to 18 years (median, 9.0 years). Before HSCT, 10 of 11 patients received a bridging therapy with ruxolitinib (dose 7.5 to 40.0 mg/m^2/d, median 24.3 mg/m^2/d; treatment duration 4-28 months, median 8.0 months). At the time of HSCT, 5 of 11 patients had partial or complete remission of their disease-related symptoms (Figs E3-E5). The previous JAKi treatment (ruxolitinib in all 11 patients) was withdrawn around the HSCT procedure, as detailed above. In 1 patient (P11), baricitinib had already been terminated several weeks before HSCT because of a mucormycosis. Ruxolitinib was reintroduced in 3 patients: in 1 patient before HSCT (P8, at day −6 after initial cessation from day −9) due to a suspected JAKi withdrawal syndrome; and in 2 patients after HSCT as a prophylactic measure, after detection of a mixed chimerism from day +60 (P37) and day +296 onward. Complete donor chimerism was reported in 7 patients (in P21 after a second HSCT procedure) and mixed (89%, 80% and >90% donor origin) in 3 patients (P31, P37, P42). Two graft failures were observed: 1 (P21) primary (which was rescued by a second procedure) and 1 secondary (P65). The latter patient died on day +93 from the sequelae of a (noninfectious) encephalitis. The overall survival after HSCT was 91% (10/11 patients: 9/9 STAT1-GOF and 1/2 STAT3-GOF) with a reported follow-up time of 0.7 to 4.8 years (median, 1.7 years). The patients' post-HSCT disease status was judged to be cured (5/10) or significantly improved (5/10) in all surviving patients.

DISCUSSION

Genetic defects resulting in impaired JAK/STAT signaling have been identified as the common pathophysiologic basis in

several IEI.[3,4] The clinical presentations of patients with GOF mutations in *STAT1* and *STAT3* are characterized by a high disease burden from various immune dysregulatory symptoms.[6,8]

Because hyperactivation of the JAK/STAT pathway is the pathophysiologic hallmark of JAK/STAT-GOF IEI, JAKi are promising pharmacologic compounds to treat affected patients. Indeed, the first successful proof of principle for treatment with ruxolitinib was reported early: in 2015, by Higgins et al[10] in an adult STAT1-GOF patient with alopecia areata. Since then, further successful treatment observations, also for various other disease manifestations, have been reported in over 30 patients with STAT1-GOF (eg, CMC, mucocutaneous inflammation),[9,10,12,14,16-18,29-42] over 50 patients with STAT3-GOF (eg, autoimmune cytopenia, lymphoproliferation),[8,11,19,20,23,24,43-45] and in single patients with other JAK/STAT IEI such as *SOCS1* haploinsufficiency,[46] JAK1-GOF,[47,48] STAT4-GOF,[49] STAT5B-GOF,[26] STAT6-GOF,[50] *STAT1* loss of function,[51] or *USP18* deficiency.[52] Despite these encouraging observations and the development of several JAKi for other autoimmune or inflammatory diseases such as rheumatoid arthritis, ulcerative colitis, and graft-versus-host disease,[2] no commercially available JAKi is currently licensed for the treatment of patients with monogenetic JAK/STAT IEI. At the time of our survey, no prospective clinical trial utilizing JAKi for these conditions was listed in the ClinicalTrials.gov database.[53] In contrast to this, the recruitment of 69 severely symptomatic patients from 32 large IEI referral centers to our study clearly document that JAKi are commonly used in an off-label setting and are broadly regarded as the standard of care to treat symptomatic JAK/STAT-GOF IEI patients. In line with this, approximately half the patients (22/45) with STAT1-GOF in our cohort received a JAKi as first-line treatment, and in 14 of these 22 patients, therapy with a JAKi had already been initiated before the year 2018, with its continuous long-term administration planned. In contrast, only 4 of 21 patients with STAT3-GOF received JAKi as a first-line approach and were previously treated with various other immunosuppressive protocols.

Similar to previous reports, ruxolitinib was the most commonly prescribed JAKi in our cohort (81% of treatment observations). At first glance, this seems surprising: ruxolitinib is a broadly acting first-generation JAKi that blocks JAK1 and JAK2, but that also affects JAK3 and TYK2 signaling.[5] Second-generation JAKi with higher specificity of anti-JAK1 (eg, filgotinib, upadacitinib) or anti-JAK2 (fedratinib) activity are emerging and may provide a more specific mode of action and possibly an improved safety profile.[2] Yet the preferential prescription routine for ruxolitinib likely reflects the commonly reported beneficial use (ie, in STAT1-GOF[10,14,16,18,29-31,33-37,39-41]) and the personal experiences of the local physicians for other treatment indications, such as graft-versus-host disease.[54] The choices of these personal physicians may have also influenced the prescription practices for other first-generation JAKi like tofacitinib and baricitinib, which were provided to single patients in our study, and previous reports on JAK/STAT-GOF IEI patients.[14,19,32,34,46,48]

Even though it is prescribed off label, ruxolitinib is considered relatively safe even in young children, and doses in malignant pediatric diseases of up to 50 mg/m^2/d have been published as being well tolerated.[55] In line with this, our data suggest a generally favorable safety profile of ruxolitinib, baricitinib, and tofacitinib for our study's JAK/STAT IEI patients. Although AEs were commonly observed (38% of patients), symptoms were usually mild (grade I-II) and transient. Nonetheless, some clinically judged low-grade AEs, such as unintentional weight gain, appeared to have an important effect on the general well-being and triggered termination of JAKi in some patients. Moreover, the treatment observation time within our study (median, 17.0 months; range, 3-57 months) is certainly too short to generate a final conclusion on the long-term safety of JAKi treatment in JAK/STAT-GOF IEI. Several severe and life-threatening AEs were previously reported in individual JAK/STAT-GOF patients receiving JAKi treatment.[34,56] Some of these (eg, potential occurrence of progressive multifocal leukoencephalopathy, deep vein thrombosis) were not routinely evaluated in the follow-up monitoring scheme of our patients. Furthermore, both the retrospective design of our study and the limited time of data capture are restricting evaluations for rare (but potentially critical) AEs.

Future prospective studies comparing the AE profile of the various specific JAKi are desirable and should ideally also include detailed quality-of-life and other patient-related outcome measures, which were lacking in our retrospective study. We were interested to note no critical inflammatory symptoms in 18 patients after ruxolitinib withdrawal. Only 1 patient with suspected (mild) withdrawal symptoms was reported within our network. However, half of these patients discontinued their JAKi therapy (all were receiving ruxolitinib) just at the start of conditioning for HSCT, which may have suppressed inflammatory responses that would otherwise have been triggered. Inflammatory symptoms related to JAKi withdrawal or discontinuation syndrome are potentially life-threatening, so gradually tapering JAKi treatment is generally advisable.[57]

Overall, JAKi treatment resulted in a marked improvement of clinical symptoms in 87% of STAT1-GOF and 90% of STAT3-GOF patients. Although treatment responses were variable among different disease manifestations, partial or complete improvement was mostly observed after 1 to 6 months. Previous case series reported faster responses of CMC.[14] However, in our larger cohort, this finding could not be confirmed.

While in the literature CMC has been the most predominantly reported symptom to initiate JAKi in STAT1-GOF, various further manifestations of immune dysregulation have also been major treatment indications in our patients. Moreover, concomitant immunosuppressive comedications could be gradually removed in most patients receiving JAKi treatment.

With a treatment median observation time of 17.0 months (range, 3-57 months), our data further suggest a sustained treatment response. However, recording the incidence of AEs accumulated over time (data not shown) and thoroughly monitoring patients remain advisable.

To evaluate treatment responses in greater detail and longitudinally, future prospective JAKi studies (as well as patient registries) should incorporate a symptom-specific disease scoring to allow for a more objective treatment assessment. These are obvious limitations of our and other retrospective studies, in which data evaluation was primarily based on retrospective patient chart analyses and individual clinical judgment. As a result of the retrospective study design and variable follow-up protocols of the participating centers (eg, lack of regular central nervous system imaging), we could also only evaluate for treatment responses of the most common clinical manifestations. Rare clinical manifestation like vascular abnormalities were not systematically assessed.

Moreover, data from our survey do not allow to provide clear recommendations for optimal JAKi dosing across variable age ranges. While JAKi treatment was generally judged to be highly efficient in controlling clinical symptoms, this response was achieved by highly variable dosing schemes. Whether the observed higher dosing of ruxolitinib in STAT3-GOF patients (median, 25 mg/m^2/d) compared to STAT1-GOF patients (median, 15 mg/m^2/d) actually reflects a higher need of JAK1/2 suppression for disease control in these patients needs to be explored in prospective trials that use a controlled dose comparison–escalation strategy. The lower ruxolitinib dosing practice among the STAT1-GOF patients in our survey may also reflect an adjustment to the higher number of coadministered drugs, in particular azoles, which are known to inhibit the cytochrome metabolic pathways. To explore optimal dosing, including the effects of comedication, future studies should ideally include PK evaluations. Overall, access to routine PK assessment for JAKi is currently limited, although it has been proven helpful to guide an optimized dosing scheme and adequate between-dose exposures in previously reported IEI patients treated with ruxolitinib.[23,27]

Although JAKi were generally well tolerated, the relevant incidence rate of AEs in some patients also highlights the need to explore further treatment options. As such, HSCT has been shown to be potentially curative—at least for the hematopoietic and immune dysregulatory disease manifestations of JAK/STAT-GOF IEI.[7,9,39,58,59] However, it remains unclear whether all disease-related manifestations, such as risk for vascular disease, can be controlled in the long term; previously published reports have demonstrated poor outcome. However, almost none of these patients received pre-HSCT JAKi treatment, and most of the patients who died had severe manifestations of JAK/STAT IEI and multiorgan damage before HSCT.[7,9] In contrast to these previously published HSCT experience, our survey could document significantly better outcomes in 11 patients after JAKi bridging treatment. These encouraging results confirm observations from single case reports.[9,39] A dedicated IEWP study analyzing HSCT outcomes in STAT1-GOF patients with and without previous JAKi bridging treatment is currently recruiting.[60]

In conclusion, our study summarizes what is to our knowledge the largest JAKi treatment observation for patients with JAK/STAT IEI published to date. Our data suggest that JAKi are highly effective in treating symptomatic JAK/STAT IEI patients. Nonetheless, AEs are common and may negatively impact affected patients. Prospective studies and registries are needed to answer open questions regarding the optimal type of JAKi, as well as timing and dosing for the variable clinical presentations and age ranges and, ideally, reaching marketing authorization for these indications. The currently used off-label treatment and monitoring regimens are highly heterogenous, even between specialized IEI centers. Harmonized protocols, ideally developed within a structured consensus process, should be pursued.

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Clinical implications:

- **JAKi are potent compounds for treating patients with JAK/STAT IEI and should be further evaluated in prospective trials.**
- **Although JAKi are generally well tolerated, long-term safety data are currently not available.**

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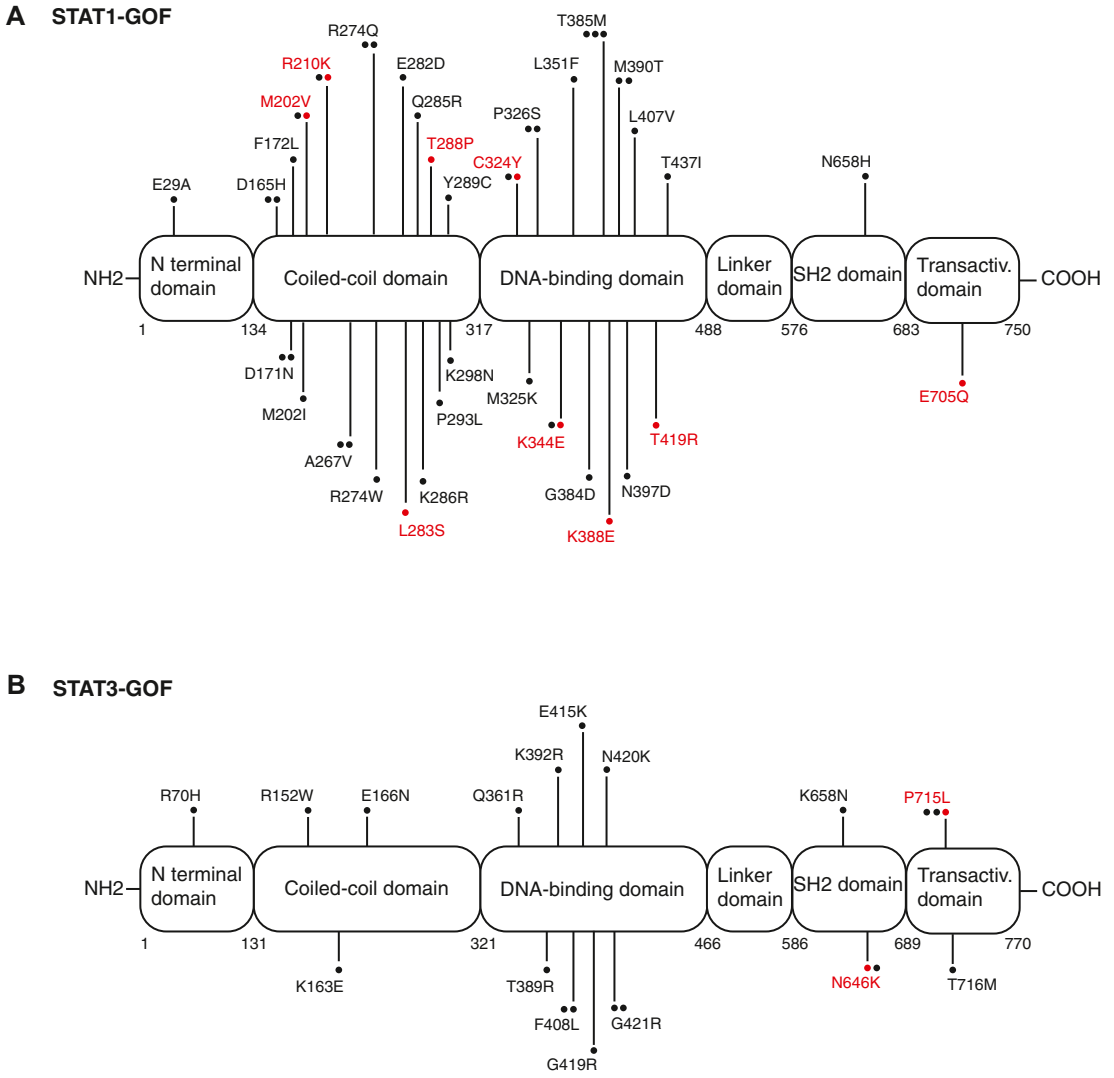


FIG E1. Schematics of *STAT1* **(A)** and *STAT3* **(B)** showing reported location of mutation. *Red dots* indicate patient received HSCT. *A,* Alanine; *C,* cysteine; *D,* aspartic acid; *E,* glutamic acid; *F,* phenylalanine; *G,* glycine; *H,* histidine; *I,* isoleucine; *K,* lysine; *L,* leucine; *M,* methionine; *N,* asparagine; *P,* proline; *Q,* glutamine; *R,* arginine; *S,* serine; *T,* threonine; *V,* valine; *W,* tryptophan; *Y,* tyrosine.

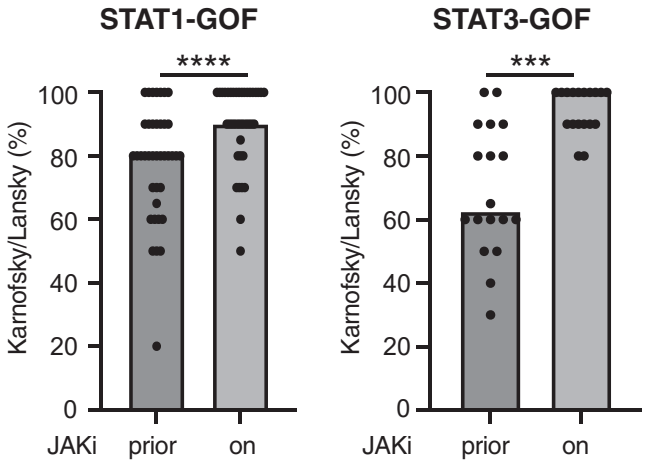
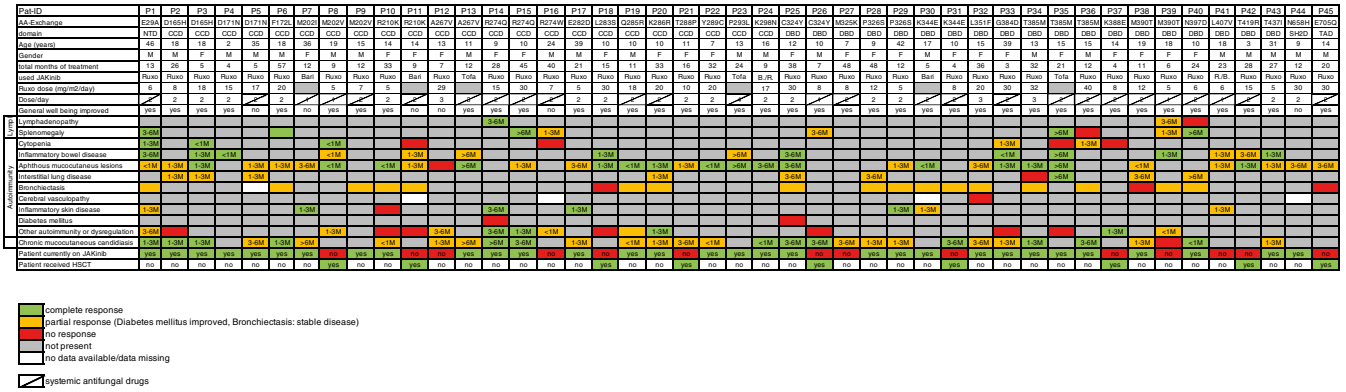


FIG E2. Bar graph of Karnofsky/Lansky scale of STAT1-GOF (n = 39, *left*) and STAT3-GOF patient (n = 18, *right*) before *(dark gray)* and while receiving *(light gray)* JAKi therapy. Data shown are medians. Statistical significance assessed by Wilcoxon matched pairs signed rank test. ***$P < .001$, ****$P < .0001$.



complete response
partial response (Diabetes mellitus improved, Bronchiectasis: stable disease)
no response
not present
no data available/data missing

systemic antifungal drugs

FIG E3. Heat map of treatment response of individual STAT1-GOF patients, each represented by a *column.* Patients were organized in order of mutation location on STAT1 protein. Treatment response was separated into complete response *(green),* partial response *(orange),* no response *(red),* not present *(gray),* or no data available *(white).*

	Pat-ID	P46	P47	P48	P49	P50	P51	P52	P53	P54	P55	P56	P57	P58	P59	P60	P61	P62	P63	P64	P65	P66
	AA-Exchange	R70H	R152W	K163E	E166N	Q361R	T389R	K392R	F408L	F408L	E415K	G419R	N420K	G421R	G421R	N646K	N646K	K658N	P715L	P715L	P715L	T716M
	domain	NTD	CCD	CCD	CCD	DBD	DBD	DBD	DBD	DBD	DBD	DBD	DBD	DBD	DBD	SH2D	SH2D	SH2D	TAD	TAD	TAD	TAD
	Age (years)	18	32	8	2	23	14	7	10	6	11	16	16	22	3	15	12	3	4	5	1	14
	Gender	F	M	M	M	F	F	M	M	M	F	F	F	F	M	M	M	M	M	M	M	F
	total months of treatment	3	22	26	19	8	42	15	16	4	52	32	7	11	20	36	7	28	34	20	6	17
	used JAKinib	Ruxo	Tofa	Tofa	Ruxo	Ruxo	Tofa	Ruxo	Tofa	Tofa	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo	Ruxo
	Ruxo dose (mg/m2/day)	8			51	20		17			20	40	30	20	8	59	30	38	40	10	54	17
	Dose/day		2	2	2	2	2	2	3	2	2	2	2	2	2	2	2	3	2	2	2	3
	General well being improved	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no
Lymph	Lymphadenopathy	1-3M					>6M	3-6M		3-6M	1-3M								1-3M	1-3M	1-3M	1-3M
Lymph	Splenomegaly		3-6M			1-3M	>6M	>6M			1-3M					>6M					1-3M	>6M
Lymph	Cytopenia	1-3M					>6M	1-3M	>6M			1-3M								1-3M		>6M
Autoimmunity	Inflammatory bowel disease		3-6M	>6M	1-3M					3-6M	1-3M							1-3M				
Autoimmunity	Aphthous mucocutaneus lesions																					
Autoimmunity	Interstitial lung disease			>6M						3-6M	>6M	3-6M				3-6M	1-3M	<1M				
Autoimmunity	Bronchiectasis																					
Autoimmunity	Cerebral vasculopathy																					
Autoimmunity	Inflammatory skin disease				1-3M			1-3M								3-6M			<1M			
Autoimmunity	Diabetes mellitus																1-3M		<1M			
Autoimmunity	Other autoimmunity or dysregulation			>6M					>6M				1-3M	1-3M	3-6M	1-3M				<1M	1-3M	
	Chronic mucocutaneous candidiasis																					
	Patient currently on JAKinib	yes	yes	yes	yes	no	yes	yes	yes	yes	yes	yes	yes	yes	yes	yes	no	yes	yes	yes	no	yes
	Patient received HSCT	no	no	no	no	no	no	no	no	no	no	no	no	no	no	no	yes	no	no	no	yes	no

complete response
partial response (Diabetes mellitus improved, Bronchiectasis: stable disease)
no response
not present
no data available/data missing

systemic antifungal drugs

FIG E4. Heat map of treatment response of individual STAT3-GOF patients, each represented by a *column.* Patients were organized in order of mutation location on STAT3 protein. Treatment response was separated into complete response *(green),* partial response *(orange),* no response *(red),* not present *(gray),* or no data available *(white).*

	Pat-ID	P67	P68	P69
	Disease	STAT5BGOF	SOCS1	JAK1GOF
	Age (years)	9	5	12
	Gender	F	F	M
	total months of treatment	23	4	24
	used JAKinib	Ruxo	Ruxo	Bari
	Ruxo dose (mg/m2/day)	30	24	
	Dose/day	2	2	2
	General well being improved	yes	yes	yes
Lympl	Lymphadenopathy			
	Splenomegaly			
Autoimmunity	Cytopenia			
	Inflammatory bowel disease	3-6M	1-3M	
	Aphthous mucocutaneus lesions			
	Interstitial lung disease			
	Bronchiectasis			
	Cerebral vasculopathy			
	Inflammatory skin disease			<1M
	Diabetes mellitus			
	Other autoimmunity or dysregulation	1-3M	1-3M	<1M
	Chronic mucocutaneous candidiasis			
	Patient currently on JAKinib	no	yes	yes
	Patient received HSCT	no	no	no

complete response
partial response (Diabetes mellitus improved, Bronchiectasis: stable disease)
no response
not present
no data available/data missing

systemic antifungal drugs

FIG E5. Heat map of treatment response of patient with underlying diseases involving JAK/STAT pathway other than STAT1-GOF or STAT3-GOF (*SOCS1,* JAK1-GOF, STAT5B-GOF). Treatment response was separated into complete response *(green),* partial response *(orange),* no response *(red),* not present *(gray),* or no data available *(white).*

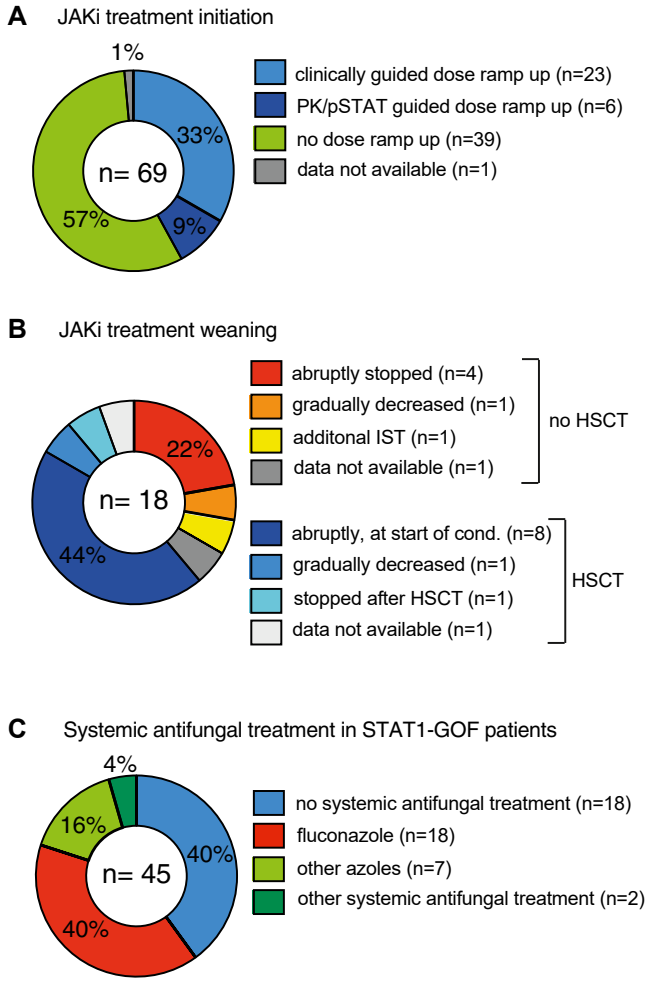


FIG E6. Additional clinical information. Percentage of JAKi treatment initiation **(A)**. Percentage of JAKi weaning strategy **(B)**. Percentage of systemic antifungal treatment in STAT1-GOF patients.

TABLE E1. Patients described in previous publications

Patient ID	Diagnosis	Age (years)	Sex	Previously published
P1	STAT1-GOF	46	M	Yes (E1)
P2	STAT1-GOF	18	M	No
P3	STAT1-GOF	18	F	No
P4	STAT1-GOF	2	M	No
P5	STAT1-GOF	35	M	No
P6	STAT1-GOF	18	M	No
P7	STAT1-GOF	36	F	Yes (E2)
P8	STAT1-GOF	19	M	No
P9	STAT1-GOF	15	M	No
P10	STAT1-GOF	14	F	No
P11	STAT1-GOF	13	F	No
P12	STAT1-GOF	13	F	No
P13	STAT1-GOF	11	M	No
P14	STAT1-GOF	9	F	No
P15	STAT1-GOF	10	F	Yes (E3)
P16	STAT1-GOF	24	M	Yes (E4)
P17	STAT1-GOF	39	M	No
P18	STAT1-GOF	10	F	Yes (E5, E6)
P19	STAT1-GOF	10	M	No
P20	STAT1-GOF	10	F	No
P21	STAT1-GOF	11	F	Yes (E3)
P22	STAT1-GOF	7	F	Yes (E3)
P23	STAT1-GOF	13	M	No
P24	STAT1-GOF	16	M	Yes (E3)
P25	STAT1-GOF	12	F	No
P26	STAT1-GOF	10	M	No
P27	STAT1-GOF	7	F	No
P28	STAT1-GOF	9	F	Yes (E3)
P29	STAT1-GOF	42	F	No
P30	STAT1-GOF	17	M	No
P31	STAT1-GOF	10	F	Yes (E3)
P32	STAT1-GOF	15	F	Yes (E3, E7)
P33	STAT1-GOF	39	F	No
P34	STAT1-GOF	13	M	No
P35	STAT1-GOF	15	F	No
P36	STAT1-GOF	15	M	No
P37	STAT1-GOF	14	F	Yes (E4)
P38	STAT1-GOF	19	F	Yes (E1)
P39	STAT1-GOF	18	F	Yes (E4, E5)
P40	STAT1-GOF	10	F	No
P41	STAT1-GOF	18	M	No
P42	STAT1-GOF	3	M	No
P43	STAT1-GOF	31	M	No
P44	STAT1-GOF	9	M	Yes (E3)
P45	STAT1-GOF	14	M	Yes (E8)
P46	STAT3-GOF	18	F	No
P47	STAT3-GOF	32	M	No
P48	STAT3-GOF	8	M	No
P49	STAT3-GOF	2	M	No
P50	STAT3-GOF	23	F	Yes (E9)
P51	STAT3-GOF	14	F	No
P52	STAT3-GOF	7	M	No
P53	STAT3-GOF	10	M	No
P54	STAT3-GOF	6	M	No
P55	STAT3-GOF	11	F	Yes (E10)
P56	STAT3-GOF	16	F	No
P57	STAT3-GOF	16	F	Yes (E9, E11)
P58	STAT3-GOF	22	F	Yes (E12)
P59	STAT3-GOF	3	M	No
P60	STAT3-GOF	15	M	Yes (E9)
P61	STAT3-GOF	12	M	Yes (E13)
P62	STAT3-GOF	3	M	Yes (E14)
P63	STAT3-GOF	4	M	Yes (E15)
P64	STAT3-GOF	5	M	No
P65	STAT3-GOF	1	M	Yes (E9)
P66	STAT3-GOF	14	F	No
P67	STAT5B-GOF	9	F	Yes (E16, E17)
P68	*SOCS1*	5	F	No
P69	JAK1-GOF	12	M	No

TABLE E2. Specific treatment response

Characteristic	STAT1-GOF (n = 45)	STAT3-GOF (n = 21)
General well-being improved	87% (39/45)	90% (19/21)
Lymphadenopathy	7% (3/45)	55% (11/20)
Complete response	33% (1/3)	64% (7/11)
Partial response	33% (1/3)	18% (2/11)
No response	33% (1/3)	18% (2/11)
Time until clinical improvement <1 month	—	—
Time until clinical improvement 1-3 months	—	67% (6/9)
Time until clinical improvement 3-6 months	100% (2/2)	22% (2/9)
Time until clinical improvement >6 months	—	11% (1/9)
Splenomegaly	20% (9/45)	43% (9/21)
Complete response	56% (5/9)	33% (3/9)
Partial response	33% (3/9)	56% (5/9)
No response	11% (1/9)	11% (1/9)
Time until clinical improvement <1 month	—	—
Time until clinical improvement 1-3 months	29% (2/7)	38% (3/8)
Time until clinical improvement 3-6 months	29% (2/7)	13% (1/8)
Time until clinical improvement >6 months	43% (3/7)	50% (4/8)
Cytopenia	20% (9/45)	38% (8/21)
Complete response	33% (3/9)	88% (7/8)
Partial response	22% (2/9)	—
No response	44% (4/9)	13% (1/8)
Time until clinical improvement <1 month	40% (2/5)	—
Time until clinical improvement 1-3 months	60% (3/5)	57% (4/7)
Time until clinical improvement 3-6 months	—	—
Time until clinical improvement >6 months	—	43% (3/7)
Inflammatory bowel disease	33% (15/45)	33% (7/21)
Complete response	60% (9/15)	71% (5/7)
Partial response	40% (6/15)	14% (1/7)
No response	—	14% (1/7)
Time until clinical improvement <1 month	20% (3/15)	—
Time until clinical improvement 1-3 months	40% (6/15)	50% (3/6)
Time until clinical improvement 3-6 months	20% (3/15)	33% (2/6)
Time until clinical improvement >6 months	20% (3/15)	17% (1/6)
Aphthous mucocutaneus lesions	73% (33/45)	0 (0/21)
Complete response	48% (16/33)	—
Partial response	48% (16/33)	—
No response	3% (1/33)	—
Time until clinical improvement <1 month	22% (7/32)	—
Time until clinical improvement 1-3 months	47% (15/32)	—
Time until clinical improvement 3-6 months	22% (7/32)	—
Time until clinical improvement >6 months	9% (3/32)	—
Interstitial lung disease	22% (10/45)	38% (8/21)
Complete response	10% (1/10)	50% (4/8)
Partial response	80% (8/10)	38% (3/8)
No response	10% (1/10)	13% (1/8)
Time until clinical improvement <1 month	—	14% (1/7)
Time until clinical improvement 1-3 months	44% (4/9)	14% (1/7)
Time until clinical improvement 3-6 months	33% (3/9)	43% (3/7)
Time until clinical improvement >6 months	22% (2/9)	29% (2/7)
Bronchiectasis	47% (21/45)	5% (1/20)
Stable disease	81% (17/21)	100% (1/1)
Progressive disease	14% (3/21)	—
No follow-up data	5% (1/21)	—
Cerebral vasculopathy	11% (5/45)	0 (0/21)
Inflammatory skin disease	18% (8/45)	19% (4/21)
Complete response	50% (4/8)	50% (2/4)
Partial response	38% (3/8)	50% (2/4)
No response	13% (1/8)	—
Time until clinical improvement <1 month	—	25% (1/4)
Time until clinical improvement 1-3 months	86% (6/7)	50% (2/4)
Time until clinical improvement 3-6 months	14% (1/7)	25% (1/4)
Time until clinical improvement >6 months	—	—

(Continued)

TABLE E2. *(Continued)*

Characteristic	STAT1-GOF (n = 45)	STAT3-GOF (n = 21)
Diabetes mellitus	4% (2/45)	14% (3/21)
Improved	—	67% (2/3)
No response	100% (2/2)	33% (1/3)
Time until clinical improvement <1 month	—	50% (1/2)
Time until clinical improvement 1-3 months	—	50% (1/2)
Time until clinical improvement 3-6 months	—	—
Time until clinical improvement >6 months	—	—
Other autoimmunity or dysregulation	38% (17/45)	52% (11/21)
Complete response	24% (4/17)	55% (6/11)
Partial response	35% (6/17)	27% (3/11)
No response	41% (7/17)	18% (2/11)
Time until clinical improvement <1 month	22% (2/9)	13% (1/8)
Time until clinical improvement 1-3 months	44% (4/9)	50% (4/8)
Time until clinical improvement 3-6 months	33% (3/9)	13% (1/8)
Time until clinical improvement >6 months	—	25% (2/8)
Chronic mucocutaneous candidiasis	69% (31/45)	—
Complete response	42% (13/31)	—
Partial response	55% (17/31)	—
No response	3% (1/31)	—
Time until clinical improvement <1 month	17% (5/30)	—
Time until clinical improvement 1-3 months	43% (13/30)	—
Time until clinical improvement 3-6 months	30% (9/30)	—
Time until clinical improvement >6 months	10% (3/30)	—

TABLE E3. Summary of AEs: Infection

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Systemic corticosteroid therapy	Infection	Time (months) until AE manifestation	Clinical course	Outcome
P2	STAT1-GOF	18	M	R	No	EBV reactivation (September 2019), persistent EBV copy numbers	1	Dose reduction, JAKi paused	Resolved
P7	STAT1-GOF	36	F	B	No	SARS-CoV-2 infection	12	No dose reduction, JAKi paused	Resolved
P9	STAT1-GOF	15	M	R	No	Sputum culture positive for penicillium	4	Dose reduction, JAKi paused	Resolved
P11	STAT1-GOF	13	F	B	No	2× onychia, perineal cellulitis, mucor	1	No dose reduction, JAKi stopped	Resolved
P12	STAT1-GOF	13	F	R	No	Chronic bronchitis: positive PCR for PCJ of uncertain significance and *Moraxella catarrhalis*	6	Dose reduction, JAKi stopped	Ongoing
P20	STAT1-GOF	10	F	R	No	Suspected mycobacterial skin disease	16	Dose reduction, JAKi paused	Resolved
P22	STAT1-GOF	7	F	R	Yes	Pneumonia, 2× suspected bacteremia (blood cultures negative), pneumonia *(Pseudomonas aeruginosa)* eradication ongoing	21	No dose reduction, no JAKi pause	Resolved
P25	STAT1-GOF	12	F	R	No	Transient EBV reactivation	3	Dose reduction, no JAKi pause	Resolved
P31	STAT1-GOF	10	F	R	No	CMV primoinfection	4	No dose reduction, no JAKi pause	Resolved
P34	STAT1-GOF	13	M	R	No	Pneumococcal pneumonia	26	No dose reduction, no JAKi pause	Resolved
P37	STAT1-GOF	14	F	R	No	Otitis media	2	No dose reduction, no JAKi pause	Resolved
P41	STAT1-GOF	18	M	R/B	No	4 episodes of sepsis-like infections during B treatment	22	Dose reduction, JAKi stopped	Resolved
P44	STAT1-GOF	9	M	R	No	Parainfluenza type 4 infection	7	No dose reduction, no JAKi pause	Resolved
P45	STAT1-GOF	14	M	R	Yes	Herpes zoster infection	17	No dose reduction, no JAKi pause	Resolved
P49	STAT3-GOF	2	M	R	No	Varicella	9	No dose reduction, no JAKi pause	Resolved
P65	STAT3-GOF	1	M	R	No	Mild viral infections*	3	No dose reduction, no JAKi pause	Resolved

B, Baricitinib; *CMV,* cytomegalovirus; *R,* ruxolitinib; *SARS-CoV-2,* severe acute respiratory syndrome coronavirus 2.
*Viral infections included astrovirus gastroenteritis, adenovirus, and human metapneumovirus respiratory infection.

TABLE E4. Summary of AEs: Unintentional weight gain

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Time (months) until AE manifestation	Clinical course	Outcome
P3	STAT1-GOF	18	F	R	3	No dose reduction, no pause	Ongoing
P9	STAT1-GOF	15	M	R	4	No dose reduction, no pause	Ongoing
P10	STAT1-GOF	14	F	R	NA	No dose reduction, no pause	Ongoing
P12	STAT1-GOF	13	F	R	NA	No dose reduction, stopped	Resolved
P43	STAT1-GOF	31	M	R	3	No dose reduction, no pause	Ongoing
P53	STAT3-GOF	10	M	T	1	Dose reduction, no pause	Ongoing
P60	STAT3-GOF	15	M	R	21	No dose reduction, no pause	Ongoing
P64	STAT3-GOF	5	M	R	16	No dose reduction, no pause	Resolved
P66	STAT3-GOF	14	F	R	2	Dose reduction, no pause	Ongoing

NA, Not applicable; *R,* ruxolitinib; *T,* tofacitinib.

TABLE E5. Summary of AEs: Neurologic symptoms

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Neurologic symptoms	Time (months) until AE manifestation	Clinical course	Outcome
P12	STAT1-GOF	13	F	R	Forgetfulness, concentration disruption, memory loss	1	JAKi stopped	Ongoing
P34	STAT1-GOF	13	M	R	Headache, vertigo, visual impairment	9	JAKi paused	Resolved
P43	STAT1-GOF	31	M	R	Mild headache	0	No pause, no dose reduction	Resolved
P56	STAT3-GOF	16	F	R	Headache, vomiting	1	Dose reduction, no pause	Resolved

R, Ruxolitinib.

TABLE E6. Summary of AEs: Cytopenia

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Cytopenia	Time (months) until AE manifestation	Clinical course	Outcome
P11	STAT1-GOF	13	F	B	Anemia (more related to disease activity than toxicity)	3	No reduction, no pause	Ongoing
P16	STAT1-GOF	24	M	R	Bicytopenia followed by tricytopenia and aplasia	40	Dose reduction, JAKi stopped	Ongoing
P50	STAT3-GOF	23	F	R	Anemia (preexisting); neutropenia (without LGL relapse)	7	Dose reduction, JAKi stopped	Resolved

B, Baricitinib; *LGL,* large granular lymphocytic leukemia; *R,* ruxolitinib.

TABLE E7. Summary of AEs: Growth and bone metabolism related

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Growth or Bone metabolism	Clinical course	Outcome
P20	STAT1-GOF	10	F	R	Osteoporosis	No dose reduction	Ongoing

R, Ruxolitinib.

TABLE E8. Summary of AEs: Grade III or higher organ toxicity

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Grade II or higher organ toxicity	Time (months) until AE manifestation	Clinical course	Outcome
P12	STAT1-GOF	13	F	R	Elevation of creatinine	6	No pause, no dose reduction	Resolved
P31	STAT1-GOF	10	F	R	Liver, hepatitis; JAKi stopped and AE resolved	3	JAKi stopped	Resolved

R, Ruxolitinib.

TABLE E9. Summary of AEs: Other AEs

Patient ID	Molecular diagnosis	Age (years) at last follow-up	Sex	JAKi	Other AE	Time (months) until AE manifestation	Clinical course	Outcome
P7	STAT1-GOF	36	F	B	Myalgia and dyspepsia	3	Dose reduction, no JAKi pause	Resolved
P41	STAT1-GOF	1	M	R	Severe mucositis, acne, fatigue	9	Dose reduction, JAKi pause	Resolved

B, Baricitinib; *R,* ruxolitinib.

TABLE E10. Patient characteristics, HSCT details, JAKi treatment, and HSCT outcome of all 11 patients receiving HSCT

	Patient ID	P8	P11	P18	P21	P26	P31	P37	P42	P45	P61	P65
	Molecular diagnosis	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT1-GOF	STAT3-GOF	STAT3-GOF
	Sex	M	F	F	F	M	F	F	M	M	M	M
HSCT details	Main HSCT indication	Multisystemic immunody sregulation	Infection and immunody sregulation	Multisystemic immunodysregulation	Infection and immunodysregulation	Infection susceptibility	Infection and immunody sregulation	Infection and immunody sregulation	Infection and immunody sregulation	Infection susceptibility	Multisystemic immunody sregulation	Multisystemic immunody sregulation
	Age (years) at HSCT	18	13	9	11	9	6	14	3	11	9	1
	HSCT, donor relation	MUD	MSD	MUD	MMUD (9, 10), MMFD (5, 10)*	MMUD (9, 10)	MFD	MUD	MRD	MUD	MUD	MUD
	HSCT, graft source	PBSC	BM	PBSC	BM+PBSC;	PBSC	BM	BM	BM	PBSC	PBSC	PBSC
	No. of HSCTs	1	1	1	2*	1	1	1	1	1	1	1
	Conditioning regimen	RIC	MAC	RIC	MAC	MAC	RIC	MAC	MAC	RIC	RIC	RIC
	Serotherapy	A	ATG	A	ATG	ATG	A	A	ATG	A	A	A
JAKi treatment	Received JAKi before HSCT	R	B	R	R	R	R	R	R	R	R	R
	JAKi dose in *x* dose	10 mg/m^2/d in 1 dose per day	6.95 m^2/d in 2 doses per day	30 mg/m^2/d in 2 doses per day	18.5 mg/m^2/d in 2 doses per day	7.5 mg/m^2/d in 1 dose per day	8 mg/m^2/d in 2 doses per day	10 mg/m^2/d in 2 doses per day	40 mg/m^2/d in 2 doses per day	30 mg/m^2/d in 2 doses per day	30 mg/m^2/d in 2 doses per day	37.5 mg/m^2/d in 2 doses per day
	Total months of JAKi treatment	9	12	15	16	7	4	4	28	20	7	6
	HSCT due to insufficient JAKi response	No	Yes	Yes (no PK)	Yes (no PK)	No	No	No	Yes (no PK)	Yes (no PK)	No	No
	JAK withdrawal strategy	At start of conditioning	At start of conditioning, reduction until day 0	At start of conditioning, abruptly stopped	At start of conditioning, abruptly stopped	At start of conditioning, abruptly stopped	Before conditioning, abruptly stopped	At start of conditioning, abruptly stopped	Stopped after day +4	At start of conditioning, abruptly stopped	At start of conditioning, abruptly stopped	At start of conditioning, abruptly stopped
	JAK withdrawal syndrome	Uncertain†	Yes	No	No	No	No	No	No	No	No	No
	JAKi reintroduction, reason	Yes, due to withdrawal syndrome†	No	No	No	No	No	Yes, to evaluate effect on chimerism	Yes, to evaluate effect on chimerism	No	No	No
Outcome	Acute GvHD (grade, manifestation)	Yes (2, gut)	No	Yes (1, skin)	No, yes (2, skin)*	Yes (1, skin)	No	No	Yes (1, skin)	Yes (1, skin)	No	No
	Chronic GvHD	No	No	No	No, no*	No	No	No	No	No	No	No
	Last chimerism, myeloid (% donor)	Complete	Complete	Complete	Complete (second HSCT)*	Complete	Complete	Mixed (70-80%)	Complete	Complete	Complete	Mixed (21%)
	Last chimerism, T cells (% donor)	Complete	Complete	Complete	Complete (second HSCT)*	Complete	Mixed (89%)	Mixed (70-80%)	Mixed (95%)	Complete	Complete	Mixed (0)
	Engraftment after HSCT	Complete	Complete	Complete	Complete (second HSCT)*	Complete	Partial	Complete	Complete	Complete	Complete	
	Graft failure	No	No	No	Primary (at first HSCT)*	No	No	No	No	No	No	
	Current status of disease	Improved	Cured	Improved	Improved*	Cured	Cured	Improved	Improved	Cured	Cured	Dead
	Alive or dead	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Alive	Dead‡
	Last follow-up (days) after HSCT	626	270	589	257*	715	1765	300	559	1530	941	93
	Age (years) at last follow-up	20	14	10	12*	11	11	15	4	15	12	1

A, Alemtuzumab; *ATG,* antithymocyte globulin; *B,* baricitinib; *BM,* bone marrow; *GvHD,* graft-versus-host disease; *MAC,* myeloablative conditioning; *MFD,* matched family donor; *MMFD,* mismatched family donor; *MMUD,* mismatched unrelated donor; *MSD,* matched sibling donor; *MUD,* matched unrelated donor; *PBSC,* peripheral blood stem cell; *R,* ruxolitinib; *RIC,* reduced-intensity conditioning.

*First HSCT (MMUD 9, 10) with primary graft failure (day +28); Second HSCT (MMFD 5, 10), complete chimeris at day +180, acute GvHD 2° skin.

†Suspected withdrawal syndrome with severe body aches within 1 week of stopping R and 1 episode of hypotension requiring fluid supplementation; R was reintroduced (day −6 to day +28).

‡Dead as a result of HSCT-induced autoimmune encephalitis.