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CLINICAL LETTER

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Clinical manifestations and treatment of STAT-1 gain-of-function: A single-center experience from India

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To the Editor,

Heterozygous, gain-of-function (GOF) mutations in *STAT1* (Signal transducer and activator of transcription-1) cause chronic mucocutaneous candidiasis (CMC), immunodeficiency, and immune dysregulation.[1] We present the clinical features of 11 patients with STAT1 GOF diagnosed and treated at our center.

Table 1 and Figure S1 detail the clinical characteristics of our cohort. Male: female ratio was 8:3. Six were symptomatic during infancy. Ten were symptomatic before their fifth birthday (median age of onset–11 months, range–1.5 –120 months). Six were diagnosed in the first decade. Median delay in diagnosis was 30 months (Range–2.5 months to 321 months). Fungal infections were the main reason for referral, work-up. All had CMC, oral mucosa being the predominant site, followed by esophagus, external genitals, nails, skin (Figure 1 and Figure S2A). Three had esophageal candidiasis causing strictures requiring endoscopic dilatations. Four had dermatophytosis. Five had invasive fungal infections (candida sepsis, persistent pneumonia with positive aspergillus galactomannan, cryptococcal meningitis).

Nine have had at least one pneumonia; four had recurrent pneumonias, and three had persistent pneumonias; one had pleural effusion, and one had empyema. Five had already developed bronchiectasis before referral. ENT manifestations included ear infections, chronic rhinitis, and maxillary sinusitis. Susceptibility to fungal, bacterial, and viral infections was depicted in our cohort (Figure S2B). *Candida albicans* was the most commonly isolated organism, followed by *Mycobacterium tuberculosis*, *Staphylococcus aureus*, and *Pseudomonas aeruginosa*. Other bacterial and fungal organisms isolated included *Klebsiella pneumoniae*, *Streptococcus pneumoniae*, *Enterococcus* species, Beta-Hemolytic *Streptococcus*, *Cryptococcus neoformans*, and *Acroneum* species. Viruses isolated were *Cytomegalovirus*, *Epstein–Barr Virus*, and *Parvovirus B19*. Though all have received live-attenuated vaccines like BCG, OPV, and MMR, none had vaccine-derived infections.

Autoimmunity seen with STAT1 GOF is thought to be due to increased cellular responses to IFN-α/β.[2] These mutations do not affect FOXP3 expression and development of T-regulatory cells.[3] Five of our patients had autoimmunity. Four patients had hematological autoimmunity (three had autoimmune hemolytic anemia (AIHA), one had Evans syndrome). Gastrointestinal autoimmunity included Crohn's disease and autoimmune hepatitis with positive anti-smooth muscle antibody and antineutrophil cytoplasmic antibody. One had autoimmune hypothyroidism positive for anti-thyroglobulin and anti-thyroid peroxidase. Two had recurrent aphthous stomatitis. None of our patients had aneurysms or malignancies. This could be as most of our patients were in their first or second decade of life,- and the

TABLE 1 Demographic features, clinical features, infection spectrum, management, and outcome details of our cohort.

Patient	Sex	Age at onset (in months)	Age at diagnosis (in months)	Delay in diagnosis (in months)	Failure to thrive	Chronic mucocutaneous candidiasis	Dermatophytosis	Invasive fungal infection	Number of episodes of LRTI	Ent symptoms
P1	Male	120	144	24	+	Oral thrush, onychomycosis, balanitis	+	–	2 episodes of pneumonia, 1 episode of pleural effusion	–
P2	Male	11	211	199	+	Oral candidiasis, esophageal candidiasis	+ Acroneum species from nail infection	–	5 episodes of pneumonia	
P3	Male	48	144	96	+	Recurrent oral thrush	–	Cryptococcal meningitis	–	Chronic rhinitis
P4	Female	6	36	30	+	Recurrent oral thrush, esophageal candidiasis	–	–	4 episodes of pneumonia	Left CSOM, chronic maxillary sinusitis
P5	Male	3	25	22	+	Oral candidiasis, esophageal candidiasis, balanitis Candida albicans from ear swab	–	–	2 episodes of pneumonia, 1 episode of persistent pneumonia	Recurrent bilateral ASOM
P6	Male	16	78	62	+	Oral thrush, esophageal candidiasis, palatal candidiasis, balanitis, skin candida infection	–	Candida albicans sepsis	2 episodes of pneumonia	
P7	Female	36	156	120	+	Oral and vaginal candidiasis	–	Persistent pneumonia–most probably Aspergillus as BAL galactomannan positive	3 episodes of pneumonia, 1 episode of pulmonary embolism	
P8	Male	6	25	19	+	Recurrent oral thrush	+	Persistent pneumonia-most probably Aspergillus as BAL galactomannan positive	6 episodes of pneumonia, 2 episodes of persistent pneumonia, necrotizing pneumonia of right lower lobe with right sided empyema thoracis requiring right thoracotomy and right lower lobectomy	–
P9	Male	3	324	321	+	Oral thrush, onychomycosis, external genitalia, esophageal candidiasis	+	–	2 episodes of pneumonia	–
P10	Male	1.5	4	2.5	+	Oral thrush, esophageal candidiasis	–	Candida albicans sepsis	–	–
P11	Female	48	68	20	+	Oral thrush	–	Persistent pneumonia–most probably Aspergillus as bronchoalveolar lavage galactomannan positive	2 episodes of pneumonia	–

Esophageal involvement	Bacterial infections (organisms isolated)	Viral infections (organisms isolated)	Mycobacterium infection	Autoimmune/ inflammatory/ endocrine manifestations	Bronchiectasis	Infection due to live attenuated vaccines (OPV/ MMR/ BCG)	Treatment and outcome
–	Right sided pneumonia–Sputum–Klebsiella, pleural fluid–Methicillin resistant Staphylococcus aureus (MRSA). Right Synpneumonic effusion, Sputum Culture–Streptococcus. Pneumoniae	Herpes zoster Epstein bar virus, Parvovirus B19 isolated from blood	CNS Tuberculoma on MRI	Crohn's disease, autoimmune hemolytic anemia	–	–	Expired, cause of death-gangrene of finger with septicemia
Esophageal candidiasis	Sputum–Pseudomonas, Enterococcus species	2 episodes of Herpes zoster		Recurrent aphthous stomatitis	+	–	On baricitinib
–	–	–	–	–	–	–	Lost to follow up
Esophageal candidiasis, deep ulcer	MRSA from ear swab, 2 episodes of sputum positive pulmonary Koch's		Mycobacterium tuberculosis isolated from gastric lavage 2 times	Autoimmune hemolytic anemia	+	–	Received baricitinib for 28 months, details in Table 2
Oropharyngeal and esophageal candidiasis, stricture formation, required 7 dilations	MRSA, Pseudomonas from ear swab, pseudomonas from esophageal biopsy	Anal wart	–	Recurrent aphthous stomatitis	–	–	On baricitinib
Esophageal candidiasis causing stricture	Mycobacterium tuberculosis isolated from sputum	CMV, EBV viremia	Mycobacterium tuberculosis isolated from gastric lavage	Evans syndrome, hypothyroidism (positive for anti–thyroglobulin and anti-thyroid peroxidase)	–	–	Started on ruxolitinib. Developed pulmonary tuberculosis 8 weeks later, ruxolitinib stopped Succumbed to fungal pneumonia
	Recurrent subcutaneous abscesses, beta hemolytic streptococcus from sputum, BAL–Pseudomonas aeruginosa	Warts, CMV viremia			+	–	Lost to follow up
–	MRSA, Klebsiella pneumoniae from empyema fluid. Nasal swab–Streptococcus pneumoniae, Mycobacterium tuberculosis from gastric lavage	–	Mycobacterium tuberculosis from gastric lavage	–	+	–	Received baricitinib for 9 months, details in Table 2
Esophageal candidiasis with stricture requiring dilation	Sputum positive for MDR (Multi drug resistant) MTb, XDR (Extensively drug resistant) MTb	–	1 episode of pulmonary and lymph node tuberculosis, MDR Mycobacterium tuberculosis isolated from sputum. 1 episode of XDR pulmonary tuberculosis	–	+	–	Succumbed to XDR Pulmonary Kochs
Esophageal candidiasis	–	Parvo viremia, molluscum contageosum	–	Autoimmune hemolytic anemia	–	–	Received baricitinib for 26 months, details in Table 2
–	–	CMV viremia	–	Autoimmune hepatitis (anti–smooth muscle antibody positive), serum antineutrophil cytoplasmic antibody (MPO-ANCA) positive	–	–	Received baricitinib for 1 week Stopped when she developed Pseudomonas putida pneumonia Expired at 6 years of age, Cause of death–hemophagocytic lymphohistiocytosis, pulmonary hemorrhage

follow-up period was short (median years of follow-up– 3.5 years, range– 6 months to 9 years).

Basic lymphocyte subset analysis was available for all (Table S1). Three had low $CD3^+$ T lymphocytes. One had elevated absolute T lymphocytes. Seven patients had $CD4^+$ T lymphopenia. Only one had low, while three had elevated $CD8^+$ T lymphocytes. Two had B lymphopenia. Two had low NK cells. None of our patients had hypogammaglobulinemia (Table S2).

All our patients had reported missense mutations in *STAT1* (Table S3). In a systematic review by Zhang, of the 111 mutations reported, 110 were missense. R274Q was the most common mutation, followed by A267V, T385M, and R274W. In our cohort, T385M was the most common mutation, affecting three patients. A267V and R274W mutations were found in one patient each. None of our patients had R274Q. Zhang reported an increased risk of bronchiectasis with T385M. One patient with the T385M mutation had bronchiectasis. Zhang reported that there was no phenotypic difference in patients according to their mutations with respect to CMC, infection profile, thyroid disease, atopy, or tumor.[1]

All patients were started on antibiotic, antifungal, and antiviral prophylaxis soon after diagnosis and counseled for hematopoietic stem cell transplant (HSCT). Seven received Janus kinase inhibitor (JAKi). One patient was started on oral ruxolitinib at 0.4 mg/kg/day at 9.5 years of age. Ruxolitinib was discontinued after 8 weeks when he developed pulmonary tuberculosis. Two months later, he succumbed to fungal pneumonia. Five were started on baricitinib. As the effective dose of baricitinib in interferonopathies was 0.01 mg/kg/day to 0.82 mg/kg/day,[4] we started baricitinib at 0.08 mg/kg/day in two divided doses and gradually increased it to 0.1 mg/kg/day. Details of JAKi therapy and response are given in Table 2.

Key message

Chronic mucocutaneous candidiasis, autoimmune and inflammatory manifestations seen in patients with STAT-1 GOF respond to baricitinib. However, the occurrence of severe infections limits its long-term usage.

Median age at starting baricitinib was 61.5 months (Range– 6 months–18 years) and median duration on baricitinib was 24 months (Range– 1 week–38 months). One patient with autoimmune hepatitis had received baricitinib for only a week when she developed *Pseudomonas putida* pneumonia requiring discontinuation. Two months later, she succumbed to CMV-induced hemophagocytic lymphohistiocytosis and pulmonary hemorrhage. The patient who has been on baricitinib for the longest duration (38 months) had recurrent painful aphthous stomatitis which resolved within 8 weeks of starting baricitinib. Of the three patients who had bronchiectasis prior to adding baricitinib, two did not have lung infections on baricitinib. One had six episodes of pneumonia, including one necrotizing pneumonia requiring right lobectomy before starting baricitinib.

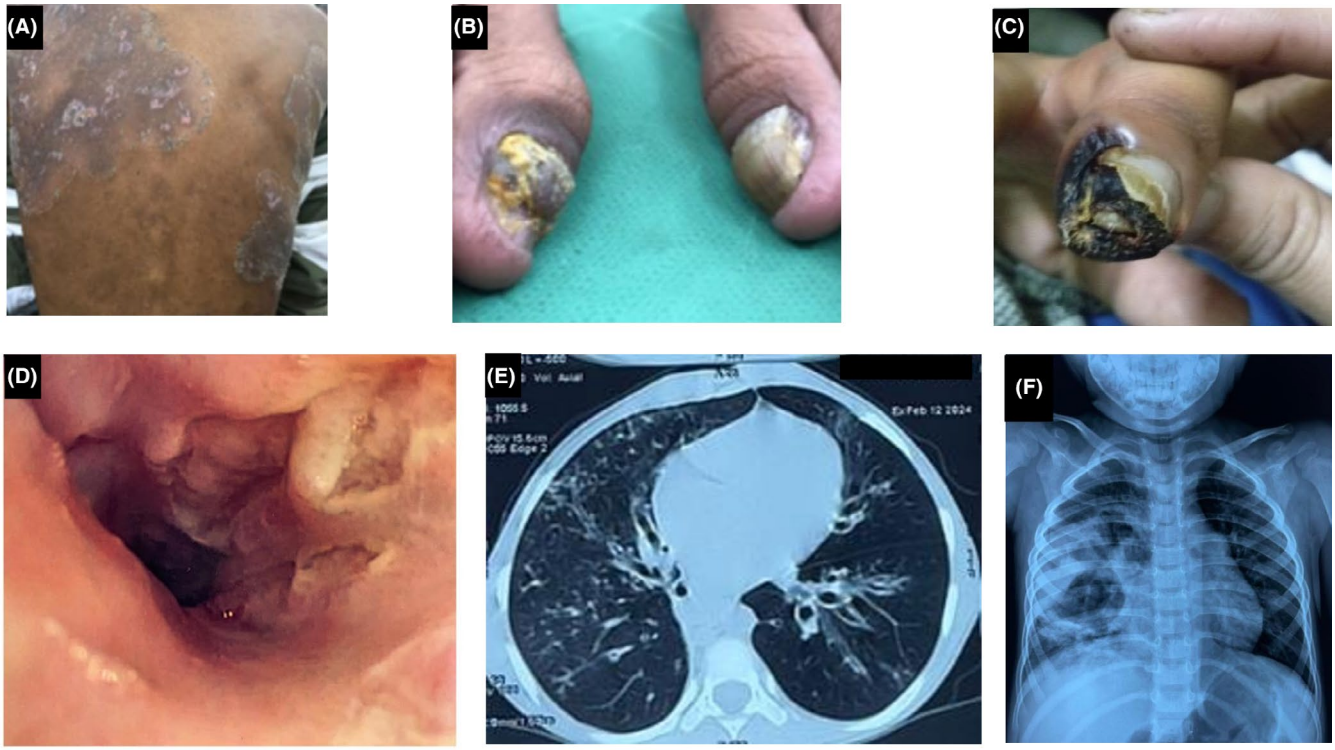

FIGURE 1 (A) Clinical picture of P9 showing extensive dermatophytosis involving the back. (B) Clinical picture of P9 showing onychomycosis of both thumbs. (C) Photo of P1 showing gangrene of the right index finger, following which he developed sepsis and succumbed. (D) Photo of upper gastrointestinal endoscopy of P4 showing multiple deep esophageal ulcers and esophageal candidiasis. (E) CT scan of P8 showing bilateral bronchiectasis. (F) Chest X-ray of P10 showing pneumonia which he developed while on baricitinib.

TABLE 2 Clinical response to JAK inhibitors.

Patient	P2	P4	P5	P6	P8	P10	P11
Age at starting JAK inhibitor and JAK inhibitor started	18 years Baricitinib	10 years Baricitinib	4 ½ years Baricitinib	9 ½ years Ruxolitinib	4 ½ years Baricitinib	6 months Baricitinib	5 years 9 months Baricitinib
Duration on JAK inhibitor	38 months	28 months	22 months	2 months	9 months	26 months	1 week
Dose range at initiation and follow-up	2 mg–4 mg (0.08 mg/kg/day to 0.1 mg/kg/day)	2 mg–4 mg (0.08 mg/kg/day to 0.1 mg/kg/day)	0.8 mg–1 mg (0.08 mg/kg/day)	5 mg (0.4 mg/kg/day)	1.4 mg–1.5 mg (0.08 mg/kg/day)	0.4 mg–1 mg (0.08 mg/kg/day to 0.1 mg/kg/day)	
Autoimmune/inflammatory manifestations before addition of JAK inhibitor	Recurrent painful stomatitis Bronchiectasis	AIHA Alopecia areata bronchiectasis	-	Evans syndrome	Bronchiectasis	AIHA	
Effect on Autoimmune/inflammatory manifestations	Stomatitis–resolved after 8 weeks Bronchiectasis–no respiratory tract infections	AIHA–Hemoglobin↑, DCT remained positive Alopecia areata resolved after 8 weeks Bronchiectasis–no respiratory tract infections	-	Stopped before response seen	Had 6 episodes of pneumonia, including one necrotizing pneumonia requiring right lobectomy prior to starting Baricitinib. On Baricitinib he had improved growth, but had 3 episodes of pneumonia	DCT turned negative after 10 weeks, Hemoglobin↑ after 16 weeks	Stopped before response seen
Effect on chronic mucocutaneous candidiasis	No new lesions	No new lesions	No new lesions	No new lesions	No new lesions	Voriconazole tapered from 18 mg/kg/day to 2 mg/kg/day over 25 weeks, stopped after 40 weeks	No new lesions
Effect on growth	Improved	Exponential increase in height and weight	Improved	Stopped before response seen	Improved	Improved	Stopped before response seen
Side effects	Urine BK virus PCR–2476 copies, blood BK virus PCR–negative, repeat urine BK virus PCR done after 2 weeks–negative	Was doing well during first 24 months. Had recurrent episodes of lymphopenia with CMV viremia and hepatitis hence baricitinib was stopped and shifted to Azathioprine. She had severe neutropenia and lymphopenia with Azathioprine, hence it was stopped. AIHA managed with Mycophenolate mofetil (MMF) and Rituximab.	-	Developed pulmonary tuberculosis	Urine BK virus PCR–36,404 copies, Blood BK virus PCR–negative, repeat urine BK virus PCR done after 2 weeks–negative. Three episodes of pneumonia. Mycobacterium Tuberculosis was isolated from bronchoalveolar lavage fluid during the 3rd episode, hence baricitinib was stopped	Developed bilateral pneumonia, Mycobacterium tuberculosis, Candida tropicalis, Influenza A, H3N2 and Adenovirus were isolated from bronchoalveolar lavage	Developed pneumonia, Pseudomonas putida isolated from bronchoalveolar lavage
Outcome	Currently doing well on baricitinib	Currently doing well on MMF	Currently doing well on baricitinib	Succumbed to pulmonary tuberculosis	Currently receiving treatment for pulmonary tuberculosis	Currently receiving treatment for pulmonary tuberculosis, off baricitinib	Baricitinib was stopped after she developed pneumonia. She succumbed to CMV infection and HLH 1 month later

During the 9 months that he was on baricitinib, he had improved growth but had three episodes of pneumonia. As *Mycobacterium tuberculosis* was isolated during the third episode, baricitinib was discontinued (Duration–9 months).

Two patients had AIHA prior to starting baricitinib. One had a gradual increase in hemoglobin; however, the Direct Coombs test (DCT) remained strongly positive (4+). She had alopecia areata, which reduced 8 weeks after starting baricitinib. She was doing well during the first 24 months, after which she had recurrent episodes of CMV viremia with lymphopenia and hepatitis; hence, baricitinib was stopped 4 months later, and azathioprine was added. She had severe neutropenia and lymphopenia with azathioprine; she responded to mycophenolate mofetil and rituximab. The other patient had a weakly positive DCT prior to starting baricitinib, which turned negative 10 weeks after starting baricitinib, and a gradual increase in hemoglobin was seen 16 weeks after initiation. He was receiving 18 mg/kg/day of voriconazole, which was tapered over 65 weeks and stopped. His total duration on baricitinib was 26 months when he developed bilateral pneumonia. *Mycobacterium tuberculosis*, *Candida tropicalis*, *Influenza A*, H3N2, and *Adenovirus* were isolated by bronchoalveolar lavage. Hence, baricitinib was discontinued. None of our patients developed CMC while on baricitinib.

Ruxolitinib and baricitinib are first-generation JAK1/2 inhibitors. As STAT1 GOF is associated with hyperresponsiveness of STAT1 to stimulation, these patients benefit from blocking the JAK–STAT pathway.[5] The multiple publications demonstrating the benefit of JAKi for STAT1 GOF have been compiled by Hadjadj. Deyà-Martínez has compiled the pediatric cases specifically. Only one patient included in each study had received baricitinib; the rest were treated with ruxolitinib.[5,6] In Deyà-Martínez's study, CMC responded 1–8 weeks after adding JAK inhibitors, while cytopenias responded within 1–2 weeks, and oral aphthous ulcers took 6–12 weeks.[6]

As seen with our cohort, the most common side effect of JAKi is increased risk of infections, especially reactivation of herpes zoster, viral infections (two patients), bacterial pneumonia (one patient), tuberculosis (one patient), BK virus nephropathy, and toxoplasmosis.[5,6] Two patients had asymptomatic, self-resolving urinary BK virus excretion. In the recently published ESID/EBMT retrospective study on JAKi treatment for IEI, 33% of patients with STAT1 GOF receiving JAKi had infections. In spite of prophylaxis, the incidence of infections with JAKi was higher in our cohort (71%), probably due to environmental factors. Three developed pulmonary tuberculosis, causing interruption of JAKi. A higher incidence of tuberculosis could be due to the endemicity of tuberculosis in India.

JAK2 inhibition has been shown to lead to reduced postprandial leptin signaling, leading to hyperphagia and weight gain in mouse models. Ruxolitinib causes weight gain and increased BMI. However, such associations with baricitinib are not clear.[5] One patient had gained 13.6 kg and grown 8 cm within 36 weeks of starting baricitinib; however, this period could have coincided with a pubertal growth spurt.

Mortality was observed in four patients. One succumbed to septicemia at 16 years. The oldest patient in our cohort succumbed to XDR (extensively drug-resistant) pulmonary tuberculosis at 28 years. One patient succumbed to pulmonary tuberculosis complicated by fungal pneumonia at 10 years. One succumbed to CMV-induced hemophagocytic lymphohistiocytosis and pulmonary hemorrhage at 6 years. The last two had received a short duration of JAKi but succumbed 2 months after stoppage. Parents of two patients refused further treatment and were lost to follow-up.

As seen in our cohort, in addition to autoimmunity and CMC, patients with STAT1 GOF also have bacterial, viral, and invasive fungal infections. Seven patients from our cohort received JAKi. Five showed initial improvement in CMC, autoimmune and inflammatory manifestations, and improved growth while on baricitinib. However, the occurrence of severe infections limited long-term usage.

AUTHOR CONTRIBUTIONS

Akshaya Chougule: Writing – original draft; formal analysis; data curation; conceptualization; investigation; methodology. **Prasad Taur:** Formal analysis; project administration. **Vijaya Gowri:** Formal analysis; project administration. **Vaishnavi Iyengar:** Data curation; software. **Manisha Madkaikar:** Validation; investigation. **Minnie Bodhanwala:** Supervision. **Mukesh Desai:** Writing – review and editing; conceptualization; investigation; methodology; supervision; visualization; validation.

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CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

PEER REVIEW

The peer review history for this article is available at https://www.webofscience.com/api/gateway/wos/peer-review/10.1111/pai.70168.

DATA AVAILABILITY STATEMENT

Authors confirm that all relevant data are included in the article, figures, and Supporting Information—S1.

ETHIC STATEMENT

Ethics approval was taken from the Institutional Ethics Committee, B. J. Wadia Hospital for Children, under the Centre of Excellence project by ICMR. Project number: IEC-BJWHC/AP/2014/003.

CONSENT

A written informed consent was taken from the patient or guardians of the children included in the study. The authors affirm that the patients and/or parents have provided informed consents for publication of the images in Figure 1.

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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