



REVIEW

# Efficacy and Safety of Janus Kinase Inhibitors in Type I Interferon-Mediated Monogenic Autoinflammatory Disorders: A Scoping Review

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## ABSTRACT

**Importance:** Type I interferon (IFN)-mediated monogenic autoinflammatory disorders (interferonopathies) are childhood-onset rare multi-systemic diseases with limited treatment options. The Janus kinase (JAK) inhibitors are

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promising potential therapeutic candidates for immune-mediated chronic inflammatory skin diseases.

**Objective:** To review the use of JAK inhibitors to improve decision-making when treating interferonopathies with cutaneous manifestations.

**Evidence Review:** The MEDLINE, EMBASE, CINAHL, Scopus, and Web of Science databases were searched for studies that used JAK protein inhibitors to treat IFN-related monogenic diseases with cutaneous manifestations in humans. The search results are reported using the scoping review approach.

**Findings:** Seventeen open-label studies assessing the efficacy of ruxolitinib, baricitinib, or tofacitinib reported variable responses in patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) and related syndromes, stimulator of IFN genes [STING]-associated vasculopathy with onset in infancy (SAVI), familial chilblain lupus (FCh-L), gain-of-function mutations of *STAT1* (GOF-STAT1), or Aicardi-Goutières syndrome. JAK inhibitors improved clinical and analytical parameters and decreased flare numbers, plasma inflammatory markers, and expression of IFN-stimulated genes. BK viremia and upper respiratory infections were the most frequent and severe adverse events. Significant heterogeneity in efficacy assessment methods and poor reporting of safety events were detected.

**Conclusions and Relevance:** Evidence of the use of JAK inhibitors in patients with interferonopathies is scarce and of low methodological quality. Future clinical trials should use validated scales and report drug safety in a more accurate way.

**Keywords:** CANDLE; SAVI; Familial chilblain lupus; JAK inhibitors; Autoinflammatory diseases; Interferon pathway; Ruxolitinib; Baricitinib; Tofacitinib

### Key Summary Points

Evidence on efficacy of Janus kinase inhibitors in patients with interferonopathies is scarce and of low methodological quality.

Future clinical trials should use validated scales and report drug safety in a more accurate way.

## DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to: <https://doi.org/10.6084/m9.figshare.14237444>.

## INTRODUCTION

Type I interferon (IFN)-mediated monogenic autoinflammatory disorders (type I interferonopathies) comprise a genetically and phenotypically heterogeneous group of autoinflammatory and autoimmune disorders characterized by constitutive activation of the antiviral type I IFN axis [1]. This activation is multifactorial, as in the case of lupus erythematosus, or is associated with monogenic, autosomal dominant, or recessive mutations [2].

There are several monogenic interferonopathies that cause significant morbidity and mortality from early stages of life, as well as skin involvement. Stimulator of interferon genes [STING]-associated vasculopathy with onset in infancy (SAVI, ORPHA:425120) is a monogenic interferonopathy due to a mutation in *TMEM173*. Patients present feet and hand involvement showing rash, blisters, pustules, or telangiectasia, in addition to fever flares, vasculitis, stunted growth, interstitial lung disease, or lymphadenopathy [2–5]. Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE, ORPHA:325004) is an interferonopathy related with proteasome dysfunction. Clinical features include cutaneous rash, acral perniosis, and annular and disseminated plaques or violaceous edema around the mouth and eyelids associated with fever flares. Joint swelling and arthralgia are also observed. A characteristic phenotype includes facial lipodystrophy, a protruding abdomen, and stunted growth [2, 6–8]. Familial chilblain lupus (FChL, ORPHA:481662) is an autosomal dominant condition due to a mutation in the three prime repair exonuclease 1 gene (*TREX1*) or in the SAM and HD domains containing deoxynucleoside triphosphate triphosphohydrolase 1 (*SAMHD1*) or *STING1*, respectively. Clinical features include chilblain acral lesions, fever, and interstitial lung disease [2, 9, 10]. Other important interferonopathies include Aicardi-Goutières syndrome (ORPHA:51), Singleton-Merten syndrome (ORPHA:85191), and gain-of-function mutations of *STAT1* (GOF-STAT1) and *SKIVL2*, an unfolded protein response or spondyloenchondrodysplasia, where neurologic, immunologic, hepatologic, or rheumatologic conditions are associated with chilblain, panniculitis, psoriasis, oral and genital ulcers, hair disorders, and acrocyanosis, respectively [11, 12].

Different treatments, most of which involve immunosuppressants, have been employed with an irregular response. Corticosteroids have shown moderate or partial success in CANDLE [6] and SAVI [13], but have not been used in FCh-L [10]. Methotrexate has been reported to produce partial improvement in CANDLE cases [14] without affecting the evolution of FCh-L

[10]. The use of cyclosporine and azathioprine is anecdotal, while isolated cases of CANDLE and SAVI treated with tumor necrosis factor alpha (TNF $\alpha$ ) inhibitors have shown poor responses [13]. Immunosuppressants (biologic disease-modifying antirheumatic drugs) used to treat other interferonopathies have been shown to lack effectiveness or cause toxicity [11, 12].

Because the major signaling pathway activated by IFNs is the Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway [3], drugs inhibiting this pathway represent a therapeutic opportunity to these patients. In recent years, drugs inhibiting different proteins of the JAK/STAT pathway have been developed; some act specifically on a single component (e.g., filgotinib, JAK1; pacritinib, JAK2; decernotinib, JAK3) and others on several components (e.g., tofacitinib, JAK1 and JAK3; ruxolitinib and baricitinib, JAK1 and JAK2) [15].

The aim of this study was to report the current evidence of JAK inhibitor treatment in autoinflammatory IFN-related monogenic diseases with cutaneous manifestations using scoping review methodology [16].

## METHODS

### Protocol Design

The protocol for the scoping review protocol used in this study has been previously published [17]. The study was conducted and reported using the methodology described in the Joanna Briggs Institute Reviewer's Manual [18] and the PRISMA Extension for Scoping Reviews [19], respectively. When necessary, the authors of the included articles were contacted to obtain more data or clarify issues.

### Eligibility Criteria

Studies that have used JAK protein inhibitors to treat IFN-related monogenic diseases with cutaneous manifestations in humans were included in the review. There were no restrictions regarding age, ethnicity, study design, or any other characteristics. IFN-related

monogenic disease studies were included if written in English, involved human participants, and described the conditions formulated in the research question, regardless of publication date or format. Articles were excluded if they did not fit into the conceptual framework of the study. Non-scientific reviews and opinion articles were excluded.

### Literature Search

Strategies for the literature search and eligibility criteria are described in detail in the Supplementary Methods of the Electronic Supplementary Material (ESM).

### Data Charting

A data charting form was jointly developed by two authors to determine the variables to extract. These reviewers independently charted the data, discussed the results, and continuously updated the data charting form in an iterative process. Finally, variables related to patients (disease, drug, treatment response, and safety profile) and to the study design and metadata from primary sources were reported.

### Collating, Summarizing and Reporting Results

The comprehensive search results are presented using a PRISMA flow diagram and references and primary studies are displayed by drug. After data extraction, a narrative and qualitative synthesis of references, studies, efficacy, and safety data was elaborated.

### Compliance with Ethics Guidelines

This scoping review relates to previously conducted studies, and does not involve any new human or animal studies performed by the authors.

## Protocol versus Overview

Our planned search strategy in the published protocol was compared to the final reported review methods.

## RESULTS

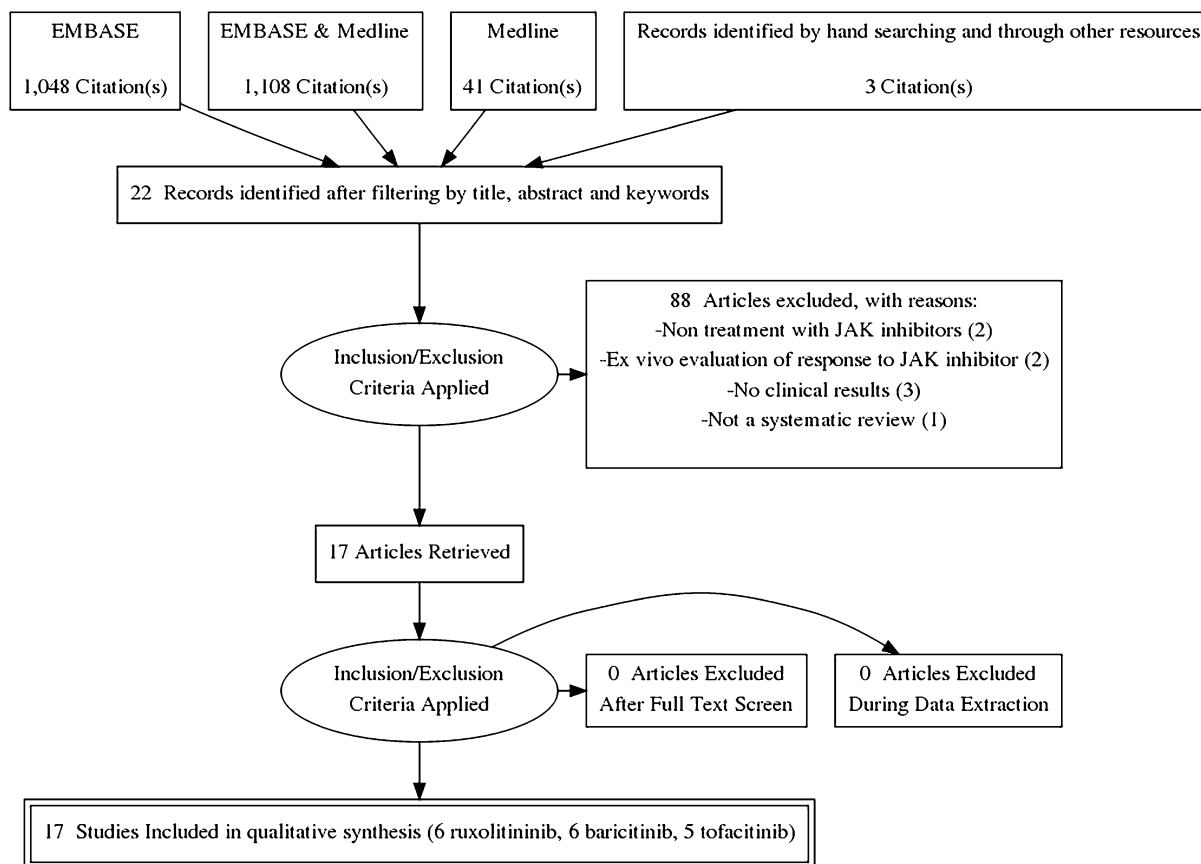
### Search Results

We found 4897 articles on the use of drugs targeting the JAK/STAT pathway in the treatment of dermatological diseases. After filtering duplicates and selecting studies according to title, abstract, and keywords, 22 studies met the criteria for full-text review. Three more articles were included after reviewing the references of other studies and conducting manual searches (Fig. 1). After applying the inclusion criteria,

only 17 studies were included in the scoping review (Fig. 1). Data related to the country, study and publication type, number of authors, and funding across all studies are presented in ESM Table S1. Lists of included and excluded articles and reasons for exclusion are given in ESM Tables S2 and S3. The JAK inhibitor drugs included in this review were baricitinib, ruxolitinib, and tofacitinib.

### Baricitinib

Six articles mentioning baricitinib were identified [11, 12, 20–23], and all were observational studies, including three case series and three case reports published in journals related to rheumatology, general medicine, immunology, and dermatology. The articles were written by an average of 26.56 (range 6–55) authors from



**Fig. 1** PRISMA flow diagram. *JAK* Janis kinase

**Table 1** Summary of efficacy and safety of baricitinib in the treatment of patients with interferonopathies

Study ID (reference)	Disease (no. of study patients) <sup>a</sup>	Sex	Age at enrollment (years)	Age at disease onset (years)	Previous treatment <sup>b</sup>	Mutation	Dosage (mg/24 h)	Duration (months)	Steroids (months)
1 [20]	CANDLE (1)	Male	6	0	GLC, MTX, HCQ	PSMB8	8	18	Yes
7 [11]	GOF STAT1 <sup>d</sup> (1)	Female	24	NA	MTX, IFX, GLC, ADA, AZA, HCQ, MCF, FCN	Heterozygous - STAT1 GOF	2	8	No
8 [11]	Aicardi-Goutières syndrome (1)	Female	22	NA	NA	SAMHD1	2 mg/kg/24 h	18	No
17 [23]	FCh-L-TREX1 (1)	Female	20	NA	GLC + HCQ	Heterozygous TREX1 H195Q	4	3	No
	FCh-L-TREX1 (2)	Male	70	NA	GLC + HCQ	Heterozygous TREX1 H195Q	4	3	No
	FCh-L-TREX1 (3)	Female	50	NA	GLC + HCQ	Heterozygous TREX1 H195Q	4	3	No
12 [23]	CANDLE (1)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	0.1–6	58.81	No
	CANDLE (2)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	0.2–6	55.43	No
	CANDLE (3)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–6	50.3	No
	CANDLE (4)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–8	50.56	No
	CANDLE (5)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–9	48.56	No
	CANDLE (6)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–4	38.97	No

Table 1 continued

Study ID (reference)	Disease (no. of study patients) <sup>a</sup>	Sex	Age at enrollment (years)	Age at disease onset (years)	Previous treatment <sup>b</sup>	Mutation	Dosage (mg/24 h)	Duration (months)	Steroids (months)
	CANDLE (7)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–4	26.65	
	CANDLE (8)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–6	39.98	
	CANDLE (9)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	3–10	35.32	
	CANDLE (10)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	7–9	29.67	
	SAVI (1)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	2–6	31.9	
	SAVI (2)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	7–10	28.34	28.34
	SAVI (3)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	3–6	29.36	
	SAVI (4)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	3–6	18.27	
	CANDLE-RELATED (1)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	0.5–8	8.02	
	CANDLE-RELATED (2)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	1–6	37.03	
	CANDLE-RELATED (3)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	3–5	2	
	CANDLE-RELATED (4)	AGD (NA)	AGD (NA)	AGD (NA)	AGD	AGD	3–9	27.11	

Table 1 continued

Study ID (reference)	Efficacy				Safety		
	Skin and/or systemic improvement	Diary score reduction criteria	Primary benefit	Secondary benefit <sup>c</sup>	Reduction	Others	
1 [20]	Yes	-	NA	NA	NA	NA	Upper respiratory infection
7 [11]	Yes	-	NA	NA	NA	RFIN	NA
8 [11]	Yes	-	NA	NA	NA	RFIN	NA
17 [23]	Yes	-	NA	NA	NA	RFIN	Upper respiratory infection
	Yes	-	NA	NA	NA	RFIN	Upper respiratory infection
	Yes	-	NA	NA	NA	RFIN	Upper respiratory infection
12 [23]	No	-	No	Yes	NA	-	Failure to thrive Osteoporosis Nephrolithiasis Herpes Zoster BK virus infection
	Yes	-	Yes	Yes	NA	-	NA
	Yes	Yes	Yes	Yes	NA	-	BK virus infection
	Yes	Yes	Yes	Yes	Yes	-	NA
	Yes	Yes	Yes	Yes	Yes	-	BK virus infection
	Yes	Yes	Yes	Yes	NA	-	Portacath infection, Urinary tract infection, Pneumonia, Influenza
	No	-	No	No	NA	-	Knee deformity
							Infections: BK, <i>Clostridium difficile</i> , Haemophilus bacteremia, Influenza, <i>Pneumocystis jirovecii</i> pneumonia, Rotavirus
	Yes	-	Yes	Yes	NA	-	Renal tubular disorder Thrombocytopenia Neutropenia Epistaxis
	Yes	-	Yes	Yes	Yes	-	Pyrexia
	Yes	-	Yes	Yes	NA	-	BK virus infection
	Yes	-	Yes	Yes	Yes	-	Jaw operation
	Yes	-	Yes	NA	Yes	-	Herpes zoster BK virus infection

Table 1 continued

Study ID (reference)	Efficacy				Safety		
	Skin and/or systemic improvement	Diary score reduction criteria	Primary benefit	Secondary benefit <sup>c</sup>	Reduction	Others	
	No	–	No	No	No	–	Rash
	Yes	–	Yes	NA	NA	–	Viral gastroenteritis
	Yes	–	Yes	NA	NA	–	Wound infection Extremity necrosis
	Yes	–	Yes	Yes	NA	–	Pneumonia, Osteomyelitis Wound infection BK virus infection
							Pneumonia Vasculitis
							BK virus infection
							NA
	Yes	–	Yes	Yes	NA	–	BK virus infection
	No	–	No	No	NA	–	Upper gastrointestinal Thrombocytopenia Osteonecrosis
	No	–	No	Yes	NA	–	Cerebrovascular disorder Pyelonephritis Urosepsis <i>Clostridium difficile</i> infection Nephrolithiasis Headache
							Hepatic adenoma

*ADA* Adalimumab, *AGD* aggregated data, *AZA* azathioprine, *FCN* fluconazole, *GLC* Glucocorticoids, *HCQ* hydroxychloroquine, *IFX* infliximab, *MCF* mycophenolate mofetil, *MTX* methotrexate, *NA* not available

<sup>a</sup> *CANDLE* Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature, *GOF-STAT1* gain-of-function mutations of *STAT1*, *Fcb-L* familial chilblain lupus, *TREX1* three prime repair exonuclease 1 gene, *SATI* stimulator of IFN genes [STING]-associated vasculopathy with onset in infancy

<sup>b</sup> Previous treatment with Janus kinase/signal transducer and activator of transcription (JAK/STAT) pathway inhibitors is underlined

<sup>c</sup> According to prednisone reduction criteria

<sup>d</sup> According to diary score reduction criteria (DSR)



the USA ( $n = 2$ ), the Netherlands ( $n = 2$ ), Bulgaria ( $n = 1$ ), and Germany ( $n = 1$ ). In one of six articles, the authors declared a conflict of interest. One article had private funding (Eli Lilly, Indianapolis, IN, USA) and one had public (US National Institutes of Health [NIH], Bethesda, MD, USA) funding (ESM Table S1).

### **Mapping Studies**

Two clinical trials on the use of baricitinib to treat patients with interferonopathies were identified that were registered in November 2012 and November 2016 (NCT01724580 and NCT02974595, respectively).

### **Efficacy and Safety**

Twenty-four patients with diagnoses of CANDLE ( $n = 11$ ), SAVI ( $n = 4$ ), CANDLE-like syndrome ( $n = 3$ ), FCh-L due to TREX1 deficiency ( $n = 3$ ), GOF mutations of *STAT1*' ( $n = 1$ ), and Aicardi-Goutières syndrome ( $n = 2$ ) were included. Of 11 patients with CANDLE syndrome, nine showed improvement in the daily diary score (DDS) and/or reduction in the use of prednisone. Four of those 11 patients with CANDLE syndrome had increased remission time. Baricitinib was used for an average of 39.5 (18–58.8) months at doses of 0.10–10 mg/24 h. In terms of safety, infections (BK viremia/respiratory tract infections) were frequently found.

On average, patients with SAVI received treatment with baricitinib for 29.6 (range 18.2–31.9) months at doses of 2–10 mg/24 h. One patient experienced a decrease in the DDS. Decreased prednisone use and remission were not reported in this case. Respiratory tract infections were the most frequent adverse events. The treatment was administered to four patients presenting CANDLE-related conditions for 17.5 (range 2–37) months at doses of 0.5–9 mg/24 h; one, two, and zero patients presented improved DDS, decreased use of corticosteroids, and remission, respectively. These patients experienced more adverse effects, including infectious and cerebrovascular or coagulation issues. Patients with FCh-L were treated on average for 3 months at doses of 4 mg/24 h. All patients achieved marked improvement in cutaneous involvement and

relief of joint pain. The most common adverse effect was repeated mild respiratory infections.

Patients suffering from Aicardi-Goutières syndrome and GOF mutations of *STAT1*' syndrome were treated at doses of 2 mg for 8 and 18 months, respectively. In both cases, skin improvement was observed. No adverse events were described in these patients (Table 1).

### **Ruxolitinib**

#### **Mapping Studies**

Two full texts, three letters to the editor, and one congress abstract of a case series or case reports using ruxolitinib were published in immunology ( $n = 3$ ) and two in rheumatology journals ( $n = 2$ ) [9, 10, 13, 24–26]. On average, 14 (range 1–27) authors located in Australia, France, Italy, and Greece contributed to each of these studies. None of the studies were registered. In one of the studies, one of the authors declared a conflict of interest. Four studies had a public funding source and one study included both public and private funding. One study did not provide funding information (ESM Table S1).

#### **Efficacy and Safety**

Nine patients were included in these studies (eight with SAVI and one with FCh-L due to TREX1 deficiency). The mean time of treatment was 13 (6–32) months. The ruxolitinib dosage range was 0.25–1.3 (range 2.5–10 mg/12 h) mg/kg/day. All patients showed improvement in clinical and respiratory symptoms. However, respiratory symptoms worsened after treatment in three cases and one patient died. Six adverse effects were reported with ruxolitinib, including respiratory infections, BK viremia, and hypercapnia-induced cerebral edema in three patients, respectively (Table 2).

### **Tofacitinib**

#### **Mapping Studies**

Five case series or case report articles (2 full text articles, 2 congress abstracts, and one 1 letter to the editor) were published in rheumatology ( $n = 3$ ) and allergy-immunology ( $n = 2$ )

**Table 2** Efficacy and safety of ruxolitinib in the treatment of patients with interferonopathies

Study ID (reference)	Disease (no. of study patients)	Sex/age at enrollment/age at disease onset	Previous treatment <sup>a</sup>	Mutation	Dosage/duration of treatment/association with steroids	Efficacy/time to achieve clinical improvement	Safety
2 [10]	FCh-L (1)	Female	HCQ, MTX,	Dominant negative	10 mg/24 h	Yes	None referred
		3 years	GLC	heterozygous mutation in	12 months	One week	
		6 months		<i>TREX1</i> (c.52G > A, p.D18N)	No		
3 [24]	SAVI (1)	Female	GLC, MCF, anti-CD20	TMEM173 V155M	2.5 mg/12 h	Yes	Papillary edema
		4 years			18 months	NA	
		12 months			Yes		
SAVI (2)	Male	GLC, MCF, MTX, CCH, HCQ, anti-CD20	TMEM173 V147M	5 mg/12 h, then 10 mg/12 h	Yes	None referred	
	8 years			6 months	NA		
	2 months			Yes			
SAVI (3)	Male	GLC, HCQ	TMEM173 V155M	5 mg/12 h, then 10 mg/12 h	Yes	None referred	
	12 years			6 months	NA		
	12 months			Yes (1 month)			
6 [25]	SAVI (1)	Male	NA	TMEM173 C206G	5–20 mg/24 h	Yes (cutaneous not systemic)	Lung dysfunction/patient died
		18 years			NA	NA	
		Early infancy			NA	NA	
10 [9]	SAVI (1)	Male	IVIG, <u>prednisone</u>	TMEM173 R284G	5 mg/24 h	Yes	None referred
		3 years			12 months	NA	
		2 months			Yes		

Table 2 continued

Study ID (reference)	Disease (no. of study patients)	Sex/age at enrollment/age at disease onset	Previous treatment <sup>a</sup>	Mutation	Dosage/duration of treatment/association with steroids	Efficacy/time to achieve clinical improvement	Safety
16 [13]	SAVI (1)	Female	AZA, ETA, GLC	TMEM173 V155M	0.3–0.6 mg/kg/24 h	Yes	BK viruria
		10 years			32 months	One week	
		8 months			NA		
SAVI (2)	Female	8 years	MTX, IFX, GLC	TMEM173 R281Q	0.25–0.7 mg/kg/24 h	Yes	Respiratory infections, worsening lung interstitial disease
		8 years			18 months	One week	
		3 months			NA		
SAVI (3)	Female	2 years	GLC	TMEM173 N154S	0.45–1.3 mg/kg/day	Yes	Relapse in pulmonary symptoms
		3 days			6 months	One week	
					NA		

<sup>a</sup> Anti-CD20 monoclonal antibodies, CCH colchicine, ETA etanercept, IVIG intravenous immunoglobuline, NA not available

<sup>b</sup> Previous treatment with JAK/STAT pathway inhibitors is underlined

**Table 3** Efficacy and safety of tofacitinib in the treatment of patients with interferonopathies

Study ID (reference)	Disease (no. of study patients) <sup>a</sup>	Sex/age at enrollment/age at onset	Previous treatment <sup>b</sup>	Mutation	Dosage/duration of treatment/association with steroids	Efficacy/skin and/or systemic improvement/efficacy comments	Safety
4 [27]	CANDLE (1)	Female 18 years NA	GLC, CyP, AZA, CFM, HCQ, IVIG, ANK, IFX, ABA, HpT	Not confirmed	15–20 mg/24 h NA NA	Yes NA Lipodystrophy, chilblains, and hair loss improvement	Increase in creatine kinase and low-density lipoprotein cholesterol levels
5 [28]	FCh-L(SM) (1)	Female 60 years 3 years	NA	TMEM173 G166E	10 mg/24 h 17 days No	Yes Yes Discomfort and pain on fingers improvement	NA
9 [29]	FCh-L(SM) (2)	Female 58 years 2 months	NA	TMEM173 G166E	10 mg/24 h 17 days No	Yes Yes Discomfort and pain on fingers improvement	NA
9 [29]	SAVI (1)	Female 6 years 1 year	NA	Not confirmed	7.5 mg/24 h 12 months Yes	Yes Yes Pulmonary, rash, arthralgias and analytical improvement	NA
13 [30]	SAVI (1)	Male 9 years 6 months	NA	De novo double-mutant TMEM173 (S102P-F279L)	5 mg/day 3 months NA	Yes NA Pulmonary defect unchanged	NA

**Table 3** continued

Study ID (reference)	Disease (no. of study patients) <sup>a</sup>	Sex/age at enrollment/age at onset	Previous treatment <sup>b</sup>	Mutation	Dosage/duration of treatment/association with steroids	Efficacy/skin and/or systemic improvement/efficacy comments	Safety
14 [31]	SAVI (1)	Female	<u>GLC + IVIG</u>	De novo	5 mg/day	Yes	Died due to acute respiratory failure
		12 months		TMEM173	10 months	Partially	
		3 months		V155M	Yes	Rash improvement, but pulmonary involvement worsening and fever	
SAVI (2)	Male	60 months	<u>GLC + IVIG</u> , CFM	De novo	5 mg/24 h	Yes	No adverse events
		54 months		TMEM173	10 months	Partially	
				V155M	Yes	Rash improvement while pulmonary involvement worsening	

*ABA* abatacept, *ANK* anakinra *CFM* cyclophosphamide, *CyP* cyclosporine, *HpT* Hyperbaric therapy, *NA* not available

<sup>a</sup> *FCB-L(SM)* Familial Chilblain Lupus due to a gain-of-function mutation in *STING*

<sup>b</sup> Previous treatment with *JAK/STAT* pathway inhibitors is underlined



**Fig. 2** Studies that have assessed the expression of interferon target genes as a tool to evaluate treatment response. See footnote to Table 1 for definitions of SAVI, CANDLE, FCh-L and GOF-STAT1

journals [27–31]. On average, 10.4 (range 5–18) authors located in Germany, Russia, Italy, China, and South Korea contributed to each study. None of the studies were registered. Two authors declared a conflict of interest for receiving public funding. Two of the studies received public funding, while a third received private and public funding (ESM Table S1).

### ***Efficacy and Safety***

Seven patients were included in these studies (4 with SAVI, 2 with FCh-L with gain-of-function in STING, and 1 with CANDLE). Tofacitinib dosage range was 5–10 mg/day. All patients showed cutaneous improvement, reducing pain and discomfort. Lipodystrophy reduction and hair regrowth were reported in the patient with CANDLE. One of four patients with SAVI showed pulmonary symptom relief and two showed rash improvement with tofacitinib treatment. Adverse effects were reported in only two patients. An increase in creatine kinase and low-density lipoprotein cholesterol plasma levels was found in one case (Table 3).

### **Standardized Type-I INF-Response Gene Score**

An INF signature (the INF-Response Gene Score [IRG-S]), using nanostring technology based on the expression of 28 target genes, was developed and validated by Kim et al. [32] to have a reliable and standardized readout to evaluate the severity and treatment response for type I interferonopathies. Nine of the 17 studies assessed the expression of INF target genes as a tool to evaluate treatment response. Overall, a maximum of seven genes were tested in these studies, with different genes tested in each study, with the exception of one study in which 25 of the 28 genes included in the IRG-S were tested (Fig. 2) [22].

## **DISCUSSION**

This is the first scoping review on the use of JAK inhibitors in monogenic type I interferonopathies, and it provides an overview of

currently available research evidence based on observational studies, most of which are cases or case series. The majority of evidence is derived from non-registered studies conducted in the USA and European countries and supported by private–public collaborative funding. In terms of treatment efficacy, baricitinib, ruxolitinib, and tofacitinib showed variable clinical and analytical improvement in most patients with these monogenic diseases, with cases of patients with CANDLE or SAVI being the most commonly reported. With the exception of studies that were registered, a low systematization was identified in both the conduct and reporting of these studies, making it difficult to synthesize their results. Specifically, the reporting of adverse events was poor. These deficiencies were more evident when the cases were reported in abstract form.

## **SUMMARY OF FINDINGS**

First, related to diagnosis, Sanchez-Montalegre et al. [22] establish criteria to define a group of patients with CANDLE-related conditions that may classify patients with undetermined interferonopathy. This may be very helpful in cases where patients present incomplete forms of the disease or to guide diagnoses in this type of rare disease. Second, related to severity measurement for these diseases, a DDS, a daily specific scale, was used to assess patients with CANDLE and SAVI in above-mentioned study. The authors of a study that explored its validity came to the conclusion that the outcome measures in SAVI should be further refined and validated across other outcome measures in unrelated pediatric inflammatory diseases [33]. Widespread use of the standardized type I IRG-S would make it possible to measure severity and treatment response for these diseases [32, 34], improving replicability and making comparison across studies feasible. Third, related to risk/benefit, important conclusions could not be drawn given the small patient numbers and follow-up times due to illness. Generally, most patients experienced improvement with these drugs, except for a group treated with baricitinib and defined as having CANDLE-like

syndrome. However, as previously mentioned, an efficacy measurement was not performed in most cases with a scale that allowed a comparison of results. Thus, although a possible publication bias has not been studied, there is evidence of the preferential publication of favorable treatment results, and this must be taken into account when evaluating that the efficacy of the treatment [35]. Fourth, regarding safety, mild-moderate respiratory infections and BK viremia were the most frequent adverse events, without any apparent differences across drugs and diseases. Finally, related to the study methodology, to our knowledge baricitinib was the only drug tested in registered clinical trials.

### Strengths and Limitations

This scope review was conducted and reported based on an a priori protocol, using the latest methodology for conducting and reporting this type of study. Two authors selected the articles for inclusion and extracted the data. The number of databases consulted was wide and authors were contacted when necessary, thus ensuring more reliable research results and increasing the internal validity. However, due to time and funding, the study was limited to articles published in English. Since this study was a sub-study, the three-step search strategy was not research-specific, so some studies might have been missed. Furthermore, despite best efforts, information on all consulted cases was not obtained. Finally, the risk of bias of the included studies was not evaluated, nor was a quantitative synthesis performed on the evidence found.

### Research Gaps

Evidence on the use of JAK-STAT pathway inhibitors in interferonopathies was scarce, but is increasing. To date, the methodology used in these studies was of a low quality; most studies were observational. Although specific efficacy scales have been developed and validated, they were not applied in most studies. Collection of adverse events should be systematized. Overall, clinical improvement was observed in patients, regardless of disease type and treatment used,

and with a safety profile in which mild-moderate respiratory infections and BK viremia were notable. However, these findings should be interpreted with caution.

## CONCLUSIONS

Studies with a more robust methodology, such as clinical trials, are necessary to evaluate efficacy and safety of JAK inhibitors in patients with interferonopathies. It is advisable to standardize outcomes evaluated and time-points for evaluating efficacy and to report drug safety in a more systematic and accurate way. Finally, efforts should be made to make these treatments accessible to developing countries.

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**Data Availability.** All data generated or analyzed during this study are included in this published article/as supplementary information files. All data generated or analyzed during this study are included in this published article/as supplementary information files.

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