DISSERTATION

Janus Kinase Inhibitors for Autoinflammatory Disease: A First Systematic Review of Effectiveness and Safety

Janus Kinase Inhibitoren für Autoinflammatorische Erkrankungen: Erste Systematische Übersichtsarbeit über Effektivität und Sicherheit

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Abkürzungsverzeichnis

AEs ..... Adverse events
AGS ..... Aicardi Goutières Syndrome
AID..... Autoinflammatory diseases; Autoinflammatorische Erkrankungen
AOSD ..... Adult Onset Still´s Disease
bDMARDs..... Biologic disease-modifying antirheumatic drugs
Behçet-Syndrom..... Behçet-Syndrom
CANDLE .....
.Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature
CAPS..... Cryopyrin-associated periodic syndromes
CSF .....Colony stimulating factors
FMF ..... Familial Mediterranean Fever; Familiäres Mittelmeerfieber
GC ..... Glucocorticoids
IFN..... Interferon
IL ..... Interleukin
IVIG .....Immunoglobulins
JAKi .....Janus Kinase inhibitors; Janus Kinase Inhibitoren
JAK-STAT..... Janus Kinase-Signal transducer and activator of transcription
MKD.....Mevalonate Kinase Deficiency
PAPA .....Pyogenic Arthritis, Pyoderma Gangrenosum and Acne
PFAPA.....Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis
PRISMA.....Preferred Reporting Items for Systematic Reviews and Meta-Analyses
SAVI .....STING associated vasculitis with onset in infancy
sJIA.....Systemic juvenile idiopathic arthritis; systemische juvenile idiopathische Arthritis
SLE.....Systemic lupus erythematodes
TRAPS..... TNF-Receptor Associated Periodic Syndrome

Zusammenfassung

Autoinflammatorische Erkrankungen (AID) sind Störungen der angeborenen Immunität, gekennzeichnet durch unprovozierte Entzündungsepisoden. Im Gegensatz zu klassischen Autoimmunerkrankungen lassen sich bei AID keine spezifischen Autoantikörper oder antigenspezifischen T-Zellen nachweisen. Obwohl für einige AID genetische Ursachen identifiziert wurden, ist die Pathophysiologie häufig unklar. Zu den AID-Symptomen gehören Fieber, Arthritis, aber auch schwere Komplikationen wie das Makrophagen-Aktivierungssyndrom. Therapien wie Glukokortikoide und Colchicin haben ihre Limitationen. Die gezielte Zytokinblockade ist zwar vielversprechend, aber nicht bei allen Patienten wirksam. Janus Kinase Inhibitoren (JAKi) bieten einen neuen Ansatz zur Beeinflussung der Zytokin-Signaltransduktion, und erste Berichte deuten auf ihren potenziellen Nutzen bei einigen AID hin.

Um die Wirksamkeit und Sicherheit von JAKi für AID zu untersuchen, erfolgte eine systematische Literaturrecherche nach den PRISMA-Richtlinien. Drei Datenbanken wurden nach relevanten Publikationen durchsucht. Aus Artikeln, die den Einschlusskriterien entsprachen, erfolgte eine Datenextraktion mit narrativer Zusammenfassung. Es wurden Kriterien für das Therapieansprechen vorabdefiniert und für die Analyse verwendet.

Es wurden Publikationen analysiert, die über insgesamt 101 mit JAKi behandelte AID-Patienten berichteten. Bei Patienten mit Typ-I-Interferonopathien führten JAKi bei 7 Patienten (7/52, 13,5%) zum vollständigen Ansprechen, wobei die meisten Patienten ein partielles Ansprechen zeigten (35/52, 67,3%). 10 Patienten (10/52, 19,2%) zeigten kein Ansprechen. Beim Adulten Morbus Still erreichten 11 (11/26, 42,3%) Patienten ein vollständiges und wiederum 11 ein partielles Ansprechen. 2 Patienten mit systemischer juveniler Arthritis erreichten ein vollständiges Ansprechen (2/4, 50 %) und in 2 Fällen (2/4, 50%) wurde ein partielles Ansprechen beschrieben. Die Hälfte der Patienten mit familiärem Mittelmeerfieber zeigte ein vollständiges Ansprechen und die andere Hälfte ein partielles (3/6, 50,0%). Von den Morbus Behçet-Patienten erreichten die meisten ein partielles Ansprechen (8/13, 61,5%). 5 Patienten zeigten kein Ansprechen auf die Therapie (5/13, 38,5%). Niemand aus dieser Gruppe erreichte ein vollständiges Ansprechen. Insgesamt waren die häufigsten Nebenwirkungen Infektionen der oberen Atemwege (17), Lungenentzündungen (10),

BK- Virämie (10) und -Virurie (4), Herpes-Zoster-Infektionen (5), virale Gastroenteritiden (2) und andere Infektionen (4).

Diese systematische Übersichtsarbeit liefert erste Ergebnisse, die den potenziellen Nutzen von JAKi zur Therapie einiger AID nahelegen. Die Behandlung mit JAKi wurde insgesamt gut toleriert, dennoch sollte ein gewisses Infektionsrisiko beim Einsatz bei AID berücksichtigt werden. Um diese Ergebnisse zu validieren und die Wirksamkeit und Sicherheit von JAKi für AID besser zu bewerten, sollten weitere klinische Studien durchgeführt werden.

Abstract

Autoinflammatory diseases (AIDs) encompass innate immunity disorders, characterized by unprovoked inflammatory attacks. Contrary to classic autoimmune diseases, in AIDs no specific autoantibodies or antigen-specific T-cells can be found. Although certain AID have identified genetic causes, many syndromes' underlying mechanisms remain elusive. The clinical manifestations range from fever and arthritis to severe complications such as the macrophage activation syndrome. Current treatments, like glucocorticoids and colchicine, have limitations, and targeted inhibition of specific cytokines, such as interleukin 1, show promise but may not be effective for all patients. JAKi offer a novel approach to interfere with cytokine signaling, and initial reports indicate their potential benefits in some AID.

To investigate the effectiveness and safety of JAKi in AID treatment, a systematic literature search following PRISMA guidelines was conducted. Three databases were explored for relevant publications. Data were extracted from the articles that met the inclusion criteria and were reported by a narrative synthesis. Criteria for treatment response were pre-defined and applied for analysis.

Publications reporting on a total of 101 AID patients treated with JAKi were analysed. In patients with type I interferonopathies, JAKi led to a complete response in 7 patients (7/52, 13.5%), with most patients showing a partial response (35/52, 67.3%). 10 patients (10/52, 19.2%) had no response. In Adult Onset Still´s Disease 11 (11/26, 42.3%) patients achieved a complete response and 11 achieved a partial response

(4). 2 patients with systemic juvenile arthritis achieved a complete response (2/4, 50 %) and in 2 cases (2/4, 50 %) a partial response was described. Half of the patients with familial Mediterranean fever showed a complete response and the other half a partial response (3/6, 50.0%). Of the Behçet´s syndrome patients, most achieved a partial response (8/13, 61.5%). 5 patients did not respond to the therapy (5/13, 38.5%). No one in this group achieved a complete response. Overall, the most common adverse events were upper respiratory tract infections (17), pneumonia (10), BK viraemia (10) and viruria (4), herpes zoster infections (5), viral gastroenteritis (2) and other infections (4).

This systematic review provides first results suggesting a potential benefit of JAKi for the treatment of some AIDs. Overall, treatment with JAKi was well tolerated, yet a risk of infection should be considered when used in AID. To validate these results and better assess the efficacy and safety of JAKi for AID, further clinical trials should be conducted.

1 Introduction

1.1 Autoinflammatory diseases

1.1.1 Overview and pathogenesis

Autoinflammatory diseases (AID) represent mono- or polygenic disorders of innate immunity. These are characterized by seemingly unprovoked inflammatory attacks in absence of autoantibodies or antigen-specific T-cells (1).

Specific underlying genetic causes for AID have been identified for certain diseases, (2-4) however the exact mechanisms behind many syndromes remain elusive. The concept of autoinflammation was first introduced in the late 20th century to differentiate these disorders from autoimmune diseases. The initial recognition of AID came with the identification of monogenic syndromes such as Familial Mediterranean Fever (FMF) and TNF receptor-associated periodic syndrome (TRAPS). These diseases were characterized by recurrent episodes of unprovoked inflammation and had a clear genetic basis.Clinical phenotypes within the autoinflammatory spectrum range from periodic fever to joint, skin, lung, neurological involvement. The genes responsible for AID pathogenesis identified to date cannot fully account for all clinical presentations. This leaves many patients lacking a certain diagnosis. Thanks to advances in gene sequencing technology and the development of diagnostic criteria, new syndromes continue emerging (5) (3).

AID can be grouped based on the dominating cytokine patterns as follows: interleukin (IL)-1 (inflammasomopathies) (6), NFκB (relopathies) (7) or type I interferon (IFN)-driven diseases (interferonopathies) (8). In multiple syndromes such as Adult-Onset Still´s Disease (AOSD; IL-1, IL-6, IL-18(9, 10)), Behçet's syndrome (BS; IL-1, IL-6 (11), IFNγ (12)) or Familial Mediterranean Fever (FMF; IL-1 (13) and IL6 (14)) more than one cytokine plays a key role in pathogenesis.

Due to the broad disturbance of cytokine signaling, AID can affect various organs and are thus associated with a high disease burden and severe physical, but also socioeconomic limitations (15). Furthermore, AID patients with persistent inflammation have a high risk of developing AA amyloidosis (16, 17).

1.1.2 Therapeutic options

Classic therapeutic option for inflammatory rheumatic diseases are glucocorticoids (GC). In AID these can be useful for managing acute inflammatory episodes (18). However, considering the chronic disease course of many AID a GC monotherapy is rarely sufficient for effective disease control and preventing systemic complications. Long known to be beneficial in certain AID is colchicine. It is still considered first line treatment in patients with Familial Mediterranean Fever (FMF) (19) and Behçet‘s Syndrome (BS) patients with active arthritis (20). It possesses a pronounced anti-inflammatory effect mediated through numerous direct and indirect effects on the innate immune system including inhibiting the formation and activation of the NLRP3 inflammasome. The NLRP3 inflammasome is a key component of the innate immune response, responsible for the production of pro-inflammatory cytokines, particularly interleukin-1 beta (IL-1β). Colchicine disrupts the assembly of the NLRP3 inflammasome, thereby reducing the production and release of IL-1β, which plays a crucial role in promoting inflammation. Furthermore, colchicine can suppress neutrophil activation and migration by interfering with microtubule polymerization. Thus, less neutrophils can be recruited to sites of inflammation. Despites its diverse effects, some patients, considered non-responders, show no satisfactory response to colchicine and other options must be considered.

Many AID share a common disturbance in IL-1 signaling. In approaching the latter currently three drugs have been shown to be effective: anakinra, canakinumab and rilonacept, engaging with the IL-1 receptor, IL-1-α or IL-1- α *and* -β, respectively (21). Anakinra is a recombinant form of the naturally occurring IL-1 receptor antagonist. It competitively binds to the IL-1 receptor, preventing IL-1 from exerting its pro-inflammatory effects. Canakinumab is a fully human monoclonal antibody that specifically targets and neutralizes IL-1β, preventing its binding to IL-1 receptors. Rilonacept is a fusion protein that combines the extracellular portion of the IL-1 receptor with the Fc portion of human IgG1. It acts as a decoy receptor, binding to IL-1 molecules and preventing their interaction with cellular receptors. While all three are administered as subcutaneous injections, they differ in their half-life and dosing frequency, with anakinra having a short half-life of circa 4-6 hours, and canakinumab having a half-life ranging from 26 to 28 days.

Targeted IL-1 inhibition has been shown to be effective for some conditions such as cryopyrin-associated periodic syndromes (CAPS) (22, 23), AOSD (24), FMF (25) and sJIA

(26, 27). For certain monogenic disorders current recommendations advise long term treatment with an IL-1 inhibitor to prevent organ damage (28) since IL-1 is involved in promoting tissue destruction and remodeling in various inflammatory conditions. Other biologic disease-modifying antirheumatic drugs (bDMARDs), such as etanercept, TNF-blockers and IL-6 inhibitors can be considered for AID treatment. Overall, in recent years, the otherwise rather limited armamentarium for treating AID has seen certain improvement. Unfortunately, some AID patients do not respond to targeted inhibition of specific cytokines as needed (29). For example, patients with mutations in the IL1RN gene show low response to IL-1 inhibition due to the functional impairment or deficiency of IL-1Ra – a naturally occurring protein acting as a competitive antagonist to IL-1 by binding to the IL-1 receptor and preventing IL-1 from exerting its effects (30, 31).

Respectively, further therapeutic options are necessary.

1.2. Janus Kinase Inhibitors

1.2.1 Mechanism of action

The development of Janus Kinase inhibitors (JAKi) as orally available small molecules offers novel treatment options for rheumatic diseases. JAKi interfere with signal transduction of the Janus Kinase-Signal transducer and activator of transcription (JAK-STAT) pathway causing effective suppression of downstream cytokine signaling(32). Janus kinases are phosphotransferases whose enzymatic function is triggered by receptor engagement by cytokines. JAK-STAT signaling can be activated by two types of cytokine receptors: type I receptors bind mainly cytokines (IL-2, -6, -9, -12, -15), hormones (growth hormone, GH) and colony stimulating factors (CSF), while type 2 receptors are activated mostly by interferon and IL-10 (33). They act as competitive antagonists at activation sites for Janus kinases and as such interrupt downstream signals along the JAK-STAT pathway, effectively leading to suppression of cytokine production. The JAK-STAT pathway includes several kinases and JAKi can be grouped by their kinase-specific effects. Several drugs have been developed and been approved for the treatment of autoimmune and inflammatory conditions, with each expressing a certain specificity towards Janus kinases: Tofacitinib - JAK1, JAK2 and JAK3, baricitinib and ruxolitinib- selective inhibition

of JAK1 and JAK2, upadacitinib and filgotinib - selective for JAK1. While JAKi are considered ‘targeted therapies’, there is almost no other substance class that exerts an effect on such a large number of cytokines.

The resulting immunomodulatory effects of JAKi can be clinically illustrated by the fact that the drugs have already been approved for a number of rheumatic diseases such as rheumatoid arthritis (RA), psoriatic arthritis (34, 35), polyarticular juvenile arthritis (tofacitinib) (36) and ankylosing spondylitis (upadacitinib, tofacitinib) (37, 38).

First reports on positive effects of JAKi in certain AID have begun to emerge. Already published are results from an expanded access program study on the beneficial effects of JAKi in type I interferonopathies (39), evidence is also available on other AID (40).

1.3. Research question

Due to their broad blockade of proinflammatory pathways, JAKi are a plausible therapeutic option in diseases driven by cytokines, signaling via the JAK-STAT pathway, as in AID. The aim of this systematic literature review is to identify and analyze the available evidence on effectiveness and safety of JAKi for the treatment of AID

2 Methods

During the preparation of the manuscript the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed (41).

2.1. Protocol and registration

A study protocol was registered at PROSPERO (CRD42021270369) prior to the systematic search (42).

2.2. Data sources and searches

To identify publications investigating the role of JAKi in AID treatment the following databases were searched: MEDLINE via PubMed, EMBASE via Ovid, Cochrane Central Register of Controlled Trials (via Cochrane Central). A primary search was conducted on 30 June 2021 and updated on 16 October 2021 as to prepare an overview as up to date as possible. References cited in the identified publications were screened to identify additional relevant reports so as not to miss publications not indexed in the electronic databases.

The search strings were built based on two components using the Boolean operator *and* (AID *and* JAKi). Within those components, multiple terms were linked by *or*. For each syndrome, the full and the abbreviated terms were used including at least one synonym for each condition. For MEDLINE both Medical Subject Headings (MeSH) terms and free-text words were used. All keywords were used to search within titles and abstracts of publications, here exemplary for Still's disease:

("Still's Disease, Adult-Onset"[Mesh] OR "adult onset Still's disease" [tiab] OR "adult onset stills disease" [tiab] OR "adult onset Still disease" [tiab] OR "Still's disease" [tiab] or "stills disease" [tiab] or "still disease" [tiab] or "Still's Disease, Adult-Onset" [tiab] OR "adult onset Still"[tiab]* ***AND*** *("Janus Kinase Inhibitors"[Mesh] OR "Janus kinase inhibitor*"[tiab] OR "JAK Kinase inhibitor*"[tiab] OR "JAKi" [tiab] or "Protein kinase inhibitor*" [tiab] OR tofacitinib [tiab] OR baricitinib OR ruxolitinib [tiab] OR filgotinib [tiab] OR upadacitinib [tiab]))*

2.3. Study selection

Defining inclusion and exclusion criteria was guided by the Patient, Intervention, Comparator, Outcome (PICO) scheme (43). Of interest were the following diseases/syndromes:

- Adult-Onset Still's disease (AOSD)
- Systemic Juvenile Idiopathic Arthritis (sJIA)
- Familial Mediterranean Fever (FMF)
- Cryopyrin-associated Periodic Syndromes (CAPS)
- TNF-Receptor Associated Periodic Syndrome (TRAPS)
- Mevalonate Kinase Deficiency (MKD)
- Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) Syndrome
- Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAP) Syndrome

- Genetic Interferonopathies: Aicardi Goutières Syndrome (AGS), Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) Syndrome, STING associated vasculitis with onset in infancy (SAVI) Syndrome
- Behçet‘s Syndrome (BS)

Acceptable as *Intervention* were following JAKi: tofacitinib, upadacitinib, baricitinib, filgotinib or ruxolitinib. No specific treatment was defined as *Comparator*. Primary outcome was treatment response (see below), of interest were also any reports on adverse events.

No restrictions were applied concerning publication date, age, and number of recruited patients. Only studies published in English were included. Considered for inclusion were both retrospective (e.g., case reports, case-series, case-control studies) and prospective studies (e.g., randomized controlled trials, non-randomized controlled trials, prospective observational studies).

Two reviewers assessed eligibility of the identified publications, according to the pre-specified inclusion criteria (**Table 1**). All references were imported into the citation manager EndNote X9. First, the software´s automated duplicate detection function was used to resolve any duplicates, during screening further duplicates were removed manually. The two reviewers screened title and abstract only, then the eligibility of the remaining publications was assessed in full text. In cases of disagreement consensus was reached by discussion with a third reviewer, who acted as an arbiter.

Table 1 Inclusion and exclusion criteria

Inclusion criteria	Exclusion criteria
(a) *Patient population*: Patients with AID (AOSD, sJIA, FMF, BS, CAPS, TRAPS, PAPA, PFAPA, Type I Interferonopathies)	(a) *Patient population*: animal/ in-vitro study, AID other than specified
(b) *Intervention*: tofacitinib, baricitinib, upadaci tinib, filgotinib, ruxolitinib, other JAKi	(b) *Intervention*: other than specified
(c) *Comparators:* any other treatment	(c) *Outcomes*: no/insufficient clinical results
(d) *Outcomes*: effectiveness, safety	(d) *Publication type:* review articles
(e) *Study design*: retrospective (e.g., case reports, case-series, case-control studies, cc hort studies); prospective studies (e.g., rar domized controlled trials, non-randomized controlled trials, prospective observational studies)	(e) *Language*: other
(f) *Language*: English	

From Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safe of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicin 2022;9.

2.4. Data collection process and data items

For data extraction and management Microsoft Excel 2016 was used. Study characteristics and outcome data were extracted into predesigned standardized data extraction sheets by one of the reviewers. Data was acquired on: (1) study characteristics; (2) patient characteristics at baseline; (3) patient characteristics after intervention.

2.5. Summary measures, synthesis

Due to the lack of randomized controlled trials and the heterogeneity of data, a narrative synthesis was carried out. Results were reported based on the Synthesis Without Meta-analysis (SWiM) guideline (44).

As described above, the primary outcome of interest in this work was treatment response. The latter was defined here as *complete, partial* or *none* based on data on clinical symptoms and laboratory parameters prior/post intervention reported in each study. Clinical response was defined as follows:

- Complete: resolution of all clinical symptoms and normalization of inflammatory parameters (erythrocyte sedimention rate, ESR, and/or C-reactive protein,CRP)
- Partial: either clinical symptoms resolved, or laboratory markers normalized.
- None: clinical symptoms and laboratory markers remained unchanged or worsened

3 Results

3.1. Overview

Using the aforementioned search strings, 582 records could be identified in a first database search. Of those 70 were removed for being duplicate records. Initially 512 were screened for eligibility. By screening of references of eligible publications additional 4 suitable articles were identified. A second updated search from June to October 2021 identified another 80 publications. After duplicate removal (5 articles), 75 records were screened for eligibility. Figure 1 provides details on the selection process of included studies.

Finally, a total of 38 original publications were included for data extraction and analysis.

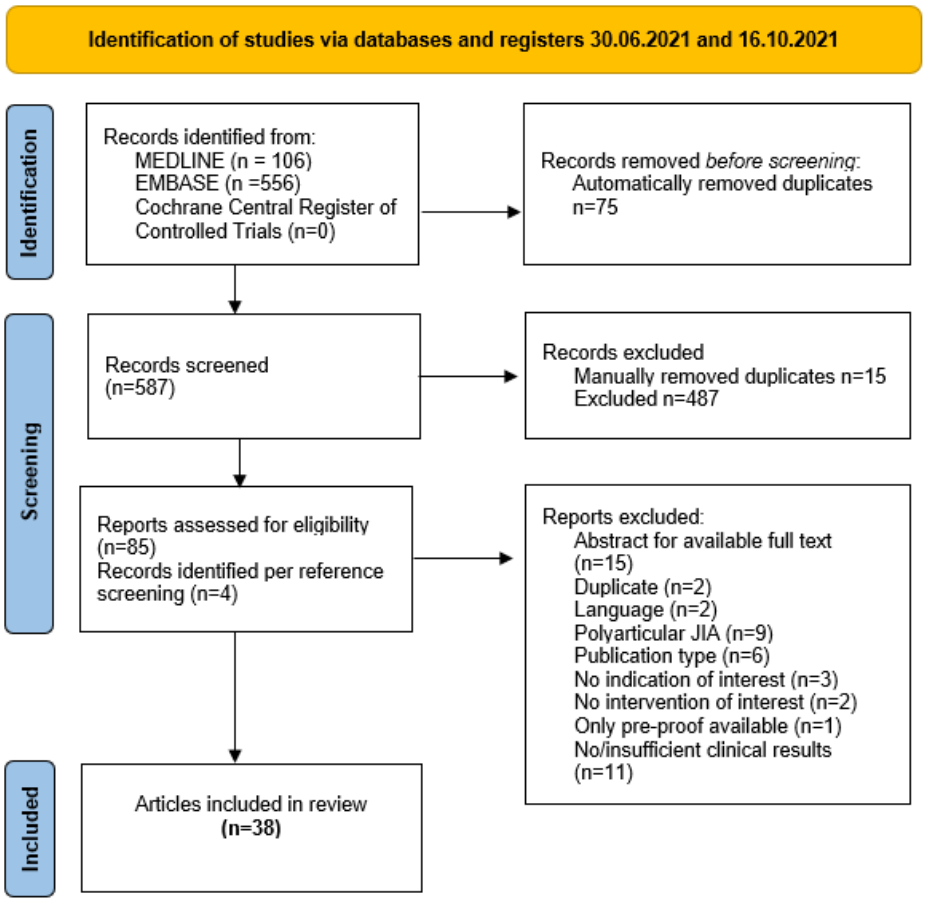

Figure 1 Prisma flow chart

From Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9

3.2. Evidence on effectiveness and safety for Chronic Atypical Neutrophilic Dermatosis with Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

Data was extracted and analyzed for overall fourteen patients. Median age of JAKi initiation was 8.5 years (1.5-17 years, reported for four patients). Most often prescribed was baricitinib (11/14, 84.6%), three patients received tofacitinib (3/14, 21.4%). Treatment duration was reported for 13 patients, for a mean of 92.4 months. Thirteen patients (13/14, 92.6%) received GC as supportive treatment. Clinical and treatment data, as well as response to therapy are reported in Table 2.

A complete response to therapy was achieved by six patients (6/14, 42.9%). Half of patients had a partial response (7/14, 50%), one patient did not respond to JAKi therapy (1/14, 7.1%).

Information on adverse events (AEs) was available for thirteen patients (13/14, 92.9%). Most AEs did not require treatment discontinuation. Those included: transient muscle pain, gamma-glutamyl transferase elevation with dyslipidemia, and infections. The latter were also the most common AEs: BK virus viremia (6/13, 46.2%), herpes zoster infection (2/13, 15.4%), upper respiratory tract infections (UTI) (10/13, 76.9%) and pneumonia (4/13, 30.8%). However, in three cases (3/25, 12%) hospitalization was required: for BK viremia, herpes zoster and pneumonia. Treatment with JAKi was discontinued in one case. Cause for discontinuation was acute kidney injury after multiple infections (pneumocystis jirovecii pneumonia, clostridium difficile, influenza and rotavirus). Further details on all AEs can be found in Table 3.

Table 2 Baseline characteristics, treatment, and response in CANDLE patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (45)	5, m	dyspnea fever, rash, periorbital swelling, hypertrichosis, lipodystrophy, polyarthritis, atrophic facial musculature, cough, hepatomegaly, arterial hypertension	BAR	6mg/d for 3 days, 8mg/d	GC	Partial no clinical symptoms, elevated CRP during follow-up
2 (46)	12, f	recurring purpuric annular plaques, recurrent fever, abdominal pain, myositis, panniculitis	TOF	10mg/d 6 Mo; 20mg/d	GC	Partial resolution of clinical symptoms, no laboratory parameters
3 (47)	17, f	skin rashes, arthritis, panniculitis, lipodystrophy, alopecia, growth delay	TOF	10 mg/d	GC	Complete
4 (48)	n/a	n/a	BAR	0.1mg/d titrated to 6mg/d	GC 0.84mg/kg/d	Partial partial resolution of clinical symptoms* GC reduction to 0.27 mg/kg/d
5 (48)	n/a	n/a	BAR	0.2mg/d titrated to 6mg/d	GC	Complete
6 (48)	n/a	n/a	BAR	1mg/d titrated to 6mg/d	GC	Partial partial resolution of clinical symptoms* GC reduction**
7 (48)	n/a	n/a	BAR	1mg/d titrated to 8mg/d	GC	Complete
8 (48)	n/a	n/a	BAR	1mg/d titrated to 9mg/d	GC	Complete
9 (48)	n/a	n/a	BAR	1mg/d titrated to 4mg/d	GC	Partial partial resolution of clinical symptoms* GC reduction**
10 (48)	n/a	n/a	BAR	1mg/d titrated to 4mg/d	GC	No

Baseline characteristics, treatment, and response in CANDLE patients

11 (48)	n/a	n/a	BAR	1mg/d titrated to 6mg/d	GC	Partial partial resolution of clinical symptoms* GC reduction**
12 (48)	n/a	n/a	BAR	3mg/d titrated to 10mg/d	GC	Complete
13 (48)	n/a	n/a	BAR	7mg/ titrated to 9mg/d	none	Complete

*Clinical symptoms were summarized in a daily diary score (DDS). A score of <0.15 showed complete resolution, <0.5 (or <1 for SAVI) was considered as partial resolution of clinical symptoms (48)

** prednisone ≥50% dose reduction or 0.15mg/kg/d

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

Table 3 Overview of adverse events

Disease	CANDLE	SAVI	AGS	other type I interferonopathies	AOSD	sJIA	FMF	BS	Total
Number of patients treated	14	28	3	7	26	4	6	13	101
Adverse events – *n**	26	17	1	9	4	0	0	2	59
JAKi dose reduction	-	2	-	-	-	-	-	-	2
JAKi discontinuation	1	2	-	-	1	-	-	2	6
requiring hospitalization	3	4	-	2	-	-	-	-	9
Deaths	-	4**	-	-	1***	-	-	-	5
Types of adverse events									
Pneumonia	4	3	-	-	3	-	-	-	10
dose reduction	-	1	-	-	-	-	-	-	1
discontinuation	-	-	-	-	-	-		-	
UTI	10	5	-	2	-	-	-	-	17
dose reduction	-	-	-	-	-	-	-	-	-
discontinuation	-	-	-	-	-	-	-	-	-
BK viremia	6	3	-	1	-	-	-	-	10
dose reduction	-	1	-	-	-	-	-	-	1
discontinuation	-		-	-	-	-	-	-	-
BK viruria	-	1	-	3	-	-	-	-	4
dose reduction	-	-	-	-	-	-	-	-	-
discontinuation	-	-	-	-	-	-	-	-	-
Herpes zoster	2	-	-	1	-	-	-	2	5
dose reduction	-	-	-	1	-	-		-	1
discontinuation	-	-	-	-	-	-	-	2	2
Viral gastroenteritis	-	2	-	-	-	-	-	-	2
dose reduction	-	-	-	-	-	-	-	-	-

Overview of adverse events									
discontinuation	-	1	--	-	-	-	-	-	1
Other infections	1[1]	2[2]	-	1[3]	-	-	-	-	4
dose reduction	-	-	-	-	-	-	-	-	-
discontinuation	-	-	-	-	-	-	-	-	-
Dyslipidemia	1	-	1	-	-	-	-	-	2
dose reduction	-	-	-	-	-	-	-	-	-
discontinuation	-	-	-	-	-	-	-	-	-
Other AEs	2	1	-	1	1[7]	-	-	-	5
dose reduction	-		-	-	-	-	-	-	-
discontinuation	1[4]	1[5]	-	1[6]	1	-	-	-	4

* Information on adverse events was available for 13 CANDLE patients, 20 SAVI patients, 1 AGS patient, 5 patients with other interferonopathies, 24 AOSD patients, 3 sJIA patients, 4 FMF patients and all 13 Behçet's Syndrome patients

** One due to ILD and heart failure; one after humoral rejection after lung transplant due to ILD; one due to acute respiratory failure; one due to ILD

*** One of the patients with bacterial pneumonia, after a 217-day long hospital stay

[1] multiple: pneumocystis jirovecii pneumonia, clostridium difficile, influenza, and rotavirus; [2]osteomyelitis; cutaneous infection with staphylococcus aureus; [3] multiple: clostridium difficile, pyelonephritis, urosepsis; [4] acute kidney injury; [5] papillary edema; [6] osteonecrosis; [7]menometrorrhagia

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.3. Evidence on effectiveness and safety for STING-associated vasculopathy with onset in infancy (SAVI)

Data was extracted and analyzed for twenty-eight patients. Median age of JAKi initiation was 7.5 years (1 month-37 years, reported for twenty-four patients). Most often prescribed was ruxolitinib (18/28, 64.3%), seven patients received baricitinib (7/28, 25%), and three (3/28, 10.7%) received tofacitinib. Treatment duration was reported for twenty-seven patients, for a mean of 23.7 months. For five patients (5/28, 17.9%) data on supportive treatment was not available. A quarter of patients (6/23, 26.1%) received JAKi monotherapy. Sixteen patients (16/23, 69.6%) received GC as supportive treatment. Of those five (5/16, 31.3%) received additional immunosuppression (e.g., hydroxychloroquine, intravenous immunoglobulins (IVIG), etanercept). One patient received only IVIG in combination with JAKi (1/23, 4.3%). Clinical and treatment data, as well as response to therapy are reported in Table 4.

No patient achieved complete remission. A partial response to therapy was achieved by twenty-one patients (21/28, 75%) seven patients did not respond to JAKi therapy (7/28, 25%). GC dosage at last follow-up was reported for twelve patients (12/16, 75%). For eight patients (8/12, 66.7% of reported cases) complete tapering was possible and in three cases (3/12, 25%) GC dose reduction was tolerated.

nformation on adverse events (AEs) was available for twenty patients (20/28, 71.4%) Most AEs did not require treatment discontinuation or dose reduction. Those included: UTI (4), pneumonia (3), osteomyelitis (1), cutaneous infection (1), BK viremia (2), BK viruria (1) and gastroenteritis (1). Dose reduction was required in two cases: after recurring respiratory infections and in one case of BK viremia. Treatment with JAKi was discontinued in two cases (severe rotavirus enteritis, papillary edema). In both cases, JAKi therapy was later reinstated and well-tolerated. Hospitalization occurred in four cases (4/17,23.5%) for gastroenteritis, two cases of pneumonia and recurring respiratory infections. Four patients (4/28, 14.3%) died during JAKi treatment. Of all AEs, one (enteritis) occurred while the patient was hospitalized. Further details on all AEs can be found in Table 3.

Table 4 Baseline characteristics, treatment and response in SAVI patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (49)	13, m	fever, rash, lipodystrophy, polyarthritis, pulmonary hypertension	RUX	10mg/d	n/a	Partial only lung function and skin improvement
2 (49)	7, w	recurring purpuric annular plaques, fever, abdominal pain, myositis, panniculitis, pulmonary hypertension	RUX	10mg/d	n/a	Partial no information on clinical symptoms except “improvement”
3 (50)	37, m	erythema, livedo reticularis, alopecia, vasculitis, vasculitis ulcer	BAR	4mg/d for 2 months; 6mg/d	Pred 0,2mg/kg	Partial ulcer - healed; improved well-being; persisting livedo, no laboratory improvement
4 (51)	10, f	fever, skin lesions, acral ulcers, arthralgia, ILD	RUX	10mg/d; 15mg/d; 20mg/d	Pred 0,4mg/kg/d	Partial GC withdrawal, resolution of skin lesions, lung function improvement
5 (51)	8, f	growth delay, livedo reticularis, ILD + oxygen support + NIV	RUX	5mg/d; 10mg/d, 15mg/d, 5mg/d	Pred 0,3mg/kg/d	Partial GC tapered to 0,2mg/kg/d; skin improvement; initial improvement in lung function, deterioration after 18 months
6 (51)	2, f	erythematosus vesicular rash, dermatitis, fever, cough, lungs - septal thickening on CT	RUX	5mg/d, 15mg/d	None	Partial resolution skin lesions, initial improvement in lung function and radiological findings, followed GC-responsive lung disease relapse
7 (52)	1, m	fever, livedoid skin lesions, ulcerated lesions on heels, ILD, oxygen dependent	BAR	2mg/d	Mpred 1mg/kg/d	Partial no oxygen dependency, resolution of skin lesions; GC tapered to

						0,5mg/kg/d; no information on ILD; ESR elevated
Baseline characteristics, treatment, and response in SAVI patients						
8 (53)	2y9mo, m	pulmonary hypertension, hypoxia, livedo racemosa, vomiting, epistaxis, failure to thrive, growth delay	RUX	5mg/d	Pred 2mg/kg/d	Partial normalization pulmonary pressure; neurodevelopmental improvement; persistence of livedo reticularis
9 (54)	37, m	dyspnea, ILD, pneumonia, finger clubbing	RUX	10mg/d	None	No patient died (ILD, heart failure)
10 (54)	13, m	growth delay, finger clubbing, recurrent migratory polyarthritis	RUX	5mg/d	None	No
11 (55)	1y1mo, m	dyspnea, cyanosis, finger clubbing, telangiectasis, Chilblain lesions, myositis, fever, growth delay	TOF	5mg/d	Pred	No patient died due to acute respiratory failure
12 (55)	5, m	cough, tachypnea, finger clubbing, arthritis	TOF	5m/d	Pred	No
13 (56, 57)	4, f	fever, scalp lesions, fatigue, ILD	RUX	5mg/d 10mg/d 5mg/d	Pred 0,5mg/kg/d	Partial GC withdrawal, disease score improvement[1], occasional fever episodes
14(56) (57)	8, m	ulcers, nail dystrophy, fatigue, ILD	RUX	5mg/d; 10mg/d; 15mg/d; 20mg/d	Pred 0,6mg/kg/d	Partial GC withdrawal, general improvement, disease score improvement[2], persisting ulcer
15 (56, 57)	12, m	fever, fatigue, ILD, erythematous skin lesions	RUX	10mg/d	Pred 0,2mg/kg/d HCQ 11mg/kg/d	Partial GC withdrawal; skin lesion improvement, weight gain, disease score improvement[3]

Baseline characteristics, treatment and response in SAVI patients

16 (58)	5y10mo, f	nasal septum perforation, growth delay; ILD;	BAR	n/a	n/a	No
17 (59)	8 mo, m	recurrent skin lesions, fever, ischemic changes of digits	RUX	2mg/d; 5mg/d	n/a	Partial less skin lesions, less hospital admissions
18 (60)	6, f	fever, cough, dyspnea, Raynaud, arthralgia, rash	TOF	7.5mg/d	Pred 0.7mg/kg/d	Partial GC withdrawal
19 (61)	18, m	fever, dyspnea, ILD, chilblain lupus-like lesions, rash, livedo reticularis	RUX	5mg/d; 20mg/d	n/a	No patient died (ILD)
20 (48)	n/a	n/a	BAR	2mg/d titrated to 6mg/d	Pred	No
21 (48)	n/a	n/a	BAR	7mg/d titrated to 10mg/d	None	Partial partial resolution of clinical symptoms*
22 (48)	n/a	n/a	BAR	3mg/d titrated to 6mg/d	None	Partial partial resolution of clinical symptoms*
23 (48)	n/a	n/a	BAR	3mg/d titrated to 6mg/d	None	Partial partial resolution of clinical symptoms*
24 (56)	14, m	dyspnea, ILD, rash, end-stage pulmonary failure;	RUX	0.28mg/kg/d	GC 0.16mg/kg/d	partial weight and height increase, significant disease score reduction** patient died after humoral rejection after lung transplant for severe ILD
25 (56)	7, m	extreme vasculopathy, dyspnea at rest, ILD, arthritis, myositis	RUX	1.10mg/kg/d	GC 0.625mg/kg/d IVIG	partial weight and height increase, significant disease score reduction**
26 (56)	12, f	severe dyspnea at rest, oxygen therapy, ILD, severe polyarthritis	RUX	0,2mg/kg/d	GC 1.5mg/kg/d IVIG	partial weight and height increase, significant disease score reduction**

Baseline characteristics, treatment and response in SAVI patients

27 (56)	8, f	fever, severe vasculopathy, dyspnea on moderate exercise; ILD, severe polyarthritis	RUX	0,83mg/kg/d	GC 0.22mg/kg/d, ETA, monthly GC pulses	partial weight and height increase, significant disease score reduction***
28 (56)	7mo	fever, severe dyspnea at rest, ILD	RUX	1mg/kg/d	IVIG	partial weight and height increase, significant disease score reduction**

Clinical symptoms were summarized in a daily diary score (DDS). A score of <0.15 showed complete resolution, <0.5 (or <1 for SAVI) was considered as partial resolution of clinical symptoms

** p<0.05; Disease score parameters: fever; skin, nail, and hair lesions; respiratory difficulties and fatigue

[1]Disease score at JAKi initiation 12 vs 2 (after 12 months)

[2]Disease score at JAKi initiation 10 vs 2.8 (after 12 months)

[3]Disease score at JAKi initiation 11.2 vs 5 (after 6 months)

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.4. Evidence on effectiveness and safety for Aicardi Goutières Syndrome (AGS)

Data was extracted and analyzed for three patients. Median age of JAKi initiation was 11 years (1.5-22years). The patients received baricitinib, tofacitinib or ruxolitinib, respectively. Mean treatment duration was 28.3 (18-43) months. Clinical and treatment data, as well as response to therapy are reported in Table 5.

All patients (3/3, 100%) showed a partial response to therapy.

Information on adverse events (AEs) was available for only one patient (1/3, 33%), who developed creatine kinase fluctuations, hypercholesterinemia, and hypertriglyceridemia, which were transient and controlled by dietary management without the need for JAKi dose reduction or hospitalization. No other AEs were reported. Further details on all AEs can be found in Table 3.

Table 5 Baseline characteristics, treatment and response in AGS patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (62)	22, f	severe chilblains	BAR	2mg/d	n/a	Partial resolution of chilblains, no laboratory parameters
2 (63)	11, m	rash, dyspnea, ILD, lower limb weakness, calcifications in cerebral cortex and basal ganglia	TOF	10mg/d	CsA + GC	Partial rash resolution, improvement of pulmonary function; persisting muscle weakness; GC dose reduction
3 (64)	1year 6 months, m	neurological (irritability, sleep disturbances, language regression, loss of postural control, axial hypotonia, extrapyramidal signs, microcephaly)	RUX	0,8mg/kg/d	Monthly IVIG 1mg/kg	Partial progressive clinical improvement*

*confirmed on standardized evaluations (Griffiths-III Developmental Scale, Gross Motor Function Classification System)

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.5. Evidence on effectiveness and safety for other type I interferonopathies

Data was extracted and analyzed for seven patients. Median age of JAKi initiation was 4 years (1 month-17 years, reported for three patients). Most often prescribed was baricitinib (5/7, 71.4%). One patient each received tofacitinib or baricitinib (1/7, 14.3% each)- Mean treatment duration was 33.4 months. Most patients (5/7,71.4%) received GC as supportive treatment. One patient each received concomitant cyclosporine A and a combination of mepacrine and hydroxychloroquine, respectively. Clinical and treatment data, as well as response to therapy are reported in Table 6.

Complete response to therapy was achieved by one patient (1/7, 14.3%), under a combination of baricitinib and cyclosporine A. A complete response was achieved by only one patient (1/7, 14.3%) under combination of baricitinib and cyclosporine A (5mg/kg/d). Four patients (4/7, 57.1%) had a partial response and two (2/7, 28.6%) showed no response to therapy. For three patients (3/5, 60%) GC dose reduction was possible and one (1/5, 20%) successfully tapered GC.

Information on adverse events (AEs) was available for five patients (5/7, 71.4%) Most AEs did not require treatment discontinuation or dose reduction. Those included: UTI (2), BK viruria (3), BK viremia (1). Intermittent dose reduction was required in one case after herpes zoster infection. Hospitalization occurred in two cases (2/9, 22.2%): for multiple infectious events (clostridium difficile infection, pyelonephritis, urosepsis) and for a case of osteonecrosis The latter discontinued JAKi therapy after 5.1 months due to this AE. Further details on all AEs can be found in Table 3.

Table 6 Baseline characteristics, treatment, and response in patients with type I interferonopathies

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (48)	n/a	n/a	BAR	0.5mg/d titrated to 8mg/d	GC	No
2 (48)	n/a	n/a	BAR	1mg/d titrated to 6mg/d	GC	Partial partial resolution of clinical symptoms* GC reduction**
3 (48)	n/a	n/a	BAR	3mg/d titrated to 9mg/d	GC	No
4 (48)	n/a	n/a	BAR	3mg/d titrated to 9mg/d	none	Partial partial resolution of clinical symptoms* GC reduction**
5 (65)	1 mo, m	rash, fever, respiratory failure, pulmonary hypertension, cluster seizures	TOF	0.2mg/kg/d 2 weeks, 0,3mg/kg/d	none	Partial rash improvement, ECMO withdrawal, pulmonary hypertension "controlled" (SIL, MAC)

Baseline characteristics, treatment and response in patients with type I interferonopathies

6 (66)	17, m	weakness, palpitations, dyspnea, joint stiffness, headache	RUX	15mg/d; 20mg/d; 15mg/d	MEP 100mg + HCQ 200mg + GC	Partial resolution of pulmonary hypertension, no laboratory parameters
7 (67)	4, m	fever, rash, abdominal pain, hepatosplenomegaly, cervical lymphadenopathy	BAR	8mg/d	CsA + GC	Complete

*Clinical symptoms were summarized in a daily diary score (DDS). A score of <0.15 showed complete resolution, <0.5 (or <1 for SAVI) was considered as partial resolution of clinical symptoms (48)

** prednisone ≥50% dose reduction or 0.15mg/kg/d

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.6. Evidence on effectiveness and safety for Adult-Onset Still´s Disease (AOSD)

Data was extracted and analyzed for twenty-six patients. Median age of JAKi initiation was 33 years (18-82 years). Most often prescribed was tofacitinib (18/26, 69.2%), one (1/26, 3.8%) patient received ruxolitinib, and the rest (7/26, 26.9%) received baricitinib. Mean treatment duration was 7.6 months. Most patients (24/26, 92.3%) received GC either alone (7/26, 26.9%) or in combination with other DMARDs (17/26, 65.4%). Two patients had methotrexate (MTX) alone as supportive treatment (2/26, 7.7%). Mean GC dose at JAKi initiation was 37.3 prednisone equivalent per day. Clinical and treatment data, as well as response to therapy are reported in Table 7.

A complete response was achieved by eleven patients (11/26, 42.3%). A partial response to therapy was seen in the same number of patients (11/26, 42.3%). Four patients did not respond to JAKi therapy (4/26, 15.4%). GC dosage at last follow-up was reported for twenty-two patients (22/24, 91.7%). For three patients (3/22, 14.3%) complete tapering was possible and most cases (18/22, 81.8%) GC dose reduction was tolerated.

Information on adverse events (AEs) was available for twenty-four patients (24/26, 92.3%). Those included: pneumonia (3) and menometrorrhagia (1). The latter required therapy discontinuation in one patient. One of the patients with bacterial pneumonia died after a 217-day long hospital stay. Otherwise no AEs required hospitalization. Further details on all AEs can be found in Table 3.

Table 7 Baseline characteristics, treatment, and response in AOSD patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (68)	18, m	fever, rash sore throat, synovitis	TOF	10mg/d	MTX 20mg/week	Partial no laboratory parameters
2 (68)	31, m	fever, rash sore throat, synovitis	TOF	10mg/d	MTX 20mg/week	Partial no laboratory parameters
3 (69)	33, f	polyarthritis, rash	TOF	10mg/d	Pred 40mg/d	Complete
4 (69)	27, f	Fever, polyarthritis	TOF	10mg/d	Pred 60mg/d + MTX	Complete
5 (69)	32, f	fever, rash, pharyngitis, myalgia	TOF	10mg/d	Pred 50mg/d + HCQ	Complete
6 (69)	58, f	polyarthritis, rash	TOF	10mg/d	Pred 15mg/d + MTX + HCQ	Complete
7 (69)	35, f	polyarthritis, rash	TOF	10mg/d	Pred 15mg/d + MTX	Partial persistence of clinical symptoms
8 (69)	29, f	polyarthritis, early joint destruction, lymphadenopathy, MAS	TOF	10mg/d	Pred 60mg/d + MTX	Complete
9 (69)	82, f	ESR elevation	TOF	5mg/d	Pred 25mg/d + HCQ	Complete
10 (69)	25, f	polyarthritis	TOF	10mg/d	Pred 50mg/d + MTX	Partial persistence of clinical symptoms
11 (69)	41, f	polyarthritis	TOF	10mg/d	Pred 60mg/d + MTX	Partial persistence of clinical symptoms
12 (69)	31, f	polyarthritis	TOF	5mg/d	Pred 20mg/d + MTX + HCQ + CsA	Complete

Baseline characteristics, treatment and response in AOSD patients

13 (69)	33, f	fever, rash, pharyngitis, myalgia, polyarthritis	TOF	10mg/d	Pred 40mg/d + MTX + HCQ	Complete
14 (69)	35, m	MAS	TOF	10mg/d	Pred 22.5mg/d + CsA + ANA	Partial persistence of clinical symptoms
15 (69)	18, m	polyarthritis, rash	TOF	10mg/d	Pred 15mg/d + HCQ	Partial clinical improvement, CRP elevated
16 (69)	18, f	polyarthritis, rash, MAS	TOF	10mg/d	Pred 50mg/d + CsA + MTX	Partial persistence of clinical symptoms
17 (70)	68, f	fever, arthritis	TOF	5mg/d	Pred 30mg/d	Partial "clinical and serological improvement", occasional CRP elevations and hyperferritinemia during follow-up; patient died (bacterial pneumonia)
18 (40)	43, f	fever, arthritis, synovitis, rash, pharyngitis, serositis, splenomegaly	BAR	4mg/d	Pred 10mg/d	Complete
19 (40)	32, m	fever, polyarthritis, rash, synovitis	BAR	4mg/d	Pred 40mgd, MTX 20mg/week	No
20 (40)	63, f	persistent fever	BAR	4mg/d	Pred 15mg/d	Complete
21 (71)	50, f	polyarthritis	BAR	4mg/d	Mpred 9mg/d + ANA	Complete
22 (72)	28, m	fever, polyarthritis, rash	BAR	4mg/d	Pred 80 mg/d	No
23 (72)	32, m	fever, polyarthritis, rash	BAR; UPA	4mg/d; 15mg/d	Pred 16mg/d; MTX 20mg/week (stop), ANA 100mg/d; COL 1.5 mg/d	Partial incomplete resolution of clinical symptoms
24 (72)	40, f	fever, polyarthritis, rash	RUX	30mg/d	Pred 60mg/d; ANA 200mg/d	No
25 (72)	48, f	fever, polyarthritis, rash	TOF	10mg/d	Pred 50mg/d	Partial CRP elevated

Baseline characteristics, treatment and response in AOSD patients						
26 (72)	50, f	fever, polyarthritis, rash	BAR	4mg/d	Pred 60 mg/d	No

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.7. Evidence on effectiveness and safety for Systemic Juvenile Idiopathic Arthritis (sJIA)

Data was extracted and analyzed for four patients. Median age of JAKi initiation was 9 years (4-13 years). Most often prescribed was ruxolitinib (2/4, 50%), one patient each (1/4, 25%) received tofacitinib or baricitinib, respectively. Mean treatment duration was 14.2 months. All patients received GC along JAKi. In two cases (2/4, 50%) GC were prescribed as monotherapy, the other two patients (2/4, 50%) also received non-steroidal anti-inflammatory drugs. Clinical and treatment data, as well as response to therapy are reported in Table 8.

Two patients (2/4, 50%) achieved complete remission. A partial response to therapy was achieved by the other two (2/4, 50%). GC dose reduction was possible in three patients (3/4, 75%) and one (1/4, 25%) successfully tapered GC to discontinuation.

Information on adverse events (AEs) was available for three patients (3/4, 75%) and none were reported. Further details on all AEs can be found in Table 3.

Table 8 Baseline characteristics, treatment and response in sJIA patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (72)	6, f	fever, polyarthritis, rash	RUX	10mg/d; 30mg/d	Pred 3mg/d, IND	Partial incomplete resolution of clinical symptoms
2 (72)	12, f	fever, polyarthritis	BAR	4mg/d; 8 mg/d	Pred 40mg/d, NAP	Partial incomplete resolution of clinical symptoms
3 (73)	4, f	recurrent fever, urticaria, arthralgia, ILD	RUX	1mg/kg/d	Pred 0,5mg/kg/d; Mpred pulse 1x/Mo (3 times)	Complete
4 (74)	13, f	polyarthritis, axillary lymphadenopathy	TOF	5mg/d; 10mg/d	Mpred 4mg/d	Complete

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.8 Evidence on effectiveness and safety for Familial Mediterranean Fever (FMF)

Data was extracted and analyzed for six patients. Median age of JAKi initiation was 35 years (16-64 years). All patients received tofacitinib 10mg/d. Mean treatment duration was 4.5 months (2-12 months). One patient received no supportive treatment (1/6, 16.7%), one (1/6, 16.7%) received a combination of GC, colchicine, and sulfasalazine. Four patients (4/6, 66.7%) were prescribed only colchicine parallel to JAKi. Clinical and treatment data, as well as response to therapy are reported in Table 9

A complete response was shown by half of the patients (3/6, 50%). The rest (3/6, 50%) developed no further flares, but acute phase reactants remained elevated, thus only a partial response was achieved.

Information on adverse events (AEs) was available for four patients (4/6, 66.7%) with none reported. Further details on all AEs can be found in Table 3.

Table 9 Baseline characteristics, treatment, and response in FMF patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (75)	16, m	recurrent fever, generalized peritonitis, monoarthritis, rash,	TOF	10mg/d	n/a	Complete
2 (76)	27, f	fever, polyarthritis, peritonitis	TOF	10mg/d	SSZ + GC + COL [1]	Partial attack-free, CRP elevated
3 (77)	28, m	fever, peritonitis, serositis, arthritis, proteinuria, AA amyloidosis	TOF	10mg/d	COL 3mg/d	Complete
4 (77)	58, f	peritonitis, fever, pleuritis, arthritis	TOF	10mg/d	COL 1.5mg/d	Complete
5 (77)	64, f	fever, arthritis	TOF	10mg/d	COL 1.5mg/d	Partial attack-free, CRP elevated
6 (77)	43, f	fever, peritonitis, arthritis	TOF	10mg/d	COL 2.5mg/d	Partial attack-free, CRP elevated

[1] 1 month after baricitinib initiation

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.9. Evidence on effectiveness and safety for Behçet's Syndrome (BS)

Data was extracted and analyzed for thirteen patients. Median age of JAKi initiation was 42 years (22-73 years). All patients received tofacitinib 10mg/d. Mean treatment duration was 10.8 months (5-21 months). Twelve patients (12/13, 92.3%) received GC parallel to JAKi. In all cases JAKi was administered in combination to other drugs (azathioprine, thalidomide, leflunomide, colchicine, sulfasalazine). Clinical and treatment data, as well as response to therapy are reported in Table 10.

Most patients achieved a partial response (8/13, 61.5). Five patients showed no response to therapy (5/13, 38.5%). Observed were two cases of herpes zoster reactivation, for which tofacitinib was discontinued. Another patient discontinued tofacitinib after nine

months of treatment due to lack of efficacy and condition worsening. Further details on all AEs can be found in Table 3.

Table 10 Baseline characteristics, treatment and response in BS patients

Patient	Age at initiation, sex	Clinical symptoms	Drug	Dosage	Supportive Treatment	Response
1 (78)	37, m	oral ulcers, skin involvement, aortic aneurysm	TOF	10mg/d	GC, AZA, CYC, LEF, COL, TCZ	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
2 (78)	42, m	oral ulcers, genital ulcers, skin involvement, aortic aneurysm	TOF	10mg/d	GC, THA, CsA, AZA, CYC	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
3 (78)	29, f	oral ulcers, pulmonary embolism	TOF	10mg/d	GC, MMF, CYC, LEF, COL	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
4 (78)	42, f	oral ulcers, genital ulcers, skin involvement, aortic valve regurgitation	TOF	10mg/d	GC, CYC	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
5 (78)	64, m	oral ulcers, genital ulcers, aortic valve regurgitation, aortic aneurysm	TOF	10mg/d	GC, LEF	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
6 (78)	42, m	oral ulcers, genital ulcers, polyarthritis	TOF	10mg/d	SSZ, LEF, THA	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
7 (78)	30, m	oral ulcers, GI ulcers, skin involvement, scleritis, polyarthritis	TOF	10mg/d	GC, SSZ, MTX, AZA, COL, THA	Partial resolution of ulcers, no newly onset imaging/endoscopic findings

Baseline characteristics, treatment and response in BS patients						
8 (78)	73, m	oral ulcers, genital ulcers, GI ulcers	TOF	10mg/d	GC; CYC, SSZ	Partial resolution of ulcers, no newly onset imaging/endoscopic findings
9 (78)	59, f	oral ulcers, GI ulcers	TOF	10mg/d	GC, CYC, SSZ, THA	No
10 (78)	48, m	oral ulcers, genital, GI ulcers	TOF	10mg/d	GC, TAC, SSZ	No
11 (78)	22, f	oral ulcers, genital ulcers, GI ulcers	TOF	10mg/d	GC, SSZ, THA, MTX	No
12 (78)	37, f	oral ulcers, genital ulcers, GI ulcers, MDS	TOF	10mg/d	GC, TAC, THA, COL	No
13 (78)	23, f	oral ulcers, genital ulcers, GI ulcers	TOF	10mg/d	GC, CYC, AZA, THA	No worsening of clinical symptoms

Adapted from Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

3.10. Evidence on effectiveness and safety for other AID

No articles regarding CAPS, TRAPS, PFAPA, PAPA or MKD could be identified.

4 Discussion

4.1 Summary of results

To our knowledge, this is the first systematic review analyzing the effectiveness and safety of JAKi in AID. The overview of the available clinical evidence is based on observational studies such as case reports and case series. Effectiveness was evaluated based on clinical response, defined by the authors of this systematic review as complete, partial or no response depending on (complete) symptom resolution and/or normalization of laboratory parameters for inflammation. Furthermore, AEs were described.

Evidence on a total of 101 patients with different AID was identified. A complete response to therapy with JAKi was seen in twenty-three patients (23/101, 22.8%). Partial response was achieved by fifty-nine patients (59/101, 58.4%). Less than a fifth of all patients showed no response to therapy (19/101, 18.8%).

4.2 Evidence on type I interferonopathies

Most reports (n=25) included in this systematic review investigated the use of JAKi for type I interferonopathies. The disruption of interferon-mediated immune responses in patients with type I interferonopathies explains the rationale behind the usage of JAKi for treating these diseases since JAKi are potent inhibitors of the JAK-STAT pathway, involved in interferon signaling (79). In this analysis, reports on SAVI, CANDLE, AGS and other interferonopathies were included.

Fifty-two patients (CANDLE n=14, SAVI n=28, AGS n=3, other interferonopathies n=7) could be identified. Overall promising results were seen: seven patients (7/52, 13.5%) showed a complete response to therapy, the majority (35/52, 67.3%) showed a partial and a minority (10/52, 19.2%) showed no treatment response.

One publication on AGS reported no individual patient data (80). Thus, results of this study are discussed only in this section of the systematic review. The publication by Vanderver, A. et al., 2020 reports preliminary results of an open-label single center study involving 35 patients with molecularly confirmed AGS. This is to our knowledge the largest AGS cohort treated with JAKi. All patients received baricitinib in doses ranging from 0.1

to 0.6 mg/kg/d. The authors report overall improvement of daily diary scores within one month of therapy initiation. Neurological function was evaluated based on key developmental milestones, with 20 patients (20/35, 57.1%) meeting new milestones and 12 (12/35, 34.3%) gaining two to seven new skills, such as sitting, rolling, head control. In the three cases presented in this systematic review, neurological symptoms were the dominant disease feature, but only in just (63) improvement was reported with ruxolitinib. Regarding the safety profile of JAKi, in this AGS cohort (80) only one case of BK viremia was described – a relatively frequent event in interferonopathy patients discussed here (10/52, 19.2%).

Notably, amongst interferonopathy patients, JAKi were most efficient for CANDLE patients: complete remission was achieved by six patients (6/14, 42.6%). Additionally, the available data suggests a GC sparing effect in this group, since seven patients (7/11, 63.6%) were able to discontinue GC and in four patients (4/11, 36.4%) GC dose reduction was possible.

One hypothesis for the difference in treatment outcome between interferonopathies is that the better treatment response was due to a higher JAKi dosage. A direct comparison is difficult since mostly pediatric patients were treated and JAKi dosage was reported as mg per kilogram without documenting weight for each individual patient. Mean baricitinib and tofacitinib dosages in CANDLE cases were 6.8 mg/d and 5 mg/d, respectively. Mean baricitinib doses for SAVI were 6 mg/d (reported for 6/7, 85.7%) up to a mean 8mg/d in other interferonopathies. Most SAVI patients were treated with ruxolitinib at a mean dose 10.8mg/d (reported for 13/18, 72.2% patients treated).

A head-to-head comparison of effectiveness is difficult due to several reasons such as the small number of patients treated, the usage of the different JAKi and the respective dosage used and partially missing individual data.

While belonging to the same drug class, the three JAKi – baricitinib, tofacitinib and ruxolitinib, differ in some respects. Firstly, growing scientific evidence has highlighted a certain selectivity of JAKi toward specific Janus kinases with ruxolitinib and baricitinib targeting primarily JAK 1 and JAK2, and tofacitinib interfering also with JAK3 (32). Furthermore, ruxolitinib and tofacitinib are primarily metabolized vie the cytochrome P450 system, while

baricitinib is primarily renally excreted (32). This suggests a lower risk of drug interactions during therapy with baricitinib. Interestingly, ruxolitinib is also available as a topical drug and was very recently approved for treating nonsegmental vitiligo by the FDA (81) after being approved for atopic dermatitis in 2021 (82).

Regarding safety it should be mentioned that most infectious AEs in this analysis occurred in patients with type I interferonopathies: seven cases of pneumonia (7/10, 70%), all UTIs (17/17, 100%) and all cases of BK viremia and viruria (10/10 and 4/4, respectively; 100%) (Table 3). The proportion of patients in this group who experienced any AE is also greater compared to other groups: 16.7% of AOSD patients (4/24), even less in BS patients (2/13, 15.4%) and none of the FMF and sJIA patients.

Of overall 59 AEs reported, 52 (88.1%) were due to infections (Table 3). In general JAKi show a heterogenous risk of infectious complications. For example, a known class effect for JAKi is an elevated risk of herpes zoster (83, 84, 85, 86). In one recent study, serious infections were more frequent with tofacitinib at a dose of 10mg twice daily compared to TNF inhibition (87), which contradicts some available evidence pointing to a similar risk of serious infections under JAKi compared to other bDMARDs (88, 89). The risk for opportunistic infections (herpes zoster, tuberculosis) under tofacitinib in this study was higher compared to a TNF-inhibitor, and even more so when tofacitinib dose was 10mg compared to 5mg. In this systematic review a total of three cases of herpes infections occurred under tofacitinib, baricitinib and ruxolitinib each. Recent case series investigated the effectiveness of tofacitinib in six patients with type I interferonopathies(90). Among these, a single transient lung infection in one patient and a cytomegalovirus infection in another were reported, both defined as non-severe.

A controversially discussed adverse effect of JAKi are thromboembolic events. This risk has been shown to be elevated relative to TNF inhibitors, along with a clinically meaningful risk of serious heart-related AEs, cancers, blood clots and death in older patients with RA (87). However, several (meta-) analyses did not provide evidence supporting an increased risk of thromboembolism with JAKi (83, 91, 92). In this systematic review, thromboembolic events were not reported. Most safety data regarding JAKi stems from RCTs

in adult patients. Although data from clinical trials in adult patients cannot be directly extrapolated to the pediatric population, special attention should still be paid to clinical experience from these trials, as they tend to have a higher level of evidence.

The discrepancy in the frequency of AEs in the different disease groups presented in this systematic review could reflect the inconsistency in reporting of AEs, commented further below. It should be considered that for FMF, sJIA and Behçet's syndrome only a few reports were available for analysis. However, one reason for the higher incidence of infections amongst interferonopathy patients might be due to a dose dependent effect. All FMF and BS patients, as well as most AOSD patients received a "standard dose" of tofacitinib (10mg/d) or baricitinib (4mg/d). As mentioned above, JAKi doses varied amongst interferonopathy patients. Nevertheless, baricitinib was often administered at doses higher than 4mg/d – up to a mean 6.8 mg/d in CANDLE patients and a mean 6 mg/d for SAVI patients. Notably, most interferonopathy patients were pediatric patients, suggesting a higher dose pro kilogram body weight.

Another hypothesis is that interferonopathy patients are generally exposed to a higher risk for infections. While infections can be considered potential triggers for disease onset or flares (8), current evidence does not suggest a predisposition for infections in interferonopathy patients. However, for other diseases with a prominent interferon signature, such as systemic lupus erythematodes (SLE) and dermatomyositis, a susceptibility for infections has been reported (93, 94). Thus, a possible explanation for the elevated incidence of infectious AEs in this subgroup could be an intrinsically dysfunctional immune system leaving patients exposed to an increased risk of infection.

4.3 Evidence on other AID

Part of the systematic database searches about JAKi for treating monogenic AID were CAPS, TRAPS, MKD and FMF. Of those, publications were identified only for FMF. In FMF patients, JAKi resulted in a complete response in half of the patients and a partial response for the rest (3/6, 50% each).
Furthermore, an analysis for the polygenetic diseases sJIA, AOSD and BS was conducted. Eleven AOSD patients had a complete response and the same number of patients a partial response (11/26, 42.3% each). Two sJIA patients completely responded

to JAKi therapy (2/4, 50%) and for the other two (2/4, 50%) a partial response was reported. Amongst BS a partial response was achieved by most (8/13, 61.5%), and five (5/13, 38.5%) showed no response to therapy.
Although JAKi did not lead to complete remission in all AOSD patients, most of them were able to taper or withdraw GC – used as supportive treatment in almost all patients (24/26, 92.3%). Dosage of GC at last follow up was reported for twenty-two patients (22/24, 91.7%). Mean GC dose at JAKi initiation was 37.3 mg prednisone equivalent per day, and 13.3 mg/d at last follow-up. This highlights the potential of JAKi as GC sparing drug in AOSD, especially in patients with articular phenotype. The majority of AOSD patients presented with arthritis (20/26, 76.9%), of whom most showed a complete or a partial response (8/20, 40% for each group). Additionally, all FMF patients included in this analysis had active arthritis. All of them showed clinical improvement under JAKi. Therefore, it can be hypothesized that JAKis are especially beneficial for patients with active arthritis

4.4 Strengths and limitations

Due to the rare nature of AID and the relatively recent availability of JAKi, there are currently no RCTs available, and most publications included were case reports or case series. Recently, it has been suggested that for *ultrarare diseases* evidence from case reports and series should be considered to be of higher quality (95). However, this can only be encouraged if treatment outcome in the reports includes *precise outcomes*, i.e. inflammatory remission. Thus, for reporting outcomes in this systematic review, a classification based on clinical symptoms *and* laboratory parameters was performed. Accordingly, treatment response was classified as complete, partial or none. Although this approach has not been validated, it has been previously used by other investigators (40, 69, 72) and serves as base for objectifying and summarizing the available evidence. The body of evidence found did not suffice for quantitative analysis due to its heterogeneity. Instead, an extensive narrative synthesis was conducted.

For observational studies to be regarded as pieces of evidence of higher quality, thorough reporting is required. To date, no universal criteria for reporting outcomes in AID patients exist. To improve and standardize reporting on treatment strategies in AID we suggest the following type of reporting (Table 11): clinical symptoms, inflammatory parameters, concomitant diseases, previous therapies; for the use of JAKi - exact dose, as well as

information on any supportive treatment, including dosage; for a precise evaluation therapeutic response statements on dynamics of clinical symptoms, as well as inflammatory parameters should be noted. AEs especially infections should be closely monitored and reported. In the publications included in this systematic review reports on AEs were sometimes insufficient – those were not documented in 18% of cases (83/101, 82.2%).

Table 11 Suggestions for future reporting on treatment outcome

Pre-JAKi	**JAKi**	**Post-JAKi**
Clinical		**Clinical**
Clinical symptoms	Dosage	Change in clinical symptoms
Disease score (if available)	Supportive treatment (including dosage)	Change in disease score (if available)
Concomitant diseases	Treatment duration	Change in dosage of supportive drugs (e.g. GC)
Previous therapies		Adverse events
Inflammatory markers		**Inflammatory markers**
CRP		CRP
ESR		ESR
others (complete blood count, ferritin, IFN gene expression, if applicable)		others (complete blood count, ferritin, IFN gene expression, if applicable)

From Boyadzhieva Z, Ruffer N, Burmester G, Pankow A, Krusche M. Effectiveness and Safety of JAK Inhibitors in Autoinflammatory Diseases: A Systematic Review. Frontiers in Medicine. 2022;9.

Here, many authors were contacted to complete missing data and meet the suggested reporting criteria. However, in some instances despite the reviewers´ best effort complete information could not be obtained. In the analysed publications a relatively low systematization in conduct and reporting was observed. To maximize potential data on JAKi in AID, abstracts were also included, which in part presented limited details on individual patient characteristics at baseline and post JAKi treatment.

Alongside defining reporting items, disease (specific) activity scores and response criteria to compare AID studies are urgently needed. For monogenetic inflammasomopathies (FMF, CAPS, TRAPS, MKD) the Auto-Inflammatory Diseases Activity Index (AIDAI) (96) is a validated score but was only reported in one study concerning JAKi use in FMF (77). An EULAR task force is currently preparing specific criteria for AOSD which should be applied for future reporting (97). Regarding type I interferonopathies Frémond, M. et al., 2016 suggested a disease activity score for SAVI patients: the Disease Activity Rating Scale of TMEM173-mutated patients (57). This score for SAVI needs to be validated and scores for the other interferonopathies need to be developed.

Regarding limitations of this analysis, the general risk of publication bias should be considered. With publication bias the decision to pursue the publication of results of an experiment is biased by the result itself, with favorable, or statistically significant results being more likely to be published than dissatisfactory ones(98). In rare, difficult to treat diseases it can be expected that this effect is even more pronounced.

Overall, given their rare nature, a considerable number of AID patients treated with a JAKi (101) could be identified. The available evidence showed most patients did respond to JAKi therapy. This review was conducted to summarize the available evidence on new therapeutic possibilities for AID patients and to highlight the need for well-designed clinical trials investigating JAKi in AID. Currently, one phase 3 clinical trial on baricitinib in CANDLE, SAVI and AGS is being conducted (99). Research is actively underway in the direction of sJIA with two ongoing phase 3 randomized double-blind, placebo-controlled studies on baricitinib and tofacitinib (100, 101).

5 Conclusions

This systematic review provides results from observational studies showing first pieces of evidence on treatment effectiveness of JAKi for AID. To validate these results and confirm efficacy and safety of JAKi for specific AID, clinical trials need to be initiated.

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Eidesstattliche Versicherung

„Ich, Zhivana Boyadzhieva versichere an Eides statt durch meine eigenhändige Unterschrift, dass ich die vorgelegte Dissertation mit dem Thema: Janus Kinase Inhibitors for Autoinflammatory Disease: A First Systematic Review of Effectiveness and Safety; *dt*. Janus Kinase Inhibitoren für Autoinflammatorische Erkrankungen: Erste Systematische Übersichtsarbeit über Effektivität und Sicherheit, selbstständig und ohne nicht offengelegte Hilfe Dritter verfasst und keine anderen als die angegebenen Quellen und Hilfsmittel genutzt habe.
Alle Stellen, die wörtlich oder dem Sinne nach auf Publikationen oder Vorträgen anderer Autoren/innen beruhen, sind als solche in korrekter Zitierung kenntlich gemacht. Die Abschnitte zu Methodik (insbesondere praktische Arbeiten, Laborbestimmungen, statistische Aufarbeitung) und Resultaten (insbesondere Abbildungen, Graphiken und Tabellen) werden von mir verantwortet.

Ich versichere ferner, dass ich die in Zusammenarbeit mit anderen Personen generierten Daten, Datenauswertungen und Schlussfolgerungen korrekt gekennzeichnet und meinen eigenen Beitrag sowie die Beiträge anderer Personen korrekt kenntlich gemacht habe (siehe Anteilserklärung). Texte oder Textteile, die gemeinsam mit anderen erstellt oder verwendet wurden, habe ich korrekt kenntlich gemacht.

Meine Anteile an etwaigen Publikationen zu dieser Dissertation entsprechen denen, die in der untenstehenden gemeinsamen Erklärung mit dem/der Erstbetreuer/in, angegeben sind. Für sämtliche im Rahmen der Dissertation entstandenen Publikationen wurden die Richtlinien des ICMJE (International Committee of Medical Journal Editors; www.icmje.og) zur Autorenschaft eingehalten. Ich erkläre ferner, dass ich mich zur Einhaltung der Satzung der Charité – Universitätsmedizin Berlin zur Sicherung Guter Wissenschaftlicher Praxis verpflichte.

Weiterhin versichere ich, dass ich diese Dissertation weder in gleicher noch in ähnlicher Form bereits an einer anderen Fakultät eingereicht habe.

Die Bedeutung dieser eidesstattlichen Versicherung und die strafrechtlichen Folgen einer unwahren eidesstattlichen Versicherung (§§156, 161 des Strafgesetzbuches) sind mir bekannt und bewusst.“

Datum Unterschrift

Anteilserklärung an den erfolgten Publikationen

Zhivana Boyadzhieva hatte folgenden Anteil an den folgenden Publikationen:

Publikation 1: Boyadzhieva, Z., Ruffer, N., Burmester, G.R., Pankow, A., Krusche, M.; Effectiveness and Safety of JAK Inhibitors in Autoinflammatory diseases: A systematic review, *Frontiers in Medicine*, 2022
Beitrag im Einzelnen:

- Entwicklung der Fragestellung und Design (gemeinsam mit Prof. Dr. Burmester und Dr. Krusche)
- Erstellung und Veröffentlichung eines Protokolls nach der PRISMA Leitlinie (gemeinsam mit Prof. Burmester, Dr. Krusche und Dr. Ruffer)
- Erarbeiten einer Suchstrategie
- Durchführung der systematischen Datenbanksuche
- Ein- und Ausschluss von den identifizierten Publikationen (gemeinsam mit Dr. Pankow)
- Datenextraktion und Synthese
- Erstellung eines Manuskriptentwurfs (gemeinsam mit Dr. Krusche)
- Erstellung aller Tabellen und Figuren
- Überarbeitung der Veröffentlichung (gemeinsam mit Prof. Burmester, Dr. Krusche, Dr. Ruffer, Dr. Pankow)

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SYSTEMATIC REVIEW
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Effectiveness and Safety of JAKInhibitors in Autoinflammatory Diseases: A Systematic Review

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Introduction: Autoinflammatory diseases (AID) are rare diseases presenting with episodes of sterile inflammation. These involve multiple organs and can cause both acute organ damage and serious long-term effects, like amyloidosis. Disease-specificanti-inflammatory therapeutic strategies are established for some AID. However, theirclinical course frequently includes relapsing, uncontrolled conditions. Therefore, new therapeutic approaches are needed. Janus Kinase inhibitors (JAKi) block key cytokines of AID pathogenesis and can be a potential option.

Methods: A systematic review of the literature in accordance with the PRISMA guidelines was conducted. Three databases (MEDLINE, Embase and Cochrane Central Register of Controlled Trials) were searched for publications regarding the use of JAKi forAID. Data from the included publications was extracted and a narrative synthesis wasperformed. Criteria for defining treatment response were defined and applied.

Results: We report data from 38 publications with a total of 101 patients describing the effects of JAKi in AID. Data on Type I Interferonopathies, Adult-Onset Still's Disease (AOSD), Systemic Juvenile Idiopathic Arthritis (sJIA), Familial Mediterranean Fever (FMF), and Behçet's Syndrome (BS) was identified. From a total of 52 patients with type I interferonopathies, in seven patients (7/52, 13.5%) a complete response was achieved, most (35/52, 67.3%) showed a partial response and a minority (10/52, 19.2%) showedno treatment response. For AOSD, a complete or a partial response was achieved byeleven (11/26, 42.3%) patients each. Two sJIA patients achieved complete response(2/4, 50%) and in two cases (2/4, 50%) a partial response was reported. Half of FMFpatients showed a complete response and the other half had a partial one (3/6, 50.0%). Amongst BS patients most achieved a partial response (8/13, 61.5%). Five patients showed no response to therapy (5/13, 38.5%). Overall, the most frequent AEs were upper respiratory tract infections (17), pneumonia (10), BK virus viremia (10) and viruria (4), herpes zoster infection (5), viral gastroenteritis (2) and other infections (4).

Conclusion: The results from this systematic review show that JAKi can be beneficialin certain AID. The risk of AEs, especially viral infections, should be considered. To accurately assess the risk benefit ratio of JAKi for AID, clinical trials should be conducted.

Keywords: autoinflammation, interferonopathy, monogenic autoinflammatory disease, Janus Kinase inhibition, *innate immunity*

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INTRODUCTION

Autoinflammatory diseases (AID) are characterized by seemingly unprovoked inflammatory attacks in absence of pathogenic autoantibodies or antigen-specific T-cells. Defined as *mono- andpolygenic disorders of innate immunity,* AID comprise a broad spectrum of rare diseases which may present with episodesof fever and sterile inflammation potentially causing severemorbidity and mortality. Due to advances in gene sequencing technology and the development of diagnostic criteria, new syndromes continue emerging (1, 2).

Depending on the dominating cytokine pattern, AID can be grouped in IL-1 (inflammasomopathies) (3), NFκB(relopathies) (4) or type I interferon (IFN)-driven diseases (interferonopathies) (5). However, in multiple syndromes such as Adult-Onset Still's Disease [AOSD; IL-1, IL-6, IL-18 (6, 7)], Behçet's syndrome [BS; IL-1, IL-6 (8), IFNγ (9)] or Familial Mediterranean Fever [FMF; IL-1 (10) and IL6 (11)] more thanone cytokine plays a key role in pathogenesis. Due to the broaddisturbance of cytokine signaling, AID can affect various organs and are thus associated with a high disease burden and severe physical, but also socioeconomic limitations (12). Furthermore, AID patients with persistent inflammation have a high risk ofdeveloping AA amyloidosis (13, 14).

Current management of AID includes targeted inhibition of specific cytokine signaling. For example, targeted IL-1 inhibitionhas been shown to be effective for some conditions such as cryopyrin-associated periodic syndromes (CAPS) (15) and AOSD (16). Unfortunately, some AID patients do not respondto targeted inhibition of specific cytokines and other treatmentoptions are needed (17).

Janus Kinase inhibitors (JAK inhibitors, JAKi) interfere withsignal transduction of the Janus Kinase-Signal transducer and activator of transcription (JAK-STAT) pathway causing effective suppression of downstream cytokine signaling. JAK-STAT signaling can be triggered by two types of cytokine receptors: type I receptors bind mainly cytokines (IL-2,−6,−9,−12,−15), hormones (growth hormone, GH) and colony stimulating factors, while type 2 receptors are activated mostly by interferon and IL-10 (18). They act as competitive antagonists at activation sites for Janus kinases and as such interrupt downstream signals along the JAK-STAT pathway, effectively leading to suppression of cytokine production. The JAK-STAT pathway includes several kinases and JAKi can be grouped by their kinase-specific effects: tofacitinib—JAK1, JAK2 and JAK3, baricitinib and ruxolitinib- selective inhibition of JAK1 and JAK2, upadacitinib and filgotinib—selective for JAK1. While JAKi are considered as "targeted therapies," there is almost no other substance class thatexerts an effect on such a large number of cytokines. The resultingimmunomodulatory effects can be clinically illustrated by the fact that the drugs have already been approved for a number ofrheumatic diseases such as rheumatoid arthritis (RA), psoriatic arthritis (19, 20), polyarticular juvenile arthritis (tofacitinib) (21)and ankylosing spondylitis (upadacitinib, tofacitinib) (22, 23).

First reports from an expanded access program study on the beneficial effects of JAKi in type I interferonopathies (24) have also been published. Due to their broad blockade of proinflammatory pathways, JAKi may ameliorate autoinflammatory processes and thus lead to clinical remission in otherwise refractory AID cases. The aim of this systematic literature review is to identify and analyze the available evidenceon JAKi for the treatment of autoinflammatory diseases.

METHODS

The Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines were followed for preparing the manuscript (25).

Protocol and Registration

A study protocol was registered at PROSPERO (CRD42021270369) prior to the systematic search (26).

Data Sources and Searches

The following databases were systematically searched for publications investigating the role of JAKi in AID treatment:MEDLINE *via* PubMed, EMBASE *via* Ovid, Cochrane Central Register of Controlled Trials (via Cochrane Library). The search was conducted on 30 June 2021 and updated on 16 October 2021. The results were supplemented by a backwards search of relevant publications (reference screening).

The search strings were built based on two componentsusing the Boolean operator *and* (AID *and* JAKi). Within those components, multiple terms were linked by *or*. For each syndrome, the full and the abbreviated terms were used including at least one synonym for each condition. For MEDLINE both Medical Subject Headings (MeSH) terms and free-text words were used. All keywords were used to search within titles and abstracts of publications.

Details of the complete search strategy for all searched databases can be found in the **Supplementary Materials**.

Study Selection

Criteria for inclusion were developed using the Patient, Intervention, Comparator, Outcome (PICO) scheme (27). Of interest were following diseases/syndromes:

- Adult-Onset Still's disease (AOSD)
- Systemic Juvenile Idiopathic Arthritis (sJIA)
- Familial Mediterranean Fever (FMF)
- Cryopyrin-associated Periodic Syndromes (CAPS)
- TNF-Receptor Associated Periodic Syndrome (TRAPS)
- Mevalonate Kinase Deficiency (MKD)
- Pyogenic Arthritis, Pyoderma Gangrenosum and Acne (PAPA) Syndrome
- Periodic Fever, Aphthous Stomatitis, Pharyngitis and Adenitis (PFAPA) Syndrome
- Genetic Interferonopathies: Aicardi Goutières Syndrome (AGS), Chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) Syndrome, STING associated vasculitis with onset in infancy (SAVI) Syndrome
- Behçet's Syndrome

TABLE 1 | Inclusion and exclusion criteria.

Inclusion criteria	Exclusion criteria
a) *Patient population*: Patients with AID (AOSD, sJIA, FMF, BS, CAPS, TRAPS, PAPA, PFAPA, Type I Interferonopathies) b) *Intervention*: tofacitinib, baricitinib, upadacitinib, filgotinib, ruxolitinib, other JAKi c) *Comparators:* any other treatment d) *Outcomes*: effectiveness, safety e) *Study design*: retrospective (e.g., case reports, case-series, case-control studies, cohort studies); prospective studies (e.g., randomized controlled trials, non-randomized controlled trials, prospective observational studies) f) *Language*: English	a) *Patient population*: animal/ *in-vitro* study, AID other than specified b) *Intervention*: other than specified c) *Outcomes*: no/insufficient clinical results d) *Publication type:* review articles e) *Language*: other

Defined as *Intervention* was the usage of JAKi (tofacitinib, upadacitinib, baricitinib, filgotinib or ruxolitinib). As *Comparator* we accepted any other treatment. For *Outcome* weanalyzed treatment response (see below) and safety (considered were reports on any adverse events).

No restrictions were applied concerning publication date,age, and number of recruited patients. Only studies publishedin English were included. Considered for inclusion were bothretrospective (e.g., case reports, case-series, case-control studies)and prospective studies (e.g., randomized controlled trials, non-randomized controlled trials, prospective observational studies). Assessment for eligibility was performed by two independent reviewers (AP and ZB), following inclusion and exclusion criteria(**Table 1**). First, only title and abstract were screened. Suitablepublications were then assessed in full text. Where there werediscrepancies in the evaluation of the eligibility of a publication by the two reviewers, a third reviewer acted as an arbiter (MK).

Data Collection Process and Data Items

Data extraction and management was performed with Microsoft Excel 2016. A standardized data extraction sheet was designed and used for extraction of study characteristics and outcome data, which was carried out by one of the reviewers (ZB). Data was extracted from each publication on: (1) study characteristics; (2) patient characteristics at baseline; (3) patient characteristics after intervention.

Summary Measures, Synthesis

Due to the lack of randomized controlled trials and the heterogeneity of data, a narrative synthesis was carried out. Results were reported based on the Synthesis Without Meta- analysis (SWiM) guideline (28).

Here, the treatment response of each patient was classified as *complete, partial* or *none* based on the available dataon clinical symptoms and laboratory parameters prior/post intervention. A *complete* response was defined as resolution of all clinical symptoms and normalization of inflammatory parameters (Erythrocyte Sedimentation Rate, ESR, and/or C-Reactive Protein, CRP); as *partial* when either clinical symptoms resolved or laboratory markers normalized, and as *none* when both remained unchanged or worsened.

RESULTS

The first database search identified 582 records of which 70 were removed (duplicate records). The 512 records were screened. Reference screening of included publications additionally identified 4 suitable publications. The updated search (June to October 2021) identified further 80 publications, of which 75 were screened.

Overall, 38 original publications were included for data extraction and analysis. A total of 101 AID patients treatedwith a JAKi could be identified. **Figure 1** provides details on the selection process of included studies.

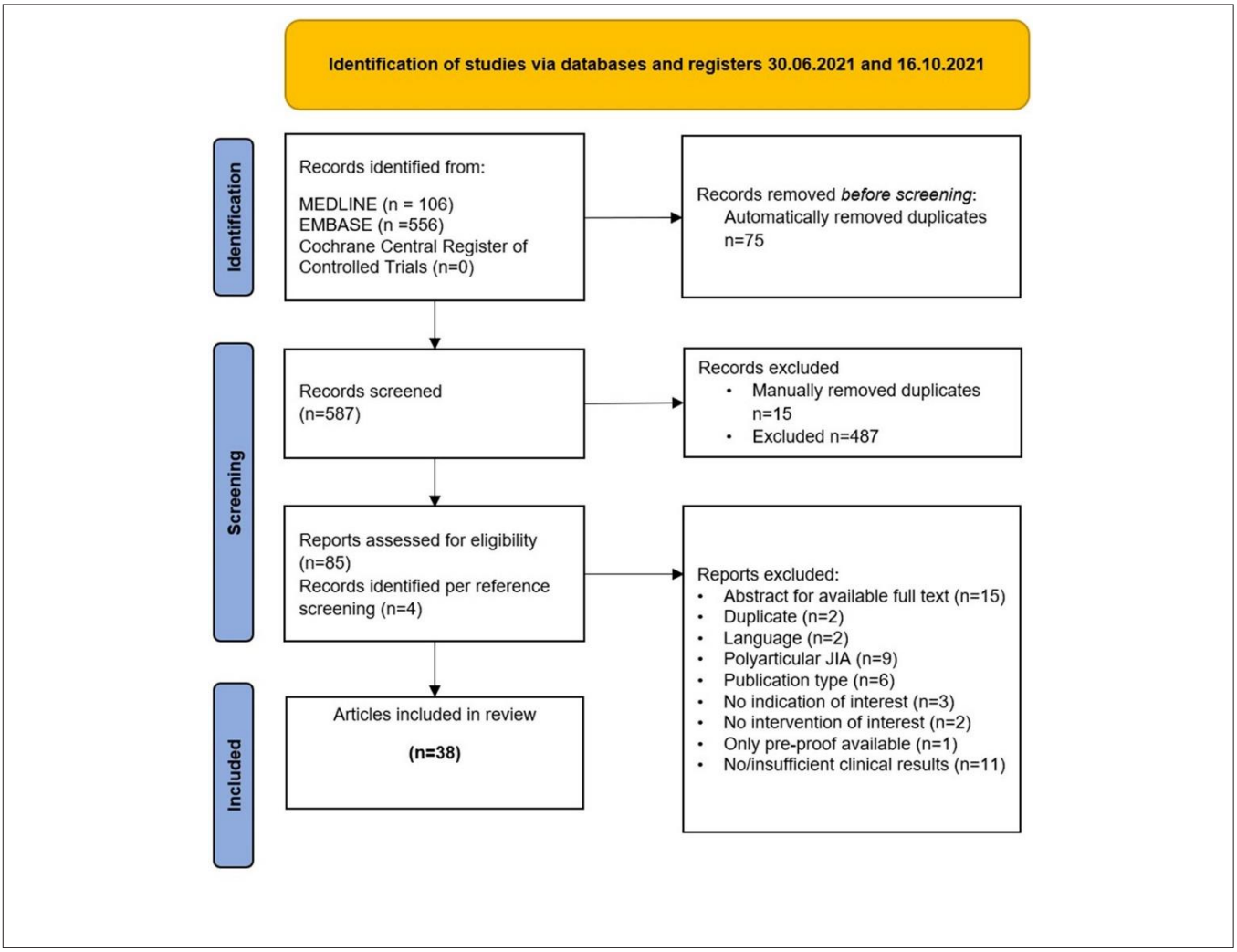
Evidence on Effectiveness and Safety for Chronic Atypical Neutrophilic Dermatosis With Lipodystrophy and Elevated Temperature (CANDLE) Syndrome

The database search identified four case reports (full text $n = 3$, conference abstracts $n = 1$) (29–32) and two articles reporting results of the same compassionate use study (24, 33). A total of fourteen patients were treated with a JAKi. Median age of JAKi initiation was 8.5 years (1.5–17 years, reported for 4 patients). Eleven patients received baricitinib (11/13, 84.6%), and three received tofacitinib (3/14, 21.4%). Mean treatment duration was 92.4 months (reported for 13 patients). All but one patientreceived glucocorticoids (GC) in addition to a JAKi. Data onbaseline characteristics, treatment and response are shown in **Supplementary Table 1**.

Six of the patients (6/14, 42.9%) had a complete response totherapy, half (7/14, 50.0%) showed a partial response and one (1/14, 7.1%) did not respond at all. GC dosage at the end of follow up was reported for eleven patients (11/13, 84.6%), of whom seven (7/11, 63.6%) successfully discontinued GC. In fourpatients (4/11, 36.4%) GC dose reduction was possible.

Data on adverse events (AEs) was available for thirteen patients (13/14, 92.9%). One patient experienced transient muscle pain. One other developed gamma-GT elevation with dyslipidemia. The latter was managed with atorvastatin. Both cases did not require therapy discontinuation. The most common AEs were infections: BK virus viremia (6/13, 46.2%), herpeszoster (2/13, 15.4%), upper respiratory tract infections (UTI) (10/13, 76.9%) and pneumonia (4/13, 30.8%) none of which required treatment discontinuation. Of all AEs hospitalization was required in 3 cases (3/25, 12%): for BK viremia, herpes zoster and pneumonia.

One patient discontinued therapy after 67.5 months because of acute kidney injury following a series of infections (pneumocystis jirovecii pneumonia, clostridium difficile, influenza, and rotavirus). Details on AEs are summarized in**Table 2**.



Evidence on Effectiveness and Safety for STING Associated Vasculopathy With Onset in Infancy (SAVI) Syndrome

Six case reports (34–39) and seven case series (40–46) reportingon SAVI could be identified (full text $n = 9$, conference abstracts$n = 1$, letters $n = 3$). Additional two articles (24, 33) reported on the same study population (patients with SAVI, CANDLE, other interferonopathies).

Data was extracted and analyzed for a total of twenty- eight patients. Median age of JAKi initiation was 7.5 years (1 month-37 years, reported for 24 patients). Eighteen patients (18/28, 64.3%) received ruxolitinib, seven patients (7/28, 25%) received baricitinib, and three (3/28, 10.7%) received tofacitinib.Mean treatment duration was 23.7 months (2.5–80.1 months, reported for 27 patients). For five patients (5/28, 17.9%) data onsupportive treatment was not available. A minority of patients (6/23, 26.1% of reported cases) received JAKi monotherapy. Most were on concomitant GC (16/23, 69.6% of reported cases)of whom six (5/16, 31.3% of reported cases) also received additional immunosuppression (e.g., hydroxychloroquine, IVIG, etanercept). One patient received only IVIG in combination with JAKi (1/23, 4.3%). A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**.A quarter of the patients (7/28, 25%) showed no clinicaland laboratory response. While most patients experienced improvement either in clinical symptoms, or in laboratory parameters of inflammation, no patient achieved complete remission. GC dosage at last follow-up was reported for twelve patients (12/16, 75%). For eight patients (8/12, 66.7% of reported cases) complete tapering was possible and in three cases (3/12,25%) GC dose reduction was tolerated.

Data on AEs was available for twenty patients (20/28, 71.4%) and were mostly infectious: UTI (4), pneumonia (3), osteomyelitis (1), cutaneous infection (1), BK viremia (2), BK viruria (1) and gastroenteritis (1) all without the need for therapy discontinuation or reports of dose reduction. JAKi dose reduction was required in two cases: after recurring respiratory infections and in one case of BK viremia. Treatment

TABLE 2 | Overview of adverse events.

Disease	CANDLE	SAVI	AGS	Other type I interferonopathies	AOSD	sJIA	FMF	BS	Total
Number of patients treated	14	28	3	7	26	4	6	13	101
Adverse events—*n**	26	17	1	9	4	0	0	2	59
JAKi dose reduction	–	2	–	–	–	–	–	–	2
JAKi discontinuation	1	2	–	–	1	–	–	2	6
requiring hospitalization	3	4	–	2	–	–	–	–	9
Deaths	–	4**	–	–	1***	–	–	–	5
Types of adverse events									
Pneumonia	4	3	–	–	3	–	–	–	10
Dose reduction	–	1	–	–	–	–	–	–	1
Discontinuation	–	–	–	–	–	–		–	
UTI	10	5	–	2	–	–	–	–	17
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
BK viremia	6	3	–	1	–	–	–	–	10
Dose reduction	–	1	–	–	–	–	–	–	1
Discontinuation	–		–	–	–	–	–	–	–
BK viruria	–	1	–	3	–	–	–	–	4
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
Herpes zoster	2	–	–	1	–	–	–	2	5
Dose reduction	–	–	–	1	–	–		–	1
Discontinuation	–	–	–	–	–	–	–	2	2
Viral gastroenteritis	–	2	–	–	–	–	–	–	2
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	1	–	–	–	–	–	–	1
Other infections	1[a]	2[b]	–	1[c]	–	–	–	–	4
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
Dyslipidemia	1	–	1	–	–	–	–	–	2
Dose reduction	–	–	–	–	–	–	–	–	–
Discontinuation	–	–	–	–	–	–	–	–	–
Other AEs	2	1	–	1	1[g]	–	–	–	5
Dose reduction	–		–	–	–	–	–	–	–
Discontinuation	1[d]	1[e]	–	1[f]	1	–	–	–	4

**Information on adverse events was available for 13 CANDLE patients, 20 SAVI patients, 1 AGS patient, 5 patients with other interferonopathies, 24 AOSD patients, 3 sJIA patients, 4 FMF patients and all 13 Behçet's Syndrome patients.*

***One due to ILD and heart failure; one after humoral rejection after lung transplant due to ILD; one due to acute respiratory failure; one due to ILD.*

****One of the patients with bacterial pneumonia, after a 217-day long hospital stay.*

[a]*multiple: pneumocystis jirovecii pneumonia, clostridium difficile, influenza, and rotavirus;* [b]*osteomyelitis; cutaneous infection with staphylococcus aureus;* [c]*multiple: clostridium difficile, pyelonephritis, urosepsis;* [d]*acute kidney injury;* [e]*papillary edema;* [f]*osteonecrosis;* [g]*menometrorrhagia.*

discontinuation occurred in two cases (severe rotavirus enteritis, papillary edema). In both cases, JAKi therapy was later reinstated and well-tolerated. Four patients (4/28, 14.3%) died during JAKi treatment. Of all AEs, one (enteritis) occurred while the patient was hospitalized. Hospitalization was otherwise required in four cases (4/17, 23.5%): for gastroenteritis, two cases of pneumonia and recurring respiratory infections. Details on AEs are summarized in **Table 2**.

Evidence on Effectiveness and Safety for Aicardi Goutières Syndrome (AGS)

The systematic searches identified three case reports on AGS (full text $n = 2$, letters $n = 1$) (47–49). One additional letter reports preliminary results of an open-label single center study involving 35 patients with AGS (50). The publication is discussed in the Discussion section since no individual patient data was available.

Here, we report the available data on two pediatric patients and one adult. The median age of JAKi initiation was 11 years (1.5–22 years). The patients were treated for a mean duration of 28.3 months (18–43 months). A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. All patients (3/3, 100%) showed a partial response to therapy.

Data on AEs was available for only one patient (1/3, 33.3%) (48) who developed creatine kinase fluctuations, hypercholesterinemia, and hypertriglyceridemia, which weretransient and controlled by dietary management without the need for JAKi dose reduction or hospitalization. No other AEs were reported. Details on AEs are summarized in **Table 2**.

Evidence on Effectiveness and Safety for Other Type I Interferonopathies

Three case reports (51–53) (conference abstracts $n = 1$, full text $n = 2$) and two articles reporting results of the same compassionate use study (24, 33) regarding type I interferonopathies were identified.

A total of seven patients were treated. One patient was diagnosed with DNase II deficiency. For the rest either only "other type I interferonopathy" was reported as diagnosis ora novel mutation was described (**Table 1**). Median age of JAKi initiation was 4 years (1 month −17 years, reportedfor 3 patients). Five patients (5/7, 71.4%) received baricitinib, and one patient each received tofacitinib or baricitinib (1/7, 14.3% each). Mean treatment duration was 33.4 months. GC were used in five patients (5/7, 71.4%), one patient received concomitant cyclosporine therapy and one patient received a combination of mepacrine and hydroxychloroquine. A summaryof baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A complete response was achieved by only one patient (1/7, 14.3%) under combination of baricitinib and cyclosporine A (5 mg/kg/d). Four patients (4/7, 57.1%) had a partial response and two (2/7, 28.6%) showed no response totherapy. For three patients (3/5, 60%) GC dose reduction was possible and one (1/5, 20%) successfully tapered GC.

Data on AEs was available for five patients (5/7, 71.4%),as follows: UTI (2/5, 40%), BK viruria (3/5, 60%), BK viremia (1/5, 20%). In neither case were dose reduction ortherapy discontinuation reported. One case of herpes zoster (1/5, 20%) required intermittent JAKi dose reduction. Of allAEs, hospitalization was required in two cases (2/9, 22.2%):in one patient after multiple infectious events (clostridium difficile infection, pyelonephritis, urosepsis) and in one case of osteonecrosis. The latter discontinued JAKi therapy after 5.1 months due to this AE. Details on AEs are summarized in **Table 2.**

Evidence on Effectiveness and Safety for Adult-Onset Still's Disease (AOSD)

For AOSD three case reports (54–56) and three case series (57–59) were identified (conference abstracts $n = 2$, letters to the editor $n = 2$, publications in full text $n = 2$).

A total of 26 patients were treated with a JAKi. Median age of JAKi initiation was 33 years (18–82 years). Most patients (18/26, 69.2%) were treated with tofacitinib, one patient (1/26,3.8%) received ruxolitinib, and the other patients (7/26, 26.9%) baricitinib. Mean treatment duration was 7.6 months (1–24months). Most patients (24/26, 92.3%) received GC either alone(7/26, 26.9%) or in combination with other disease modifying antirheumatic drugs (DMARDs) (17/26, 65.4%). Two patients had methotrexate (MTX) alone as supportive treatment (2/26, 7.7%). Mean GC dose at JAKi initiation was 37.3 mg prednisone equivalent per day. A summary of baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A complete response was seen in eleven patients (11/26, 42.3%), with the same number of patients showing a partial response (11/26, 42.3%). No response was seen in a minority of patients (4/26, 15.4%). GC dosage at the end of follow-up was reported for twenty-two patients (22/24, 91.7%). Mean GC dose was 13.3 mg prednisone equivalent per day. GC dose reduction was possible for most patients (18/22, 81.8% of reported cases) and completeGC tapering was achieved by three patients (3/21, 14.3% of reported cases).

Data on AEs was available for 24 patients (24/26, 92.3%)and were overall rare: pneumonia (3/24, 12.5%) and menometrorrhagia (1/24, 4.2%); the latter required therapydiscontinuation in one patient. One of the patients with bacterialpneumonia died after a 217-day long hospital stay. Otherwise noAEs required hospitalization. Details on AEs are summarized in **Table 2**.

Evidence on Effectiveness and Safety for Systemic Juvenile Idiopathic Arthritis (SJIA)

Two case reports (60, 61) and one case series (57) (publishedas conference abstracts $n = 1$, letters $n = 1$, in full text $n = 1$) were identified.

Four patients with sJIA were treated with a JAKi. Medianage at JAKi initiation was 9 years (4–13 years). Two patients received ruxolitinib (2/4, 50%), and one each received tofacitinibor baricitinib (1/4, 25% each). Mean treatment duration was 14.2 months (8–25 months). All received GC as supportive treatment. Two patients (2/4, 50%) received GC only alongJAKi, and two patients—in combination with non-steroidal anti-inflammatory drugs and two patients (2/4, 50%). Data on baseline characteristics, treatment and response are shown in **Supplementary Table 1**. **Two** patients showed a completeresponse to therapy (2/4, 50%) and for the other two (2/4, 50%) a partial response was reported. GC dose reduction was possible for three patients (3/4, 75%) and one (1/4, 25%) successfully tapered GC to discontinuation. Data on AEs was available for three patients (3/4, 75%), and none were reported (**Table 2**).

Evidence on Effectiveness and Safety for FMF

Two case series (62, 63) and one case report (64) (full text $n = 2$, letters $n = 1$) were identified.

A total of six patients with FMF were treated with a JAKi. Median age at JAKi initiation was 35.5 years (16–64 years). All patients were treated with tofacitinib 10 mg/d. Meantreatment duration was 4.5 months (2–12 months). One patientreceived no supportive treatment (1/6, 16.7%), one (1/6, 16.7%) received a combination of GC, colchicine, and sulfasalazine. Four patients (4/6, 66.7%) were prescribed colchicine. A summaryof baseline characteristics, treatment and response is shown in **Supplementary Table 1**. A complete response was shown by halfof the patients (3/6, 50%). The other three patients (3/6, 50%) developed no further flares, but acute phase reactants remainedelevated, thus only a partial response was achieved.

Data on AEs was available for four patients (4/6, 66.7%) withnone reported (**Table 2**).

Evidence on Effectiveness and Safety for Behçet's Syndrome

Only one publication on BS could be identified (65). Thirteen patients were treated with a JAKi. Median age at JAKi initiation was 42 years (22–73 years). All patients received tofacitinib10 mg/d. Patients were treated for a mean duration of 10.8 months (5–21 months). All but one patient received concomitant GC therapy (12/13, 92.3%). Tofacitinib was administeredas additional therapy to other drugs such as azathioprine, thalidomide, leflunomide, colchicine, salazosulfapyridin. A summary of baseline characteristics, treatment and response isshown in **Supplementary Table 1.**

According to the criteria used in this systematic review, most patients achieved a partial response (8/13, 61.5%). Five patients showed no response to therapy (5/13, 38.5%), of whomone patient's condition worsened (1/13, 7.7%) and tofacitinib was withdrawn after 9 months of treatment. Two cases of herpes zoster reactivation were observed, both of which ledto discontinuation of tofacitinib. No other AEs were reported (**Table 2**).

Evidence on Effectiveness and Safety for Other Syndromes

No articles regarding CAPS, TRAPS, PFAPA, PAPA or MKD could be identified.

DISCUSSION

To our knowledge, this is the first systematic review analyzing the safety and effectiveness of JAKi in AID. The overview ofthe available clinical evidence is based on observational studiessuch as case reports and case series. Effectiveness was evaluated based on clinical response, defined by the authors of this systematic review as complete, partial or no response depending on (complete) symptom resolution and/or normalization of laboratory parameters for inflammation. Furthermore, AEs were described.

Type I Interferonopathies

Most reports ($n = 25$) included in this systematic review investigated the use of JAKi for type I interferonopathies. Interferonopathies represent a group of rare monogenic AID, characterized by a disturbed control of interferon-mediatedimmune responses, especially of type I interferons. JAKi are potent inhibitors of the JAK-STAT pathway, involved in interferon signaling (66). Thus, the application of JAKi ininterferonopathies seems rational. In this analysis, reports on SAVI, CANDLE, AGS and other interferonopathies were included. Fifty-two patients (CANDLE $n = 14$, SAVI $n = 28$, AGS$n = 3$, other interferonopathies $n = 7$) could be identified. Overall promising results were seen: seven patients (7/52, 13.5%) showed a complete response to therapy, the majority (35/52, 67.3%) showed a partial and a minority (10/52, 19.2%) showed no treatment response.

For AGS, one publication (50) was identified but individual patient data was not available. This article reported preliminaryresults of an open-label single center study involving 35 patientswith molecularly confirmed AGS. This is to our knowledge the largest AGS cohort treated with JAKi. All patients received baricitinib. The authors report overall improvement of dailydiary scores within 1 month of therapy initiation. Neurological function was evaluated based on key developmental milestones,with 20 patients (20/35, 57.1%) meeting new milestones and12 (12/35, 34.3%) gaining two to seven new skills. In the three cases presented in this systematic review, neurological symptoms were leading in just one case (49) showing improvement under ruxolitinib. Regarding the safety profile of JAKi, in this AGScohort (50) only one case of BK viremia was described—a relatively frequent event in interferonopathy patients discussedhere (10/52, 19.2%).

Notably, amongst interferonopathy patients, JAKi was most efficient for CANDLE patients: complete remission was achievedby six patients (6/14, 42.6%). Additionally, a GC sparing effect inthis group is suggested by the available data, since seven patients (7/11, 63.6%) were able to discontinue GC and in four patients (4/11, 36.4%) GC dose reduction was possible.

One hypothesis for the difference in treatment outcomebetween interferonopathies is that the better treatment response is owed to a higher JAKi dosage. A direct comparison is difficult since mostly pediatric patients were treated and JAKi dosage was reported as mg per kilogram without documenting weight for each individual patient. Mean baricitinib and tofacitinib dosagesin CANDLE cases were 6.8 and 5 mg/d, respectively. Mean baricitinib doses for SAVI were 6 mg/d (reported for 6/7, 85.7%)up to a mean 8 mg/d in other interferonopathies. Most SAVI patients were treated with ruxolitinib at a mean dose 10.8 mg/d(reported for 13/18, 72.2% patients treated).

A head-to-head comparison of effectiveness is difficult due to (1) the small number of patients treated (2) the different choiceof JAKi and the respective dosage used and (3) partial missing individual data.

Regarding safety it should be mentioned that most infectious AEs in this analysis occurred in patients withtype I interferonopathies: seven cases of pneumonia (7/10, 70%), all UTIs (17/17, 100%) and all cases of BK viremia and viruria (10/10 and 4/4, respectively; 100%) (**Table 2**). The proportionof patients in this group who experienced any AE is also greatercompared to other groups: around 17% of AOSD patients (4/24,

16.7%), even less in BS patients (2/13, 15.4%) and none of the FMF and sJIA patients.

Of overall 59 AEs reported, 52 (88.1%) were due to infections(**Table 2**). In general JAKi show a heterogenous risk of infectiouscomplications. For example, a known class effect for JAKi isan elevated risk of herpes zoster (67–70). In one recent study, serious infections were more frequent with tofacitinib at a doseof 10 mg twice daily compared to TNF inhibition (71), which contradicts some available evidence pointing to a similar riskof serious infections under JAKi compared to other biological disease-modifying antirheumatic drugs (bDMARDs) (72, 73). The risk for opportunistic infections (herpes zoster, tuberculosis)under tofacitinib in this study was higher compared to a TNF- inhibitor, and even more so when tofacitinib dose was 10 mg compared to 5 mg. In this systematic review two cases of herpes infections occurred under tofacitinib and baricitinib each. One case occurred under ruxolitinib.

A controversially discussed adverse effect of JAKi arethromboembolic events. This risk has been shown to be elevatedrelative to TNF inhibitors, along with a clinically meaningfulrisk of serious heart-related AEs, cancers, blood clots and death in older patients with RA (71). However, several (meta-) analyses did not provide evidence supporting an increased risk of thromboembolism with JAKi (67, 74, 75). In this systematic review, thromboembolic events were not reported.

The discrepancy in the frequency of AEs in the differentdisease groups here could reflect the inconsistency in reportingof AEs, commented further below. It should be considered that for FMF, sJIA and Behçet's syndrome only a few reports were available for analysis. However, one reason for the higherincidence of infections amongst interferonopathy patients mightbe due to a dose dependent effect. All FMF and Behçet's syndromepatients, and most AOSD patients received a "standard dose"of tofacitinib (5 mg/d) or baricitinib (4 mg/d). As mentioned above, JAKi doses varied amongst interferonopathy patients. Nevertheless, baricitinib was often administered at doses higherthan 4 mg/d—up to a mean 6.8 mg/d in CANDLE patients and amean 6 mg/d for SAVI patients. Notably, most interferonopathypatients were pediatric patients, suggesting a higher dose pro kilogram body weight.

Another hypothesis is that interferonopathy patients generally have a higher risk for infections. While infections can be considered potential triggers for disease onset or flares (5),a predisposition for infections in interferonopathy patients is currently not proven. However, for other diseases witha prominent interferon signature, such as systemic lupus erythematosus (SLE) and dermatomyositis, a susceptibility for infections has been reported (76, 77). Thus, a possible explanation for the elevated incidence of infectious AEs in this subgroup could be an intrinsically dysfunctional immune systemleaving patients exposed to an increased risk of infection.

Other AID

Part of the systematic database searches about JAKi for treating monogenic AID were CAPS, TRAPS MKD and FMF. Of those, publications were identified only for FMF. In FMF patients, JAKiresulted in a complete response in half of the patients and a partial response for the rest (3/6, 50% each). Eleven AOSD patients hada complete response and the same number of patients a partialresponse (11/26, 42.3% each). Two sJIA patients completely responded to JAKi therapy (2/4, 50%) and for the other two (2/4, 50%) a partial response was reported. Amongst BS a partialresponse was achieved by most (8/13, 61.5%), and five (5/13, 38.5%) showed no response to therapy.

Although JAKi did not lead to complete remission in all AOSD patients, the majority of them were able to taper orwithdraw GC—used as supportive treatment in most patients (24/26, 92.3%). Dosage of GC at last follow up was reportedfor 22 patients. Mean GC dose at JAKi initiation was 37.3 mg prednisone equivalent per day, and 13.3 mg/d at last follow- up. This highlights the potential of JAKi as GC sparing drugin AOSD, especially in patients with articular phenotype. The majority of AOSD patients presented with arthritis (20/26, 76.9%), of whom most showed a complete or a partial response (8/20, 40% for each group). Additionally, all FMF patients included in this analysis had active arthritis. All of them showed clinical improvement under JAKi. Therefore, it can be hypothesized that JAKis are especially beneficial for patients with active arthritis.

Limitations and Considerations for the Future

Due to the rare nature of AID and the relatively recent availability of JAKi, there are currently no RCTs available, and most publications included were case reports or series. Therefore, conducting a risk of bias assessment was not possible. Many authors were contacted to complete missing data, however in some instances despite our best effort complete information could not be obtained. In the analyzed publications a relatively low systematization in conduct and reporting was observed, which in part resulted in limited details on individual patient characteristics at baseline and post JAKi treatment. In orderto include as much information as possible on the topic, congress abstracts were also included in the analysis. Abstracts are generally considered to potentially lower the overall evidence level in a systematic review. Therefore, only abstracts providingsufficient clinical data were included in the final analysis (78).

To present the results of this systematic review, a classification based on clinical symptoms and laboratory parameters wasperformed. Accordingly, treatment response was classified as complete, partial or none. Although this approach has not beenvalidated, it has been previously used by other investigators (57–59) and serves as base for objectifying and summarizing the available evidence. The body of evidence found did not suffice for quantitative analysis due to its heterogeneity. Instead, an extensive narrative synthesis was conducted.

To this date, no universal criteria for reporting outcomesin AID patients exist. To improve and standardize reportingon treatment strategies in AID we suggest the following type of reporting (**Table 3**). clinical symptoms, inflammatory parameters, concomitant diseases, previous therapies; for the use of JAKi—exact dose, as well as information on any supportive treatment, including dosage; for a precise evaluation therapeutic

TABLE 3 | Suggestions for future reporting on treatment outcome.

Pre-JAKi	JAKi	Post-JAKi
Clinical		Clinical
Clinical symptoms	Dosage	Change in clinical symptoms
Disease score (if available)	Supportive treatment (including dosage)	Change in disease score (if available)
Concomitant diseases drugs (e.g. GC)	Treatment duration	Change in dosage of supportive
Previous therapies		Adverse events
Inflammatory markers		Inflammatory markers
CRP		CRP
ESR		ESR
others (complete blood count, ferritin, IFN gene expression, if applicable)		others (complete blood count, ferritin,IFN gene expression, if applicable)

response statements on dynamics of clinical symptoms, as well as inflammatory parameters should be noted. AEs especially infections should be closely monitored. In the publications included in this systematic review reports on AEs were sometimes insufficient—those were not documented in around 15% of cases (83/101, 82.2%).

Furthermore, disease (specific) activity scores and response criteria to compare AID studies are urgently needed. For monogenetic inflammasomopathies (FMF, CAPS, TRAPS, MKD) the Auto-Inflammatory Diseases Activity Index (AIDAI) (79) is a validated score but was only reported in one study concerning JAKi use in FMF (63). An EULAR task forceis currently preparing specific criteria for AOSD which should be applied for future reporting (80). Regarding typeI interferonopathies Frémond, M. et al., 2016 suggested a disease activity score for SAVI patients: the Disease Activity Rating Scale of TMEM173-mutated patients (42). This score for SAVI needs to be validated and scores for the otherinterferonopathies need to be developed. Overall, given their rare nature, a considerable number of AID patients treated with a JAKi (101) could be identified. The available evidence showed most patients did respond to JAKi therapy. This review was conducted to summarize the available evidence on new therapeutic possibilities for AID patients and to highlight the need for well-designed clinical trials investigating JAKi in AID.Currently, one phase 3 clinical trial investigating baricitinib inCANDLE, SAVI and AGS is being conducted (81). Research is actively underway in the direction of sJIA with two ongoing phase 3 randomized double-blind, placebo-controlled studies onbaricitinib and tofacitinib (82, 83).

CONCLUSION

This systematic review provides results from observational studies showing first pieces of evidence on treatment effectivenessof JAKi for AID. To validate these results and confirm efficacy and safety of JAKi for specific AID, clinical trials need tobe initiated.

DATA AVAILABILITY STATEMENT

The original contributions presented in the study are includedin the article/**Supplementary Material**, further inquiries can be directed to the corresponding author/s.

AUTHOR CONTRIBUTIONS

ZB, GB, and MK: systematic review concept and design.ZB, NR, and MK: systematic review protocol. ZB: database search. ZB and AP: study selection. MK: arbiter during publications screening. ZB: data extraction and synthesis. ZB and MK: manuscript drafting. ZB, MK, NR, GB, and AP: manuscript revision and final review. All authors approved the final version.

SUPPLEMENTARY MATERIAL

The Supplementary Material for this article can be found online at: https://www.frontiersin.org/articles/10.3389/fmed.2022.930071/full#supplementary-material

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Komplette Publikationsliste

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