



REVIEW

Scoping Review on the Use of Drugs Targeting JAK/STAT Pathway in Atopic Dermatitis, Vitiligo, and Alopecia Areata

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ABSTRACT

Introduction: The JAK/STAT signaling pathway is involved in the immune-mediated inflammatory skin diseases atopic dermatitis (AD), vitiligo, and alopecia areata (AA), and represents a potential target when developing treatments. So far, no drugs targeting this pathway have been approved for the treatment of dermatological diseases. We reviewed the use of drugs

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blocking the JAK/STAT pathway in the aforementioned diseases.

Methods: An a priori protocol was published. We used Joanna Briggs Institute Reviewer's Manual methodology to conduct the review and PRISMA Extension for Scoping Review (PRISMA-ScR) to report results. MEDLINE, EMBASE, CINAHL, Scopus, and Web of Science databases were searched in a three-step approach on April 2019 by two researchers.

Results: Ninety-six mainly multicenter observational studies were included (66, 10, and 20 studies on AA, vitiligo, and AD, respectively). Tofacitinib and ruxolitinib were mainly used for the three diseases, and also upadacitinib, abrocitinib, baricitinib, cerdulatinib, delgocitinib, gusacitinib for AD, and baricitinib, PF-06700841, and PF-06651600 for AA. All patients with AD improved, whereas patients with vitiligo and patients with AA showed varied responses, including unresponsive cases. The safety profiles were similar for all drugs and diseases, mainly comprising mild or no adverse events.

Conclusions: Evidence on the efficacy and safety of drugs targeting the JAK/STAT pathway for the treatment of patients with AD, vitiligo, or AA is increasing but is still of low quality.

Keywords: Alopecia areata; Atopic dermatitis; Baricitinib; Cerdulatinib; Immune-mediated inflammatory skin diseases; JAK/STAT

pathway; Ruxolitinib; Tofacitinib;
Upadacitinib; Vitiligo

INTRODUCTION

Immune-mediated inflammatory skin diseases are a group of frequently associated disorders comprising atopic dermatitis (AD), vitiligo, and alopecia areata (AA), among others. AD is a chronic inflammatory skin disease associated with skin barrier dysfunction, intense pruritus, and eczematous skin lesions. Its estimated prevalence in industrialized countries is 15–30% in the pediatric population and 2–10% in the adult group [1]. Vitiligo is a chronic autoimmune disorder characterized by cutaneous depigmentation as a result of the destruction of melanocytes via cell-mediated immunity, affecting 1–2% of the population worldwide including children and adults [2]. AA is a multifactorial autoimmune disease in which an immune-mediated destruction of hair follicles in conjunction with genetic predisposition lead to non-scarring hair loss, typified by alopecic patches that can encompass the entire scalp in alopecia totalis or body in alopecia universalis [3]. It is one of the most prevalent autoimmune diseases with approximately 2% lifetime risk [4, 5].

These three diseases cause significant impairment in the quality of life of the patient and marked psychological distress derived from their associated symptoms and the stigma related to a highly visible skin condition [6–8]. This profound impact is not completely avoidable because the currently existing therapies are limited in efficacy and not exempt from undesirable side effects, which is the reason behind performing further research.

Since multiple molecules are involved in their pathogenesis, further knowledge of molecular cell biology has permitted the design of new drugs directed against key targets in signaling pathway regulation. In this sense, the Janus kinases (JAKs) and signal transducer and activator of transcription (STAT) proteins (JAK/STAT) pathway is one of a handful of pleiotropic routes used to transduce multiple extracellular signals involved in cell proliferation,

differentiation, migration, and apoptosis [9]. The JAK pathways are believed to play an important role in inflammatory processes as they are involved in signaling for over 50 cytokines and growth factors, many of which drive immune-mediated conditions.

The JAK family is constituted by four types of cytoplasmic tyrosine kinases: JAK1, JAK2, JAK3, and TYK2 [10]. STAT, of which there are seven different subtypes (STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6), is the other fundamental component of the cascade [11]. After being phosphorylated by JAK, STAT translocates to the nucleus to induce the transcription of specific genes (Fig. S1 of Supplementary Material). Alterations in the JAK/STAT pathway have been related to the pathophysiology of AD, vitiligo, and AA. In fact, some molecules, such as interleukins (IL)-2 and its family, IL-23, interferon alpha [12], and IL-17 [13], have demonstrated their importance in the development of dermatological diseases by direct or indirect regulation of this pathway. Therefore, drugs that act on this pathway [14] by selectively inhibiting one (filgotinib, JAK1; pacritinib, JAK2; decernotinib, JAK3) or more than one (tofacitinib, JAK1 and JAK3; ruxolitinib, baricitinib, JAK1 and JAK2) JAK protein [15] are promising for the treatment of the aforementioned diseases [14] (Table S7 of Supplementary Material).

So far, no JAK/STAT inhibitors have been approved for the treatment of dermatological diseases, although some of them (ruxolitinib and tofacitinib) are used in other illnesses, such as myelofibrosis and rheumatoid arthritis [16, 17]. However, the off-label use of these drugs showed promising results in the treatment of different skin diseases, including AA, AD, and vitiligo. Broadening our knowledge on the efficacy and safety profiles of these drugs and their application in dermatological diseases is essential to establish their risk–benefit balance.

A scoping review is a form of scientific methodology that addresses an exploratory research question, with the aim of mapping key concepts and gaps related to a defined area or field [18]. The development of JAK inhibitors for the treatment of AA, AD, and vitiligo is still in

its early stages. In order to avoid the extensive efforts that would be needed to conduct studies aimed at answering specific questions, we considered it necessary to review the literature available to date. Therefore, we performed a scoping review to broadly summarize all the available evidence presented to date on the use of inhibitors of the JAK/STAT pathway in the treatment of AA, AD, and vitiligo diseases.

METHODS

Protocol and Registration

We conducted this scoping review in accordance with the recently published a priori protocol [19]. Methodology to conduct scoping reviews by the Joanna Briggs Institute was followed [20] and results were presented using the recent Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Reviews (PRISMA-ScR) [21].

Literature Search and Eligibility Criteria

Strategies for literature search and eligibility criteria are broadly described in the Supplementary Methods (Supplementary Material).

Data Chart

The relevant information for this review was extracted and summarized in a data chart developed by two reviewers. Characteristics of the studies, including information about author(s), year of publication, country, study design, registration, conflict of interest (COI), and funding, were displayed in separate tables for AA, AD, and vitiligo. Epidemiological aspects of the studies, including a classification based on the type (experimental or observational) and sub-type of study, study population, sample size, as well as an evaluation of the efficacy and safety of drugs for each disease (intervention type, details of comparators, duration of the intervention, dosage, outcomes, and adverse events) were collected and displayed in tables. Finally, a table linking randomized clinical trial (RCT)

protocols and the subsequently published articles was also created.

Report of Results

Results of the comprehensive search were presented in a PRISMA flow diagram. We organized the extracted data in several categories: indications, mechanism of action, efficacy, and safety and provided a clear explanation for each category. Finally, the results of the scoping review were presented in both diagrammatic and tabular forms, and in a descriptive format, accompanied by a narrative summary of the relation between the results and the review objective and question(s).

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any studies with human participants or animals performed by any of the authors; thus, no ethical approval from institutional committees was required.

Protocol versus Overview

Our planned search strategy published in *BMJ Open* was compared with the final reported review methods. No differences were found.

RESULTS

From 2197 articles (EMBASE + MEDLINE 1108; EMBASE 1048; MEDLINE 41) regarding the use of JAK/STAT-targeting drugs in dermatological diseases, after filtering duplicates and selecting studies according to title, abstract, and keywords, 116 studies met the criteria for full-text review (Fig. 1). Of these, 95 articles fulfilled the inclusion criteria and one article was included after reviewing the references of those studies. Thus, 96 studies, which included 66, 20, and 10 reports describing AA, AD, and vitiligo, respectively, were finally analyzed in the scoping review. A reference list of all articles with reasons for inclusion and exclusion is presented in Tables S2 and S3 of Supplementary Material.

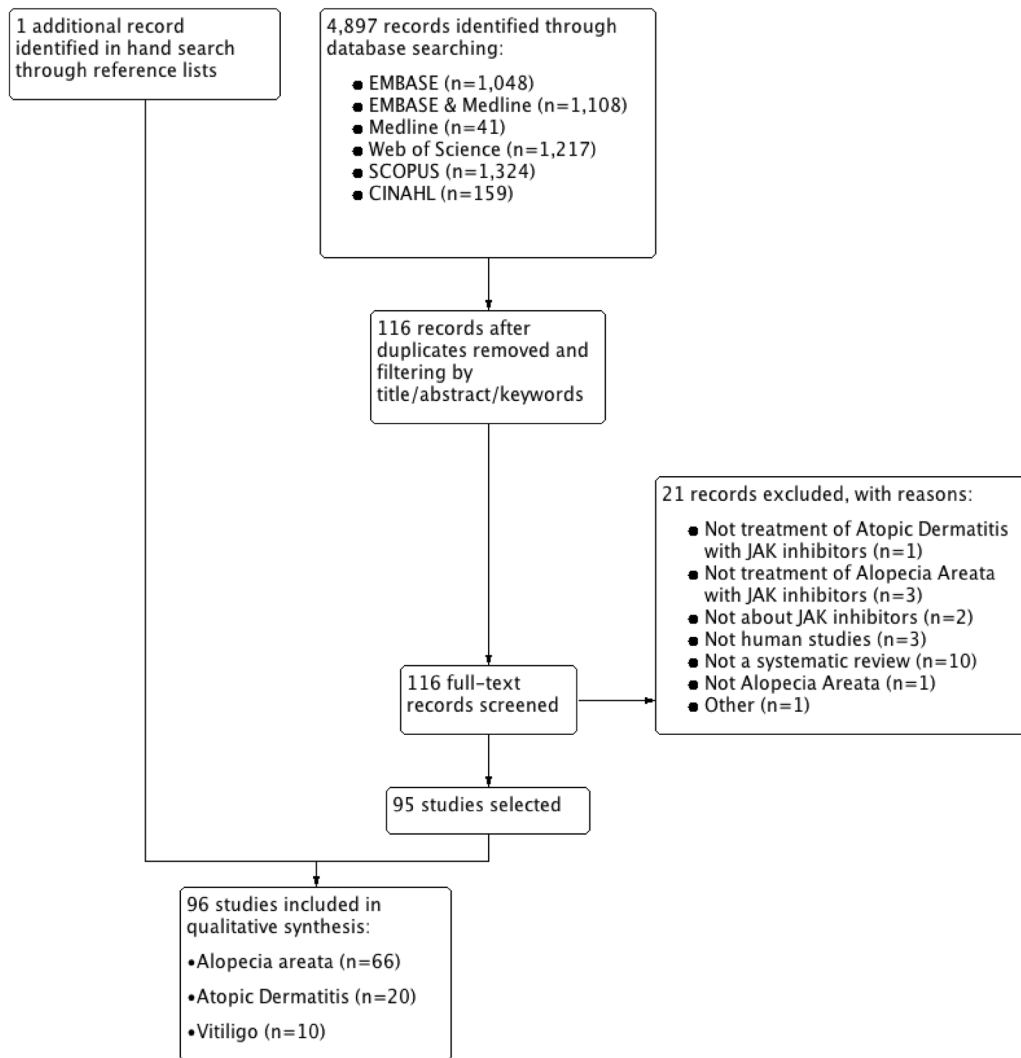


Fig. 1 PRISMA flow diagram

Mapping Studies on Use of JAK Inhibitors

Atopic Dermatitis

Twenty studies [22–41] comprising 1851 patients with AD were published from 2015 to 2019 as full-text publications of abstracts presented at congresses ($n = 11$) or scientific manuscripts ($n = 9$) (Tables S4 and S8 of Supplementary Material). Seven studies (35%) previously registered an a priori protocol in a public registry. Sixteen (80%) were multicenter studies involving up to 38 different institutions. The average number of authors and affiliations

per article was 7 (range 3–18) and 6 (range 1–38), respectively. Sixteen articles (80%) had at least one author who was working for a pharmaceutical company, with an average of five authors per article (range 0–16). Eight studies (40%) declared that one or more authors had conflicts of interest (CoIs), while another article (5%) denied any CoIs and 11 papers did not mention CoI (55%). Disclosures related to the funding sources were detailed only in seven articles (35%), including public sources ($n = 1$), pharmaceutical sources ($n = 5$), or none ($n = 1$).

Vitiligo

Ten studies [42–51] comprising 62 patients with vitiligo were published between October 2015 and June 2018 as full manuscripts ($n = 7$), full-text publications of abstracts presented at congresses ($n = 2$), or letters ($n = 1$) (Tables S5 and S8 of Supplementary Material). Only three studies (30%) had an a priori protocol. Six (60%) were multicenter studies with up to four centers participating. The average number of authors and affiliations per article was 5 (range 2–13) and 2 (range 1–4), respectively. Authors from pharmaceutical industries were involved in three studies with an average number of one author (range 1–2). Three studies (30%) declared the existence of an author's CoI, five articles (50%) declared having no CoI, and in another two (20%) this information was not available. Funding sources were described in five articles (50%) and were divided into public sources ($n = 3$), both public and pharmaceutical sources ($n = 1$), or none ($n = 1$).

Alopecia Areata

Sixty-six studies [49, 50, 52–114] comprising 950 patients with AA were published between May 2013 and May 2019 as full papers ($n = 39$), letters ($n = 14$), or full-text publications of abstracts presented at congresses ($n = 11$) (Tables S6 and S8 of Supplementary Material). Of those, 16 studies (24.2%) had previously published or registered an a priori protocol. The majority of studies were performed in the USA ($n = 41$) and 37 studies (56%) were multicenter involving up to five institutions. The number of authors per article ranged from 1 to 15, with an average of 4. Only 17 studies declared CoIs among their authors, whereas 29 studies stated not to have any, and 20 articles did not make any reference to this topic. Information on funding sources was available in 32 manuscripts, of which 15 were funded by public sources, one by academic and pharmaceutical industry, and 16 did not receive any funding.

Evidence of Efficacy and Safety of Treatment with JAK Inhibitors

Atopic Dermatitis

Twenty studies on the use of JAK inhibitors for the treatment of AD were identified, four of

which followed an observational design (two case reports and two case series) and 16 followed an experimental design (three phase I and 13 phase II RCTs) (Table 1). The duration of observational studies ranged from 6 to 10 months. The phase I RCT study was performed for 7 days and phase II RCTs lasted for 4–16 weeks. The reviewed articles explored the efficacy and safety of a wide variety of drugs such as tofacitinib (three systemic, three topical), upadacitinib (five systemic), ruxolitinib (three topical), abrocitinib (two systemic), gusacitinib (one systemic), delgocitinib (one topical), baricitinib (one systemic), and cerdulatinib (one topical). Efficacy outcomes were assessed using several validated scales, such as Eczema Area and Severity Index (EASI), pruritus Numerical Rating Scale (NRS) score, Investigator's Global Assessment (IGA), body surface area (BSA), Severity Scoring of Atopic Dermatitis Index (SCORAD), or Patient-Oriented Eczema Measure (POEM).

Significant improvement across all efficacy endpoints was evidenced in both experimental and observational studies. Furthermore, some studies evaluated relapse rate after a treatment discontinuation. Most studies did not report adverse events. Where they were reported, the majority were mild cases of upper respiratory tract infections, nasopharyngitis, AD exacerbation, erysipelas, headache, nausea, diarrhea, white cell count decrease (neutropenia, lymphopenia), or mild hypertension. There were four reports of severe adverse events: herpes zoster-associated encephalitis, appendicitis, pericoronitis, and skin infection.

Vitiligo

We identified ten studies about the use of JAK inhibitor drugs in vitiligo therapy. Seven of them were observational (four case reports, three case series), whereas three were open-label experimental studies (Table 2). Study length ranged from 3 to 10 months for observational studies and from 5 to 13 months for experimental studies. Regarding drug and administration route, seven articles were about tofacitinib (three systemic, one topical, three systemic/topical) and three were about ruxolitinib (two topical, one systemic). Seven studies

Table 1 Characteristics of primary clinical studies on atopic dermatitis

Study [references]	Type	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
1 [22]	RCT phase IIb	Upadacitinib	7.5/15/30 mg PO	Systemic	16	167	At week 16 EASI score Pruritus NRS score EASI-75	EASI: 39.4%/61.7%/74.4% for UPA vs 23.0% placebo NRS: 39.6%/48.0%/68.9% UPA vs 9.7% placebo EASI-75: 28.6%/52.4%/69.0% UPA vs 9.8% placebo	Mild: Upper respiratory tract infection, AD exacerbation Severe: appendicitis, pericoronitis, skin infection (all of them $n = 1$)
2 [23]	Case report	Tofacitinib	5 mg BID PO	Systemic	40	1	NRS score	NRS score changed from 8/10 to 3/10	None
3 [24]	RCT phase II	Upadacitinib	7.5/15/30 mg QD PO	Systemic	16	163	At week 16 SCORAD POEM ≥ 4 improvement in NRS	SCORAD: 33%/47%/60% UPA vs 12% placebo POEM: 5.5/8.6/12.3 UPA vs 1.6 placebo NRS: 24%/59%/53% UPA vs 6% placebo	Upper respiratory tract infection, AD exacerbation
4 [25]	RCT phase I	Tofacitinib	0.03%; 0.1%; 0.3%; 1%; 3%	Topical	1	66	EASI score Pruritus NRS score	Clear and rapid improvement	White blood cell count decreased ($n = 1$ with 3% tofacitinib) Erysipela ($n = 1$ with 1% tofacitinib) AD exacerbation ($n = 1$ with 1% and $n = 1$ with 3%)
5 [26]	Case series	Ruxolitinib	NA	NA	NA	4	Clinical endpoints	Remarkable improvement	–
6 [27]	RCT phase II	Cerdulatinib	0.25%, 0.5%, 1%, or 3%	Topical	4	327	EASI score Pruritus NRS score IGA score BSA	All doses had greater efficacy than vehicle in all studied efficacy parameters. Rapid significant pruritus NRS score reduction	Mild
7 [28]	Case report	Tofacitinib	5 mg BID PO	Systemic	24	1	EASI score	EASI = 0 (complete remission) within 3 months	Upper respiratory tract infection Diarrhea
8 [29]	RCT phase IIa	Tofacitinib	2%	Topical	4	69	EASI score Pruritus NRS score IGA score BSA	Significant improvements vs vehicle across all efficacy endpoints	Mild and infrequent
9 [30]	Case series	Tofacitinib	5 mg/day or BID PO	Systemic	29	6	SCORAD index	Increase in SCORAD for all patients, maintained during follow-up period	None

Table 1 continued

Study [references]	Type	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
10 [31]	RCT phase IIb	Ruxolitinib	1.5% QD; 1.5% BID	Topical	8	65	Serum proteomic changes from baseline	NA	Suspected herpes zoster-associated encephalitis during oral treatment with tofacitinib in alopecia universalis
11 [32]	RCT phase II	Upadacitinib	7.5 mg/15 mg/30 mg QD PO vs placebo	Systemic	16	167	EASI score Pruritus NRS score Histological changes	NA Mean % improvements in EASI (39.4%, 61.7%, 74.4% vs 2.3% placebo) and pruritus NRS (39.6%, 48%, 68.9% vs 9.7% placebo) Lesional and non-lesional biopsies from 50 patients: reduction of epidermal hyperplasia and number of dendritic cells, associated with clinical improvements, in upadacitinib 15 mg and 30 mg	NA
12 [33]	RCT phase II	Baricitinib	2/4 mg QD vs placebo PO	Systemic	16	124	EASI-75 Pruritus NRS score SCORAD IGA DLQI POEM	Achievement of EASI-50 (61% 4 mg, 37% placebo) was significant as early as week 4, although it was not significant for 2 mg vs placebo EASI reduction at week 16: 65% for 2 mg and 4 mg vs 46% for placebo Significant improvement in pruritus and sleep loss, as well as HRQoL measures	Adverse events were reported in 24 (49%) placebo, 17 (46%) baricitinib 2 mg, and 27 (71%) baricitinib 4 mg cases Placebo: Lymphopenia (<i>n</i> = 3) and eczema Baricitinib 2 mg: neutropenia (<i>n</i> = 1)
13 [34]	RCT phase Ib	Gusacitinib	20/40/80 mg PO vs placebo	Systemic	4	36	EASI-50 EASI-75 BSA Pruritus NRS score IGA POEM	EASI-50 (20%, 100%, 83% vs 22% placebo) EASI-75 (0%, 71%, 33% vs 22% placebo) Change in pruritus NRS score (− 1.3 ± 2.1, − 3.1 ± 2.7, − 4.7 ± 2.1 vs − 1.6 ± 1.8 placebo)	Baricitinib 4 mg: neutropenia (<i>n</i> = 5), white cell count decreases (<i>n</i> = 2), abnormal lymphocyte count, headache, eczema, benign polyp of the large intestine (<i>n</i> = 1) Adverse events were mild and similar across all groups, including headache, nausea, diarrhea, nasopharyngitis, back pain, mild hypertension, and low lymphocyte levels

Table 1 continued

Study [references]	Type	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
14 [35]	RCT phase II	Upadacitinib	7.5/15/30 mg QD PO	Systemic	16	36	EASI score Pruritus NRS score AEC Serum IgE	Mean percentage EASI reduction at week 16: 39.4%, 61.7%, 74.4% vs 23% placebo, all of them significant Mean percentage pruritus NRS reduction at week 16: 39.6%, 48%, 68.9% vs 9.7% placebo, all significant Week 16 AEC significantly lowered with 15 mg and 30 mg vs placebo, as early as week 2 (these changes strongly correlated with EASI) Changes in IgE levels were <i>not</i> significant	NA
15 [36]	RCT phase II	Ruxolitinib	0.15% QD; 0.5% QD; 1.5% QD; 1.5% QD; 1.5% BID	Topical	8	111	EASI score TARC/CCLL17 levels AEC Serum IgE	Significant reduction of TARC/CCLL17 levels with ruxolitinib 1.5% BID Total serum IgE levels reduction with ruxolitinib 1.5% QD or BID These changes did not predict ruxolitinib treatment response (percentage reductions in EASI)	NA
16 [37]	RCT phase IIb	Upadacitinib	7.5/15/30 mg QD PO	Systemic	16	166	SCORAD Pruritus NRS score POEM	Mean improvement in SCORAD itch VAS: 3.3, 3.4, 4.7 vs 1.2 placebo	NA
17 [38]	RCT phase IIa	Tofacitinib	2%	Topical	4	67	Pharmacokinetics	NA	For adult and pediatric patients with > 70% BSA, concentrations could exceed 12.4 ng/mL for ointment application rates > 2 mg/cm ² Additional safety monitoring requirements may have to be considered
18 [39]	RCT phase Ib	Cerdulatinib	0.4% BID	Topical	2	8	EASI Histological, immune, and gene expression analyses	Significant clinical improvements (EASI improvement 65%), reversal of epidermal hyperplasia, reduced immune cell infiltration and AD-related inflammatory gene expression	All treatment-related adverse events were grade 1 (34/35 events) or grade 2 (1/35 events), with no safety-related withdrawals

Table 1 continued

Study [references]	Type	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
19 [40]	RCT phase IIb	Abrocitinib	10/30/100/200 mg QD PO	Systemic	12	267	EASI-50/75/90 Pruritus NRS score SCORAD	Significant changes in SCORAD (40.7% for 100 mg), in EASI (47.4% for 100 mg), and in pruritus NRS (25.4% for 200 mg; 20.7% for 100 mg) EASI-50 achievement: 78.5% for 200 mg, 55.3% for 100 mg, and 27.4% for placebo EASI-75 achievement: 63.7% for 200 mg, 41.6% for 100 mg, and 15.6% for placebo EASI-90 achievement: 51.6% for 200 mg, 26.8% for 100 mg, and 10.3% for placebo 200 mg significantly improved ALL outcomes. 100 mg only pruritus NRS, DLQI, and POEM	Adverse events and laboratory anomalies were found in 184 patients (68.9%). Serious AE were observed in 9 patients (3.4%). No deaths were registered
20 [41]	RCT phase IIb	Abrocitinib	10/30/100/200 mg QD PO	Systemic	12	267	Pruritus NRS score PtGA POEM DLQI	200 mg significantly improved ALL outcomes. 100 mg only pruritus NRS, DLQI, and POEM	NA

AEC absolute eosinophil count, *SCORAD* Severity Scoring of Atopic Dermatitis Index, *EASI* Eczema Area and Severity Index, *NRS* Numerical Rating Scale, *EASI-75* $\geq 75\%$ reduction of basal EASI value, *POEM* Patient Oriented Eczema Measure, *PGA* Physician's Global Assessment, *PGA* Patient's Global Assessment, *HRQL* Health-Related Quality of Life, *IGA* Investigator's Global Assessment, *VAS* visual analogue scale, *QD* once a day, *BID* twice a day, *PO* per os (oral), *DLQI* Dermatology Life Quality Index, *BSA* body surface area, *NA* not acquired

Table 2 Characteristics of primary clinical studies on vitiligo

Article	Type, subtype of study	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
1 [42]	Open label	Ruxolitinib	1.5% BID	Topical	52	8	VASI score PGA score DLQI score BSA	5/8 patients responded (facial VASI—mean improvement 92% ± 7.1 [n = 4], VASI—mean improvement: non-acral upper extremities 12.6% ± 19.5 [n = 3], trunk 16.7% ± 16.7 [n = 2]) Not statistically significant: PGA, DLQI, and BSA	Minor (erythema [n = 3], transient acne [n = 2])
2 [43]	Open label	Tofacitinib	2.5 mg BID PO	Systemic	NA	25	Repigmentation	NA	NA
3 [44]	Case series	Tofacitinib	5 mg BID PO	Systemic	12–18	2	Repigmentation	Facial repigmentation: nearly complete in case #1; 75% case #2 Body repigmentation: > 75% in case #1, 0% case #2	None
4 [45]	Case series	Tofacitinib	Topical 1.5%; 5 mg BID PO	Topical	12	2	Repigmentation	Facial and body repigmentation, preferential in sun-exposed areas	NA

Table 2 continued

Article	Type, subtype of study	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
5 [46]	Case series	Tofacitinib	5–10 mg BID PO	Systemic	40	10	Repigmentation	5/10 patients responded (BSA 5.4% decrease, 3 of them only in sun-exposed areas)	Upper respiratory tract infection [n = 2], weight gain [n = 1], arthralgia [n = 1], mild lipid elevation [n = 4] NA
6 [47]	Case report	Tofacitinib	Topical	Topical	NA	1	NA	NA	NA
7 [48]	Open label	Ruxolitinib	1.5% BID	Topical	20	11	VASI score Repigmentation	8/11 patients responded (VASI 23% mean improvement, facial repigmentation [n = 8], periocular repigmentation [n = 2], non-acral upper extremities repigmentation [n = 3])	Erythema [72%], transient acne [n = 2]
8 [49]	Case report	Tofacitinib	5 mg BID PO	Systemic	24	1	VASI score	Only marginal improvement (VASI from 4.68 at baseline to 3.95 at 5 months)	Upper respiratory tract infection and diarrhea
9 [50]	Case report	Ruxolitinib	20 mg BID PO	Systemic	20	1	Repigmentation	51% facial repigmentation, repigmentation on other areas	NA

Table 2 continued

Article Type, subtype of study	Drug	Dosage	Administration route	Period (weeks)	Number of patients	Outcomes	Efficacy	Safety
10 [51]	Tofacitinib	5 mg PO every other day; later, daily	Systemic	20	1	Repigmentation	Partial facial and upper extremities repigmentation, nearly complete in forehead and hands	None

BSA body surface area, *DLQI* Dermatology Life Quality Index, *PGA* Physician Global Assessment, *VASI* Vitiligo Area Severity Index, *QD* once a day, *BID* twice a day, *PO* per os (oral), *NA* not acquired

(five observational, two experimental) set the percentage change in repigmentation (or percentage decrease in BSA) as their primary endpoint. Out of 17 patients in whom facial repigmentation was specifically studied, 14 (82%) showed different degrees of response. Concerning body repigmentation, which was assessed in 27 patients, 13 (48%) of them had an improvement; meanwhile, five patients experienced preferential repigmentation in sun-exposed areas. Three studies (one observational, two experimental) considered the improvement in Vitiligo Area Scoring Index (VASI) score as their main goal. These studies found that from a total of 20 patients, 14 (70%) had some improvement in VASI score, although with varied degrees, and one patient only showed a marginal improvement. Overall, 14 out of 20 patients (70%) responded to ruxolitinib and 11 out of 16 (68%) to tofacitinib.

Adverse events, though infrequent and mild, included application-site irritation, folliculitis, hypertension, upper respiratory tract infections, herpes zoster infection, increased appetite, weight gain, or diarrhea.

Alopecia Areata

Sixty-six studies on drugs targeting the JAK/STAT pathway in AA were selected (Table 3). Most of them followed an observational design (30 case reports and 23 case series). There were also 13 experimental studies (7 open-label, 1 phase I, 5 phase II RCTs). Both observational and experimental studies lasted between 3 months and 3 years. Most manuscripts focused on the treatment with tofacitinib (41 systemic, 3 topical), ruxolitinib (9 systemic, 2 topical), or both tofacitinib vs ruxolitinib (4, both as topical and/or systemic). Two studies were found for baricitinib (systemic) and for both PF-06700841 and PF-06651600, two dual TYK2/JAK1 and JAK3/TYK2 family kinase inhibitors, respectively.

Efficacy outcomes were mainly measured by using Severity of Alopecia Tool (SALT) score in experimental studies, while the percentage of hair regrowth, at least 50% regrowth achievement, or HRQoL assessed by Skindex-16 scores were used to determine treatment efficacy in observational studies. Hair regrowth was

Table 3 Characteristics of primary clinical studies on alopecia areata

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
1 [52]	Case report	Tofacitinib	5 mg BID PO; later, 15 mg/day	Systemic	40	1	Hair regrowth	Near complete by 6 months, loss of regrown hair at 8 months	Herpes zoster
2 [53]	RCT phase II	Tofacitinib	5 mg to 10 mg BID PO	Systemic	72	12	≥ 50% regrowth SALT score	≥ 50% regrowth ($n = 8$), overall SALT improvement ($n = 11$)	Hypertension ($n = 1$)
3 [23]	Case report	Tofacitinib	5 mg BID PO	Systemic	40	1	Hair regrowth	Hair regrowth on all affected body parts	None
4 [54]	Case series	Tofacitinib	2%	Topical	–	11	SALT score	Average SALT reduction of 32.3%	Application-site irritation ($n = 1$)
5 [55]	Open label	Tofacitinib	2.5 mg QD PO, modified according to response	Systemic	24/72	200	% change in SALT score	Eleven out of 12 patients attained a global overall improvement in SALT score at the end of treatment with results ranging from 12.1% to 100% regrowth, with an average 56.8% regrowth	None
6 [56]	Case series	Tofacitinib	10 mg PO	Systemic	≥ 16	33	Nail improvement	Improvement in nail changes in 11/15 patients (73.3%)	NA
7 [57]	Case report	Ruxolitinib	20 mg BID PO	Systemic	48	1	Hair regrowth	Complete regrowth (beard) and partial (50%) regrowth (scalp), maintained after 1 year	NA
8 [58]	RCT phase II	Tofacitinib	5 mg BID PO	Systemic	12	30	HRQoL scale Skindex-16 scale	Significant improvement for all subjects	NA
9 [59]	Open label	Tofacitinib	2% BID	Topical	24	10	Hair regrowth SALT score	Hair regrowth in 3 patients (61%, 18%, 25% improvement in SALT score)	Skin irritation, folliculitis
10 [60]	Case series	Tofacitinib	5 mg QD or BID PO	Systemic	20	2	SALT score	Patient 1: SALT 100 to 15 (85% change); Patient 2: SALT 100 to 10 (90% change)	Increased appetite, weight gain
11 [61]	RCT phase I	Tofacitinib, Ruxolitinib	Tofacitinib 2% Ruxolitinib 1% Tofacitinib 5 mg PO	Topical/systemic	28	16	Hair regrowth Global photography IGA score PtGA	Partial regrowth ($n = 6$ with 2% T, $n = 5$ with 1% R, $n = 10$ with clobetasol propionate 0.05%, $n = 0$ with placebo)	None

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
12 [23]	Case report	Tofacitinib	5 mg BID PO	Systemic	24	1	Hair regrowth	Hair regrowth on scalp, beard, extremities, eyebrows, and eyelashes	Upper respiratory tract infections, diarrhea
13 [62]	Open label	Tofacitinib	5 mg BID PO 10 mg QD PO 20 mg QD PO	Systemic	30	32	SALT50	18/32 patients achieved SALT50	None
14 [63]	Case series	Ruxolitinib	5 mg BID to 30 mg QD	Systemic	56	2	Hair regrowth	Complete or nearly complete regrowth	None
15 [64]	Case series	Tofacitinib Ruxolitinib	Tofacitinib 1% Ruxolitinib 2%	Topical	NA	6	Hair regrowth	Partial regrowth in 4 patients (20%, 75%, 95%, 80%, respectively)	None
16 [65]	Case report	Ruxolitinib	0.6% nightly to BID	Topical	14	1	SALT score	Lack of improvement	None
17 [66]	Case report	Tofacitinib	5 mg PO	Systemic	20	1	Hair regrowth	Regrowth on scalp, eyebrows, and extremities	Increased appetite, weight gain
18 [67]	Case series	Tofacitinib	5 mg BID PO, increased by 5 mg per month	Systemic	36	13	Regrowth rate, response time	Rate 2–90%, mean (sd) 44.3% (31.9), median 50.5%. Response time 1–9 months, mean (sd) 4.2 (2.6) months	Morbiliform eruption, peripheral edema, lipid and liver abnormalities
19 [68]	Case report	Tofacitinib	NA	NA	40	1	Hair regrowth	Near complete regrowth, mild nail improvement	None
20 [69]	Case series	Tofacitinib	NA	NA	16–52	13	Hair regrowth	Regrowth range 2–90%, mean 44.3%, median 50.5%	NA
21 [70]	Case report	Tofacitinib	5 mg BID PO	Systemic	32	1	Hair regrowth	Complete regrowth in scalp	None
22 [71]	Case series	Tofacitinib	5 mg BID PO	Systemic	48	8	Hair regrowth	> 50% regrowth in scalp, eyebrows, eyelashes, and body hair (<i>n</i> = 8)	None
23 [72]	Case report	Tofacitinib	15 mg QD PO to 10 mg QD PO	Systemic	36	1	Hair regrowth	Significant regrowth in scalp and body. No regrowth in eyebrows and eyelashes	Herpes zoster
24 [73]	Case series	Tofacitinib	5 mg BID to 10 mg BID PO	Systemic	16–52	90	Hair regrowth	69/90 patients with response, 52/90 patients achieved > 50% change in SALT score	Upper respiratory (28.9%) and urinary tract (3.3%) infections, tonsillitis (2.2%), headache (14.4%), acne (7.8%), fatigue (6.7%), Leukopenia (<i>n</i> = 1), LDL-c increase (<i>n</i> = 15)

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
25 [74]	Case report	Tofacitinib	5 mg BID PO	Systemic	12	1	Hair regrowth	No hair regrowth	NA
26 [75]	Case report	Tofacitinib	5 mg BID to 10 mg am + 5 mg nightly	Systemic	24	1	Hair regrowth	Complete hair regrowth throughout the entire body	None
27 [76]	Case report	Tofacitinib	5 mg BID PO	Systemic	36	2	Hair regrowth	Partial regrowth on scalp, eyebrows, and axillae	NA
28 [77]	Case series	Tofacitinib	NA		26	13	Hair regrowth SALT score	Clinically significant regrowth ($n = 9$), mean SALT change 93%	Headache, upper respiratory infections, mild and transient increase in transaminases
29 [78]	RCT phase II	Tofacitinib	5 mg BID PO	Systemic	12	66	SALT score	36% were non-responders (< 5% SALT change), 32% intermediate responders (5–50% change), 32% strong responders (> 50% SALT change)	Grade I and grade II leukopenia
30 [79]	RCT phase II	Ruxolitinib	20 mg BID PO	Systemic	12–24	12	$\geq 50\%$ regrowth Changes in mean SALT score	9/12 $\geq 50\%$ regrowth 7/9 responders achieved > 95% regrowth. Mean SALT from 65.8% \pm 28.0% (baseline) to 7.3% \pm 13.5% (end of treatment)	Minor bacterial skin infections, upper respiratory or urinary infections, allergy, pneumonia, conjunctival hemorrhage, mild gastrointestinal symptoms. Lowered Hb ($n = 1$)
31 [80]	Case report	Tofacitinib	5 mg BID PO	Systemic	40	1	Hair regrowth Nail improvement	At 10 months, complete hair regrowth, nail growth, and nail plate normalization	None
32 [81]	Case report	Tofacitinib	5 mg BID PO	Systemic	16	1	Hair regrowth	Nearly complete scalp hair regrowth. Significant regrowth in eyebrows and eyelashes. Near-complete hair loss at treatment cessation	None
33 [82]	Case report	Tofacitinib	5 mg BID PO	Systemic	128	1	Hair regrowth	Beard, body, scalp, eyebrow, and eyelash hair regrowth	None
34 [83]	Case report	Ruxolitinib	5 mg BID to 20 mg/day PO	Systemic	24	1	Hair regrowth	Progressive regrowth until complete recovery. Relapse after 6 months of durable remission after treatment end	Mild anemia
35 [84]	Case report	Ruxolitinib	0.6% BID	Topical	12	1	Hair regrowth	Nearly complete eyebrow regrowth, 10% scalp hair regrowth	None

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
36 [85]	Case report	Ruxolitinib	5 mg BID to 15 mg/day PO	Systemic	24	3	Hair regrowth Nail improvement	Remission of nail changes ($n = 3$), hair regrowth ($n = 2$)	None
37 [49]	Case report	Ruxolitinib	20 mg BID PO	Systemic	20	1	Hair regrowth	85% scalp hair regrowth, maintained after 12 weeks from end of treatment	NA
38 [86]	Case report	Tofacitinib	5 mg BID PO	Systemic	16	1	Hair regrowth	Growth of short terminal pigmented hair after 3 months, which then completely disappeared within a month	NA
39 [87]	Case series	Tofacitinib	5 mg BID PO	Systemic	32	2	Hair regrowth	Beard, body, scalp, eyelash, and eyebrow hair regrowth in both patients	Viral infections, fatigue
40 [88]	Case report	Baricitinib	7 mg/day, later 7 mg am + 4 mg pm PO	Systemic	60	1	Hair regrowth	Complete scalp hair regrowth	NA
41 [89]	Case report	Ruxolitinib	15 mg BID PO	Systemic	40	1	Hair regrowth	Nearly complete regrowth durable at > 50 months	NA
42 [90]	Case series	Ruxolitinib	20 mg BID PO	Systemic	12–18	3	Hair regrowth	Nearly complete hair regrowth in all patients	NA
43 [91]	Case report	Tofacitinib	5 mg BID to 10 mg am + 5 mg nightly PO	Systemic	32	1	Hair regrowth	Complete hair regrowth at all body sites except extremities	None
44 [92]	Case series	Tofacitinib	5 to 10 mg BID PO	Systemic	12–18	6	Hair regrowth Photography SALT score Physical examination	Nearly complete regrowth. Mean SALT score went from 77.9% to 25.5%	Acneiform eruptions ($n = 2$)
45 [93]	RCT phase II	PF-06651600, PF-06700841	PF-06651600: 200 mg QD during induction and 50 mg QD during maintenance PF-06700841: 60 mg QD during induction and 30 mg QD during maintenance	Systemic	24	46	To evaluate changes in lesional scalp biomarkers	Gene-level changes (PF-06651600 and PF-06700841, respectively): 62% and 115% at week 12, 162% and 104% at week 24, vs 18% and 6% placebo. Downregulation of Th1, Th2 and IL-12/23 immune responses and upregulation of hair keratins. These changes correlated with clinical (SALT score) improvement	NA

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
46 [94]	Case report	Tofacitinib	5 mg BID PO	Systemic	36	1	Efficacy	Hair regrowth: complete hair regrowth at 5 months, maintained after 4 months of follow-up. Regrowth started in the area of contact dermatitis	NA
47 [95]	Case series	Tofacitinib	2.5 mg QD, then 2.5 mg QD for 4 days and 5 mg QD for 3 days each week	Systemic	48	3	Efficacy and safety	With 2.5 mg: unsatisfactory hair regrowth (< 20%) When 2.5/5 mg: patient #1 > 90% regrowth; patient #2 > 50% by month 6; patient #3 > 50% by 21 months (complete regrowth of eyebrows and eyelashes and partial scalp hair)	Mild diarrhea. Upper respiratory tract infection
48 [96]	Case series	Tofacitinib	Patient #1: 5 mg BID. Then cycles of 5 mg BID PO 8 weeks/5 mg once daily 4 weeks/no treatment 10–12 weeks. Then 5 mg once daily 5 months/off drug 8 weeks/5 mg BID 8 weeks. Patient #2: 5 mg BID PO	Systemic	3 years	2	Efficacy and safety	Patient #1: almost complete regrowth at 3 months, relapsing after 8–10 weeks of stopping drug. With the 3rd cycling pattern, almost complete regrowth and no relapses Patient #2: complete regrowth after 2 months	No adverse effects
49 [97]	Case series	Tofacitinib, ruxolitinib	Tofacitinib 5 mg BID PO Ruxolitinib 1.5% BID topical	Systemic/topical	52/16	2	Rebound effect after JAK inhibitor treatment discontinuation	Patient #1 on tofacitinib: SALT improvement from 60% to 25%. After discontinuation, relapse and SALT 90% Patient #2 on ruxolitinib: SALT score improvement from 80% to 7%. After discontinuation, relapse and SALT > 99%	
50 [98]	Case series	Ruxolitinib	10 to 25 mg BID PO	Systemic	20/124	8	Efficacy and safety	5/8 patients achieved complete or nearly complete regrowth. Mean SALT improvement of 98% (SD 4%). 3/8 patients: no regrowth	Mild adverse effects: upper respiratory infections, weight gain, acne, easy bruising, fatigue. One patient had decreased white blood cell count

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
51 [99]	Open label	Tofacitinib, ruxolitinib	Tofacitinib 5 mg BID PO Ruxolitinib 20 mg BID PO	Systemic	36	75	Efficacy and safety	% change in SALT score: 93.8 ± 3.25 for ruxolitinib/95.2 ± 2.69 for tofacitinib. ^a RUXO group (38 patients): 3 low, 3 medium, 6 good, 18 excellent, 8 complete. Relapse: 28 (73.3%) ^a TOFA group (n = 35): 4 low, 4 medium, 5 good, 16 excellent, 8 complete. Relapse: 26 (74.2%)	Adverse effects were infrequent and minor: leukopenia (n = 4), AST/ALT mild elevation (n = 5), serum triglycerides elevation (n = 2), cholesterol elevation (n = 1), acute infections (n = 25), mild gastrointestinal symptoms, headache, weight gain, fatigue
52 [100]	Case series	Tofacitinib	5 mg BID PO	Systemic	24/60	4	Efficacy	Hair regrowth: complete (n = 2) after 3–6 months, 62% (n = 1), scarce (n = 1)	No differences between both drugs NA
53 [101]	Case series	Tofacitinib	5 mg BID PO, then decreased to 7.5 mg daily	Systemic	NA	63	Efficacy and safety	25/63 patients had > 90% SALT score change. Of these, 15/24 achieved 100% change in SALT score	Mild adverse effects: hyperseborrhea, upper respiratory infections, acneiform eruptions
54 [102]	Case report	Tofacitinib	5 mg BID PO	Systemic	24	1	Hair regrowth	40% regrowth	NA
55 [103]	Case report	Ruxolitinib	5 mg BID then 10 mg BID PO	Systemic	40	1	Hair regrowth	Nearly complete hair regrowth	NA
56 [104]	Case report	Tofacitinib	2% BID	Topical	32	1	Eyelashes regrowth	Nearly complete eyelashes regrowth	NA
57 [105]	Case report	Tofacitinib	5 mg BID PO	Systemic	24	1	Efficacy and safety	Complete regrowth of eyebrows and scalp hair (SALT of 0)	Mild headaches

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
58 [106]	Case series	Tofacitinib	5 mg QD PO 5 mg BID PO	Systemic	16/108	11	Efficacy and safety	The mean SALT score improvement from baseline was calculated to be 61.18% ($n = 10$, range, 0–100%)	One patient developed hyperlipidemia and weight gain while on 11 mg extended release twice daily, which improved with exercise and diet changes while remaining on treatment. Other side effects included gastrointestinal symptoms and mild acne. One patient stopped treatment because of new-onset multiple sclerosis
59 [107]	Case series	Tofacitinib	Tofacitinib 5 mg BID PO, increased to 5 mg 3 times daily for 4 unresponsive patients, and then to 10 mg BID for one of these Comparators: oral conventional treatment (steroids + cyclosporine) and diphenylcyclopropenone (DPCP)	Systemic/topical	24	74	Efficacy and safety	Median SALT change: 3rd month: tofacitinib 34.6 (range 0–80), conventional 34.7 (0–89.2), and DPCP 0 (0–53.0) 6th month: tofacitinib 36.5 (0–91.5), conventional 39.9 (0–91.6), and DPCP 0 (0–80) SALT50 3rd month: Tofacitinib: 9 patients (50%), conventional: 7 patients (26.9%), DPCP: 1 patient (3.6%) SALT50 6th month: Tofacitinib: 8 (44.4%), conventional: 9 (37.5%), DPCP: 3 (11.1%)	In the tofacitinib group, 6 patients (33.3%) suffered abdominal discomfort and acneiform eruption, most of them mild and transient
60 [108]	Case series	Tofacitinib	5 mg BID PO	Systemic	64	9	Efficacy and safety	3/9 patients responded (showing 25–75% regrowth at 6 months)	No significant clinical or laboratory adverse events
61 [109]	Open label	Tofacitinib	5 mg BID PO, increased to 10 mg BID PO in non-responders	Systemic	24	12	Efficacy	8/12 patients \geq 50% hair regrowth, 3/12 partial < 50% regrowth, and 1 patient no regrowth	NA

Table 3 continued

Study [references]	Type, subtype of study	Drug	Dosage	Administration route	Follow-up (weeks)	Number of patients	Outcomes	Efficacy	Safety
62 [110]	Case series	Tofacitinib	5 mg BID PO	Systemic	28/36	4	Efficacy	Patient #1: progressive hair growth after 9 months Patient #2: partial growth of scalp, eyebrow, and axillary hair Patient #3: hair growth on scalp, eyebrows, and skin after 7 months Patient #4: complete regrowth	NA
63 [111]	Case report	Tofacitinib	5 mg BID PO	Systemic	32	1	Efficacy and safety	Almost complete full body hair regrowth	No adverse effects or laboratory abnormalities
64 [112]	Open label	Tofacitinib	5 mg BID PO, then escalated to 10 mg BID PO	Systemic	24	12	Efficacy	7/12 patients achieved \geq 50% regrowth (60% response rate)	NA
65 [113]	Open label	Tofacitinib	5 mg BID PO, then escalated to 10 mg BID PO	Systemic	24	12	Efficacy	8/12 patients \geq 50% improvement (hair regrowth). Skin gene expression profiles and ALADIN scores correlated with clinical response	NA
66 [114]	Case report	Tofacitinib	5 mg BID PO	Systemic	20 + 8	1	Efficacy and safety	Complete hair regrowth. At 5 months treatment discontinuation because of herpes zoster infection. When resolved, tofacitinib was restarted but without clinical response at 2 months, then it was discontinued	Herpes zoster-associated encephalitis

ALADIN Alopecia Areata Disease Activity Index, *HRQoL* Health-Related Quality of Life, *IGA* Investigator's Global Assessment, *LDL-c* low density lipoprotein cholesterol, *PGA* Patient Global Assessment, *SALT* Severity of Alopecia Tool, *BID* twice a day, *AST* aspartate transaminase, *ALT* alanine transaminase, *NA* not acquired

^a Grade of treatment response based on SALT reduction: low 0–24%, medium 25–49%, good 50–74%, excellent 75–99%, complete 100%

observed in around 50% of patients, with some studies finding at least 50% hair regrowth. Some studies found a median frequency of hair regrowth of 50.5% (2–90%), and a mean response time of 4.2 (range 1–9) months. In some cases, relapse was observed after drug withdrawal. JAK inhibitors were generally safe and well tolerated in all AA studies. Reported adverse events included minor bacterial skin infections, peripheral edema, acneiform eruptions, upper respiratory or urinary tract infections, viral infections, tonsillitis, allergy, pneumonia, conjunctival hemorrhage, mild gastrointestinal symptoms, lipid and liver abnormalities, mild anemia, headache, fatigue, increased appetite, weight gain, and one case of leukopenia.

DISCUSSION

Summary of Findings

This is the first scoping review which summarizes the available evidence on the use of JAK inhibitor drugs in patients with AD, vitiligo, and AA. Our results provide more insight about the gap that exists between specific therapeutic needs not covered by current therapies and the strategical value of these diseases in the R&D pipeline of pharmaceutical companies.

Some patterns were found after systematically reviewing evidence of using JAK-targeting drugs for AD, vitiligo, and AA. Most reviewed studies were related to AA disease, and just a few published studies about vitiligo were identified. In both cases, studies followed an observational design, mostly as small case series. Also, they mainly used systemic drugs, with tofacitinib followed by ruxolitinib, as the JAK inhibitors most frequently used. Although there are some planned or ongoing early phase RCTs for AA, no vitiligo study was associated with any current or completed RCT. Response to treatment was very variable among studies. In most vitiligo studies a positive therapeutic response was noted in 50% of patients, especially in sun-exposed areas. However, not standardized methods were used to assess the efficacy, and the period of follow-up was less than 6 months in most cases. In AA

studies, a validated scale (SALT) was frequently used and the follow-up period was longer than in vitiligo studies. We noted two observations of JAK inhibitor response in many AA studies: first, many patients that achieved therapeutic efficacy needed to scale up or maintain treatment for an extended period of time; secondly, in many of these cases the achieved effect was lost after treatment was discontinued. As we observed different responses with different agents in different diseases, we shall consider selecting some specific types of JAK/STAT in different diseases on the basis of their pathogenic features. Finally, the number of published AD studies was intermediate between vitiligo and AA and mostly were associated with phase I/II RCTs, involving up to seven drugs/pharma companies and enrolling a total of 2098 patients. Improved methodological procedures were implemented (i.e., using several standardized tools for each study) to assess efficacy and safety outcomes more rigorously in AD studies as compared to those used for AA and vitiligo. Studies were mainly multicenter and multidisciplinary, especially related to AA, as they involved the largest number of medical specialties and were performed in a higher number of countries, most of them developed countries and mainly represented by the USA. Private funding sources were scarce, and most studies received financial support either from public sources or from none. Conflicts of interest were minimal.

Some factors may explain differences between clinical needs and pharma initiatives: prevalence, burden of disease, and current therapeutic options. The prevalence of vitiligo and AA is lower than that of AD. The burden of disease is higher for AD and AA, compared to that of vitiligo. Therapeutic options are not specifically targeted in any of the three cases. However, there are more current therapeutic options for AD as compared to those for AA and vitiligo. These facts could explain why most the pharmaceutical industry is more interested in developing clinical trials to assess targeted therapies with different drugs in the case of AD, as compared to AA and vitiligo. The increased burden of disease associated with AA could

explain the great number of physician-initiated off-label observational studies.

Strengths and Limitations

Some years ago, a systematic review was published about the available data on the use of JAK inhibitors in cutaneous diseases [115]. Recently, two systematic reviews about JAK inhibitors were published, both of them focused on patients with AA and included 30 studies [116, 117]. After assessing these reviews using A MeaSurement Tool to Assess systematic Reviews (AMSTAR) 2 instrument [118], we found that the overall confidence in their results was critically low (data not shown). These reviews had more than one critical flaw and did not provide an accurate and comprehensive summary of the available studies. There are also some non-systematic reviews or literature reviews about JAK inhibitors for AA, AD, and vitiligo, all of them with an intrinsic lower methodological quality as compared with systematic reviews [119–134].

In contrast to all the above, our review was conducted systematically according to the methodology planned in an a priori protocol published prior to study performance. This methodology followed the latest guidelines for conducting scoping reviews and at least two researchers participated in each of the phases. Authors were contacted to clarify certain details about primary data when necessary. Reporting was based on recommendations from the PRISMA Extension for Scoping Reviews. However, funding and time limitations only allowed for the inclusion of studies published in English in our analysis. Even though we believe that the literature search was complete and the performance of a three-stage search approach minimized the potential loss of relevant papers, there is still a possibility that we missed some manuscripts. Additionally, it was not possible to obtain all missing data or clarification of poorly detailed data from some articles we reviewed, even after contacting the authors. This was especially relevant in studies published in the form of abstracts, which we did not exclude. Furthermore, most of these selected studies were of low quality, owing to their

observational designs and the high proportion of observational studies and their diversity of efficacy endpoints and outcome reporting forced us to organize and analyze the information into broader and less detailed categories. As a result of the large amount of information extracted from the search and the different designs of the included studies we were not able to do analysis comprising individual patients. Finally, we did not assess the quality of the studies included here, in terms of risk of bias, quality of evidence, and statistical analysis techniques.

Research Gaps

The small number of studies about the use of drugs targeting the JAK/STAT pathway in the treatment of AD and vitiligo contrasts with the great amount of available information on the use of these drugs in AA. Most of the reviewed studies were observational, which translated into a low quality of evidence, according to the GRADE system for grading the quality of evidence [117]. In addition to this, the absence of an a priori design published in a public repository, as occurs in the majority of included studies, could increase the bias risk and reduce analysis transparency, thus limiting the validity and reproducibility of results. Therefore, future studies should focus on improving study quality in order to achieve reliable evidence that could be applicable to clinical practice.

Considering these limitations, the use of JAK inhibitors for the treatment of AD, vitiligo, and AA is promising. The conditions of most participants with AD improved to some extent, while in vitiligo and AA studies both responders and non-responders were identified. Given the preferential repigmentation in sun-exposed areas that some patients with vitiligo experienced when treated with JAK inhibitors, the concomitant or sequential treatment of these patients with UV exposure and these drugs may result in a greater improvement compared to administration of the drug. Response rates to tofacitinib and ruxolitinib were similar in all the studied diseases, while efficacy evidence for

other drugs (upadacitinib, baricitinib, cerdulinib, abroticininib, delgocitinib, and gusacitinib) was scarce because of the small number of studies in which they were applied. It is imperative to establish a consensus on the best methodology (outcomes, validated scales, and time point for assessment) to measure efficacy, which will allow comparison of results between studies, especially in the case of vitiligo and AA, and AD to a lesser extent. Overall, JAK inhibitor drugs have shown short-term acceptable safety, even though they are not completely without adverse events. However, further phase III/IV RCTs are required to ensure more accurate efficacy and safety profiles of these drugs. In fact, there are currently several protocols of RCTs registered in ClinicalTrials.gov about JAK inhibitors for AA, AD, and vitiligo treatment, most of them promoted by the industry and still active and recruiting (Table S8 of Supplementary Material).

CONCLUSIONS

Evidence on the use of drugs targeting the JAK/STAT pathway for the treatment of dermatological diseases such as AD, vitiligo, and AA is growing but still mainly focused on observational or early phase experimental studies. Although existing results are promising, further studies are needed to ensure that the efficacy and safety parameters of these drugs are optimal for their use in clinical practice. These clinical trials studies should provide more accurate results by improving their design, standardization of scales, and the time of outcome measurement.

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

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