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SYSTEMATIC REVIEW

Safety of Janus Kinase inhibitors in Patients with Alopecia Areata: A Systematic Review

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Abstract

Background and Objectives Janus kinase (JAK) inhibitors are emerging as a therapeutic option for alopecia areata. The risk of potential adverse events is currently debated. In particular, several safety data for JAK inhibitors are extrapolated from a single study in elderly patients with rheumatoid arthritis treated with tofacitinib or adalimumab/etanercept as a comparator. The population of patients with alopecia areata is clinically and immunologically different from persons with rheumatoid arthritis and tumor necrosis factor (TNF) inhibitors are not effective in these patients. The objective of this systematic review was to analyze available data on the safety of various JAK inhibitors in patients with alopecia areata.

Methods The systematic review was performed according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. A literature review was performed by searching PubMed, Scopus and EBSCO databases with the last search on March 13, 2023.

Results In total, 36 studies were included. The frequency and odds ratio (OR) for most common adverse events versus placebo were: for baricitinib hypercholesterolemia (18.2% vs 10.5%, OR = 1.9) and headache (6.1% vs 5.1%, OR = 1.2), for brepocitinib elevated creatinine level (27.7% vs 4.3%, OR = 8.6) and acne (10.6% vs 4.3%, OR = 2.7), for ritlecitinib acne (10.4% vs 4.3%, OR = 2.6) and headache (12.5% vs 10.6%, OR = 1.2) and for deuruxolitinib headache (21.4% vs 9.1%, OR = 2.7) and acne (13.6% vs 4.5%, OR = 3.3). The respective numbers for upper respiratory infections were: baricitinib (7.3% vs 7.0%, OR = 1.0) and brepocitinib (23.4% vs 10.6%, OR = 2.6); for nasopharyngitis: ritlecitinib (12.5% vs 12.8%, OR = 1.0) and deuruxolitinib (14.6% vs 2.3%, OR = 7.3).

Conclusions The most common side effects of JAK inhibitors in patients with alopecia areata were headache and acne. The OR for upper respiratory tract infections varied from over 7-fold increased to comparable to placebo. The risk of serious adverse events was not increased.

1 Introduction

Alopecia areata is an autoimmune chronic disorder, resulting in non-scarring hair loss. The estimated lifetime prevalence of the disease is 2% [1]. The course of alopecia areata is unpredictable. Spontaneous remissions may occur; however, the overall rate of relapses is high [2]. Due to frequent recurrence of hair loss in alopecia areata, prolonged treatment is often required. There are numerous traditional therapeutic options for alopecia areata (e.g., topical, intralesional and oral glucocorticosteroids, cyclosporine, methotrexate) [3]. However, their efficacy is limited, especially in patients with negative prognostic factors (such as alopecia totalis or universalis [4] and long duration of the disease) [5].

The pathogenesis of alopecia areata is not fully understood. However, the role of Janus kinase (JAK)-signal transducer and activator of transcription (STAT) signaling pathways is described [6]. The JAK family composes four intracellular enzymes: JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2), which transmit signals for different cytokine receptors. Activation of the JAK-STAT pathway promotes expression of genes involved into production of the pro-inflammatory cytokines. It results in activation of CD8+ T-cells, which attack hair follicles during anagen phase [7, 8].

JAK inhibitors have been described as the most effective therapeutic option for alopecia areata [9]. In 2022, baricitinib (JAK1/2 inhibitor) was approved by the United States Food and Drug Administration (FDA) and European

Extended author information available on the last page of the article

Key Points

The two most common adverse effects of JAK inhibitors in patients with alopecia areata are headache and acne.

The odds ratio for upper respiratory tract infections varied from over 7-fold increased (deuruxolitinib) to comparable to placebo (baricitinib, ritlecitinib).

The risk of serious adverse events, including major adverse cardiovascular events, is not increased.

Medicines Agency (EMA) as the first systemic drug for alopecia areata and received a breakthrough therapy status.

A study of Ytterberg et al [10], performed in a cardiovascular risk-enriched population of patients with rheumatoid arthritis aged ≥ 50 years indicated that the risk of major adverse cardiovascular events (MACE) and cancers was higher in the group treated with tofacitinib compared to the group treated with adalimumab and etanercept. On the basis of these results, the FDA required warnings about an increased risk of serious heart-related events, cancer, blood clots, and death for JAK1 inhibitors (tofacitinib, baricitinib and upadacitinib). Earlier, the FDA warned about an increased risk of blood clots and death in patients with rheumatoid arthritis receiving tofacitinib at a dose of 10 mg twice daily [11]. In November 2022, the EMA issued a statement to minimize the risk of serious side effects with JAK inhibitors for chronic inflammatory disorders. According to this document, JAK inhibitors should be used only if no suitable treatment alternatives are available in the following groups of patients: ≥ 65 years, patients at increased risk of major cardiovascular problems, patients who smoke or have done so for a long time in the past, and patients at increased risk of cancer. Special caution is suggested for patients at risk for thromboembolic events.

2 Objectives

The aim of this systematic review was to summarize adverse effects and assess safety of systemic and topical JAK inhibitors in patients with alopecia areata.

3 Methods

A literature review was performed by searching PubMed, Scopus and EBSCO databases with the last search on March 13, 2023. The terms used for search were: "alopecia areata", "alopecia totalis", "alopecia universalis" combined with "JAK inhibitors", "tofacitinib", "ruxolitinib", "ritlecitinib", brepocitinib", "baricitinib", "CTP-543". Moreover, references of all relevant articles were checked for further publications. Studies with incomplete data, such as unknown number of adverse effects, case reports, in vitro studies, animal studies, reviews, book chapters, articles in language other than English, were rejected. The exclusion criteria were also: adjuvant therapies, alopecia of beard or eyebrows, previous treatment with JAK inhibitors, no division between adults and children. If data were duplicated in more than one study, the most recent placebo-controlled study was included in the analysis.

4 Results

Among retrieved articles, 36 studies (27 original studies and 9 case series) were found eligible for quantitative synthesis. Data flow diagram is presented in Fig. 1.

Systemic JAK inhibitors used in adults with alopecia areata were tofacitinib (JAK 1/3 inhibitor), ruxolitinib (JAK 1/2 inhibitor), baricitinib (JAK 1/2 inhibitor), ritlecitinib (JAK 3 inhibitor), brepocitinib (JAK 1/TYK2 inhibitor), and deuruxolitinib (JAK 1/2 inhibitor). In pediatric populations, only oral tofacitinib was used. In both adults and children, topical tofacitinib and ruxolitinib were evaluated.

4.1 Common Adverse Effects in All JAK Inhibitors

The most common adverse effects of systemic JAK inhibitors were mild and consisted of upper respiratory infections (mean for all studies: 10.3%), headache (6.5%), and acne (6.5%). Nasopharyngitis (4.3%), gastrointestinal symptoms (3.4%), urinary tract infections (2.7%), herpes infections, including herpes zoster (1.1%), and hyperseborrhea (1.2%) were also reported. Folliculitis (0.9%) and bacterial skin infections (0.5%), weight gain (0.7%), fatigue (0.7%), and allergy symptoms (0.6%) were also present. The most common laboratory abnormalities were hypercholesterolemia (10.8%), creatine phosphokinase elevation (2.1%), and elevated liver enzymes (1.7%).

In studies concerning topical JAK inhibitors, the most common adverse effects were scalp skin irritation (11.2%), folliculitis (1.2%) and laboratory abnormalities such as hypercholesterolemia (4.1%), elevated liver enzymes (1.0%), and leukopenia (1.0%).

Studies concerning baricitinib, brepocitinib, ritlecitinib and deuruxolitinib were randomized clinical trials with a control arm receiving placebo. In studies on tofacitinib and ruxolitinib in alopecia areata, control groups were not present.

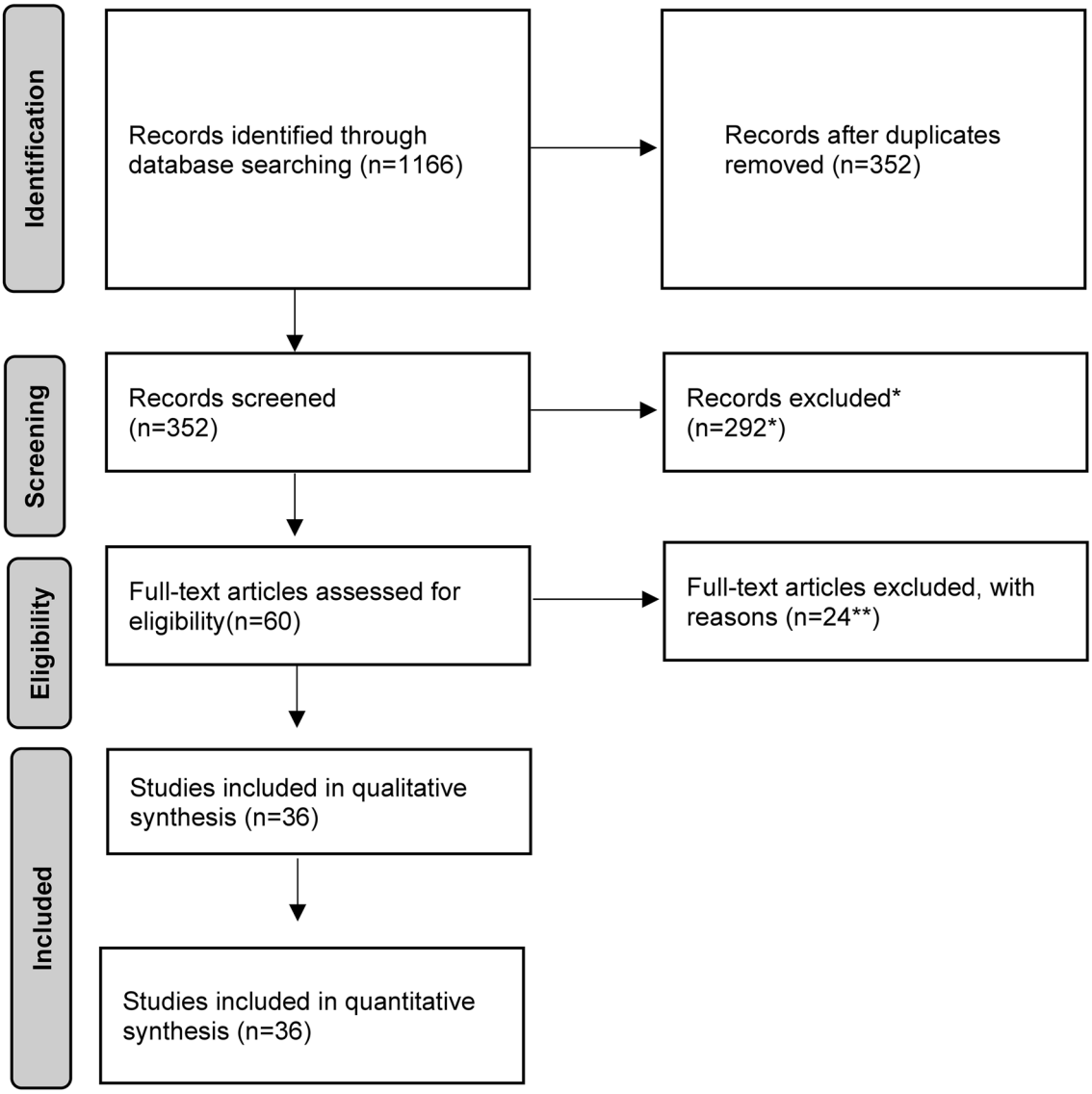

Fig. 1 Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flowchart. *Excluded records: reviews, book chapters, case reports, articles concerning animals, in vitro studies, articles in languages other than English. **Excluded records: lack of data about adverse effects ($n = 10$), adjuvant therapies ($n = 3$), alopecia of beard or eyebrows ($n = 3$), studies with duplicated data ($n = 3$), previous treatment with JAK inhibitors ($n = 2$), no division between adults and children ($n = 3$)

All results and detailed data are summarized in Tables 1, 2, 3 and 4 and Supplementary Tables 1 to 4.

4.2 Serious Adverse Events

Serious adverse events were reported in 4 studies and included hypertensive urgency in 1 patient receiving oral tofacitinib (0.2%) [12], cellulitis in 1 patient exposed to deuruxolitinib (1.0% vs 0% in placebo group, odds ratio (OR) = 1.3) [13] and rhabdomyolysis in 2 patients receiving brepocitinib (4.3% vs 0%, OR = 5.21) [14]. In two Phase 3 trials of baricitinib for alopecia areata, 22 patients experienced serious adverse events (2.4% vs 1,6%, OR = 1.5), including acute myocardial infarction in 1 patient (0.1% vs 0%, OR = 1.23), ventricular tachycardia in 1 patient (0.1% vs 0%, OR = 1.23), cardiac failure congestive in 1 patient (0.1% vs 0%, OR = 1.23), hypertension in 1 patient (0.1% vs 0%, OR = 1.23), food poisoning in 1 patient (0.1% vs 0%, OR = 1.23), hernia in 2 patients (0.2% vs 0%, OR = 2.1), chest pain in 1 patient (0.1% vs 0%, OR = 1.23), asthenia in 1 patient (0.1% vs 0%, OR = 1.23), acute cholecystitis in 2 patients (0.2% vs 0.3%, OR = 0.8), pyelonephritis in 2 patients (0.2% vs 0%, OR = 2.1), COVID-19 pneumonia in 1 patient (0.1% vs

0%, OR = 1.23), bone fractures in 6 patients (0.7% vs 0.3%, OR = 2.5), SARS-CoV-2 test positive in 1 patient (0.1% vs 0%, OR = 1.23), B-cell lymphoma in 1 patient (0.1% vs 0%, OR = 1.23), Guillain-Barre syndrome in 1 patient (0.1% vs 0%, OR = 1.23), missed abortion in 1 patient (0.1% vs 0%, OR = 1.23) and device dislocation in 1 patient (0.1% vs 0%, OR = 1.23) [15]. Overall, among all patients exposed to any baricitinib dose at any time in BRAVE-AA1 and BRAVE-AA2 clinical trials, there was 1 myocardial infarction (incidence ratio, IR = 0.1), 1 pulmonary embolism (IR = 0.1), 3

Table 1 Summary of adverse effects of systemic JAK inhibitors in adults with alopecia areata

JAK isomer	Name of drug	No. patients	AEs (%)
JAK 1/3	Tofacitinib	511	URI (12.9%), acne (7.4%), headache (4.1%), hyperseborrhea (4.1%), hypercholesterolemia (3.1%), elevated liver enzymes (2.7%), UTI (1.8%), weight gain (2.3%), abdominal pain (2.2%), fatigue (2.2%), leukopenia (1.6%), diarrhea (1.6%), H. zoster (1.4%), anemia (1.0%), bacterial skin infection (0.8%), folliculitis (1.0%), night sweats (0.8%), warts (0.8%), blood in urine (0.8%), joint aches (0.6%), skin rash (0.6%), bronchitis (0.6%), nausea (0.6%), hot flashes (0.6%), conjunctivitis (0.6%), numbness (0.6%), asymptomatic bacteriuria (0.4%), peripheral edema (0.4%), palpitations (0.4%), hypertriglyceridemia (0.4%) pruritus (0.4%), tonsillitis (0.4%), acute kidney injury (0.2%), urinary retention (0.2%), mononucleosis (0.2%), paronychia (0.2%), dizziness (0.2%), neuropathic pain (0.2%), palmoplantar desquamation (0.2%), urticaria (0.2%), bloating (0.2%), verruca vulgaris (0.2%), tinnitus (0.2%), cough (0.2%), amenorrhea (0.2%), vaginal spotting (0.2%), hypertensive urgency (0.2%), bruising (0.2%), dry eyes (0.2%), proteinuria (0.2%), neutropenia (0.2%)
JAK 1/2	Ruxolitinib	58	URI (17.2%), allergy symptoms (12.1%), UTI (10.3%), bacterial skin infection (6.9%), elevated liver enzymes (5.2%), leukopenia (5.2%), H. zoster (3.4%), headache (3.4%), fatigue (3.4%), conjunctival hemorrhage (1.7%), pneumonia (1.7%), abdominal pain (1.7%), diarrhea (1.7%), weight gain (1.7%), anemia (1.7%)
	Baricitinib	905	Hypercholesterolemia (18.2%), URI (7.3%), headache (6.1%), acne (5.6%), nasopharyngitis (5.5%), UTI (3.5%), CPK elevations (3.2%), H. simplex (1.9%), H. zoster (1.2%), hypertriglyceridemia (0.6%), nausea (0.4%), neutropenia (0.1%), new malignancy (0.1%), myocardial infarction (0.1%)
	Deuruxolitinib (CTP-543)	103	Headache (21.4%), nasopharyngitis (14.6%), acne (13.6%), URI (10.7%), nausea (8.7%), cough (6.8%), folliculitis (5.8%), CPK elevations (5.8%), elevated lipase (4.9%), hypercholesterolemia (3.9%), oropharyngeal pain (3.9%), diarrhea (3.9%), elevated phosphate (2.9%), hyperkalemia (1.9%), elevated urea (1.9%), neutropenia (1.9%), elevated amylase (1.9%), hyperglycemia (1.0%), elevated liver enzymes (1.0%), hypertriglyceridemia (1.0%)
JAK 1/TYK2	Brepocitinib	47	Elevated creatinine level (27.7%), URI (23.4%), acne (10.6%), nasopharyngitis (8.5%), headache (8.5%), oropharyngeal pain (6.4%), sinusitis (6.4%), abdominal pain (6.4%), nausea (6.4%), rhabdomyolysis (4.3%), neutropenia (4.3%), elevated liver enzymes (4.3%), allergy symptoms (2.1%), diarrhea (2.1%), folliculitis (2.1%), CPK elevations (2.1%), hypercholesterolemia (2.1%)
JAK 3	Ritlecitinib	48	Nasopharyngitis (12.5%), headache (12.5%), acne (10.4%), URI (8.3%), diarrhea (8.3%), allergy symptoms (6.3%), folliculitis (6.3%), nausea (6.3%), lymphopenia (2.1%)

AEs adverse effects, *CPK* creatine phosphokinase, *H. simplex* Herpes simplex, *H. zoster* Herpes zoster, *JAK* Janus kinase, *TYK* tyrosine kinase, *URI* upper respiratory infection, *UTI* urinary tract infection

Table 2 Summary of adverse effects of topical JAK inhibitors in adults with alopecia areata

JAK isomer	Name of drug	No. patients	AEs (%)
JAK 1/3	Tofacitinib	14	Scalp skin irritation (28.6%), hypercholesterolemia (28.6%), folliculitis (7.1%)
JAK 1/2	Ruxolitinib	67	Scalp skin irritation (10.4%)

AEs adverse effects, *CPK* creatine phosphokinase, *H. simplex* Herpes simplex, *H. zoster* Herpes zoster, *JAK* Janus kinase, *TYK* tyrosine kinase, *URI* upper respiratory infection, *UTI* urinary tract infection

Table 3 Summary of adverse effects of systemic JAK inhibitors in children with alopecia areata

JAK isomer	Name of drug	No. patients	AEs (%)
JAK 1/3	Tofacitinib	73	URI (17.4%), elevated liver enzymes (14.5%), eosinophilia (7.2%), headache (4.3%), abdominal pain (4.3%), hypercholesterolemia (4.3%), hyperkalemia (4.3%), elevated urea (4.3%), hypertriglyceridemia (2.9%), diarrhea (1.4%), hyperbilirubinemia (1.4%), low total protein (1.4%), lymphopenia (1.4%), elevated alkaline phosphatase (1.4%), acne (1.4%)

AEs adverse effects, *CPK* creatine phosphokinase, *H. simplex* Herpes simplex, *H. zoster* Herpes zoster, *JAK* Janus kinase, *TYK* tyrosine kinase, *URI* upper respiratory infection, *UTI* urinary tract infection

Table 4 Summary of adverse effects of topical JAK inhibitors in children with alopecia areata

JAK isomer	Name of drug	No. patients	AEs (%)
JAK 1/3	Tofacitinib	15	Leukopenia (6.7%), elevated liver enzymes (6.7%)
JAK 1/2	Ruxolitinib	2	No serious AEs were observed

AEs adverse effects, *CPK* creatine phosphokinase, *H. simplex* Herpes simplex, *H. zoster* Herpes zoster, *JAK* Janus kinase, *TYK* tyrosine kinase, *URI* upper respiratory infection, *UTI* urinary tract infection

malignancies other than non-melanoma skin cancer (IR = 0.2) and 1 gastrointestinal perforation (IR = 0.1) [58]. There were no cases of death in these studies.

4.3 Common Side Effects Depending on the JAK Inhibitor

4.3.1 Adverse Effects of Tofacitinib in Alopecia Areata

The most common adverse effects of oral tofacitinib in adults were upper respiratory infections (12.9%), acne (7.4%), headache (4.1%), and hyperseborrhea (4.1%), whereas in children upper respiratory infections (17.4%), elevated liver enzymes (14.5%), and eosinophilia (7.2%) were most commonly observed. Topical tofacitinib was associated with scalp irritation (28.6%), hypercholesterolemia (28.6%), and folliculitis (7.1%) in adults, while leukopenia (6.7%) and elevated liver enzymes (6.7%) were reported in children.

4.3.2 Adverse Effects of Ruxolitinib in Alopecia Areata

In adults receiving oral ruxolitinib, upper respiratory infections (17.2%), allergy symptoms (12.1%), and urinary tract infections (10.3%) were most commonly observed. In the studies on topical ruxolitinib, scalp skin irritation (10.4%) was reported in adults; there were no adverse effects reported in children.

4.3.3 Adverse Effects of Baricitinib in Alopecia Areata

The most commonly reported adverse effects of baricitinib were: hypercholesterolemia (18.2% vs 10.5%, OR = 1.9), upper respiratory infections (7.3% vs 7.0%, OR = 1.0), and headache (6.1% vs 5.1%, OR = 1.2).

4.3.4 Adverse Effects of Brepocitinib in Alopecia Areata

In patients receiving brepocitinib, the most frequently reported adverse effects and the respective OR versus placebo were: elevated creatinine level (27.7% vs 4.3%, OR = 8.6), upper respiratory infections (23.4% vs 10.6%, OR = 2.6), and acne (10.6% vs 4.3%, OR = 2.7).

4.3.5 Adverse Effects of Ritlecitinib in Alopecia Areata

The most commonly reported adverse effects of ritlecitinib and the respective OR versus placebo were: nasopharyngitis (12.5% vs 12.8%, OR = 1.0), headache (12.5% vs 10.6%, OR = 1.2), and acne (10,4% vs 4.3%, OR = 2.6).

4.3.6 Adverse Effects of Deuruxolitinib in Alopecia Areata

In patients receiving deuruxolitinib, the most commonly reported adverse effects were headache (21.4% vs 9.1%, OR = 2.7), nasopharyngitis (14.6% vs 2.3%, OR = 7.3), and acne (13.6% vs 4.5%, OR = 3.3).

4.4 Common Adverse Effects Divided by Groups of Symptoms

4.4.1 Upper Respiratory Infections

Upper respiratory infections were most commonly reported in patients with alopecia areata treated with oral brepocitinib (23.4% of adults) [14], tofacitinib (12.9% of adults, 17.4% of children) [12, 16–27] and ruxolitinib (17.2% of adults) [18, 28, 29]. Upper respiratory infections were less commonly

presented in adult patients who received deuruxolitinib (10.7%) [13], ritlecitinib (8.3%) [14], and baricitinib (7.3%,) [15, 30]. Specifically, nasopharyngitis was reported in 14.6% [13] and 12.5% [14] of adults treated with oral deuruxolitinib and ritlecitinib, respectively. Moreover, it was observed in 8.5% [14] and 5.5% [15] of adults who received brepocitinib and baricitinib, respectively. Cough was reported only in adult patients treated with deuruxolitinib with the frequency 6.8% [13]. Oropharyngeal pain occurred in 6.4% [14] and 3.9% [13] of adults with alopecia areata who received brepocitinib and deuruxolitinib, respectively. Sinusitis was reported only in adults treated with brepocitinib (6.4%) [14].

4.4.2 Urinary Tract Infections

Urinary tract infections occurred in adult patients treated with oral ruxolitinib (10.3%) [18, 28], baricitinib (3.5%) [15, 24], and tofacitinib (1.8%) [18, 22, 24].

4.4.3 Acne and Hyperseborrhea

Acne was reported in 13.6% [13] and 10.6% [14] of adults treated with oral deuruxolitinib and brepocitinib, respectively. The disease was observed in 7.4% [12, 17, 22, 24, 31, 32, 56] and 5.6% [15, 30] of adult patients receiving tofacitinib and baricitinib, respectively. Hyperseborrhea was reported in adult patients treated with oral tofacitinib at the frequency 4.1% [17].

4.4.4 Scalp Irritation

Scalp irritation was the most commonly reported adverse effect of topical tofacitinib (28.6%) [33] and ruxolitinib (10.4%) [34] in adults.

4.4.5 Bacterial Skin Infection and Folliculitis

Bacterial skin infection was only reported in adults treated with oral ruxolitinib (6.9%) [18, 28], whereas folliculitis occurred in adult patients receiving oral ritlecitinib (6.3%) [14], deuruxolitinib (5.8%) [13], brepocitinib (2.1%) [14], and topical tofacitinib (7.1%) [33].

4.4.6 Allergic Symptoms

Allergic symptoms (such as atopic dermatitis and allergic rhinitis) were the second most commonly reported adverse effects in adults treated with oral ruxolitinib (12.1%) [28]. They were also described in adults receiving oral ritlecitinib (6.3%) [14] and brepocitinib (2.1%) [14].

4.4.7 Headache

Headache was the most commonly reported adverse effect of oral deuruxolitinib (21.4%) [13] and the third most common adverse effect of oral tofacitinib (4.1%) [12, 18, 22, 24] in adults. Headache was also described in adult patients treated with oral ritlecitinib (12.5%) [14], brepocitinib (8.5%) [14], baricitinib (6.1%) [15], and ruxolitinib (3.4%) [18]. In children receiving oral tofacitinib headache occurred in 4.3% [23] of cases.

4.4.8 Weight Gain

Weight gain was reported in adult patients treated with oral tofacitinib (2.3%) [12, 18, 22, 24, 35] and ruxolitinib (1.7%) [18, 29].

4.4.9 Fatigue

Fatigue was reported only in adults with alopecia areata who were treated with oral ruxolitinib (3.4%) [18, 29] and tofacitinib (2.2%) [22, 24, 56].

4.4.10 Gastrointestinal Symptoms

Diarrhea was observed in adult patients treated with oral ritlecitinib (8.3%) [14], deuruxolitinib (3.9%) [13], brepocitinib (2.1%) [14], tofacitinib (1.6%) [12, 22, 24], and ruxolitinib (1.7%) [18]. Diarrhea was also reported in 1.4% [24] of children treated with oral tofacitinib.

Nausea was observed in 8.7% [13] and 6.4% [14] of adults treated with deuruxolitinib and brepocitinib, respectively. Abdominal pain occurred in 6.4% [14], 2.2% [12, 16, 22, 24], and 1.7% [18] of adult patients receiving oral brepocitinib, tofacitinib and ruxolitinib, respectively. Moreover, abdominal pain was also reported in 4.3% [27] of children treated with oral tofacitinib.

4.4.11 Herpes Infections

Herpes zoster was described in adult patients receiving oral ruxolitinib (3.4%) [18], tofacitinib (1.4%) [18, 21, 22, 24, 36, 56], and baricitinib (1.2%) [15, 30], whereas herpes simplex was reported in 1.9% [15, 30] of adults treated with baricitinib.

4.4.12 Conjunctival Hemorrhages

Conjunctival hemorrhages were reported in adults who were treated with oral ruxolitinib at the frequency 1.7% [28].

4.4.13 Rhabdomyolysis

Rhabdomyolysis was reported in adult patients receiving systemic brepocitinib at the frequency 4.3% [14].

4.4.14 Laboratory Abnormalities

The most common laboratory abnormalities reported in patients treated with JAK inhibitors were hypercholesterolemia (10.5%), creatine phosphokinase elevation (2.0%), elevated liver enzymes (1.7%), leukopenia (0,7%), hypertriglyceridemia (0.4%). Also, anemia (0.3%) neutropenia (0.3%), eosinophilia (0.3%), elevated lipase (0.3%), hyperkalemia (0.3%), elevated urea (0.3%), low total protein (0.1%), lymphopenia (0.1%), elevated alkaline phosphatase (0.1%) and hyperbilirubinemia (0.1%) were reported.

Hypercholesterolemia was the most commonly reported adverse effect in patients treated with oral baricitinib at the frequency 18.2% [15]. It was observed in 3.9% [13], 3.1% [18, 20, 21, 24, 35, 36, 56], and 2.1% [14] of adult patients treated with oral deuruxolitinib, tofacitinib and brepocitinib, respectively. Hypercholesterolemia was observed in 4.3% [26] of children receiving oral tofacitinib. Additionally, hypercholesterolemia was the second most commonly reported adverse effect in adults treated with topical tofacitinib at the frequency 28.6% [33].

Elevated liver enzymes were reported in 5.2% [18], 4.3% [14], 2.7% [12, 18, 20–22, 24, 32, 36, 37], and 1.0% [13] of adults treated with oral ruxolitinib, brepocitinib, tofacitinib, and deuruxolitinib, respectively. In children treated with oral and topical tofacitinib, liver enzymes were elevated in 14.5% [26, 38, 39] and 6.7% [40] of cases, respectively.

Leukopenia was reported in adults treated with oral ruxolitinib (5.2%) [18, 29] and tofacitinib (1.6%) [18, 21, 24, 36] as well as in children treated with topical tofacitinib (6.7%) [40]. Lymphopenia was reported in 2.1% [14] of adults receiving oral ritlecitinib and in 1.4% [39] of children receiving oral tofacitinib. In 4.3% [14] and 1.9% [13] of adults treated with oral brepocitinib and deuruxolitinib, respectively neutropenia was observed. Eosinophilia was described in 7.2% [26] of children receiving systemic tofacitinib.

An increased level of creatine phosphokinase were observed in 5.8% [13], 3.2% [15, 30], and 2.1% [14] of adults treated with oral deuruxolitinib, baricitinib and brepocitinib, respectively. An elevated lipase level was only described in adults treated with deuruxolitinib at the frequency 4.9% [13]. Hyperkalemia, an elevated level of urea and hypertriglyceridemia were reported in children receiving oral tofacitinib (4.3%, 4.3%, and 2.9%, respectively) [26] and in adults receiving deuruxolitinib (1.9%, 1.9%, and 1.0%, respectively) [13]. A low total protein level, hyperbilirubinemia and an elevated alkaline phosphatase level were only observed in children treated with oral tofacitinib (1.4%, 1.4%, 1.4% respectively) [26, 39].

5 Discussion

JAK inhibitors are the most effective therapeutic option for alopecia areata. A good response, defined as 50% improvement in Severity of Alopecia Tool (SALT) score, is observed in 63% of patients treated with systemic JAK inhibitors [41]. However, the discontinuation of JAK inhibitors results in the disease recurrence in 82.7% of cases [42]; thus, life-long treatment is usually required.

Alopecia areata has been considered an organ-specific disorder limited to the hair follicles. However, recent studies have indicated that the disease is associated with systemic dysregulation of cytokines [43], which leads to the presence of numerous inflammatory and metabolic comorbidities [44].

Considering the presence of numerous systemic disorders in patients with alopecia areata and a need to usually prolong therapy, awareness of safety profile of JAK inhibitors in these patient group is especially important [45].

It has been described that obesity and hyperlipidemia are more frequently observed in patients with alopecia areata compared to healthy controls [46]. In previously published studies, all systemic JAK inhibitors used in patients with alopecia areata were associated with an increased risk of hyperlipidemia. The highest frequency of hypercholesterolemia was reported in adults receiving baricitinib. Moreover, in patients treated with baricitinib, hypercholesterolemia was the most common adverse event. Hypercholesterolemia was also reported in children treated with oral tofacitinib and adults treated with topical tofacitinib. On the contrary, no hyperlipidemia was reported in adults receiving oral ruxolitinib and ritlecitinib. Weight gain was only reported in adults treated with oral tofacitinib and ruxolitinib. According to these observations, in patients with alopecia areata with coexisting hyperlipidemia and obesity, oral ritlecitinib may be considered as the safest therapeutic option.

An association between alopecia areata and atopy is well described. In the study performed by Kridin et al [47], an increased prevalence of asthma, atopic dermatitis, allergic rhinitis and allergic conjunctivitis in patients with alopecia areata compared to control group was observed. Allergy symptoms were also reported in adult patients with alopecia areata treated with oral ruxolitinib, ritlecitinib, and brepocitinib. According to these observation, in patients with alopecia areata with coexisting atopy, oral tofacitinib and deuruxolitinib may be recommended as the first-line therapeutic options.

The role of gut microbiota in pathophysiology of alopecia areata has been suggested [48]. Recently, it was shown that

JAK inhibitors affect gut microbiota [59]. The influence of JAK inhibitors on gut microbiota in patients with alopecia areata may result in hair regrowth but also causes gastrointestinal adverse effects. In patients with alopecia areata, all systemic JAK inhibitors, except for baricitinib, were associated with an increased risk of gastrointestinal side effects.

It has been suggested that alopecia areata may be associated with an increased risk of acne due to the lack of hair, which is important for follicular orifice opening and sebum removal [49]. In patients with alopecia areata treated with tofacitinib, baricitinib, brepocitinib, ritlecitinib, and deuruxolitinib an increased risk of acne was reported. On the contrary, acne was not presented in patients with alopecia areata treated with oral ruxolitinib.

It has been shown that alopecia areata is associated with a higher risk of migraine and vice versa [50]. In the present analysis, all systemic JAK inhibitors were associated with a risk of headache. However, the highest prevalence of headache was observed in adults treated with oral deuruxolitinib.

It is worth emphasizing that upper respiratory tract infections are the most common adverse effects in patients treated with oral tofacitinib and ruxolitinib. Also in patients treated with JAK inhibitors, herpes infections and urinary tract infections may occur.

In 2021, the FDA required warnings about an increased risk of serious heart-related events, cancer, blood clots, and death for JAK inhibitors (tofacitinib, baricitinib, upadacitinib) [11]. In our analysis, no increased risk of severe adverse events was observed in patients with alopecia areata treated with JAK inhibitors.

6 Conclusions

The most common adverse effects of systemic JAK inhibitors in alopecia areata are upper respiratory infections, headache, acne, and hypercholesterolemia. In studies that included a placebo arm, the OR for upper respiratory tract infections varied from over 7-fold increased (deuruxolitinib) to comparable to placebo (baricitinib, ritlecitinib). The most common adverse effects of topical JAK inhibitors are skin irritation and folliculitis. Although adverse effects of different JAK inhibitors in alopecia areata follow a similar group pattern, the frequency of particular adverse effects varies between different drugs. Available data on treatment of alopecia areata with JAK inhibitors indicate that this treatment is not associated with an increased risk of severe adverse events.

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