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Title: Adverse events in patients treated with Jak-inhibitors for alopecia areata: a systematic review

Running head: Safety profile of Jak-inhibitors in alopecia areata

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Keywords: alopecia areata, biologics, drug studies, hair disorders

Tables: 3

Figures: 1

Word Count: 3169

Funding sources: None

Conflict of interest: None declared

Data availability statement: The data that support the findings of this study are available on request from the corresponding author, [JS].

Abstract:

Recently, the impressive efficacy of JAK-inhibitors (JAK-I) in alopecia areata (AA) has been described in several studies; however, to date, there is limited information on the safety of JAK-I in AA patients. For this reason, on the August 18th 2022, a systematic review was performed to collect the pre-marketing and post-marketing data on the safety of JAK-I in patients treated for AA, evaluating for each molecule the reported adverse events (AEs) in indexed literature and their frequency. The keywords "alopecia areata" AND "Jak-inhibitors OR Janus-kinase Inhibitors" were searched on PubMed, Embase, and Cochrane databases.

Of 407 studies retrieved, 28 papers met the requirements and were used in our review, including 5 RCTs and 23 case series, overall 1719 patients were included and the safety of 6 JAK-I was assessed (baricitinib, brepocitinib, deuruxolitinib, ritlecitinib, ruxolitinib, tofacitinib). Systemic JAK-I were well tolerated, most of the AEs were mild, and the withdrawal rate for AEs was very low and inferior to placebo in controlled studies (1.6% vs. 2.2%). Laboratory abnormalities represented 40.1% of AEs associated with oral JAK-I, which mostly included the rise in cholesterol, transaminase, triglycerides, creatine phosphokinase (CPK), and sporadic cases of neutro/lymphocytopenia. The remaining AEs involved the respiratory tract (20.8%), the skin (17.2%), the urogenital (3.8%), or the gastroenterological (3.4%) tract. Increased rates of infections involved not only the upper (19.0%) and lower (0.3%) respiratory tract, but also the urogenital system (3.6%), and the skin (4.6%). Isolated cases of grade 3 to 4 AEs have been reported, including myocardial infarction, hypertensive urgencies, cellulitis, rhabdomyolysis, neutropenia, and high elevation of creatinine kinase. No fatal outcomes were reported. AEs reported with topical formulation included scalp irritation and folliculitis.

The main limit of this review is the lack of data related to post-marketing surveillance, which should be maintained on a long-term basis.

MAIN TEXT

Introduction

Alopecia areata (AA) is an autoimmune non-scarring alopecia that affects up to 2% of the general population worldwide. AA does not show ethnic variations or gender-specific predominance, and may start at any age, with a peak in the third and fourth decade of life.[1] A single AA episode has a 34-50% probability of undergoing spontaneous resolution within 1 year[2], however, many patients expect wax and wane course, characterized by clinical remission and sudden relapse. Some cases become chronic, especially when the hair loss is extensive. About 14-25% of patients may progress to complete loss of hairs on the scalp (AA totalis), sometimes in combination with loss of hairs in all body areas (AA Universalis).[1,2] Traditional treatments for AA include the use of topical, intralesional, and systemic corticosteroids, minoxidil, contact immunotherapy, and conventional immunosuppressants. Still, their efficacy is limited and none of these treatment have been shown to maintain prolonged remission with hair regrowth.[2,3] Recently, the impressive efficacy of Janus-kinase inhibitors (JAK-I) targeting JAK 1,2, 3, and TYK2 in AA has been described in several studies.[4] Therefore, the popularity of prescription of JAK-I for AA is rising in adult and pediatric patients, making the evaluation of safety profiles mandatory, since AA treatment is long-term. Limited information is available concerning the safety of JAK-I in AA and their benefit-risk profiles.

Our aim is to review the adverse events (AEs) associated with JAK-I used in the treatment of AA, including both commercially available JAK-I (tofacitinib, baricitinib, ruxolitinib) and experimental ones, evaluating, for each one, the reported events in the AA treated population. The final aim is to gain a better understanding of the benefit-risk profile of each JAK-I used in AA.

Material and methods

We conducted a systematic review of AEs attributed to JAK-I inhibitors in the treatment of AA, either in an oral or topical formulation. Papers published in English up to the 18th of August 2022, were retrieved via Pubmed, Embase, and the Cochrane Library, using the term "alopecia areata" AND "JAK inhibitors" OR "Janus-kinase Inhibitors". Two authors (JS and AS) assessed the papers independently. Information sources of the search were processed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyzes (PRISMA). All studies published in English until the search date were included. Furthermore, a manual search of references cited by screened reports was conducted to include potential relevant studies. Studies reporting information on AEs were eligible. Randomized controlled trials (RCTs) and observational studies, including cohort, case-control, cross-sectional studies, and case series with 5 or more patients, were included in the review. Data related to non-exposed patients (placebo or controls) coming from included RCTs or observational comparative studies were equally collected in a separate file. Exclusion criteria were: review articles, case series with fewer than 5 patients, commentaries, conference abstracts, studies involving non-human subjects, or studies that did not provide sufficient information of safety in the treated groups. Any incongruence in data screening and collection among the two independent assessors was resolved through discussion with the senior authors (BMP and LN). For the included articles, we collected any single AE separately and classified using a standardized excel sheet to fit within the following categories (cardiovascular, respiratory, dermatologic, urogenital, laboratory and others). In case of pooled data regarding safety or missing data, the corresponding author was contacted to obtain the not-specified data. The Cochrane risk of bias tool was used to assess RCT, whereas the updated risk of bias in nonrandomized studies of interventions (ROBINS-I) was used to assess case series and cohort studies.

Results

A total number of 407 articles were identified, of which 107 were duplicated across the selected databases (Fig 1).

In the screening process, 203 articles were excluded due to the following reasons: language other than English (12), review articles (101), conference abstracts (48), not relevant topics, or not including human subjects (42). The full texts of the remaining 97 articles were assessed for eligibility: 48 articles were excluded as they do not detail AEs data and 21 articles were excluded as they included less than 5 subjects. At the end of the process, 28 articles, including 5 RCTs and 23 case series were selected, with 5 studies (all RCTs) having a control group treated with a placebo. In these articles, 1719 patients, mean age 35.65 years, female ratio 60.33, were treated with JAK-I (1668 oral and 51 topical), and 490 received a placebo (mean age of 37.58, female ratio of 60.56%). A total of 6 JAK-I (baricitinib, brepocitinib, deuruxolitinib, ritlecitinib, ruxolitinib, tofacitinib) were administered orally according to 14 dosing schedules for a median duration of 36 weeks (interquartile range: 24-48) to 1668 patients with a mean age of 36.59 years, and female percentage of 60.80% (Table 1).

Alopecia Universalis was the most common presentation among both the interventional and control groups (68% vs.74.5%), followed by patchy type (22% vs. 20.8%), totalis (8.9 vs. 4.8%) and ophiasis (1.1% vs. 0%). Data on the types of AA were missing in 38.8% and 52.9% of treated and placebo patients.

A total of 1360 AEs were reported with oral JAK-I use, varying according to the specific drug, while 6 AEs were associated with topical formulations (Table 2).

The top 5 most commonly encountered AEs in 909 patients with oral baricitinib at doses of 2mg QD or 4mg QD were increased high-density lipoprotein cholesterol (HDLC) (21.8%) and low-density lipoprotein cholesterol (LDLC) (18.2%), upper respiratory infection (URI) (7.3%), headache (6.1%) and acne (5.6%).

The incidence rate of URI increased to 20.9% in the 67 patients treated with brepocitinib 30mg QD. Also, this drug was associated with the possible onset of acne (7.5%), nasopharyngitis (7.5%), abdominal pain (6%), and headache (6%).

The incidence of AEs in 105 patients treated with deuruxolitinib tended to increase proportionally with the dosing schedule (4,8,12mg BID) and included among the most common: headache (21.0%), creatine phosphokinase (CPK) increase (20%), nasopharyngitis (14.5%), acne (13.3%), URI (10.5%) and nausea (8.6%).

Ritlecitinib 50mg QD the most commonly reported AEs among 780 treated patients were nasopharyngitis (11.5%), URI 7.7%, headache 7.7%, acne 6.4%, and diarrhea 5.1%.

Fifty patients who were administered Ruxolitinib 20mg BID reported most frequently URI (14%), urinary tract infection (UTI) (12%), herpes zoster infection (4%), headache, and fatigue (4%) and showed a mild increase of aspartate aminotransferase/alanine aminotransferase (AST/ALT) ratio in laboratory tests (6%).

Oral tofacitinib was administered to 459 patients with different dosing schedules depending on studies (4, 5, 10, 15 mg QD, and 5, 10 mg BID). The top 5 most common AEs were URI (14.8%), acne (8.9%), headache (5.4%), and lab abnormalities, including elevated transaminase levels (5.2%) and raised levels of cholesterol (3.5%).

The topical formulation of tofacitinib cream 2% applied to the scalp twice daily by 51 patients, which caused scalp irritation in 5 (9.8%) and folliculitis in one (2%).

Data related to drug withdrawal can be categorized as permanent discontinuation or transitory interruption. The percentage of patients treated with oral JAK-I who discontinued the drug for AEs was 1.6%, compared to 2.2% in the control group. The percentage of patients treated with oral JAK-I who interrupted the drug for AEs was 1.9% in the oral-treated patients and 2.9% in controls (Table 1).

Most of the AEs were mild and no fatal AE was reported. Isolated clinical and laboratory grade 3-4 AEs were reported in 5 cases, including 1 myocardial infarction in a patient exposed to baricitinib 2mg BID (out of 367 patients), 1 hypertensive urgency in the group receiving tofacitinib 5mg BID

(out of 459 patients), 1 case of cellulitis occurring under deuruxolitinib treatment (out of 105 patients), and 2 rhabdomyolyses with brepocitinib (out of 67 patients). Laboratory grade 3-4 AEs were 2.2% (37/1668) with the most frequent event being CPK elevation (0.7%) and neutropenia (0.5%) in baricitinib, brepocitinib, deuruxolitinib and ritlecitinib exposed groups. No grade 3-4 AE was reported with the use of Ruxolitinib. All severe AEs are summarized in Table 3.

Laboratory AEs were the most frequently reported among all the oral JAK-I accounting for 40.1% of the total number of AEs, followed by respiratory (20.8%), dermatologic (17.2%), urogenital (3.8%) and gastroenterological (3.4%) AEs.

The most frequent laboratory abnormalities mainly involved the hepatic and metabolic panels, including the increase in cholesterol (28.5% of all AEs), transaminase (2.9%), triglycerides (1.2%) and CPK (0.4%). Complete blood count (CBC) abnormalities were rare and limited to 10 cases of neutropenia (0.7%) and 5 of leukopenia (0.4%).

The most common respiratory, dermatologic, urogenital and gastroenterological AEs were: URI (19.0%, of which nasopharyngitis 5.9%), acne (8.7%), UTI (3.6%), and diarrhea (1.1%). Urogenital AEs were reported in the cohorts treated with baricitinib (3.5%), ruxolitinib (12%) and tofacitinib (5%), with UTI being the most frequent.

Increased rate of infections involved not only the upper (19.0%), and lower (0.3%) respiratory tract, but also urogenital system (3.6%), and the skin (4.6%) with herpes zoster accounting for 1.5% of events.

Subjective symptoms most commonly consisted of headache (8.5%), nausea (1.6%), and fatigue (1.0%).

To investigate the distribution of AEs caused by oral JAK-I among the recruited populations according to sex and age, we were able to extract the available data from 4 out of 28 papers, which included 41 patients who were all treated with oral tofacitinib. The incidence of AEs showed a male

to female ratio of 1.2:1 in this group (p=0.70). However, no further data regarding demographic trends of AEs could be collected, due to the lack of availability of individual patient's records.

The RCT clinical trials were sponsored by the pharmaceutical industry, and a population-choice bias could have occurred. All case series recruited non-consecutive patients and are prone to selection bias and to confounding factors (such as concomitant disease and relative treatment).

Discussion

The etiopathogenesis of AA is multifactorial and is driven by genetic, immunologic, and environmental factors. Recent studies have revealed the pivotal role of IFN-γ, IL-15, CD8+ and NKG2D+ T cells in the pathogenesis of AA, with the Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathway at the base of their interactions.

Research studies on murine models have shown that IFN-γ produced by CD8+NKG2D+T cells acts on hair follicle keratinocytes, binding to JAK1 and JAK2 molecules and stimulating the production of IL-15. IL-15, in turn, binds to the surface of CD8+NKG2D+T cells via JAK1 and JAK3 pathways, inducing further production of IFN-γ. This positive feedback of IFN-γ and IL-15 production through the JAK-STAT pathway enhances inflammation and progression of AA.[2,5-7] These advances support the strong rationale for the clinical use of JAK-I in AA.[5-8]

In June 2022, based on the results of two RCTs, namely BRAVE-AA1 and BRAVE-AA2, baricitinib became the first drug approved by the European Medicine Agency (EMA) and Food and Drug Administration (FDA) for the treatment of severe AA in adult patients.[9,10] However, FDA and EMA have placed several warnings concerning the risk of thromboembolic events and infectious complications related to JAK-I. In September 2021, FDA issued a black box warning about an increased risk of serious heart-related events, such as heart attack or stroke, cancer, blood clots, and death in patients treated with JAK-I used for rheumatoid arthritis and ulcerative colitis.[11] In February 2022, EMA launched a call to review the safety of JAK-I used to treat rheumatoid arthritis, psoriatic

arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, ulcerative colitis, and atopic dermatitis. This call was prompted by the results obtained in a clinical trial and preliminary findings from an observational study, which showed that patients administered with tofacitinib or baricinitib for rheumatoid arthritis were at a higher risk of major cardiovascular adverse events and venous thromboembolism compared to control patients treated with TNF-alpha inhibitors.[12]

This systematic review on AEs of JAK-I in AA included 28 studies (5 RCTs, 23 case series) with a total of 1668 patients with AA treated with oral JAK-I and 51 treated with topical JAK-I. Five of the studies included pediatric patients. Three studies reported topical application. Overall, oral JAK-I were well tolerated, and drug interruption due to adverse events was less than placebo in controlled studies. No fatal adverse events were reported. Overall, 0.3% developed severe or life-threatening events, with 2 cases of rhabdomyolysis (brepocitinib), 1 case of myocardial infarction (baricitinib), 1 case of cellulitis (deuruxolitinib), and 1 case of hypertensive urgency (tofacitinib). These data, even if somewhat reassuring, should be taken with caution. The overall duration of the studies was limited and AEs occurring after a latency period cannot be properly evaluated. Moreover, given the limited number of patients analyzed, rare but severe AEs could not be ruled out with confidence. Finally, most of the data come from RCTs with a high degree of patient selection and close patient monitoring. We combined data from different sources in an unadjusted way, and our summary measure should only be taken as rough indication of the actual frequency of the AEs.

The most frequently reported adverse events for all JAK-I were infections, particularly infections of the upper respiratory tract, with the highest rate reported for beprocitinib, followed by tofacitinib, ruxolitinib, and baricitinib. In baricitinib, in contrast to tofacitinib, there was a slight trend for higher number of infections with increased doses, as previously described in a retrospective analysis of the World Health Organization (WHO) pharmacovigilance data.[13] However, in controlled studies, no relevant difference could be found compared to the placebo group. The same observation was made

in a previous meta-analysis.[4] Nasopharyngitis has been associated with treatment with all types of JAK-I except tofacitinib, but no higher risk was observed compared to the control groups.[4]

Other infections reported with all types of JAK-I included urinary tract infections (3.5% for baricitinib, 12% for ruxolitinib, and 2.6% for tofacitinib) and rarely viral infections, such as herpes zoster (1.2%) and herpes simplex (1.0%). The rate of herpes simplex infection reported in patients receiving baricitinib for AA was not higher than that seen in the placebo group in randomized controlled trials.[14,15] Herpes zoster has already been identified as a possible complication of JAK-I in clinical trials and pharmacovigilance studies.[13,15] In our review, we found that herpes zoster occurred in 1.4% of patients treated with baricitinib 2mg QD, 1.1% of patients treated with baricitinb 4mg QD, 4% of patients treated with ruxolitinib 20mg BID, and 1.8% of patients treated with tofacitinib 5mg BID. It would be interesting to know the race of patients who developed herpes zoster, as its occurrence may differ by race.[16] Moreover, the risk of herpes zoster should be considered in the light of other risk factors, including older age, glucocorticoid exposure, and underlying immunologic dysregulation.[13] Several reports highlighted a higher incidence of herpes zoster in Asian patients exposed to baricitinib.[17,18]

Besides infections, the most frequent AE reported in all types of JAK-I treated patients was headache, with the highest rate in deuruxolitinib, followed by ritlecitinib, baricitinib, brepocitinib, tofacitinib, and ruxolitinib. However, a recent meta-analysis of the 5 RCTs showed a similar incidence of this side effect in the placebo groups.[4]

Acne was a possible side-effect of all types of JAK-I, expect Ruxolitinib, with an average prevalence of 6.7%. This side-effect was higher in baricitinib compared to control group. The data were not matched by age, making an assessment difficult.[14] An isolated case report described acne onset in a 59-years old woman during baricinitib treatment, which regressed after she was switched to upadacitinib.[19]

In a large retrospective observational analysis of WHO pharmacovigilance data, gastrointestinal perforation has been described in patients treated with tofacitinib mainly affected by inflammatory bowel disease.[13] The IR was estimated at 0.1 events/100 patient-years in patients with rheumatoid arthritis exposed to tofacitinib up to 9.5 years.[20] In patients with AA, no such event has been reported; in the included studies, gastrointestinal side effects were limited to nausea, diarrhea, functional dysregulation, and abdominal pain.

Several studies have reported safety warnings about thromboembolism with JAK-I, with the highest rates seen in baricitinib, followed by ruxolitinib and tofacitinib in patients with previous cardiovascular risk factors.[13,21] Interestingly, in our review focusing on AA, no thromboembolic events were identified. Long-term safety analyses of baricinitib and tofacitinib for the treatment of rheumatoid arthritis showed incidence rates (IR) of major adverse cardiovascular events of 0.5 and 0.4 per 100 patient-years at risk, respectively. The IR for deep venous thrombosis (DVT)/pulmonary embolism (PE), DVT, and PE were 0.49, 0.35, and 0.26 for baricitinib and 0.3, 0.2, and 0.1 for tofacitinib.[18,20] Several factors could have influenced the lack of observed thromboembolic events in our survey. Follow-up duration was limited in AA studies, and patients with AA are usually young and healthy, without recognized cardiovascular risk factors. Systemic inflammation, as found in rheumatoid arthritis, and older age are risk factors for thrombosis.[13,22] A previous review about the safety of baricitinib in dermatologic and rheumatologic diseases already reported that venous thromboembolism was generally within or below the ranges reported for the respective disease populations.[22]

Additionally, a WHO pharmacovigilance report found no association between JAK-I and major cardio/cerebrovascular events.[13]

As for laboratory findings, the most significant abnormality was hypercholesterinemia, consisting of an elevation of HDLC and LDLC in 11.5% and 9.8% of patients, respectively. These findings, along with grade 3-4 adverse events in laboratory findings, underline the usefulness and importance of

laboratory screening in younger patients and the recommendation to repeat a complete metabolic panel after treatment initiation, as recommended for baricitinib.[23]

JAK-I have been suspected to be associated with a higher risk of malignancy. None of the patients in our review developed cancer during the study periods. An analysis of baricitinib use for diverse indications showed that the number of malignancies in treated patients was generally within or below the ranges reported for the respective disease populations.[22]

A total of 5 studies involved pediatric and adolescent patients, 4 with oral and 1 with topical tofacitinib.[24-28] Side effects were comparable to those reported in adults, including headache, upper respiratory tract infections, gastrointestinal distress, and mild increase of liver transaminase as well as hypertriglyceridemia and one case of lymphopenia.[24-26] All side effects resolved spontaneously after the drug was stopped. In topical application, only local irritation and folliculitis have been reported, similar to the reports in adults using the same topic.[28]

This review did not include two JAK-1 inhibitors which proved effective in stimulating hair regrowth in AA, due to the small population size. Oral abrocitinib (100/200 mg daily) was administered to 3 patients (2 females and 1 male aged 14, 46 and 33 years) suffering from AA and atopic dermatitis, for a median period of 56 weeks with no reported side effects.[29,30]

5 cases (3 males and 2 females meanly aged 36years) affected by AA, and in 4 out of 5 cases by moderate-severe atopic dermatitis, were treated with oral upadacitinib 30mg/daily (not specified in 1 case) for a mean time of 13 weeks with no reported AEs.[19,31-33] Interestingly, one patient had previously ceased baricitinib due to AEs including severe acne, migraine, orolabial herpes simplex infection and lethargy.[20]

Conclusion

The major concern of cardiovascular events has never been documented in AA patients receiving JAK-I. Our review has shown that adverse events in patients taking JAK-I for severe AA are

infrequent, self-limited, and mostly mild or moderate. Their use for AA is thus justified by making patients' quality of life achievable by improving the disease. However, the limited available data, the isolated cases of severe adverse events, especially in laboratory findings and the safety signals in previous studies, prompt a benefit-risk assessment, and regular safety checks on each patient being treated. Reporting bias could have occurred in those case series that did not recruit consecutive patients, impacting the real number of AEs. Also, the available data cannot rule out even severe AEs occurring after a latency period or with a rate of less than 1 per 1000 treated patients. Collaborative registries to assess the long-term efficacy and safety of JAK-I inhibitors for AA in a real-world setting are advocated.

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Tables

Randomized control trial								
Source (Year)	Jak Inhibitor drug	Dose	AEs/tot pt (intervention group)	AEs/tot pt (control group, placebo)	Age (years)	Sex (female %)	Duration (weeks)	% discontinuation (intervention; control)
King et al,[34] (2022)	Deuruxolitinib (oral)	4mg BID 8mg BID 12mg BID	25/30 31/38 30/37	31/44	M: 36.8 (SD: 12.9)	70.5	24	Discontinuation 1.9%; 6.8% Interruption 4.9%;11.4%
King et al,[15] (2022)	Baricitinib (oral)	2mg QD 4mg QD	199/338 321/513	194/343	M: 37.6 (SD: 12.9)	60.7%	36	2% ; 1.7% 2.1% ; 1.7%
Peeva et al,[35] (2022)	Ritlecitinib (oral)	50mg QD	19/30	12/17	N/A	N/A	24	3.3% ; 0%
Peeva et al,[35] (2022)	Brepocitinib (oral)	30mg QD	13/20	10/12	N/A	N/A	24	5% ; 0%
King et al,[14] (2021)	Baricitinib (oral)	2mg QD 4mg QD	19/27 21/27	17/27	M: 42.5 (SD: 14.4)	88.9%	36	0% ; 0% 4.6% ; 0%
King et al,[36] (2021)	Ritlecitinib (oral)	50mg QD	32/48	35/47	M: 37 (SD: 13)	77%	24	Discontinuation 0% ; 4% Interruption 4% ; 6%
King et al,[36] (2021)	Brepocitinib (oral)	30mg QD	36/47	35/47	M: 34 (SD: 11)	68%	24	Discontinuation 4% ; 4% Interruption 8% ; 6%
Case series								
Zhang et al,[37] (2022)	Tofacitinib (oral)	5mg BID	7/20		m: 26.1	65%	54	0%
Sanchez-Diaz et al,[38] (2022)	Tofacitinib (oral)	5mg BID	7/17		M: 32.6 (SD: 18.7)	76.4%	57	0%, 0%
Kibbie et al,[26] (2022)	Tofacitinib (oral)	5mg BID 5mg QD +10mg QD 10mg BID	2/4 2/6 0/1		M: 17 (SD: 2.59)	63.6%	139	0% 0% 0%
Kerkemeyer et al,[39] (2021)	Tofacitinib (Topical)	2% BID	0/26		M: 30	34.6%	35	0%
McKenzie et al,[27] (2022)	Tofacitinib (oral)	10mg QD	7/21		M: 15.5	52.4%	135	0%

Dincer Rota et al,[40] (2021)	Tofacitinib (oral)	10mg QD	10/13		M: 32.1 (SD: 8.04)	61.5%	13~52	7.7%
Jerjen et al,[25] (2021)	Tofacitinib (oral)	4mg QD	5/11		M: 9.5	54.5%	64	0%
Chen et al,[41] (2019)	Tofacitinib (oral)	5mg QD	0/6		M: 32.8 (SD: 14.3)	66.7%	24	0%
Akdogan et al,[42] (2019)	Tofacitinib (oral)	10mg QD	3/9		M: 27.8 (SD: 14.8)	11.1%	26	0%
Wambier et al,[43] (2021)	Tofacitinib (oral)	5mg BID	6/12		M: 39.6	58.3%	39	0%
Serdaroglu et al,[44] (2019)	Tofacitinib (oral)	5mg BID	21/63		M: 27	47.6%	26~130	0%
Almutairi et al,[45] (2019)	Ruxolitinib (oral)	20mg BID	21/38		M: 35.5 (SD: 13.8)	44.7%	26	0%
Almutairi et al,[45] (2019)	Tofacitinib (oral)	5mg BID	27/37		M: 47.4 (SD: 16.1)	40.5%	26	0%
Shivanna et al,[46] (2018)	Tofacitinib (oral)	5mg BID	2/6		M: 27.7 (SD: 5.1)	50%	13~26	0%
Cheng et al,[47] (2018)	Tofacitinib (oral)	5mg BID	4/11		M: 38.3 (SD: 12.7)	72.7%	61	0%
Cheng et al,[47] (2018)	Tofacitinib (Topical)	2% BID	0/4		M: 42.5 (SD: 14.5)	25%	30	0%
Putterman et al,[28] (2018)	Tofacitinib (Topical)	2% BID	1/11		M: 11.5 (SD: 3.9)	81.8%	35	0%
Jabbari et al,[48] (2018)	Tofacitinib (oral)	5mg BID	11/12		M: 34.7 (SD: 9.2)	66.7%	26~78	8.3%
Liu et al,[49] (2018)	Tofacitinib (topical)	2% BID	5/10		M: 36.9 (SD: 14.2)	40%	24	0%
Park et al,[50] (2017)	Tofacitinib (oral)	5mg BID	0/32		m: 30 (R: 18-54)	50%	33	0%
Ibrahim et al,[51] (2017)	Tofacitinib (oral)	5mg BID	3/13		N/A	92.3%	28	0%
Liu et al,[52] (2017)	Tofacitinib (oral)	5mg BID	35/90		m: 34.5 (R: 18~70)	55.6%	52	0%
Craiglow et al,[24] (2017)	Tofacitinib (oral)	5mg BID	7/13		m: 15 (R: 12~17)	23.1%	22	0%
Mackay-Wiggan et al,[53] (2016)	Ruxolitinib (oral)	20mg BID	9/12		M: 43.7 (SD: 14.4)	58.3%	20	0%
Kennedy Crispin et al,[54] (2016)	Tofacitinib (oral)	5mg BID	17/66		m: 37 (R: 19~65)	53.0%	13	0%

Table 1: Characteristics of the included studies.

Table legend: Summary of the identified studies of JAK-I for AA. Abbreviations:

AEs = Adverse events, QD= quaque die, BID= bis in die, M= mean, SD= standard deviation, m=median, R=interquartile range. N/A= not available data.

Drug name	Dose (pt)	Cardiovascular (pt)	Respiratory (pt)	Dermatologic (pt)	Urogenital (pt)	Laboratory (pt)	Gastrointestinal (pt)	Others (pt)
Baricitinib	2mg QD[14,15] (367)	Myocardial infarction 0.3% (1)	URI 6.5% (24) Nasopharyngitis 3.8% (14)	Acne 5.7% (21) Herpes simplex 2.5% (9) Herpes zoster 1.4% (5)	UTI 3.8% (14)	↑ HDL 19.6% (72) ↑ LDL 14.7% (54) ↑ CPK 0.8% (3) Neutropenia 0.5% (2) Thrombocytosis 0.3% (1) ↑ Triglyceride 0.3% (1)		Headache 5.4% (20) Nausea 0.5% (2)
	4mg QD[14,15] (542)		URI 7.7% (42) Nasopharyngitis 6.6% (36)	Acne 5.5% (30) Herpes simplex 1.5% (8) Herpes zoster 1.1% (6)	UTI 3.3% (18)	↑ HDL 23.2% (126) ↑ LDL 20.5% (111) ↑ CPK 4.2% (23) ↑ Triglyceride 0.7% (4) Neutropenia 0.6% (3) Thrombocytosis 0.4% (2) Anemia 0.2% (1)		Headache 6.5% (35) Nausea 0.4% (2) B-cell Lymphoma 0.2% (1)
Brepocitinib	30mg QD[35,36] (67)		URI 20.9% (14) Nasopharyngitis 7.5% (5) Sinusitis 4.5% (3) Oropharyngeal pain 4.5% (3)	Acne 7.5% (5) Folliculitis 1.5% (1) Atopic dermatitis 1.5% (1) Unspecified 1.5% (1)		↑ ALT 4.5% (3) Neutropenia 4.5% (3) Rhabdomyolysis 3% (2)	Abdominal pain 6.0% (4) Unspecified 4.5% (3) Diarrhea 1.5% (1)	Headache 6.0% (4) Nausea 4.5% (3) Unspecified nervous system 3.0% (2) Musculoskeletal disease 1.5% (1)
Deuruxolitinib	4mg BID[36] (30)		Cough 13.3% (4) Oropharyngeal pain 10% (3) Nasopharyngitis 10% (3) URI 6.7% (2)	Acne 13.3% (4) Folliculitis 10% (3)		↑ CPK 20% (6) Neutropenia 3.3% (1) ↑ ALT 3.3% (1) ↑ Glucose 3.3% (1) ↑ Lipase 3.3% (1) ↑ Potassium 3.3% (1)	Diarrhea 10% (3)	Headache 16.7% (5) Nausea 13.3% (4)
	8mg BID[36] (38)		Nasopharyngitis 7.9% (3) URI 5.3% (2) Cough 2.6% (1) Oropharyngeal pain 2.6% (1)	Acne 10.5% (4) Folliculitis 5.3% (2)		↑ CPK 16.8% (6) ↑ LDL 10.5% (4) Neutropenia 2.6% (1) ↑ ALT 2.6% (1) ↑ Amylase 2.6% (1) ↑ Lipase 2.6% (1) ↑ Phosphate 2.6% (1)	Diarrhea 2.6% (1)	Headache 26.3% (10) Nausea 10.5% (4)
	12mg BID[36] (37)		Nasopharyngitis 24.3% (9) URI 18.9% (7)	Acne 16.2% (6) Folliculitis 2.7% (1) Cellulitis 2.7% (1)		↑ Lipase 8.1% (3) ↑ Phosphate 5.4% (2) ↑ Urate 5.4% (2)		Headache 18.9% (7) Nausea 2.7% (1)

			Cough 5.4% (2)			↑ Creatine kinase 5.4% (2) ↑ Potassium 2.7% (1) ↑ Triglycerides 2.7% (1) ↑ Amylase 2.7% (1)		
Ritlecitinib	50mg QD[35,36] (78)		Nasopharyngitis 11.5% (9) URI 7.7% (6)	Acne 6.4% (5) Folliculitis 3.8% (3) Atopic dermatitis 3.8% (3) Unspecified 3.8% (3)		↑ ALT 3.8% (3)	Diarrhea 5.1% (4) Unspecified 2.6% (2)	Unspecified nervous system 7.7% (6) Headache 7.7% (6) Nausea 3.8% (3)
Ruxolitinib	20mg BID[45,53] (50)		URI 14% (7) Tonsillitis 2% (1) Mild pneumonia 2% (1)	Herpes zoster 4% (2) Folliculitis 2% (1) Minor bacterial skin infection 2% (1)	UTI 12% (6)	↑ Mild AST/ALT 6% (3) Leukopenia 4% (2) ↓ Hemoglobin 2% (1)	Abdominal pain 2% (1) Diarrhea 2% (1) Gastrointestinal symptoms 2% (1)	Headache 4% (2) Fatigue 4% (2) Weight gain 2% (1) Conjunctival hemorrhage 2% (1)
Tofacitinib	4mg QD[25] (11)					↑ Transaminase 90.9% (10) Eosinophilia 45.5% (5) ↑ Cholesterol 27.3% (3) ↑ Urea 27.3% (3) Hyperkalemia 27.3% (3) ↓ Protein 9.1% (1) ↑ Triglycerides 9.1% (1) persistent, asymptomatic hyperbilirubinemia 9.1% (1)		
	5mg QD[41] (6)							
	10mg QD[27,40,42] (43)		URI 14.0% (6)	Acne 18.6% (8) Oily skin 18.6% (8)		↑ Transaminase 7.0% (3) Proteinuria 2.3% (1)	Gastrointestinal upset 7.0% (3)	
	5mg BID[24,26,37,38,43-48,50-52,54] (392)	Hypertensive urgency 0.3% (1) Palpitation 0.3% (1)	URI 15.8% (62) Tonsillitis 1.3% (5) Bronchitis 0.8% (3) Cough 0.3% (1)	Acne 8.4% (33) Hyperseborrhea 5.4% (21) Folliculitis 2.3% (9) Herpes zoster 1.8% (7) Hypertrichosis (usually upper lip, preauricular) 1.5% (6) Hot flash 0.8% (3) Genital warts 0.8% (3) Pruritus 0.5% (2) Morbilliform eruption 0.3% (1)	UTI 2.6% (10) Vaginal spotting (post-menopause) 0.3% (1) Urinary retention 0.3% (1) Amenorrhea 0.3% (1)	↑ Cholesterol 4.1% (16) ↑ LDL 3.8% (15) ↑ Transaminase 2.8% (11) ↑ Triglycerides 2.0% (8) ↑ AST/ALT 1.0% (4) Blood on urinalysis 1.0% (4) Hyperlipidemia 0.8% (3) Leukopenia 0.8% (3) Asymptomatic bacteriuria 0.5% (2) Lymphocytopenia 0.3% (1) ↑ Serum creatine 0.3% (1)	Abdominal pain 1.5% (6) Diarrhea 1.3% (5) Bowel movement frequency ↑ 1.0% (4) Digestive complication 0.8% (3) Loose stool 0.8% (3) Bloating 0.3% (1)	Headache 6.1% (24) Weight gain 3.1% (12) Fatigue 2.8% (11) Night sweat 1.0% (4) Conjunctivitis 0.8% (3) Nausea 0.8% (3) Numbness 0.8% (3) Knee soreness 0.3% (1) Joint ache 0.3% (1)

				Peripheral edema 0.3% (1) Bruising 0.3% (1) Verruca vulgaris 0.3% (1) Paronychia 0.3% (1)		↑ Blood urea nitrogen 0.3% (1) ↑ Lipid 0.3% (1)	Constipation 0.3% (1)	Multiple sclerosis 0.3% (1) Dizziness 0.3% (1) Neuropathic pain 0.3% (1) Tinnitus 0.3% (1) Dry eyes 0.3% (1) Arthralgia 0.3% (1) Mononucleosis 0.3% (1)
	5mg + 10mg[26] (6)					↑ ALP 16.6% (1) ↑ Triglyceride 16.6% (1)		Headache 16.6% (1) Dizziness 16.6% (1)
	10mg BID[26] (1)							
Tofacitinib 2% cream	BID[28,39,47,49] (51)			Scalp skin irritation 9.8% (5) Folliculitis 2.0% (1)				

Table 2: Characteristics of adverse events recorded per each drug and dosage

Table legend: Summary of AEs. Abbreviations: (pt)= number of patients, QD= quaque die, BID= bis in die, URI= upper respiratory tract infection, UTI=urinary tract infection, HDL=high-density lipoprotein, LDL=low-density lipoprotein, CPK=creatine phosphokinase, AST= aspartate aminotransferase, ALT= alanine aminotransferase, ALP=alkaline phosphatase.

Drug name	Dose (pt)	Grade 3-4 Disease (pt)	Grade 3-4 Laboratory (pt)
Baricitinib	2mg QD[14,15] (367)	Myocardial infarction (1)	Neutropenia (2) ↑ CPK (3)
	4mg QD[14,15] (542)		Anemia (1) Neutropenia (3)
Brepocitinib	30mg QD[34,35] (67)	Rhabdomyolysis (2)	Neutropenia (1)
Deuruxolitinib	4mg BID[34] (30)		Neutropenia (1) ↑ ALT (1) ↑ CPK (3) ↑ Glucose (1) ↑ Lipase (1) ↑ Potassium (1)
	8mg BID[34] (38)		Neutropenia (1) ↑ Amylase (1) ↑ CPK (4) ↑ Lipase (1) ↑ Phosphate (1)
	12mg BID[34] (37)(	Cellulitis (1)	↑ Amylase (1) ↑ CPK (1) ↑ Lipase (3) ↑ Phosphate 2 ↑ Potassium 1 ↑ Triglycerides (1) ↑ Uric acid (2)
Ritlecitinib	50mg QD[34,35] (78)		Lymphocytopenia (1)
Ruxolitinib	20mg BID[45,53] (50)		
Tofacitinib	5mg BID[24,26,37,38,43-48,50-52,54] (392)	Hypertensive Urgency (1)	

Table 3: Characteristics of serious clinical and laboratory adverse events recorded per single drug and dosage

Table legend: Summary of grade 3-4 AEs. Abbreviations: (pt)= number of patients, QD= quaque die, BID= bis in die, CPK=creatine phosphokinase, ALT= alanine aminotransferase.

Figure

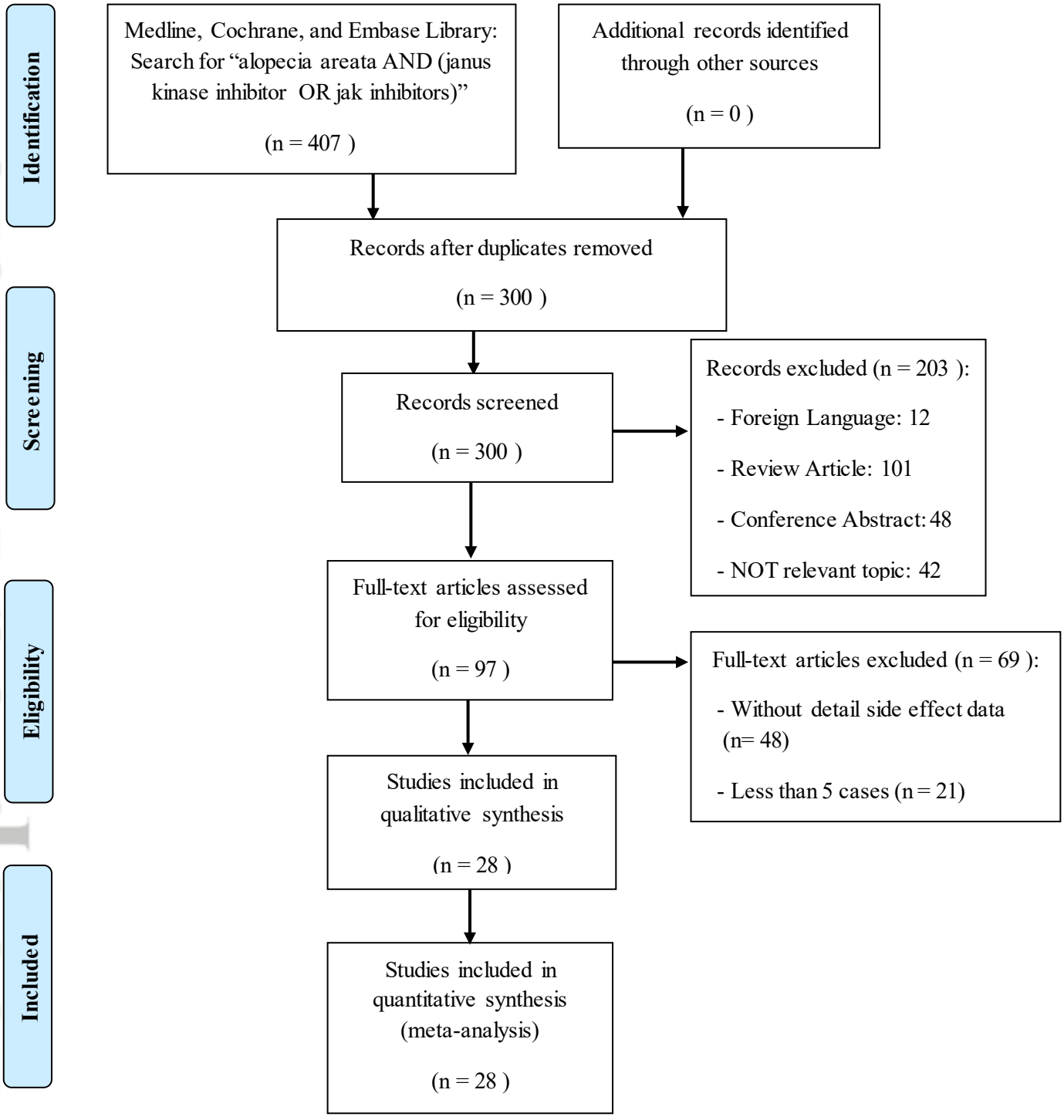

Figure 1: Flowchart for article selection according to PRISMA guideline