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ORIGINAL ARTICLE

Benefit and risk profile of tofacitinib for the treatment of alopecia areata: a systemic review and meta-analysis

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Abstract

Background Recent insights showed the possibility of using JAK inhibitors for the treatment of alopecia areata (AA). Most of the previous articles evaluated the overall efficacy of existing JAK inhibitors rather than evaluating one of them alone. Currently, the benefit and risk profile of tofacitinib for the treatment of AA is still not clear.

Objective To estimate the safety and efficacy of tofacitinib in patients with AA based on summarizing the clinical outcomes.

Methods The systematic review and meta-analysis was performed according to PRISMA guidelines. ROBINS-I (Risk of Bias in Non-randomized Studies-of Interventions) was used for quality assessment.

Results We enrolled 14 studies including six clinical trials and eight observational studies with 275 patients. The result of meta-analysis showed that tofacitinib has reasonable effectiveness in patients with AA. The pooled good/complete hair regrowth rate of tofacitinib treating patient with AA was 54.0% (95% CI: 46.3%–61.5%), and the pooled rate of partial response in patients with AA taking tofacitinib was 26.1% (20.7–32.2%). Approximately a quarter of patients had experience of relapse, most of which was reported due to discontinuation of tofacitinib. In terms of toxicity, reported adverse effects included only mild symptoms. Upper respiratory infection, headache and acne were the most common adverse events.

Conclusion Tofacitinib seems to be a promising drug for the treatment of AA with only mild adverse effects. More thorough larger sized randomized clinical trials are required to further assess the safety and clinical efficacy of tofacitinib for the treatment of AA.

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Conflicts of Interest

None declared.

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Introduction

Alopecia areata (AA) is an autoimmune condition that is meditated by the attack of hair follicles resulting in non-scarring hair loss.[1,2] For both aesthetic and medical purposes, AA has an unpredictable evolution in each patient.[3] In general, ~two per cent of the general population will be affected by AA sometimes in their lifetime.[4,5] However, prevalence can vary from 0.1% to 6.9% depending on the population and area of study.[6] AA can occur at any age, and the lifetime incidence appears at a linear rate with a median age of diagnosis at 33.[7] AA does not distinguish between gender, although some studies point towards a slight female-to-male gender bias.[8,9] In addition, diagnosis of AA for male patients is more likely during childhood compared with females during adolescence. It is generally agreed that AA can be further classified into three different groups depending on severity and the areas where the hair loss occurs: (i) alopecia areata in patches (AA), considered the most common form seen in clinic. This form of AA has characteristic round and oval

patches on the head or in different part of the body. (ii) Alopecia totalis (AT) representing the total loss of hair on the scalp. (iii) Alopecia universalis (AU), the most severe of the 3, represents total hair loss all over the body in addition to the face and scalp.[10,11]

Unfortunately, there is no cure and no universally proven treatment that induces sustained remission for AA, traditional medical therapies include corticosteroids, immunotherapy and light therapy.[12,13] Of the three traditional medical therapies, corticosteroids seem to be the most common treatment. Topical, intralesional or systemic corticosteroids are used with an aim to eliminate inflammation, preventing hair loss and controlling symptoms. Studies showed around 60% rate of hair regrowth using corticosteroids.[14] However, the use of corticosteroids needs constant clinical monitoring due to the adverse effects that can be generated such as weight gain, avascular necrosis, hypertension, diabetes, sleep disturbances, mood changes, acne, sensitivity to allergies and atypical hair coloration.[15,16] In addition to the adverse effects, the response rate to the treatment varies greatly among patients. Many factors may affect the treatment outcome of patients with AA, such as age, family history, onset of disease and other clinical conditions that could be associated. Therefore, more effective and safe treatment options are urgently needed for the treatment of AA.

Tofacitinib is a small molecule oral selective inhibitor of JAK1 and JAK3. JAK signalling pathway is important in cytokine regulation, normal cell growth and immunoregulations.[17] Tofacitinib was approved and is currently used for the treatment of moderate-to-severe rheumatoid arthritis. The efficacy and safety of tofacitinib have been extensively studied in a series of phase II and phase III randomized controlled trials. Two global long-term extension studies, including 4967 RA patients, have confirmed the sustained efficacy (>6 years) and consistent safety profile (>8 years) of tofacitinib.[18,19] Researches using animal models of AA elucidated key factors in AA pathogenesis.[3,20] An important discovery was made that blockade of cytokine receptors, in particular JAK/STAT, could reverse AA in mice.[21] This led to clinical explorations of using tofacitinib in the treatment of AA. Numerous small studies with using 1–3 patients tested the effect of tofacitinib on AA.[21–23] Similar results were seen with inflammatory remission and hair regrowth. To explore the potential clinical value of tofacitinib for the treatment of AA, we conducted this study to find out the most meaningful efficacy and safety outcomes of tofacitinib.

Methods

This systematic review and meta-analysis was performed according to PRISMA guidelines.

Search strategy

We searched the PubMed, EMBASE and Cochrane library databases from their inception dates to 7 December 2018, using the keywords *tofacitinib and alopecia areata* to identify clinical reports in which tofacitinib was used to treat alopecia areata patients. In addition, references from all retrieved articles were screened for potential eligible studies, assessed according to the inclusion and exclusion criteria. Studies of all languages were included for assessment.

Study inclusion/Exclusion criteria

Studies were selected for the final analysis based on the following inclusion criteria: (i) studies enrolling patients with alopecia areata or alopecia totalis or alopecia universalis; (ii) studies in which patients received oral tofacitinib or scalp topical tofacitinib treatment; (iii) studies providing efficacy outcome including scalp hair regrowth data or recurrence data, or safety outcome including adverse events; and (iv) studies of clinical trials or observational studies, and case series in observational studies should include more than three patients. Exclusion criteria were (i) studies in which tofacitinib was topically applicated on eyelashes of patients; (ii) studies of case reports (less than 4 cases), reviews, conference presentations and abstracts; (iii) studies not reporting relevant outcomes or data not available; and (iv) studies of repeated publications or repeated report of same study group.

Data extraction

Two investigators (L.G. and Y.L.) independently screened literatures, extracted the study information from each study and cross-checked, with disagreements resolved by consensus discussion with the third investigator (S.F.). The lack of information

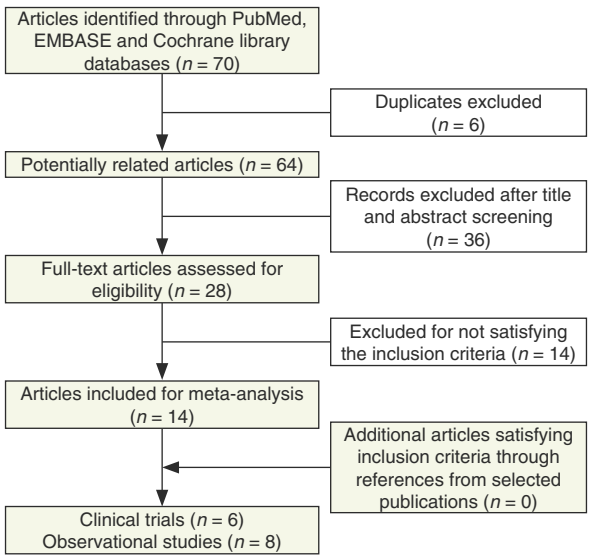

Figure 1 Flow diagram of the literature search and selection process.

Table 1 Characteristics of included studies in this systematic review and meta-analysis

Study	Study Type	Disease	Total Patient	Treatment Regimen	Treatment Duration, mo	Age (median, range, y)	Sex (M: F)	Duration of Alopecia (mean/ median, range, y)	Concomitant Comorbidity	SALT Improvement (median, range)
Bokhari 2018	Phase I RCT	AU 16	16	Tofacitinib 2% ointment twice daily, placebo (ointment base)	3	NR	NR	NR	NR	NR
Putterman 2018	CT	AA 1 AT 4 AU 6	11	Non-patented formulations of 2% topical tofacitinib	7 (2–19)	12 (4–16)	2 : 9	3 (2–10)	NR	32.3% (−10 to 92%)
Jabbari 2018	CT	AA 7 AT/AU 5	12	Tofacitinib 5 mg to 10 mg twice daily	6–18	36.5 (18–52)	4 : 8	16.5 (3–33.5)	NR	56.8% (12.1–100%)
Liu 2018	CT	AA 10	10	Tofacitinib 2% ointment twice daily	6	36.9 (19–58)	6 : 4	9.4	NR	10% (0–61%)
Bayart 2017	CT	AA 1 AT 2	3	Topical tofacitinib 2% to scalp (2 patients BID, 1 patient QOD)	3–12	5 (3–15)	0 : 3	2 (1–3.5)	NR	NR
Kennedy 2016	CT	AA (with > 50% scalp hair loss) 11 AT 6 AU 46	66	Tofacitinib 5 mg twice daily	3	37 (19–65)	31:35	5 (0.5–43)	Atopic dermatitis, allergic rhinitis, thyroid disease, asthma, vitiligo, psoriasis	21% (−)
Shin 2019	R, OS	AT 8 AU 10	18	Tofacitinib 5 mg twice daily initially, increased to 5 mg 3 times a day, then increased to 10 mg twice daily, the median total tofacitinib dose was 1680 mg	6	28 (19–51)	7 : 11	8 (2–17)	NR	36.5% (0–91.5%)
Ibrahim 2017	R, OS	AA 4 AT 2 AU 7	13	Tofacitinib 5 mg twice daily initially, holding dosage 15.8 mg(mean)	6.3	50 (20-50)	1 : 12	18	NR	50.5% (0–90%)
Liu 2017	R, OS	AA (at least 40% scalp hair loss) 13 AT/AU 52	65	Standard monotherapy group: Tofacitinib 5 mg BID (*N* = 28); Adjuvant therapy group: Tofacitinib > 5 mg BID (N = 19), Tofacitinib 5 mg BID plus prednisone (*N* = 9), Tofacitinib > 5 mg BID plus prednisone (*N* = 9)	12 (4–18)	32 (18-69)	33 : 32	18 (2–54)	Atopic dermatitis, allergic rhinitis, asthma, thyroid disease, vitiligo, psoriasis, rheumatoid arthritis, HLA-B27 spondyloarthropathies	64.7% (10–88%)
Craiglow 2017	R, OS	AA 6 AT 1 AU 6	13	Tofacitinib 5 mg twice daily	6.5 (2–16)	15 (12–17)	10 : 3	8 (1.5–15)	Atopic dermatitis, thyroid disease	61% (0–100%)
Craiglow 2019	CS	AT 1 AU 3	4	Tofacitinib 5 mg twice daily (N = 3); tofacitinib 5 mg daily 3 mo, then 5 mg bid (*N* = 1)	6–15	9 (8–10)	1 : 3	13 (7–17)	Atopic dermatitis, lichen sclerosis	81% (1–100%)
Park 2017	CS	AA 11 AT 10 AU 11	32	Tofacitinib 5 mg twice daily, in 6 patients the dose increased up to 20 mg/day, total median dose 2065 mg	7.5 (4–17)	30 (18–54)	16 : 16	8 (1–35)	NR	NR
Schinberg 2017	CS	AU 4	4	Tofacitinib 5 mg twice daily	NR	41.5 (20–60)	2 : 2	NR	Rheumatoid arthritis	NR
Castelo-Soccio 2017	CS	AU 8	8	Tofacitinib 5 mg twice daily	7.5 (5–18)	15.5 (12–19)	NR	4 (1–12)	NR	63% (52–79%)

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis; CS, case series; CT, clinical trial; mo, month; NR, not report; OS, observational study; R, retrospective; RCT, randomized clinical trial; SALT, Severity in Alopecia Tool scoring.

Table 2 Quality assessment of 11 studies included for meta-analysis

ROBINS-I assessment									
Study	**Study type**	**Bias due to confounding**	**Bias in selection of participants into the study**	**Bias in classification of interventions**	**Bias due to deviations from intended interventions**	**Bias due to missing data**	**Bias in measurement of outcomes**	**Bias in selection of the reported result**	**Overall assessment**
Jabbari 2018	CT	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Kennedy 2016	CT	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Liu 2018	CT	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Putterman 2018	CT	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Craiglow 2017	OS	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Ibrahim 2017	OS	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Liu 2017	OS	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Shin 2019	OS	Low	–	–	–	–	–	–	Low
Craiglow 2019	OS	Serious	Low	Low	Low	Low	Moderate	Low	Serious
Park 2017	OS	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate
Castelo-Soccio 2017	OS	Moderate	Low	Low	Low	Low	Moderate	Low	Moderate

CT, clinical trial; OS, observational study.

was supplemented by contact with the study author. Study characteristics data included lead author, publication year, study type, disease subtype, patients' number, treatment regimen, treatment duration, median age, sex ratio, duration of alopecia, concomitant comorbidity and SALT score improvement. If the study had multiple comparative groups, we only extracted the data of interest.

Clinical endpoints extracted from studies included efficacy outcomes and safety outcomes. For efficacy endpoints, the incidence of therapeutic hair regrowth and recurrence was recorded. For safety endpoints, the patient number of different types of adverse events and total treatment patients were extracted to calculate adverse event ratio. Only adverse events reported by at least two studies were included.

Quality assessment

ROBINS-I (Risk of Bias In Non-randomized Studies-of Interventions), an emerging useful tool for quality assessment of non-randomized studies, was used to estimate the risk of bias of included studies.[24] Two researchers independently answered signalling questions and judged risk of bias of each study within seven domains including bias due to confounding, bias in selection of participants into the study, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. Each domain was graded as low risk, moderate risk, serious risk, critical risk or no information. An overall assessment of each study was generated based on grades of the seven domains.

Statistical analysis

Statistical analysis of pooled efficacy data and adverse effects was performed using the Comprehensive Meta-analysis (CMA) software 3.3.0 (Biostat, Englewood, NJ). Retrospective studies and case series were combined as observational studies for analysis. In the present study, proportions of partial hair regrowth (SALT5-50, representing SALT score change between 5 and 50%), good/complete hair regrowth (SALT50, representing SALT score change > 50%) and disease relapse were meta-analysed for efficacy evaluation. For safety assessment, the incidence of adverse events was meta-analysed. Heterogeneity was evaluated by Cochrane Q statistic (significant at $P < 0.10$) and the I^2 test (significant at $I^2 > 50\%$). Subgroup analysis was performed according to administration route (oral medication or topical medication), oral dose (>5 mg twice daily or ≤ 5 mg twice daily), treatment duration (>6 months or ≤ 6 months), disease subtype (AA or AT/AU) and age (adults or paediatric populations). A random effects model was used when there was a significant heterogeneity, and a fixed-effect model was adopted when heterogeneity was low. P value < 0.05 was considered statistically significant.

Results

Search results and study characteristics

A total of 70 references were identified after initial search. After exclusion of duplicates, 64 potentially relevant articles were retrieved. Titles and abstracts of these studies were screened. Full text of 28 studies was reviewed, and 14 studies[25–38] including six

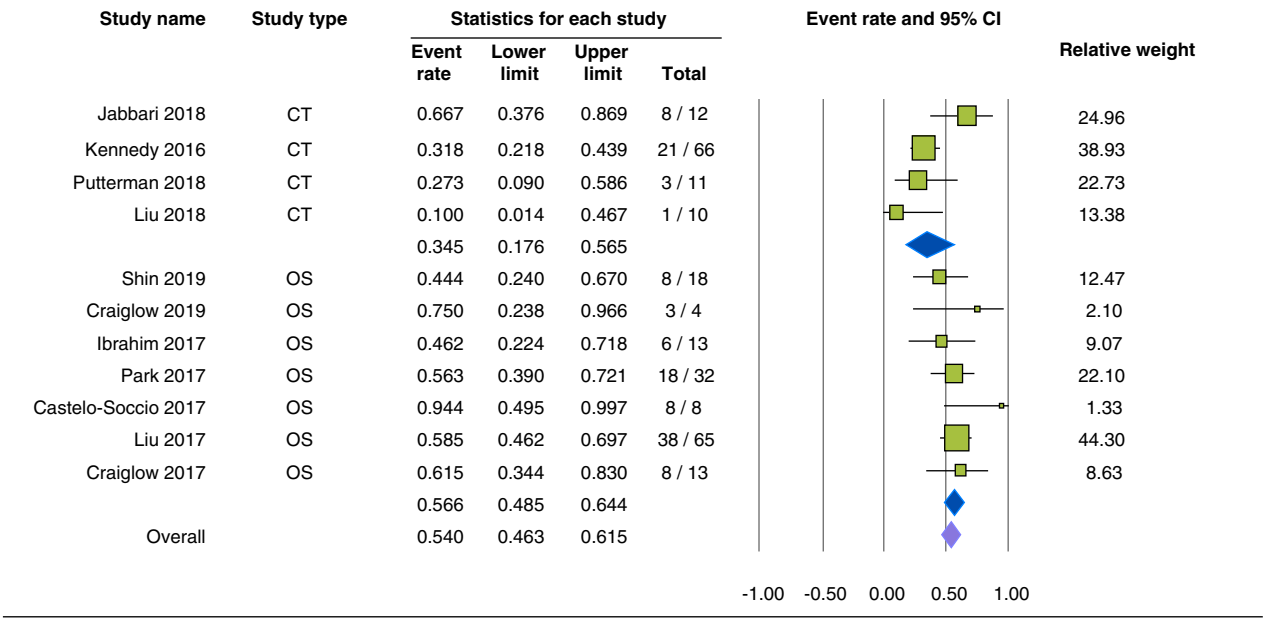

Figure 2 Forest plot of good/complete hair regrowth rate of tofacitinib treatment in patients with AA. CT, clinical trials; OS, observational study.

clinical trials and eight observational studies with 275 patients which met the inclusion criteria were selected (Fig. 1). Among them, 11 studies which reported patients SALT score change were enrolled for meta-analysis. The search of reference list did not supplement any additional records.

Study characteristics of the 14 studies were shown in Table 1, and quality assessment of the 11 meta-analysed studies was summarized in Table 2. One study was at low risk of bias; six studies were at moderate risk; and four studies were at high risk.

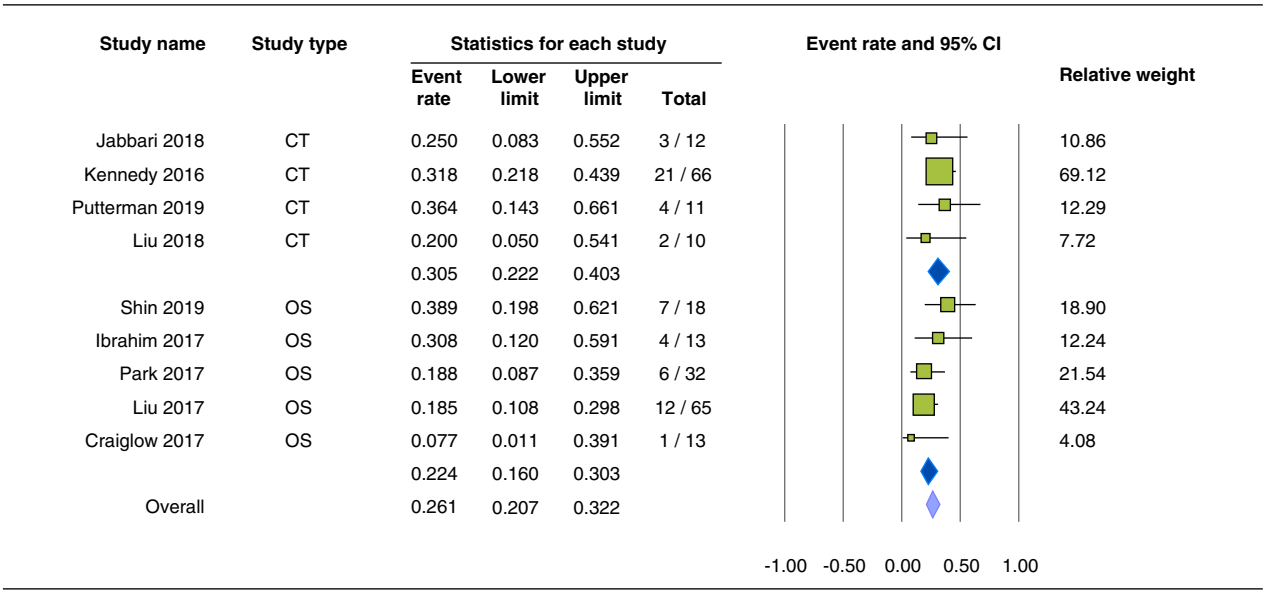

Figure 3 Forest plot of partial therapeutic hair regrowth rate in patients with AA receiving tofacitinib treatment.

Table 3 Subgroup analysis based on administration route, oral dose, treatment duration, disease subtype and age

Variable	No. of Studies	No. of Participants		Event Rate, % (95% CI, %)	Heterogeneity		*P* Value
		$SALT_{50}$	Total		*P*	I^2	
Clinical trials							
Administration route							
Oral tofacitinib	2	29	78	46.5 (17.5–78.1)	0.029	79.0	0.195
Topical tofacitinib	2	4	21	20.8 (7.9–44.5)	0.332	0	
Oral dose							
>5 mg twice daily	1	8	12	66.7 (37.6–86.9)	1	0	0.029
≤5 mg twice daily	1	21	66	31.8 (21.8–43.9)	1	0	
Treatment duration							
>6 months	1	8	12	66.7 (37.6-86.9)	1	0	0.029
≤6 months	1	21	66	31.8 (21.8-43.9)	1	0	
Disease subtype							
AA	2	5	17	30.0 (3.6–82.9)	–	–	0.569
AT/AU	2	7	15	52.4 (11.2–90.5)	–	–	
Age							
Adults	3	30	88	36.0 (13.7–66.6)	0.028	71.9	0.663
Paediatric populations	1	3	11	27.3 (9.0–58.6)	1	0	
Observational studies							
Oral dose							
>5 mg twice daily	4	70	128	54.7 (45.9–63.1)	0.674	0	0.155
≤5 mg twice daily	3	20	25	72.0 (49.1–87.3)	0.214	35.1	
Treatment duration							
>6 months	5	74	122	58.2 (49.0–66.9)	0.255	25	0.511
≤6 months	2	16	31	51.5 (34.2–68.5)	0.35	0	
Disease subtype							
AA	2	13	17	74.5 (46.9–90.6)	–	–	0.132
AT/AU	4	40	72	52.0 (40.0-63.7)	–	–	
Age							
Adults	4	70	128	54.7 (45.9–63.1)	0.674	0	0.155
Paediatric populations	3	20	25	72.0 (49.1–87.3)	0.214	35.1	

AA, alopecia areata; AT, alopecia totalis; AU, alopecia universalis.

Assessment of efficacy

Overall, 11 studies including 4 clinical trials and 7 observational studies investigated patient response to tofacitinib treatment assessed by SALT, and 1 study reported therapeutic regrowth assessed by IGA and PtGA (Investigator's and patient's global assessment). Two studies did not mention the assessment method.

Proportions of good/complete response to tofacitinib were calculated from 11 studies including 252 patients (Fig. 2). The meta-analysis results of random-effect model showed the overall good/complete response rate was 54.0% (95% CI: 46.3%–61.5%). In seven clinical trials, the pooled rate of good/complete regrowth was 34.5% (17.6%–56.5%) among patients with alopecia areata. However, in seven observational studies, the overall proportion was significantly higher (56.6%, 48.5%–64.4%).

A partial response was defined as 5–50% regrowth in hair. Proportions of partial regrowth of hair were analysed from nine studies including four clinical trials and five observational studies (Fig. 3). The meta-analysis results of fixed-effect model showed the pooled rate of partial response in patients with alopecia areata taking tofacitinib was 26.1% (20.7–32.2%). From subgroup analysis, the pooled proportion of partial regrowth in four clinical trials was 30.5% (22.2–40.3). The pooled partial regrowth rate was found to be 22.4% (16.0–30.3%) in five observational studies.

In addition, within the three non-SALT assessment studies, the phase I randomized controlled trial by Bokhari *et al.* showed six partial regrowth AU patients (total $N = 16$), and Bayart *et al.* reported that one patient with AA demonstrated 95% hair regrowth and one patient with AT showed 80% hair regrowth (total $N = 3$). Schinberg *et al.* observed hair regrowth in four patients with AU (total $N = 4$).

Subgroup analysis

Subgroup analysis suggested the efficacy comparisons in treatment dose group and duration group in clinical trials were statistically significant (Table 3). The good/complete rate in oral tofacitinib group (46.5%) was higher than that in topical

tofacitinib group (20.8%), but the difference was statistically insignificant ($P = 0.195$).

Disease relapse

The rates of recurrence were investigated in four studies including two clinical trials and two observational researches (Fig. 4). The overall pooled proportion of recurrence was 24.0% (17.9%–31.3%). The pooled recurrence rates were 33.5% (23.8%–44.8%) and 13.5% (8.0%–21.8%) in clinical trials and observational studies, respectively. The vast majority of relapses were due to discontinuation of tofacitinib. Only one study reported recurrence occurred during treatment.

Assessment of safety

Safety analysis was based on seven studies including three clinical trials and four observational studies (Fig. 5). In clinical trial group, the overall pooled rate of any adverse events was 7.2% (4.3%–11.8%). The highest risk was found for upper respiratory infection (URI) (56.8%), followed by acne (13.2%), headache (7.7%), weight gain (5.7%), folliculitis (4.5%) and conjunctivitis (3.5%). With regard to observational study group, the overall pooled proportion of any adverse events was 22.7% (17.5–29.0). URI (29.1%), headache (15.7%) and liver enzyme abnormalities (7.7%) were the most common in decreasing order of frequency. Detailed information about adverse events included for meta-analysis was shown in Figures S1 and S2. A summary of all the adverse events reported in the included studies was present in Table S1.

Discussion

Currently, there is no uniform treatment for hair loss with guaranteed efficacy. Topical corticosteroids are often used as first-line therapy, but had limited response.[39] In recent years, increasing evidence suggests that tofacitinib, a JAK inhibitor, might be of potentially therapeutic use for alopecia areata.[40] Results of several clinical trials suggested patients with AA were responsive to tofacitinib treatment.[27,30] However, the sample size of each clinical trial was small and the response rate varied greatly (0%–100%). In the present study, we enrolled 14 studies including 6 clinical trials and 8 observational studies with 275 patients. Meta-analysis was performed based on 11 studies which adopted SALT score for treatment assessment. The result of meta-analysis showed that the pooled good/complete hair regrowth rate of tofacitinib treating patient with AA was 54.0% (95% CI: 46.3%–61.5%). The pooled rate of partial response in patients with alopecia taking tofacitinib was 26.1% (20.7–32.2%). Oral dose of tofacitinib and duration of treatment may be the factors influencing the therapeutic effect. In addition, the recurrence rate was 24.0% (17.9%–31.3%), most of which was reported due to discontinuation of tofacitinib. In terms of toxicity, reported adverse effects included only mild symptoms. URI, headache and acne were the most common adverse events.

Our results indicated that the addition of tofacitinib in treatment regimen conferred therapeutic hair regrowth benefit. AA is an autoimmune-related hair loss disorder which targets hair follicle epithelium.[41] Over the past few years, JAK inhibitors are emerging as promising treatments for various autoimmune disorders including rheumatoid arthritis,[42] psoriasis[43] and AA. Among them, tofacitinib was the most studied and has varied therapeutic effect. Previous studies have demonstrated that JAK-STAT pathway played a crucial role in the pathogenesis of AA by modulating the CD8+NKG2D+T cell reaction and hair growth cycle.[44,45] When the immune system is disrupted, hair follicle will lose immune privilege during anagen phase and will be attacked by CD8+NKG2D+T cell, resulting in hair follicle dystrophy.[21,46] Therefore, by inhibiting JAK-dependent STAT

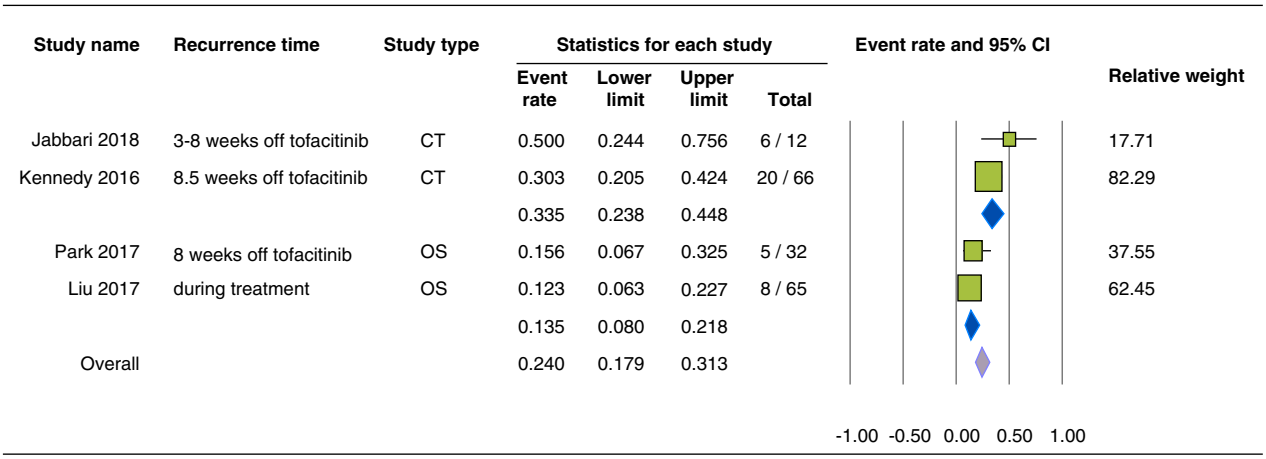

Figure 4 Recurrence rate and time in patients treated with tofacitinib.

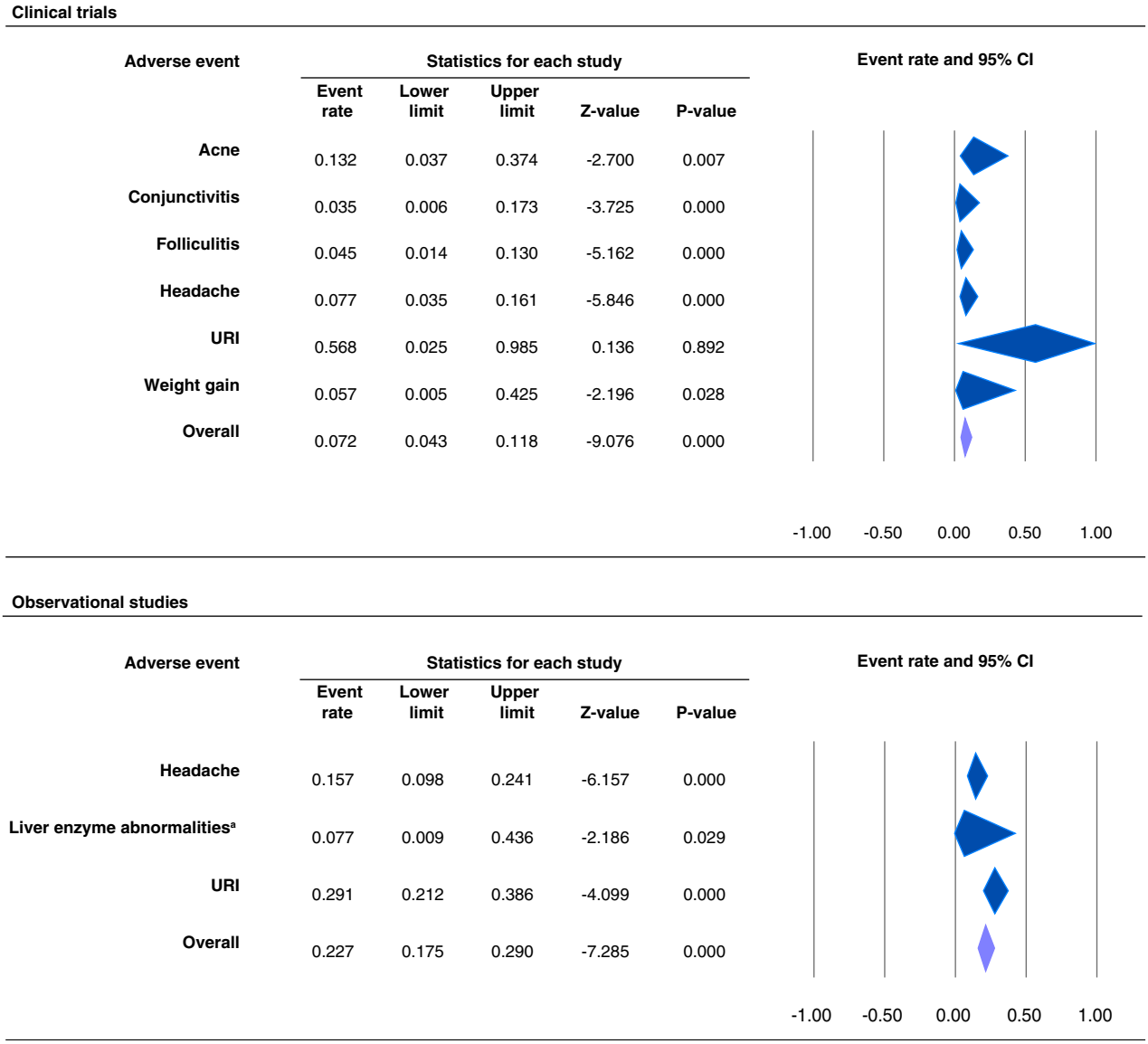

Figure 5 Adverse events and event rate in clinical trials and observational studies.

activation, tofacitinib potentially has a positive effect on treatment of AA. Several studies have investigated the specific underlying mechanism of tofacitinib in stimulating hair growth. Meephansan J *et al.* found hair regrowth and anagen extension in mice treated with tofacitinib.[45] They also proved the inhibition of JAK-STAT pathway was beneficial to angiogenesis by upregulating vascular endothelial growth factor. In addition, tofacitinib has been reported to have anti-inflammatory effects.[47] In the current study, approximately half of patients achieved good/complete hair regrowth and more than a quarter of patients showed partial hair regrowth. Our results were consistent with prior studies. In a retrospective study of 65 severe AA patients treated with tofacitinib, 77% clinical response was achieved and 58% satisfactory regrowth (>50% SALT score change) was reported.[33] In addition, in an open-label pilot study which evaluated the efficacy of tofacitinib in AA, about 67% patients demonstrated > 50% hair regrowth.[27]

Considering the differences of study design and quality between clinical trials and observational studies, we performed subgroup analysis, respectively. In clinical trials, we found the pooled good/complete response rates in oral tofacitinib > 5 mg twice daily group and treatment duration > 6 months group were higher than those in oral tofacitinib ≤ 5 mg twice daily group and treatment duration ≤ 6 months group respectively,

with statistical significance. However, increasing the dose of tofacitinib might result in rising risk of adverse effect.[48] Within the 14 enrolled studies in our meta-analysis, 10 studies adopted oral tofacitinib for patients with AA. Patients in six of the studies received 5 mg tofacitinib twice daily, which was associated with better response outcome with lower toxicity. More dose-related studies of tofacitinib are needed to elucidate the maximum tolerated dose and suggested treatment dose for treating patients with AA. In addition, our results showed that there was no significant difference with subgroups based on the administration route (oral tofacitinib vs. topical tofacitinib), disease subtype (AA vs. AT/AU) and age (adults vs. paediatric populations). However, due to inadequate data of subgroup analysis, the results need to be further verified.

Approximately a quarter of patients showed signs of shedding after hair regrowth. Three studies reported hair loss recurs after 2–8.5 weeks of tofacitinib.[27,30,36] However, in another study, a total of 8 patients (12.3%) experienced disease relapse, 3 of whom exhibited hair shedding on tapered dose after complete response and 5 of whom experienced spontaneous relapse during treatment. Remarkably, 7 patients achieved hair regrowth again when continuing with tofacitinib treatment.[33] The above observations suggested that maintenance therapy in the treatment strategy might be necessary for reducing recurrence and obtaining continued remission. However, most clinical trials did not include maintenance therapy in treatment regimens and few studies discussed the detailed protocol of maintenance treatment. Therefore, it is difficult to directly compare the relapse rate between patients not receiving maintenance therapy and those receiving maintenance therapy. Further work is needed to explore optimal maintenance therapies of tofacitinib for treating patients with AA.

In terms of safety, our results revealed that the reported adverse effects were mostly limited to mild symptoms and relatively manageable. The most frequently observed adverse events were upper respiratory infections, headache, acne and liver enzyme abnormalities. Mild infection was found to have the highest risk. However, most studies did not elaborate underlying mechanisms of adverse effects. The possible mechanism of infection was derived indirectly from clinical trials of tofacitinib treating patients with rheumatoid arthritis. Tofacitinib users had higher incidence of opportunistic infection than non-users. It may result from JAK inhibition, which reduced type 1 and 2 antiviral responses.[49]

Our study has several limitations. First, most of the included studies reported low-to-moderate quality evidence. The sample size of most studies was small. In addition, the majority of reports included in the meta-analysis described non-comparative studies, which limited us to calculate single-arm rate instead of estimating comparative efficacy. Thus, more thorough larger sized randomized controlled trials are needed. Second, the disease subtypes, dosage and duration of treatment varied from study to study, which make it difficult to perform subgroup analysis. Therefore, we grouped disease subtypes and drug-related designs based on summarized information and conducted subgroup comparison of efficacy. Third, few studies gave information about the long-term efficacy and safety of tofacitinib treatment. Finally, there were limited data on maintenance therapy which could be of great importance in reducing recurrence and obtaining continued remission.

In conclusion, our current study suggested that tofacitinib treatment for patients with AA conferred favourable therapeutic hair regrowth benefit with mild adverse effect. Due to the limitation of study quality and insufficient data, the results of subgroup analysis need to be further verified. Disease relapse often occurred after withdrawal of tofacitinib, which suggested the maintenance therapy might be necessary in treatment regimens. More large-sample randomized trials with in-depth studies of drug efficacy, dosage form, dose and duration of treatment are needed.

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Supporting information

Additional Supporting Information may be found in the online version of this article:

Figure S1. Detailed information about adverse events rate in clinical trails.

Figure S2. Detailed information about adverse events rate in observational studies.

Table S1. Adverse events reported in included studies.