Meta-Analysis and Systematic Review

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Efficacy and safety of tofacitinib for the treatment of chronic plaque psoriasis: a systematic review and meta-analysis

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Abstract

Background: Tofacitinib is an oral Janus kinase (JAK) inhibitor that targets JAK1 and JAK3, and thus regulates immune response. Therefore, tofacitinib is used to treat immune-mediated inflammatory diseases such as chronic plaque psoriasis. The objective of this study was to systematically assess the efficacy and safety of tofacitinib in treating chronic plaque psoriasis.

Objective: To systematically review the efficacy and safety of tofacitinib in the treatment of chronic plaque psoriasis, we performed a meta-analysis to evaluate the efficacy and safety of tofacitinib in patients with chronic plaque psoriasis.

Methods: Databases including PubMed, Embase, and The Cochrane Library were searched for randomized controlled trials about the efficacy and safety of tofacitinib in treating chronic plaque psoriasis from inception to August 2017 (PROSPERO Code No: CRD42017076587).

Results: Six articles (seven randomized controlled trial studies) involving 3743 patients were included. The meta-analysis results showed that for efficacy, tofacitinib (5 mg or 10 mg) compared with placebo can significantly improve the Physician's Global Assessment response, PASI75, and PASI90 after treatment. For safety, the incidence of adverse reactions was statistically significantly higher for tofacitinib compared with placebo.

Conclusion: Treatment of chronic plaque psoriasis with tofacitinib is effective, but there may be more adverse reactions.

Keywords

Tofacitinib, chronic plaque psoriasis, randomized controlled trial, systematic review, safety, adverse reactions, efficacy

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Learning points

1. Tofacitinib is efficacious in treating chronic plaque psoriasis, but there may be a higher incidence of adverse reactions.
2. The included studies only compared the efficacy and safety of tofacitinib and placebo, and did not compare these with other drugs that are used to treat chronic plaque psoriasis.

Introduction

Chronic plaque psoriasis is an inflammatory, immune-mediated systemic disease that impacts patients both physically and psychologically, leading to major quality of life impairment.[1] The prevalence of psoriasis is about 0.47% in China, but the disease incidence is higher in Europe and North America, at approximately 2%.[2,3] Patients with moderate to severe plaque psoriasis usually need phototherapy or systemic agents for treatment.[4,5] Prolonged use of classical systemic agents is associated with organ toxicity to the liver, kidney, and mucocutaneous organs, thus limiting their long-term use.[6–10]

The Janus kinase (JAK) intracellular signaling pathway has been implicated in the pathogenesis of chronic immune-mediated and inflammatory diseases, including psoriasis.[11] The JAK family includes JAK1, JAK2, JAK3, and TYK2. Tofacitinib is an oral JAK inhibitor that mainly interferes with JAK1 and JAK3 signaling. Tofacitinib was approved by the FDA on November 6, 2012 for the treatment of moderate to severe rheumatoid arthritis, and tofacitinib was approved by the Chinese Food and Drug Administration on March 16, 2017 for the treatment of adult patients with moderate to severe active rheumatoid arthritis in whom methotrexate is not effective or who are intolerant to methotrexate treatment. In addition to rheumatoid arthritis, clinical data suggests that tofacitinib has a good effect on the treatment of chronic plaque psoriasis. **However, no relevant studies have evaluated the efficacy of tofacitinib in treating chronic plaque psoriasis.**

Therefore, we conducted a systematic evaluation to analyze and evaluate data from randomized controlled trials (RCTs) on the treatment of chronic plaque psoriasis to provide a reference for its safe and optimal use in the clinic.

Methods

Eligibility criteria

Only RCTs studying the effects and safety of tofacitinib on patients with chronic plaque psoriasis were included in this study. The co-primary efficacy endpoints were the proportion of patients achieving at least a 75% reduction in the Psoriasis Area and Severity Index (PASI) score (PASI75 response) from baseline and the proportion of patients achieving a Physician's Global Assessment (PGA) score (on a five-point severity scale where 0 is "clear"; 1 is "almost clear"; 2 is "mild"; 3 is "moderate"; and 4 is "severe") of "clear" or "almost clear" (PGA response). The main secondary endpoints were the proportion of patients achieving at least a 90% reduction in the PASI score (PASI90 response) from baseline. Safety was assessed based on the incidence of adverse events. All studies included were published in English. The protocol was registered with the International Prospective Register of Systematic Reviews (identification number: CRD42017076587).

Search strategy

We searched the PubMed, Embase, and Cochrane databases from their earliest dates up to August 2017. The final search

string was "tofacitinib" [Mesh] OR "tasocitinib" OR "Xeljanz" AND "psoriasis" [Mesh] OR "psoriasis" AND randomized controlled trial [ptyp]. No additional filters were used. This search resulted in 151 articles (Figure 1). No additional articles were found by searching through article references, resulting in the final 151 articles. Using the titles and abstracts of these 151 articles, we eliminated studies that were unrelated to psoriasis, basic science research articles, pilot studies, commentaries, and reviews. This strategy narrowed down the list to 24 articles. The full text of these articles was reviewed to assess their eligibility for inclusion.

Quality assessment

The Cochrane System Evaluator Manual 5.1.0 was used to assess the bias risk of the included RCTs, and the following seven aspects are included: random sequence generation was correct, allocation concealment, blinding status, blinded evaluation results, completeness of information, whether selective reporting was used, and any other risk of bias implementation.

Patient and public involvement

Patients and the public were not involved in this study.

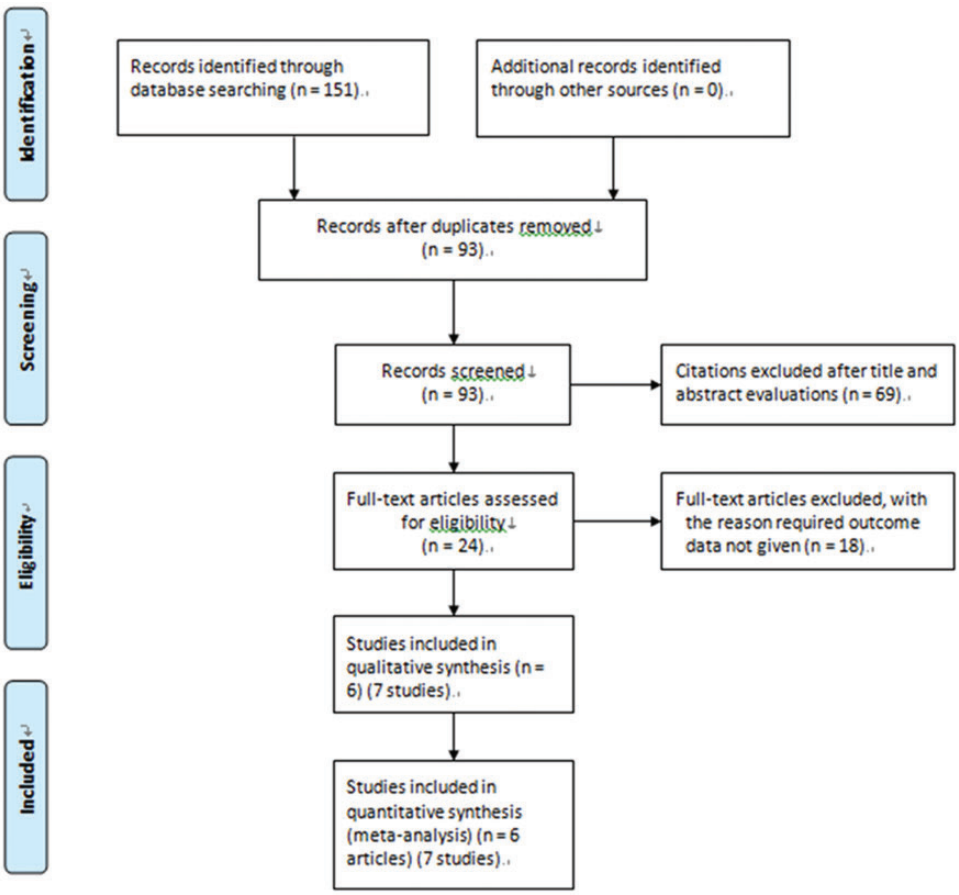

Figure 1. Article identification, assessment, and selection

Data synthesis

Descriptive information was collected for each study, including the country of origin, clinical trial number, and diagnostic criteria. Quantitative information included the pooled risk ratio and 95% confidence intervals (CI). The measures of consistency (I^2) for each meta-analysis were described. Subgroup analyses were performed based on the different interventions.

Results

Study selection and study characteristics

Studies were selected by two researchers in accordance with the inclusion and exclusion criteria. There were 45 articles initially identified and subjected to literature screening, data extraction, and crosscheck. Any differences were resolved through consultation or by a third researcher. In the case of missing data, the researchers contacted the authors to obtain more information. For literature screening, the titles and abstracts were analyzed first. After excluding reports that were clearly irrelevant, the researchers read the remaining full texts and determined whether the articles met the criteria. This process excluded 18 of the 24 articles, with six articles (seven RCTs) that were available for inclusion (see flow diagram, Figure 1). Two researchers extracted data from the seven RCTs (see Table 1).

Risk of bias assessment

There were seven studies that described using the random assignment method and allocation concealment. All seven studies were double-blind, which resulting in a low risk of bias (see Figure 2).[12–17]

Meta-analysis

Efficacy. We compared the seven RCTs to the different doses of tofacitinib (5 mg or 10 mg twice daily) and to the placebo in adults with chronic plaque psoriasis.[12–17] Pooled data from the seven RCTs showed that the tofacitinib 5 mg group had a superior PGA response compared with the placebo group (adjusted RR, 3.77; 95% CI, 3.01–4.71; $I^2 = 0\%$; $P < 0.00001$) and PASI75 (adjusted RR, 5.31; 95% CI, 4.04–6.97; $I^2 = 18\%$; $P < 0.00001$). However, the 5 mg dose of tofacitinib appeared to be less effective compared with the 10 mg dose of tofacitinib on the PGA response (adjusted RR, 0.70; 95% CI, 0.63–0.79; $I^2 = 67\%$; $P < 0.00001$) and PASI75 (adjusted RR, 0.68; 95% CI, 0.64–0.73; $I^2 = 35\%$; $P < 0.00001$). Four studies reported the PASI90.[12,13,16,17] A meta-analysis of those four RCTs showed that the tofacitinib 5 mg group had a greater effect compared with the placebo group on PASI90 (adjusted RR, 14.88; 95% CI, 5.59–39.60; $I^2 = 0\%$; $P < 0.00001$), but the effect was lower compared with the tofacitinib 10 mg group (adjusted RR, 0.60; 95% CI, 0.49–0.72; $I^2 = 0\%$; $P < 0.00001$). The differences were statistically significant for these three outcome indicators (Table 2).

Safety. The incidence of adverse events (AEs) was higher in the tofacitinib group compared with the placebo group (tofacitinib 5 mg, 54.8% vs. placebo, 50.2%, $P < 0.04$; tofacitinib 10 mg, 59.5% vs. placebo, 49.3%; $P < 0.0001$). All studies examined showed that there were no statistical differences in serious AEs (tofacitinib 5 mg, 2.39% vs. placebo, 0.97%; tofacitinib 10 mg, 1.72% vs. placebo, 1.58%), AEs leading to discontinuation (tofacitinib 5 mg, 2.58% vs. 4.23%; tofacitinib 10 mg, 2.84% vs. placebo, 4.22%), or the rate of infection (tofacitinib 5 mg, 10.9% vs. placebo, 10.2%; tofacitinib 10 mg, 12.7% vs. placebo, 9.11%) compared with placebo (Table 3).

Table 1. Basic characteristics of included studies

Article	Country	Race	Clinical trial Number	Diagnostic criteria	Male	Mean age (years)	Disease severity	Intervention group		Control
								tofacitinib 5 mg	tofacitinib 10 mg	
Zhang et al. 2017[12]	China	China, Taiwan, Korea	NCT01815424	PASI score ≥12 and PGA score of "moderate" or "severe" at baseline	65/67/62	40.7±11.3/ 41.0±12.0/ 41.7±13.7	moderate to severe	tofacitinib 5 mg twice daily for 16 weeks (n=88)	tofacitinib 10 mg twice daily for 16 weeks (n=90)	placebo (n=88)
Asahina et al. 2016[13]	Japan	Japanese	NCT01519089	PASI score ≥12 or more and PGA score of 3 (moderate) or 4 (severe)	35/36	50.9/46.6	moderate to severe	tofacitinib 5 mg twice daily for 16 weeks (n=43)	tofacitinib 10 mg twice daily for 16 weeks (n=44)	none
OPT1-Papp et al. 2015[14]	Canada	Blacks, whites, Asians	NCT01276639	PASI score ≥12, PGA score of 3 (moderate) or 4 (severe)	261/261/121	46/46/45	moderate to severe	tofacitinib 5 mg twice daily for 16 weeks (n=363)	tofacitinib 10 mg twice daily for 16 weeks (n=360)	placebo (n=177)
OPT2-Papp et al. 2015[14]	Canada	Black, white, Asian, other	NCT01309737	PASI score ≥12, PGA score of 3 (moderate) or 4 (severe)	268/257/123	47/44/45	moderate to severe	tofacitinib 5 mg twice daily for 16 weeks (n=382)	tofacitinib 10 mg twice daily for 16 weeks (n=381)	placebo (n=196)
Bissonnette et al. 2015[15]	Canada	White, other	NCT01186744	PASI score ≥12, PGA score of 3 (moderate) or 4 (severe)	228/230	45/47	mild, moderate, severe	tofacitinib 5 mg twice daily for 16 weeks (n=331)	tofacitinib 10 mg twice daily for 16 weeks (n=335)	none
Bachelez et al. 2015[16]	France	White, Asian, other	NCT01241591	PASI score ≥12 or more and PGA score of "moderate" or "severe" at baseline	236/238/71	44/44/46	mild, moderate, severe	tofacitinib 5 mg twice daily for 12 weeks (n=329)	tofacitinib 10 mg twice daily for 12 weeks (n=330)	placebo (n=107)
Papp et al. 2012[17]	Canada	Black, white, Asian, other	NCT00678210	PASI score ≥13	29/36	44/43.9	mild, moderate, severe	tofacitinib 5 mg twice daily for 12 weeks (n=49)	none	placebo (n=50)

PASI, Psoriasis Area and Severity Index; PGA, Physician's Global Assessment

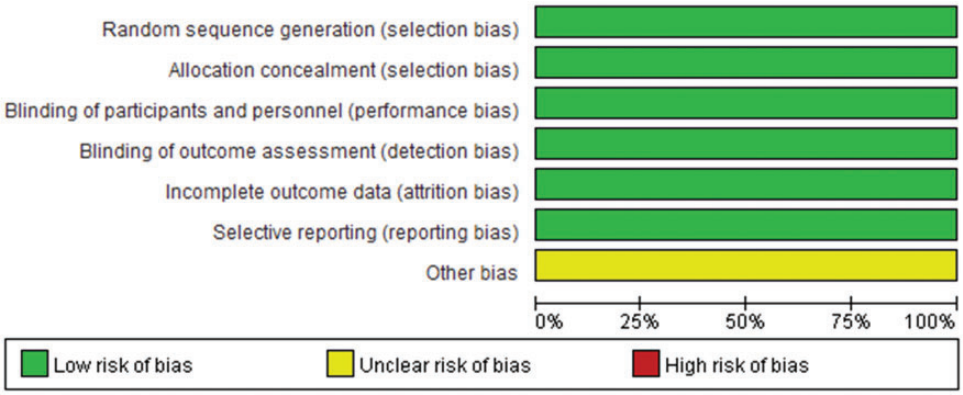

Figure 2. Risk of bias graph

Table 2. Analysis of efficacy and the association between tofacitinib and placebo

Outcome or Subgroup	Studies	Participants	I^2, %	Adjusted risk ratio (95% CI)	*P*
1.1 PGA response[12–17]	7	6634			
1.1.1 tofacitinib 5 mg vs. placebo[12,14,16,17]	5	1829	0	3.77 (3.01, 4.71)	<0.00001
1.1.2 tofacitinib 10 mg vs. placebo[12,14,16]	4	1729	0	5.17 (4.12, 6.48)	<0.00001
1.1.3 tofacitinib 5 mg vs. tofacitinib 10 mg[12–16]	6	3076	67	0.70 (0.63, 0.79)	<0.00001
1.2 PASI75[12–17]	7	6634			
1.2.1 tofacitinib 5 mg vs. placebo[12,14,16,17]	5	1829	18	5.31 (4.04, 6.97)	<0.00001
1.2.2 tofacitinib 10 mg vs. placebo[12,14,16]	4	1729	39	7.30 (5.55, 9.59)	<0.00001
1.2.3 tofacitinib 5 mg vs. tofacitinib 10 mg	6	3076	35	0.68 (0.64, 0.73)	<0.00001
1.3 PASI90[12,13,16,17]	4	2250			
1.3.1 tofacitinib 5 mg vs. placebo[12,16,17]	3	711	0	14.88 (5.59, 39.60)	<0.00001
1.3.2 tofacitinib 10 mg vs. placebo[12,16]	2	615	0	24.57 (8.75, 69.06)	<0.00001
1.3.3 tofacitinib 5 mg vs. tofacitinib 10 mg[12,13,16]	3	924	0	0.60 (0.49, 0.72)	<0.00001

PASI, Psoriasis Area and Severity Index

Discussion

JAK was identified in the early 1990s[18] and is a core member of the protein tyrosine kinase family. The JAK family includes JAK1, JAK2, JAK3, and TYK2. JAK is a receptor-related intracellular protein that plays a key role in cytokine receptor signaling.[19] JAK is involved in cell growth, survival, development, and differentiation, and it is also important for immune and hematopoietic functions.[20] Tofacitinib is an oral JAK1 and JAK3 inhibitor. Partial inhibition of JAK signaling by tofacitinib leads to a multi-tiered intervention in the cycle of psoriasis pathogenesis, with a direct impact on dysregulated keratinocytes, a reduction in inflammatory infiltrates, and normalization of the interleukin (IL)-23/Th17 axis.[21]

Seven RCTs involving 3743 patients were included in this study. The

Table 3. Analysis of safety and the association between tofacitinib and placebo

Outcome or Subgroup	Studies	Participants	I^2, %	Adjusted risk ratio (95% CI)	*P*
1.1 Adverse reactions[12–17]	7	6634			
1.1.1 tofacitinib 5 mg vs. placebo[12,14,16,17]	5	1829	3	1.10 (1.00, 1.21)	0.04
1.1.2 tofacitinib 10 mg vs. placebo[12,14,16]	4	1729	0	1.21 (1.10, 1.33)	<0.0001
1.1.3 tofacitinib 5 mg vs. tofacitinib 10 mg[12–16]	6	3076	12	0.90 (0.85, 0.96)	0.0007
1.2 Serious adverse events[12–17]	7	6634			
1.2.1 tofacitinib 5 mg vs. placebo[12,14,16,17]	5	1829	0	1.51 (0.75, 3.03)	0.25
1.2.2 tofacitinib 10 mg vs. placebo[12,14,16]	4	1729	0	1.01 (0.46, 2.19)	0.99
1.2.3 tofacitinib 5 mg vs. tofacitinib 10 mg[12–16]	6	3076	34	0.91 (0.60, 1.39)	0.67
1.3 Discontinuations because of adverse events[12–16]	6	6535			
1.3.1 tofacitinib 5 mg vs. placebo[12,14,16]	4	1730	32	0.65 (0.38, 1.09)	0.10
1.3.2 tofacitinib 10 mg vs. placebo[12,14,16]	4	1729	0	0.65 (0.38, 1.10)	0.11
1.3.3 tofacitinib 5 mg vs. tofacitinib 10 mg[12–16]	6	3076	12	0.84 (0.56, 1.26)	0.41
1.5 Infection[12,14,15,17]	5	5017			
1.5.1 tofacitinib 5 mg vs. placebo[12,14,17]	4	1393	57	0.99 (0.55, 1.79)	0.97
1.5.2 tofacitinib 10 mg vs. placebo[12,14]	3	1294	8	1.25 (0.88, 1.77)	0.21
1.5.3 tofacitinib 5 mg vs. tofacitinib 10 mg[12,14,15]	4	2330	33	0.79 (0.61, 1.03)	0.08

meta-analysis showed that tofacitinib 10 mg twice daily was effective in treating chronic plaque psoriasis as measured by PGA responses, PASI75, and PASI90. Although a substantial number of patients who received tofacitinib 5 mg twice daily achieved PGA responses, PASI75, and PASI90, this dose did not meet the statistical criterion for non-inferiority to tofacitinib 10 mg twice daily. However, tofacitinib compared with placebo increased the incidence of adverse reactions, and the incidence of AEs related to tofacitinib 10 mg twice daily was higher compared with tofacitinib 5 mg twice daily.

This study was conducted via a comprehensive search of relevant literature on these topics, and the researchers carefully performed data extraction and rigorously assessed the quality of the included research to reduce bias. Additionally, these RCTs were analyzed by methodology used in evidence-based medicine. Although the selected studies were randomized, had large sample sizes, were multicenter clinical studies, and were high quality, this review has some limitations because of the small number of studies included, which may produce false-positive results. Additionally, the included studies only compared the efficacy and safety of tofacitinib and placebo and did not involve comparisons with other drugs for the treatment of chronic plaque psoriasis. Therefore, the efficacy and safety of tofacitinib in the treatment of chronic plaque psoriasis still requires large and high-quality studies for further confirmation.

Conclusions

Treatment of chronic plaque psoriasis with tofacitinib is efficacious, but the incidence of adverse reactions is higher with tofacitinib compared with placebo.

Author contributions

Conceived and designed the experiments: TX. Performed the experiments: FYT, ZYC.

Analyzed the data: FYT, ZYC. Contributed reagents/materials/analysis tools: FYT, ZYC. Wrote the paper: FYT.

Declaration of conflicting interest

The authors declare that there is no conflict of interest.

Data sharing statement

No additional data are available.

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