Efficacy and Safety of JAK-STAT Inhibitors in the Treatment of Moderate to Severe Plaque Psoriasis: a Meta Analysis

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Abstract: **Objective:** To systematically evaluate the efficacy and safety of JAK-STAT inhibitors in the treatment of moderate to severe plaque psoriasis. **Methods:** We conducted a computerized search of relevant published literature in the PubMed, EMBASE, and Cochrane Library databases from their inception to May 2024. We included randomized controlled trials comparing JAK-STAT inhibitors to placebo. Two researchers independently screened the literature and extracted data. The quality of the included studies was assessed using the bias risk assessment tool provided in the Cochrane Systematic Reviews Handbook 5.1.0. We performed a meta-analysis on the effectiveness and safety of JAK-STAT inhibitors for treating moderate to severe plaque psoriasis using RevMan 5.4 software. **Results:** Seven studies with a total of 1830 patients were included. Meta-analysis revealed that in the JAK-STAT inhibitors group, the proportion of patients achieving a 75% reduction in Psoriasis Area and Severity Index (PASI) scores [RR=6.49, 95% CI (4.07, 10.34), P<0.0001], a Static Physician Global Assessment (sPGA) score of 0 or 1 [RR=4.60, 95% CI (3.08, 6.85), P<0.0001], a Dermatology Life Quality Index (DLQI) score of 0 or 1 [RR=2.73, 95% CI (2.16, 3.44), P<0.0001], and an Itching Scale (ISS) score of 0 or 1 [RR=5.84, 95% CI (3.69, 9.24), P<0.0001] was significantly higher than in the placebo group; The incidence of Total AEs in the JAK-STAT inhibitors group was marginally higher than in the placebo group [RR=1.19, 95% CI (1.01, 1.41), P=0.04], with no statistically significant difference in SAEs between the two groups (P=0.05). **Conclusion:** JAK-STAT inhibitors demonstrate significant clinical efficacy in treating moderate to severe plaque psoriasis, with most adverse reactions being mild to moderate. Patients exhibit good adherence and tolerability, suggesting their potential as an alternative therapy in clinical practice.

Keywords: JAK-STAT inhibitor, Plaque psoriasis, Meta-analysis.

1. Introduction
Psoriasis is a chronic inflammatory skin disease mediated by the immune system, influenced by both genetic and environmental factors. The primary clinical features include scaly erythema or plaques, with plaque psoriasis being the most prevalent clinical type, comprising approximately 90% of all cases [1]. Global epidemiological studies indicate that the prevalence of psoriasis reaches up to 3%, affecting over 125 million individuals [2]. Due to its frequent comorbidity with psychological, metabolic, and cardiovascular diseases, it significantly impairs patients' physical and mental health, as well as their quality of life [3]. To date, the pathogenesis of psoriasis remains unclear. Research indicates that the IL-23/IL-17 axis is a critical pathway in the pathogenesis of psoriasis, with the signal transduction of many cytokines in this pathway linked to the Janus kinase (JAK)/signal transducer and activator of transcription (STAT) pathway [4]. Currently, biologics and small molecule targeted drugs represent novel and effective treatments for chronic plaque psoriasis; however, they often cannot simultaneously address efficacy, adverse reactions, and affordability [5]. Therefore, the ongoing exploration and development of psoriasis treatment options with enhanced efficacy, improved safety, and broad patient acceptance remains a persistent challenge in medical research. Tofacitinib, peficitinib, baricitinib, upadacitinib, and other novel JAK-STAT inhibitors have been approved by the European Medicines Agency and the US Food and Drug Administration for the treatment of moderate to severe chronic plaque psoriasis [6]. This study conducted a meta-analysis on the efficacy and safety of JAK-STAT inhibitors in the treatment of moderate to severe plaque psoriasis by reviewing randomized controlled trials (RCTs) published internationally, aiming to provide evidence-based medical support for clinical practice.

2. Materials and Methods

2.1 Retrieval Strategy
The databases of PubMed, Cochrane Library, and EMBASE were electronically searched using the keywords ‘psoriasis / moderate to severe plaque psoriasis / baricitinib / tofacitinib / peficitinib / upadacitinib’. Relevant Randomized Controlled Trials (RCTs) from the inception of each database to May, 2024 were retrieved using a combination of subject headings and free-text keywords.

2.2 Inclusion Criteria
The inclusion criteria for the study required a confirmed diagnosis of moderate to severe plaque psoriasis. The experimental group received oral JAK-STAT inhibitors, while the control group was treated with a placebo.

2.3 Outcome Measure
The primary outcome measures encompassed the proportion of patients achieving a 75% reduction from baseline in Psoriasis Area and Severity Index scores at weeks 6, 12, or 16 (PASI 75), the percentage of patients with a static Physician’s Global Assessment score of 0 or 1 (sPGA 0/1), the proportion of patients with a Dermatology Life Quality Index score of 0 or 1 (DLQI 0/1), the percentage of patients with an Itch
Severity Scale score of 0 or 1 (ISS 0/1). Total adverse events, and Serious adverse events.

2.4 Data Extraction and Quality Assessment

Two researchers independently conducted the literature screening based on the inclusion criteria. Initially, they screened by reading titles and abstracts, followed by a re-screening after reviewing the full texts. In case of disagreement, a third researcher resolved the conflict through discussion. The extracted contents include the name and year of publication of the researcher, patient age, intervention measures, course of treatment and outcome indicators, etc. The Cochrane Collaboration tool assessed the quality of the included studies regarding random sequence generation, allocation concealment, blinding, completeness of outcome data, selective reporting, and other sources of bias.

2.5 Statistical Processing Method

We employed Review Manager 5.4 software for the meta-analysis. The binary variables were expressed by risk ratio (RR), and each effect quantity was expressed by 95% confidence interval (CI). Q test and I² test were used to evaluate the heterogeneity among the studies. If P was greater than 0.1 and I² was less than 50%, it was considered that the heterogeneity between the studies was small, and the fixed effect model was used for analysis; Otherwise, the random effect model is used for analysis.

3. Results

3.1 Literature Search Results

After preliminary retrieval, we obtained 654 relevant literatures, removed 183 duplicate literatures by endnote 20 software, and finally included 7 literatures after further reading [7-13]. The retrieval process is shown in figure 1.

![Figure 1: PRISMA study flow chart.](image_url)

3.2 Characteristics of Included Studies

A total of 7 literatures with a total sample size of 1830 were included in this study. The specific contents of the included literatures include the name and year of publication of the researcher, patient age, intervention measures, course of treatment and outcome indicators, etc. As shown in Table 1.

<table>
<thead>
<tr>
<th>Study</th>
<th>Intervention</th>
<th>Sample capacity</th>
<th>Average age(years)</th>
<th>Intervention cycle</th>
<th>Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>Papp 2012</td>
<td>Tofacitinib 2mg BID</td>
<td>49</td>
<td>45.7</td>
<td>12 weeks</td>
<td>PASI75, sPGA</td>
</tr>
<tr>
<td>Papp 2012</td>
<td>Tofacitinib 5mg BID</td>
<td>49</td>
<td>44.0</td>
<td>12 weeks</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>Papp 2012</td>
<td>Tofacitinib 15mg BID</td>
<td>49</td>
<td>43.6</td>
<td>12 weeks</td>
<td>DLQI</td>
</tr>
<tr>
<td>Mamolo 2014</td>
<td>Tofacitinib 2mg BID</td>
<td>49</td>
<td>45.7</td>
<td>12 weeks</td>
<td>sPGA</td>
</tr>
<tr>
<td>Mamolo 2014</td>
<td>Tofacitinib 5mg BID</td>
<td>49</td>
<td>44.0</td>
<td>12 weeks</td>
<td>DLQI</td>
</tr>
<tr>
<td>Mamolo 2014</td>
<td>Tofacitinib 15mg BID</td>
<td>49</td>
<td>43.6</td>
<td>12 weeks</td>
<td>sPGA</td>
</tr>
<tr>
<td>Papp 2015</td>
<td>Pefacitinib 25mg BID</td>
<td>21</td>
<td>47.5</td>
<td>6 weeks</td>
<td>PASI75</td>
</tr>
<tr>
<td>Papp 2015</td>
<td>Pefacitinib 100mg BID</td>
<td>17</td>
<td>51.1</td>
<td>6 weeks</td>
<td>Total adverse events</td>
</tr>
<tr>
<td>Feldman 2016</td>
<td>Tofacitinib 5mg BID</td>
<td>363</td>
<td>45.6</td>
<td>16 weeks</td>
<td>DLQI</td>
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<td>Feldman 2016</td>
<td>Tofacitinib 10mg BID</td>
<td>360</td>
<td>45.2</td>
<td>16 weeks</td>
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<td>Feldman 2016</td>
<td>Placebo</td>
<td>177</td>
<td>45.0</td>
<td>16 weeks</td>
<td></td>
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<tr>
<td>Papp 2016</td>
<td>Baricitinib 8mg MQD</td>
<td>64</td>
<td>47.4</td>
<td>12 weeks</td>
<td>PASI75</td>
</tr>
<tr>
<td>Papp 2016</td>
<td>Baricitinib 10mg MQD</td>
<td>69</td>
<td>47.4</td>
<td>12 weeks</td>
<td>Serious adverse events</td>
</tr>
<tr>
<td>Masatoshii 2017</td>
<td>Tofacitinib 5mg BID</td>
<td>22</td>
<td>47.5</td>
<td>16 weeks</td>
<td>PASI75</td>
</tr>
<tr>
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<td>24</td>
<td>47.5</td>
<td>16 weeks</td>
<td>sPGA</td>
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<td>40.7</td>
<td>16 weeks</td>
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<td>83</td>
<td>41.0</td>
<td>16 weeks</td>
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<tr>
<td>Zhang 2017</td>
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<td>77</td>
<td>41.7</td>
<td>16 weeks</td>
<td>Total adverse events</td>
</tr>
</tbody>
</table>

3.3 Included in Research Quality Evaluation

The included studies underwent quality assessment, with all reporting the use of randomization methods and rated as "low risk". Three documents failed to mention the allocation concealment and were assessed as "unclear risk". One study was rated as "high risk" due to the absence of blinding. Another study reported case dropout and was rated "high risk". No selective reporting was detected in the included studies, leading to a rating of "low risk"; Furthermore, no other
potential sources of bias were identified through the review, thus the risk was rated as "low". Refer to Figure 2 for the detailed risk assessment results.

3.4 Efficacy of JAK-STAT Inhibitors

Efficacy of JAK-STAT inhibitors in achieving PASI 75 Five studies reported PASI 75 [7,8,11,12,13], with heterogeneity test results of P=0.30 and I²=19%. There was no significant heterogeneity among the groups. A fixed-effect model was employed for the meta-analysis. According to the meta-analysis results, the PASI 75 in the JAK-STAT inhibitors group was significantly higher than in the placebo group, with the difference being statistically significant [RR=6.49, 95% CI (4.07, 10.34), P<0.00001]. See Figure 3.

![Figure 3](image3.png)

**Figure 3:** Meta-analysis of efficacy of JAK-STAT inhibitors for patients achieving at least 75% reduction in the Psoriasis Area and Severity Indexscore.

Efficacy of JAK-STAT inhibitors in achieving sPGA 0/1 Four studies reported sPGA 0/1 [7,8,12,13], with heterogeneity test results of P=0.44 and I²=0%. There was no significant heterogeneity among the groups. A fixed-effect model was employed for the meta-analysis. According to the meta-analysis results, the sPGA 0/1 in the JAK-STAT inhibitors group was significantly higher than in the placebo group, with the difference being statistically significant [RR=4.60, 95% CI (3.08, 6.85), P<0.00001]. See Figure 4.

![Figure 4](image4.png)

**Figure 4:** Efficacy of JAK-STAT inhibitors in achieving static Physician’s Global Assessment (0/1).
Efficacy of JAK-STAT inhibitors in achieving ISS 0/1 Two studies reported on ISS0/1 [10,12], with heterogeneity test results of P=0.84 and I²=0%, indicating no significant heterogeneity among the groups. A fixed-effect model was employed for the meta-analysis, revealing that the ISS 0/1 in the JAK-STAT inhibitors group was significantly higher than in the placebo group, with a statistically significant difference [RR=5.84, 95% CI (3.69, 9.24), P<0.00001]. See Figure 6.

Figure 6: Efficacy of JAK-STAT inhibitors in achieving Itch severity scale (0/1).

3.5 Safety of JAK-STAT Inhibitors
Total AEs Three studies reported on Total AEs [7,9,13], with heterogeneity test results of P=0.16 and I²=45%, indicating no significant heterogeneity among the groups. A fixed-effect model was utilized for the meta-analysis, which showed that the incidence of Total AEs was slightly higher in the JAK-STAT inhibitors group compared to the placebo group, with a statistically significant difference [RR=1.19, 95% CI (1.01, 1.41), P=0.04]. See Figure 7.

Figure 7: Meta analysis forest chart of Total AEs of JAK-STAT inhibitors vs placebo.

SAEs Three studies reported on SAEs [7,11,13], with heterogeneity test results of P=0.62 and I²=0%, indicating no significant heterogeneity among the groups. A fixed-effect model was employed for the meta-analysis, showing no statistically significant difference in the incidence of SAEs between the JAK-STAT inhibitors group and the placebo group [RR=1.42, 95% CI (0.32, 6.40), P=0.65]. See Figure 8.

Figure 8: Meta analysis forest chart of SAEs of JAK-STAT inhibitors vs placebo.

4. Discussion
JAKs are part of the tyrosine kinase family, which comprises four members: Janus kinase 1 (JAK1), JAK2, JAK3, and tyrosine-protein kinase Tyk2 [14]. The transcription factor STAT family comprises seven members: STAT1, STAT2, STAT3, STAT4, STAT5A, STAT5B, and STAT6. Various STAT proteins share common structural features, including an amino terminal, a helical domain, a DNA binding domain (DBD), a linker region, a SH2 domain, and a transcriptional activation domain (TAD) [15]. The JAK-STAT pathway is a common signal transduction pathway for many cytokines, involved in immune regulation, cell proliferation, and differentiation [16]. JAKs function differently depending on the receptor they bind to. JAK1 can pair with the other three
JAK members to mediate the expression of signals from IFN-α, IFN-γ, IL-6, and IL-10. JAK2 primarily produces the hematopoietic factor (EPO) and is associated with hormones. JAK3 is primarily expressed specifically in hematopoietic tissues and can be activated by cytokines of the IL-2 family. TYK2 is primarily involved in the responses to cytokines including IL-10, IFN-α, IL-6, and IL-23 [17]. Various STAT proteins can be activated by specific extracellular signals, with STAT1 activated by IFN, STAT3 specialized in responding to activation by IL-6 family cytokines, STAT4 activated by IL-12, and STAT6 activated by IL-4 [18]. Each STAT protein can associate with different members of the JAK family to exert specific biological effects [19].

Research indicates that the pathogenesis of psoriasis is closely associated with inflammatory cytokines such as IL-2, IL-6, IL-17, IL-23, TNF-α, and IFN-γ [20]. Research has found that JAK, STAT1, and STAT3 signals are overexpressed in psoriatic lesions. STAT1 regulates the signaling of IFN-γ and IFN-α through JAK1/JAK2, leading to the production of multiple pro-inflammatory cytokines and the activation and maturation of dendritic cells (DCs). STAT3 is involved in the differentiation of Th17 and the proliferation of keratinocytes (KC). In summary, the JAK-STAT signaling pathway is involved in the inflammatory response of psoriasis, T cell differentiation, and excessive keratinocyte proliferation, among others. Currently, JAK-STAT inhibitors (baricitinib, tofacitinib, peficitinib, upadacitinib) primarily target the JAK family, effectively reducing cytokine expression in the JAK-STAT pathway by inhibiting JAK activity, thus emerging as a new and effective treatment for psoriasis.

This paper conducted a meta-analysis on the efficacy and safety of JAK-STAT inhibitors for moderate to severe plaque psoriasis. The results demonstrate that the efficacy of JAK-STAT inhibitors in terms of PASI 75, SPQA 0/1, DLQI 0/1, and ISS 0/1 is significantly greater than that of the placebo group (P<0.05). These findings indicate that JAK-STAT inhibitors can significantly reduce the lesion area in psoriasis patients, alleviate itching symptoms, and enhance their quality of life. In terms of safety, the incidence of serious adverse reactions was not statistically different between the JAK-STAT inhibitor and placebo groups, with the overall incidence of adverse reactions being slightly higher in the former. Across the seven included studies, both groups reported various degrees of adverse reactions, including nasopharyngitis, herpes zoster, infections, cardiovascular events, and malignancies. Generally, the adverse reactions associated with JAK-STAT inhibitors are mostly mild to moderate and well-tolerated by patients. Additionally, the current treatment of psoriasis with JAK-STAT inhibitors predominantly involves oral formulations, significantly enhancing patient compliance without posing risks for immunogenicity or adverse reactions at the injection site [21]. The seven included studies are of high overall quality; however, this paper is limited by: a. the small sample size, encompassing only 1830 patients; b. the limited number of included studies and varying drug dosages across groups, which preclude subgroup analysis by factors such as dosage, race, and gender; c. the absence of comparative analysis with other positive treatments.

In conclusion, JAK-STAT inhibitors demonstrate efficacy in treating moderate to severe plaque psoriasis, with mostly mild to moderate adverse reactions and good patient tolerance and compliance. Nonetheless, further large-scale, high-quality, multicenter research is necessary to validate their clinical efficacy and safety, thereby providing a more robust foundation for their use in treating moderate to severe plaque psoriasis.

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**References**


