A Systematic Review and Meta-analysis of Efficacy and Safety of Novel Interleukin Inhibitors in the Management of Psoriatic Arthritis

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Objective: The aim of this study was to systemically review the efficacy and safety of inhibitors of interleukin 6 (IL-6): clazakizumab, IL-12/23: ustekinumab, and IL-17A: secukinumab, brodalumab, and ixekizumab in psoriatic arthritis (PsA).

Methods: The literature search was conducted using MEDLINE, EMBASE, Cochrane Library, Scopus, and Web of Science. We included randomized controlled trials that assessed the efficacy of IL inhibitors and reported American College of Rheumatology 20 response at 24 weeks. Meta-analysis was done using random-effects model utilizing the DerSimonian and Laird method. Quality assessment was done using RobotReviewer Cochrane Risk-of-Bias Assessment Tool. Heterogeneity was assessed with Q statistic and quantified with $I^2$. Publication bias was assessed with a funnel plot.

Results: Eight studies including 2722 subjects demonstrate the efficacy of IL inhibitors clazakizumab, secukinumab, ixekizumab, brodalumab, and ustekinumab in the treatment of PsA. The American College of Rheumatology 20/50/70 risk ratios were 2.02 (95% confidence interval [CI], 1.65–2.47; $P = 0.000$), 2.95 (95% CI, 2.32–3.73; $P = 0.000$), and 5.14 (95% CI, 3.28–8.06; $P = 0.000$), respectively, in favor of treatment versus placebo. There was no evidence of significant heterogeneity between trials. Subgroup analysis showed efficacy in patients who were tumor necrosis factor naïve, as well as tumor necrosis factor nonresponders or inadequate responders. The number of adverse events was higher in the treatment groups versus placebo, the majority were mild and did not require treatment adjustment (risk ratio, 1.17; 95% CI, 1.06–1.28; $P = 0.001$). There was no significant difference in drug withdrawals.

Conclusions: Our meta-analysis shows that the inhibitors of IL-6 (clazakizumab), IL-12/23 (ustekinumab), and IL-17A (secukinumab, brodalumab, and ixekizumab) are efficacious and generally well tolerated when used to treat patients with PsA.

Key Words: biologics, interleukin inhibitors, psoriatic arthritis, spondyloarthropathies

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J.B. and I.B.R. have equally contributed as co-first authors for this project. This research received no specific grant from any funding agency in the public, commercial, or not-for-profit sectors.

M.A.K. has received speaking fees from AbbVie and Novartis and honoraria as a consultant for Janssen, Novartis, and Pfizer. The other authors declare no conflict of interest.

Supplemental digital content is available for this article. Direct URL citation appears in the printed text and is provided in the HTML and PDF versions of this article on the journal’s Web site (www.jclinrheum.com).

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ISSN: 1076-1608
DOI: 10.1097/RHU.000000000000583

P soriatic arthritis (PsA) is an inflammatory arthritis with no gender preference and has an estimated incidence of 6 per 100,000 per year and a prevalence of 1 to 2 per 1000 in the general population.1,2 It is a heterogeneous clinical entity that may involve peripheral joints, axial skeleton, or both. Polyarthritis is the predominant clinical pattern, observed by approximately 60% of the affected individuals, with an equal incidence of symmetric and asymmetric patterns.3 Tenosynovitis, enthesitis, and dactylitis are commonly associated rheumatologic features. Articular, tendon, and joint swelling and range of motion may sometimes overcome this problem.4 The advent of biologics, including tumor necrosis factor α (TNF-α) inhibitors, has advanced the treatment of PsA.5–9 However, TNF-α inhibitors may also have primary inefficacy or lose efficacy with time in some patients. Switching to an alternative TNF-α inhibitor or increasing the dose or frequency of administration may sometimes overcome this problem.10–12 To circumvent this issue, recent studies have focused on medications with novel modes of action, such as the phosphodiesterase 4 inhibitor apremilast, the T-cell activation inhibitor abatacept, and newer biologics inhibiting interleukin 6 (IL-6; i.e., clazakizumab), IL-12/23 (i.e., ustekinumab), IL-17 (i.e., secukinumab, ixekizumab, and brodalumab), and IL-23 (i.e., guselkumab and tildrakizumab).13 These agents are either recently approved or being tested in clinical trials that have demonstrated encouraging results. The emergence of these agents warrants dynamic updated treatment guidelines for PsA.

Recently conducted reviews have evaluated such novel treatment options in PsA.6,14–16 We present here an updated meta-analysis that includes the most recent data and compares the efficacy and safety of newer therapies for patients who have previously used TNF inhibitors alone or in combination with synthetic disease-modifying antirheumatic drugs.

METHODS

Search Strategy

The meta-analysis was designed in accordance with the principles set by the Preferred Reporting Items for Systematic Reviews and Meta-analyses checklist.17 Literature search was performed using the following electronic bibliographic databases: MEDLINE
(Ovid SP and PubMed), EMBASE, The Cochrane Library (Cochrane Database of Systematic Reviews) and Cochrane Central Register of Controlled Trials (CENTRAL), Scopus, and Web of Science. The initial search was not restricted to English. The searches were repeated just before the final analyses, and further studies were retrieved for inclusion until March 2017. The bibliographies of retrieved articles and previous review articles were hand searched to obtain additional articles (Fig. 1).

**Condition or Domain Being Studied**

The targets of our investigation were randomized clinical trials of adult patients with active PsA treated with biologic inhibitors of IL-6: clazakizumab; IL-12/23: ustekinumab; IL-17A: secukinumab, ixekizumab, and brodalumab; and IL-23: guselkumab and tildrakizumab, and their results published before March 2017. There were no trials available for guselkumab and tildrakizumab. We did not include tofacitinib because it was a drug of the Janus kinase inhibitor class. For the purpose of statistical analysis, we excluded studies with no placebo arm.

**Primary Analysis**

The primary outcome was the American College of Rheumatology (ACR) 20% response reported at 24 weeks.

**Subgroup Analysis**

We performed prespecified subgroup analysis to assess efficacy of IL inhibitors in the TNF inhibitor–exposed versus TNF inhibitor–naive patients, as well as concomitant use of methotrexate versus no methotrexate.

**Data Extraction**

Using the search strategy, we obtained titles and/or abstracts of retrieved studies and imported them to endnote. Two investigators independently screened the titles and abstracts; the full texts were screened if the articles met the inclusion criteria. Full texts of these selected articles were obtained and evaluated by 2 investigators to confirm eligibility for inclusion. Discrepancy was resolved via discussion. Two independent reviewers, using a structured template, performed data extraction from the included studies, and any disagreements were resolved with consensus. A standardized data extraction form was used to extract the following fields: year of study, country of study, disease duration, study design, number of patients, study phase, study duration, disease duration, age, gender, body mass index (BMI), body surface area affected by the Psoriasis Area Severity Index (PASI), C-reactive protein levels, swollen joint score, tender joint score, and percentage of patients with enthesis and dactylitis, along with enthesis score and dactylitis score.

**Risk-of-Bias Assessment**

Risk of bias for the included trials was assessed using the RobotReviewer, a Cochrane Collaboration’s tool.

**Strategy for Data Synthesis**

We calculated the risk ratio (RR) as an effect measure to compare efficacy and safety between treatment and control arms.

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**FIGURE 1.** Preferred Reporting Items for Systematic Reviews and Meta-analyses flow diagram describing literature search strategy.
<table>
<thead>
<tr>
<th>Study (Author, Year) and Phase</th>
<th>Treatment vs. Control</th>
<th>Patient No. (Treatment/Placebo)</th>
<th>Study Duration, wk</th>
<th>Disease (PsA) Duration, y</th>
<th>Age, y</th>
<th>Women, n (%)</th>
<th>BMI, kg/m²</th>
<th>CRP, mg/dL</th>
<th>Swollen Joint Score</th>
<th>Tender Joint Score</th>
<th>Enthesitis, n (%)</th>
<th>Dactylitis, n (%)</th>
<th>Enthesitis Score</th>
<th>Dactylitis Score</th>
<th>PASI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gottlieb et al., 2009</td>
<td>Ustekinumab vs. placebo</td>
<td>146 (76 vs. 70)</td>
<td>36</td>
<td>6.2 vs. 4.9</td>
<td>50.0 vs. 47.5</td>
<td>31 (41.0%) vs. 33 (47.0%)</td>
<td>NR</td>
<td>4.0 vs. 7.0</td>
<td>10.0 vs. 7.0</td>
<td>19.5 vs. 16.0</td>
<td>34 (45%) vs. 32 (46%)</td>
<td>33 (43%) vs. 22 (31%)</td>
<td>NR</td>
<td>4.0 (2.0–9.0)</td>
<td>NR</td>
</tr>
<tr>
<td>Ritchlin et al., 2014</td>
<td>Ustekinumab vs. placebo</td>
<td>312 (208 vs. 104)</td>
<td>60</td>
<td>4.9 vs. 5.5</td>
<td>48.5 vs. 48.0</td>
<td>111 (53.4%) vs. 53 (51.0%)</td>
<td>30.3 vs. 30.5</td>
<td>11.6 vs. 8.5</td>
<td>11.5 vs. 11.0</td>
<td>22.0 vs. 21.0</td>
<td>148 (71.2%) vs. 73 (70.2%)</td>
<td>99 (47.6%) vs. 38 (36.5%)</td>
<td>5.5 vs. 4.0</td>
<td>6.0 vs. 7.0</td>
<td>8.7 vs. 7.9</td>
</tr>
<tr>
<td>McInnes et al., 2013</td>
<td>Ustekinumab vs. placebo</td>
<td>615 (409 vs. 206)</td>
<td>52</td>
<td>4.2 vs. 3.6</td>
<td>47.5 vs. 48.0</td>
<td>187 (45.7%) vs. 98 (47.6%)</td>
<td>29.7 vs. 29.7</td>
<td>11.2 vs. 9.6</td>
<td>10.0 vs. 12.0</td>
<td>19.0 vs. 22.0</td>
<td>296 (72.4%) vs. 145 (70.4%)</td>
<td>200 (48.9%) vs. 96 (46.6%)</td>
<td>4.5 vs. 4.0</td>
<td>4.0 vs. 4.5</td>
<td>7.6 vs. 8.8</td>
</tr>
<tr>
<td>McInnes et al., 2014</td>
<td>Ustekinumab vs. placebo</td>
<td>168 (113 vs. 55)</td>
<td>52</td>
<td>8.8 vs. 8.4</td>
<td>52.0 vs. 53.0</td>
<td>77 (68%) vs. 30 (55)</td>
<td>33 vs. 31</td>
<td>5.1 vs. 3.8</td>
<td>12.5 vs. 12.8</td>
<td>24.0 vs. 25.0</td>
<td>73 (65%) vs. 45 (82%)</td>
<td>67 (59%) vs. 37 (67%)</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
</tr>
<tr>
<td>Mease et al., 2015</td>
<td>Brodalumab vs. placebo</td>
<td>42 (28 vs. 14)</td>
<td>24</td>
<td>6.3 vs. 5.4</td>
<td>46.7 vs. 47.6</td>
<td>19 (68%) vs. 8 (57)</td>
<td>31.9 vs. 27.5</td>
<td>4.9 vs. 6.2</td>
<td>8.3 vs. 9.5</td>
<td>23.5 vs. 22.6</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>NR</td>
<td>3.5 vs. 2.4</td>
</tr>
<tr>
<td>McInnes et al., 2015</td>
<td>Secukinumab vs. placebo</td>
<td>397 (299 vs. 98)</td>
<td>52</td>
<td>NR</td>
<td>43.3 vs. 49.9</td>
<td>156 (51.2%) vs. 59 (60)</td>
<td>84.4 vs. 80.0 kg²</td>
<td>NR</td>
<td>11.3 vs. 12.1</td>
<td>22.2 vs. 23.4</td>
<td>188 (62.9%) vs. 111 (37.1%)</td>
<td>31.1 vs. 3.1</td>
<td>3.7 vs. 2.7</td>
<td>13.4 vs. 11.6</td>
<td></td>
</tr>
<tr>
<td>Mease, 2015</td>
<td>Secukinumab vs. placebo</td>
<td>606 (404 vs. 202)</td>
<td>52</td>
<td>NR</td>
<td>49.2 vs. 48.5</td>
<td>226 (55.9%) vs. 106 (52.5)</td>
<td>87.4 vs. 86.2 kg²</td>
<td>NR</td>
<td>12.6 vs. 14.9</td>
<td>23.6 vs. 25.1</td>
<td>255 (63.2%) vs. 117 (57.9)</td>
<td>116 (57.4)</td>
<td>NR</td>
<td>13.2 vs. 15.1</td>
<td></td>
</tr>
<tr>
<td>McInnes et al., 2017</td>
<td>Ixekizumab vs. placebo³</td>
<td>417 (210 vs. 106)</td>
<td>52</td>
<td>NR</td>
<td>49.5 vs. 50.6</td>
<td>117 (55.7%) vs. 58 (54.7)</td>
<td>29.4 vs. 29.212</td>
<td>14 vs. 15.1</td>
<td>11.6 vs. 10.6</td>
<td>21 vs. 19.2</td>
<td>129 (61.4%) vs. 57 (53.8)</td>
<td>95 (45.2%) vs. 39 (36.8)</td>
<td>NR</td>
<td>6.5 vs. 6.2</td>
<td></td>
</tr>
<tr>
<td>Mease et al., 2016</td>
<td>Clazakizumab vs. placebo</td>
<td>165 (124 vs. 41)</td>
<td>24</td>
<td>6.6 vs. 8.5</td>
<td>47.9 vs. 48.0</td>
<td>63 (50.8%) vs. 23 (36.1)</td>
<td>86.7 vs. 82.3 kg²</td>
<td>15.6 vs. 11.0</td>
<td>12.3 vs. 11.2</td>
<td>19.5 vs. 11.2</td>
<td>32.3 (78.1%) vs. 33 (80.5%)</td>
<td>10 (32.5%) vs. 17 (41.5%)</td>
<td>NR</td>
<td>9.1 vs. 7.9</td>
<td></td>
</tr>
</tbody>
</table>

All the studies were randomized controlled trials.

*Only weight in kilograms is reported.

³The data of 101 patients treated with adalimumab were not included in the analysis.

CRP indicates C-reactive protein; NR, not reported.
We conducted the meta-analysis using random-effects model utilizing the DerSimonian and Laird method. Heterogeneity was assessed using $Q$ statistic, and it was quantified using $I^2$ statistic, which, expressed as a percentage, represents the proportion of between-study variation that is not random, that is, variation due to differences in study design, interventions, or populations. Heterogeneity was considered negligible if $I^2$ was less than 25%; moderate if $I^2$ was approximately 50%; and substantial if $I^2$ was 70% or more. Publication bias was assessed with a funnel plot.

RESULTS

A total of 1265 titles were retrieved using initial database search. One thousand one hundred eighty-two studies were selected after removing duplicates, and 42 studies were considered eligible for further review after reviewing titles and abstracts. A total of 9 randomized clinical trials were found to have outcomes of interest, and 8 were included in the primary analysis. Twenty-four trials were included in 5 trials, were 31.0 and 29.6 kg/m², in 7 trials, were 6.1 and 6.08 years; average BMIs, as reported in 8 trials, averaged 45.6% and 43.1%, respectively. Mean disease durations, as reported in 45.6% and 43.1%, respectively. Mean disease durations, as reported in 4 trials, were 47.3 years in the former and 49.1 years in the latter group; female percentages were 54.5% and 53.1%; baseline average swollen joint counts were 11.12 and 11.23, and baseline average tender joint counts were 21.58 and 20.6, respectively. Prevalence of enthesis, as reported in 8 trials, averaged 64.9% and 65.85%, and that of dactylitis averaged 45.6% and 43.1%, respectively. Mean disease durations, as reported in 7 trials, were 6.1 and 6.08 years; average BMIs, as reported in 5 trials, were 31.0 and 29.6 kg/m², and the average weights, as reported in 3 trials, were 86.16 and 82.83 kg, respectively.

Quality assessment of the included studies is summarized in Table 2. The included studies were well conducted across all assessed domains. There was no evidence of significant publication bias (see supplementary material, Figure 1, http://links.lww.com/RHU/A75).

Results of meta-analysis paralleled that of the individual studies. The patients in the treatment group achieved ACR20/50/70 responses at a significantly higher rate as compared with placebo, with RRs of 2.02 (95% confidence interval [CI], 1.65–2.47; $P = 0.000$), 2.95 (95% CI, 2.32–3.73; $P = 0.00$), and 5.14 (95% CI, 3.28–8.06; $P = 0.00$), respectively (Figs. 2A–C). We also did a sensitivity analysis based on the sample size of the included trials, and removal of the phase 2 trial with $n < 100$ by McInnes et al. did not impact the results of our analysis. The RR of achieving an ACR20 response in the 2 studies of ustekinumab was 2.060 (95% CI, 1.641–2.585; $P = 0.000$) (see supplementary material, Figure 2A, http://links.lww.com/RHU/A75). The RR of achieving an ACR20 response in the 3 studies of secukinumab was 2.823 (95% CI, 2.177–3.661; $P = 0.000$) (see supplementary material, Figure 2B, http://links.lww.com/RHU/A75).

There was no increase in the incidence of serious adverse effects in the treatment versus control groups (RR, 1.25; 95% CI, 0.73–2.15; $P = 0.39$). There was negligible heterogeneity between these trials ($I^2 = 12.406, Q = 7.991$) (see supplementary material, Figure 3A, http://links.lww.com/RHU/A75). Withdrawals due to toxicity were seen less in the active treatment group as compared with the control group in 6 trials with an RR of 0.59 (95% CI, 0.32–1.22; $P = 0.11$) (see supplementary material, Figure 3B, http://links.lww.com/RHU/A75). There was no evidence of heterogeneity...
between these trials ($I^2 = 0.000$, $Q = 4.953$). There was an increased incidence of overall adverse effects in the treatment arm, although the increase in risk was small (RR, 1.17; 95% CI, 1.06–1.30; $P = 0.001$). There was no evidence of heterogeneity between these trials ($I^2 = 0.000$, $Q = 5.962$) (see supplementary material, Figure 3C http://links.lww.com/RHU/A75).

We performed several subgroup analyses. The RR of achieving an ACR20 response in the TNF-α inhibitor–naive group in 5 trials was 2.293 (95% CI, 1.510–3.482; $P = 0.000$) in favor of treatment (Fig. 3A). There was no evidence of heterogeneity between these trials ($I^2 = 0.000$, $Q = 3.453$). The RR of achieving an ACR20 response in patients with prior TNF-α inhibitor exposure in 5 trials was 1.926 (95% CI, 1.392–2.665; $P = 0.000$) (Fig. 3B). There was no evidence of heterogeneity between these trials ($I^2 = 0.000$, $Q = 3.965$). The RR of achieving an ACR20 response in the concomitant methotrexate group versus no-methotrexate group in 4 trials was 1.29 (95% CI, 1.14–1.46; $P = 0.012$) (Fig. 3C). There were no adverse events in the treatment arm (see supplementary material, Figure 4 http://links.lww.com/RHU/A75). There was negligible heterogeneity between these trials ($I^2 = 16.365$, $Q = 5.978$).

**DISCUSSION**

This meta-analysis demonstrates the efficacy of IL-6/12/17/23 inhibitors (clazakizumab, secukinumab, brodalumab, ixekizumab, ustekinumab) in the treatment of PsA regardless of prior TNF-α inhibitor exposure. A subgroup analysis showed that the combination of methotrexate and IL inhibitors did not result in significantly increased benefit as compared with IL inhibitors alone for the duration of these trials (Fig. 4). Moreover, effectiveness of these agents in patients with prior TNF-α inhibitor exposure makes them a promising choice filling an unmet need.

Results of this systematic review are consistent with recent clinical trials and systematic reviews.

![FIGURE 2. Risk ratio of achieving an ACR20 response at 24 weeks (IL inhibitors vs. placebo) (A). Risk ratio of achieving an ACR50 response at 24 weeks (B). Risk ratio of achieving an ACR70 response at 24 weeks (C).](http://links.lww.com/RHU/A75)

The IL inhibitors were generally safe and well tolerated by the patients for the duration of the clinical trials. Adverse events were noted to be higher in the treatment group as compared with placebo, but most adverse events were mild and did not require treatment adjustment. There was no significant increase in serious adverse events. Interestingly, withdrawal rates were actually lower in the treatment group, probably because subjects stayed in the treatment group despite adverse effects because it was working so well for their disease. These results suggest that the safety profile of these novel agents is likely favorable. However, future
studies looking at the long-term adverse effects are of paramount importance to verify or uncover less common adverse effects (such as suicidal ideation reported with brodalumab) and to address concerns of increased infection risks associated with biologic therapies.\textsuperscript{34,35} Recently, Candida infections are increasingly reported with the use of IL-17 agents, that is, secukinumab, brodalumab, and ixekizumab.\textsuperscript{36} Lipid abnormalities have been common with IL-6 inhibitors in patients with rheumatoid arthritis, and it is very important to have follow-up data in patients with PsA, especially given the higher prevalence of metabolic syndrome in this patient population.

This is the most up-to-date and comprehensive systematic review of IL inhibitors for PsA reporting both efficacy and safety profiles. Our analysis has several strengths, including precise results with no significant heterogeneity, and subgroup analyses. Moreover, we have demonstrated consistent efficacy of IL inhibitors for 24 weeks without significant increase in adverse effects observed during the relatively short duration of the studies. Furthermore, our analysis further supports the view that IL inhibitors are effective as monotherapy (without concomitant methotrexate) in clinically relevant and sometimes challenging situations or unmet needs, such as treatment of PsA patients who cannot receive TNF-\(\alpha\) inhibitors because of contraindications, prior lack of adequate response, or untoward effects of such treatment.

Our meta-analysis is limited by the lack of individual patient data, and it is based on the outcomes reported (selectively) in the published trials and is subject to the limitations of the individual trials. Moreover, subgroup analysis does not follow the design of the clinical trials. For example, none of these trials were designed to compare IL inhibitor monotherapy to combination therapy with methotrexate. We were unable to include complete data from all studies for subgroup analysis because of unavailability, and one of the studies was available only in abstract form. We plan to assess in the future the comparative efficacy and safety of IL inhibitors. A networking meta-analysis can compare different IL inhibitors for their efficacy and safety and answer the question whether these agents differ in their efficacy and safety. Moreover, the current evidence regarding efficacy of clazakizumab is weak, and there is a concern for lack of dose response. Further studies are needed to elucidate the therapeutic role of clazakizumab in PsA. Similarly, current safety data are limited to short-term clinical trial reports, and longitudinal data predicting infections and
malignancy risk are not yet available. Lastly, inherent heterogeneity of PsA demands individualized treatment for diverse clinical manifestations, while this review addresses only synovitis. Therefore, there is a need for clinical trials that also address the effects of the drugs on the individual components of the wide clinical spectrum of PsA.

In summary, our systematic review demonstrates the efficacy of IL-6, IL-12, IL-17, and IL-23 inhibitors in the management of PsA. Although there are no head-to-head comparisons, the response rate to these IL inhibitors is similar to that previously reported with TNF-α inhibitors. The results of subgroup analyses should be tested in well-designed randomized controlled trials that should also allow investigators to address the optimal timing of commencing treatment and its duration, identification of predictors of response, switching between different IL inhibitors, response to extra-articular manifestations, and discontinuation strategy on re-commencing treatment and its duration, identification of predictors of response rate to these IL inhibitors is similar to that previously reported in the literature with a meta-analysis. Moreover, there is a need for dynamic changes in the treatment strategies for psoriasis and PsA considering emerging suite of newer biologics, that is, Janus kinase inhibitor tofacitinib and IL-23 inhibitors tildrakizumab and guselkumab.29,37

REFERENCES


