Objective and Background
We evaluated the comparative effectiveness of targeted immunomodulators for adults with moderate-to-severe plaque psoriasis.

Clinical interest in targeted immunomodulators is high, as many patients with moderate-to-severe chronic plaque psoriasis do not achieve adequate or durable benefit from older systemic therapies or phototherapy. The newer targeted immunomodulators are generally more expensive than older medications and there are questions regarding their relative effectiveness.

Methods
We performed a systematic literature review of randomized controlled trials of targeted immunomodulators that evaluated the comparative clinical benefits and harms relative to placebo or each other. We abstracted evidence from available clinical studies, whether in published, unpublished, or abstract form.

The key clinical outcome reported in plaque psoriasis trials included response on the Psoriasis Area and Severity Index (PASI). The most consistently reported primary outcome in clinical trials was the “PASI 75,” the proportion of patients who had a 75% reduction in the PASI score from baseline to follow-up. Many trials reported other PASI thresholds: PASI 50, PASI 90, and PASI 100 (equivalent to a follow-up PASI score of zero). We summarized comparative findings qualitatively and quantitatively synthesized evidence for PASI 50, 75, and 90, and measures through the conduct of a Bayesian network meta-analysis. For the base-case analysis, the placebo response rate in each trial was included as a covariate to account for between-study population variability.

Results
We included both placebo-controlled and head-to-head trials of the targeted immunomodulators. We excluded studies that evaluated targeted immunomodulators as part of a combination treatment, as well as studies evaluating the recently approved biosimilar forms of the TNF-α inhibitors since they are assumed to be functionally equivalent to the reference product.

Our literature search identified 1,618 potentially relevant references. A total of 34 Phase III RCTs met our inclusion criteria, including 26 placebo-controlled and eight head-to-head trials of targeted immunomodulators for plaque psoriasis.

All targeted immunomodulators had a statistically significantly higher PASI 75 response rate compared to placebo. In individual placebo-controlled RCTs, the incremental proportion of patients achieving PASI 75 above placebo within trials was:

- 13.8% for adalimumab (2 trials),
- 33%-54% for etanercept (7 trials),
- 62%-64% for adalimumab (2 trials),
- 63%-64% for ustekinumab 45 mg (2 trials),
- 63%-72% for ustekinumab 90 mg (2 trials),
- 72%-84% for secukinumab at 12 weeks (4 trials),
- 74%-77% for infliximab (2 trials),
- 78%-80% for brodalumab (3 trials), and
- 80%-88% for ixekizumab (3 trials).

In the NMA, the targeted immunomodulators, ordered by an increasing relative risk (demonstrating greater likelihood) of achieving PASI 75 relative to placebo were adalimumab (9.6), etanercept (13.0), ustekinumab (14.0), secukinumab (15.4), infliximab (16.2), brodalumab (17.3), and ixekizumab (17.9). In addition, ixekizumab, brodalumab, and infliximab were all statistically superior to ustekinumab, adalimumab, etanercept, and placebo.

The eight head-to-head RCTS all showed statistically-significant differences between treatments in PASI 75 response.

- In four trials, three agents were superior to etanercept: ustekinumab, secukinumab, and ixekizumab.
- In four trials, three agents were superior to ustekinumab: secukinumab, ixekizumab, and brodalumab.
- Finally, in a recently published report of 52-week data from the CLEAR study, the rate of achieving PASI 75 for secukinumab and ustekinumab was 93% vs. 80%, respectively.

Harms and Long Term Adverse Events
We abstracted data on adverse events that occurred in at least 5% of patients in any treatment group, particularly serious infections or other events leading to study discontinuation, which have been abstracted and presented as trial-weighted averages. Most adverse events were mild or moderate.

- Compared to other drugs, infliximab appears to have higher rates of infection, and adalimumab was associated with a higher incidence of nausea and diarrhea.
- Findings suggest an increased rate of serious infections for biologic agents relative to placebo, although not for ustekinumab.
- Other severe adverse effects, death, and events leading to discontinuation were rare and comparable between the treatment and placebo groups.

In longer-term follow-up, there were no substantive differences between secukinumab and etanercept or ustekinumab, or between ustekinumab and brodalumab up to one year of follow-up. For newer targeted immunomodulators – ixekizumab and apremilast – no long-term safety data beyond the duration of clinical trials have been published.

Table 1: Head to Head Trials

<table>
<thead>
<tr>
<th>Trial</th>
<th>Treatment</th>
<th>PASI 75 (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Head to Head with Etanercept</td>
<td>Etanercept</td>
<td>57</td>
</tr>
<tr>
<td></td>
<td>Ustekinumab</td>
<td>68-74</td>
</tr>
<tr>
<td>FIXTURE</td>
<td>Etanercept</td>
<td>44</td>
</tr>
<tr>
<td></td>
<td>Secukinumab</td>
<td>77</td>
</tr>
<tr>
<td>UNCOVER 2 &amp; 3</td>
<td>Etanercept</td>
<td>42-53</td>
</tr>
<tr>
<td></td>
<td>Ixekizumab</td>
<td>87-90</td>
</tr>
</tbody>
</table>

Table 2: Base case NMA: League Table of Relative Risk (Likelihood) of PASI 75 Response

<table>
<thead>
<tr>
<th>Drug</th>
<th>PASI 50</th>
<th>PASI 75</th>
<th>PASI 90</th>
<th>PASI 100</th>
<th>Ustekinumab</th>
<th>Secukinumab</th>
<th>Ixekizumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Adalimumab</td>
<td>2.15</td>
<td>2.72</td>
<td>2.99</td>
<td>3.31</td>
<td>2.90</td>
<td>2.79</td>
<td>2.70</td>
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<tr>
<td>Brodalumab</td>
<td>1.73</td>
<td>1.81</td>
<td>1.69</td>
<td>1.76</td>
<td>1.81</td>
<td>1.73</td>
<td>1.70</td>
<td>1.15</td>
</tr>
<tr>
<td>Ixekizumab</td>
<td>1.10</td>
<td>1.28</td>
<td>1.67</td>
<td>2.18</td>
<td>1.80</td>
<td>1.73</td>
<td>1.70</td>
<td>1.15</td>
</tr>
<tr>
<td>Placebo</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
<td>1.00</td>
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<td>1.00</td>
</tr>
</tbody>
</table>

References
- The findings of our review suggest that, in general, IL-23A inhibitors (brodalumab, ixekizumab, secukinumab) are more effective than ustekinumab, which is, in turn, more effective than etanercept, adalimumab, and apremilast with acceptable safety profiles.

- Although infliximab, an outlier of the TNF-α class, was among the most effective agents, it is intravenous infusion rather than intramuscular injection and there are concerns over a greater rate of infections compared to other drugs.

- The key clinical outcome reported in plaque psoriasis trials included response on the Psoriasis Area and Severity Index (PASI). The most consistently reported primary outcome in clinical trials was the “PASI 75,” the proportion of patients who had a 75% reduction in the PASI score from baseline to follow-up. Many trials reported other PASI thresholds: PASI 50, PASI 90, and PASI 100 (equivalent to a follow-up PASI score of zero).