Ustekinumab for the treatment of psoriasis: an evidence update

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Abstract

Ustekinumab is an interleukin-12/23 inhibitor used for the treatment of moderate-to-severe psoriasis. Here, we review new evidence since ustekinumab was licensed for relative efficacy in comparison with other biologic therapies from head-to-head randomized controlled trials and network meta-analyses for the treatment of psoriasis. We also review observational data emerging from psoriasis registries reporting the effectiveness and safety of ustekinumab. Overall, new evidence suggests that ustekinumab has a favorable balance between efficacy/effectiveness, safety, and tolerability and should remain a first-line biologic therapy option for patients with severe psoriasis at present.

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The introduction of ustekinumab as a treatment option for patients with moderate-to-severe psoriasis represented a major step forward at its time of launch. In contrast to tumor necrosis factor inhibitors, ustekinumab was the first biologic therapy to specifically modulate what is now recognized as the pivotal cytokine pathway of pathogenesis of psoriasis, the T-helper 17 pathway, paving the way for subsequent research, introduction, and testing of the interleukin (IL)-17 and -23 inhibitors.

Since ustekinumab was licensed, several other biologic therapies for psoriasis have been launched. These include secukinumab, ixekizumab, and brodalumab, which are IL-17 inhibitors, and tildrakizumab and guselkumab, which are IL-23 inhibitors. In some instances, these therapies have been evaluated directly against ustekinumab in head-to-head randomized controlled trials (RCTs), showing direct superiority in terms of efficacy. With these newer therapies pushing the boundaries, however, what role does ustekinumab play in the treatment ladder for psoriasis now and in the near future? Here, we review the new clinical trial evidence since the pivotal licensing phase 3 trials were published. We also review and appraise the emerging observational data reflecting the increasing experience with using ustekinumab for the treatment of psoriasis in the real world. Based on the clinical evidence accumulated thus far, we will suggest the place of ustekinumab in the expanding treatment ladder for severe psoriasis now and in the future.

Efficacy: from systematic reviews, network meta-analyses, and new head-to-head randomized controlled trials

Since the pivotal licensing trials of ustekinumab for psoriasis, PHOENIX 1 and 2,1,2 were published, further RCTs have helped researchers place the relative efficacy and safety of ustekinumab in comparison to other treatments for moderate-to-severe psoriasis (Table). Two major network meta-analyses (NMAs) have been published to aid these comparisons. NMAs help clinical decision-making by connecting a network of evidence together, enabling relative comparisons of all available interventions to be made. In a comparison against other biologic therapies, methotrexate, and placebo,3 ustekinumab had a higher probability of achieving clear or nearly clear disease and a reduction in Psoriasis Area and Severity Index (PASI) score of at least 75% (PASI 75) at week 12 to 16 compared with placebo, methotrexate, etanercept, and adalimumab, but it had a lower probability compared with secukinumab, ixekizumab, and infliximab. However, ustekinumab was ranked the best in having the lowest probability of withdrawal due to adverse events compared with the same treatments. In a hierarchical cluster analysis considering efficacy (clear or nearly clear) and tolerability (withdrawal due to adverse events) jointly, ustekinumab was clustered with adalimumab and secukinumab as having both high efficacy and tolerability. This NMA included head-to-head trials such as the ACCEPT trial comparing ustekinumab to etanercept,4 data from ustekinumab arms from AMAGINE-2 and AMAGINE-3 comparing brodalumab to ustekinumab,5 and the CLEAR trial comparing secukinumab to ustekinumab,6 enriching and enabling these comparisons to be made (Table).

A second recent Cochrane systematic review and NMA compared all systemic treatments for psoriasis.7 At the time of review, evidence for IL-23 inhibitors tildrakizumab and guselkumab, but not risankizumab, were available for inclusion. This NMA found that ustekinumab had a higher probability of achieving PASI 90 at week 12 to 16 compared with tildrakizumab, adalimumab, itolizumab, infliximab, etanercept, tofacitinib, apremilast, ponesimod, alefacept, fumaric acid esters, ciclosporin, methotrexate, and acitretin and considered all trials irrespective of dose and duration of treatment. Where possible, the outcomes were evaluated at the end of induction therapy and at the end of maintenance therapy. It found that ustekinumab had a lower probability of achieving the same outcome compared with ixekizumab, secukinumab, brodalumab, guselkumab, and certolizumab. Although the authors concluded that there were no clear differences between the treatments for safety profile of serious adverse events, methotrexate, ciclosporin, infliximab, certolizumab, alefacept, apremilast, and fumaric acid esters had a lower...
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**TABLE. Summary of efficacy outcomes from new RCTs involving ustekinumab for the treatment of psoriasis since the drug was licensed**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Phase</th>
<th>Primary endpoint</th>
<th>PASI 90 for ustekinumab</th>
<th>PASI 90 for comparator</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACCEPT</td>
<td>3</td>
<td>Week 12</td>
<td>36.4% (45 mg); 44.7% (90 mg)</td>
<td>Etanercept: 23.1%</td>
</tr>
<tr>
<td>AMAGINE-3</td>
<td>3</td>
<td>Week 12</td>
<td>PASI 100</td>
<td>Brodalumab: 27.0% (140 mg)</td>
</tr>
<tr>
<td>CLEAR</td>
<td>3</td>
<td>Week 16</td>
<td>57.6%</td>
<td>Secukinumab: 79.0%</td>
</tr>
<tr>
<td>IXORA-S</td>
<td>3</td>
<td>Week 12</td>
<td>42.2%</td>
<td>Ixekizumab: 72.8%</td>
</tr>
<tr>
<td>Risankizumab trial</td>
<td>2</td>
<td>Week 12</td>
<td>40.0%</td>
<td>Risankizumab: 77.0%</td>
</tr>
<tr>
<td>NAVIGATE</td>
<td>3</td>
<td>Week 16 after randomization</td>
<td>22.6%</td>
<td>Guselkumab: 48.1%</td>
</tr>
</tbody>
</table>

**Abbreviations:** PASI, Psoriasis Area and Severity Index; RCT, randomized controlled trial.

The authors recommended caution in interpretation of this data due to the low number of serious adverse events, as well as conclusions based on low to very low or moderate certainty evidence for this outcome. The authors concluded that ustekinumab, along with infliximab and certolizumab, appeared to have the best trade-off between efficacy and tolerability. This NMA also included the same head-to-head RCTs involving ustekinumab as the previous NMA.

**Other head-to-head RCTs**

Since the cut-off for the literature search for the 2 NMAs, 3 more head-to-head RCTs involving ustekinumab in the treatment of psoriasis have been published, with congruent results (Table). IXORA-S is a phase 3 study comparing ixekizumab to ustekinumab with the primary endpoint of PASI 90 at week 12. The RCT found that ustekinumab had a lower PASI 90 response (n = 70; 42.2%) at week 12 compared with ixekizumab (n = 99; 72.8%), with a response difference of 32.1% (97.5% confidence interval [CI], 19.8%-44.5%). There were no significant differences in serious adverse events between the 2 treatment arms. A phase 2 trial of 166 patients compared risankizumab, an IL-23 inhibitor, with ustekinumab, with a primary endpoint of PASI 90 at week 12. This trial found that ustekinumab had a lower PASI 90 response (n = 40; 40%) compared with risankizumab (n = 43; 77%), with again little significant difference in serious adverse events between the comparators. It is likely that the choice of 12 weeks as a primary endpoint may be too early for ustekinumab to achieve its potential overall efficacy. Finally, NAVIGATE is a phase 3 RCT comparing guselkumab, another IL-23 inhibitor, with ustekinumab in patients with inadequate response to ustekinumab. Ustekinumab was shown to have a lower Investigator’s Global Assessment 0/1 response 16 weeks after randomization (0.7 ± 1.3 versus 1.5 ± 1.6; P ≤ .001) as well as a lower PASI 90 response (22.6% versus 48.1%; P ≤ .001) compared with guselkumab, although this response is an unfair comparison for ustekinumab given the preselected nature of the population. Safety of ustekinumab is also difficult to assess in this trial given that a prerandomization open-label phase would have pre-selected out patients with early adverse events to ustekinumab.

**Summary from update of trial data**

Since ustekinumab was approved and made available on the market, new IL-17 and IL-23 inhibitors have emerged with higher efficacy for the treatment of psoriasis. However, 2 recent NMAs have both concluded that ustekinumab has a favorable trade-off between efficacy and tolerability. This is highly important because utility and tolerability, along with efficacy, are crucial factors for patients and are likely to aid adherence to medication. However, it should be noted that both NMAs and the head-to-head RCTs mostly report on short-term outcomes (week 12), and interpretation of longer-term outcomes from these data is made difficult given the lack of comparator arms in most RCTs. In our opinion, ustekinumab may have its maximum efficacy after loading later than week 12, and there is therefore the probability that this timepoint may underestimate its efficacy. The low external validity due to stringent exclusion and inclusion criteria of RCTs also affects interpretability of the true safety of ustekinumab and other biologic therapies in the real world.

**Observational data evidence: effectiveness**

Real-world data are extremely helpful for clinicians because they have high external validity and evaluate the effectiveness of medicines, or how medicines perform in the clinics, rather than efficacy, or how medicines perform in idealized settings. Psoriasis treatment registries around the world help to provide this data to enable clinicians to further scrutinize the performance of ustekinumab and other biologic therapies.

Psoriasis Longitudinal Assessment and Registry (PSOLAR) is a large, multinational single-sponsor prospective observational registry of patients with psoriasis on systemic treatments. PSOLAR collects data from predominantly US dermatology centers but also includes data from Europe and other countries. A recent study looked at effectiveness outcomes for patients initiating ustekinumab, infliximab, adalimumab, or etanercept, with the Physician Global Assessment (PGA) and percent body surface area (BSA) used as outcome measures. The Dermatology Life Quality Index (DLQI) was used as the health-related quality of life score.

The study found that 1,041 patients on ustekinumab had a PGA 0/1 proportion of 57.1% at 6 months and 59.2% at 12 months.
Adjusted logistic regression found that all tumor necrosis factor (TNF) inhibitors had a lower probability of achieving a PGA score of 0/1 at 6 months, although at 12 months the equivalent estimates were nonsignificant apart from the infliximab versus ustekinumab comparison. There was also a mean decrease of percent BSA of −14.7 (SD 19.65) at 6 months and −16.3 (SD 18.53) at 12 months. Analysis of covariance found that ustekinumab was significantly better at reducing percent BSA than adalimumab and etanercept, but not infliximab, at 6 months. At 12 months, ustekinumab was significantly better than infliximab and etanercept but not adalimumab. Regarding quality of life, the DLQI 0/1 for ustekinumab was 47.6% at 6 months and 54.8% at 12 months. The study report did not state whether there were any significant differences between the treatment groups for this outcome, so it can be assumed that there was no significant difference between ustekinumab and the other outcomes.

Although this study provides some useful comparative data, it is somewhat difficult to interpret the raw proportions of patients achieving the outcomes because the study uses a generous per-protocol or complete case analysis approach to missing outcome data. This means that only those with no missing outcome data are analyzed, rather than the whole starting cohort. The study report states that the background characteristics of patients with missing data were comparable to those evaluated, but these data are not given in the manuscript. If the missing data were not at random but associated with effectiveness and/or quality of life, this could introduce a bias to both the raw proportions and the adjusted point estimates. Nonetheless, assuming that missing data were missing for the same reasons for all comparator arms (nondifferential misclassification), the adjusted relative risk estimates suggest that ustekinumab was more effective for treating clinical signs of psoriasis than TNF inhibitors at 6 months but was not more effective at quality of life measures than the same comparators. It is also notable that PSOLAR is sponsored by the manufacturers of ustekinumab, and analysis of data is not independent.

The British Association of Dermatologists Biologic Interventions Register (BADBIR) is a United Kingdom and Republic of Ireland national prospective safety psoriasis registry that, similar to PSOLAR, recruits patients with psoriasis on systemic treatments. A study in BADBIR investigated self-reported outcome measures of DLQI and EuroQoL-5D (EQ5D) after 6 and 12 months of follow-up on etanercept, adalimumab, and ustekinumab. Out of a total of 396 patients on ustekinumab, 46.8% achieved a DLQI 0/1 at 6 months, and 50.2% achieved a DLQI 0/1 at 12 months. Patients on all 3 treatments experienced significant improvements in both the DLQI and EQ5D scores at both timepoints. Multivariable regression modelling found that ustekinumab had no significant difference in odds of achieving a DLQI score of 0 or 1 compared to adalimumab after adjustment of a range of potential confounders (6-month odds ratio [OR] 0.86; 95% CI, 0.59-1.25), but etanercept had lower odds compared to adalimumab (OR 0.37; 95% CI, 0.28-0.50); none of the treatments were significantly different from one another in mean change in EQ5D score after 6 or 12 months.

Similar to the previous study, there is a complete case analysis approach to missing data, especially of the outcome. It is therefore difficult to extrapolate a conclusive relative difference between ustekinumab and the other biologic therapies solely from the percentages of patients achieving the outcomes, but the multivariable regression result suggests that ustekinumab may also have a more beneficial effect for quality of life (DLQI) compared with etanercept.

The Continuous Assessment of Psoriasis Treatment Use Registry with Biologicals (BioCAPTURE) is a registry based in the Netherlands that contains data from consecutive patients with psoriasis treated with biologics in 1 academic and 8 nonacademic centers. This smaller study investigated 90 treatment episodes with ustekinumab and, in a multilevel linear regression analysis, found a significantly higher probability of achieving a lower mean PASI for ustekinumab compared with etanercept at 5 years (P = .019) but not adalimumab (mean PASI 5 years: ustekinumab, 4.7; 95% CI, 3.9-5.5; etanercept, 5.9; 95% CI, 5.4-6.5). There were no significant differences in mean PASI between the 3 treatments at 1 year. The per-protocol PASI 75 data are also shown, with a 45.3% PASI 75 for ustekinumab after 1 year of treatment and a higher probability of achieving PASI 75 for ustekinumab compared with etanercept (P = .048).

Given that those who persisted on the drug after 1 year have directed the difference between ustekinumab and etanercept in the above analysis, ustekinumab could have a higher long-term effectiveness compared with etanercept. An alternative interpretation could be that those who have persisted and were treated with ustekinumab early (to enable a follow-up of 5 years) have a lower mean PASI than the equivalent patients selected on etanercept, and therefore any difference could be due to selection bias. The per-protocol PASI 75 results are hard to interpret given the same missing data concerns as listed in the above analysis.

Summary from effectiveness data in observational studies
Although an interpretation of observational data is difficult due to the per-protocol approach necessitated by missing outcome data, there is a suggestion that ustekinumab is superior to etanercept for effective treatment of psoriasis when the outcome is either objective (disease severity scores) or subjective (patient-reported quality of life scores). However, there is less consistent evidence for a difference in treatment effectiveness between ustekinumab and adalimumab.

Drug survival
It is now well established that ustekinumab has a higher drug survival compared with the TNF inhibitors as a first-line therapy. Analyses in the BADBIR, PSOLAR, and BioCAPTURE registries all found that, after adjustment for potential confounding factors, ustekinumab has a higher drug survival as a first-line therapy compared with infliximab, etanercept, and adalimumab. The PSOLAR registry also investigated drug survival by different lines of therapy and found similar results, with ustekinumab having the highest drug survival as a second- and third-line therapy. A recent study specifically investigated second-line therapy in the BADBIR database and found similar overall drug survival as first-line therapy, with drug survival highest at year 1 for ustekinumab (85%; 95% CI, 82%-87%). In the multivariable Cox regression model,
second-line ustekinumab therapy also had significantly higher drug survival than etanercept or adalimumab (hazard ratio [HR] 0.46; 95% CI, 0.33-0.64). Importantly, the discontinuation of a prior TNF inhibitor due to ineffectiveness was not associated with a higher probability of discontinuation due to ineffectiveness of a second biologic, and this therefore suggests that ustekinumab may perform well also as a second-line biologic.

Adherence
One of the factors by which ustekinumab is thought to encourage drug survival is a favorable 12-weekly dosing regimen. A study of a subset of patients in the BADBIR cohort investigated medication nonadherence, classified into intentional and unintentional nonadherence. Only 11 out of 160 (7.3%) patients on ustekinumab were classified as nonadherent compared to 52 out of 331 (16.4%) of those prescribed either etanercept or adalimumab. Part of this is due to the fact that ustekinumab is often nurse-administered in the United Kingdom compared with self-administration for etanercept and adalimumab.

Pharmacogenetics
Moving on from overall markers of treatment response or adherence, there is a growing interest in personalized medicine, in which an individual’s characteristics direct treatment choice in order to maximize the probability of treatment effectiveness and also avoid adverse effects. Although clinically the individual tailoring of therapies is central to the art of medicine, the advent of the availability of big data enables utilization of “omics” data to objectively personalize treatment options.

Pharmacogenetics is a field of intense interest for psoriasis biologic therapies at the moment. A recent systematic review identified several candidate genetic predictors. Three out of five studies identified the presence of the human leukocyte antigen–Cw6 allele as a predictor for higher response rates to ustekinumab. One study also found a higher response rate with a TT genotype for rs763780 in the IL17F gene, while another found associations of higher efficacy with ustekinumab for 2 variants in the ERAP1 gene (rs26653 and rs151823) in patients with psoriasis. Further research to identify relevant genetic markers for ustekinumab is needed, and it is likely that genetics will play a supporting role among other clinical and “omic” predictors that, together, will explain more of the variability in treatment response and thus allow for accurate prediction.

Serious infection
There have now been several studies utilizing registry data to assess the risk of serious infection associated with ustekinumab compared with non-biologic systemic therapies. The PSOLAR registry investigated the following 3 populations of patients on ustekinumab: an overall (including prevalent) population of 3,474 patients on ustekinumab with a follow-up of 5,923 person-years (median follow-up 1.6 years), an incident population of 1,519 patients with a follow-up of 2,489 person-years (median follow-up 1.4 years), and a biologic-naïve population of 376 patients with a follow-up of 585 person-years (median follow-up 1.4 years). They reported a crude incidence rate of 8.3 per 1,000 person-years for the overall population, but the crude incidence rates were not reported for the other two populations. In an adjusted Cox regression, ustekinumab was found to have an HR of 0.96 (95% CI, 0.56-1.65), 1.26 (95% CI, 0.66-2.42), and 1.29 (95% CI, 0.43-3.87) for the respective overall, incidence, and biologic-naïve populations when compared to a group of patients on acitretin and/or phototherapy. The Spanish Registry of Adverse Events Associated With Biologic Drugs in Dermatology (BIOMBADERMI), a smaller single-country registry, reported a crude incidence rate of 5.9 per 1,000 person-years in 560 patients and 1,194 person-years of follow-up. This gave an adjusted HR of 0.75 (95% CI, 0.18-3.13) when compared to methotrexate. All patients were incident users of ustekinumab, and no separate estimate was given for the biologic-naïve population in this registry. Finally, the authors were involved in a study utilizing the BADBIR database, and we found a crude incidence rate of 15.1 per 1,000 person-years in 994 biologic-naïve patients and 2,256 person-years of follow-up (median follow-up 2 years). We found an adjusted HR of 0.92 (95% CI, 0.60-1.41) comparing against a cohort on any nonbiologic systemic therapy and an adjusted HR of 1.22 (95% CI, 0.75-1.99) comparing against methotrexate. It is therefore reassuring that, despite the different comparators and use of different types of ustekinumab starters in the different analyses of registry data across the world (ie, incident, prevalent, biologic-naïve), the relative risk of serious infection for ustekinumab was consistent and was not shown to be elevated.

Malignancy
In contrast to infection, the risk of malignancy associated with ustekinumab is not as well established. A recent systematic review identified only 1 study investigating the risk of malignancy in patients on ustekinumab—an open-label extension of combined safety data from 4 large RCTs. The standardized incidence ratios (SIRs) did not show an increased risk of malignancies overall (excluding nonmelanoma skin cancer; SIR, 0.98; 95% CI, 0.74-1.29) or across a range of specific cancers, including prostate, melanoma, colorectal, lymphoma, and breast cancers. Since the systematic review was published, the PSOLAR has published a nested case-control analysis with 252 cases of malignancy and 1,008 controls. The primary analysis including exposure within 12 months did not show any increase in the risk of malignancy for any length of exposure (≥3 to <12 months of exposure: OR 1.12; 95% CI, 0.63-2.01; ≥12 months: OR 0.98; 95% CI, 0.63-1.53) although the CIs were wide.

Summary from observational studies
As real-world evidence for biologic therapies in the treatment of psoriasis has gradually emerged over time, ustekinumab has been shown to be a drug with favorable effectiveness and safety profile. In our opinion, ustekinumab has several properties that give it a high real-world utility. The regular dosing regimen of 12 weeks in conjunction with drug administration by nurses helps encourage good adherence and a high drug survival as a first- or second-line biologic drug. The licensed higher dose of 90 mg for patients over 100 kg also helps both effectiveness and drug survival given that BMI is a predictor for drug discontinuation due to ineffectiveness in multiple-registry drug survival studies. Data from psoriasis
registries are consistent in showing that ustekinumab does not have an elevated risk of serious infection compared to the nonbiologic systemic therapies, while early data on the risk of malignancy are also promising. Further observational data are needed, however, to fully understand the true risk of malignancy associated with ustekinumab and to assess other safety outcomes.

**Conclusion**

It is undeniable that the IL-17 and IL-23 inhibitors have a higher efficacy when compared head-to-head with ustekinumab. However, there are several reasons why ustekinumab should remain a first-line biologic option. Two large meta-analyses have both concluded that trial data show that ustekinumab strikes a good balance between efficacy and tolerability. There is a substantial body of evidence from observational studies to indicate that ustekinumab is effective, safe, and associated with high drug survival and adherence. Importantly, no observational evidence has suggested the emergence of any new adverse event signal after 9 years of use in the clinic. Coupled with favorable drug administration and a weight-based dosing profile, we believe that ustekinumab should remain a first-line option for patients until further real-world and trial evidence is available for IL-23 inhibitors. It is a particularly important option for patients who are more concerned about safety of treatments over other aspects, such as the onset of action or the probability of obtaining complete clearance.

**References**


