Network meta-analyses of systemic treatments for psoriasis: a critical appraisal

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Summary

Aim There are numerous systemic medications in use for psoriasis, with additional investigational agents being studied. However, head-to-head, randomized clinical trials are rare and cannot feasibly compare all treatments. A network meta-analysis (NMA) synthesizes the available evidence to provide estimates for all pairwise comparisons. Here, we summarize and appraise two recent NMAs that assessed systemic therapies for moderate-to-severe psoriasis.

Setting and design Two systematic reviews searched databases and the grey literature to identify relevant randomized clinical trials.

Study participants The reviews mostly included trials that involved adults with moderate-to-severe psoriasis. One of the reviews also included two trials involving children.

Study exposure Interventions common to both reviews include adalimumab, etanercept, infliximab, ustekinumab, ixekizumab, secukinumab and methotrexate. One of the reviews included additional interventions, primarily other biological agents along with new small-molecule treatments and systemic conventional treatments.

Primary outcomes One review focused on ‘clear/nearly clear’ and withdrawals from adverse events as study outcomes, while the second review focused on improvement of ≥ 90% measured on the Psoriasis Area and Severity Index (PASI 90) and serious adverse events.

Outcomes Additional outcomes included quality of life, PASI 75, Physician’s Global Assessment of 0/1 and any adverse event.

Results Overall, both NMAs are of high quality and provide a comprehensive summary of the evidence base and treatment effects. Results, in terms of both estimates and rankings, suggest that newer biologics targeting the interleukins (IL)-12/23 and IL-17 axes appear to be more effective than older biologics and oral agents.

Conclusions Patients, clinicians and policy makers can use the relative efficacy assessments of NMAs to inform decision making regarding the clearance of psoriasis skin lesions at relevant time points and improvement in quality of life.

Comment

What is already known about this topic?

Over the last two decades, the treatment for psoriasis has been revolutionized, particularly for patients with more severe disease refractory to topical therapies. There are now numerous biological and systemic small-molecule agents that have been approved by various regulatory bodies and further investigational agents are currently being assessed in clinical trials. These new agents have improved our ability to treat the signs and symptoms of psoriasis and have improved quality of life for many patients. However, many of these medications are
associated with important safety concerns, including the risk of serious infections. Furthermore, they are expensive, posing a significant burden on healthcare resources.

Given the many competing benefits, risks and costs associated with these medications, it is imperative that patients, clinicians and policy makers have high-quality comparative evidence to aid prescribing practice. Ideally, head-to-head randomized clinical trials (RCTs) would be performed comparing each and every treatment option, but this is not feasible. In reality, there are several trials that assess the same two therapies (e.g. secukinumab vs. ustekinumab) and there is a lack of head-to-head trials for other comparisons (e.g. secukinumab vs. ixekizumab).

It may be tempting to make informal comparisons of different treatments by, for instance, comparing the proportion of patients achieving ≥ 90% on the Psoriasis Area and Severity Index (PASI 90) using different treatments in different trials. While this informal estimate may give a rough idea of how relatively effective two treatments are, the approach is problematic as it does not respect randomization, which underpins RCTs. Randomization is an assignment mechanism such that, on average, the distribution of patient characteristics is similar between the groups at baseline. Any subsequent difference in outcomes between the groups can therefore be attributed to the treatment assignment. However, characteristics of the patients, nature of the interventions and outcome assessments often vary between trials, meaning that the results cannot be directly compared. The informal comparison above cannot distinguish whether the difference in PASI 90 is due to the treatment or a result of the differences in other characteristics that vary between trials. Hence, a formal comparison that takes randomization into account is preferred.

One formal approach that preserves randomization is a network meta-analysis (NMA). An NMA combines both direct (e.g. trials comparing secukinumab with ustekinumab) and indirect evidence (e.g. trials comparing secukinumab with placebo and ustekinumab with placebo) for the relative safety and efficacy of treatments, providing more robust estimates than direct comparisons alone. For treatment pairs that have not been compared in RCTs, an NMA uses indirect evidence (e.g. secukinumab vs. placebo and ixekizumab vs. placebo) to provide comparative estimates (e.g. secukinumab vs. ixekizumab). An NMA provides estimates of all pairwise treatment comparisons that are connected within a network, including those that have never been directly compared in RCTs. While there are key assumptions that must be met in order for the results of an NMA to be valid, the technique can be very useful for diseases such as psoriasis with a large and growing therapeutic armamentarium. Recently, NMAs assessing systemic therapies for moderate-to-severe psoriasis have been published.1,2

Here, we summarize and appraise two NMAs, both of which conclude that newer biological agents have higher efficacy relative to older targeted agents and traditional systemic agents.1,2 In Jabbar-Lopez et al.,1 ixekizumab and secukinumab were found to be the two best medications (among those available at the time of the analysis) regarding the clearance of patients’ skin disease. In Shidian et al.,2 ixekizumab and secukinumab were also ranked as the top two medications, but were followed closely by additional newer agents targeting the interleukin (IL)-17 and (IL)-12/23 pathways, which were not included in the review by Jabbar-Lopez et al.

**Strengths of the research**

Both reviews followed best practices for conduct and reporting of systematic reviews and NMAs.3,4 The authors prospectively registered the review protocols (PROSPERO or Cochrane),5–7 with protocol deviations described in the publications. The reviews comprehensively summarized the comparative efficacy and safety of systemic therapies to treat moderate-to-severe psoriasis. In the review by Jabbar-Lopez et al., the included therapies were limited to biologics and methotrexate.1 In Shidian et al., this list was expanded to include other systemic medications, including traditional systemic agents (e.g. ciclosporin) and new oral agents (e.g. apremilast).2 Furthermore, by the time of publication, new biological interventions had been approved by some regulators (e.g. brodalumab) that were not included in the review by Jabbar-Lopez et al. This situation is inevitable outside of a living systematic review8 because, as noted earlier, the evidence base in psoriasis is rapidly expanding with RCTs being published and interventions being approved on an ongoing basis. Nevertheless, the literature searches in each systematic review were thoroughly conducted using several electronic databases and other sources. Both sets of authors followed best practices for screening (e.g. independent dual screening) and data abstraction (e.g. pilot testing forms, independent quality checking).

For the quantitative analyses, the authors conducted NMAs for a pre-established list of outcomes (Table 1). Each paper presented pairwise results [odds ratios (ORs) or risk ratios (RRs)] with 95% confidence intervals and also used surface under the cumulative ranking curve (SUCRA) to rank and compare all included treatments. To provide insights on the trade-off between benefits and risks of the therapies, the reviews presented two-dimensional plots of SCURAs for the pair of primary outcomes (‘clear/nearly clear’ vs. withdrawals from adverse events in Jabbar-Lopez et al. and PASI 90 vs. serious adverse events in Shidian et al.). The authors conducted appropriate assessments of heterogeneity and the key NMA assumptions (e.g. transitivity, inconsistency). Overall, both reviews were of high quality and provide a comprehensive summary of the evidence base and treatment effects.

**Assessment of validity**

**Internal validity**

**Research questions**

In systematic reviews, research questions are typically defined in terms of population, intervention, comparator, outcomes and study design (PICOS) elements. Explicitly defining these elements enables appraisers to judge the
Table 1  Summary of the network meta-analyses

<table>
<thead>
<tr>
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<th>Jabbar-Lopez et al.</th>
<th>Shidian et al.</th>
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<tbody>
<tr>
<td>Population</td>
<td>Children or adults with moderate-to-severe psoriasis (any type of psoriasis)</td>
<td>Adults with moderate-to-severe psoriasis</td>
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<td>Intervention/comparators</td>
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<td></td>
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<td>Adalimumab, certolizumab, etanercept, infliximab</td>
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<td>Anti-IL-12/23</td>
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<td>Anti-IL-17</td>
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<td>Ixekizumab, secukinumab</td>
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<td>Anti-IL-23</td>
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<td></td>
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<td>Placebo</td>
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<td>Outcomes</td>
<td>Efficacy</td>
<td>Safety</td>
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<td></td>
<td>Primary: clear/nearly clear defined as PASI 90 or PGA 0/1</td>
<td>Primary: withdrawal from AEs</td>
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<td></td>
<td>Secondary: DLQI, PASI 75</td>
<td>Secondary: PASI 0/1, PASI 75, quality of life (including DLQI)</td>
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<td>SUCRA, pairs of outcomes</td>
<td>1. Clear/nearly clear and withdrawals from AEs</td>
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<td>2. DLQI and withdrawals from AEs</td>
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<td>3. Clear/nearly clear and DLQI</td>
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AE, adverse event; DLQI, Dermatology Life Quality Index; FAE, fumaric acid esters; NNT, number needed to treat; PASI, Psoriasis Area and Severity Index; PGA, Physician’s Global Assessment; SUCRA, surface under the cumulative ranking curve; TNF, tumour necrosis factor; IL, interleukin.

selection of studies and allows decision makers to determine the applicability of the results to their particular context. Table 1 lists the clearly defined PICOS elements from each review. The populations were similar, i.e. patients with moderate-to-severe psoriasis. Although the scope of the NMA carried out by Jabbar-Lopez et al. included a larger population of patients with psoriasis (any age, any psoriasis phenotype), the included trials enrolled adults (except for two trials involving children) with plaque psoriasis, which was consistent with Shidian et al.

The prespecified outcomes differed between the reviews, which was in part a result of the absence of a defined existing core outcome set for psoriasis (one is currently being developed). In Jabbar-Lopez et al., the choice of outcomes was based on majority voting from a guideline development group that included patient representatives. In Shidian et al., the authors stated that they selected outcomes deemed to be most important to patients, but details about that determination were not provided.

The primary efficacy outcomes were ‘clear/nearly clear’ in Jabbar-Lopez et al., defined as either PASI 90 or 0/1 (clear/nearly clear) on the Physician’s Global Assessment, and PASI 90 in Shidian et al. However, Jabbar-Lopez et al. did not specify what data were used when an individual RCT reported both outcomes. In Jabbar-Lopez et al., primary safety outcomes were withdrawals owing to adverse events and in Shidian et al. primary safety outcomes were serious adverse events. Common to both reviews were the secondary outcomes PASI 75 and quality of life, including the Dermatology Life Quality Index. Although PASI 75 is commonly reported across RCTs, both sets of authors commented that this measure is less stringent and hence considered less important than the primary efficacy outcomes.

**Literature search, screening and data abstraction**

The authors of each review searched at least three electronic databases (e.g. PubMed/MEDLINE, Embase, Cochrane), appropriately using both free-text and database-specific tags (e.g. medical subject headings terms in MEDLINE) pertinent to the specified PICOS criteria. Shidian et al. also searched for unpublished literature including trial registries and conference proceedings. In addition, the authors of both reviews screened references from systematic reviews. Title/abstract screening was conducted independently by two researchers. The full-text articles were screened by one researcher in Jabbar-Lopez et al. and in duplicate in Shidian et al. Excluded references along with primary reasons for exclusion were provided in the appendix of both reviews.

In both reviews one researcher abstracted data, which was checked by another researcher. If additional details or results from a trial were missing, the authors contacted the primary
the differences in the individual domain ratings. For example, having an ‘unclear’ RoB. Many trials included in both reviews and those with up to two ‘unclear’ domains were classified as domains classified as ‘low’ were given an overall ‘low’ RoB were ‘unclear’. In the results, only those trials with all methods state that trials would be given a ‘low’ RoB assess consistent with the results. For example, in Sbidian et al. the criteria specified in the methods section does not appear to be consistent with the results. For example, in Sbidian et al., the methods state that trials would be given a ‘low’ RoB assessment if none of the domains were ‘high’ and if two or fewer were ‘unclear’. In the results, only those trials with all domains classified as ‘low’ were given an overall ‘low’ RoB and those with up to two ‘unclear’ domains were classified as having an ‘unclear’ RoB. Many trials included in both reviews were given different overall RoB assessments, partly owing to the differences in the individual domain ratings. For example, Gordon et al.12 was given a ‘low’ RoB assessment in Sbidian et al. with all domains given ‘low’ ratings. In Jabbar-Lopez et al., this trial was given a ‘high’ RoB assessment with the attrition bias domain given a ‘high’ rating and selection and detection biases were given ‘unclear’ RoBs. While the primary results of the two NMAs are not impacted by these discrepancies, the different RoB classifications point to subjectivity inherent in RoB assessments. Furthermore, Sbidian et al. conducted a sensitivity analysis, excluding studies with a high RoB. While this is a useful approach, the RoB discrepancies with Jabbar-Lopez et al. raise questions about the external validity of this sensitivity analysis. If the RoB of studies were classified differently, the studies included vs. those excluded in the sensitivity analysis would change, potentially impacting the results.

Risk of bias assessments

Both reviews used the Cochrane risk of bias (RoB) tool to assess each included trial.10 Owing to the overlap in scope, many trials (n = 38) were included in both reviews. When we compared RoB domain assessments between the two NMAs, only 10 of the 38 trials were given the same ratings for all domains. For example, the reviewers in Sbidian et al. gave Cai et al.11 a ‘low’ RoB rating for all six domains, whereas the reviewers in Jabbar-Lopez et al. gave the same study a ‘low’ RoB rating in only one domain, and gave one domain an ‘unclear’ RoB rating and four domains a ‘high’ RoB rating. While Sbidian et al. provided justification for the ratings, Jabbar-Lopez et al. did not and hence the reasons for the discrepant ratings are unclear.

In each review, results from individual RoB domains informed an overall RoB of ‘low’, ‘moderate’ or ‘high’ for each study. However, Jabbar-Lopez et al. did not specify the criteria used to classify each study, and in Sbidian et al. the criteria specified in the methods section does not appear to be consistent with the results. For example, in Sbidian et al., the methods state that trials would be given a ‘low’ RoB assessment if none of the domains were ‘high’ and if two or fewer were ‘unclear’. In the results, only those trials with all domains classified as ‘low’ were given an overall ‘low’ RoB and those with up to two ‘unclear’ domains were classified as having an ‘unclear’ RoB. Many trials included in both reviews were given different overall RoB assessments, partly owing to the differences in the individual domain ratings. For example, Gordon et al.12 was given a ‘low’ RoB assessment in Sbidian et al. with all domains given ‘low’ ratings. In Jabbar-Lopez et al., this trial was given a ‘high’ RoB assessment with the attrition bias domain given a ‘high’ rating and selection and detection biases were given ‘unclear’ RoBs. While the primary results of the two NMAs are not impacted by these discrepancies, the different RoB classifications point to subjectivity inherent in RoB assessments. Furthermore, Sbidian et al. conducted a sensitivity analysis, excluding studies with a high RoB. While this is a useful approach, the RoB discrepancies with Jabbar-Lopez et al. raise questions about the external validity of this sensitivity analysis. If the RoB of studies were classified differently, the studies included vs. those excluded in the sensitivity analysis would change, potentially impacting the results.

Analyses

For each outcome, both sets of authors analysed the study-level data using NMA models with random effects for the treatment parameters.13 Note that for dichotomous outcomes (e.g. PASI 75), the metric of choice differed between the reviews. Sbidian et al. presented results in terms of RRs, whereas Jabbar-Lopez et al. used ORs and number needed to treat (NNT). When results are statistically significant, the NNT may be easy to interpret for some clinicians. However, when results are not statistically significant and cross the null, the NNT is no longer interpretable and hence Jabbar-Lopez et al. do not present NNT estimates in those cases.

In addition to presenting the treatment effect results (OR, RR) from the NMA, the authors also present treatment rankings. Using the (posterior) distributions for all treatment effect estimates resulting from an NMA, the proportion of times a treatment is ranked as the best, second best, etc. can be obtained. Authors graphically present these probabilities of each treatment for each rank (e.g. Fig. 14 in Sbidian et al.) or the cumulative rankings (e.g. Figs S11–S14 in Jabbar-Lopez et al.). Both NMAs utilize a common approach to summarizing the cumulative rankings, i.e. calculating the SUCRA curve.14 Although treatment rankings can provide insights into how the treatments compare, they are conditional on the set of treatments included. For example, evaluating a subset of treatments would produce different SUCRAs for those treatments than when evaluating a larger set of treatments. Hence, SUCRAs cannot be compared between the two reviews. Furthermore, neither the rankings nor the SUCRAs can be easily generalized or interpreted and do not replace treatment effect estimates.14

Sbidian et al. conducted sensitivity analyses to test their assumptions. For example, an analysis was conducted that included only observed participants in the studies and assumed missing data were missing at random. Overall, results were consistent with the primary analyses. Furthermore, both Jabbar-Lopez et al. and Sbidian et al. conducted subgroup analyses to explore the effect of excluding studies with prespecified characteristics. For example, Jabbar-Lopez et al. conducted an analysis using only the licensed dosages of biologics, with results also similar to that of the primary analyses.

Heterogeneity and inconsistency assessments

Heterogeneity is the variation in the true treatment effect between the underlying studies.15,16 Given that trials in an evidence base are conducted by different investigators, in different populations, in different locations, at different points in time and using different methods, some degree of heterogeneity is expected. To analyse a set of heterogeneous trials, a random effect NMA model is typically used, which assumes that the study-specific treatment effects are different but related.13 As noted above, both reviews appropriately used random effect NMA models in their analyses.

In addition, Sbidian et al. compared heterogeneity assessments with empirical distributions, although their methods section did not provide much detail on how this was done. For example, they state in the methods that comparing the magnitude of an estimated heterogeneity parameter with empirical distributions would determine the presence or absence of important heterogeneity. However, specifics are not provided (e.g. what is ‘important’ heterogeneity, what distribution was used in the cited empirical studies), and the
results section notes only whether the authors considered the estimate to be ‘low’ heterogeneity.

Another key assumption in NMAs is that of consistency, which considers how the direct and indirect estimates of a particular comparison agree.\(^{15,16}\) If the estimates do not agree, there is said to be inconsistency in the network and the reasons for inconsistency should be explored. Plainly, one would expect the indirect estimates in a network to agree with the direct estimates from RCTs – if they do not and the direct and indirect estimates are contradictory, there is a problem. Jabbar-Lopez et al. and Sbidian et al. both assessed inconsistency using standard approaches (e.g. node-splitting, estimating inconsistency factors, design-by-treatment interactions).\(^{15,17,18}\) Both sets of authors found that most ‘loops’ (i.e. treatment comparisons in which both direct and indirect estimates exist) were consistent, while a small minority had evidence of inconsistency. However, tests for inconsistency are generally underpowered such that a lack of statistical significance does not imply consistency.\(^ {18}\)

As noted above, many reasons for heterogeneity and inconsistency may exist, including differences of key patient characteristics, study designs and outcome definitions. In order to investigate the reasons for heterogeneity or inconsistency in the evidence base, Sbidian et al. assessed the distribution of key characteristics across the trials and provided visual plots of these characteristics (mean age, proportion of male patients, mean weight, baseline PASI score) by treatment comparison. Jabbar-Lopez et al. briefly described the evidence base but did not detail any difference in these characteristics across the studies. Owing to inconsistent reporting across the trials, the authors from both reviews did not conduct subgroup or metaregression analyses incorporating these characteristics.

**External validity**

Generalizability of results

The evidence base consisted of a set of RCTs that enrolled mostly adults with moderate-to-severe plaque psoriasis. These eligible patients may differ from patients in clinical practice in ways that may affect the treatment effect estimates (e.g. age, other psoriasis subtypes, presence of comorbidities). For example, results from the British Association of Dermatologists Biologic Interventions Register (BADBIR) suggest that patients with psoriasis taking biologics who are otherwise ineligible for RCTs may have lower PASI responses and higher rates of serious adverse events compared with patients who meet RCT eligibility criteria.\(^ {19}\) Hence, the results of the NMAs may not be generalizable to patients in clinical practice. This limitation arises from the underlying RCTs and not the NMAs themselves.

As psoriasis is a chronic condition, patients may receive treatment over many years. However, the authors analysed outcomes for a short time period (12–16 weeks). In terms of efficacy, the NMAs suggest treatment benefits in the short term, but the persistence of effects was not assessed owing to limited longer-term data from the RCTs. In terms of safety, NMAs may be able to detect differences in rates of common adverse events that occur in the early stages of treatment. However, latent harmful events will not be detected in short-term trials nor in NMAs of such trials. Hence, the longer-term efficacy and safety of these treatments cannot be generalized from the results of the NMAs. Treatment registers are a more suitable study vehicle for such data.

**Relevance of outcomes to inform decision making**

The outcomes used in both NMAs are relevant to patients, clinicians and policy makers. Core outcome domains identified for psoriasis are skin manifestations, symptoms, health-related quality of life, investigator and patient global assessment and treatment satisfaction.\(^ {9}\) Although Jabbar-Lopez et al. and Sbidian et al. take slightly different approaches to assessing skin manifestations (Table 1), both do so in a reasonable manner translatable to clinical practice. Both also incorporate investigator global assessment. Regarding patient-reported outcomes, both NMAs assessed quality of life, measured using the Dermatology Life Quality Index,\(^ {20}\) and Sbidian et al. also included the Psoriasis Disability Index (which also assesses elements of quality of life)\(^ {21}\) and Psoriasis Symptom Inventory (PSI) (which, as the name suggests, assesses symptoms rather than quality of life).\(^ {22}\) Jabbar-Lopez et al. did not include a measure of symptoms such as the PSI, which may be because this outcome measure is relatively new. Neither NMA assessed patient global assessment or treatment satisfaction.

The different approaches to the assessment of adverse events were notable. Jabbar-Lopez et al. assessed tolerability (withdrawal owing to adverse events) and Sbidian et al. assessed serious adverse events and overall adverse event rates. In our opinion, both tolerability and serious adverse events are important outcomes. Serious adverse events give end users an idea of the potential for the included medications to cause substantial harm, which is important for patients to understand when making an informed decision to start a potentially risky therapy. Tolerability, on the other hand, gives a sense of the benefit-to-risk ratio associated with adverse events that may occur more commonly than serious adverse events, i.e. how often an adverse event occurs or whether an adverse event is serious or a ‘nuisance’ that might lead a patient to forego the current or future benefits of a medication. In our opinion, overall adverse event rates are less informative for clinical decision making.

**Overall assessment**

The results of the two NMAs are valid and useful for clinical practice, shared decision making and policy making. Specifically, stakeholders can make use of the relative efficacy assessments regarding the clearance of psoriasis skin lesions at relevant time points and improvement in quality of life – newer biologics targeting the IL-12/23 and IL-17 axes appear to be more effective than older biologics and oral agents. As individual patients prioritize outcomes differently and the evidence does not suggest an overall ‘best’ treatment, shared
decision making that involves both patients and clinicians is encouraged.

Elements missing from these analyses that would be helpful for decision making include longer-term assessments of the outcomes, particularly for newer medications that have shown excellent results in trials of short duration. This is the product of the included trials rather than the NMAs themselves. Additionally, neither analysis incorporates real-world data, in particular from treatment registers such as BADBIR, which could improve the generalizability of the results.\textsuperscript{23} Incorporating individual patient data could also enhance the usability of the results by enabling analyses focused on specific patient subgroups (e.g. older vs. younger patients, patients with more vs. less severe psoriasis at baseline). We are unaware of any publications using these approaches to analyse studies of patients with psoriasis, which may be due to data-sharing concerns. However, these types of analyses are becoming more common and the methods are described elsewhere.\textsuperscript{23,24}

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Conflicts of interest

The authors do not have any conflicts of interest to report that are relevant to psoriasis treatment. In the last 3 years, A.M.D. served as an investigator and has received research funding from Sanofi and Regeneron and has been a consultant for Sanofi, RTI Health Solutions, the Eczema Society of Canada and the Canadian Agency for Drugs and Technology in Health. A.M.D. has received honoraria from Prime Inc., Spire Learning, CME Outfitters and the Eczema Society of Canada. C.F. is Chief Investigator of the British Association of Dermatologist’s U.K.–Irish Atopic Eczema Systemic Therapy Register (A*STAR) and the Treatment of Severe Atopic Eczema Trial (TREAT). His department has received research funding from Sanofi. He serves as a member of the Allergy U.K. Health Advisory Board and has been a consultant for Sanofi/Regeneron and Roche/Genentech.

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