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Comparing the efficacy and tolerability of biologic therapies in psoriasis: an updated network meta-analysis

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ABSTRACT

Background/Objectives: The rapid expansion of psoriasis biologics has led to an urgent need to understand their relative efficacy and tolerability to better inform treatment decisions and specifically, to inform guideline development.

Methods: We searched MEDLINE, PubMed, EMBASE and Cochrane databases for randomized controlled trials (RCTs), published up to 7th September 2018, of 11 licensed, NICE-approved biologics targeting TNF (adalimumab, etanercept, infliximab, certolizumab pegol), IL-12/IL-23p40 (ustekinumab), IL-17A (secukinumab, ixekizumab), IL-17RA (brodalumab) and IL-23p19 (guselkumab, tildrakizumab, risankizumab). Data were extracted and synthesised using RevMan 5.3. A frequentist network meta-analysis, conducted using Stata13 (StataCorp), ascertained direct/indirect evidence comparing biologics with one another, methotrexate, or placebo. This was combined with hierarchical cluster analyses to consider efficacy (PASI90 or PGA0/1; PASI75; DLQI improvement) and tolerability (drug withdrawal due to adverse events) outcomes at 10-16 weeks, followed by study quality, heterogeneity, and inconsistency assessments.

Results: We identified 62 RCTs presenting data on direct comparisons (n=31,899 participants). All biologics were efficacious compared with placebo or methotrexate at 10-16 weeks. Hierarchical cluster analyses revealed that adalimumab, brodalumab, certolizumab pegol, guselkumab, risankizumab, secukinumab, tildrakizumab and ustekinumab were comparable with respect to high short-term efficacy and tolerability. Infliximab and ixekizumab clustered together, with high short-term efficacy but relatively lower tolerability compared with other agents, although the number of drug withdrawal events across the network was low, so these findings should be treated with caution.

Conclusions: Using our methodology, we find most biologics cluster together with respect to short-term efficacy and tolerability, and we do not identify any single agent as 'best'. These data need to be

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interpreted in the context of longer-term efficacy, effectiveness data, safety, posology, and drug acquisition costs when making treatment decisions.

INTRODUCTION

Psoriasis is a chronic inflammatory skin disease that affects 2-4% of individuals worldwide,¹ and is associated with increased mortality and multimorbidity.² An improved understanding of the molecular pathogenesis of psoriasis has led to the introduction of powerful targeted biologic therapies, which have transformed patient outcomes.³ Eleven biologics are now licensed for use in Europe and USA that target TNF (adalimumab, certolizumab pegol, etanercept, infliximab), IL-12/IL-23p40 (ustekinumab), IL-17A (ixekizumab, secukinumab), IL-17 receptor (brodalumab) and IL-23p19 (guselkumab, risankizumab, tildrakizumab).^{4,5} This rapid expansion of treatment options has led to an urgent need for comparative efficacy research to inform clinical decision making.

Head-to-head randomized trials are considered the gold standard for comparative evidence, and increasingly active comparator trial data are available.⁶ However, randomized controlled trials (RCTs) involving all possible pairwise combinations of biologics, or a simultaneous direct comparison of multiple agents, are not feasible. To address this, a network meta-analysis (NMA) can synthesise direct/indirect evidence from multiple RCTs simultaneously.⁷ The relative efficacy of two treatments can be estimated even if no studies compare them directly. Indirect evidence from studies comparing treatments with a common reference arm is used. If head-to-head trial data are available, pooled estimates derived from direct/indirect evidence can provide greater precision compared with using direct evidence alone. The treatments can also be ranked to produce a hierarchy. NMAs are thus a powerful source of evidence for informing clinical guidelines and practice.

Recent NMAs have assessed the relative efficacy of newer biologics with respect to psoriasis area and severity index (PASI) response, i.e. >90% improvement in PASI from baseline (PASI90).⁸⁻¹⁹ Patient-reported outcomes such as change in dermatology life quality index (DLQI) and treatment tolerability measures are also vital considerations for clinical decision making. These data can be synthesised in a hierarchical cluster analysis, whereby outcomes related to both efficacy and tolerability are analysed simultaneously.²⁰ Although not performed in many recent NMAs,^{8-11,14-17,19} hierarchical cluster analysis may help inform treatment choice since it identifies clusters of agents that are similar with regard to both outcomes.^{12,13,18} Our last NMA in 2017 included six biologics.^{18,21} Since the number of biologics has nearly doubled since this study, we updated the NMA and hierarchical cluster analyses using the outcome set defined by our multi-stakeholder guideline development group. These findings, which have in part informed the updated BAD clinical guidelines,²² provide a comprehensive evidence base to support clinicians when choosing from the expanded range of biologics.

METHODS

Following our 2017 NMA,¹⁸ we conducted an updated systematic review.²³ Our 2017 NMA protocol (PROSPERO 2015:CRD42015017538) was amended to incorporate recently licensed biologics (covering all doses published in RCTs). Funding was independent of the pharmaceutical industry. Search and study selection strategy are presented in Supplementary Appendix S1.

Outcomes of interest

The primary efficacy outcome was clear/nearly clear (i.e. PASI90 where available and if not reported, the corresponding Physician Global Assessment [PGA] score of 0 or 1). PASI90 was used as a stringent correlate of PGA clear/nearly clear for this analysis, which is supported by recent observations from a U.K. real-world dataset of 13,422 patients showing that PGA clear/nearly clear correctly classified nearly all PASI90 responses.²⁴ Secondary efficacy outcomes were mean change in DLQI and PASI75. The primary safety outcome was tolerability, measured by withdrawal due to adverse events. Specific adverse events could not be reported due to insufficient detail in the literature. Where studies only presented the mean and standard deviation (SD) for drug doses, a weighted average was taken. All outcomes were extracted at 10-16 weeks. Consistent with other recent NMAs,^{8,13,15} there were insufficient studies to analyse 52-week outcomes.

Data analysis and quality assessment

Data analysis was performed using a random-effects model within a frequentist approach in Stata13 (StataCorp) using the network command.^{20,25} Equal heterogeneity across all comparators was assumed and correlations due to multi-arm studies were accounted for. Multi-arm trials were separated into their constituent pairwise comparisons. Summary results were presented as an odds ratio (OR).

Cumulative ranking probability plots were inspected visually. Rankings were quantified by the Surface Under Cumulative Ranking Curve (SUCRA).²⁰ The larger the treatment's SUCRA value, the better its rank. Outcomes were jointly ranked using hierarchical cluster analyses of SUCRA values. The clustering metric and linkage method was chosen based on the cophenetic correlation coefficient. The optimal number of clusters was chosen based on optimization of clustering gain.

Absolute effects were calculated from multiplication of the NMA-derived relative effects estimates by an assumed control risk based on the weighted control event rate across all studies. Numbers needed to treat to benefit/harm (NNTB/NNTH) were calculated as the reciprocal of the corresponding risk. Absolute

as opposed to relative effects were presented to optimise the interpretability and hence clinical utility of the findings for informing shared decision making by clinicians and patients.²²

Individual studies were assessed for selection, performance, attrition, detection/measurement and outcome reporting bias using criteria in the Cochrane Handbook for Systematic Reviews of Interventions²⁶ and information reported in the published papers.²⁰ Heterogeneity and inconsistency (differences between direct/indirect effect estimates) were evaluated using visual inspection of the forest plots. Inconsistency was also tested using an overall Chi-squared test of inconsistency, and through loop-specific inconsistency plots and inconsistency factors (IF). IF is the logarithm of the ratio of two odds ratios from direct/indirect evidence in the loop: values close to 1 suggest the two sources are in agreement.²⁰ To understand the potential impact of differing drug doses on outcomes, subgroup analysis was performed considering only data on licensed biologic doses. It is beyond the scope of this project to conduct a multivariate network meta-analysis.

RESULTS

Study selection and baseline characteristics

In addition to the studies included in our 2017 NMA,¹⁸ database searches identified a further 3727 recently published articles. Following de-duplication, 2491 titles were screened (Figure 1). Twenty-six studies met the inclusion criteria: 19 were new RCTs and five were previously identified trials with data that are now in-scope (i.e. from three-armed trials). Combined with the 2017 NMA, the overall analysis included 63 studies (31,899 participants) reporting on 62 RCTs (Table 1, Supplementary Table S1).

Patient characteristics were similar across the studies. The mean age of participants was 44.7 years and 68.7% were male. Up to 50% in any treatment arm had concurrent psoriatic arthritis. All studies included patients with moderate-to-severe psoriasis and baseline PASI scores, where stated, ranged from 8 to 30 in any treatment arm. Forty-nine RCTs (79%) included patients with a PASI ≥ 12 and ten (16.1%) with a PASI ≥ 10 . Where reported, all studies included patients with prior conventional systemic treatment use, and all patients were candidates for conventional systemic therapy and phototherapy. Forty-one RCTs (66%) included patients with prior biologic exposure.

Placebo-controlled trial data were available for all biologics. Active comparator trial data were available for etanercept (versus infliximab, ustekinumab, secukinumab, ixekizumab, certolizumab pegol and tildrakizumab); ustekinumab (versus secukinumab, ixekizumab and brodalumab); adalimumab (versus methotrexate and guselkumab); and infliximab (versus methotrexate). Thirty-seven RCTs reported (or

supplied upon request) the mean change from baseline in DLQI; two further studies reported incomplete data and were excluded.

Networks were built for the four main outcomes (Figure 2, Supplementary Figure S1). Each network involved the 11 biologics, methotrexate, and placebo, except for DLQI, for which there was no data on risankizumab published by the literature search date.

Risk of bias

The risk of bias for most studies was low (Supplementary Figure S2). Fifty-three (84%), 50 (79%), 51 (81%), 54 (86%), 57 (90%) and 63 (100%) of RCTs had a low risk of selection bias due to random sequence generation, selection bias due to allocation concealment, as well as performance, detection, attrition and reporting bias, respectively. Most studies were double-blinded. Patient characteristics were similar between treatment arms at baseline, and most studies used an intention-to-treat or modified intention-to-treat approach. Comparison-adjusted funnel plots of all outcomes were largely symmetrical (with a slight increase in asymmetry for the DLQI outcome), indicating low risk of publication bias (Supplementary Figure S3).

Efficacy of biologics at 10-16 weeks

Both clinician-evaluated ('clear/nearly clear', i.e. PASI90 or PGA 0/1; and PASI75) and patient-reported (mean change in DLQI) measures of efficacy at 10-16 weeks were analysed. All biologic treatments had increased odds of clinician- and patient-reported efficacy relative to placebo or methotrexate (Supplementary Figure S4). Cumulative ranking probabilities (Supplementary Figure S5) for clear/nearly clear showed that ixekizumab performed best (SUCRA 91), closely followed by risankizumab (SUCRA 90) (Table 2). Tildrakizumab performed best with respect to improvement in DLQI (SUCRA 86), closely followed by guselkumab (SUCRA 83) (Table 2). PASI75 outcomes were similar to the results for clear/nearly clear (Supplementary Table S2).

Compared with placebo, risankizumab had the lowest number needed to treat to benefit (NNTB) to achieve clear/nearly clear skin (NNTB1, 95% CI 1-2), followed by eight biologics with NNTB 2; adalimumab (95% CI 2-3), brodalumab (95% CI 2-2), certolizumab pegol (95% CI 2-3), guselkumab (95% CI 1-2), infliximab (95% CI 2-2), ixekizumab (95% CI 1-2), secukinumab (95% CI 2-3) and ustekinumab (95% CI 2-3) (Table 1). Etanercept and methotrexate had the highest NNTB (5 [95% CI 4- 6] and 5 [95% CI 3-11], respectively) and lowest odds of response (OR 11.0 [95% credible interval [CrI] 8.9-13.6] and OR 13.0 [95% CrI 7.5-22.4], respectively) compared with placebo.

Tolerability of biologics at 10-16 weeks

Although tolerability of treatments is not directly measured in trials, it can be inferred from withdrawal due to adverse events. Compared with placebo, there were highest odds of withdrawal with infliximab (OR 2.59 [95% CI 1.3-5.3], NNTH29 [95% CI 19-73]) and ixekizumab (OR 1.76 [95% CI 1.0-3.1], NNTH 103 [95% CI 58-488]). Since the drug withdrawal event rates were low across the whole network of agents, these results should be interpreted with caution. Relative treatment rankings indicated that risankizumab had the highest tolerability (SUCRA 94), followed by guselkumab (SUCRA 80) (Table 2).

Hierarchical cluster analysis

Three clusters of treatments were identified when considering both efficacy (clear/nearly clear) and tolerability (Figure 3a). Adalimumab, certolizumab pegol, ustekinumab, secukinumab, brodalumab, guselkumab, risankizumab and tildrakizumab formed a large cluster of biologics with high efficacy and tolerability. Infliximab and ixekizumab demonstrated high efficacy but lower tolerability when compared with other agents. Methotrexate and etanercept formed the third cluster (with placebo) since these agents demonstrated moderate tolerability and poor efficacy. Similar clusters were identified when considering mean change in DLQI and tolerability (Figure 3b).

Hierarchical cluster analyses identified three distinct clusters of agents with respect to both clinician-evaluated (clear/nearly clear) and patient-reported (mean change in DLQI) efficacy outcomes (Supplementary Figure S6). All biologics were similar with respect to these parameters and demonstrated high efficacy, except etanercept, which formed a distinct cluster with methotrexate due to relatively lower efficacy. Placebo formed a third cluster due to low efficacy.

Inconsistency

Analysis of the triangular closed loops in the NMA indicated inconsistency for clear/nearly clear in 1 of 15 loops (etanercept-ustekinumab-secukinumab; IF 0.63, 95% CI 0.08-1.18), and for mean change in DLQI in 1 of 4 loops (placebo-etanercept-ixekizumab; IF 2.10, 95% CI 0.15-4.06) (Supplementary Figure S7). There was consistency between direct/indirect estimates for drug withdrawal due to adverse events. Marked loop-specific inconsistency was suggested for PASI75 in 1 of 15 loops (placebo-infliximab-methotrexate; IF 2.31, 95% CI 1.24-3.39).

Subgroup analysis of licensed doses of biologics

Subgroup analysis of studies that compared only licensed doses of biologics showed similar findings to the primary analysis of all doses. Ixekizumab and risankizumab were ranked highest with respect to clear/nearly clear (SUCRA 96 and 92, respectively; Supplementary Table S5). Guselkumab and secukinumab performed the best with respect to improvement in DLQI (SUCRA 87 and 85, respectively). With respect to tolerability, risankizumab again ranked highest, followed by ustekinumab (SUCRA 96 and 77, respectively). Infliximab and ixekizumab ranked lowest (SUCRA 3 and 9, respectively), however these results should be interpreted with caution due to the low absolute numbers of drug withdrawal events. Results for PASI75 were similar to those for all biologic doses, with ixekizumab ranking highest (SUCRA 98) followed by guselkumab (SUCRA 81).

Hierarchical cluster analyses identified similar clusters of agents to those for all biologic doses. All biologics were similar with respect to both efficacy outcomes (clear/nearly clear and mean change in DLQI), except for etanercept, which formed a separate cluster with methotrexate due to its lower efficacy (Supplementary Figure S6). The same three clusters of treatments as in the analyses for all doses were identified when considering efficacy (clear/nearly clear or mean change in DLQI) and tolerability for only licensed doses. Adalimumab, certolizumab pegol, ustekinumab, secukinumab, brodalumab, guselkumab, tildrakizumab and risankizumab clustered together due to high efficacy and tolerability. Infliximab and ixekizumab showed high efficacy but lower tolerability. Methotrexate, etanercept and placebo formed a final cluster due to moderate tolerability and poor efficacy.

There was consistency between direct/indirect estimates for clear/nearly clear and drug withdrawal due to adverse events (Supplementary Figure S7). There was again evidence of inconsistency for mean change in DLQI in 1 of 4 loops (placebo-etanercept-ixekizumab; IF 2.11, 95% CI 0.13-4.09) and for PASI75 in 1 of 15 loops (placebo-infliximab-methotrexate; IF 2.55, 95% CI 1.47-3.64).

DISCUSSION

This NMA represents a valuable comparison of all currently licensed and NICE-approved (U.K.) psoriasis biologics (i.e. newer IL-17 and IL-23p19 inhibitors and more established IL-12/IL-23p40 and TNF antagonists) and the commonly used conventional systemic agent methotrexate. Our findings are largely consistent with, and build on, evidence from previously published NMAs.⁸⁻¹⁹ Importantly, we consider both efficacy and tolerability outcomes together in hierarchical cluster analyses, suggesting the majority of biologics (8 of 11) broadly cluster together and demonstrate short-term efficacy and tolerability.²²

Since our 2017 NMA,¹⁸ IL-23p19 antagonists and further IL-17 inhibitors have been approved for use in Europe and USA, and recent NMAs have analysed their relative PASI response.^{9,11,13,16} Our rank ordering of efficacy of all available biologics also illuminates these agents as the most highly efficacious. These findings may relate to their targeted action on the central IL-23/IL-17 pathogenic axis.³ There are, however, notable efficacy differences between agents within each class (despite a common biological target) that may be attributable, at least in part, to their distinct pharmacokinetic and pharmacodynamic properties (e.g. variation in dosing schedules/injection frequency and target binding affinities, respectively).²⁷ For example, ixekizumab and secukinumab both target IL-17A, however, the NMA suggests that ixekizumab has superior efficacy than secukinumab. This may be attributable to the higher binding affinity to human IL-17A of ixekizumab (dissociation constant [K_D] <3 pM) compared to secukinumab (K_D ~200 pM).²⁸⁻³⁰ The induction dosing schedule is also more intensive for ixekizumab (2 weekly until week 12) compared to secukinumab (weekly until week 4, then monthly). Similarly, despite having a common target of IL-23p19, tildrakizumab has lower efficacy rates than risankizumab and guselkumab. Tildrakizumab has a lower target binding affinity (K_D 297 pM) than risankizumab (K_D ≤29 pM) or guselkumab (K_D 3.3 pM).³¹⁻³³ An improved understanding of the underlying molecular basis for these differences may inform the future design of highly efficacious therapies.

Despite the rank order of comparative efficacy of biologics, hierarchical cluster analyses of clinician-evaluated and patient-reported short-term efficacy outcomes suggest that the older and newer biologics broadly cluster together (with the exception of etanercept). In other words, the agents appear more aligned than they are different based on statistical correlation, and there is no 'overall best' treatment highlighted when considering all 10-16 weeks' outcomes. Given the cost variation between biologics, this becomes relevant in cost-effectiveness analyses.

Psoriasis has a large impact on quality of life,³⁴ so our consideration of DLQI increases the clinical relevance of our findings. It also addresses limitations of previous NMAs, which have analysed PASI response without consideration for patient-reported outcomes.^{8-11,15,17,19} A recent NMA¹³ analysed heterogeneous quality of life measures together (DLQI, Skindex, Psoriasis Disability Index and Psoriasis Symptom Inventory), thus limiting interpretability of the results and underscoring the need for harmonisation of outcome measures.

The tolerability of treatment was not captured in all previous NMAs,^{9,10,15,16,19} but is an important consideration for a condition that may require life-long treatment. Ixekizumab and infliximab were shown to have high efficacy but lower tolerability in our NMA, however, these data should be treated with

caution due to the low number of withdrawal events across the whole network within the short time period analysed. U.K. pharmacovigilance registry data (3843 patients across 153 centres) showed a two-fold increase in the observed rate of serious infections for those receiving infliximab compared to non-biologic systemic therapies (follow-up 941 and 6419 person-years, respectively).³⁵ Although a degree of selection bias is likely since patients receiving infliximab had more severe/recalcitrant psoriasis, this study underscores the value of real-world data in understanding drug tolerability.

The outcome 'serious adverse events' (as opposed to withdrawal due to adverse events) was selected for a recent comprehensive NMA¹³ and no significant differences were found between any of the included 19 systemic interventions and placebo. However, infliximab, ixekizumab and secukinumab were found to have a higher risk of serious adverse events compared with methotrexate (RR 2.55, 95% CI 1.26-5.18; RR 2.52, 95% CI 1.03-6.15; RR 2.58, 95% CI 1.07-6.20, respectively).¹³ Methotrexate had the lowest risk of serious adverse events, in contrast to our analysis demonstrating only moderate tolerability. Since we defined tolerability as withdrawal due to *any* adverse event, it is possible that flaring disease was included as an adverse effect. Therefore, our tolerability data may be influenced, in part, by drug efficacy. Similarly, etanercept demonstrates moderate tolerability and efficacy in our NMA. Detailed analysis of the reasons for drug withdrawal/adverse events could not be performed due to insufficient reporting in the literature.

We adopted a broad approach by not restricting our primary analysis to licensed doses to include all available information in a more densely populated network. Dose-comparison studies were considered as single-arm studies and therefore excluded, however, since these studies can add indirect evidence to the estimate of effect for licensed doses, they should be considered in future analyses. Pooling of doses may obscure differences in the rank order of efficacy of drugs, so restricting the primary analysis of NMAs to only licensed doses will be a preferred approach as more trial data becomes available. Reassuringly for the current NMA, however, our sensitivity analyses showed comparable findings for both licensed and all doses. Since biologics dose optimisation (escalation/reduction) via therapeutic drug monitoring is increasingly viable clinically,^{36,37} our broader dose analysis may be relevant for future practice.

The current analysis is limited to outcomes at 10-16 weeks, which is in contrast to a recent NMA summarising long-term efficacy evidence from 17 RCTs.¹⁰ This analysis required imputation of missing long-term outcomes for placebo, which is often stopped after the induction phase. IL-17 inhibitors demonstrated a higher likelihood of a sustained PASI response at week 52 compared with TNF inhibitors and ustekinumab,¹⁰ however, IL-23p19 inhibitors, tolerability or patient-reported quality of life outcomes

were not considered. Longer-term follow up, increasingly captured in trials,³⁸ will enable future NMAs to deliver insight into the longevity of efficacy and tolerability of biologics.

The evidence-to-recommendation discussions in the updated BAD guidelines for biologic therapy for psoriasis (in Appendix D; Supporting information file S2)²² recommend that any of the currently licensed biologics can be offered as first-line therapy (with special considerations for etanercept and infliximab), however, a paucity of long-term data is recognised. It emphasises that patient- and drug-specific factors should be considered to achieve the optimal choice for each individual. Psoriatic arthritis is highly prevalent in psoriasis;² although not captured here, it is important to consider arthritis outcomes following biologic treatment. Other comorbid diseases (which are likely under-represented in trial cohorts) may preclude certain treatments, for example multiple sclerosis (TNF antagonists) and inflammatory bowel disease (IL-17 antagonists). Drug-specific factors, such as dosing frequency, are also an important consideration for patients with a chronic disease that requires prolonged treatment. This information is summarised in the guideline's decision aid.²² Emerging data on genetic biomarkers of biologics treatment response in psoriasis also hold the promise of personalisation of treatment choice, which may become an important consideration in future practice.³⁹

Our study provides comprehensive comparative data on all licensed and NICE-approved psoriasis biologics for guiding treatment selection. Future analyses of real-world safety and effectiveness data captured in large-scale pharmacovigilance registries (e.g. BADBIR)⁴⁰ will determine the generalisability of our NMA findings for routine clinical practice and deliver insights on long-term outcomes/drug survival. As the therapeutic armamentarium for psoriasis continues to expand and innovative trial design (e.g. multi-arm, multi-stage platform protocols)⁴¹ opens avenues for simultaneously analysing multiple agents, future NMAs will provide increasingly precise relative efficacy and safety comparisons.

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Table 1. Network meta-analysis results summary for the three main outcomes at 10 to 16 weeks for biologics vs. placebo, and biologics vs. adalimumab as a clinically relevant reference point: clear/nearly clear (PASI90 or PGA 0 or 1), mean change in DLQI, withdrawal due to adverse events (*all doses*). See Supplementary TableS1 for the full set of tabulated results. ADA, adalimumab; BRO, brodalumab; CrI, credible interval; CI, confidence interval; CZP, certolizumab pegol; DLQI, dermatology life quality index; ETA, etanercept; GUS, guselkumab; INF, infliximab; IXE, ixekizumab; MTX, methotrexate; NNTB, number needed to treat to benefit; NNTH, number needed to treat to harm; PASI, psoriasis area and severity index; PBO, placebo; PGA, physician's global assessment; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.

Biologics	Comparison	Anticipated absolute effect (95% CrI)				No. of participants, direct evidence (no. of studies)	NNTB ^b /NNTH ^h (95% CI)
		OR (95% CrI)	Without intervention	With intervention	Difference		
CLEAR/NEARLY CLEAR (PASI 90/ PGA 0 OR 1) AT 10-16 WEEKS (ALL DOSES)							
ETANERCEPT	ETA vs. PBO	10.99 (8.89, 13.58)	17 per 1000	225 per 1000	208 more per 1000 (166 more to 249 more)	5924 (16 studies)	5 (4,6) ^b
ADALIMUMAB	ADA vs. PBO	20.88 (14.46, 30.15)	17 per 1000	445 per 1000	428 more per 1000 (366 more to 491 more)	3204 (8 studies)	2 (2,3) ^b
	ADA vs. ETA	1.90 (1.25, 2.90)	225 per 1000	445 per 1000	220 more per 1000 (146 more to 295 more)	0 (0 studies)	5 (3,7) ^b
INFLIXIMAB	INF vs. PBO	38.17 (21.53, 67.67)	17 per 1000	517 per 1000	500 more per 1000 (421 more to 578 more)	1591 (4 studies)	2 (2,2) ^b
	INF vs. ADA	1.83 (1.09, 3.07)	445 per 1000	517 per 1000	72 more per 1000 (25 less to 169 more)	0 (0 studies)	NS
METHOTREXATE	MTX vs. PBO	13.00 (7.53, 22.43)	17 per 1000	217 per 1000	200 more per 1000 (89 more to 311 more)	163(1 study)	5 (3,11) ^b
	MTX vs. ADA	0.62 (0.39, 1.00)	445 per 1000	217 per 1000	228 less per 1000 (342 less to 115 less)	332 (2 studies)	4 (3,9) ^h
USTEKINUMAB	UST vs. PBO	19.41 (15.77, 23.88)	17 per 1000	435 per 1000	418 more per 1000 (369 more to 466 more)	4663 (11 studies)	2 (2,3) ^b
	UST vs. ADA	0.93 (0.61, 1.42)	445 per 1000	435 per 1000	10 less per 1000 (90 less to 69 more)	0 (0 studies)	NS
SECUKINUMAB	SEC vs. PBO	26.56 (21.33, 33.09)	17 per 1000	473 per 1000	456 more per 1000 (385 more to 527 more)	2481 (5 studies)	2 (2,3) ^b

	SEC vs. ADA	1.27 (0.83, 1.95)	445 per 1000	473 per 1000	28 more per 1000 (66 less to 122 more)	0 (0 studies)	NS
IXEKIZUMAB	IXE vs. PBO	32.66 (26.05, 40.95)	17 per 1000	653 per 1000	636 more per 1000 (561 more to 711 more)	3268 (4 studies)	2 (1,2) ^b
	IXE vs. ADA	1.56 (1.02, 2.40)	445 per 1000	653 per 1000	208 more per 1000 (110 more to 306 more)	0 (0 studies)	5 (3,9) ^b
BRODALUMAB	BRO vs. PBO	24.63 (19.79, 30.65)	17 per 1000	571 per 1000	554 more per 1000 (480 more to 629 more)	4109 (5 studies)	2 (2,2) ^b
	BRO vs. ADA	1.18 (0.77, 1.81)	445 per 1000	571 per 1000	126 more per 1000 (29 more to 223 more)	0 (0 studies)	8 (4,35) ^b
GUSELKUMAB	GUS vs. PBO	30.27 (20.90, 43.84)	17 per 1000	644 per 1000	627 more per 1000 (544 more to 711 more)	1689 (4 studies)	2 (1,2) ^b
	GUS vs. ADA	1.45 (1.32, 1.59)	445 per 1000	644 per 1000	199 more per 1000 (108 more to 290 more)	1658 (3 studies)	5 (3,9) ^b
CERTOLIZUMAB	CZP vs. PBO	18.19 (13.10, 25.27)	17 per 1000	442 per 1000	424 more per 1000 (336 more to 512 more)	1026 (4 studies)	2 (2,3) ^b
PEGOL	CZP vs. ADA	0.87 (0.53, 1.42)	445 per 1000	442 per 1000	4 less per 1000 (112 less to 104 more)	0 (0 studies)	NS
TILDRAKIZUMAB	TIL vs. PBO	19.10 (14.19, 25.69)	17 per 1000	357 per 1000	340 more per 1000 (245 more to 434 more)	1904 (3 studies)	3 (2,4) ^b
	TIL vs. ADA	0.91 (0.57, 1.46)	445 per 1000	357 per 1000	88 less per 1000 (201 less to 25 more)	0 (0 studies)	NS
RISANKIZUMAB	RIS vs. PBO	31.50 (24.58, 40.36)	17 per 1000	721 per 1000	704 more per 1000 (601 more to 807 more)	798 (2 studies)	1 (1,2) ^b
	RIS vs. ADA	1.51 (0.97, 2.35)	445 per 1000	721 per 1000	276 more per 1000 (155 more to 397 more)	0 (0 studies)	4 (3,6) ^b
MEAN CHANGE IN DLQI AT 10-16 WEEKS (ALL DOSES)							
ETANERCEPT	ETA vs. PBO	-5.65 (-6.86, -4.43)				1920 (4 studies)	
ADALIMUMAB	ADA vs. PBO	-7.27 (-8.40, -6.14)				2610 (6 studies)	
	ADA vs. ETA	-1.62 (-3.28, -0.04)				0 (0 studies)	
INFLIXIMAB	INF vs. PBO	-8.43 (-9.79, -7.06)				1591 (4 studies)	
	INF vs. ADA	-1.16 (-2.94, 0.62)				0 (0 studies)	
METHOTREXATE	MTX vs. PBO	-4.33 (-6.51, -2.15)				163 (1 study)	
	MTX vs. ADA	2.94 (0.89, 4.98)				332 (2 studies)	
USTEKINUMAB	UST vs. PBO	-7.60 (-8.55, -6.65)				3027 (7 studies)	

	UST vs. ADA	-0.33 (-1.81, 1.15)				0 (0 studies)	
SECUKINUMAB	SEC vs. PBO	-8.31 (-9.38, -7.24)				2282 (5 studies)	
	SEC vs. ADA	-1.05 (-2.60, 0.51)				0 (0 studies)	
IXEKIZUMAB	IXE vs. PBO	-7.87 (-9.41, -6.23)				1830 (2 studies)	
	IXE vs. ADA	-0.60 (-2.51, 1.34)				0 (0 studies)	
BRODALUMAB	BRO vs. PBO	-4.69 (-7.03, -2.34)				349 (2 studies)	
	BRO vs. ADA	2.58 (-0.02, 5.18)				0 (0 studies)	
GUSELKUMAB	GUS vs. PBO	-8.64 (-9.91, -7.36)				1689 (4 studies)	
	GUS vs. ADA	-1.37 (-2.75, 0.00)				1658 (3 studies)	
CERTOLIZUMAB	CZP vs. PBO	-6.80 (-9.00, -4.61)				461 (2 studies)	
PEGOL	CZP vs. ADA	0.46 (-2.01, 2.93)				0 (0 studies)	
TILDRAKIZUMAB	TIL vs. PBO	-9.30 (-12.40, -6.20)				351 (1 study)	
	TIL vs. ADA	-2.03 (-5.33, 1.26)				0 (0 studies)	
WITHDRAWAL DUE TO ADVERSE EVENTS AT 10-16 WEEKS (ALL DOSES)							
ETANERCEPT	ETA vs. PBO	1.18 (0.81, 1.71)	19 per 1000	23 per 1000	5 more per 1000 (1 less to 11 more)	5148 (14 studies)	NS
ADALIMUMAB	ADA vs. PBO	0.70 (0.44, 1.09)	19 per 1000	15 per 1000	4 less per 1000 (13 less to 5 more)	3204 (8 studies)	NS
	ADA vs. ETA	0.59 (0.33, 1.06)	23 per 1000	15 per 1000	8 less per 1000 (19 less to 2 more)	0 (0 studies)	NS
INFLIXIMAB	INF vs. PBO	2.59 (1.26, 5.30)	19 per 1000	53 per 1000	34 more per 1000 (14 more to 54 more)	964 (2 studies)	29 (19, 73) ^h
	INF vs. ADA	3.72 (1.64, 8.44)	15 per 1000	53 per 1000	38 more per 1000 (16 more to 59 more)	0 (0 studies)	27 (17, 62) ^h
METHOTREXATE	MTX vs. PBO	1.08 (0.46, 2.55)	19 per 1000	11 per 1000	8 less per 1000 (33 less to 18 more)	163 (1 study)	NS
	MTX vs. ADA	1.56 (0.62, 3.93)	15 per 1000	11 per 1000	4 less per 1000 (29 less to 21 more)	332 (2 studies)	NS
USTEKINUMAB	UST vs. PBO	0.65 (0.43, 0.99)	19 per 1000	15 per 1000	3 less per 1000 (9 less to 3 more)	3837 (10 studies)	NS

	UST vs. ADA	0.94 (0.51, 1.74)	15 per 1000	15 per 1000	1 more per 1000 (10 less to 11 more)	0 (0 studies)	NS
SECUKINUMAB	SEC vs. PBO	0.69 (0.38, 1.26)	19 per 1000	15 per 1000	4 less per 1000 (11 less to 4 more)	2686 (6studies)	NS
	SEC vs. ADA	0.99 (0.47, 2.11)	15 per 1000	15 per 1000	0 more per 1000 (12 less to 12 more)	0 (0 studies)	NS
IXEKIZUMAB	IXE vs. PBO	1.76 (1.00, 3.11)	19 per 1000	28 per 1000	10 more per 1000 (2 more to 17 more)	3126 (3 studies)	103 (58,488) ^h
	IXE vs. ADA	2.54 (1.23, 5.23)	15 per 1000	28 per 1000	13 more per 1000 (2 more to 25 more)	0 (0 studies)	74 (40,585) ^h
BRODALUMAB	BRO vs. PBO	0.84 (0.45, 1.57)	19 per 1000	21 per 1000	2 more per 1000 (4 less to 8 more)	4109 (5 studies)	NS
	BRO vs. ADA	1.20 (0.55, 2.60)	15 per 1000	21 per 1000	6 more per 1000 (5 less to 17 more)	0 (0 studies)	NS
GUSELKUMAB	GUS vs. PBO	0.51 (0.25, 1.01)	19 per 1000	17 per 1000	2 less per 1000 (13 less to 9 more)	1689 (4studies)	NS
	GUS vs. ADA	0.73 (0.37, 1.44)	15 per 1000	17 per 1000	2 more per 1000 (9 less to 13 more)	1658 (3studies)	NS
CERTOLIZUMAB	CZP vs. PBO	0.66 (0.25, 1.69)	19 per 1000	17 per 1000	2 less per 1000 (16 less to 13 more)	1026 (4 studies)	NS
PEGOL	CZP vs. ADA	0.94 (0.33, 2.70)	15 per 1000	17 per 1000	2 more per 1000 (15 less to 19 more)	0 (0 studies)	NS
TILDRAKIZUMAB	TIL vs. PBO	0.72 (0.30, 1.75)	19 per 1000	17 per 1000	2 less per 1000 (11 less to 8 more)	1904(3 studies)	NS
	TIL vs. ADA	1.04 (0.39, 2.80)	15 per 1000	17 per 1000	2 more per 1000 (11 less to 16 more)	0 (0 studies)	NS
RISANKIZUMAB	RIS vs. PBO	0.27 (0.09, 0.85)	19 per 1000	9 per 1000	10 less per 1000 (22 less to 3 more)	798 (2 studies)	NS
	RIS vs. ADA	0.39 (0.12, 1.33)	15 per 1000	9 per 1000	6 less per 1000 (21 less to 10 more)	0 (0 studies)	NS

Figure 1. Flow diagram showing the identification of *additional* literature in the PRISMA format. RCT, randomized controlled trial.

Figure 2 (a) – (c). Network maps for the main outcomes considered in the review at 10-16 weeks (**all doses**). Nodes and edges are weighted according to number of studies including that treatment or comparison. ADA, adalimumab; BRO, brodalumab; CZP, certolizumab pegol; ETA, etanercept; GUS, guselkumab; INF, infliximab; IXE, ixekizumab; MTX, methotrexate; PASI, psoriasis area and severity index; PBO, placebo; PGA, physician's global assessment; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab. N.B. There were no DLQI data for RIS published by the cut-off date for the literature searches.

(a) Clear/nearly clear (PASI 90/PGA 0 or 1)

(b) Mean change in the dermatology life quality index, DLQI

(c) Withdrawal due to adverse events

Table 2. Relative treatment rankings based on the three main outcomes (*all doses*, outcomes at 10-16 weeks); tolerability is the inverse of ‘withdrawal due to adverse events’; see Supplementary Table S2 for treatment rankings based on PASI 75 outcome. DLQI, dermatology life quality index; PASI, psoriasis area and severity index; Pr. Best, probability of being best; SUCRA, surface under the cumulative ranking curve.

Treatment	Clear/nearly clear			Mean change in DLQI			Tolerability		
	SUCRA	Pr. Best	Mean rank	SUCRA	Pr. Best	Mean rank	SUCRA	Pr. Best	Mean rank
Adalimumab	42.6	0	7.9	50.1	0.1	6.5	63.6	0.5	5.4
Brodalumab	60.7	0	5.7	17.9	0	10	49.7	0.7	7
Certolizumab pegol	37.2	0	8.5	44.4	1.5	7.1	63.8	6.9	5.3
Etanercept	10.8	0	11.7	26	0	9.1	25.8	0	9.9
Guselkumab	80.3	8.6	3.4	83.3	18.6	2.8	79.9	12.7	3.4
Infliximab	83.5	25.6	3	78.1	12.4	3.4	2	0	12.8
Ixekizumab	91.1	33.4	2.1	65	4.6	4.9	10.4	0	11.8
Methotrexate	16.1	0	11.1	15	0	10.3	35.9	0.6	8.7
Placebo	0	0	13	0	0	12	35.6	0	8.7
Risankizumab	90.1	32.3	2.2	N/A	N/A	N/A	94.1	71.9	1.7
Secukinumab	68.2	0.1	4.8	76.4	6.9	3.6	62.8	1.7	5.5
Tildrakizumab	33.5	0	9	86.1	55.7	2.5	58.6	4.3	6

Ustekinumab	36.1	0	8.7	57.8	0.3	5.6	67.8	0.8	4.9
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Figure 3 (a) – (b). Plot of joint rankings based on hierarchical clustering of the surface under the cumulative ranking curve (SUCRA) estimates. ADA, adalimumab; BRO, brodalumab; CZP, certolizumab pegol; ETA, etanercept; GUS, guselkumab; INF, infliximab; IXE, ixekizumab; MTX, methotrexate; PASI, psoriasis area and severity index; PBO, placebo; PGA, physician's global assessment; RIS, risankizumab; SEC, secukinumab; TIL, tildrakizumab; UST, ustekinumab.

(a) Combined estimates of efficacy (clear/nearly clear –PASI 90/PGA 0 or 1) and tolerability (inverse of withdrawal due to adverse events) for **all doses** at 10-16 weeks

(b) Combined estimates of efficacy (mean change in DLQI) and tolerability (inverse of withdrawal due to adverse events) for **all doses** at 10-16 weeks

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