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ORIGINAL RESEARCH

Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis

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Objective: To evaluate the comparative effectiveness of available tumor necrosis factor-α inhibitors (anti-TNFs) for the management of psoriatic arthritis (PsA) in patients with an inadequate response to disease-modifying antirheumatic drugs (DMARDs).

Methods: We used an exhaustive search strategy covering randomized clinical trials, systematic reviews and health technology assessments (HTA) published on anti-TNFs for PsA. We performed indirect comparisons of the available anti-TNFs (adalimumab, etanercept, golimumab, and infliximab) measuring relative risks (RR) for the psoriatic arthritis response criteria (PsARC), mean differences (MDs) for improvements from baseline for the Health Assessment Questionnaire (HAQ) by PsARC responders and non-responders, and MD for the improvements from baseline for the psoriasis area and severity index (PASI). When the reporting of data on intervention group response rates and improvements were incomplete, we used straightforward conversions based on the available data.

Results: We retrieved data from 20 publications representing seven trials, as well as two HTAs. All anti-TNFs were significantly better than control, but the indirect comparison did not reveal any statistically significant difference between the anti-TNFs. For PsARC response, golimumab yielded the highest RR and etanercept the second highest; adalimumab and infliximab both yielded notably smaller RRs. For HAQ improvement, etanercept and infliximab yielded the largest MD among PsARC responders. For PsARC nonresponders, etanercept, infliximab, and golimumab yielded similar MDs, and adalimumab a notably lower MD. For PASI improvement, infliximab yielded the largest MD and golimumab the second largest, while etanercept yielded the smallest MD. In some instances, the estimated magnitudes of effect were notably different from the estimates of previous HTA indirect comparisons.

Conclusion: There is insufficient statistical evidence to demonstrate differences in effectiveness between available anti-TNFs for PsA. Effect estimates seem sensitive to the analytic approach, and this uncertainty should be taken into account in future economic evaluations.

Keywords: anti-tumour necrosis factor drugs, biologic DMARDs, indirect comparison meta-analysis, psoriatic arthritis, health assessment questionnaire, psoriatic arthritis response criteria, psoriasis area and severity index

Introduction

Psoriatic arthritis (PsA) is an inflammatory disease affecting joints and connective tissues.[1] PsA affects up to 30% of individuals with psoriasis, a chronic skin condition affecting 1%–2% of the general population.[1] It can be a destructive disabling joint disease, with the severity increasing over time.[1] There are no cures for PsA and so the focus of treatment has been on controlling symptoms and preventing damage to joints.

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Patients are typically treated first with nonsteroidal anti-inflammatory drugs (NSAIDS), that help to reduce pain and inflammation of the joints.[2] In patients with more severe disease, disease-modifying antirheumatic drugs (DMARDs), such as methotrexate, are often a first course of treatment.[2] More recently, therapies that inhibit the pro-inflammatory protein – tumor necrosis factor (TNF) – are increasingly being used in patients who have failed traditional DMARD therapy.[2]

Currently, four anti-TNFs are indicated for the treatment of PsA in combination with methotrexate (MTX). So far two comparative effectiveness assessments of available anti-TNFs for PsA have been conducted, both in connection with a health technology assessment (HTA).[3,4] However, because of methodological shortcomings and limitations, the inferences from these analyses are weakened. The first HTA included adjusted indirect comparisons of only three of the four indicated anti-TNFs (adalimumab, infliximab, and etanercept).[3] In addition, although this HTA provided summary tables of the trial outcomes at different time points (eg, 14 weeks and 24 weeks), it was not clear which time points were used for producing the pooled comparative effectiveness estimates. The second HTA attempted to model only a few outcomes that lend themselves well to an economic model (ie, PsA response criteria [PsARC], Health Assessment Questionnaire [HAQ] by PsARC responders and nonresponders, and Psoriasis Area and Severity Index [PASI] mean change as a continuous variable).[4] However, the shortage in available data on these outcomes led the authors to conduct what was effectively a Bayesian imputation analysis. Given the scarcity of the data used, it is evident that the effectiveness estimates and any accompanying cost-effectiveness estimates will be sensitive to the imputation assumptions, and that the "noninformative" priors elicited in the model may carry a relatively high degree of information, and thus bias the estimates of effect.[5,6]

To address the shortcomings of previous indirect comparisons, and in particular the most recent HTA report, we performed an exhaustive literature search and data extraction of all trial publications, data available in published meta-analyses, and data available from HTAs. We used all available data on outcomes to calculate previously missing trial results, and thereby obviated the shortcomings of the Bayesian approach. We then re-ran the indirect comparison to obtain "improved" estimates of effect on the outcomes used to derive quality-adjusted life year (QALY) estimates in a recent National Institute for Health and Clinical Excellence (NICE) HTA.[4]

Methods

Eligibility criteria

We included randomized controlled trials (RCTs) examining the efficacy of anti-TNF biological agents (adalimumab, etanercept, golimumab, and infliximab) for the treatment of PsA. RCTs studying adult populations with active and progressive PsA with an inadequate response to previous DMARD therapy were eligible. We included RCTs of any treatment dose and duration of the above-specified anti-TNF biologics. We excluded trials conducted among PsA populations that had an adequate response to DMARD therapy, or were naïve to DMARD therapy. We also excluded trials conducted among PsA populations with prior experience with anti-TNF agents, including an inadequate response. Furthermore, trials that did not have a placebo control and that examined non-anti-TNF biological agents were excluded.

Search strategy

In consultation with a medical librarian, two investigators (ED, KT) independently conducted a systematic literature search for RCTs. The search terms included "psoriatic arthritis," "biologic," "anti-TNF," and the generic and brand names of each of the agents (eg, "adalimumab," "etanercept," "golimumab," "infliximab"). The following electronic databases (from inception to week 15 [April 9–15], 2012) were searched: MEDLINE, EMBASE, and Cochrane CENTRAL. Searches were limited to RCTs in humans, but not limited by language. Additionally, we searched for published HTAs and systematic reviews to further identify completed RCTs and/or obtain additional data on the published clinical trials. Lastly, some additional data were provided by Merck-Shire-Dome, UK. The exact search strategy is available from the authors upon request.

Study selection

Following the systematic literature searches, the same two investigators (ED, KT) obtained the full manuscripts of relevant trials, and independently assessed the relevance of each to determine whether or not it fit the eligibility criteria listed above. Any discrepancies between the two investigators were resolved by consulting a third investigator (EM) if necessary. Trials that did not meet the eligibility criteria were excluded and their reference listed with reasons for exclusion. Eligible trials underwent a quality assessment by one investigator (ED), using a modified Jadad scale.[7]

Data abstraction

Data were extracted by one investigator (ED) and independently checked by a second investigator (KT). Disagreements between

the data extracted were resolved by consulting a third investigator (EM) if necessary. We abstracted data on anti-inflammatory response as derived from the PsARC. Response of psoriatic skin lesions, as determined by the PASI, was also abstracted. Finally, functional status, as determined by the HAQ score, was abstracted overall, and by PsARC response, where possible. Definitions of each for the outcomes are presented in the Supplementary materials (Table S1). The following trial characteristics were also abstracted: study design, number of subjects, trial duration, outcome measures used, treatment dose and duration, concomitant therapies, and participant characteristics.

Data synthesis

Outcomes

We considered the same three outcomes as a previous HTA: the PsARC response, the HAQ mean change from baseline for PsARC responders and nonresponders, and the PASI mean change from baseline. Our primary endpoint was the last observed time point in the trial, before allowed dose escalation or treatment cross-over. We chose this because patients with escalated dose and patients that have crossed over are no longer comparable to patients on a fixed dose treatment in terms of estimating efficacy.

Dealing with incomplete data

The PsARC response was reported completely across all trial publications, and thus did not require any transformations or imputations. The HAQ mean change by PsARC responders and non-responders were made available to us through the full version of a recently published HTA.[4] However, the HAQ scores from the Mease 2000[8] and Mease 2004[9] studies had been combined in this HTA, and the available placebo HAQ response had been compiled across Mease 2000, Mease 2004, and the IMPACT trials.[16–18] For this reason we made use of the overall HAQ baseline and mean change scores extracted from the trial publications to calculate the summary statistics which were not reported (note all missing data points were fully derived and no imputations were needed). Table S2 provides a detailed overview of necessary data conversions for the HAQ outcome.

For the PASI mean change only IMPACT and IMPACT 2 had complete data. For the remaining trials except for Mease 2004, baseline PASI and associated standard deviations (SDs) as well as PASI50, PASI70, and PASI90 were available. We assumed that the absolute percentage mean change approximately followed a normal distribution and approximated the mean and standard deviation from the PASI50, PASI70, and PASI90 data. We then used the approximated distribution with the available baseline distribution to produce PASI mean changes, using simulations. For Mease 2004, where no baseline data was available, we imputed data by random sampling from the other trials. Appendix 2 provides a detailed overview of necessary data conversions and imputations for the PASI outcome.

Statistical models

We performed frequentist indirect comparison meta-analyses using random-effects models.[13] We obtained comparative relative risks (RR) with 95% confidence intervals for PsARC, and mean difference (MD) estimates with 95% confidence intervals for HAQ (PsARC responders and nonresponders) and PASI. All analyses were performed using StatsDirect (StatsDirect Ltd, Altrincham, UK) and R v. 2.14 (The R Project for Statistical Computing; http://www.R-project.org/).

For PsARC we pooled the response rate in the placebo group from all trials, and used simulation to produce the expected response rate with each of the treatments using the indirect RR estimates and associated (log) standard error estimates. For HAQ and PASI we pooled the control group mean responses from baseline across trials, and used simulation to produce the expected mean response with each of the treatments using the indirect MD estimates and associated standard error estimates. Our primary analysis was of the outcomes observed at last time point (before allowed dose escalation or cross-over). However, since the last observed time points across trials were not consistent, we performed sensitivity analysis where possible. For PsARC we performed sensitivity analysis using similar "short-term" (ie, 12–16 weeks) outcomes, and, separately, "long-term" (ie, 24 weeks) outcomes where available. These analyses were not possible for the HAQ and PASI outcomes as we only had data on one time point.

Results

Identified studies

Nineteen studies, representing seven RCTs, met our inclusion criteria.[14–27] Two of these RCTs used adalimumab,[14–19] two used etanercept,[8–27] two used infliximab,[10–24] and one used golimumab.[20] Table 1 presents the characteristics of each RCT, and Table S3 presents the demographic characteristics of the patients included in each RCT. Twenty-nine studies examined in detail were excluded; reasons for exclusion are presented in Table S4. A schematic of the study selection process is presented in Figure 1.

Indirect comparisons

For all treatments for all outcomes (except for adalimumab for HAQ nonresponders), there was a statistically significant difference in favor of the treatment (allowing for 5% type I error).

Table 1 Characteristics of the included trials

Trial	Intervention	Setting	Blinded period	No of patients randomized	Quality score	Outcomes of interest
Mease et al[8]	ETN (25 mg twice weekly)	NS	12 weeks	60	5/5	HAQ, PASI, PsARC
Mease et al[25–27]	ETN (25 mg twice weekly)	17 sites in USA	24 weeks	205	4/5	PASI, PsARC
IMPACT[10–12]	INF (5 mg/kg at weeks 0, 2, 6, 14)	9 sites in Europe, Canada, USA	16 weeks	104	4/5	HAQ, PsARC
IMPACT 2[21–24]	INF (5 mg/kg at weeks 0, 2, 6, 14, 22)	36 sites in Europe, Canada, USA	16 weeks	200	4/5	HAQ, PASI, PsARC
ADEPT[14–18]	ADA (40 mg every other week)	50 sites in Europe, Australia, Canada, USA	24 weeks	313	3/5	HAQ, PASI, PsARC
Genovese et al[19]	ADA (40 mg every other week)	16 sites in Canada, USA	24 weeks	100	5/5	HAQ, PsARC
GO-REVEAL[20]	GOL (50 mg or 100 mg every fourth week)	52 sites in Europe, Canada, USA	24 weeks	405	5/5	HAQ, PASI, PsARC

Abbreviations: ADA, adalimumab; ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; ETN, etanercept; GOL, golimumab; GO-REVEAL, Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody; HAQ, Health Assessment Questionnaire; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, inflizimab; NS, not stated; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria.

Figure 2 presents the direct estimates for each of the anti-TNF treatments compared with placebo. For PsARC response, golimumab yielded the highest relative risk (RR 3.45, 95% CI: 2.39, 4.99) and etanercept the second highest (RR 3.19, 95% CI: 2.31, 4.42). Adalimumab and infliximab both yielded notably smaller RRs. Sensitivity analysis using different time points did not reveal any difference in PsARC response RRs (results not shown, but available from the authors upon request). For HAQ improvement, etanercept and infliximab yielded the largest MD among PsARC responders (0.43 and 0.41, respectively). For PsARC nonresponders, etanercept, infliximab, and golimumab yielded similar MDs, and adalimumab yielded a notably lower MD. For PASI improvement, infliximab yielded the largest MD and golimumab the second largest (6.44 and 4.90, respectively), while etanercept yielded the smallest MD (3.13).

Table 2 presents the indirect estimates between anti-TNF treatments. None of the four treatments were statistically significantly different for any of the outcomes.

Lastly, Table 3 presents the pooled control group responses and the expected intervention group responses using the indirect RR and MD estimates from the placebo comparison.

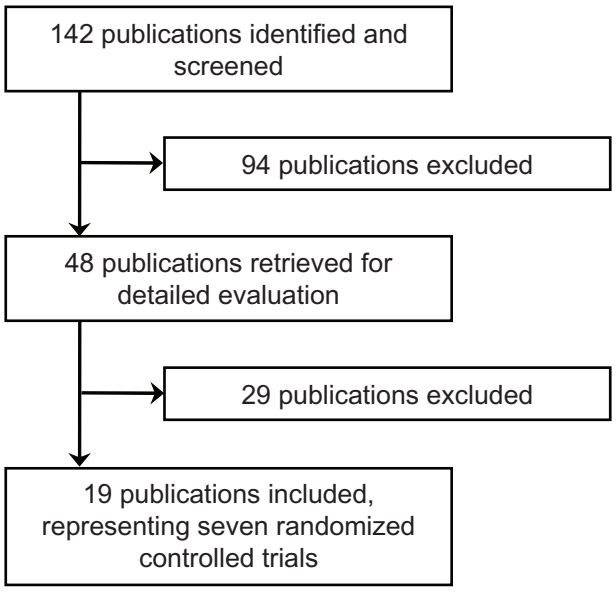

Figure 1 Schematic of the publication selection process.

Discussion

Our indirect comparison of anti-TNF drugs for PsA was based on an extensive literature search and data extraction that allowed us to calculate trial results that were missing in previous indirect comparisons. No statistically significant difference was detected between the four anti-TNF drugs. When considering only the magnitude of estimated effect, the three anti-TNF drugs etanercept, infliximab, and golimumab seem to perform comparably better than adalimumab. When compared with each other, each of these three anti-TNFs performed better for one or two outcomes, but worse for one or two other outcomes (eg, golimumab yields the highest PsARC response, but the lowest average HAQ among PsARC nonresponders). In some instances, the treatment effect point estimates were also notably different from the estimates used to inform the recent NICE cost-effectiveness analysis.[4]

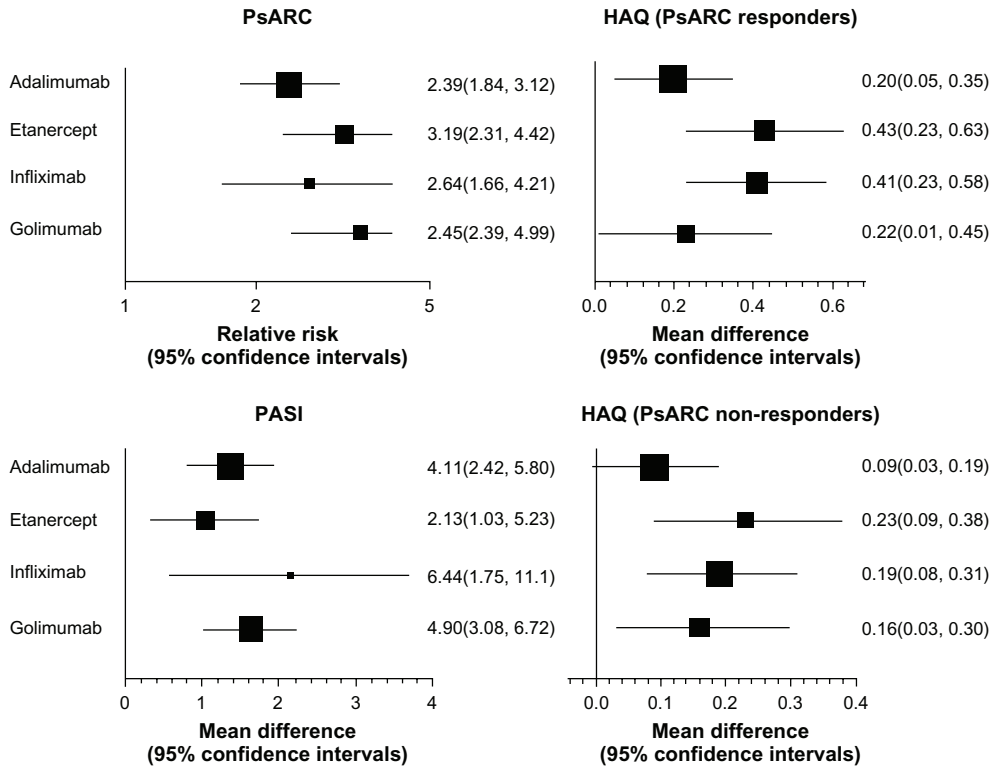

Figure 2 Forest plots of direct estimates for anti-TNFs versus placebo comparisons.
Abbreviations: anti-TNF, anti-tumor necrosis factor; HAQ, Health Assessment Questionnaire; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria.

Our indirect comparison comes with a number of strengths and limitations. We performed an extensive search of all trial publications (several reports have been published for each trial[14–29]), previous systematic reviews, and HTAs. This allowed us to extract enough data to calculate the results of the outcomes of interest when missing. This also removed the necessity for Bayesian imputation models driven by priors. Despite the extensive data search and extraction, one cannot avoid the fact that the trial data are relatively sparse. Thus, calculations made for missing values and inferences regarding comparative effectiveness may be considerably impacted by random error. Some data may also have been suboptimal. For HAQ improvement by PsARC responders, our etanercept data were a pooled analysis of the Mease 2000 and Mease 2004 trials. Although we were able to use trial reported HAQ scores to calculate and validate these results, some bias concerns exist with regards to Mease 2000, which we were not able to perform sensitivity analysis on. For PASI improvement, we only had continuous data available for about half of the trials. The conversion based on reported PASI50, PASI75, and PASI90 is only approximate, and may thus introduce some error. However, we do not believe this potential error is worse than the bias introduced by using falsely labeled "noninformative" priors in a Bayesian imputation model.

Table 2 Head-to-head indirect estimates of the anti-TNF drugs

Comparison	PsARC RR (95% CI)	HAQ MD (95% CI)		PASI MD (95% CI)
		Responders	Nonresponders	
ADA versus ETN	0.75 (0.49, 1.24)	–0.23 (–0.51, 0.05)	–0.15 (–0.33, 0.03)	0.98 (–1.72, 3.68)
ADA versus INF	0.91 (0.53, 1.32)	–0.21 (–0.48, 0.06)	–0.11 (–0.27, 0.05)	–2.33 (–7.30, 2.64)
ADA versus GOL	0.69 (0.44, 1.26)	–0.03 (–0.33, 0.27)	–0.08 (–0.25, 0.09)	–0.79 (–3.27, 1.69)
ETN versus INF	1.21 (0.69, 1.34)	0.02 (–0.26, 0.30)	0.04 (–0.15, 0.23)	–3.31 (–8.44, 1.82)
ETN versus GOL	0.92 (0.57, 1.28)	0.20 (–0.10, 0.50)	0.07 (–0.13, 0.26)	–1.77 (–4.55, 1.01)
INF versus GOL	0.76 (0.42, 1.35)	0.18 (–0.11, 0.47)	0.03 (–0.15, 0.21)	1.54 (–3.48, 6.56)

Abbreviations: ADA, adalimumab; anti-TNF, anti-tumor necrosis factor; CI, confidence interval; ETN, etanercept; GOL, golimumab; HAQ, Health Assessment Questionnaire; INF, infliximab; MD, mean difference; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; RR, relative risk.

Table 3 Expected response rates and 95% confidence intervals for the three considered outcomes with the four anti-TNF drugs

Outcome	Placebo response	Anti-TNF treatment response			
		ADA	ETN	INF	GOL
PsARC response (proportion)	0.25 (0.21, 0.28)	0.60 (0.50, 0.70)	0.80 (0.70, 0.88)	0.66 (0.48, 0.81)	0.86 (0.76, 0.93)
HAQ responders (mean response)	0.24 (0.18, 0.31)	0.44 (0.29, 0.51)	0.67 (0.47, 0.87)	0.65 (0.47, 0.83)	0.47 (0.24, 0.69)
HAQ nonresponders (mean response)	0.01 (–0.3, 0.04)	0.09 (–0.02, 0.18)	0.24 (0.10, 0.39)	0.19 (0.09, 0.32)	0.17 (0.04, 0.31)
PASI (mean response)	0.68 (0.31, 1.04)	4.79 (3.10, 6.48)	3.81 (1.71, 5.91)	7.12 (2.43, 11.78)	5.58 (3.76, 7.40)

Note: Confidence intervals are derived assuming a fixed placebo response.
Abbreviations: ADA, adalimumab; anti-TNF, anti-tumor necrosis factor; ETN, etanercept; GOL, golimumab; HAQ, Health Assessment Questionnaire; INF, infliximab; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria.

This incongruence between magnitudes of effect estimates in our indirect comparison and previous indirect comparisons, strongly suggests sensitivity to analytic approaches that should not be overlooked in related economic evaluations. Patient utility can be derived by already established mathematical relationships between generic quality of life instruments such as the EQ-5D and the disease outcomes of interest (PsARC, HAQ, and PASI). While previous health economic assessments did perform a wide array of sensitivity analyses, these did not cover sensitivity to different analytic approach such as the 'imputation' used for our indirect comparison. Given that adalimumab, etanercept, golimumab, and infliximab are approved for use in PsA in many major settings, it is unlikely that we will see additional trials assessing the efficacy of these therapies, and so, economic evaluations will need to rely on the current available evidence. As such, it seems important to undertake a revision of current cost-effectiveness models to assess whether current drug indications are based on robust results, or need reconsideration.

Conclusion

Our indirect comparison did not demonstrate any significant difference between anti-TNF drugs for the treatment of PsA. In some instances, the magnitudes of effect in our indirect comparison differed from others. Since the analyzed outcomes play an important role informing quality adjusted life years (QALYs, and thus cost per QALY) in cost-effectiveness analyses, it seems reasonable to insist that the cost-effectiveness analyses on which the current drug indications are based be revised to check the robustness of their findings.

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Author contributions

KT and EM conceived the design of the study. KT drafted the first manuscript. KT and ED extracted the data. KT performed the statistical analyses. All authors contributed to the interpretation of the findings and to the writing of the final version of the manuscript.

Disclosure

Kristian Thorlund and Edward Mills have consulted either Merck and Co, Inc, Pfizer Ltd, Nycomed, Takeda, Novartis or GlaxoSmithkline on multiple treatment comparison and systematic review issues. Kristian Thorlund and Edward Mills have received grant funding from the Canadian Institutes of Health Research (CIHR) Drug Safety and Effectiveness Network to develop methods and educational materials on MTCs. Edward Mills receives salary support from the Canadian Institutes of Health Research through a Canada Research Chair. Kristian Thorlund receives salary support from the CIHR Drug Safety and Effectiveness Network. The above authors report no other conflicts of interest in this work. Eric Druyts and Antonio Avina-Zubieta report no conflicts of interest in this work.

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Supplementary materials

Table S1 Outcomes included in the analysis

Outcome	Definition
Psoriatic arthritis response criteria (PsARC)	PsARC is defined as an improvement in at least two of the following four measures: patient self-assessment, physician assessment, joint pain/tenderness score, and joint swelling score. One of the two measures must be joint pain/tenderness score or joint swelling score. No worsening can occur in any of the four measures.
Psoriasis area and severity index (PASI)	PASI combines the assessment of the severity of lesions and the area affect into a score that spans from 0 (no disease) to 72 (maximal disease). At least 3% of the body surface area has to be affected by the psoriasis in order for the PASI measure to be used.
Health assessment questionnaire (HAQ)	The HAQ focuses on two dimensions of health status: physical disability and pain, generating a score of 0 (least disability) to 3 (most severe disability).

Table S2 Imputations solutions and assumptions employed to construct PASI mean changes

Trial	Data format	Imputation solutions and employed assumptions
Mease et al[13]	Baseline median and range (assumed range = 2 × 3 SEs) Percentage change from baseline	Assume similar percentage change SD as Mease 2004 Assume mean percentage change is normally distributed Simulate PASI mean change scores from available baseline and % change data
Mease et al[25–27]	Baseline not reported Percentage change (SE)	Assume similar baseline score as Mease 2000 Assume mean percentage change is normally distributed Simulate PASI mean change scores from assumed baseline and available % change data
IMPACT[10–12]	PASI (BSA > 3%) reported by PsARC responders and nonresponders	Take weighted average of PsARC responders and non-responders
IMPACT 2[21–24]	PASI (BSA > 3%) reported by PsARC responders and nonresponders	Same as IMPACT
ADEPT[14–18]	Baseline PASI mean and SE Percentage achieving 50%, 75%, and 90% PASI improvement	Assume percentage change is normally distributed Approximate normal distribution mean and SE using available percentiles (PASI50, PASI75, and PASI90 transformed) Simulate PASI mean change scores from assumed baseline and available % change data
GO-REVEAL[20]	PASI (BSA > 3%) reported by PsARC responders and non-responders	Same as IMPACT

Abbreviations: ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; BSA, body surface area; GO-REVEAL, Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; PASI, Psoriasis Area and Severity Index; PsARC, Psoriatic Arthritis Response Criteria; SD, standard deviation; SE, standard error.

Table S3 Demographic characteristics of participants in the included randomized controlled trials

	Mease[8]		Mease[9,25–27]		IMPACT[10–12]		IMPACT 2[21–24]		ADEPT[14–18]		Genovese et al[19]		GO-REVEAL[20]		
	ETN 25 mg twice weekly	Placebo	ETN 25 mg twice weekly	Placebo	INF 5 mg/kg at weeks 0, 2, 6, 14	Placebo	INF 5 mg/kg at weeks 0, 2, 6, 14, 22	Placebo	ADA 40 mg every other week	Placebo	ADA 40 mg every other week	Placebo	GOL 50 mg every forth week	GOL 100 mg every forth week	Placebo
Patients randomized, no	30	30	101	104	52	52	100	100	151	162	51	49	146	146	113
Male sex, %	53	60	57	45	58	58	71	51	56	55	57	51	61	59	61
Caucasian, %	90	83	90	91	–	–	–	–	97	94	98	94	97	97	97
Age, years	46.0*	43.5*	47.6**	47.3**	45.7**	45.2**	47.1**	46.5**	48.6**	49.2**	50.4**	47.7**	45.7**	48.2**	47.0**
Psoriasis duration, years	19.0*	17.5*	18.3**	19.7**	16.9**	19.4**	NS	NS	17.2**	17.1**	18.0**	13.8**	NS	NS	NS
PsA duration, years	9.0*	9.5*	9.0**	9.2**	11.7**	11.0**	8.4**	7.5**	9.8**	9.2**	7.5**	7.2**	7.2**	7.7**	7.6**
PsA type, %															
Distal interphalangeal joint arthritis	NS	NS	51	50	NS	NS	NS	NS	10	5	6	0	16	15	14
Arthritis mutilans	NS	NS	1	2	NS	NS	NS	NS	1	0	0	0	1	1	0
Asymmetric peripheral arthritis	NS	NS	41	38	NS	NS	NS	NS	25	25	10	14	30	34	24
Polyarticular arthritis	NS	NS	86	83	100	100	NS	NS	64	70	82	84	43	38	51
Ankylosing spondylitis	NS	NS	3	4	NS	NS	NS	NS	1	0	2	2	10	12	11
Swollen joint count	NS	NS	NS	NS	14.6**,†	14.7**,†	13.9**,†	14.4**,†	14.3**,††	14.3**,††	18.2**,††	18.4**,††	14.1**,†	12.0**,†	13.4**,†
Tender joint count	NS	NS	NS	NS	23.7**,†	20.4**,†	24.6**,†	25.1**,†	22.7**,††	19.1**,††	29.3**,††	25.3**,††	24.0**,†	22.5**,†	21.9**,†
Prior number of DMARDs	1.5*	2.0*	NS	NS	NS	NS	NS	NS	1.5**	1.5**	NS	NS	NS	NS	NS
Concomitant therapies during study, %															
Corticosteroid	20	40	19	15	NS	NS	10	15	NS	NS	8	18	13	18	17
NSAID	67	77	88	83	NS	NS	73	71	NS	NS	73	86	75	75	78
MTX	47	47	42	41	NS	NS	45	47	51	50	47	47	49	47	48

Notes: *Median; **mean; †0–66 (swollen joints), 0–68 (tender joints); ††0–76 (swollen joints), 0–78 (tender joints).

Abbreviations: ADEPT, Adalimumab Effectiveness in Psoriatic Arthritis Trial; ADA, adalimumab; DMARDs, disease-modifying antirheumatic drugs; ETN, etanercept; GOL, golimumab; GO-REVEAL, Golimumab-Randomized Evaluation of Safety and Efficacy in Subjects with Psoriatic Arthritis Using a Human Anti-TNF Monoclonal Antibody; IMPACT, Infliximab Multinational Psoriatic Arthritis Controlled Trial; INF, infliximab; MTX, methotrexate; NSAID, nonsteroidal anti-inflammatory drugs; PsA, psoriatic arthritis; NS, not stated.

Table S4 Publications excluded after detailed evaluation

Study	Reason for exclusion
Baranauskaite et al[28]	Included patients naïve to methotrexate
Kimball et al[29]	Does not exclusively include psoriatic arthritis patients; sub-analysis to randomized controlled trial
Mease et al[30]	Treatment not of interest; included inadequate responders to adalimumab, entanercept, or infliximab
Prinz et al[31]	Does not include a control arm; post hoc analysis to randomized controlled trial
Asahina et al[32]	Does not exclusively include psoriatic arthritis patients
Atteno et al[33]	Not a randomized controlled trial
Mease et al[34]	Pooled analyses of randomized controlled trials
Sterry et al[35]	Does not include a control arm
Torii et al[36]	Does not exclusively include psoriatic arthritis patients
Van Kuijk et al[37]	Does not include outcomes of interest
Bongiorno et al[38]	Not a randomized controlled trial
Brodszky et al[39]	Not a randomized controlled trial
Feldman et al[40]	Does not exclusively include psoriatic arthritis patients
Kristensen et al[41]	Not a randomized controlled trial
Ravindran et al[42]	Not a randomized controlled trial
Revicki et al[43]	Does not exclusively include psoriatic arthritis patients
Saad et al[44]	Not a randomized controlled trial
Spadaro et al[45]	Not a randomized controlled trial
Strober et al[46]	Does not include outcomes of interest
Frankel et al[47]	Not a randomized controlled trial
Kimball et al[48]	Not a randomized controlled trial
Romero-Maté et al[49]	Not a randomized controlled trial
Vander Cruyssen et al[50]	Not a randomized controlled trial
Fransen et al[51]	Not a randomized controlled trial
Gottlieb et al[52]	Not a randomized controlled trial
Mease et al[25]	Not a randomized controlled trial
Ritchlin[53]	Not a randomized controlled trial
Kvien et al[54]	Not a randomized controlled trial
Rinaldi et al[55]	Not a randomized controlled trial