Review

Treatment modifying factors of biologics for psoriatic arthritis: a systematic review and Bayesian meta-regression

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ABSTRACT

Objective. *The aim of this study was to explore factors that modify treatment effects of non-conventional biologics versus placebo in patients with psoriatic arthritis.*

Methods. *A systematic literature review and meta-regression was conducted. The biologics included etanercept, infliximab, adalimumab, golimumab, certolizumab, ustekinumab, tocilizumab, anakinra, abatacept, rituximab, and secukinumab. Outcomes included American College of Rheumatology (ACR) 20 and 50, Psoriasis Area Severity Index (PASI) 75, and 36-Item Short Form Health Survey (SF-36) Physical and Mental Component Summaries (PCS and MCS).*

Results. *Twelve RCTs were eligible for meta-regression. Treatment effects for ACR-20 at 12 weeks were higher in trials with longer disease durations (OR=2.94), and lower in trials enrolling older patients (OR=0.48), and those recently published (OR=0.49). Treatment effects for ACR-50 at 12 weeks were higher in trials with more males (OR=2.27), but lower in trials with high prior anti-TNF use (OR=0.28) and recently published trials (OR=0.37). For PASI-75, trials with more male patients (24 weeks: OR=2.56), and with higher swollen and tender joint counts (12 weeks: OR=8.33; 24 weeks: OR=14.44) showed higher treatment effects, and trials with high prior anti-TNF use had lower effects (OR=0.41). Treatment effects for SF-36 PCS at 24 weeks were higher in trials with longer psoriasis disease durations (OR=2.95) and PsA disease durations (OR=4.76), and those published earlier (OR=4.19).*

Conclusion. *Our analyses show that differences in baseline characteristics may explain some of the differences in response to biologics versus placebo across different trials. Accounting for these factors in future studies will likely be important.*

Introduction

Psoriatic arthritis (PsA) is a type of chronic inflammatory arthritis frequently occurring in association with psoriasis (1, 2). PsA may involve painful inflammation of peripheral joints, peripheral entheses, synovial tendon sheaths, as well as the spine and sacroiliac joint (3). Due to the potential for progressive joint damage, PsA can have considerable impact on functional status and quality of life (4, 5).

Early stage PsA can initially be treated with non-steroidal anti-inflammatory drugs (NSAIDs) or low-dose systemic glucocorticoids (2). More severe forms of PsA are typically initially treated with conventional disease-modifying anti-rheumatic drugs (DMARDs, *e.g.* methotrexate, leflunomide, and sulfasalazine) to minimise the risk of disease progression (6). Biologic disease-modifying anti-rheumatic drugs (DMARDs) or other biologics are indicated for moderate to severe PsA after failure with conventional DMARDs (7). Currently, etanercept, infliximab, adalimumab, golimumab, certolizumab, and ustekinumab are approved for the treatment of PsA. These biologics have been shown to reduce inflammation and enhance quality of life (8-11). Other biologics evaluated for PsA include tocilizumab, anakinra, abatacept, rituximab, and secukinumab (12).

Although biologic treatments have demonstrated superior efficacy when compared to placebo in clinical trials, not all patients show adequate response. Presently, it is unclear which factors influence the probability of a positive clinical response. Therefore, the objective of this study was to per-

form a systematic review of the literature and meta-regression analysis to explore factors that potentially modify treatment effects of biologics *versus* placebo in PsA.

Methods

Systematic review

Literature search

Relevant studies were identified by conducting a systematic literature search following a search protocol developed according to Cochrane collaboration's recommendations for systematic literature review (13). The search was carried out via OvidSP platform in the following databases (from inception to October 2014): MEDLINE®, Embase, and Cochrane Central Register of Controlled Trials. In addition, clinicaltrials.gov database was also searched to identify potentially eligible studies not yet catalogued in any of the searched databases and not published in a peer-reviewed format. The literature search strategies employed are provided in Appendix 1, consultable on line at *www.clinexprheumatol*.org.

Criteria for study inclusion

The selection of studies was guided according to the population, interventions, comparisons, and outcomes (PICO criteria) outlined in Table I. In brief, adults above the age of 18 diagnosed with psoriatic arthritis and on a treatment of etanercept, infliximab, adalimumab, golimumab, certolizumab, tocilizumab, anakinra, abatacept, rituximab, ustekinumab, or secukinumab as monotherapy or in combination with a conventional DMARDs were considered eligible. Comparisons of interest included placebo or no treatment for any of the above mentioned interventions. Outcomes of interest included the American College of Rheumatology (ACR) 20 and 50 responses (14), the Psoriasis Area Severity Index (PASI) 75 response (15), and the SF-36 Physical Component Summary (PCS) and Mental Component Summary (MCS) at 12 and 24 week time points (14-16). The search included randomised controlled trials (RCTs) and comparative retrospective or prospective observational studies.

Study selection

Two reviewers working independently scanned all abstracts and proceedings identified in the literature searches. The same two investigators independently reviewed abstracts potentially relevant in full-text. If any discrepancies occurred between the studies selected by the two investigators, a third reviewer provided arbitration.

Assessment of study quality

In this systematic review, the risk of bias in the included RCTs was assessed using the Cochrane risk-of-bias tool (17) (Appendix 2).

Data extraction

Two reviewers working independently extracted data on study characteristics, interventions, patient characteristics at baseline, and outcomes for the study population of interest for the final list of selected eligible studies. Any discrepancies observed between the data extracted by the two reviewers were resolved by consensus through discussion. Data was stored in a Microsoft Excel Workbook with sheets corresponding to the different information categories.

For dichotomous outcomes, such as the ACR response, the number of patients with the event, the number of patients at risk, and the time point of follow-up in each treatment group were extracted. For continuous outcomes, such as the SF-36 score, the change from baseline in the intervention groups was extracted. If change from baseline was not provided, the score at end of follow-up and baseline was extracted and used to

Table I. Population, interventions, comparisons, outcomes, study design.

Criteria	Definition
Population	The population of interest was adult patients with psoriatic arthritis (PsA)
Interventions	The following treatments as monotherapy or in combination with a conventional disease-modifying anti-rheumatic drugs (DMARDs*) were considered eligible: • Etanercept • Infliximab • Adalimumab • Golimumab • Certolizumab • Tocilizumab • Anakinra • Abatacept • Rituximab • Ustekinumab • Secukinumab
Comparators	The following comparisons as monotherapy or in combination with a conventional DMARD were considered eligible: • Placebo or no treatment • Any of the above mentioned interventions
Outcomes	The following outcomes at 12 and 24 weeks (continuous, categorical or both) were considered: *Efficacy* • 20% improvement in the American College of Rheumatology response criteria (ACR 20 response) • 50% improvement in the American College of Rheumatology response criteria (ACR 50 response) • 75% improvement in the Psoriasis Area and Severity Index (PASI 75 response) *Quality of Life* • SF-36 Physical Component Summary (PCS) • SF-36 Mental Component Summary (MCS)
Study design	The eligible studies included randomised controlled trials (RCTs) and retrospective or prospective comparative observational studies

*Conventional DMARDS: methotrexate, leflunomide and sulfasalazine.

calculate the change from baseline. The standard error of the change from baseline was calculated by assuming a conservative 0.50 correlation. However, if estimates of the correlation between baseline and end of treatment/follow-up were available, these were used to calculate the standard error. Furthermore, corresponding sample sizes, standard deviation, and measures of uncertainty (*i.e.* standard error, 95% confidence intervals, and *p*-values) were extracted. If the standard error was not reported for a particular outcome, it was calculated according to the following hierarchy: based on the reported 95% confidence interval by intervention group; standard deviation by intervention group along with sample size; 95% confidence interval of the difference between intervention groups; *p*-values by intervention groups; *p*-values for the difference between intervention groups.

Analyses

As a first step, the *exploratory* stage, graphical representations of the data were constructed to determine the factors that could act as potential effect modifiers in the assessment of biologics *versus* placebo. Forest plots with study level covariates in ascending order were used to examine the between-study variation of these factors in relation to reported treatment effects. L'Abbé plots were also used to investigate this relationship while accounting for differences in strength of evidence. Identification of factors of relevance at this exploratory phase was based on p-value and graphical trend (*e.g.* significant *p*-values due to a clear outlier were ignored).

As a second step, the relationship between each of these characteristics potentially associated with the treatment effects of biologics *versus* placebo identified in the exploratory stage were estimated using meta-regression analysis (18). Given that meta-regression methods are susceptible to the ecological fallacy when using continuous explanatory variables reflecting patient characteristics reported at the study level, all analyses were performed using dichotomised versions of continuous measures (dichotomised at the median) (19). The meta-regression was applied within a network meta-analysis framework that considered three nodes: placebo or no treatment, anti-TNF therapies, and non-anti-TNF therapies (20, 21). As such, it was necessary to assume that the effect of such factors on treatment effects of biologics *versus* placebo would be similar for all anti-TNF treatments. This approach was favored over network meta-analyses using the individual treatments because the latter tended to lead to sparse networks that did not allow for meta-regression to be used. Sensitivity analyses were performed where meta-regression was restricted to placebo/ no treatment and only anti-TNF treatments.

Analyses were performed in the Bayesian framework, which involves data, a likelihood distribution, a model with parameters, and prior distributions. For each outcome and covariate of interest, fixed effects meta-regression analysis was performed. Fixed effects instead of random effects modeling was used because random-effects models did not produce stable estimates due to limited trials with head-to-head comparisons.

For dichotomous outcomes, a logistic regression model with the logit link function and a binomial likelihood was used (22). Non-informative prior distributions were used for all model parameters. The parameter estimates reflecting the association between the covariate and treatment effect were transformed into odds ratios (OR) reflecting the ratio of the treatment effect (in terms of OR) between different levels of the covariate. For continuous outcomes, linear models with an identity link and normal likelihood were used. The parameter estimates representing the association between the covariate and treatment effect were presented as mean differences in treatment effect between the different levels of the covariate. The posterior distributions of each association measure of interest were summarised by the median as reflection of the "point estimate" of effect and 95% credible intervals (CrIs), which are constructed from the 2.5^{th} and 97.5^{th} percentiles of the posterior distribution. Given the use of non-informative prior distributions for all analyses, the 95% CrIs are similar to what 95% confidence intervals (CIs) would have been if the analyses were performed in a frequentist framework. Accordingly, one can interpret the 95% CrI in a similar way as 95% CIs with regards to relative treatment effect.

The forest and L'Abbé plots were created using R v. 3.1.1 (www.r-project.org; Vienna, Austria). The parameters of the different models were estimated using a Markov Chain Monte Carlo (MCMC) method as implemented in the OpenBUGS v. 3.2.3 (OpenBUGS Project Management Group) (23, 24). A first series of iterations from the OpenBUGS sampler were discarded as 'burn-in' and the inferences were based on additional iterations using two chains. Convergence of two chains was confirmed by the Gelman-Rubin statistic (25).

Results

Evidence base

A total of 4608 abstracts were identified from the literature searches. After the removal of 512 duplicates, each of the abstracts was screened and consequently 148 studies were further examined via their full-text publications. In total, 16 publications representing 12 RCTs were identified as eligible for inclusion. No observational studies were eligible for inclusion. Table II provides a summary of the studies included in the analyses. The flowchart of study selection is provided in Figure 1, and details regarding the patient demographics, treatment characteristics, and trial characteristics are provided in Appendix 3.

The two time points of interest were 12 weeks and 24 weeks. Eleven studies were included for the 12-week time point (9-11, 26-33), of which eight reported data at 12 weeks and three at 14 weeks (9, 26, 27, 34, 35). Data for the 14- and 12-week time points were combined. Nine studies reported data at the 24-week time point (9-11, 26, 29-31, 33-40). Adalimumab *versus* placebo was reported in two trials (10, 28), etanercept *versus* placebo was reported in two trials (11, 32), infliximab *versus* placebo was reported in two trials (26, 27), and ustekinumab *versus* placebo was reported in two trials (29, 33). Abatacept *versus* placebo was reported

Table II. Summary of trials included in analyses.

Study	Source	Treatment	Publication type	Time points available (weeks)	Outcomes reported
ADEPT	Mease *et al*. 2005 (10)	Adalimumab	Principal	12, 24	ACR, PASI, SF-36 PCS, SF-36 MCS
	Genovese *et al*. 2007 (28)	Adalimumab	Principal	12	ACR, SF-36 PCS, SF-36 MCS
GO-REVEAL	Kavanaugh *et al*. 2009 (9)	Golimumab	Principal	12, 24	ACR, PASI, SF-36 PCS
	Kavanaugh *et al*. 2013 (41)	Golimumab	Subsequent	12, 24	SF-36 MCS
IMPACT	Antoni *et al*. 2005 (26)	Infliximab	Principal	12, 24	ACR, PASI
IMPACT 2	Antoni *et al*. 2005 (27)	Infliximab	Principal	12	ACR, PASI
	Kavanaugh *et al*. 2007 (8)	Infliximab	Subsequent	12	SF-36 PCS, SF-36 MCS
	McInnes *et al*. 2014 (30)	Secukinumab	Principal	12, 24	ACR, SF-36 PCS
Mease *et al*. 2000	Mease *et al*. 2000 (32)	Etanercept	Principal	12	ACR, PASI
Mease *et al*. 2004	Mease *et al*. 2004 (11)	Etanercept	Principal	12, 24	ACR, PASI
	Mease *et al*. 2010 (42)	Etanercept	Subsequent	12, 24	SF-36 PCS, SF-36 MCS
	Mease *et al*. 2011 (34)	Abatacept	Principal	24	ACR, PASI, SF-36 PCS, SF-36 MCS
PSUMMIT 1	McInnes *et al*. 2013 (29)	Ustekinumab	Principal	12, 24	ACR, PASI, SF-36 PCS, SF-36 MCS
PSUMMIT 2	Ritchlin *et al*. 2014 (33)	Ustekinumab	Principal	12, 24	ACR, PASI, SF-36 PCS, SF-36 MCS
RAPID-PsA	Mease *et al*. 2014 (31)	Certolizumab	Principal	12, 24	ACR, PASI
	Gladman *et al*. 2014 (45)	Certolizumab	Subsequent	12, 24	SF-36 PCS, SF-36 MCS

in one trial (34) certolizumab *versus* placebo was reported in one trial (31, 45), golimumab *versus* placebo was reported in one trial (9), and secukinumab *versus* placebo was reported in one trial (30). No RCTs compared any treatments of interest head-to-head. Of the outcomes of interest, 12 studies reported on ACR responses (9-11, 26-33, 36), 10 studies reported on PASI (9-11, 26, 27, 29, 31-33, 36), 10 studies reported on SF-36 PCS (9-11, 27-31, 33, 36), and 9 studies reported on SF-36 MCS (9-11, 27-29, 31, 33, 36).

ACR 20

The exploratory analyses suggested that age, psoriasis disease duration, PsA disease duration, prior anti-TNF use, and year of publication were associated with treatment effects (i.e. the odds ratio of a biologic *versus* placebo) for ACR 20 response at both the 12 and 24-week time points (see Appendix 4 and 5). Estimating the strength and statistical significance of the relationships with meta-regression analyses, we found that treatment effects for ACR 20 response at 12 weeks were significantly lower in trials enrolling older *versus* younger patients (OR=0.48) and trials published more recently *versus* earlier (OR=0.49). Furthermore, treatment effects for ACR 20 at 12 weeks were significantly higher in trials with longer *versus* shorter psoriasis disease durations (OR=2.94). At 24 weeks, trials with longer *versus* shorter PsA duration showed significantly higher treatment effects for ACR 20 response (OR=1.88) (Table III).

In a sensitivity analysis considering only anti-TNF treatments, the meta-regression results were similar to the main analysis, but there was no longer statistically significant results for psoriasis disease duration for ACR 20 response at 12 weeks and for PsA disease duration for ACR 20 response at 24 weeks. However, treatment effects for ACR 20 response at 12 weeks were significant for trials with higher *versus* lower proportions of prior anti-TNF use (OR=0.46) in this sensitivity analysis.

ACR 50

Exploratory analyses suggested that proportions of males, disease duration, swollen joint counts, baseline disease activity score (DAS), prior anti-TNF use, and year of publication are associated with treatment effects for ACR 50 response (see Appendix 4 and 5). Meta-regression analyses to estimate the strength of these associations showed treatment effects at 12 weeks that were significantly greater in trials with a larger *versus* smaller proportion of males (OR=2.27), but significantly smaller in trials with higher *versus* lower proportions of prior anti-TNF use (OR=0.28) and in trials published more recently *versus* earlier (OR=0.37) (Table III). A similar association between treatment effects and year of publication was observed when looking at 24-week effects (Table III), but the statistical significance disappeared in the sensitivity analyses considering only trials of anti-TNF treatments (see Appendix 6).

PASI 75

The exploratory analyses suggested that proportion of males, tender and swollen joint counts, prior anti-TNF use, and Caucasian patients were associated with treatment effects for PASI 75 (see Appendix 7 and 8).

In meta-regression, we found that treatment effects for PASI 75 were significantly higher in trials with higher *versus* lower proportions of male patients (OR=2.56 at 24 weeks), and in trials

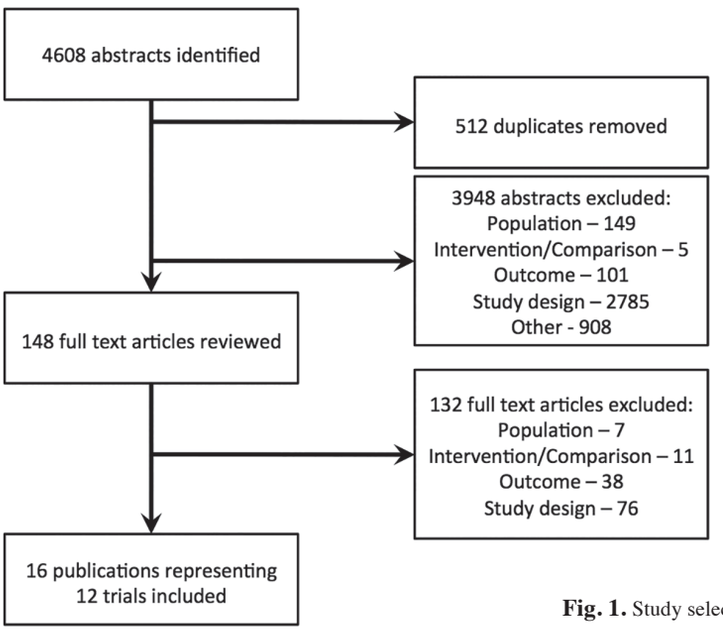

Fig. 1. Study selection flowchart

with patients with higher *versus* lower swollen joint counts and higher *versus* lower tender joint counts (OR=8.33 at 12 weeks; OR=14.44 at 24 weeks) (Table III). Trials with a high *versus* low proportion of prior anti-TNF use showed significantly smaller treatment effects (OR=0.41 at 24 weeks) (Table III). Trends were comparable in the sensitivity analyses considering the subset of trials assessing anti-TNF treatments in the meta-regression; however, trials with a high *versus* low proportion of Caucasian patients showed significantly smaller treatment effects (OR=0.21 at 12 weeks). Swollen joint count, tender joint count, and sex were no longer significantly associated with treatment effects at 24 weeks.

SF-36 PCS

The exploratory analyses suggested that age, disease duration, baseline DAS scores, and year of publication were associated with treatment effects for SF-36 PCS scores (see Appendix 9 and 10). In meta-regression, we found that treatment effects for SF-36 PCS scores at 24 weeks were significantly higher in trials with patients with a longer *versus* shorter psoriasis disease duration (OR=2.95) and longer *versus* shorter PsA disease duration (OR=4.76), and in trials published in an earlier *versus* later year (OR=4.19) (Table IV). In the meta-regression analysis considering only the subset of trials assessing anti-TNF treatments, results were generally comparable; however, treatment effects for SF-36 PCS scores at 24 weeks were now significantly higher in trials with patients with a high *versus* low baseline DAS (OR=2.00).

SF-36 MCS

The exploratory analyses suggested that age and proportion of Caucasian patients were associated with treatment effects for SF-36 MCS scores (see Supplementary Figure 55, Appendix 9). However, in the meta-regression analysis, there were no significant associations observed (Table IV).

Discussion

This study was conducted to explore effect modification of treatment effects on biologics for PsA. Using a systematic review and meta-regression, we demonstrated that systematic differences in trial and patient characteristics may be helpful in explaining some of the differences in response to biologics *versus* placebo across different PsA trials. Several factors were assessed for their impact on the effect of biologics *versus* placebo on both efficacy and quality of life outcomes, and the found trends were generally consistent across the investigated outcomes. Demographic and disease characteristics known to be surrogate markers for disease severity were positively correlated with increased therapeutic benefit from biologics, perhaps due to having more room for improvement, and later publication dates were found to negatively impact the estimated efficacy of biologics *versus* placebo.

Significant associations between demographic risk factors, *i.e.* age and sex, and efficacy outcomes were evident in our analysis. In particular, treatment effects for ACR 20 tended to be lower in trials enrolling older patients, and treatment effects for ACR 50 and PASI 75 tended to be lower in trials enrolling a lower proportion of male patients. With respect to age, previous studies have shown that patients with a late onset of psoriasis have a milder form of the disease, and patients that have an onset after 50 years of age will have a less severe form of the disease (41, 42). Furthermore, it may be the case that older patients may have more advanced disease and may have been on previous treatments leading to lower response. With respect to sex, many studies have suggested that hormones influence the pathogenesis of the PsA. For instance, some studies have shown the potential protective effects of estrogen against the development of PsA (38-40), and the risk of PsA being higher in men with psoriasis compared to women (40).

Significant associations between PsA disease characteristics and efficacy and quality of life outcomes were also observed in our analysis. For instance, trials with longer psoriasis and PsA disease durations tended to have higher ACR 20 treatment effects, and higher physical quality of life scores. Furthermore, trials with high tender and swollen joint counts tended to have higher treatment effects for PASI 75, and trials with low prior anti-TNF use tended to have higher treatment effects for ACR 50 and PASI 75. These findings exemplify the reality that disease characteristics known to be surrogate markers for disease severity are positively correlated with increased therapeutic benefit from biologics, and are likely due to having more room for improvement. Publication year was shown to be negatively associated with treatment effect. Specifically, trials with later study year

Table III. Estimated covariate effect on ACR 20, ACR 50 and PASI 75: fixed effects meta-regression.

Covariate	ACR 20		ACR 50		PASI 75	
	12 weeks	24 weeks	12 weeks	24 weeks	12 weeks	24 weeks
Older age *vs*. younger	**0.48 (0.28, 0.79)**	0.84 (0.51, 1.36)	-	-	-	-
High % male *vs*. low	-	-	**2.27 (1.06, 4.81)**	1.46 (0.84, 2.56)	-	**2.56 (1.23, 5.37)**
High % Caucasian *vs*. low	-	-	-	-	0.46 (0.11, 1.55)	-
Longer psoriasis duration vs. shorter (years)	**2.94 (1.02, 8.00)**	1.34 (0.00, 314.19)	-	1.14 (0.00, 292.95)	-	-
Longer PsA duration *vs*. shorter (years)	1.45 (0.74, 2.69)	**1.88 (1.13, 3.25)**	1.34 (0.00, 314.19)	0.84 (0.00, 292.95)	-	-
High swollen joint count *vs*. low	-	-	1.21 (0.00, 292.95)	1.58 (0.85, 2.97)	**8.33 (2.92, 25.28)**	**14.44 (4.18, 53.52)**
High tender joint count *vs*. low	-	-	-	-	**8.33 (2.92, 25.28)**	**14.44 (4.18, 53.52)**
High % steroid use *vs*.low	-	-	-	-	-	-
High % methotrexate use *vs*. low	-	-	-	-	-	-
High prior anti-TNF use *vs*. low	0.66 (0.43, 1.03)	0.82 (0.54, 1.23)	**0.28 (0.12, 0.63)**	-	-	**0.41 (0.20, 0.88)**
High baseline DAS *vs*. low	-	-	-	0.89 (0.50, 1.55)	-	-
Later study year *vs*. early	**0.49 (0.30, 0.79)**	0.66 (0.38, 1.16)	**0.37 (0.17, 0.76)**	**0.44 (0.21, 0.92)**	-	-

Values are represented as odds ratio (95% credible interval). All bolded values are statistically meaningful at the 0.05 significance level. Analyses were performed using dichotomised versions of continuous measures (dichotomised at the median). Direction of values: Values above 1.00 indicate an increase in the treatment effect due to the selected covariate; values below 1.00 indicate a decrease in the treatment effect due to the selected covariate.

tended to have lower treatment effects for ACR 20, ACR 50, and SF-36 PCS. This appears to be a counter-intuitive finding, as more recent trials studying newer treatments may be thought to be more effective than older treatments. However, this anomaly may be due to a previously reported bias known as eligibility creep (43). Due to the improvements in treatments over time, newer trials may have less strict eligibility criteria allowing for inclusion of patients with a less severe baseline disease state, thus minimising opportunity for improvement. This phenomenon has also been observed in trials assessing biologics for rheumatoid arthritis (44).

The strength of our study is its use of network meta-regression, which helps disentangle the contribution of the potential effect modifiers on observed treatment effects. The meta-regression showed that some of these investigated characteristics could be responsible for some of the observed differences. Additionally, our study assessed a comprehensive set of clinical and quality of life outcomes that are meaningful to both clinicians and patients. By identifying effect modifiers of these outcomes, our study could aid in future study planning for PsA.

However, despite comprehensive analyses that were undertaken, the sparse existing evidence base limited our study. It would have been ideal to assess each individual treatment as a separate node within the network meta-regression, but this was not feasible due to the scarce data in the network. This was addressed by grouping treatments (as placebo or no treatment, anti-TNF therapies, and non-anti-TNF therapies). This approach assumes that the covariate effects are similar for all treatments; however, it is not possible to make conclusions about the covariate effects on individual treatment effects because the

Table IV. Estimated covariate effect on SF-36 PCS and SF-36 MCS: fixed effects meta-regression.

Covariate	SF-36 PCS		SF-36 MCS	
	12 weeks	24 weeks	12 weeks	24 weeks
Older age vs. younger	-1.36 (-3.15, 0.45)	-	-1.84 (-3.82, 0.15)	-1.08 (-2.70, 0.56)
High % male *vs*. low	-	-	-	-
High % Caucasian *vs*. low	-	-	1.51 (-0.66, 3.64)	-
Longer psoriasis duration *vs*. shorter (years)	-	**2.95 (1.62, 4.29)**	-	-
Longer PsA duration *vs*. shorter (years)	-	**4.76 (3.50, 6.00)**	-	-
High swollen joint count *vs*. low	-	-	-	-
High tender joint count *vs*. low	-	-	-	-
High % steroid use *vs*. low	-	-	-	-
High % methotrexate use *vs*. low	-	-	-	-
High prior anti-TNF use *vs*. low	-	-	-	-
High baseline DAS28 *vs*. low	-	-0.06 (-1.39, 1.26)	-	-
Later study year *vs*. early	-	**-4.19 (-5.36, -3.01)**	-	-

Values are represented as odds ratio (95% credible interval). All bolded values are statistically meaningful at the 0.05 significance level. Analyses were performed using dichotomised versions of continuous measures (dichotomised at the median). Direction of values: Positive values indicate an increase in the treatment effect due to the selected covariate; negative values indicate a decrease in the treatment effect due to the selected covariate.

treatment classes were grouped together. Furthermore, it should be recognised that the low numbers of trials in each analysis might compromise the stability of the results obtained with the meta-regression. Another important limitation is that results obtained from the meta-regression provide insight into what drives trial success and thus extrapolating these results to individuals should be done with utmost care. Finally, no one variable was found to be strongly related to publication year, thus limiting the conclusions on what actions should be taken to minimise the bias caused by eligibility creep.

These analyses explain treatment effects of biologics on efficacy and quality of life outcomes. Accounting for these factors in future real world studies may be important to ensure that the best evidence is used for biologic coverage and treatment decision-making.

Conclusion

Our analyses demonstrated that systematic differences in trial and patient characteristics may explain some of the differences in response to biologics *versus* placebo across different psoriatic arthritis trials. Demographic and disease characteristics known to be surrogate markers for disease severity were positively correlated with increased therapeutic benefit from biologics. Accounting for these factors in future real world studies will likely be important.

References

1. GOLDENSTEIN-SCHAINBERG C, FAVARATO MH, RANZA R: Current and relevant concepts in psoriatic arthritis. *Rev Bras Reumatol* 2012; 52: 98-106.
2. MEASE P: A short history of biological therapy for psoriatic arthritis. *Clin Exp Rheumatol* 2015; 33: S104-8.
3. MORTEZAVI M, THIELE R, RITCHLIN C: The joint in psoriatic arthritis. *Clin Exp Rheumatol* 2015; 33: S20-5.
4. GLADMAN DD, STAFFORD-BRADY F, CHANG CH, LEWANDOWSKI K, RUSSELL ML: Longitudinal study of clinical and radiological progression in psoriatic arthritis. *J Rheumatol* 1990; 17: 809-12.
5. MCHUGH NJ, BALACHRISHNAN C, JONES SM: Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology* (Oxford) 2003; 42: 778-83.
6. CASO F, COSTA L, DEL PUENTE A *et al*.: Pharmacological treatment of spondyloarthritis: exploring the effectiveness of non-steroidal anti-inflammatory drugs, traditional disease-modifying antirheumatic drugs and biological therapies. *Ther Adv Chronic Dis* 2015; 6: 328-38.
7. GOSSEC L, SMOLEN JS: Treatment of psoriatic arthritis: management recommendations. *Clin Exp Rheumatol* 2015; 33: S73-7.
8. KAVANAUGH A, KRUEGER GG, BEUTLER A *et al*.: Infliximab maintains a high degree of clinical response in patients with active psoriatic arthritis through 1 year of treatment: results from the IMPACT 2 trial. *Ann Rheum Dis* 2007; 66: 498-505.
9. KAVANAUGH A, MCINNES I, MEASE P *et al*.: Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60: 976-86.
10. MEASE PJ, GLADMAN DD, RITCHLIN CT *et al*.: Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3279-89.
11. MEASE PJ, KIVITZ AJ, BURCH FX *et al*.: Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; 50: 2264-72.
12. CASO F, DEL PUENTE A, PELUSO R *et al*.: Emerging drugs for psoriatic arthritis. *Expert Opin Emerg Drugs* 2016; 21: 69-79.
13. HIGGINS J, GREEN S: Cochrane Handbook for Systematic Reviews of Interventions, Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. Available from www.cochrane-handbook.org.
14. FELSON DT, ANDERSON JJ, BOERS M *et al*.: American college of rheumatology preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995; 38: 727-35.
15. BERTH-JONES J, GROTZINGER K, RAINVILLE C *et al*.: A study examining inter- and intrarater reliability of three scales for measuring severity of psoriasis: Psoriasis Area and Severity Index, Physician's Global Assessment and Lattice System Physician's Global Assessment. *Br J Dermatol* 2006; 155: 707-13.
16. FARIVAR S, CUNNINGHAM W, HAYS R: Correlated physical and mental health summary scores for the SF-36 and SF-12 Health Survey, V.1. *Health Qual Life Outcomes* 2007; 5: 54.
17. HIGGINS JP, ALTMAN DG, GOTZSCHE PC *et al*.: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
18. THOMPSON SG, HIGGINS JP: How should meta-regression analyses be undertaken and interpreted? *Stat Med* 2002; 21: 1559-73.
19. JANSEN JP, FLEURENCE R, DEVINE B *et al*.: Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011; 14: 417-28.
20. LU G, ADES AE: Assessing evidence inconsistency in mixed treatment comparisons. *J Am Stat Assoc* 2006; 101: 447-59.
21. MILLS EJ, IOANNIDIS JP, THORLUND K, SCHÜNEMANN HJ, PUHAN MA, GUYATT GH: How to use an article reporting a multiple treatment comparison meta-analysis. *JAMA* 2012; 308: 1246-53.
22. LU G, ADES AE: Combination of direct and indirect evidence in mixed treatment comparisons. *Stat Med* 2004; 23: 3105-24.
23. SPIEGELHALTER D, THOMAS A, BEST N, LUNN D: WinBUGS user manual version 1.4. 2003. Available from http://www.mrc-bsu.cam.ac.uk/wp-content/uploads/manual14.pdf.
24. LUNN D, SPIEGELHALTER D, THOMAS A, BEST N: The BUGS project: Evolution, critique and future directions. *Stat Med* 2009; 28: 3049-67.
25. GELMAN A, RUBIN DB: Inference from Iterative Simulation Using Multiple Sequences. *Statist Sci* 1992; 7: 457-72.
26. ANTONI CE, KAVANAUGH A, KIRKHAM B *et al*.: Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: Results from the Infliximab Multinational Psoriatic Arthritis Controlled Trial (IMPACT). *Arthritis Rheum* 2005; 52: 1227-36.
27. ANTONI C, KRUEGER GG, DE VLAM K *et al*.: Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005; 64: 1150-7.
28. GENOVESE MC, MEASE PJ, THOMSON GT *et al*.: Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. [Published erratum appears in *J Rheumatol* 2007; 34: 1439]. *J Rheumatol* 2007; 34: 1040-50.
29. MCINNES IB, KAVANAUGH A, GOTTLIEB AB *et al*.: Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; 382: 780-9.
30. MCINNES IB, SIEPER J, BRAUN J *et al*.: Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: A 24-week, randomised, double-blind, placebo-controlled, phase ii proof-of-concept trial. *Ann Rheum Dis* 2014; 73: 349-56.
31. MEASE PJ, FLEISCHMANN R, DEODHAR AA *et al*.: Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73: 48-55.
32. MEASE PJ, GOFFE BS, METZ J, VANDERSTOEP A, FINCK B, BURGE DJ: Etanercept in the treatment of psoriatic arthritis and psoriasis: A randomised trial. *Lancet* 2000; 356: 385-90.
33. RITCHLIN C, RAHMAN P, KAVANAUGH A *et al*.: Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month

and 1-year results of the phase 3, multicentre, double-blind, placebo controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014; 73: 990-9.

34. MEASE P, GENOVESE MC, GLADSTEIN G *et al*.: Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum* 2011; 63: 939-48.
35. HENSELER T, CHRISTOPHERS E: Psoriasis of early and late onset: characterization of two types of psoriasis vulgaris. *J Am Acad Dermatol* 1985; 13: 450-6.
36. LANGLEY RG, KRUEGER GG, GRIFFITHS CE: Psoriasis: epidemiology, clinical features, and quality of life. *Ann Rheum Dis* 2005; 64: ii18-23; discussion ii4-5.
37. THUMBOO J, URAMOTO K, SHBEEB MI *et al*.: Risk factors for the development of psoriatic arthritis: a population based nested case control study. *J Rheumatol* 2002; 29: 757-62.
38. MCHUGH NJ, LAURENT MR: The effect of pregnancy on the onset of psoriatic arthritis. *Br J Rheumatol* 1989; 28: 50-2.
39. OSTENSEN M: Pregnancy in psoriatic arthritis. *Scand J Rheumatol* 1988; 17: 67-70.
40. WILSON FC, ICEN M, CROWSON CS, MCEVOY MT, GABRIEL SE, KREMERS HM: Incidence and clinical predictors of psoriatic arthritis in patients with psoriasis: a population-based study. *Arthritis Rheum* 2009; 61: 233-9.
41. KAVANAUGH A, MCINNES IB, KRUEGER GG *et al*.: Patient-reported outcomes and the association with clinical response in patients with active psoriatic arthritis treated with golimumab: findings through 2 years of a phase III, multicenter, randomized, double-blind, placebo-controlled trial. *Arthritis Care Res* (Hoboken) 2013; 65: 1666-73.
42. MEASE PJ, WOOLLEY JM, SINGH A, TSUJI W, DUNN M, CHIOU CF: Patient-reported outcomes in a randomized trial of etanercept in psoriatic arthritis. *J Rheumatol* 2010; 37: 1221-7.
43. HICK J, FELDMAN SR: Eligibility creep: a cause for placebo group improvement in controlled trials of psoriasis treatments. *J Am Acad Dermatol* 2007; 57: 972-6.
44. KANTERS S, DRUYTS E, MILLS EJ, THORLUND K: What drives the comparative effectiveness of biologics vs. methotrexate in rheumatoid arthritis? Meta-regression and graphical inspection of suspected clinical factors. *Rheumatology* (Oxford) 2014; 53: 1264-73.
45. GLADMAN D, FLEISCHMANN R, COTEUR G, WOLTERING F, MEASE PJ: Effect of certolizumab pegol on multiple facets of psoriatic arthritis as reported by patients: 24-week patient-reported outcome results of a phase III, multicenter study. *Arthritis Care Res* (Hoboken) 2014; 66: 1085-92.