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Original article

What drives the comparative effectiveness of biologics *vs* methotrexate in rheumatoid arthritis? Meta-regression and graphical inspection of suspected clinical factors

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Abstract

Objective. The aim of this study was to explore which clinical factors and patient characteristics are associated with the magnitude of comparative efficacy between biologics *vs* MTX in RA patients with inadequate response to MTX.

Methods. We included randomized controlled trials assessing the efficacy of a biologic plus MTX *vs* MTX alone. We examined several clinical factors and patient characteristics potentially associated with magnitude of response, measured as ACR20 (20% improvement in ACR criteria) and ACR50 (16–26 weeks). We employed meta-regression for formal estimates and statistical significance of effect modification. We produced regression and forest plots to further inspect potential associations.

Results. For ACR50, a 1-year increment on the average patient disease duration was statistically significantly associated with a 16% relative increase in the pooled odds ratio (OR) estimate ($P = 0.003$). A 1-year increment in patient age and a 1 mg/week increment in MTX dose were marginally statistically significantly associated with a 9% ($P = 0.056$) and 22% ($P = 0.092$) relative increase in the OR. For ACR20, the average number of swollen and tender joints was marginally statistically associated with a 3% relative decrease. The associations for age and MTX dose appeared to be partly driven by significant negative associations between these two factors and the control group response.

Conclusion. Our analyses identified key variables associated with the magnitude of comparative effects for ACR outcomes. Our findings provide valuable insights for future trial designs and systematic reviews as well as decision-making and clinical practice.

Key words: rheumatoid arthritis, biologics, effect modifiers, indirect treatment comparison, meta-analysis, meta-regression, comparative efficacy.

CLINICAL SCIENCE

Introduction

RA is the cause of one the greatest disease-specific health care expenditures in North America and Europe [1, 2]. These expenditures are predominantly driven by the high costs associated with the use of biologic DMARDs (bDMARDs or biologics). Therefore regulatory agencies have great interest in ensuring that decisions to approve and fund these biologics are founded on rigorously conducted analyses of comparative efficacy that utilize the best available evidence. Further, as the diversity of patients expands, there is an increasing need to explore which patient groups are more likely to respond well to one treatment more than others.

Biologics are typically used after patients have failed one or more conventional DMARDs, such as MTX. Approximately 100 trials have been conducted to examine the efficacy of biologics among such patients, suggesting

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a strong evidence base [3, 4]. However, these trials cover various doses and durations of eight approved biologics as well as other not currently (August 2013) approved biologics. In addition, there are several important variations in the designs of these trials (e.g. the length of follow-up may differ from 14 to 52 weeks or patient disease duration may differ from a few years to >10 years). These issues of heterogeneity in trial patient populations create serious challenges in establishing comparative efficacy and safety across biologics because a key premise for synthesizing the evidence from multiple trials is that trial designs and populations are similar [5]. Simultaneously, the heterogeneous trial evidence base also offers opportunities for exploring the impact of several clinical factors on the comparative efficacy and safety of biologics. For example, previous meta-analytic studies have explored the association between treatment efficacy and factors like patient disease duration, recorded disease severity biomarkers (e.g. CRP) and backbone MTX dose [5–8]. However, as these studies are either based on older data sets, do not consider all potentially important clinical factors and/or combine trials of vastly different population groups, uncertainty still exists as to what clinical factors predict the likelihood of a good treatment outcome.

Patients with inadequate response to MTX are the RA patient population that is most well informed by randomized clinical trials and of key interest to decision-makers and practicing clinicians. Therefore, in this article we examine the potential effect modification associated with most suspected sources of heterogeneity in RA trials and meta-analytic studies on MTX inadequate responders. We examine effect modifications on comparative treatment effects as well as baseline risks and present our findings graphically, using regression plots and forest plots, and numerically, using meta-regression.

Methods

Materials

We assessed all randomized controlled trials (RCTs) previously identified as eligible in published systematic reviews and multiple treatment comparisons of biologics for RA [4]. These comprised a total of 64 RCTs investigating any one of the following biologics *vs* control: abatacept (Bristol-Myers Squibb, New York, NY, USA), adalimumab (Abbott Laboratories, North Chicago, IL, USA), certolizumab (UCB, Brussels, Belgium), etanercept (Pfizer, New York, NY, USA), golimumab (Johnson & Johnson, New Brunswick, NJ, USA), infliximab (Janssen Biotech, Horsham, PA, USA), rituximab (IDEC Pharmaceuticals, Weston, MA, USA) and tocilizumab (Hoffmann-La Roche, Basel, Switzerland). From this list we only included RCTs that (i) had an MTX control arm and gave MTX concomitantly with a biologic in the active intervention arm and (ii) reported a 20% improvement in ACR20 criteria and/or an ACR50 between 16 and 26 weeks. We excluded RCTs of patients with early RA (i.e. disease duration of ⩽3 years) and RCTs that included patients who were MTX naive or had previous experience with a biologic. We also excluded trials where only a subset of patients received MTX. Using these criteria, a total of 22 trials were eligible [9–30]. For each trial we recorded efficacy data on ACR20 and ACR50 at the last reported time point between 16 and 26 weeks. We recorded ACR70, but did not pursue any analyses for this outcome because the event rate for this outcome is very low, especially in the control group, where zero events are frequent. Finally, we recorded data on the following potentially important clinical and methodological factors: dropout proportion, dose of biologic, dose of MTX, proportion of females, age, number of tender joints, number of swollen joints, disease duration, HAQ score, DAS [i.e. the 28-joint DAS (DAS28) scale], number of previous DMARDs failed, proportion of patients on concomitant NSAIDs and proportion of patients on concomitant corticosteroids.

Data analysis

For ACR20, ACR50 and for each clinical or methodological variable we (i) produced a forest plot where trials were in ascending order by the average variable value across intervention arms, (ii) conducted a univariate meta-regression to estimate the association between the variable and the ACR outcome, and (iii) produced a l'Abbé meta-regression plot. We only performed these analyses for covariates that were reported in at least 10 trials, since a minimum of 10 trials is typically required for reliable estimation of a covariate association within meta-regression. Meta-regression was performed with (i) odds ratios (ORs) or log ORs as the dependent variable and (ii) control (MTX) group responses as the dependent variable. Meta-regression on control group responses was carried out to assess the extent to which the association between covariates and treatment effect modification depended on the response in the control group. For the meta-regression on ORs we report the estimated effect modification as a relative (percentage) increase per variable unit increment (e.g. relative change for 1-year increment in disease duration), its 95% CI and the associated *P*-value. For example, an effect modification of 1.20 would correspond to a 20% relative increase in the OR for each covariate unit (e.g. year) increase. For each meta-regression on MTX-group proportions, we report the estimated effect modification as an absolute increase in proportion of ACR responders per variable unit increment, its 95% CI and the associated *P*-value. Furthermore, we report predicted ORs based on a spectrum of key values for the variables where significant or important effect modifications were detected.

We used imputation on two variables, MTX dose and DAS. These imputed variables were used throughout the analyses in conjunction with the non-imputed variables. For trials where the average MTX dose was not reported (i.e. missing), we imputed the median of average doses across other trials with the same allowed dose range. For example, the trial by Kay *et al.* [14] did not report average doses, but had an allowed MTX dose range of ⩾10 mg/week. The median average dose among

other trials with the same specification of allowed dose was 15 mg/week, so we imputed this value for Kay *et al*. For trials where the average baseline DAS score was not reported, we approximated this by using an online DAS28 calculator and the extracted results for the mean/median number of swollen and tender joints, CRP or ESR, as well as patient's global assessment (physician's assessment if patient's assessment was not reported) [31]. In other words, when the DAS score was not reported, trial-level average values of the components used to calculate the DAS score for individuals were used to estimate the average trial-level DAS score.

Results

Covariate data were reported in all trials for dropout proportion, proportion of females, age and disease duration [9–30]. All but one trial reported on the number of tender joints and swollen joints [9–29], 18 trials reported the average MTX dose [9, 11–13, 15–22, 24–29], 18 trials reported HAQ [9, 12–22, 24–29], 15 trials reported DAS [9–16, 19–21, 23–26] and 10 trials reported concomitant use of corticosteroids [11, 13, 16, 19, 20, 22, 24, 25, 28, 29]. Only eight trials reported the number of previous DMARDs failed and only four trials reported concomitant use of NSAIDs. Therefore the number of previous DMARDS failed and concomitant use of NSAIDs were not included in the analysis. Table 1 provides an overview of the covariate values for each arm used in the meta-regression.

The results of the meta-regression for both ORs and control group proportions are presented in Table 2. For ACR50, the regression analyses of ORs yielded a positive significant association for disease duration ($P = 0.003$). Here the estimated relative increase in the OR was 1.16 (95% CI 1.06, 1.27) per 1-year increment. A marginally significant association was also observed for MTX dose (reported data only, $P = 0.056$) and for age ($P = 0.092$). The estimated relative increase in the OR associated with a 1 mg/week increment in MTX dose was 1.22 (95% CI 1.00, 1.47) and the estimated relative increase in the OR associated with a 1-year increment in age was 1.09 (95% CI 0.99, 1.19). However, when using imputed data for the three trials with missing average MTX doses, the association between MTX dosage and magnitude of OR dissipated and was no longer marginally significant ($P = 0.196 > 0.1$). Inspection of the corresponding regression plots and forest plots further suggests that the associations identified in the meta-regression hold true (see Figs. 1 and 2). For ACR20, the mean number of tender joints and swollen joints had marginally significant associations ($P = 0.077$ and $P = 0.093$, respectively). For tender joints, a single joint increment was associated with a relative decrease in the OR of 0.97 (95% CI 0.93, 1.00). For swollen joints, a single joint increment was associated with a relative decrease in the OR of 0.96 (95% CI 0.91, 1.00). The estimated magnitudes of associations between all variables and the meta-analysis ORs are presented in Table 2. Moreover, Table 3 presents predicted ORs for ACR50 based on a pertinent spectrum of values for the variables: age, disease duration and MTX dose (note that the results based on MTX data with imputed doses were used, as these provide a more complete data set for prediction).

For ACR50, the regression analyses of control group proportions yielded significant associations for age ($P = 0.031$), percentage of patients on corticosteroids ($P = 0.028$) and MTX dose (including imputed data, $P = 0.039$). However, MTX dose using complete data only was not significant. For ACR20, both age and percentage of patients on corticosteroids yielded marginally significant associations ($P = 0.056$ and $P = 0.053$, respectively). The estimated magnitudes of association between all variables and the control group proportions are presented in Table 2.

For ORs, the degree of heterogeneity appeared only moderate after (visually) discounting the variation caused by the significant variables. For proportions, however, the degree of heterogeneity still appeared substantial. For this reason, some large but non-significant estimates of association under the proportion regression may still be important (e.g. disease duration). Forest plots and l'Abbé plots for all considered variables, for ACR20, ACR50 and ACR70, and for comparative ORs and control group proportions are available as supplementary data at *Rheumatology* Online.

Discussion

We have examined associations between commonly reported variables and the magnitude of estimated effects in RA clinical trials. These associations concern both comparative efficacies between biologics and MTX and response rates in the control group (i.e. MTX group). Our analyses only identified clear associations among a few of the variables that were previously suspected to yield important associations [5, 6]. Nonetheless, our analyses showed a clear effect modification from age, a previously unrecognized variable.

Mean disease duration and age in patients enrolled in RA trials appear to have strong associations with the magnitude of the estimated comparative efficacy when ACR50 is the outcome of interest. The effect of age may be largely due to its effect on the control group response. The effect of MTX dose was estimated using both complete data and imputed data. MTX dose was only a significant effect modifier of the comparative effects of biologics with the non-imputed data, whereas the association between MTX dose and control group response was significant with imputed data only. This suggests some association for MTX dose, but the strength of the association remains uncertain. Lastly, the percentage of corticosteroids was associated with the control group response for ACR20 and ACR50, but did not affect the OR.

Our study has a number of strengths and limitations. It is the most comprehensive examination of important covariates in RA patients with previous inadequate response to MTX. Our analysis is also based on a comprehensive and complete search, including detailed evaluation of bibliographies from many published systematic reviews. Our examination employed both formal statistical testing

Table 1 Overview of regression covariate values for each intervention group in the included trials

Trial	Arm	*n*	Age, years	On CSTs, %	DAS	Disease duration, years	Dropouts, %	Females, %	HAQ	MTX dose, mg/week	Tender joints, *n*	Swollen joints, *n*
Schiff *et al.* (2008) [24]	Placebo	110	48.4	70.0	6.8	8.4	3	87.3	1.8	16.6	30.3	20.1
	ABA 10 mg/kg	156	49.0	75.6	6.9	7.9	6	83.3	1.8	16.5	31.6	21.3
	INF 3 mg/kg	165	49.1	71.5	6.8	7.3	8	82.4	1.8	16.3	31.7	20.3
Kremer *et al.* (2006) [20]	Placebo	219	50.4	68.5	6.4	8.9	26	81.7	1.7	15.7	32.3	22.1
	ABA 10 mg/kg	433	51.5	72.1	6.4	8.5	11	77.8	1.7	16.1	31.0	21.4
Kremer *et al.* (2003) [21]	Placebo	119	54.7	NR	5.5	8.9	34	66.0	1.0	15.8	29.2	21.8
	ABA 2 mg/kg	105	54.4	NR	5.4	9.7	22	63.0	1.0	15.8	28.2	20.2
	ABA 10 mg/kg	115	55.8	NR	5.5	9.7	14	75.0	1.0	15.0	30.8	21.3
Kim *et al.* (2007) [18]	Placebo	63	49.8	NR	5.4[a]	6.9	6	85.7	1.3	16.3	20.3	12.8
	ADA 40 mg	65	48.5	NR	5.2[a]	6.8	9	95.4	1.4	16.6	19.2	12.2
Keystone *et al.* (2004) [17]	Placebo	200	56.1	NR	5.5[a]	10.9	8	73.0	1.5	16.7	28.1	19.0
	ADA 20 mg	212	57.3	NR	5.4[a]	8.8	4	75.5	1.4	16.3	27.9	19.6
	ADA 40 mg	207	56.1	NR	5.5[a]	9.4	4	76.3	1.5	16.7	27.3	19.3
Weinblatt *et al.* (2003) [27]	Placebo	62	56.0	NR	5.7[a]	11.1	7	82.3	1.6	16.5	28.7	16.9
	ADA 20 mg	69	53.5	NR	5.8[a]	13.1	7	75.4	1.5	16.9	28.5	17.6
	ADA 40 mg	67	57.2	NR	5.6[a]	12.2	7	74.6	1.6	16.4	28.0	17.3
	ADA 80 mg	73	55.5	NR	5.9	12.8	7	75.3	1.6	17.2	30.3	17.0
Choy *et al.* (2012) [9]	Placebo	121	55.6	NR	6.3	9.9	46	66.1	1.5	16.6	31.0	22.2
	CER 400 mg	126	53.0	NR	6.2	9.4	22	72.2	1.4	16.9	29.0	22.8
Keystone *et al.* (2008) [15]	Placebo	199	52.2	NR	7.0	6.2	8	83.9	1.7	13.4	29.8	21.2
	CER 200 mg	393	51.4	NR	6.9	6.1	4	82.4	1.7	13.6	30.8	21.7
	CER 400 mg	390	52.4	NR	6.9	6.2	4	83.6	1.7	13.6	31.1	21.5
Weinblatt *et al.* (1999) [28]	Placebo	30	53.0	70.0	5.0[a]	13.0	20	73.0	1.5	18.0	28.0	17.0
	ETA 25 mg	59	48.0	53.0	4.9[a]	13.0	3	90.0	1.5	19.0	28.0	20.0
Kay *et al.* (2008) [14]	Placebo	35	52.0	NR	5.3	5.6	17	74.3	1.3	15.5[a]	22.0	13.0
	GOL 50 mg/4 weeks	35	57.0	NR	5.3	8.2	11	85.7	1.7	15.5[a]	28.0	14.0
	GOL 50 mg/2 weeks	34	48.0	NR	4.8	8.2	18	67.7	1.6	15.5[a]	28.0	14.0
	GOL 100 mg/4 weeks	34	57.5	NR	5.4	6.3	15	76.5	1.8	15.5[a]	32.0	20.0
	GOL 100 mg/2 weeks	34	53.5	NR	5.1	9.0	6	79.4	1.3	15.0	22.0	14.0
Keystone *et al.* (2009) [16]	Placebo	133	52.0	65.4	4.9	6.5	4	82.0	1.3	15.0	21.0	12.0
	GOL 50 mg	89	52.0	75.3	5.1	4.5	2	80.9	1.4	15.0	26.0	13.0
	GOL 100 mg	89	50.0	69.7	4.9	6.7	3	80.9	1.4	15.0	23.0	12.0
Tanaka *et al.* (2012) [26]	Placebo	88	51.1	NR	5.6	8.7	5	83.0	1.0	7.0[b]	13.2	11.4
	GOL 50 mg	86	50.4	NR	5.5	8.8	6	84.9	1.0	7.0[b]	13.1	11.8
	GOL 100 mg	87	50.0	NR	5.5	8.1	6	89.7	0.9	7.0[b]	12.9	11.5

(continued)

Table 1 Continued

Trial	Arm	*n*	Age, years	On CSTs, %	DAS	Disease duration, years	Dropouts, %	Females, %	HAQ	MTX dose, mg/week	Tender joints, *n*	Swollen joints, *n*
Westhovens *et al.* (2006) [29]	Placebo	363	52.0	59.0	4.2[a]	8.4	18	83.2	1.5	15.0	22.0	15.0
	INF 3 mg/kg	360	53.0	59.2	4.4[a]	7.8	13	80.0	1.5	15.0	22.0	15.0
	INF 10 mg/kg	361	52.0	59.1	4.4[a]	6.3	13	77.8	1.5	15.0	22.0	15.0
Zhang *et al.* (2006) [30]	Placebo	86	48.9	NR	5.9[a]	8.0	17	84.9	NR	—	NR	NR
	INF 3 mg/kg	87	47.9	NR	5.9[a]	7.1	10	85.1	NR	—	NR	NR
Maini *et al.* (1999) [22]	Placebo	88	51.0	64.0	5.0[a]	8.9	54	80.0	1.8	15.0	24.0	19.0
	INF 3 mg/8 weeks	86	56.0	63.0	5.2[a]	8.4	23	81.0	1.8	15.0	32.0	19.0
	INF 3 mg/4 weeks	86	51.0	53.0	5.0	7.2	17	77.0	1.8	15.0	31.0	20.0
	INF 10 mg/4 weeks	87	55.0	57.0	5.0	9.0	9	77.0	1.8	15.0	30.0	20.0
	INF 10 mg/8 weeks	81	52.0	65.0	5.1	8.7	20	73.0	1.5	15.0	35.0	23.0
Emery *et al.* (2010) [11]	Placebo	172	52.2	47.7	6.0	7.5	8	85.5	NR	16.6	30.2	20.9
	RIT 2 × 500 mg	168	51.9	47.9	5.8	7.1	4	79.6	NR	15.4	27.1	18.6
	RIT 2 × 1000 mg	172	51.3	39.4	5.9	6.5	4	81.2	NR	16.1	28.7	19.5
Emery *et al.* (2006) [12]	Placebo	122	51.1	NR	6.8	9.3	31	80.0	1.7	15.6	35.0	21.0
	RIT 2 × 500 mg	123	51.4	NR	6.8	11.1	6	83.0	1.8	16.0	33.0	22.0
	RIT 2 × 1000 mg	122	51.1	NR	6.7	10.8	8	80.0	1.7	14.9	32.0	22.0
Edwards *et al.* (2004) [10]	Placebo	40	54.0	NR	6.9	11.0	8	80.0	NR	14.0[a]	32.0	19.0
	RIT 1000 mg	40	54.0	NR	6.9	12.0	3	75.0	NR	14.0[a]	32.0	23.0
Kremer *et al.* (2011) [19]	Placebo	393	51.3	70.0	6.5	9.0	4	83.0	1.5	15.0	27.9	16.6
	TOC 4 mg/kg	399	51.4	69.0	6.5	9.4	7	84.0	1.5	15.4	27.9	17.0
	TOC 8 mg/kg	398	53.4	62.0	6.6	9.3	9	82.0	1.5	15.0	29.3	17.3
Smolen *et al.* (2008) [25]	Placebo	204	50.6	54.0	6.8	7.8	6	78.0	1.5	14.8	32.8	20.7
	TOC 4 mg/kg	213	51.4	55.0	6.8	7.4	12	88.0	1.6	14.7	33.2	20.0
	TOC 8 mg/kg	205	50.8	55.0	6.8	7.5	6	85.0	1.6	14.5	31.9	19.5
Maini *et al.* (2006) [23]	Placebo	48	50.9	NR	6.8	11.2	23	78.0	NR	15.5[a]	16.0	12.0
	TOC 4 mg/kg	52	50.2	NR	6.3	9.3	14	76.0	NR	15.5[a]	13.0	11.0
	TOC 8 mg/kg	49	50.1	NR	6.5	10.6	15	78.0	NR	15.5[a]	15.0	11.0
Genovese *et al.* (2008) [13]	Placebo	415	54.0	54.6	6.6	9.8	10	84.0	1.5	14.7	29.1	18.7
	TOC 8 mg/kg	805	53.0	51.2	6.7	9.8	7	81.0	1.5	15.0	30.1	19.7

CST: corticosteroid use; NR: not reported; ABA: abatacept; ADA: adalimumab; CER: certolizumab; ETN: etanercept; GOL: golimumab; INF: infliximab; RIT: rituximab; TOC: tocilizumab. [a]Imputed. [b]Excluded from meta-regression on MTX dose (considered an outlier).

Table 2 Meta-regression results

Variable	Unit of change	ACR20 Coefficient[a] (95% CI)	ACR20 *P*-value	ACR50 Coefficient[a] (95% CI)	ACR50 *P*-value
Odds ratio regression analyses					
Age	Years	1.03 (0.95, 1.12)	0.419	**1.09 (0.99, 1.19)**	**0.092**
Corticosteroid use	% of patients	0.98 (0.97, 1.00)	0.109	1.00 (0.96, 1.04)	0.942
DAS (crude)	Instrument unit	0.87 (0.70, 1.07)	0.212	0.96 (0.74, 1.25)	0.771
DAS (imputed)	Instrument unit	0.86 (0.72, 1.04)	0.132	0.95 (0.74, 1.21)	0.678
Disease duration	Years	1.07 (0.99, 1.16)	0.114	**1.16 (1.06, 1.27)**	**0.003**
Drop-outs	% of patients	0.99 (0.97, 1.02)	0.630	1.01 (0.99, 1.04)	0.285
Drop-outs (controls)	% of patients	1.00 (0.99, 1.01)	0.796	1.01 (0.99, 1.02)	0.219
Females	% of patients	1.01 (0.97, 1.04)	0.707	0.98 (0.94, 1.02)	0.363
HAQ	Instrument unit	0.74 (0.30, 1.85)	0.533	0.95 (0.33, 2.71)	0.928
MTX dose (crude)	mg/week	1.11 (0.95, 1.29)	0.200	**1.22 (1.00, 1.47)**	**0.056**
MTX dose (imputed)	mg/week	0.98 (0.91, 1.05)	0.554	1.06 (0.97, 1.15)	0.196
Tender joints	Count	**0.97 (0.93, 1.00)**	**0.077**	0.99 (0.95, 1.03)	0.561
Swollen joints	Count	**0.96 (0.91, 1.00)**	**0.093**	0.99 (0.93, 1.05)	0.777
Baseline proportion regression analyses					
Age	Years	**−1.68 (−3.29, −0.06)**	**0.056**	**−0.96 (−1.81, −0.11)**	**0.040**
Corticosteroid use	% of patients	**0.59 (0.09, 1.09)**	**0.053**	**0.43 (0.13, 0.74)**	**0.028**
DAS (crude)	Instrument unit	−0.10 (−5.27, 5.08)	0.972	0.78 (−1.67, 3.22)	0.544
DAS (imputed)	Instrument unit	0.14 (−4.10, 4.39)	0.948	0.92 (−1.27, 3.12)	0.419
Disease duration	Years	−0.61 (−2.43, 1.21)	0.520	−0.51 (−1.42, 0.40)	0.287
Dropouts	% of patients	0.03 (−0.41, 0.47)	0.897	−0.08 (−0.30, 0.14)	0.465
Dropouts (controls)	% of patients	−0.06 (−0.31, 0.20)	0.677	−0.08 (−0.20, 0.05)	0.250
Females	% of patients	0.20 (−0.53, 0.93)	0.598	0.22 (−0.15, 0.58)	0.259
HAQ	Instrument unit	3.42 (−26.6, 33.5)	0.827	7.18 (−7.88, 22.2)	0.366
MTX dose (crude)	mg/week	1.44 (−2.12, 5.01)	0.441	−0.32 (−2.03, 1.39)	0.721
MTX dose (imputed)	mg/week	−0.84 (−2.46, 0.78)	0.323	**−0.93 (−1.74, −0.11)**	**0.039**
Tender joints	Count	0.05 (−0.66, 0.76)	0.892	−0.12 (−0.48, 0.23)	0.499
Swollen joints	Count	−0.04 (−1.07, 0.99)	0.943	−0.23 (−0.73, 0.27)	0.381

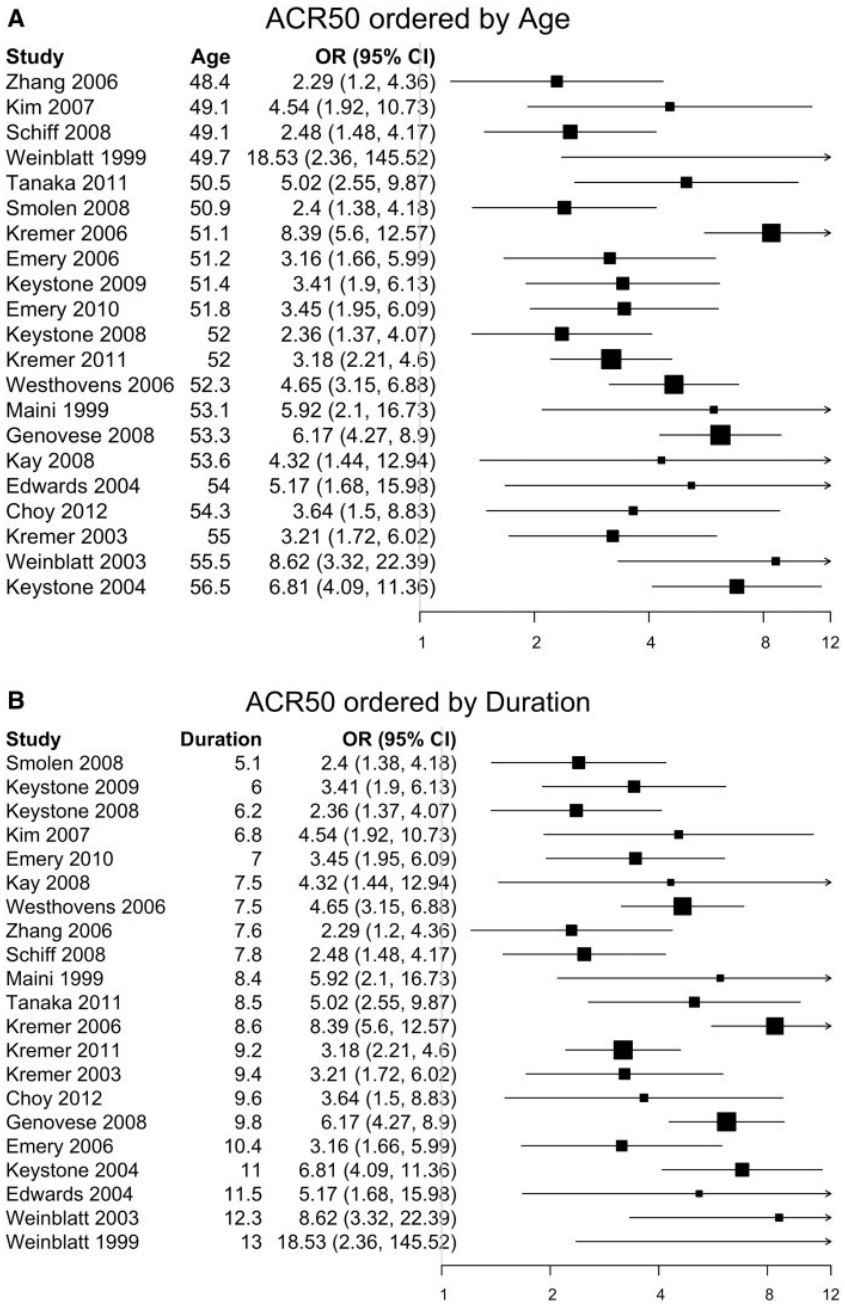
ACR20 and ACR50: 20% and 50% improvement on ACR criteria, respectively. All results in bold type are statistically significant ($P < 0.05$) or marginally statistically significant ($P < 0.10$). [a]Regression coefficient for the relative change for odds ratios and the absolute change for proportions.

(meta-regression) and elaborate graphical exploration using both regression (l'Abbé) plots and forest plots. Lastly, our analyses examined both associations between ORs (comparative efficacy) as well as control group responses. This approach allowed us to gauge the extent to which associations were driven by altered response in the control group.

For some covariates, data were missing. The percentage of patients on corticosteroids was the least frequently reported covariate, and thus the meta-regression may lack some validity. Baseline DAS score and MTX dose were both imputed using sensible approaches. However, it is possible that the imputation may have resulted in more conservative estimates of association. Lastly, there may be unmeasured confounders that bias the results of our analyses. For example, the worse outcomes associated with higher MTX dose may be due to confounding by indication, since most patients receiving higher doses of MTX could well have been patients with more severe disease activity and poor response to medications.

Our study findings may be applied to gauge the expected level of covariate effect modification and confounding in meta-analysis and multiple treatment comparisons. The estimated magnitudes of association can be directly applied to individual trials in meta-analyses and multiple treatment comparisons to gauge the expected degree of confounding away from the mean. For example, if an outlier trial has an average disease duration of 3 years above the average, then by our results, one would expect this trial to yield a $1.16^3 = 1.56$ times larger OR than trials with the average disease duration (across all trials). Our results also implied some previously unrecognized associations. First, age has typically not been a variable of concern under heterogeneity analysis. While this variable may exhibit some co-linearity with disease duration, the clear difference in association estimates strongly suggests that age should be considered as an individually important variable. Moreover, our analyses suggest that MTX dose is positively associated with the ACR50 OR and has little association with the ACR20 OR. This finding is in stark contrast to previous (but unproven)

FIG. 1 Forest plots of trial odds ratios for ACR50 where trials are ordered by (**A**) age and (**B**) disease duration



suspicions about large effect modifications occurring in trials using MTX doses <15 mg/week. Further insights are therefore needed on the effect of MTX dose. Yet, our analysis falls short in that the regression and graphical plots are limited to summary statistics. Future individual patient data analyses are needed to explore the extent to which MTX dose and other variables (e.g. disease duration) predict the likelihood of ACR responses or other efficacy outcomes.

In summary, our analyses have identified four key variables associated with the magnitude of reported comparative treatment effects on the ACR outcome in RA trials. In particular, attention should be paid to four variables—age, disease duration, corticosteroid use and MTX

FIG. 2 Meta-regression (l'Abbé) plots of log odds ratios (*y*-axis) against the underlying covariate value: age, disease duration, MTX dose (complete cases only) and MTX dose (complete and imputed data)

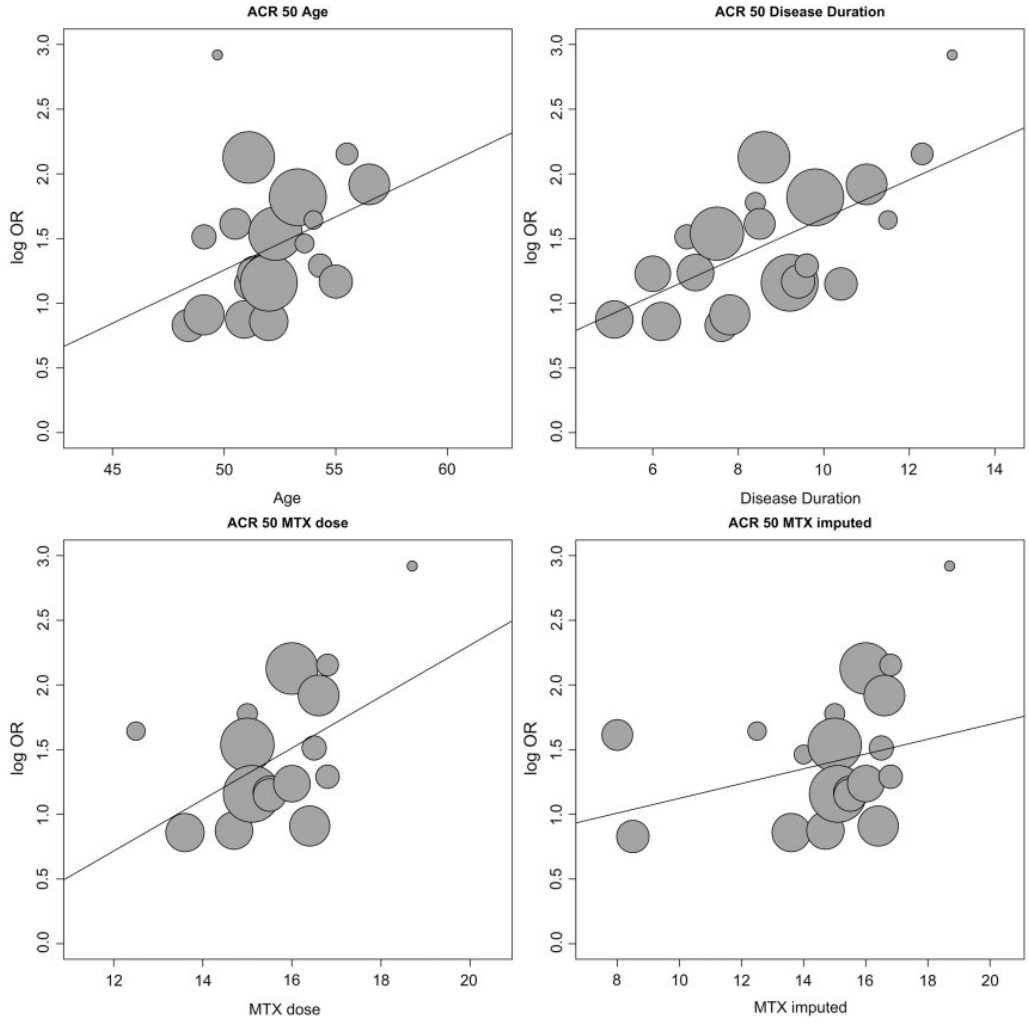


TABLE 3 Predicted ACR50 ORs based on a spectrum of common and pertinent values for the key variables

Age, years		Disease duration, years		MTX dose (imputed)	
Values of prediction	Predicted OR (95% CI)	Values of prediction	Predicted OR (95% CI)	Values of prediction	Predicted OR (95% CI)
48	14.5 (10.2, 18.9)	5	12.3 (8.2, 16.3)	10	15.2 (10.4, 20.0)
51	11.7 (9.5, 13.8)	7	11.2 (8.7, 13.7)	12.5	12.9 (10.0, 15.8)
52[a]	10.7 (8.9, 12.5)	8.5[a]	10.5 (8.5, 12.4)	15[a]	10.6 (8.7, 12.5)
53	9.8 (7.9, 11.6)	9	10.2 (8.3, 12.2)	16	9.7 (7.6, 11.7)
55	7.9 (4.9, 10.9)	10	9.7 (7.4, 12.1)	17	8.7 (6.2, 11.2)
57	5.9 (1.4, 10.5)	13	8.2 (3.5, 12.9)	18	7.8 (4.6, 11.0)

ACR50: 50% improvement in ACR criteria; OR: odds ratio. [a]Median sample value. First and last rows correspond to approximate minimum and maximum sample values, respectively.

dose—when exploring heterogeneity between ACR outcomes in RA trials. The magnitude and direction of confounding can be used to assess the extent to which some estimates of comparative effectiveness incur bias and to inform whether individual trials should be excluded from the analyses.

Rheumatology key messages

- The observed efficacy of biologics in RA clinical trials depends on patient population and treatment characteristics.
- Two prominent predictors of RA treatment efficacy are patient disease duration and administered MTX dose.
- The established effect modifiers should be considered in evidence synthesis (e.g. network meta-analysis) of biologics for RA.

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Supplementary data

Supplementary data are available at *Rheumatology* Online.

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