Efficacy of biologic agents in improving the Health Assessment Questionnaire (HAQ) score in established and early rheumatoid arthritis: a meta-analysis with indirect comparisons

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Abstract

Objective

The Health Assessment Questionnaire (HAQ) is a validated physical function measure. It is predictive for disability and mortality. The objective of this study was to determine the comparative efficacy of biologic agents in improving HAQ in patients with established RA who failed DMARDs or anti-TNF agents and in early RA (ERA).

Methods

We performed random effects meta-analyses of published randomised, placebo-controlled trials. Outcome was the mean difference in change in HAQ for biologic agents compared to controls (ΔHAQ_B-ΔHAQ_C). Indirect comparisons of the different biologic drugs were conducted using the Q-test based on analysis of variance. Meta-regression was performed using the method of moments.

Results

Twenty-eight trials were included: 19 with DMARD-failures; 4 with anti-TNF-failures and 5 ERA. The following biologics were represented: abatacept, adalimumab, certolizumab, etanercept, golimumab, infliximab, rituximab and tocilizumab. Efficacy of biologics at reducing HAQ was significantly different based on prior treatment ($p=0.001$). In RA patients with DMARD failures, ΔHAQ_B-ΔHAQ_C was -0.22; 95%CI: -0.24, -0.20 ($I^2=55\%$). Infliximab, abatacept and tocilizumab had lower ΔHAQ_B-ΔHAQ_C compared to other biologics ($p<0.02$). In anti-TNF-failures, ΔHAQ_B-ΔHAQ_C was -0.36; 95%CI: -0.42, -0.30 ($I^2=0\%$). In ERA, methotrexate-naïve trials, ΔHAQ_B-ΔHAQ_C was -0.19; 95% CI: -0.26, -0.13 ($I^2=0\%$). There were no significant differences in the efficacy of different biologics for anti-TNF failures and ERA.

Conclusions

Biologic agents were efficacious at lowering HAQ in RA. Differences between agents in RA with DMARD failures were less than the minimally clinically important difference for HAQ; therefore, the clinical significance of these differences is unclear.

Key words

rheumatoid arthritis, physical function, meta-analysis, biologics, Health Assessment Questionnaire

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Introduction

Randomised controlled trials (RCTs) have demonstrated the efficacy of biologics in Rheumatoid Arthritis (RA). Currently, there are eight biologic drugs approved for the treatment of RA: infliximab, etanercept, adalimumab, golimumab, certolizumab (anti-tumour necrosis factor-alpha), rituximab (anti-CD20), abatacept (anti-CTLA-4) and tocilizumab (anti-Interleukin-6). Anakinra (anti-Interleukin-1) is also approved for use in RA, but it is rarely used in RA. Meta-analyses of these RCTs generally report efficacy using the standard primary outcomes of the American College of Rheumatology-20, 50 or 70 score (ACR20, ACR50, ACR70) (1). This composite measure is defined as the proportion of patients with at least 20%, 50% or 70% improvement in swollen joint count, tender joint count and in 3 of the 5 variables: physician global assessment, patient global assessment, patient pain, patient function and a laboratory marker for inflammation (erythrocyte sedimentation rate or C-reactive protein) (2, 3). Since the ACR20/50/70 score is a composite measure, it is unclear what the direction of the effect is for important patient-centered components, such as physical function which, is usually assessed using the validated Health Assessment Questionnaire (HAQ) (3). Determining whether biologic agents can significantly improve HAQ scores is important because HAQ is known to predict future morbidity, mortality, and hospitalisations (4). In addition, decreases in HAQ scores are associated with less disability and improved quality of life (5).

It is unclear whether certain biologics are more efficacious than others at improving HAQ. Head-to-head RCTs of biologics are scarce and evidence synthesis using meta-analysis methods either do not report HAQ or have only compared anti-TNF agents (6-12). We have used a frequentist meta-analysis approach to compare the efficacy of different biologics at improving HAQ in established RA for (i) DMARD-failures (ii) anti-TNF-failures and (iii) in early RA (ERA) .

Methods

Literature search and study selection

We performed a search of the following bibliographic databases from 1990 up to and including August 2012: Medline Pubmed, Embase and the Cochrane Library. Our search strategy combined terms for 'Rheumatoid Arthritis', 'Biologics' and 'the Health Assessment Questionnaire' (for full search strategy, see Supplementary Fig. 1). Four independent reviewers (L, AH, LS, CF) conducted the search and study selection by title/abstract. Hand searches of the references in relevant papers were conducted to identify any additional articles. Two independent reviewers (LB and AH or LS and CF) subsequently reviewed the full text articles. If there were discrepancies, consensus was reached after the material was reviewed by the other 2 reviewers.

Inclusion criteria were: (i) randomised controlled trials, (ii) trial follow-up of at least 6 months, (iii) patients met ACR or ACR/EULAR criteria for RA (13-14); (iv) patients were >15 years of age, (v) baseline and at least one follow-up HAQ score at 6 and/or 12 months were reported. Doses of biologics used in clinical practice were included (and usual loading doses where applicable): adalimumab 40 mg every 2 weeks, infliximab 3mg/kg every 4 or 8weeks up to 10 mg/kg every 8 weeks, etanercept 50 mg every week, golimumab 50 mg every 4 weeks, certolizumab 200 mg every 2 weeks or 400 mg every 4 weeks, rituximab 1000 mg day 1 and 15 (with repeat dosing allowed as often as every 6 months), abatacept 500 mg (patient weight <60 kg), 750 mg (60–100 kg) and 1000 mg (>100 kg) every 4 weeks, and tocilizumab 4 or 8 mg/kg every 4 weeks. For studies that included both approved and unapproved drug doses, the study arm with the unapproved dose was omitted from the analysis. Open label extension studies were excluded. Other exclusions included: patients with non-RA inflammatory arthritis (such as Juvenile inflammatory arthritis, psoriatic arthritis, ankylosing spondylitis and connective tissue disease), studies combining biologic agents, case reports, case series, cross-sectional studies, reviews, editorials, letters and data published only as abstracts.

The PRISMA checklist was followed for reporting this meta-analysis. The protocol for this meta-analysis was not registered.

Data extraction and quality appraisal

The outcome measure chosen was improvement in HAQ, which we defined as the difference in the mean change in HAQ (SD) for the biologic group compared to the mean change in HAQ (SD) for the control group (ΔHAQ_B-ΔHAQ_C). The minimally clinically important difference in ΔHAQ_B-ΔHAQ_C was considered to be >0.22 (15). Absolute improvement in HAQ was chosen to allow for comparison with other meta-analyses, which more commonly report change in HAQ and for ease of interpretation with respect to the minimally clinically important difference, an important patient-centered outcome. If both 6 and 12 month data were available, we used 12 month data. In studies where median ΔHAQ scores with interquartile range was reported, the median ΔHAQ was set equal to the mean ΔHAQ score based on the assumption of normal HAQ distribution in the study sample. Similarly, the SD of ΔHAQ was calculated using: $SD_{\Delta HAQ} \approx IQR / 1.35$. For studies, only reporting *p*-values, SD was imputed based on the table for distribution of the t-statistic. When exact *p*-values were not reported, we set the *p*-value to be equal to the estimated reported value (*e.g.* if *p* was reported as <0.001, *p* was made = to 0.001).

Other extracted information included: study design (intervention administration and doses, co-interventions, prior treatment, controls, length of follow-up, number of patients in each study arm, cross-over/escape and intention to treat) and baseline characteristics of patients (mean age, mean disease duration, and baseline HAQ scores). Four reviewers collected data using a standardised form. Quality assessment of studies was conducted using guidelines published by the Cochrane group (16), as well as, the Jadad score (17).

Statistical analysis

Random-effects meta-analyses (DerSimonian and Laird method) were performed on the following groups (established *a priori*): studies with established RA patients (i) failing DMARDs or (ii) failing anti-TNF at enrolment and (iii) patients with ERA. ERA trials were defined by the trial authors as symptoms <2 years. If a study had <10% prior exposure to a biologic agent, it was included in group (i). Re-analysis of the DMARD-failure subgroup excluding studies with patients exposed to biologics was conducted *post hoc*. DMARD-naïve and methotrexate-naïve patients were also biologic naïve. Some methotrexate-naïve studies included patients exposed to other DMARDs, such as sulfasalazine and hydroxychloroquine. For studies with multiple treatment arms of the same biologic (*i.e.* multiple clinically used doses, co-interventions or comparators), the ΔHAQ for the treatment arms were averaged together. Heterogeneity was reported using the I^2. Indirect comparisons of the different drugs compared to the control group were conducted using the Q-test based on analysis of variance and reported as a *p*-value (*p*-value <0.05 was considered significant). Indirect comparisons assumed that the efficacy of each biologic was consistent across studies. Other subgroup analyses decided *a priori* included: different clinically used doses, co-intervention (DMARD *vs.* none), control (placebo alone *vs.* DMARD + placebo) and follow-up (6 months v*s.* 12 months). Meta-regression was performed using the method of moments including the following variables that were decided *a priori*: disease duration, baseline HAQ score, % cross-over from control to intervention arms, year of publication and Jadad score.

Publication bias was assessed using Funnel plots and the *Trim and Fit* method. All statistical analyses were performed using Comprehensive Meta-Analysis version 2 software.

Results

Review of the literature and included studies

Search results and reasons for exclusion are summarised in Figure 1. A total of 28 studies were included: 17 reporting on anti-TNF agents (7 adalimumab, 3 certolizumab, 4 etanercept, 1 golimumab and 2 infliximab), 4 on abatacept, 3 on rituximab and 4 on tocilizumab. Nineteen trials reported on patients failing DMARDs (n=8115), 4 on anti-TNF failures (n=1694) and 5 on ERA (n=2492). There was no significant publication bias identified (Suppl. Fig. 2). Characteristics of the trials are presented in Table 1: mean age 47-56, disease duration 6 months to 13 years and baseline HAQ score of 1 to 1.9. Quality assessment using the Jadad score revealed 4 trials of poor quality (score <3). Three studies had a high risk of bias because incomplete data was not addressed. Exclusion of these trials did not change the results (data not shown). The majority of trials (n=19) had >20% cross-over from the control group to intervention groups and these studies used intention-to-treat analyses.

Efficacy of biologic agents at lowering HAQ in established RA patients failing DMARDs

Meta-analysis of trials reporting on patients failing DMARDs yielded a pooled difference in mean ΔHAQ in biologics compared to control (ΔHAQ_B-ΔHAQ_C) of -0.22; 95%CI: -0.24, -0.20 (I^2=55%), with the upper limit of the 95% confidence interval not meeting the minimally clinically important difference (MCID) for change in HAQ (24) (Fig. 2). However, 4 trials had up to 10% of patients with a previous anti-TNF exposure. With these trials excluded, the ΔHAQ_B-ΔHAQ_C was -0.25; 95%CI: -0.29, -0.22 (I^2=60%), meeting the MCID for change in HAQ. Because of the significant heterogeneity, we analysed whether the type of biologic contributed to the heterogeneity.

Subgroup analysis of the different biologics revealed a significant difference in mean difference in change in HAQ (p<0.0001). The ΔHAQ_B-ΔHAQ_C for abatacept (-0.20; 95% CI:-0.28, -0.12; I^2=0%), and infliximab (-0.11; 95% CI: -0.17, -0.05; I^2=0%) were lower than the other anti-TNF agents with ΔHAQ_B-ΔHAQ_C of -0.32 to -0.35; I^2=0% for all) (p<0.02) (Fig. 2). The ΔHAQ_B-ΔHAQ_C for tocilizumab (-0.20; 95% CI:-0.24, -0.17; I^2=0%) was lower compared to adalimumab and certolizumab (p<0.001) (Fig. 2).

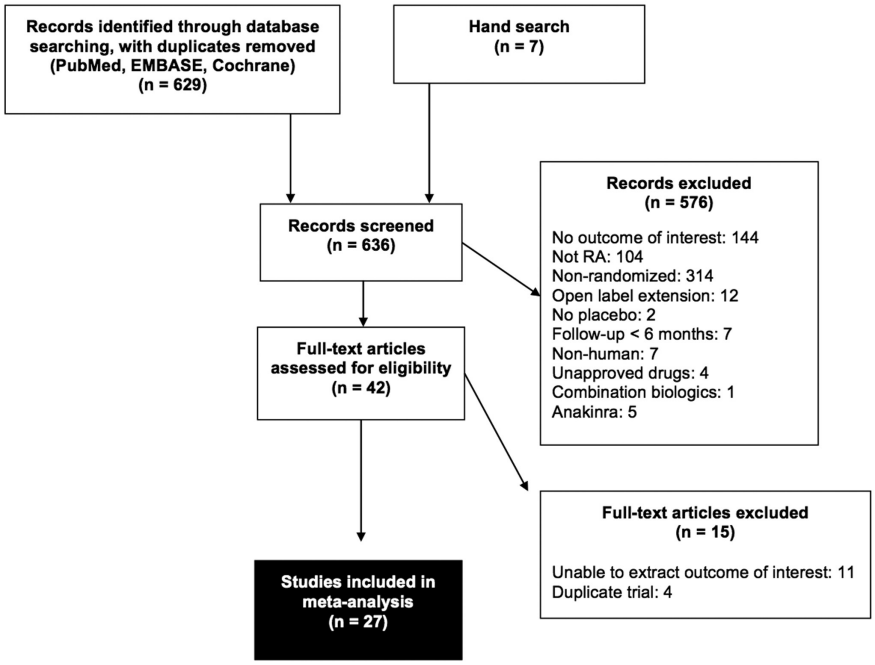


Fig. 1. Search results.

Efficacy of biologic agents at lowering HAQ in established RA patients failing anti-TNF agents

Four of the included trials required failure of an anti-TNF agent at enrollment. Meta-analysis of these trials revealed a pooled ΔHAQ_B-ΔHAQ_C of -0.36; 95%CI: -0.43, -0.30 (I^2=92%) (Fig. 3). There were no significant differences in the efficacy of the different biologics at improving HAQ: ΔHAQ_B-ΔHAQ_C for abatacept of -0.40; 95% CI:-0.51, -0.29), rituximab (-0.37; 95% CI: -0.46, -0.27) and tocilizumab (-0.36; 95% CI: -0.42, -0.30).

Efficacy of biologic agents at lowering HAQ in early RA (ERA) patients

ERA trials included DMARD-naïve (n=1 trial investigating infliximab) and MTX-naïve patients (subjects could have been exposed to other DMARDs previously; n=4 trials). The pooled ΔHAQ_B-ΔHAQ_C of all five trials was -0.23; 95% CI: -0.32, -0.14 (I^2=0%), with the upper limit of the 95% CI not meeting MCID for change in HAQ (Fig. 4). There was no significant difference in HAQ improvement for the different biologic agents. The ΔHAQ_B-ΔHAQ_C for adalimumab was -0.20; 95%CI: -0.34, -0.06; etanercept -0.3; 95%CI: -0.52, -0.07; infliximab -0.2; 95%CI: -0.40, 0; and rituximab -0.23; 95%CI: -0.32, -0.14) (Fig. 4).

Effect of baseline patient characteristics, study design and study quality on HAQ

There was a significant difference in HAQ improvement in established RA patients previously failing DMARDs (n=19 trials), patients failing anti-TNF agents (n=4 trials) and ERA (n=5 trials); p=0.001 (Table II). Most trials combined biologic therapy with a DMARD agent (21/23 with methotrexate, 1/23 with sulfasalazine, 1/23 with other DMARD). Five trials used biologic monotherapy (adalimumab, etanercept, golimumab, infliximab and abatacept), which appeared as efficacious at lowering HAQ as combination therapy. There was no detectable difference in HAQ improvement at 6 months (n=19) compared to 12 months (n=9) (Table II). Using meta-regression, mean difference in change in HAQ was not significantly affected by baseline disease duration and baseline HAQ scores. Similarly, study quality as measured by the Jadad score, had no significant effect on results. Patient cross-over from control groups to intervention groups and year of publication was also not found to impact HAQ (data not shown).

Discussion

This is the first meta-analysis with indirect comparisons to specifically assess the comparative efficacy of all clinically available biologic therapies in improving physical function as measured by the Health Assessment Questionnaire (HAQ) in RA. Other indirect comparison studies of HAQ have included only anti-TNF agents in DMARD-failures (6, 8, 10). We also evaluated improvement in HAQ in patients failing anti-TNF agents and DMARD/methotrexate -naïve patients (primarily the ERA subgroup). These groups were selected *a priori* because we felt that they represented populations with significant clinical differences, such as disease severity (including baseline HAQ score), duration of symptoms, extent of radiographic damage co-morbidities and potentially different responsiveness to treatment. In our study we found significant differences in HAQ improvement in the group with prior anti-TNF failures, which had higher baseline HAQ scores, and the same per cent change in HAQ compared to the DMARD failure group (data not shown).

We chose the HAQ score as our outcome of interest for several reasons: (1) it is a patient-centred, clinically-relevant validated score that correlates highly with disability and quality of life (3-5); (2) it is a continuous outcome, which is more sensitive to detect change than the traditionally used binary ACR20/50/70 score (2); and (3) it can be used in economic evaluations, which are crucial when assessing expensive therapies.

All biologics in patients failing DMARDs were efficacious at improving HAQ. The pooled mean difference in change in HAQ for biologics compared to control was -0.22, which meets the minimally clinically important difference (MCID) for HAQ (15). With respect to the DMARD-failure group, the detectable heterogeneity could be accounted for by differences in the efficacy of the different biologic agents. The least effective biologic was infliximab, which is consistent with the findings of other meta-analyses (6-7). Only one infliximab study was included in the DMARD-failure group and it had various study arms with different doses. If

Table I. Characteristics of included studies.

Study	Total number	Age (years)	Disease duration (years)	Previous* treatment	Baseline HAQ	Follow-up (months)	Jadad score
Anti-TNF:							
Adalimumab:							
Bejarano *et al*. (18)	148	47	0.75	MTX-naïve	1.3	12	5
Breedveld *et al*. (PREMIER) (19)	799	52	0.7	MTX-naïve	1.5	12	4
Van de Putte *et al*. (20)	544	53	11	DMARD	1.9	6	3
Weinblatt *et al*. (ARMADA) (21)	271	56	12	DMARD	1.6	6	3
Keystone *et al*. (22)	619	56	11	DMARD	1.9	12	3
Miyasaka *et al*. (CHANGE) (23)	352	56	7	DMARD	1.6	6	3
Kim *et al*. (24)	128	49	7	DMARD	1.3	6	2
Certolizumab:							
Keystone *et al*. (RAPID1) (25)	982	52	6	DMARD	1.7	12	3
Smolen *et al*. (RAPID2) (26)	619	52	6	DMARD	1.6	6	3
Fleischmann *et al*. (FAST4WARD) (27)	220	54	10	DMARD	1.5	6	4
Etanercept:							
Emery *et al*. (COMET) (28)	542	51	0.75	MTX-naïve	1.7	12	4
Moreland *et al*. (29)	234	52	12	DMARD	1.7	6	4
Weinblatt *et al*. (30)	89	50	13	DMARD	1.5	6	4
Combe *et al*. (31)	254	51	7	DMARD	1.7	6	3
Golimumab:							
Keystone *et al*. (GO-FORWARD) (32)	444	50	8	DMARD	1.4	12	5
Infliximab:							
Goekoop-Ruiterman *et al*. (BeSt) (33)	508	54	0.5	DMARD-naïve	1.4	12	3
Maini *et al*. (ATTRACT) (34)	428	53	8	DMARD	1.7	6	4
Anti-CTLA4:							
Abatacept:							
Kremer *et al*. (AIM) (35)	652	51	9	DMARD	1.7	6	5
Kremer *et al*. (36)	339	55	10	DMARD†	1.0	6	5
Weinblatt *et al*. (ASSURE) (37)	1450	52	10	DMARD†	1.5	12	2
Westhovens *et al*. (ATTAIN) (38)	391	53	12	Anti-TNF	1.8	6	2
Anti-CD20:							
Rituximab:							
Tak *et al*. (IMAGE) (39)	755	48	1	MTX-naïve	1.8	12	5
Cohen *et al*. (REFLEX) (40)	520	53	12	Anti-TNF	1.9	6	3
Emery *et al*. (DANCER) (41)	465	51	10	Anti-TNF	1.8	6	2
Anti-IL-6							
Tocilizumab:							
Jones *et al*. (AMBITION) (42)	673	51	6	DMARD†	1.6	6	3
Smolen *et al*. (OPTION) (43)	623	51	7	DMARD†	1.6	6	4
Genovese *et al*. (TOWARD) (44)	1220	53	10	DMARD	1.5	6	3
Emery *et al*. (RADIATE) (45)	499	53	12	Anti-TNF	1.7	6	4

*All MTX-naïve and DMARD-naïve populations were also biologic-naïve; MTX-naïve populations included patients treated with other DMARDs
†Exposure to previous biologic <10%. HAQ: Health Assessment Questionnaire; MTX: methotrexate; DMARD: disease-modifying anti-rheumatic drug.

for some subjects the lower doses were suboptimal, this could have underestimated the effect of infliximab on HAQ. Subgroup analysis of the different infliximab doses was conducted and we did not find a difference, but the sample size was small (data not shown).

The other anti-TNF agents were not significantly different in improving HAQ in DMARD failures. A recently published meta-analysis by *Schmitz et al*. (6) found that etanercept was superior to adalimumab at improving HAQ. Results of meta-analyses may vary depending on inclusion criteria, analyses used and the outcome selected. Our results may also differ because *Schmitz et al*. used a Bayesian approach and a different outcome for HAQ: % change in HAQ to account for variations in baseline HAQ values. We used meta-regression and did not find that baseline HAQ affected our outcome of interest. Similar to *Shmitz et al*., we found no benefit of certolizumab over other anti-TNF agents for HAQ improvement (6). Other studies demonstrated an increased likelihood of achieving ACR20/50 responses with certolizumab (7, 9, 11, 12). Two of the certolizumab trials had a different study design where patients who did not achieve an ACR20 at 12 weeks were considered non-responders and were withdrawn from the trial, which could overestimate the effect of active treatment. In contrast, some tri-

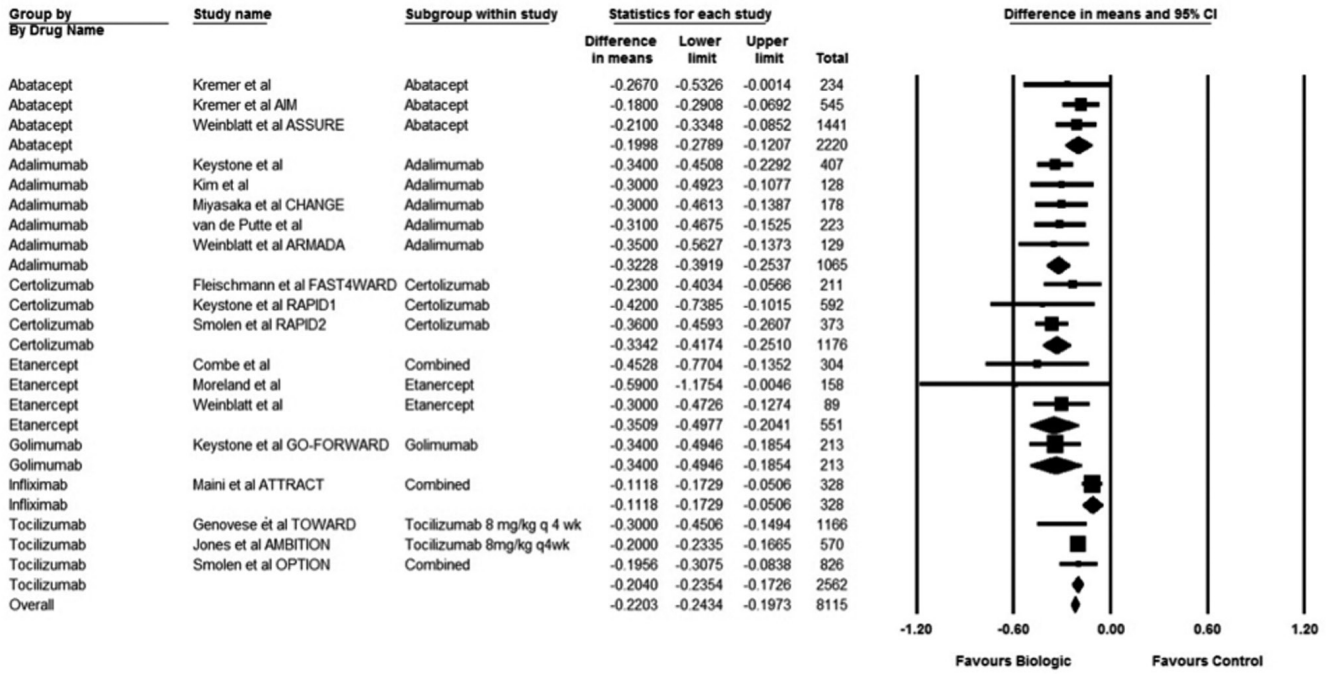


Fig. 2. Difference in mean change in HAQ in patients previously failing DMARD agents subsequently treated with biologic agents compared to control

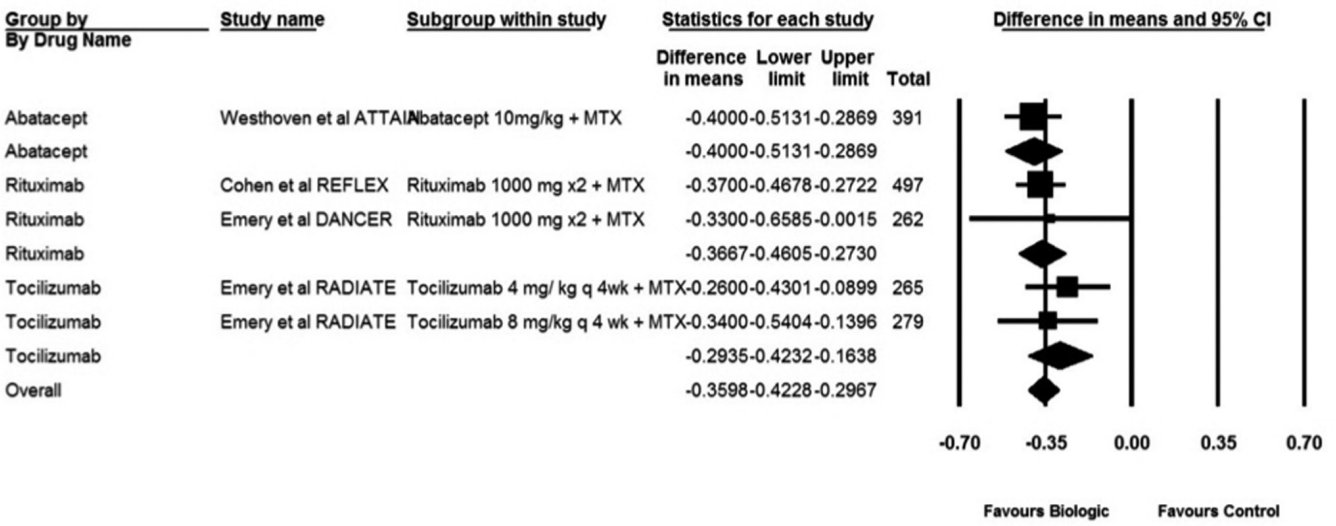


Fig. 3. Difference in mean change in HAQ in patients previously failing anti-TNF agents subsequently treated with biologic agents compared to control.

als of other biologic therapies allowed for cross-over between study arms with intention-to-treat analysis, which could underestimate the effect of the biologic. We found that abatacept and tocilizumab was not as effective at improving HAQ in DMARD-failures over the time frame of the trials. However, some of the trials included patients previously exposed to biologics (<10% of total subjects in a trial). HAQ improvement in the tocilizumab trial that only included patients with no prior anti-TNF exposure was higher than the other tocilizumab trials and not different than the HAQ improvement seen with non-infliximab anti-TNF agents. This is consistent with the recently published RCT of tocilizumab *versus* adalimumab that reported no difference in change in HAQ for the 2 drugs (46).

With respect to abatacept, excluding trials that included patients previously exposed to biologics did not change results. *Salliot et al*. also found that abatacept was inferior to other biologics at achieving ACR50 (7). The ATTEST trial (47), a head-to-head RCT of abatacept *versus* infliximab (3mg/kg every 8 weeks), did not find a difference between these two biologic drugs, which is similar to our results given the inferiority of infliximab compared to other anti-TNF agents. We were unable to analyse rituximab in the DMARD-failure group because of incomplete HAQ data in those trials. The magnitude of the difference in HAQ improvement for abatacept, infliximab or tocilizumab compared to the other anti-TNF agents was <0.22, therefore, it may not be clinically significant.

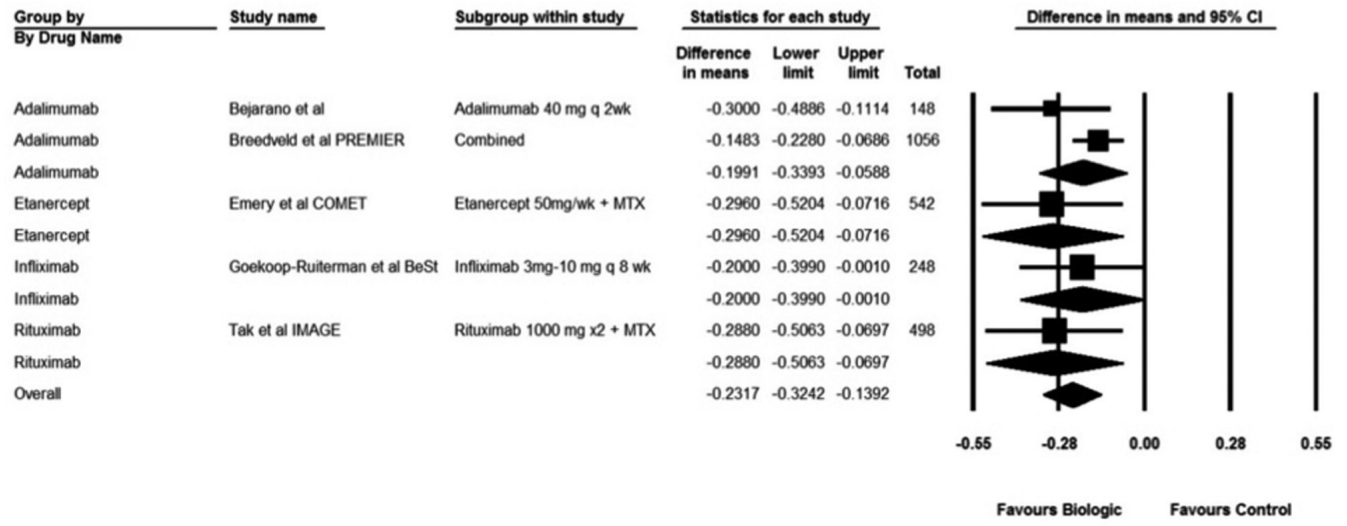


Fig. 4. Difference in mean change in HAQ in DMARD-naive or MTX-naïve patients with biologic agents compared to control.

In the anti-TNF-failure group, all drugs showed benefit compared to the control group, which met MCID. A small number of studies included patients with ERA. Only one study investigating infliximab had no previous exposure to DMARDs. Therefore, there is insufficient evidence in support of the use of biologic therapies in DMARD-naïve patients for HAQ improvement. For MTX-naïve ERA trials, where patients were exposed to other DMARDs (predominately sulfasalazine), the different biologics (adalimumab, etanercept and rituximab) were equally efficacious at improving HAQ compared to control. Mean difference in change in HAQ was -0.23 for biologics compared to DMARD, which was similar to the studies investigating DMARD-failures in established RA. Patients in these ERA studies had failed at least 1 DMARD and had similar age and baseline HAQ to the patients in the DMARD-failure established RA group. The ERA studies in this meta-analysis represent a population of ERA patients with severe disease, which may explain why the HAQ was not more modifiable in ERA studies.

Indirect comparisons using meta-analysis have several limitations. Although data are from RCTs, comparative analyses can be considered observational studies and subject to biases and confounders. We have tried to reduce biases by selecting subgroup analyses and the outcome of interest *a priori*. We accounted for possible sources of heterogeneity including patient age, disease duration, baseline HAQ, drug doses, follow-up time, co-intervention, percentage of cross-over from control to intervention arms, publication date and Jadad score. By subgroup analyses or meta-regression, these variables were not found to affect the comparative change in HAQ. Nevertheless there are other potential sources of heterogeneity that we did not control for because of incomplete information. Also, some of the analyses included a small number of trials, which may have been underpowered to detect effects. Although we did not detect any publication bias, several RCT were excluded because of insufficient information to determine change in HAQ.

In conclusion, biologics improve physical function in established RA patients failing DMARDs and anti-TNF agents. The mean improvement in HAQ at 6-12 months follow-up compared to DMARDs is at least the minimally clinically important difference for HAQ of 0.22. The role of biologic agents in improving HAQ in DMARD/methotrexate-naïve ERA is unclear. In the absence of head-to-head randomised controlled trials comparing biologic agents, comparative meta-analysis provides a means for examining differences in biologic efficacy. We found that in anti-TNF failures, the included biologics (abatacept, tocilizumab and rituximab) appeared equally efficacious. In DMARD-failures, there were differences in HAQ reduction for some biologics. These differences should be interpreted in the context of the doses used, the populations studied and the design of the included studies. Future studies should confirm the differences with head-to-head comparisons.

Table II. Subgroup analyses on mean difference in change in HAQ for biologic therapies compared to control (ΔHAQ_B-HAQ_C).

	Number of studies	ΔHAQ_B-HAQ_C (95% CI)	*p*-value between groups	I^2 (%)
Prior treatment failure:				
DMARD	19	-0.26 (-0.31, -0.22)	0.001	55.0
Anti-TNF	4	-0.36 (-0.42, -0.30)		0
DMARD/MTX-naïve	5	-0.19 (-0.26, -0.13)		0
Co-intervention				
DMARD	23	-0.23 (-0.25,-0.21)	0.987	58.6
None	5	-0.27 (-0.35, -0.19)		87.2
Follow-up				
6 months	19	-0.23 (-0.26, -0.21)	0.1731	65.6
12 months	9	-0.22 (-0.27, -0.18)		28.5

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