Efficacy of initial methotrexate monotherapy versus combination therapy with a biological agent in early rheumatoid arthritis: a meta-analysis of clinical and radiographic remission

B Kuriya, E V Arkema, V P Bykerk, et al.

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B Kuriya,[1,2] E V Arkema,[1] V P Bykerk,[2] E C Keystone[2]

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[1]Harvard School of Public Health, Boston, Massachusetts, USA
[2]Rebecca MacDonald Centre for Arthritis and Autoimmune Diseases, Mount Sinai Hospital, University of Toronto, Toronto, Canada

Correspondence to
Dr B Kuriya., Rebecca MacDonald Centre for Arthritis and Autoimmune Diseases, Mount Sinai Hospital, Joseph and Wolf Lebovic Building, Toronto, Ontario M5T 3L9, Canada;
bindee.kuriya@gmail.com

ABSTRACT

Objective The target outcome in early rheumatoid arthritis (ERA) is now remission. This meta-analysis compared the efficacy of initial methotrexate monotherapy versus combination therapy (methotrexate plus biological agent) for clinical remission and radiographic non-progression among ERA patients with minimal or no previous methotrexate exposure.

Methods A systematic search was performed for randomised controlled trials of ERA using predefined criteria. A random effects model was used to pool the risk ratio (RR) for clinical and radiographic remission at 52–56 weeks of follow-up.

Results Seven trials of combination therapy with infliximab, adalimumab, etanercept or abatacept were included. The majority of studies defined clinical remission as a 28-joint disease activity score (DAS28) of 2.6 or less. Radiographic non-progression was primarily defined as a modified total Sharp score change of less than 0.5 units. All trials demonstrated risk estimates in favour of combination therapy: the pooled RR for achieving clinical remission was 1.74 (95% CI 1.54 to 1.98) and for radiographic non-progression was 1.30 (95% CI 1.01 to 1.68). Significant heterogeneity among studies for the latter outcome was detected ($p<0.001$).

Conclusions The efficacy of combination therapy with a biological agent is superior to methotrexate monotherapy for remission. Combination therapy has a greater initial effect on clinical remission than radiographic non-progression. Uniform definitions of remission are needed and the proportion of subjects who achieve the combined endpoint of clinical and radiographic remission should be considered as a meaningful outcome in future studies of ERA.

The merits of early diagnosis and aggressive treatment of rheumatoid arthritis (RA) with disease-modifying antirheumatic drugs (DMARD) is well recognised. Clinical studies have repeatedly highlighted the detrimental effects of withholding therapy. Even in the early years of disease, rapid joint destruction, functional disability and impaired quality of life may ensue if disease activity is not adequately controlled.[1–3]

The past decade of clinical research has advanced this concept of low disease activity one step further. Now, the main goal of RA treatment after cure is the induction and maintenance of remission, which is typically accepted to mean a lack of detectable disease activity.[4] However, the concept of remission is complex. Clinical remission is generally synonymous with the absence of synovitis or elevated acute phase reactants, whereas radiographic remission is defined by non-progression of structural damage.[5 6] Complicating matters further is the observation that some patients exhibit dissociation between clinical and radiographic remission.[7 8] Various scoring methods and clinical tools have been developed to predict and estimate remission, each with its own sensitivity and specificity for these clinical and radiographic outcomes.[9 10]

Randomised controlled trials (RCT) of biological agents, including anti-tumour necrosis factor (TNF) alpha agents, abatacept and rituximab, have demonstrated superiority in achieving American College of Rheumatology (ACR) clinical responses and suppressing radiographic joint damage in combination with or compared with methotrexate monotherapy among subjects with established and early rheumatoid arthritis (ERA).[11–15] What has been less frequently reported is whether combination therapy with methotrexate plus a biological agent is better at inducing a state of clinical and/or radiographic remission if used as initial therapy in newly diagnosed patients. Currently, biological agents in most countries are only reimbursed for patients who have failed a minimum of two traditional DMARD, and some have questioned whether this delay impedes the opportunity to achieve remission.[16]

With mounting evidence in favour of remission as a target outcome, we sought to examine the efficacy of methotrexate monotherapy compared with combination therapy (methotrexate plus biological agent) when used as initial treatment in ERA patients with minimal or no previous methotrexate exposure. We conducted a systematic review and meta-analysis of RCT to summarise the proportion of subjects who achieve clinical remission and/or radiographic non-progression with either therapeutic strategy.

METHODS

This study was developed according to the Cochrane collaboration guidelines (http://www.cochrane.org) and followed a protocol that prespecified study selection, eligibility criteria, quality assessment, data abstraction and statistical analysis.

Search strategy

We conducted a systematic review of articles using MEDLINE (Ovid, PubMed) from 1950 to April 2009, EMBASE from 1980 to April 2009 and

the Cochrane Controlled Trials Register from 1990 to 2009. Additional studies were identified by hand searching reference lists and abstracts presented at the ACR and European League Against Rheumatism from 2007 to 2008. Medical subject heading terms included RA: rheumatoid arthritis; methotrexate therapy: antirheumatic agent, methotrexate (see supplementary appendix A, available online only, for full list of terms); biological agents: tumour necrosis factor α, monoclonal antibody and keywords for individual agents (see supplementary appendix B, available online only); with outcome: treatment outcome, remission, disease course, disease activity and trials: randomised-controlled trial or controlled-clinical trial.

Inclusion/exclusion criteria

We included double-blind, randomised, active-comparator, controlled clinical trials that studied the efficacy of initial combination therapy (methotrexate plus biological agent) compared with methotrexate monotherapy in adult patients with clinically active ERA, defined as disease duration less than 3 years. Subjects had no or minimal previous exposure to methotrexate (≤4 weeks). Previous treatment with corticosteroids, sulfasalazine or hydroxychloroquine/chloroquine was permitted. Our primary outcome measures were the proportion of patients achieving clinical remission and radiographic non-progression following a minimum of 1 year of treatment (table 1).

We excluded non-English studies, non-active comparator RCT and animal studies. Trials of established RA (>3 years disease), those with subjects who received methotrexate for more than 4 weeks, were treated with DMARD other than sulfasalazine or antimalarials or any biological agent, or those that did not report at least one remission outcome were further excluded. When multiple publications of a trial existed, we selected the publication with the most complete data for the outcomes of interest.

Data extraction

Data regarding the proportion of patients achieving clinical remission and/or radiographic non-progression were analysed at weeks 52, 54 or 56 of follow-up before subjects and investigators were un-blinded in the individual trials. All data were independently extracted by two investigators (EVA and BK) and discrepancies were resolved by discussion.

Quality assessment

We assessed the following methodological features most relevant to the control of bias in RCT: randomisation, baseline comparability of the participants, blinding of care providers, patients and outcome assessors, handling of withdrawals and intention-to-treat analyses.

Statistical analysis

Outcomes were analysed on an intention-to-treat basis. For each trial, the risk ratio (RR) and 95% CI of the effects of combination therapy compared with methotrexate monotherapy were calculated. The DerSimonian and Laird random effects model was used to pool the data, allowing for both within and between-study variation. Heterogeneity among studies was evaluated by the Q statistic (considered significant for $p<0.10$) and I^2 statistics. We also examined the potential of publication bias using the Begg and Egger tests. In addition, a sensitivity analysis was performed to examine the influence of individual studies. Statistical analyses were performed with STATA version 10.0.

RESULTS

Trials included

The literature search identified 2801 studies that matched the predefined search terms. Of the potentially relevant studies retrieved, the majority was excluded because the study population had RA for more than 3 years and/or had previous DMARD exposure (figure 1). A total of seven trials was included in the final analysis.

Trial characteristics

The characteristics of included trials are displayed in table 1. The studied biological agents were abatacept, adalimumab, etanercept and infliximab. St Clair *et al*[17] included two combination therapy groups with different doses of infliximab (3 and 6 mg/kg). Because 3 mg/kg is the standard initial dose used in clinical practice, and the other trials of infliximab studied this dose, we only analysed the 3 mg/kg infliximab comparison group.

Six studies reported a clinical remission outcome, defined as a 28-joint disease activity score (DAS28) score of 2.6 or less and one classified remission according to the ACR definition. Remission outcomes were reported, on average, after 1 year of follow-up. Five studies reported radiographic non-progression. Subjects in both the monotherapy and combination therapy groups in the study by Quinn *et al*[18] did not have

Table 1 Characteristics of studies included in the meta-analysis

Author, year (study acronym)	Subjects randomly assigned (n)	Biological agent studied (dose, frequency)	Combination therapy group (n)	Methotrexate monotherapy group (n)	Study duration (weeks)	Clinical remission outcome	Radiographic non-progression outcome
St Clair *et al*, 2004[17] (ASPIRE)	1004	Infliximab (3 mg/kg, q 8 weekly)	359	282	54	DAS28 ≤2.6	SDD ≤9.03 units
Quinn *et al*, 2005[18]	20	Infliximab (3 mg/kg, q 8 weekly)	10	10	54	ACR criteria	mTSS ≤0.5 units
Breedveld *et al*, 2006[19] (PREMIER)	525	Adalimumab (40 mg, q 2 weekly)	268	257	52	DAS28 ≤2.6	mTSS ≤0.5 units
Durez *et al*, 2007[20]	29	Infliximab (3 mg/kg, q 8 weekly)	15	14	52	DAS28 ≤2.6	–
Emery *et al*, 2008[21] (COMET)	528	Etanercept (50 mg, q weekly)	265	263	52	DAS28 ≤2.6	mTSS ≤0.5 units
Bejarano *et al*, 2008[22]	148	Adalimumab 40 mg, q 2 weekly)	75	73	56	DAS28 ≤2.6	
Westhovens *et al*, 2009[23] (AGREE)	509	Abatacept, (10 mg/kg, q 4 weekly)	256	253	52	DAS28 ≤2.6	mTSS* ≤0 units

*Genant-modified Sharp scoring system.
ACR, American College of Rheumatology; DAS28, 28-joint disease activity score; mTSS, van der Heijde-modified total Sharp score; SDD, smallest detectable difference in van der Heijde-modified total Sharp score.

any subjects who achieved radiographic non-progression, so that study was removed from the analysis for this outcome. Radiographic non-progression in the remaining four studies was primarily determined by means of the modified total Sharp scoring method.

The results of the quality assessment are presented in table 2. All trials were judged to be of sufficiently high quality. However, Quinn *et al*[18] did not report all important baseline characteristics such as disease activity. In the trial by Breedveld *et al*,[19] there were small but statistically significant differences in the health assessment questionnaire disability index, patient global assessment of disease activity/pain and erosion score at baseline and Westhovens *et al*[23] reported an as-treated proportion of subjects achieving radiographic non-progression.

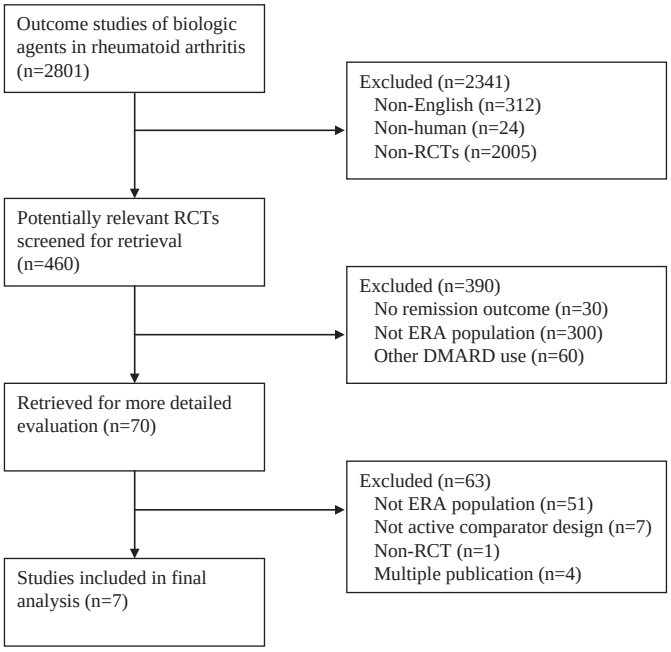

Figure 1 Flow chart for studies evaluated for inclusion in the meta-analysis. DMARD, disease-modifying antirheumatic drug; ERA, early rheumatoid arthritis; RCT, randomised controlled trial.

The manufacturers of the biological agent studied sponsored six of the seven trials.

Patients

The included studies involved 2763 patients, 1152 randomised to methotrexate monotherpay and 1248 to combination therapy. Average age ranges of the study groups were between 47 and 53 years and the proportion of women was between 53% and 79%. All subjects had active disease at baseline evidenced by the mean swollen joint count (range 9.4–22.9), mean tender joint count (range 11.6–34.0) and DAS28 score (range 5.9–6.3). Four studies reported the presence of baseline radiographic damage among this early disease population (table 3).

Corticosteroid use at baseline was identified in four studies and ranged from 35% to 51% of subjects. Four studies reported previous DMARD use ranging from 4% to 32%. Subjects enrolled by Bejarano *et al*[22] had minimal DMARD exposure at study entry (mean number 0.2). The mean dose of methotrexate (mg) at the end of follow-up was comparable between the monotherapy (range 15.1–19.0) and combination therapy (range 14.9–18.1) groups.

Four studies provided details about the proportion of withdrawals due to adverse events in the monotherapy groups (range 3.2–7.4%) and the combination therapy groups (range 3.1–11.9%). Withdrawals due to lack of efficacy were higher in the monotherapy (range 3.2–36.0%) than the combination therapy (range 0–17.0%) groups.

Data synthesis

The pooled RR for clinical remission was 1.74 (95% CI 1.54 to 1.98), suggesting that the ability to achieve remission at 1 year is significantly higher with combination therapy than methotrexate monotherapy (figure 2). No significant heterogeneity was identified among studies reporting a clinical remission outcome (I^2 0%; 95% CI 0% to 75%; p=0.496).

The pooled estimate for radiographic non-progression also favoured combination therapy, with a RR of 1.30 (95% CI 1.01 to 1.68; figure 3). However, significant heterogeneity was found for this outcome (I^2 95%; 95% CI 89% to 95%; p<0.001). Furthermore, the 95% CI of the studies minimally overlapped each other in the forest plots, supporting the presence of heterogeneity. The reasons for heterogeneity were not explored

Table 2 Quality assessment of included studies

	Randomisation		Baseline comparability			Blinding			Withdrawals	
Author, year	Number stated	Treatment concealment	All important characteristics presented	Achieved	Co-interventions specified	Providers	Subjects	Outcome assessors	Reasons stated	Intention-to-treat analysis
St Clair *et al*, 2004[17]	√	√	√	√	√	√	√	√	√	√
Quinn *et al*, 2005[18]	√	√	–	√	√	√	√	√	√	√
Breedveld *et al*, 2006[19]	√	√	√	Differences in HAQ-DI, patient global assessment of disease activity and pain, erosion score	√	√	√	√	√	√
Durez *et al*, 2007[20]	√	√	√	√	√	√	√	√	√	√
Emery *et al*, 2008[21]	√	√	√	√	√	√	√	√	√	√
Bejarano *et al*, 2008[22]	√	√	√	√	√	√	√	√	√	√
Westhovens *et al*, 2009[23]	√	√	√	√	√	√	√	√	√	As-treated analysis for radiographic outcome

HAQ-DI, health assessment questionnaire disability index.

Table 3 Baseline characteristics of subjects in studies included in the meta-analysis

Author, year	Disease duration, months	Age, years	% Female	Swollen joint count	Tender joint count	DAS28	HAQ	% RF +	% Anti-CCP+	CRP	% Corticosteroid use	Radiographic changes
St Clair *et al*, 2004[17]	Combo: 9.6 (8.4)	Combo: 51 (12)	Combo: 71	Combo: 21 (10)	Combo: 32 (15)	Combo: 6.6 (1.0)	Combo: 1.5 (0.7)	Combo: 71	–	Combo: 2.9 (3.3)	Combo: 37	Combo: 11.6 (15.2)*
	Mono: 10.8 (8.4)	Mono: 50 (13)	Mono: 75	Mono: 22 (11)	Mono: 34 (15)	Mono: 6.7 (1.0)	Mono: 1.5 (0.6)	Mono: 71	–	Mono: 2.6 (2.9)	Mono: 35	Mono: 11.3 (15.9)*
Quinn *et al*, 2005[18]	Combo: 7.4 (4.6)	Combo: 51.3 (9.5)	–	–	–	–	Combo: 1.3 (0.88)†	Combo: 70	–	Combo: 4.7 (2.8)	–	–
	Mono: 6.0 (3.7)	Mono: 53.1 (13.7)	–	–	–	–	Mono: 1.3 (0.88)†	Mono: 60	–	Mono: 3.7 (3.9)	–	–
Breedveld *et al*, 2006[19]	Combo: 8.4 (9.6)	Combo: 51.9 (14.0)	Combo: 72.0	Combo: 21.1 (11.2)	Combo: 30.7 (14.2)	Combo: 6.3 (0.9)	Combo: 1.5 (0.64)	Combo: 85	–	Combo: 3.9 (4.2)	Combo: 36	Combo: 18.1 (20.1)*
	Mono: 9.6 (10.8)	Mono: 52.0 (13.1)	Mono: 73.9	Mono: 22.1 (11.7)	Mono: 32.3 (14.3)	Mono: 6.3 (0.9)	Mono: 1.5 (0.67)	Mono: 84	–	Mono: 4.0 (4.0)	Mono: 36	Mono: 21.9 (22.2)*
Durez *et al*, 2007[20]	Combo: 4.3 (3.7)	–	–	Combo: 12.5 (5.4)	Combo: 15.9 (8.0)	Combo: 5.3 (1.1)	Combo: 1.5 (0.8)	Combo: 66	Combo: 73	Combo: 4.8 (5.2)	–	Combo: 13‡
	Mono: 5.4 (3.5)	–	–	Mono: 10.3 (5.5)	Mono: 11.6 (7.5)	Mono: 5.2 (0.8)	Mono: 1.3 (0.6)	Mono: 64	Mono: 42	Mono: 2.5 (3.5)	–	Mono: 36‡
Emery *et al*, 2008[21]	Combo: 8.8 (0.4)	Combo: 50.5 (0.9)	Combo: 74	Combo: 17.1 (10)	Combo: 25.1 (14.6)	Combo: 6.5 (1.0)	Combo: 1.7 (0.7)	–	Combo: 67	Combo: 3.70 (3.85)	Combo: 49	–
	Mono: 9.4 (0.4)	Mono: 52.3 (0.8)	Mono: 73	Mono: 17.6 (10)	Mono: 24.8 (14.5)	Mono: 6.5 (1.0)	Mono: 1.6 (0.7)	–	Mono: 70	Mono: 3.65 (3.35)	Mono: 50	–
Bejarano *et al*, 2008[22]	Combo: 9.5 (6)	Combo: 47 (9)	Combo: 58.4	Combo: 10.4 (5.5)	Combo: 12.9 (7.4)	Combo: 5.9 (1.4)	Combo: 1.3 (0.6)	Combo: 96	Combo: 63	Combo: 2.87 (3.36)	–	–
	Mono: 7.9 (5.4)	Mono: 47 (9)	Mono: 53.4	Mono: 9.4 (5.8)	Mono: 12.8 (7.8)	Mono: 6.0 (1.5)	Mono: 1.3 (0.6)	Mono: 95	Mono: 64	Mono: 3.82 (4.84)	–	–
Westhovens *et al*, 2009[23]	Combo: 6.2 (7.5)	Combo: 50.1 (12.4)	Combo: 78.6	Combo: 22.9 (11.3)	Combo: 31.3 (14.8)	Combo: 6.3 (1.0)	Combo: 1.7 (0.7)	Combo: 96.8	Combo: 92.2	Combo: 3.1 (3.1)	Combo: 51	Combo: 7.5 (9.7)§
	Mono: 6.7 (7.1)	Mono: 49.7 (13.0)	Mono: 78.7	Mono: 21.9 (10.1)	Mono: 30.8 (14.0)	Mono: 6.2 (1.0)	Mono: 1.7 (0.7)	Mono: 96.1	Mono: 85.8	Mono: 3.6 (5.0)	Mono: 49	Mono: 6.7 (8.8)§

Values are mean ± (SD).
*Modified total Sharp score.
†Median ± (interquartile range).
‡Percentage erosions.
§Genant-modified total Sharp score.
anti-CCP, anti-cyclic citrullinated peptide; Combo, combination therapy group; CRP, C-reactive protein; DAS28, 28-joint disease activity score; HAQ, health assessment questionnaire (range 0–3); Mono, monotherapy group; RF, rheumatoid factor.

because of the small number of studies and lack of statistical power.

There was no evidence of publication bias tested by constructing Begg's funnel plot or by Egger's test (p=0.95). Furthermore, the sensitivity analysis revealed that no individual study appeared to change the pooled RR dramatically.

DISCUSSION

Biological therapy is highly effective in ERA. To our knowledge, this is the first systematic review comparing the degree to which biological agents impact the ability to achieve the important goals of clinical and radiographic remission.

Individual RCT demonstrate that biological agents successfully reduce disease activity and retard radiographic progression when used as initial treatment for patients with no or minimal previous DMARD exposure. Irrespective of their immunological target, the results of this meta-analysis suggest that clinical remission is 74% more likely and radiographic non-progression is 30% more likely at 1 year when a biological agent is used in combination with methotrexate compared with methotrexate monotherapy.

All of the biological agents studied had approximately the same efficacy for clinical remission as evidenced by the overlapping CI for the point estimates. Within TNF inhibitors, RR varied as a result of differences in sample size, seen most clearly among RCT of infliximab. However, this summary strengthens previous findings that biological therapy may have a greater initial effect on clinical remission compared with methotrexate. There are plausible mechanisms for this observation. Biological agents have demonstrated a dramatic reduction in acute phase reactants through the inhibition of TNFα and have a rapid onset of action and sustained efficacy when used early in the disease process.[11–13] Individual trials also demonstrate a greater improvement in the swollen joint count and perception of general health with biological agents compared with methotrexate monotherapy.[24 25] This reduction in acute phase reactants and clinically detected synovitis in turn drives the DAS28 score below 2.6 to a larger extent than with methotrexate alone.

A similar, but less pronounced, protective trend among biological agents was seen for radiographic non-progression. There may be several explanations for the more modest effect of combination therapy compared with methotrexate. First, patients with ERA benefit from early DMARD use, especially methotrexate. When the initial dose is rapidly escalated and therapy is maintained at maximally tolerated doses, methotrexate monotherapy has been shown to halt radiographic progression substantially. This impact is evidenced by the finding that 50–60% of methotrexate-treated patients do not progress radiographically.[26] Recent studies demonstrate that even among patients with an inadequate clinical response to methotrexate, a significant proportion experience relatively small changes in the total Sharp score and fail to demonstrate structural progression over time.[27–29] This suggests that a window of opportunity to delay structural damage with DMARD exists. If this is exploited in trials of ERA, the result will be a smaller proportion of patients progressing overall with any therapy, and less of an absolute difference between groups will be detected. An alternative explanation is that a greater divergence between therapies would have

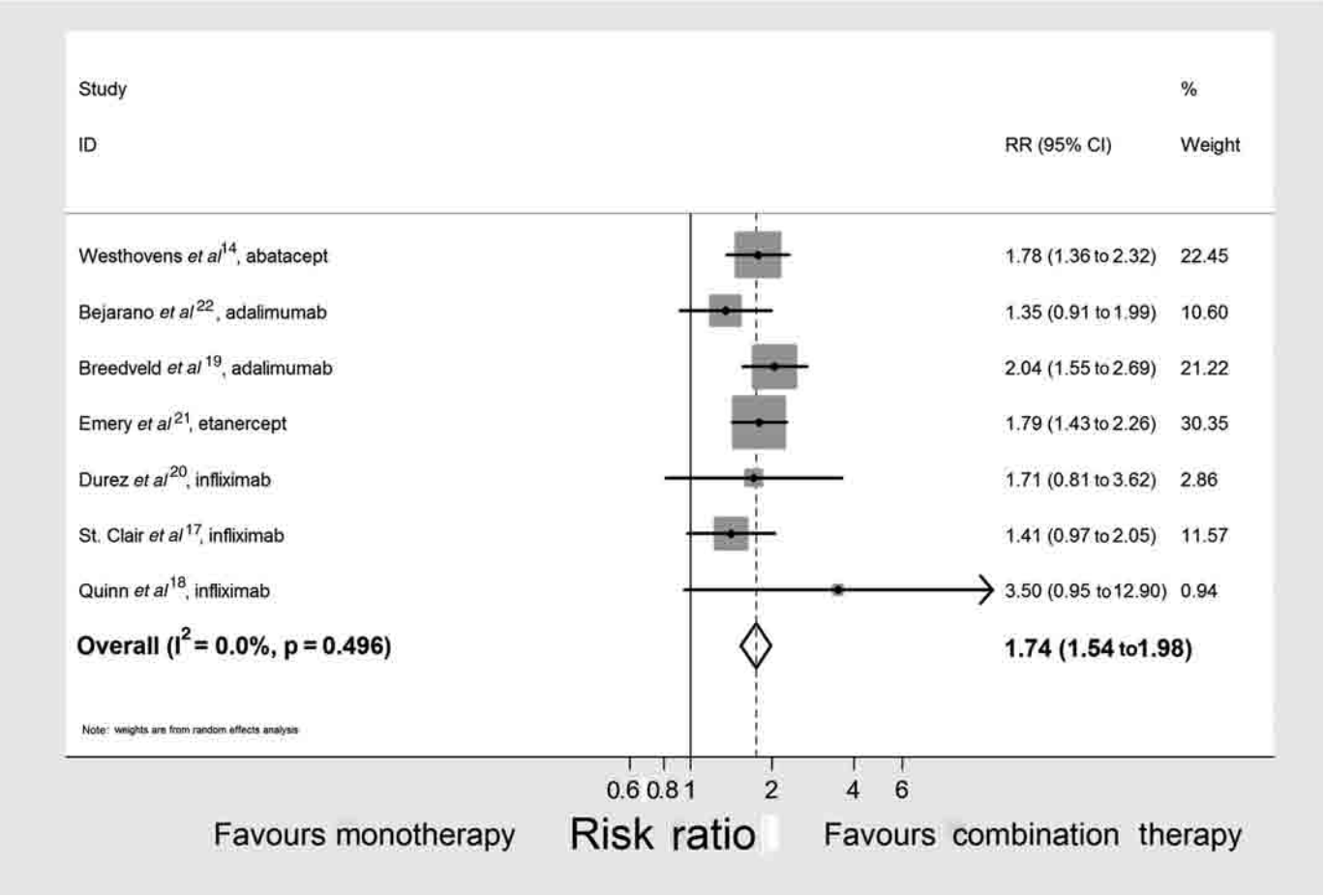

Figure 2 Forest plot of the risk ratio for attaining clinical remission using combination therapy versus monotherapy at follow-up.

been detected if more sensitive modalities to detect progression, such as magnetic resonance imaging or ultrasound were used. Prospective studies suggest that synovial hypertrophy and bone marrow oedema predict structural damage with greater accuracy and are more responsive to inhibition with biological therapy.[30 31] Despite the possible mechanisms, consideration must be given to the heterogeneity of the data included in this study, which resulted in a pooled estimate for radiographic remission with only borderline statistical significance. This may partly be explained by the different scoring systems used to measure radiographic progression.

Our results indicating only modest benefit of combination therapy with respect to radiographic non-progressors stand in stark contrast to individual RCT measuring a change in the van der Heijde-modified total Sharp score (TSS) as a primary outcome. Such studies have consistently identified marked suppression of radiographic progression (ie, reduced change in TSS) with combination therapy compared with that achieved with methotrexate monotherapy. It is of significance that the change in TSS is a reflection of progression among those who are radiographic progressors. In contrast, this meta-analysis evaluated the proportion of patients not progressing radiographically. The main incremental benefit of biological agents may thus lie in their ability to inhibit progression among those who will be rapid radiographic progressors, possibly by influencing the receptor activator of the natural killer κB ligand or osteoclast activation and differentiation.[8 32 33] This benefit of biological agents compared with methotrexate should be emphasised and evaluated in future trials.

The results of this meta-analysis also highlight how the magnitude of benefit observed for clinical and radiographic outcomes can differ in clinical trials. One reason for this disparity is that the DAS28 and ACR definitions of clinical remission used in these studies allow for residual tender and swollen joints and exclude evaluation of the feet. Synovitis is thus underestimated with the consequence that joint damage may occur even among patients deemed to be in a state of remission.[34] This difference might also be explained by insensitive techniques used to detect tender and swollen joints. In one study, close to 50% of patients with no clinical synovitis had readily detectable bone marrow oedema by magnetic resonance imaging.[35] The persistence of swelling is particularly relevant as swollen joints are a strong predictor of radiographic progression.[36]

There were some limitations to this study. Despite the approval of several biological agents for RA, our search retrieved only one eligible study of the selective co-stimulator blocker, abatacept, and no studies of rituximab or newer biological agents. The observed effect may thus not be true of all biological agents. Furthermore, the inclusion of subjects with very high disease activity, rendering them eligible for enrollment in RCT, may not reflect typical patients seen in real-world practice. The 1-year duration of follow-up also does not allow us to conclude whether remission can be sustained in the long term, although extension studies for many of the trials are now becoming available.[34] Our results may not be generalisable to populations with established disease, those with an inadequate response to methotrexate or those treated with previous DMARD/biological therapy. In addition, in the absence of cumulative probability plots and individual

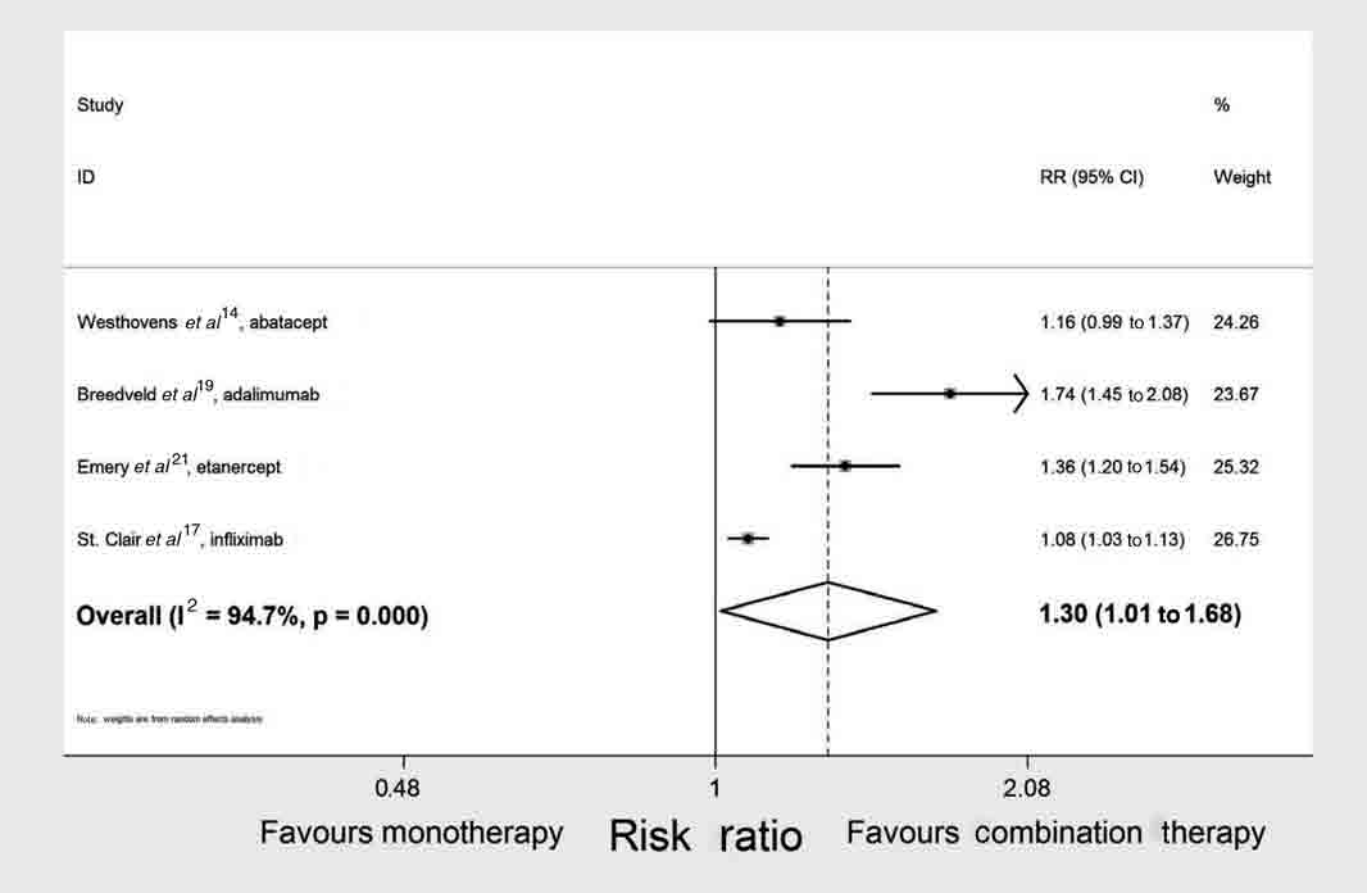

Figure 3 Forest plot of the risk ratio for attaining radiographic remission using combination therapy versus monotherapy at follow-up.

patient data, we are unable to comment on the concurrent risk of radiographic progression among those in a state of clinical remission. Finally, the focus of this review was efficacy and not safety endpoints. The risk–benefit profile appeared similar across RCT and the low risk of serious adverse events has been confirmed in a recent meta-analysis of this topic.[37]

In summary, the key findings of our study are as follows: (1) remission is an achievable goal in ERA; (2) initial combination therapy consisting of methotrexate plus a biological agent has superior efficacy for the induction of remission at 1 year; and (3) combination therapy has a greater initial effect on achieving clinical remission compared with radiographic non-progression.

Uniform definitions of remission will greatly enhance the reporting and interpretation of remission as a target outcome in future studies. Prediction of those who are most likely to benefit from this aggressive but costly form of therapy is needed. Attention should also be paid to the proportion of subjects who achieve the combined endpoint of clinical and radiographic remission, as this will provide important clues on how best to optimise the treatment of ERA.

Contributors All the authors meet the criteria for authorship, participated in the writing of the manuscript, and have seen and approved the submitted version.

Competing interests ECK has in the past received funding for research from Abbott, Amgen, Schering Plough and UCB, all companies that market anti-TNF therapies. VPB has received research funding from Amgen/Wyeth.

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