Arthritis Care & Research
Vol. 67, No. 11, November 2015, pp 1487–1495
DOI 10.1002/acr.22618

ORIGINAL ARTICLE

Combination Therapy With and Without Tumor Necrosis Factor Inhibitors in Rheumatoid Arthritis: A Meta-Analysis of Randomized Trials

NIELS GRAUDAL,[1] THORBJØRN HUBECK-GRAUDAL,[2] MIKKEL FAURSCHOU,[1] BO BASLUND,[1] AND GESCHE JÜRGENS[3]

Objective. **The costs of biologic treatment per patient with rheumatoid arthritis (RA) are approximately 100 times the costs of treatment with a combination of conventional disease-modifying antirheumatic drugs (DMARDs). Despite this, biologic agents have not been proven superior. We compared the effects of combination DMARD therapies with and without biologic agents as therapy for patients with RA.**

Methods. **Eight randomized controlled trials published in 10 articles were selected from a systematic literature search of 1,674 identified studies and integrated in a meta-analysis. These trials compared combinations of DMARDs versus a tumor necrosis factor (TNF) inhibitor plus methotrexate. Two reviewers independently entered data into standardized extraction forms. The combined effect measures were compared by means of the inverse variance method (continuous data) and the Mantel-Haenszel method (dichotomous data) using a random-effects model.**

Results. **The primary outcome, radiographic progression score, did not differ between the combination DMARD group and the TNF inhibitor group, neither during the second year (−0.09 units [−0.61, 0.44]) of treatment or during the first 2 years (0.66 units [−0.12, 1.43]). There were significant differences in the radiographic progression score, the American College of Rheumatology criteria for 50% improvement (ACR50), and the ACR70 response criteria at 6 months in favor of TNF inhibitor treatment, but these differences were not present in patients treated with an initial steroid course and disappeared at 24 months, irrespective of the use of steroids.**

Conclusion. **The difference between DMARD combination treatments, including or excluding TNF inhibitors, is small. Due to the enormous cost differences, RA guidelines should recommend combination DMARD treatment before initiation of TNF inhibitors.**

INTRODUCTION

In patients with rheumatoid arthritis (RA), treatment with a biologic agent plus a disease-modifying antirheumatic drug (DMARD) is superior to a single DMARD (1). Furthermore, a combination of 2 or more DMARDs is superior to a single DMARD (1). A recent indirect comparison network meta-analysis indicated that the effects of combination treatments with and without biologic agents might have similar properties to reduce radiographic joint destruction (2). Until recently, only 1 randomized controlled trial (RCT) directly supported this hypothesis (3,4). The 4 most sold drugs in the world with regard to sales (but not defined daily doses) are biologic agents primarily indicated for RA (adalimumab, infliximab, rituximab, and etanercept). The total yearly sales of these are approximately 36 billion US dollars (5). Some RA patients can experience successful treatment with half a dose of rituximab once per year, costing only 25% of other biologic treatments, but they are still more expensive than conventional inexpensive DMARDs. When giving priority to these treatments, it is therefore essential to know the relative effect on disease activity and progression of the inexpensive DMARDs compared to the effect of biologic agents. The objective of the present meta-analysis of RCTs in RA patients was to compare combination treatments with biologic drugs versus combination treatments without biologic drugs, using progression of radiographic joint de-

Supported by the A. P. Møller Foundation for the Advancement of Medical Science.

[1]Niels Graudal, MD, DMSc, Mikkel Faurschou, MD, PhD, Bo Baslund, MD, PhD: Copenhagen University Hospital, Rigshospitalet, Copenhagen, Denmark; [2]Thorbjørn Hubeck-Graudal, MD: Copenhagen University Hospital, Bispebjerg, Denmark; [3]Gesche Jürgens, MD, PhD: Roskilde University Hospital, Roskilde, Denmark.

Dr. Jürgens has received royalties for textbooks in clinical pharmacology.

Address correspondence to Niels Graudal, MD, DMSc, Department of Rheumatology IR4242, Copenhagen University Hospital, Rigshospitalet, Blegdamsvej 9, DK-2100 Copenhagen, Denmark. E-mail: graudal@dadlnet.dk.

Submitted for publication December 4, 2014; accepted in revised form May 5, 2015.

Significance & Innovations

- Three of the 4 most sold drugs in the world are tumor necrosis factor inhibitors for rheumatoid arthritis (RA). The total yearly costs for these are approximately 28 billion dollars (US).
- Effects comparable to the effects of these expensive drugs can be obtained by means of a combination of conventional disease-modifying antirheumatic drugs (DMARDs) at much lower costs.
- The inexpensive combination DMARD treatment should be appealing not only in regions with low health budgets, but everywhere.
- Guidelines should recommend combination treatment with synthetic DMARDs as a standard treatment of RA before the use of biologic agents, which should be considered second-line drugs for patients with inadequate response to combination DMARD treatment.

struction as primary outcome, and American College of Rheumatology 20%, 50%, and 70% (ACR 20/50/70) improvement criteria (6), the disease activity score in 28 joints (DAS28), and the Health Assessment Questionnaire (HAQ) scores as secondary outcomes.

MATERIALS AND METHODS

Protocol and registration. The analysis is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) (7). The protocol has been registered in PROSPERO and can be accessed at http://www.crd.york.ac.uk/PROSPERO; registration number CRD42014008896.

Eligibility criteria. *Types of studies.* We included full-length studies published in peer-reviewed journals that were performed according to a randomized controlled trial design, irrespective of language, sample size, and publication year, and within the limits of the electronic databases.

Participants. Patients with RA diagnosed according to the 1987 or later criteria of the ACR were included.

Types of interventions. Studies that compared a combination of conventional DMARDs versus a combination of biologic drugs plus a DMARD were included. As our previous meta-analysis showed no statistically significant differences between methotrexate, sulfasalazine, cyclosporine, leflunomide, and injectable gold (1), we included studies in which the combination DMARD treatment arm included at least 1 of these effective DMARDs. A low-dose glucocorticoid (GC) is not a DMARD, but it is suitable for shorter-term treatment during the initial treatment phase and during flares. It is an open question whether a low-dose GC is acceptable for longer-term treatment, but there is no definitive evidence to prove that longer-term treatment with a low-dose GC is harmful. As low-dose GCs are inexpensive, and as we previously showed that low-dose GC, defined as maximally 7.5 mg prednisone or prednisolone per day, had an effect similar to the effective DMARDs (1), low-dose GCs were included as a DMARD equivalent. Subcutaneous or intraarticular depot steroid doses, corresponding to a daily dose of maximally 7.5 mg prednisolone, were also accepted as a DMARD equivalent in the combination DMARD arm. The second/third/fourth/fifth drug could be one of these effective DMARDs or low-dose GCs or one of the less effective DMARDs (chloroquine, D-penicillamine, azathioprine, cyclophosphamide, and orally administered gold). In the biologic treatment arm, we accepted combination treatments of a single DMARD plus a tumor necrosis factor (TNF) inhibitor (etanercept, infliximab, adalimumab, certolizumab, and golimumab), a single DMARD plus abatacept, a single DMARD plus tocilizumab, and a single DMARD plus a CD20 inhibitor (rituximab).

Types of outcome. The following outcomes were intended to be recorded: joint radiograph scores at $\geq$2 separate time points within a time interval of at least 3 months (primary outcome), ACR 20/50/70 response criteria, changes in C-reactive protein (CRP) level and erythrocyte sedimentation rate (ESR), joint swelling score, DAS28 score, HAQ score, adverse events, and dropouts (secondary outcomes). Any of these outcomes that turned out to be only sporadically reported would be eliminated from the final analysis.

Conventional DMARDs achieve their potential effect after 3–6 months, whereas biologic drugs often achieve this effect after days or weeks. Furthermore, in many trials the synthetic DMARD arm is a "step-up" arm, which means that the maximal dose is achieved after several months of treatment in this arm. As these biases favor the biologic treatment, we defined the primary level of outcome to be the difference between the last followup measure of the radiographic score and the previous measure of the radiographic score (progression rate), because this level would exclude the initial values obtained at a stage where the DMARD-treated patients did not yet experience maximal therapeutic effect. The radiographic outcome was also shown as a difference to baseline value at all measurement points, as were all other outcomes.

Information sources. The last search date was September 12, 2014. Our previous search, which covered 1955 to December 30, 2009 (1), revealed that at this time point, only 1 study comparing combination treatments with and without biologic agents had been published. To ensure that we did not overlook studies published during 2009, we searched the electronic databases (PubMed, the Cochrane Central database, and ClinicalTrials.gov) from January 1, 2009 up to September 12, 2014. Furthermore, we scanned the lists of references from the identified randomized trials.

Search methods for identification of studies. In order to ensure as broad a search as possible, the search in PubMed and in Cochrane Central was based on the following combination of search terms: "rheumatoid arthritis and randomized OR rheumatoid arthritis and randomized." In the randomized search in ClinicalTrials.gov, we used

rheumatoid arthritis as a search term, limited by completed intervention studies with results. The searches were performed successively and independently. The primary search was in PubMed, the second in Clinicaltrials.gov, and the third in Cochrane Central.

Data collection. *Selection of trials.* Titles were screened, abstracts read, and possible papers were retrieved. Trials fulfilling eligibility criteria were included in the systematic review.

Data extraction. Four authors were involved in the selection of trials and data extraction. Eligibility assessment (NG and GJ), data collection (NG, THG, MF, and BB,), and risk of bias assessment (NG and THG) were performed independently by at least 2 authors and disagreement resolved by consensus. All data were entered into standardized extraction forms (piloted by NG) on the basis of experience from a previous analysis (1).

Data items. Mean measurements and SDs of outcomes were recorded at all measurement times for continuous variables (radiographic score, CRP level, ESR, joint swelling score, DAS28, HAQ score) and absolute numbers for dichotomous variables (ACR20, ACR50, ACR70, adverse events, serious adverse events, and dropouts). If the dichotomous values were reported as percentages, they were transformed to absolute values.

In addition, the following variables were recorded: study identification, year of publication, type of intervention in treatment arms, number of patients in each treatment arm, mean age of patients, duration of RA at baseline, duration of study, DMARD inadequate response (i.e., whether included patients previously had had an inadequate response to a least 1 DMARD), strategy change (i.e., whether a change of treatment strategy was allowed during the course of the study), mean daily GC use in all treatment arms, and percentage of IgM rheumatoid factor (RF)–positive patients.

Risk of bias in individual studies. Six different risk of bias domains, as defined by Cochrane (8), were assessed on the study level: sequence generation, allocation concealment, study blinding, outcome assessor blinding, incomplete outcome data, and selective outcome reporting. In addition, we included radiographic sequence blinding and company sponsoring as risk of bias domains. Each of the above 8 assessed risk of bias domains were evaluated in 3 groups: A, low risk; B, unclear risk; and C, high risk (8).

Measures of treatment effect. For each randomized combination drug group, the difference between followup measurement and previous measurement and the corresponding SD were recorded for continuous variables. The difference between the mean effect in the combination drug group with and without a biologic drug was the treatment effect. The ACR20/50/70 response outcomes were recorded as measured and compared directly between the combination drug group with and without biologic treatment.

Data analysis. *Unit of analysis issues.* In trials with several dose arms of biologic agents, only the defined standard dose arm was included.

Missing data. In articles where the median, but not the mean, was given, the median value was used in the calculations. If the SD was not given, it could often be calculated from a 95% confidence interval, an SE, or a *P* value (8). An interquartile range (2 quartiles) was made equivalent to $1.35 \times$ SD (8).

Heterogeneity. Heterogeneity between studies was examined for all studies and each intervention by a chi-square test (8). Potential heterogeneity would be explored by means of subgroup analyses of extracted data.

Outcome data synthesis. A continuous outcome was analyzed as a weighted mean difference, and a dichotomous outcome was analyzed as a relative risk (8).

Risk of bias across studies. Differences across studies were explored in sensitivity analyses. In addition, publication bias was evaluated visually by means of a funnel plot, in which the effect of each trial was plotted by the inverse of its SE (8).

Additional analyses. Randomized trials of a biologic drug plus methotrexate versus combination DMARD treatment are generally performed in DMARD-inadequate responders, which introduce a bias in favor of the biologic drug. This bias was opposed by separate analyses of studies of DMARD-naive and DMARD-inadequate patients.

Data synthesis method. The combined effect measures of the direct comparisons of the individual combination treatments were compared by means of the inverse variance method (continuous data) and the Mantel-Haenszel method (dichotomous data) in Review Manager (RevMan; Cochrane Collaboration), version 5.1. As we accumulated data from a series of studies that had been performed by researchers operating independently, and as the goal of the analysis was to extrapolate to other populations, we used a random-effects model in our primary analysis to estimate the summary measure as the mean of a distribution of effects. In a secondary analysis, we used a fixed-effects model, assuming that the true effect size for all studies is identical. As we move from random effect to fixed effect, extreme studies will gain influence if they are large, and they will lose influence if they are small. If there is no heterogeneity ($tau^2 = 0$ and $I^2 = 0$), the 2 models are identical.

RESULTS

Study selection. A flow chart of the study selection is shown in Figure 1. Fifty-one retrieved papers were excluded because they did not compare combination treatments versus combination treatment, and 3 were excluded because they compared add-on biologic agents or placebo to combination treatment. Twenty papers were included; these represented 8 studies. The data to be included were reported in 10 of these 20 papers. These 10 papers representing 8 studies were included in the final analysis (3,4,9–16).

Study characteristics. Baseline characteristics of included studies are shown in Supplementary Table 1 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract). The mean patient age and the HAQ scores were similar, and in 7 of

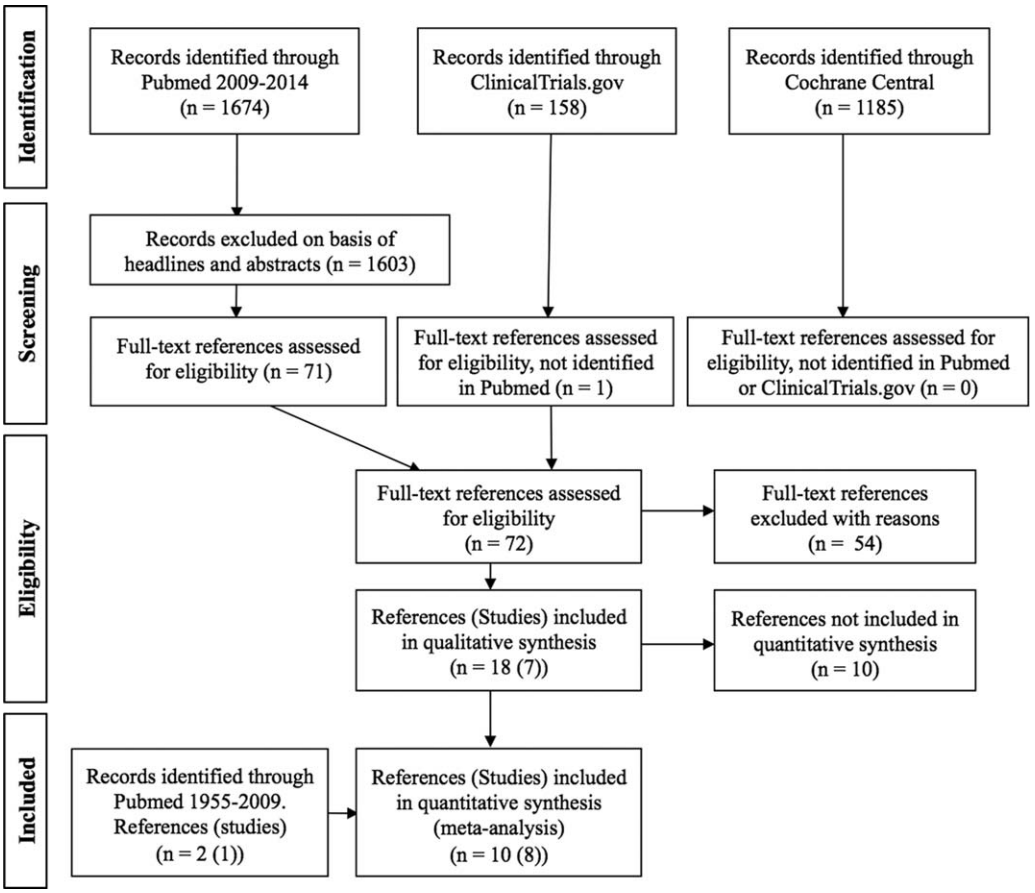

Figure 1. Flow chart of study selection.

8 studies there was a female predominance, but the other variables varied significantly. Five studies were performed in early arthritis patients, whereas 3 were performed in patients with a mean disease duration of ≥5 years. Three studies were performed in DMARD-naive patients. The baseline disease activity estimated by DAS28 varied with a factor 2, and the fraction of RF-positive patients varied between 50% and 90%. Finally, there was a large variation in the use of steroids, some of which, however, was a consequence of the study designs.

The within-study risks of bias on the study level are shown in Supplementary Table 2 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract). The most obvious bias source was lack of blinding in 5 studies. The primary outcome (radiographic score) was, however, blinded in all 7 studies, which measured radiographic outcome. All studies used the same method (a modified Sharp scoring method) to score the radiographs. Two studies were company sponsored.

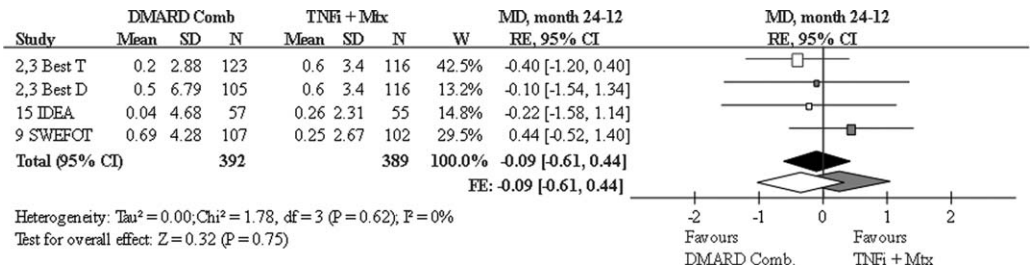

Figure 2. Primary outcome during second year: change in radiographic score from month 12 to month 18–24. White diamond/square = disease-modifying antirheumatic drugs (DMARDs) + initial glucocorticoid; grey diamond/square = DMARDs only; black diamond = combined; Comb = combination; Best = Treatment Strategies for Rheumatoid Arthritis; T = triple; D = double; IDEA = Infliximab as Induction Therapy in Early Rheumatoid Arthritis; SWEFOT = Swedish Farmacotherapy; TNFi = tumor necrosis factor inhibitor; Mtx = methotrexate; W = weight; MD = mean difference; RE = random effect; 95% CI = 95% confidence interval; FE = fixed effect.

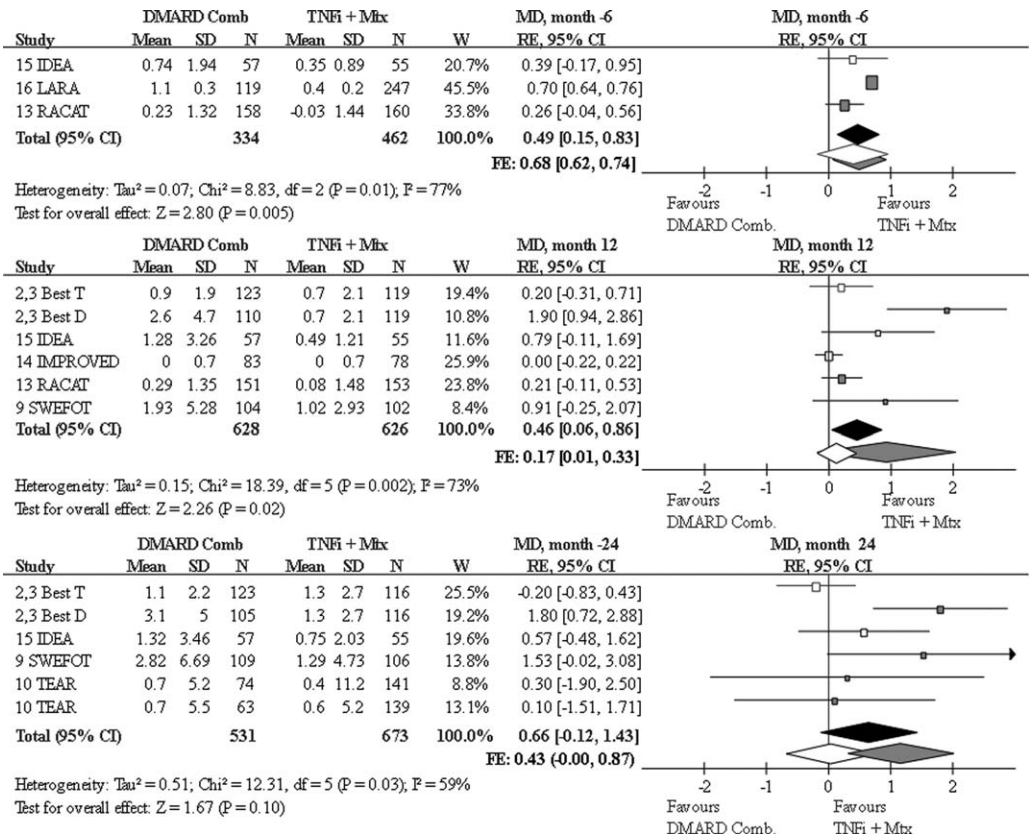

Figure 3. Primary outcome at months 6, 12, and 24. Change in radiographic score at months 6, 12, and 18–24. Elimination of heterogeneity: exclusion of LARA study at month 6: 0.29 (0.02, 0.56), $P = 0.03$; exclusion of Treatment Strategies for Rheumatoid Arthritis (Best; double [D]) study at month 12: 0.17 (−0.05, 0.40), $P = 0.13$ (random effect [RE]) or 0.12 (−0.04, 0.29), $P = 0.15$ (fixed effect [FE]); exclusion of Best D study at month 24: 0.26 (−0.32, 0.84) (RE) or 0.17 (−0.30, 0.64) (FE). White diamond/square = disease-modifying antirheumatic drugs (DMARDs) + initial glucocorticoid; grey diamond/square = DMARDs only; black diamond = combined; Comb = combination; IDEA = Infliximab as Induction Therapy in Early Rheumatoid Arthritis; LARA = Latin America RA Study; RACAT = Rheumatoid Arthritis of Active Comparison Therapies; TNFi = tumor necrosis factor inhibitor; Mtx = methotrexate; W = weight; MD = mean difference; 95% CI = 95% confidence interval; T = triple; IMPROVED = Induction Therapy With MTX and Prednisone in Rheumatoid or Very Early Arthritis Disease; SWEFOT = Swedish Farmacotherapy; TEAR = Treatment of Early Aggressive Rheumatoid Arthritis Trial.

Concerning outcomes, only 1 study presented ESRs (14), 1 study presented CRP levels (11), and 3 studies presented joint swelling scores (10,14,16). Consequently, these outcomes, which we defined in the protocol, were not summarized in the present analysis.

Interventions, results of individual studies, and synthesis of results. Only the 2 TNF inhibitors, infliximab and etanercept, were identified as biologic drugs being compared with combinations of DMARDs. The results of individual studies are shown in Figures 2–5 and Supplementary Figures 1–3 (available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract). Data were reported at 3, 6, 12, 18, and 24 months. Not all studies gave data at all 5 time points. Only 1 study delivered data at 3 months and 1 study at 18 months. Consequently, the 3 months' data were combined with the 6 months' data, and the 18 months' data were combined with the 24 months' data, and the data were synthesized at 3 time points (3/6, 12, and 18/24 months).

The main outcome is shown in Figures 2 and 3. There was no difference in radiographic progression between the 2 treatment groups in the period between month 12 and month 24 (Figure 2). When comparing with the baseline, there were significant differences in favor of a TNF inhibitor at 6 and 12 months, but the difference disappeared at 24 months (Figure 3). In studies using an intermediate GC treatment, there was no difference at any time (Figure 3). Figures 4 and 5 and Supplementary Figures 1–3 show similar patterns for the secondary outcomes. At 3/6 months, there were significant or borderline significant results in favor of TNF inhibitors plus methotrexate. At 12 months ACR 20/50/70 outcomes were still significant in favor of a TNF inhibitor, but at 18/24 months there were no statistically significant differences between the treatments.

There was no difference in number of side effects (Figure 6 and Supplementary Figure 4), whereas the number of dropouts in the DMARD group exceeded the TNF inhibitor group (Supplementary Figure 5, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract).

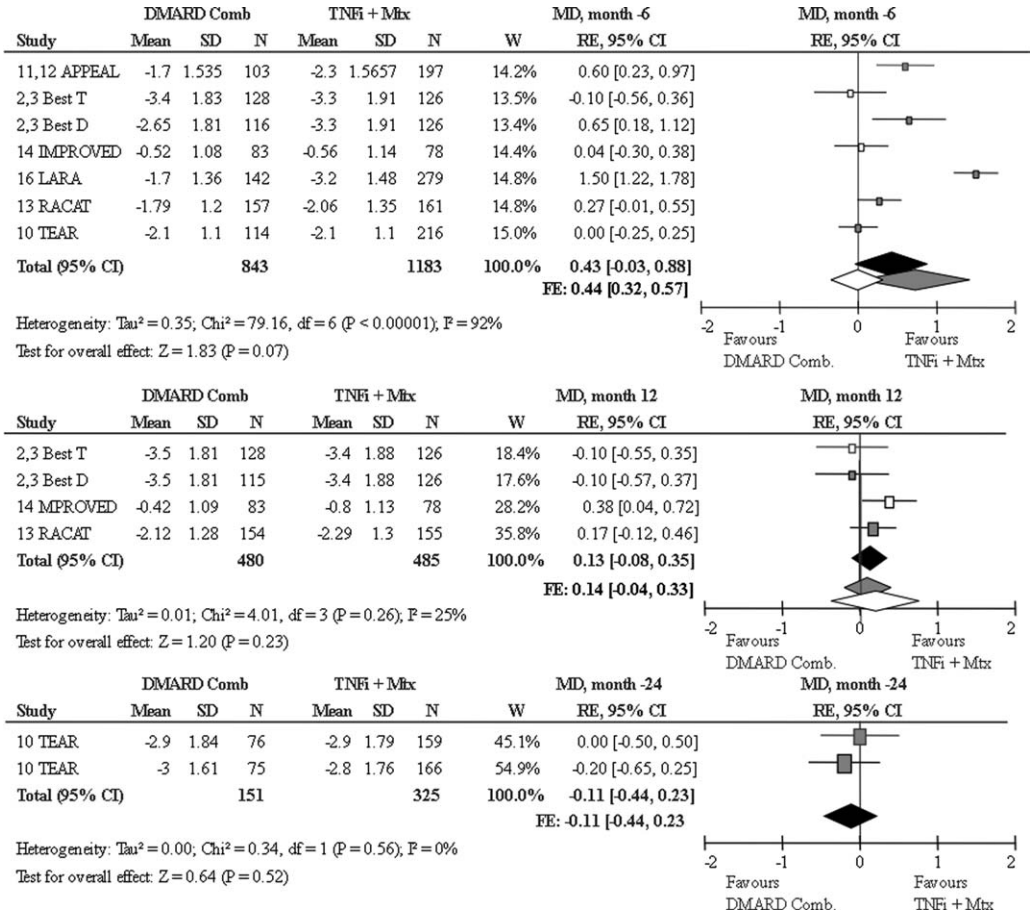

Figure 4. Change in Disease Activity Score in 28 joints score at months 6, 12, and 18–24. Elimination of heterogeneity: exclusion of APPEAL, LARA, and Treatment Strategies for Rheumatoid Arthritis (Best; double [D]) studies at month 6 reduces the difference: 0.08 (−0.08, 0.23), $P = 0.32$ (fixed effect [FE] and random effect [RE]). White diamond/square = disease-modifying antirheumatic drugs (DMARDs) + initial glucocorticoid; grey diamond/square = DMARDs only; black diamond = combined. See Figure 3 for definitions.

Risk of bias across studies. All analyses showed heterogeneity at 6 months, but few at 12 and 24 months. At 6 months, heterogeneity disappeared after the elimination of studies or treatment arms not using GC (3,11,12,16), which resulted in nonsignificant differences between a TNF inhibitor plus methotrexate and combination DMARD treatment (Figures 4 and 5, and Supplementary Figures 1 and 2), with the exception of radiographic progression (Figure 3) and ACR70 response, (Supplementary Figure 3).

Additional analyses. After exclusion of the company-sponsored studies, there were no significant differences between studies using initial steroids and those that did not, but there was a trend to reduce the difference in favor of studies using steroids (Supplementary Table 3, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract). The effects of studies using GC and those that only use DMARDs, are separated on Figures 2–6 and Supplementary Figures 2–5). There were no differences between double-blind and open studies (Supplementary Table 4).

DISCUSSION

The only identified biologic drugs, which were compared versus combination DMARD treatment, were 2 TNF inhibitors (infliximab and etanercept). A study adding adalimumab/placebo (17) and a study adding infliximab/placebo (18) to combination treatment were not included, as these studies essentially compared a biologic versus placebo and not versus combination treatment. We chose radiographic joint destruction as the main outcome. Radiographic destruction is progressive during the full course of RA, irreversible, and approximately linear (1,19–21), and consequently reflects as well the physiologic end point as the course of RA. Our analysis showed that the effect of a TNF inhibitor plus methotrexate was significantly superior to combination DMARD treatment during the first 6 months, but this difference almost disappeared after 12 months, and especially after 18/24 months (no outcomes differed). Furthermore, in 3 studies using an initial course of steroids (3,4,14,15), there was no difference between the 2 treatment principles at any time (Figures 2–5 and Supplementary Figures 1–3, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract).

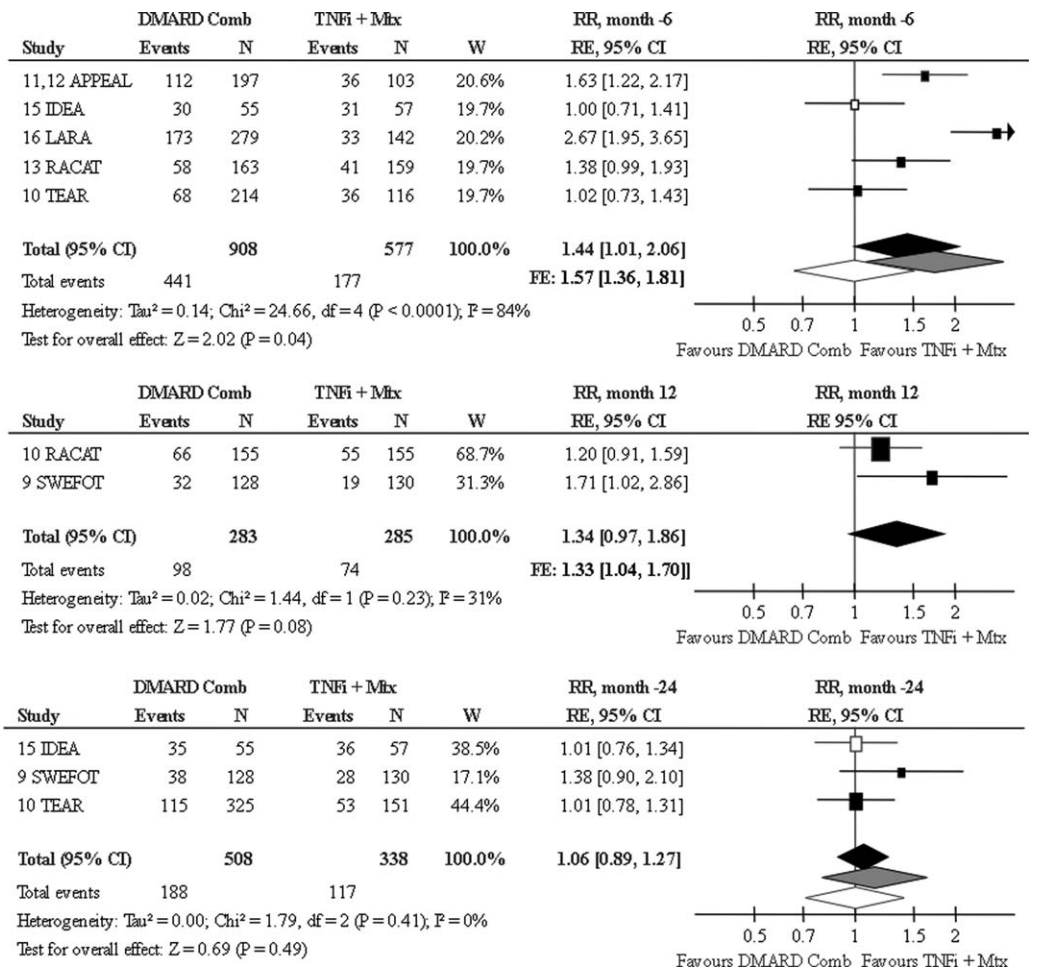

Figure 5. Change in American College of Rheumatology 50% improvement criteria (ACR50) at months 6, 12, and 18–24. Elimination of heterogeneity: exclusion of LARA and APPEAL studies at month 6 reduces the difference: 1.14 (0.94, 1.39), $P = 0.18$ (fixed effect [FE]) or 1.12 (0.92, 1.38), $P = 0.26$ (random effect [RE]). White diamond/square = disease-modifying antirheumatic drugs (DMARDs) + initial glucocorticoid; grey diamond/square = DMARDs only; black diamond = combined; RR = relative risk. See Figure 3 for definitions.

The BEST (Behandelstrategieën voor Reumatoide Artritis; Treatment Strategies for Rheumatoid Arthritis) study (3,4) was the first to indicate that a combination of conventional DMARDs might have the same effect as a TNF inhibitor plus methotrexate. As recently reviewed, 13 very similar network meta-analyses have shown similarity of different biologic agents (22), but the relative effects of a combination of conventional DMARDs versus biologic agents have only been compared indirectly in 1 network meta-analysis (2) and in 2 conventional meta-analyses (1,23). Consequently, the present analysis is the first to integrate all available evidence directly comparing a combination of DMARDs versus a biologic treatment plus methotrexate, and is also the first to estimate the effect at consecutive time points during a period of 2 years. Although only TNF inhibitors were investigated, it is likely that the present results could be extended to other biologic agents, as the biologic agents in general have been shown to be equally efficacious (2,22,24).

Considering the approximately 200 studies comparing biologic drugs versus placebo (25), the identification of only 8 studies directly comparing a biologic drug versus a combination of DMARDs reflects the insufficient focus within this treatment area and the general lack of fair control arms in available studies (1,2,26).

A recent study showed that 86% of published RCTs of RA patients found a significant effect of the tested intervention, in contrast to approximately 30% of unpublished studies (27). The potential elimination of such a classic possible publication bias against less significant results would strengthen the present results, further indicating that the difference between the 2 treatment principles, with and without biologic agents, is small.

Our analysis has several strengths: 1) the primary outcome (radiographic score) was evaluated blindly, even in the open studies, 2) all outcome definitions were identical across studies, 3) all outcomes, which in principle should be mutually dependent, generally had trends in the same direction, although not consistently significant, and 4) in contrast to most previous studies involving biologic treatments, most (6 of 8) studies were investigator-initiated.

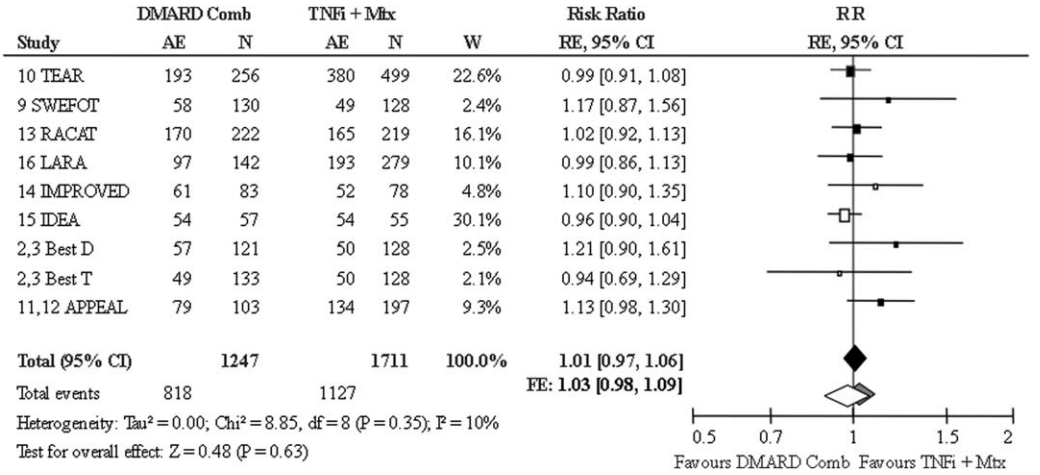

Figure 6. Adverse events (AEs): total number of AEs in each treatment arm. White diamond/square = disease-modifying antirheumatic drugs (DMARDs) + initial glucocorticoid; grey diamond = DMARDs only; black diamond/square = combined; RR = relative risk. See Figure 3 for definitions.

It was a potential disadvantage that GC was necessary to obtain complete equal efficacy of inexpensive treatments, but this GC use was limited to a relatively short period. Furthermore, in several of the studies, where GC was not included in the randomized treatment, there was still a significant use of GC, even in participants treated with TNF inhibitors.

Our analysis has limitations, but it is unlikely that these limitations should hide differences in favor of TNF inhibitors big enough to justify the enormous cost differences. Consequently, it may be reasonable to classify the biologic drugs as high-cost drugs and the DMARDs as low-cost drugs, as the cost is a more important factor for the determination of treatment than the molecular structure and the potential effect. The combination of our previous search with a new search from the date of the previous search may be considered a limitation, but this method is accepted when updating Cochrane reviews. On the outcome level, the patient populations varied across studies (see Supplementary Tables 1 and 2, available in the online version of this article at http://onlinelibrary.wiley.com/doi/10.1002/acr.22618/abstract). In spite of this, only 1 bias factor contributed to heterogeneity and had a statistically significant impact on the outcomes. This bias involved 2 studies, which were performed in Asia and Latin America, in patients with long disease duration, an inadequate response to previous DMARDs, and no treatment with a course of GC (11,12,16). In contrast, the other studies (3,4,9,10,13,15) were performed in North America and Europe, and generally in DMARD-naive early arthritis patients.

In conclusion, combination treatment with at least 2 DMARDs, 1 of which could be low-dose GC, prevents inflammatory symptoms and structural joint damage to the same degree as a TNF inhibitor combined with methotrexate after 2 years of treatment. During the first year, the equal efficacy is delayed, but the delay can be eliminated by an initial high-dose steroid course. The result is important because of its potential to reduce health care expenses and to change clinical practice, at least in some countries. Future studies should not compare biologic agents with placebo or single DMARD therapy, but should have sufficient power to investigate equal efficacy or superiority of biologic agents to a combination of conventional DMARDs. Combination treatment with synthetic DMARDs should be introduced as a standard treatment of RA and given a higher priority than in the present guidelines (28,29). Expensive drugs should still, as originally intended, be reserved for patients that are insufficiently treated with a combination of at least 2–3 conventional DMARDs.

AUTHOR CONTRIBUTIONS

All authors were involved in drafting the article or revising it critically for important intellectual content, and all authors approved the final version to be submitted for publication. Dr. Graudal had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study conception and design. Graudal, Hubeck-Graudal, Faurschou, Baslund, Jürgens.

Acquisition of data. Graudal, Hubeck-Graudal, Faurschou, Baslund, Jürgens.

Analysis and interpretation of data. Graudal, Hubeck-Graudal, Faurschou, Baslund.

REFERENCES

1. Graudal N, Jurgens G. Similar effects of disease-modifying antirheumatic drugs, glucocorticoids, and biologic agents on radiographic progression in rheumatoid arthritis: meta-analysis of 70 randomized placebo-controlled or drug-controlled studies, including 112 comparisons. Arthritis Rheum 2010;62:2852–63.
2. Graudal N, Hubeck-Graudal T, Tarp S, Christenden R, Jurgens G. Effect of combination therapy on joint destruction in rheumatoid arthritis: a network meta-analysis of randomized controlled trials. Plos One 2014;9:e106408.
3. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Clinical and radiographic outcomes of four different treatment strategies in patients with early rheumatoid arthritis (the BeSt study): a randomized, controlled trial. Arthritis Rheum 2005;52:3381–90.

4. Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, van Zeben D, Kerstens PJ, Hazes JM, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. Ann Intern Med 2007;146:406–15.
5. King S. FirstWord lists: top 50 growth driver drugs in 2013. URL: http://www.firstwordpharma.com/node/1192742#axzz3IHhNi1Ft.
6. Felson DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C, et al. American College of Rheumatology preliminary definition of improvement in rheumatoid arthritis. Arthritis Rheum 1995;38:727–35.
7. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gotzsche PC, Ioannidis JP, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. BMJ 2009;339:b2700.
8. The Cochrane Collaboration. Higgins JP, Green S, editors. Cochrane handbook for systematic reviews of interventions, version 5.0.1., section 7.7.3. 2009. URL: www.cochrane-handbook.org.
9. Van Vollenhoven RF, Geborek P, Forslind K, Albertsson K, Ernestam S, Petersson IF, et al. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 year follow-up of the randomised, non-blinded, parallel-group Swefot trial. Lancet 2012;379:1712–20.
10. Moreland LW, O'Dell JR, Paulus HE, Curtis JR, Bathon JM, St Clair EW, et al, for the TEAR Investigators. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: the Treatment of Early Aggressive Rheumatoid Arthritis Trial. Arthritis Rheum 2012;64:2824–35.
11. Kim HY, Hsu PN, Barba M, Sulaiman W, Robertson D, Vlahos B, et al. Randomized comparison of etanercept with usual therapy in an Asian population with active rheumatoid arthritis: the APPEAL trial. Int J Rheum Dis 2012;15:188–96.
12. Bae SC, Gun SC, Mok CC, Khandker R, Nab HW, Koenig AS, et al. Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis. BMC Musculoskelet Disord 2013;14:13.
13. O'Dell JR, Mikuls TR, Taylor TH, Ahluwalia V, Brophy M, Warren SR, et al, for the CSP 551RACAT Investigators. Therapies for active rheumatoid arthritis after methotrexate failure. N Engl J Med 2013;369:307–18.
14. Heimans L, Wevers-de Boer KV, Visser K, Goekoop RJ, van Oosterhout M, Harbers JB, et al. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. Ann Rheum Dis 2014;73:1356–61.
15. Nam JL, Villeneuve E, Hensor EM, Conaghan PG, Keen HI, Buch MH, et al. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). Ann Rheum Dis 2014;73:75–85.
16. Machado DA, Guzman RM, Xavier RM, Simon JA, Mele L, Pedersen R, et al. Open-label observation of addition of etanercept versus a conventional disease-modifying antirheumatic drug in subjects with active rheumatoid arthritis despite methotrexate therapy in the Latin American region. J Clin Rheumatol 2014;20:25–33.
17. Axelsen MB, Eshed I, Horslev-Petersen K, Stengaard-Pedersen K, Hetland ML, Moller J, et al, for the OPERA Study Group. A treat-to-target strategy with methotrexate and intra-articular triamcinolone with or without adalimumab effectively reduces MRI synovitis, osteitis and tenosynovitis and halts structural damage progression in early rheumatoid arthritis: results from the OPERA randomised controlled trial. Ann Rheum Dis 2015;74:867–75.
18. Leirisalo-Repo M, Kautiainen H, Laasonen L, Korpela M, Kauppi MJ, Kaipiainen-Seppanen O, et al, for the NEO-RACo Study Group. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). Ann Rheum Dis 2013;72:851–7.
19. Graudal NA, Jurik AG, de Carvalho A, Graudal HK. Radiographic progression in rheumatoid arthritis: a long-term prospective study of 109 patients. Arthritis Rheum 1998;41:1470–80.
20. Graudal N, Tarp U, Jurik AG, Galloe AM, Garred P, Milman N, et al. Inflammatory patterns in rheumatoid arthritis estimated by the number of swollen and tender joints, the erythrocyte sedimentation rate, and hemoglobin: long-term course and association to radiographic progression. J Rheumatol 2000;27:47–57.
21. Graudal N. The natural history and prognosis of rheumatoid arthritis: association of radiographic outcome with process variables, joint motion and immune proteins. Scand J Rheumatol 2004; Suppl 118:1–37.
22. Thorlund K, Druyts E, Avina-Zubieta JA, Wu P, Mills EJ. Why the findings of published multiple treatment comparison meta-analyses of biologic treatments for rheumatoid arthritis are different: an overview of recurrent methodological shortcomings. Ann Rheum Dis 2013;72:1524–35.
23. Ma MH, Kingsley GH, Scott D. A systematic comparison of combination DMARD therapy and tumour necrosis inhibitor therapy with methotrexate in patients with early rheumatoid arthritis. Rheumatology (Oxford) 2010;49:91–8.
24. Weinblatt ME, Schiff M, Valente R, van der Heijde D, Citera G, Zhao C, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. Arthritis Rheum 2013;65:28–38.
25. Ioannidis JP, Karassa FB, Druyts E, Thorlund K, Mills EJ. Biologic agents in rheumatology: unmet issues after 200 trials and $200 billion sales. Nat Rev Rheumatol 2013;9:665–73.
26. Estellat C, Ravaud P. Lack of head-to-head trials and fair control arms: randomized controlled trials of biologic treatment for rheumatoid arthritis. Arch Intern Med 2012;172:237–44.
27. Khan NA, Singh M, Spencer HJ, Torralba KD. Randomized controlled trials of rheumatoid arthritis registered at ClinicalTrials.gov: what gets published and when. Arthritis Rheum 2014;66:2664–74.
28. Smolen JS, Landewe R, Breedveld FC, Buch M, Burmester G, Dougados M, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis 2014;73:492–509.
29. Singh JA, Furst DE, Bharat A, Curtis JR, Kavanaugh AF, Kremer JM, et al. 2012 Update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken) 2012;64:625–39.