Added value of combining methotrexate with a biological agent compared to biological monotherapy in rheumatoid arthritis patients:

A systematic review and meta-analysis of randomised trials

Simon Tarp[1*], Tanja S. Jørgensen[1*], Daniel E. Furst[2], Anna Dossing[1], Peter C. Taylor[3], Ernest H. Choy[4], Maria E. Suarez-Almazor[5], Anne Lyddiatt[6], Lars E. Kristensen[1], Henning Bliddal[1], and Robin Christensen[1]

Author details:

[1]Musculoskeletal Statistics Unit, The Parker Institute, Bispebjerg and Frederiksberg Hospital, Copenhagen, Denmark
[2]Division of Rheumatology, Department of Medicine, David Geffen School of Medicine, 10833 Le Conte Avenue, Los Angeles, CA 90095, USA
[3]Nuffield Department of Orthopaedics, Rheumatology and Musculoskeletal, Sciences, Botnar, Research Centre, University of Oxford, Headington, Oxford, UK
[4]Section of Rheumatology, Arthritis Research UK and Health and Care Research Wales CREATE Centre, Cardiff University School of Medicine, Cardiff, UK.
[5]Section of Rheumatology and Clinical Immunology, University of Texas MD Anderson Cancer Center, Houston, TX, USA
[6]Musculoskeletal Group, Cochrane Collaboration, Ottawa, ON K1H 8L6, Canada

**Dr. T.S. Jørgensen and Dr. S. Tarp contributed equally to the work.*

Corresponding author:

Dr. Simon Tarp, MSc, PhD

Musculoskeletal Statistics Unit, the Parker Institute

Bispebjerg and Frederiksberg Hospital;

Nordre Fasanvej 57, 2000 Copenhagen, Denmark,

Email: simon.tarp@regionh.dk,

Fax: +45 3816 4159

Word count: 2.979

ABSTRACT

Objectives: To assess the efficacy and safety of methotrexate (MTX) in combination with an approved biological agent compared to biological monotherapy, in the management of patients with rheumatoid arthritis (RA).

Methods: MEDLINE, EMBASE, CENTRAL and other sources were searched for randomised trials evaluating a biological agent plus MTX versus the same biological agent in monotherapy. Co-primary outcomes were ACR50 and the number of patients who discontinued due to adverse events (AEs). Random-effects models were applied for meta-analyses with risk ratio and 95% confidence intervals and the GRADE approach was used to assess confidence in the estimates.

Results: The analysis comprised 16 trials (4,965 patients), including all biological agents approved for RA except anakinra and certolizumab. The overall likelihood of responding to therapy (i.e. ACR50) after 6 months was 32% better when MTX was given concomitantly with biological agents (1.32 [1.20 to 1.45]; P<0.001) corresponding to 11 more out of 100 patients (7 to 16 more); Moderate Quality Evidence. Discontinuing due to AEs from concomitant use of MTX was potentially 20% increased (1.21 [0.97 to 1.50]; P=0.09) compared to biological monotherapy corresponding to 1 more out of 100 patients (0 to 3 more); Moderate Quality Evidence.

Conclusions: Randomised trials provide Moderate Quality Evidence for a favourable benefit-harm balance supporting concomitant use of MTX rather than monotherapy when prescribing a biological agent in patients with RA although in absolute terms only 7 to 16 more out of 100 patients will achieve an ACR50 response after 6 months of this combination therapy.

Registration: PROSPERO identifier: CRD42014014633.

INTRODUCTION

The primary goal of therapy in patients with RA is to maximise long-term health-related quality of life through control of symptoms, prevention of structural damage, normalisation of function and social participation (1). Initiating disease-modifying anti-rheumatic drug (DMARD) therapy as soon as possible improves the disease course and helps to attain this goal.

Among the conventional synthetic DMARDs (csDMARDs), methotrexate (MTX) is considered the anchor drug in RA treatment both in csDMARD naïve patients, as well as in patients treated in combination with biological DMARDs (bDMARDs). The '*American College of Rheumatology*' (ACR) and the '*European League Against Rheumatism*' (EULAR) recommend use of bDMARDs with concomitant use of MTX in patients who have high disease activity with poor prognostic features (2;3). The nine bDMARDs currently approved for RA therapy include: five tumour necrosis factor inhibitors (TNFi) – adalimumab, certolizumab pegol, etanercept, golimumab, and infliximab; also available but with different modes of action are abatacept, anakinra, rituximab, and tocilizumab.

Registries of routine clinical practice treatment indicate that approximately one third of RA patients are being treated with a bDMARD in monotherapy (4-9). Although MTX has one of the most favourable efficacy:toxicity ratios among the csDMARDs (10-13), analyses from health care claims suggest that when MTX is prescribed in combination with a bDMARD, more than half of the patients do not collect the MTX prescription (14) and overall patients seem to taper MTX intake over time (15). Despite the current understanding about clinical use of the combination of a bDMARD and MTX, the actual benefit-harm associated with this combination compared to bDMARD in monotherapy has not been evaluated extensively.

Our objective was to assess the efficacy and safety of combining MTX to a bDMARD compared to bDMARD in monotherapy in the management of patients with RA. Secondarily we wanted to explore whether the potentially added value of MTX varies across the different bDMARDs.

METHODS

Study selection, assessment of eligibility criteria, data extraction, and statistical analyses were performed, based on a predefined protocol (PROSPERO: CRD42014014633) in accordance with the current methodology guidelines (16). The reporting of the systematic review and meta-analysis follows the recommendations from the PRISMA (Preferred Reporting Items for Systematic reviews and MetaAnalyses) statement (17).

Eligibility criteria

All RA randomised controlled trials (RCTs) evaluating the effect of combination therapy with any approved bDMARDs and MTX versus the same bDMARD alone (i.e. bDMARD monotherapy) qualified for inclusion. The bDMARDs of interest included all currently approved for RA (abatacept, adalimumab, anakinra, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, and tocilizumab). No restrictions on dose, treatment duration, and administration procedures were imposed on either bDMARDs or MTX. The eligible comparator group was the same bDMARD in the same dose as the intervention group (i.e. within each trial) administered without concomitant MTX (i.e. bDMARD monotherapy).

Identification and selection of studies

The Cochrane Central Register of Controlled Trials, Medline (via PubMed), Embase, and ClinicalTrials.gov were searched for published RCTs from inception of each database to April 19, 2016 (Supplement Table 1). Additional RCTs identified in relevant systematic reviews not retrieved through the electronic databases were then collated. Relevant RCTs on FDA's and EMA's websites, and relevant pharmaceutical companies' websites were scrutinized to identify unpublished trial data. Search results and full-text articles were independently assessed by two reviewers with disagreements resolved through consensus or referral to a third reviewer.

Data collection and study appraisal

A priori a benefit outcome and a harm outcome were selected from among the recommended major outcomes from the Cochrane Musculoskeletal Group (CMSG) (18). These co-primary outcomes were ACR50 for benefit (defined as a 50% improvement in the American College of

Rheumatology criteria [ACR50]) (19), with the number of withdrawals due to adverse events being applied as a proxy for harm (20). Outcome data collection was at 6 months if possible or at the time point closest to 6 months according to the individual trials. ACR50 is a validated, clinically meaningful, binary measure of benefit (19); for safety, we chose to include withdrawals due to adverse events, which is a proxy measure for patients' tolerance of treatment and should be reported consistently (20;21). Other outcomes for benefit included ACR20, health assessment questionnaire (HAQ) for function, and radiographic progression. Safety were further evaluated with risk of serious adverse events (SAE), serious infections, and gastrointestinal adverse events.

For each trial, we collected: type and doses of both the intervention and comparator (bDMARD dose was categorized according to the product labelling as recommended, below recommended [low] or above recommended dose [high]); study duration; disease duration; and whether the RA population was MTX naïve or experienced.

Study selection and data extraction were done independently by two reviewers (TSJ & ST). Disagreements were resolved by consensus with a third reviewer (RC). Internal validity was judged independently by two reviewers (TSJ & ST), using the Cochrane Collaboration's risk-of-bias tool (22).

Synthesis of results

Standard pairwise meta-analysis was performed using Review Manager (RevMan) version 5.3. Meta-analysis was conducted for trials comparing a bDMARD in combination with MTX (intervention) vs. bDMARD monotherapy (comparator). In cases where a study only compared different doses of MTX in combination with a bDMARD, the meta-analysis was conducted comparing the highest MTX-dose with the lowest MTX-dose if the MTX dose in the comparator group was considered very low (i.e. below 10 mg). Sensitivity analysis for the primary outcomes where conducted to analyse the impact of including studies comparing different MTX-doses. Dichotomous outcomes were expressed as risk ratios (RR) and the corresponding 95% confidence intervals (95% CIs) for each study. For continuous variables, net differences were estimated using the standardised mean difference (SMD) with 95% CI for each study (23).

Evidence synthesis was based on standard inverse variance random effects for meta-analysis (24). We tested for heterogeneity with the Cochran's Q-test and used the method proposed by Higgins *et al* to measure inconsistency, I^2, i.e., the percentage of total variation

across studies due to heterogeneity (25). At the protocol stage, anticipating important heterogeneity, we pre-specified a number of stratified and meta-regression analyses, stratifying the available studies according to trial characteristics and continuous variables at study-level. To explore the quantitative impact of these patient/trial characteristics, stratified analyses were performed. Adalimumab, golimumab, infliximab, and rituximab are more immunogenic than other bDMARDs for RA and anti-drug antibody formation is associated with reduced clinical efficacy (26). For these agents (except rituximab) concomitant MTX is associated with lower rates of anti-drug antibody formation (26). Post hoc analyses of the primary outcomes were conducted to explore impact of these known differences in immunogenicity (i.e. adalimumab, golimumab, infliximab, and rituximab vs. other bDMARDs).

Finally, *post hoc* analyses of the primary outcomes were conducted to explore efficacy and safety of approved Janus kinase (JAK) inhibitors (baricitinib and tofacitinib) in combination with MTX vs. as monotherapy. Medline (via PubMed) was searched for published RCTs from database inception to July 19, 2018 (Supplement Table 2).

GRADE (Grading of Recommendations Assessment, Development and Evaluation) was used to rate the overall quality of the evidence for each outcome based on risk of bias, publication bias, imprecision, inconsistency, indirectness, and magnitude of effect. The GRADE ratings of very low–, low-, moderate-, or high-quality evidence reflecting the extent to which we are confident that the true effect lies close to that of the estimate of the effect in the meta-analysis (27;28).

RESULTS

Searches of 4 primary electronic databases (Cochrane Central Register of Controlled Trials, Medline, Embase, and ClinicalTrials.gov) and reviews identified 5,127 unique references. Of the total, 675 underwent full-text review and 23 references were included in the final review. Of these, 3 references were excluded from the meta-analysis: 2 had a bDMARD+MTX run-in period before one group was randomised to bDMARD monotherapy (29;30) and one included RA patients with hepatitis C (31). Twenty references that reported 16 unique RCTs, comparing a bDMARD in combination with MTX with the same bDMARD in monotherapy, proved eligible for inclusion in the meta-analysis (**Figure 1**). All approved bDMARDs except anakinra and certolizumab pegol

were represented among the included trials. Search for JAK inhibitor trials returned 165 references. Of these 2 unique RCTs were eligible for inclusion.

The 16 bDMARD RCTs, comprised a total of 42 unique trial-arms, and included 4,965 patients with RA: abatacept (1 trial; 351 patients)(32), adalimumab (3 trials; 1,503 patients)(33-35), etanercept (2 trials; 837 patients)(36;37), golimumab (3 trials; 1,724 patients)(38-40), infliximab (1 trial; 105 patients)(41), rituximab (1 trial; 161 patients)(42), and tocilizumab (5 trials; 2,519 patients)(43-47) (**Table 1**). The 2 JAK inhibitor RCTs included 1,134 patients with RA: tofacitinib (1 trial; 760 patients)(48), baricitinib (1 trial; 374 patients)(49) (**Table 2**).

Benefit and harm of bDMARDs according to major outcomes

The GRADE Evidence Profile (Figure 2) includes the quality of the available evidence, the judgments that bear on the quality rating, and the combined effect sizes of interest presented both in relative and absolute terms for all major outcomes. The results of the meta-analyses for each outcome are provided in Supplement figure 1-8. In the GRADE approach, RCTs start as high-quality evidence supporting estimates of intervention effects. However, as illustrated in Figure 2, five factors may lead to rating down the quality of evidence. Ultimately, the quality of evidence for each outcome was either moderate or low.

ACR50 response

After on average 6 months ACR50 response was statistically significantly in favour of concomitant use of MTX compared to bDMARD monotherapy (RR=1.32 [95%CI: 1.20 to 1.45], with a small-to-moderate degree of inconsistency [I^2=39%; P=0.04]) (Supplement figure 1). In absolute terms this corresponds to 11 (95%CI: 7 to 16) extra patients out of 100 patients treated who will achieve the ACR50 goal due to concomitant MTX. The analysis indicated that the added value of MTX varied with the choice of bDMARD (Test for subgroup differences P=0.07); a subgroup difference likely driven by infliximab (3.54 [1.38 to 9.08]). It was decided to rate down (-1) our confidence in the estimate to Moderate Quality Evidence, due to heterogeneity of possible importance (test for homogeneity, P=0.04). When excluding comparisons not evaluating recommended dose of bDMARD or a MTX dose below 10 mg heterogeneity was reduced and not statistically significant (I^2=21%; P=0.24) with no apparent influence in the overall estimate (1.30 [1.20 to 1.41] (Supplement figure 9). When excluding comparisons evaluating different doses of MTX heterogeneity was increased and statistical significant (I^2=45%; P=0.02) though with no apparent influence in the overall estimate (1.33 [1.20 to 1.48] (Supplement figure 10). When stratifying by immunogenicity (high immunogenic [adalimumab, golimumab, infliximab, and rituximab] vs. low immunogenic [other bDMARDs]) the analysis indicated no differences (Test for subgroup differences P=0.09) (Supplement figure 11).

Withdrawal due to adverse events

The overall estimate of discontinuing therapy due to adverse events from concomitant use of MTX was 1.20 [0.96 to 1.49] compared to bDMARD monotherapy - corresponding to a possible 20% increased risk (P=0.09; I^2=0%) (Supplement figure 2). Although not statistically significant, this relative effect would potentially translate into 1 patient out of 100 patients treated who will discontinue therapy due to adverse events from MTX. There was no statistical signal suggesting a difference between the different bDMARDs (Test for subgroup differences P=0.43). It was decided to rate down (-1) our confidence in the estimate to Moderate Quality Evidence, because of the imprecision (low statistical power to detect a difference) around the pooled relative estimate (95%CI: 0.96 to 1.49). Excluding comparisons not evaluating recommended dose of bDMARD or a MTX dose below 10 mg heterogeneity had no apparent influence in the overall estimate (1.23 [0.96 to 1.58]; I^2=0%) (**Supplement figure 12**). Excluding comparisons evaluating different doses of MTX did not influence the overall estimate (1.21 [0.97 to 1.53]; I^2=0%) (**Supplement figure 13**). When stratifying by immunogenicity (high immunogenic [adalimumab, golimumab, infliximab, and rituximab] vs. low immunogenic [other bDMARDs]) the analysis indicated no differences (Test for subgroup differences P=0.74) (**Supplement figure 14**).

ACR20 response

The overall likelihood of achieving an ACR20 responding was 1.20 (1.12 to 1.29) – with considerable inconsistency (I^2=61%) - in favour of concomitant use of MTX when treated with a bDMARD (Supplement figure 3); corresponding to 12 (7 to 17) extra patients out of 100 patients treated who will achieve the ACR20 goal due to MTX. However, due to the important difference among bDMARDs (i.e. reason to suspect that the added value of MTX varies with the choice of bDMARD [Test for subgroup differences P=0.01]) we decided to rate down (-2) our confidence in the estimate to Low Quality Evidence for very serious inconsistency. When excluding comparisons not evaluating recommended dose of bDMARD or a MTX dose below 10 mg heterogeneity was reduced and not statistically significant (I^2= 44%; P = 0.06) along with no statistically significant difference among bDMARDs (Test for subgroup differences P=0.07) with only limited influence in the overall estimate (1.12 [1.06 to 1.20] (**Supplement figure 15**).

Function

difference between the different bDMARDs concerning risk of serious infections (Test for subgroup differences P = 0.16).

Gastrointestinal adverse events

Risk of gastrointestinal adverse events (i.e. nausea) was 65% higher with concomitant use of MTX (1.65 [1.27 to 2.14]) corresponding to 6 (3 to 11) more patient out of 100 patients treated will experience gastrointestinal adverse events due to MTX (Supplement figure 8). Due to the important heterogeneity (I^2= 46%; p=0.04), difference among bDMARDs (Test for subgroup differences p=0.009), and reporting bias we decided to rate down (-2) our confidence in the estimate to Low Quality Evidence.

Benefit and harm of JAK inhibitors according to primary outcomes

After 6 months ACR50 response was not statistically significantly different between concomitant use of MTX compared to JAK inhibitor monotherapy (1.13 [0.99 to 1.28]), with a low degree of inconsistency [I^2=11%] (**Supplement Figure 16**). In absolute terms this corresponds to 6 (0 to 12) extra patients out of 100 patients treated will achieve the ACR50 goal due to MTX. There was no significant difference between the two different JAK inhibitors (Test for subgroup differences P=0.29). It was decided to rate down (-1) our confidence in the estimate to Moderate Quality Evidence, due to imprecision.

The overall estimate of discontinuing therapy due to adverse events from concomitant use of MTX compared to JAK inhibitor monotherapy was not statistically significantly increased (1.30 [0.82 to 2.08]; P=0.27; I^2=0%) (**Supplement Figure 17**). There was no statistical signal suggesting a difference between the two JAK inhibitors (Test for subgroup differences P=0.39). It was decided to rate down (-1) our confidence in the estimate to Moderate Quality Evidence, because of the imprecision.

DISCUSSION

To our knowledge, this is the first systematic review with evidence synthesis comparing the value of adding MTX to a bDMARD compared to bDMARD monotherapy when evaluating the efficacy and safety in patients with RA. When combining trial data, we found evidence indicating moderate to low confidence in the estimates that combining the prescribed bDMARD with MTX improves the effectiveness of the bDMARD. The present meta-analysis suggests that using a bDMARD in combination with MTX increases the possibility of achieving an ACR50 by 32% compared to bDMARD monotherapy. In addition to the apparent benefit of using MTX concomitantly with a bDMARD, some unwanted effects may occur e.g. gastrointestinal adverse events. Also, our analysis revealed combining MTX with a bDMARD appears to increase the risk of discontinuing therapy due to unwanted side effects (a potential 20% increased risk). Moreover, the analyses showed infliximab being the bDMARD most dependent on concomitant use of MTX for achieving clinical efficacy. The efficacy and safety of JAK inhibitors (baricitinib and tofacitinib), was evaluated in a *post hoc* analysis. With moderate quality evidence we found that JAK inhibitors as a class were more effective in combination with MTX compared as monotherapy although the ACR50 estimate was not statistical significant.

According to the EULAR guidelines and ACR recommendations, based on its established efficacy and safety (2;3), MTX is the appropriate first-line DMARD for treating active RA either administrated orally or subcutaneously at a tolerated dose. If gastric issues arise from oral MTX a switch to injectable MTX may be a relevant option. It has been estimated that MTX monotherapy achieves satisfactory disease control in only approximately one-third of patients and that two-thirds of patients requiring more active therapy which may include addition of a bDMARD (2;3). Further, international guidelines state that monotherapy with a bDMARD should be a treatment option for patients with RA only when they have toxicities to, or are intolerant of, MTX and other csDMARDs (2;3).

The empirical evidence from this systematic review clearly demonstrated improved efficacy of concomitant MTX compared to bDMARD monotherapy. These findings are consistent with observations from the CONCERTO trial that demonstrated increasing doses of MTX in combination with adalimumab resulted in improved clinical outcomes (35).

An observational study showed that, in Denmark, close to one in five bDMARD treatments for RA were prescribed as monotherapy (50). Of these, 70% were on monotherapy

from bDMARD therapy initiation and 30% were on monotherapy after cessation of concomitant csDMARDs. Apart from infliximab, there was no statistically significant difference between the various bDMARDs in remission rates and drug adherence in patients treated with a bDMARD in monotherapy (50). The better performance of infliximab when added to MTX was expected, since infliximab is not recommended or approved as monotherapy (51). Thus, the patients who received infliximab as monotherapy were likely to be a highly selected subgroup (50).

Our evidence synthesis also has limitations. The included 16 bDMARD studies span an 18-year period, from 1998 through 2016; so, patients enrolled in early studies may differ from those included in more recent studies. Moreover, the RA patients enrolled in the different studies are to some extent heterogeneous (encompassing different duration of diseases and differences in the extent of prior MTX failure). Further, we were not able to include anakinra and certolizumab pegol in the analysis. The time points at which ACR50 was assessed in the 16 studies included in our analysis varied from 16-52 weeks (14 trials 24-26 weeks; on average 26 weeks). Therefore, whether our results can be extrapolated to longer-term efficacy and safety is not clear. This may also be of relevance to interpreting our findings as one potential reason for improved efficacy observed when MTX is given concomitantly with bDMARD is that MTX may diminish the immunogenicity of the administered bDMARD. However, other synergistic mechanisms of action may also contribute (14). Finally, there remains a certain amount of reporting bias with MTX consumption at the side of the patients, which may not adhere to the prescriptions (15) and the actual percentage of patients remaining in combination therapy with bDMARDs and MTX may be lower than the numbers stated in the registries.

In conclusion, in the management of RA, evidence from RCTs supports the added value for efficacy of combining the prescribed bDMARD with the concomitant use of MTX as recommended in current clinical practice. Although the precision around the estimate of concomitant MTX use does not rule out an increased risk of clinically important harm, the efficacy findings justify the recommendation that all patients prescribed bDMARD should be encouraged to continue MTX therapy although in absolute terms only 7 to 16 more out of 100 patients will achieve an ACR50 response after 6 months of therapy.

ACKNOWLEDGEMENT

FUNDING

Musculoskeletal Statistics Unit, The Parker Institute receives support via unrestricted grants from The Oak Foundation. This study was initially supported by a grant from AbbVie (Denmark); the AbbVie grant was provided as an unrestricted grant to Musculoskeletal Statistics Unit, The Parker Institute. The sponsors of the study had no role in writing this protocol, and will not influence data collection, data analysis, data interpretation, or writing of the subsequent manuscript.

AUTHOR CONTRIBUTIONS

Dr. Tarp and Dr. Jørgensen had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.
Study concept and design: Tarp, Jørgensen, Furst, Dossing, Taylor, Kristensen, Bliddal, and Christensen.
Acquisition, analysis, or interpretation of data: Jørgensen, Tarp, Taylor, and Christensen.
Drafting of the manuscript: Jørgensen, Tarp, and Christensen.
Critical revision of the manuscript for important intellectual content: Tarp, Jørgensen, Furst, Dossing, Taylor, Choy, Suarez-Almazor, Lyddiatt, Kristensen, Bliddal, and Christensen
Statistical analysis: Jørgensen, Tarp, and Christensen.
Obtained funding: Bliddal, Kristensen, and Christensen.

DISCLOSURES

All authors have completed the ICMJE Form for Disclosure of Potential Conflicts of Interest which can be found in the online version of this article.

REFERENCES

(1) Smolen JS, Aletaha D, Bijlsma JW, Breedveld FC, Boumpas D, Burmester G et al. Treating rheumatoid arthritis to target: recommendations of an international task force. Ann Rheum Dis 2010; 69(4):631-7.

(2) Smolen JS, Landewe R, Bijlsma J, Burmester G, Chatzidionysiou K, Dougados M et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2016 update. Ann Rheum Dis 2017; 76(6):960-77.

(3) Singh JA, Saag KG, Bridges SL, Jr., Akl EA, Bannuru RR, Sullivan MC et al. 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. Arthritis Rheumatol 2015.

(4) Heiberg MS, Koldingsnes W, Mikkelsen K, Rodevand E, Kaufmann C, Mowinckel P et al. The comparative one-year performance of anti-tumor necrosis factor alpha drugs in patients with rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: results from a longitudinal, observational, multicenter study. Arthritis Rheum 2008; 59(2):234-40.

(5) Soliman MM, Ashcroft DM, Watson KD, Lunt M, Symmons DP, Hyrich KL. Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. Ann Rheum Dis 2011; 70(4):583-9.

(6) Listing J, Strangfeld A, Rau R, Kekow J, Gromnica-Ihle E, Klopsch T et al. Clinical and functional remission: even though biologics are superior to conventional DMARDs overall success rates remain low--results from RABBIT, the German biologics register. Arthritis Res Ther 2006; 8(3):R66.

(7) Askling J, Fored CM, Brandt L, Baecklund E, Bertilsson L, Feltelius N et al. Time-dependent increase in risk of hospitalisation with infection among Swedish RA patients treated with TNF antagonists. Ann Rheum Dis 2007; 66(10):1339-44.

(8) Mariette X, Gottenberg JE, Ravaud P, Combe B. Registries in rheumatoid arthritis and autoimmune diseases: data from the French registries. Rheumatology (Oxford) 2011; 50(1):222-9.

(9) Lee SJ, Chang H, Yazici Y, Greenberg JD, Kremer JM, Kavanaugh A. Utilization trends of tumor necrosis factor inhibitors among patients with rheumatoid arthritis in a United States observational cohort study. J Rheumatol 2009; 36(8):1611-7.

(10) Felson DT, Anderson JJ, Meenan RF. The comparative efficacy and toxicity of second-line drugs in rheumatoid arthritis. Results of two metaanalyses. Arthritis Rheum 1990; 33(10):1449-61.

(11) Felson DT, Anderson JJ, Meenan RF. Use of short-term efficacy/toxicity tradeoffs to select second-line drugs in rheumatoid arthritis. A metaanalysis of published clinical trials. Arthritis Rheum 1992; 35(10):1117-25.

(12) Fries JF, Williams CA, Ramey DR, Bloch DA. The relative toxicity of alternative therapies for rheumatoid arthritis: implications for the therapeutic progression. Semin Arthritis Rheum 1993; 23(2 Suppl 1):68-73.

(13) Pincus T, Marcum SB, Callahan LF. Longterm drug therapy for rheumatoid arthritis in seven rheumatology private practices: II. Second line drugs and prednisone. J Rheumatol 1992; 19(12):1885-94.

(14) Emery P, Sebba A, Huizinga TW. Biologic and oral disease-modifying antirheumatic drug monotherapy in rheumatoid arthritis. Ann Rheum Dis 2013; 72(12):1897-904.

(15) Bliddal H, Eriksen SA, Christensen R, Lorenzen T, Hansen MS, Ostergaard M et al. Adherence to methotrexate in rheumatoid arthritis: a danish nationwide cohort study. Arthritis 2015; 2015:915142.

(16) Shamseer L, Moher D, Clarke M, Ghersi D, Liberati A, Petticrew M et al. Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015: elaboration and explanation. BMJ 2015; 349:g7647.

(17) 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.

(18) Ghogomu EA, Maxwell LJ, Buchbinder R, Rader T, Pardo PJ, Johnston RV et al. Updated method guidelines for cochrane musculoskeletal group systematic reviews and metaanalyses. J Rheumatol 2014; 41(2):194-205.

(19) Chung CP, Thompson JL, Koch GG, Amara I, Strand V, Pincus T. Are American College of Rheumatology 50% Response Criteria (ACR 50) Superior to 20% Criteria (ACR20) to Distinguish Active Aggressive Treatment in Rheumatoid Arthritis Clinical Trials Reported Since 1997? A Metaanalysis of Discriminant Capacities. Ann Rheum Dis 2006.

(20) Ioannidis JP, Evans SJ, Gotzsche PC, O'Neill RT, Altman DG, Schulz K et al. Better reporting of harms in randomized trials: an extension of the CONSORT statement. Ann Intern Med 2004; 141(10):781-8.

(21) Singh JA, Christensen R, Wells GA, Suarez-Almazor ME, Buchbinder R, Lopez-Olivo MA et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. CMAJ 2009; 181(11):787-96.

(22) Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ 2011; 343:d5928.

(23) Normand SL. Meta-analysis: formulating, evaluating, combining, and reporting. Stat Med 1999; 18(3):321-59.

(24) DerSimonian R, Laird N. Meta-Analysis in Clinical Trials. Controlled Clinical Trials 1986; 88:177-88.

(25) Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. Stat Med 2002; 21(11):1539-58.

(26) Strand V, Balsa A, Al-Saleh J, Barile-Fabris L, Horiuchi T, Takeuchi T et al. Immunogenicity of Biologics in Chronic Inflammatory Diseases: A Systematic Review. BioDrugs 2017; 31(4):299-316.

(27) Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J et al. GRADE guidelines: 3. Rating the quality of evidence. J Clin Epidemiol 2011; 64(4):401-6.

(28) Mustafa RA, Santesso N, Brozek J, Akl EA, Walter SD, Norman G et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. J Clin Epidemiol 2013; 66(7):736-42.

(29) van Riel PL, Taggart AJ, Sany J, Gaubitz M, Nab HW, Pedersen R et al. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. Ann Rheum Dis 2006; 65(11):1478-83.

(30) Pope JE, Haraoui B, Thorne JC, Vieira A, Poulin-Costello M, Keystone EC. The Canadian methotrexate and etanercept outcome study: a randomised trial of discontinuing versus continuing methotrexate after 6 months of etanercept and methotrexate therapy in rheumatoid arthritis. Ann Rheum Dis 2014; 73(12):2144-51.

(31) Iannone F, La MG, Bagnato G, Gremese E, Giardina A, Lapadula G. Safety of etanercept and methotrexate in patients with rheumatoid arthritis and hepatitis C virus infection: a multicenter randomized clinical trial. J Rheumatol 2014; 41(2):286-92.

(32) Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barre E et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis 2015; 74(1):19-26.

(33) Kaeley GS, Evangelisto AM, Nishio MJ, Goss SL, Liu S, Kalabic J et al. Methotrexate Dosage Reduction Upon Adalimumab Initiation: Clinical and Ultrasonographic Outcomes from the Randomized Noninferiority MUSICA Trial. J Rheumatol 2016; 43(8):1480-9.

(34) Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van VR et al. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. Arthritis Rheum 2006; 54(1):26-37.

(35) Burmester GR, Kivitz AJ, Kupper H, Arulmani U, Florentinus S, Goss SL et al. Efficacy and safety of ascending methotrexate dose in combination with adalimumab: the randomised CONCERTO trial. Ann Rheum Dis 2015; 74(6):1037-44.

(36) Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Mod Rheumatol 2010; 20(6):531-8.

(37) Klareskog L, van der HD, de Jager JP, Gough A, Kalden J, Malaise M et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. Lancet 2004; 363(9410):675-81.

(38) Emery P, Fleischmann RM, Moreland LW, Hsia EC, Strusberg I, Durez P et al. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. Arthritis Rheum 2009; 60(8):2272-83.

(39) Keystone EC, Genovese MC, Klareskog L, Hsia EC, Hall ST, Miranda PC et al. Golimumab, a human antibody to tumour necrosis factor {alpha} given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. Ann Rheum Dis 2009; 68(6):789-96.

(40) Kremer J, Ritchlin C, Mendelsohn A, Baker D, Kim L, Xu Z et al. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study. Arthritis Rheum 2010; 62(4):917-28.

(41) Maini RN, Breedveld FC, Kalden JR, Smolen JS, Davis D, Macfarlane JD et al. Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor alpha monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. Arthritis Rheum 1998; 41(9):1552-63.

(42) Edwards JC, Szczepanski L, Szechinski J, Filipowicz-Sosnowska A, Emery P, Close DR et al. Efficacy of B-cell-targeted therapy with rituximab in patients with rheumatoid arthritis. N Engl J Med 2004; 350(25):2572-81.

(43) Bijlsma JW, Welsing PM, Woodworth TG, Middelink LM, Petho-Schramm A, Bernasconi C et al. Early rheumatoid arthritis treated with tocilizumab, methotrexate, or their combination (U-Act-Early): a multicentre, randomised, double-blind, double-dummy, strategy trial. Lancet 2016; 388(10042):343-55.

(44) Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis 2016; 75(6):1081-91.

(45) Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis 2013; 72(1):43-50.

(46) Kaneko Y, Atsumi T, Tanaka Y, Inoo M, Kobayashi-Haraoka H, Amano K et al. Comparison of adding tocilizumab to methotrexate with switching to tocilizumab in patients with rheumatoid arthritis with inadequate response to methotrexate: 52-week results from a

prospective, randomised, controlled study (SURPRISE study). Ann Rheum Dis 2016; 75(11):1917-23.

(47) Maini RN, Taylor PC, Szechinski J, Pavelka K, Broll J, Balint G et al. Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. Arthritis Rheum 2006; 54(9):2817-29.

(48) Fleischmann R, Mysler E, Hall S, Kivitz AJ, Moots RJ, Luo Z et al. Efficacy and safety of tofacitinib monotherapy, tofacitinib with methotrexate, and adalimumab with methotrexate in patients with rheumatoid arthritis (ORAL Strategy): a phase 3b/4, double-blind, head-to-head, randomised controlled trial. Lancet 2017; 390(10093):457-68.

(49) Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M et al. Baricitinib, Methotrexate, or Combination in Patients With Rheumatoid Arthritis and No or Limited Prior Disease-Modifying Antirheumatic Drug Treatment. Arthritis Rheumatol 2017; 69(3):506-17.

(50) Jorgensen TS, Kristensen LE, Christensen R, Bliddal H, Lorenzen T, Hansen MS et al. Effectiveness and drug adherence of biologic monotherapy in routine care of patients with rheumatoid arthritis: a cohort study of patients registered in the Danish biologics registry. Rheumatology (Oxford) 2015; 54(12):2156-65.

(51) 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(5):625-39.

Figure legends:

Figure 1: Study selection
Legend: RCT = randomised controlled trial; bDMARD = biologic disease-modifying anti-rheumatic drug; RA = rheumatoid arthritis; MTX = methotrexate.

Figure 2: GRADE Evidence Profile
Legend: ACR = American College of Rheumatology criteria [ACR20: 50% improvement; ACR50: 50% improvement); HAQ = health assessment questionnaire for function; CI = confidence interval; RR = risk ratio; SMD = standardised mean difference; bDMARD = biologic disease-modifying anti-rheumatic drug; MTX = methotrexate.
a. Statistically significant heterogeneity P = 0.04 (I^2 = 39%); b: Lower limit of CI indicate no differences (P=0.09); c: Statistically significant heterogeneity and statistically significant differences among bDMARDs; d: Three bDMARDs were not represented in the analysis (abatacept, infliximab and rituximab); e: Infliximab was not included in the analysis due to lack of reporting; f: Not statistically significant. Based on the lower and upper confidence limits a potential increased or decreased risk of the addition of MTX could not be ruled out; g: Reporting bias.

Table 1: Study characteristics of included biological disease-modifying anti-rheumatic drug trials

Study information					bDMARD§			MTX intervention		MTX comparator		Risk of bias†
Author	**Acronym**	**Duration* (weeks)**	**Disease duration (years)**	**MTX history**	**Drug**	**Dose mg.**	**Dose cat.**	**Dose mg.**	**No. pts.**	**MTX dose mg.**	**No pts.**	
Emery(32)	AVERT	24/52	0.6	Naïve¶	ABA	125 QW	R	15-20	119	0	116	L,L,L,L,L,L
Breedveld(34)	PREMIER	52/104	0.7	Naïve	ADA	40 Q2W	R	20**	268	0	274	L,L,L,L,L,L
Burmester(35)	CONCERTO	26/26	0.3	Naïve	ADA	40 Q2W	R	20	98	2.5	98	L,L,L,L,L,L
Kaeley(33)	MUSICA	24/24	5.3	Exp.	ADA	40 Q2W	R	20	155	7.5	154	L,L,H,H,L,L
Klareskog(37)	TEMPO	24/52	6.5	Naïve/Exp.	ETA	25 BIW	R	20**	229	0	228	L,L,L,L,L,L
Kameda(36)	JESMR	24/24	9.3	Exp.	ETA	25 BIW	R	8	77	0	74	L,L,H,H,L,H
Emery(38)	GOBEFORE	24/24	3.9	Naïve	GOL	100 Q4W	H	20**	159	0	159	L,L,L,L,L,L
Keystone(39)	GOFORWARD	24/24	6.3	Exp.	GOL	100 Q4W	H	15-25	89	0	133	L,L,L,L,L,L
Kremer(40)	GOLIVE	24/16	8.3	Exp.	GOL	2/kg Q12W	R	15-25	129	0	128	L,L,L,L,L,H
						4/kg Q12W	H		128		129	
Maini(41)		26/14	10.4	Exp.	INF	1 x 5††	L	7.5	14	0	15	L,L,L,L,L,L
						3 x 5††	H		15		14	
						10 x 5††	H		14		15	
Edwards(42)		24/24	10.5	Exp.	RIT	1000 x 2§§	R	≥10	40	0	40	L,L,L,L,L,L
Maini(47)	CHARISMA	16/20	0.8	Exp.	TOC	2/kg Q4W	L	10-25	52	0	53	L,L,L,L,L,H
						4/kg Q4W	L		49		54	
						8/kg Q4W	R		50		52	
Dougados(45)	ACT-RAY	24/24	8.3	Exp.	TOC	8/kg Q4W	R	≥15	279	0	277	L,L,L,L,L,L
Burmester(44)	FUNCTION	24/52	0.5	Naïve	TOC	8/kg Q4W	R	20**	291	0	292	L,L,L,L,L,L
Kaneko(46)	SURPRISE	24/52	3.7	Exp.	TOC	8/kg Q4W	R	8.6	118	0	115	L,U,H,H,L,L
Bijlsma(43)	U-ACT-EARLY	24/104	0.1	Naïve	TOC	8/kg Q4W	R	30**	106	0	103	L,L,L,L,L,L

Exp. = experienced; bDMARD = biological DMARDs; NR = not reported; QW = every week; Q2W = every 2 weeks; Q4W = every 4 weeks; Q12W = every 12 weeks; BIW = twice a week; Dose cat. = dose category [L= below recommended, R=recommended dose, H=above recommended]; ABA = abatacept; ADA = adalimumab; ETA = etanercept; GOL = golimumab; INF = infliximab; RIT = rituximab; TOC = tocilizumab; MTX = methotrexate. †: Risk of Bias: Random sequence generation (selection bias), Allocation concealment (selection bias), Blinding of participants and personnel (performance bias), Blinding of outcome assessment (detection bias), Incomplete outcome data, Selective reporting (reporting bias). L = Low risk of bias. U = unclear risk of bias. H = high risk of bias. *: benefit/harm. **: maximum end dose if titration regime was necessary. §: In all individual trials bDMARD and dose were the same in the intervention and comparator groups. ¶: MTX naïve or receiving less than 10 mg/week for ≤ 4 weeks with no MTX for 1 month prior to screening. ††: on week 0, 2, 6, 10, and 14. §§: on day 1 and 15.

Table 2: Study characteristics of included Janus kinase inhibitor trials

Study information					JAK inhibitor§			MTX intervention		MTX comparator		Risk of bias†
Author	**Acronym**	**Duration* (weeks)**	**Disease duration (years)**	**MTX history**	**Drug**	**Dose mg.**	**Dose cat.**	**Dose mg.**	**No. pts.**	**MTX dose mg.**	**No pts.**	
Fleischmann (48)	ORAL Strategy	24/52	5.8	Exp.	TOF	5 BD	R	15-25	376	0	384	L,L,L,L,L,L
Fleischmann (49)	RA-BEGIN	24/24	0.7	Naïve¶	BAR	4 OD	R	20**	215	0	159	L,L,L,L,L,L

Exp. = experienced; BD = twice daily; OD = once daily; JAK = Janus kinase; TOF = tofacitinib; BAR = baricitinib MTX = methotrexate; Dose cat. = dose category [L= below recommended, R=recommended dose, H=above recommended]. *: benefit/harm. §: In all individual trials JAK inhibitor and dose were the same in the intervention and comparator groups. †: Risk of Bias: Random sequence generation (selection bias), Allocation concealment (selection bias), Blinding of participants and personnel (performance bias), Blinding of outcome assessment (detection bias), Incomplete outcome data, Selective reporting (reporting bias). L = Low risk of bias. U = unclear risk of bias. H = high risk of bias. ¶: up to 3 weekly MTX doses permitted. **: maximum end dose if titration regime was necessary.