A Systematic Review and Network Meta-analysis of the Efficacy and Safety of Tumor Necrosis Factor Inhibitor–Methotrexate Combination Therapy Versus Triple Therapy in Rheumatoid Arthritis

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Supplementary Appendix

METHODS

Search terms

PICOS	Search Terms
Population	Arthritis, rheumatoid (MeSH); rheumatoid arthritis
Intervention and comparators	Different terms for methotrexate; hydroxychloroquine; sulfasalazine; infliximab; adalimumab; etanercept; certolizumab; golimumab; infliximab biosimilars
Study design	SIGN filter for RCTs
Filters	English only

MeSH=Medical Subject Headings; PICOS=population, intervention, comparison, outcomes, and study design; RCT=randomized controlled trial; SIGN=Scottish Intercollegiate Guidelines Network.

Search terms used

EMBASE (1974–9/9/2014)

Numbers in parentheses refer to number of articles retrieved per line

RCT search filter used: SIGN filter for RCTs 2013

1. exp rheumatoid arthritis/ (152,770)
2. *caplans syndrome/ (5673)
3. *feltys syndrome/ (550)
4. *rheumatoid nodule/ (636)
5. *sjogrens syndrome/ (8993)
6. *stills disease, adult-onset/ (788)
7. (felty$ adj2 syndrome).tw. (761)
8. (caplan$ adj2 syndrome).tw. (146)
9. (rheumatoid adj nodule).tw. (288)
10. (sjogren$ adj2 syndrome).tw. (14,052)
11. still$ disease.tw. (2156)
12. (arthritis adj2 rheumat$).tw. (108,764)
13. methotrexate.tw. (44,346)
14. mexate.tw. (66)
15. amethopterin$.tw. (530)
16. trexall.tw. (52)
17. rheumatrex.tw. (186)
18. adalimumab.tw. (7289)
19. humira.tw. (2257)
20. infliximab.tw. (13,475)
21. remicade.tw. (3700)

22. etanercept.tw. (7842)

23. enbrel.tw. (2924)

24. certolizumab.tw (1234)

25. cimzia.tw (539)

26. golimumab.tw (1083)

27. simponi.tw (306)

28. sulfasalazine.tw. (3489)

29. salazosulfapyridine.tw. (327)

30. azulfidine.tw. (665)

31. sulfazine.tw. (6)

32. salazopyrin.tw. (573)

33. hydroxychloroquine.tw. (3484)

34. plaquenil.tw. (1030)

35. clinical trial/ (838,031)

36. Randomized controlled trial/ (351,806)

37. randomization/ (63,204)

38. single blind procedure/ (18,777)

39. double blind procedure/ (117,759)

40. crossover procedure/ (40,150)

41. placebo/ (258,176)

42. randomi?ed controlled trial$.tw. (102,980)

43. rct.tw. (14,729)

44. random allocation.tw. (1376)

45. randomly allocated.tw. (20,951)

46. allocated randomly.tw. (1965)

47. (allocated adj2 random).tw. (797)

48. single blind$.tw. (14,871)

49. double blind$.tw. (149,736)

50. ((treble or triple) adj blind$).tw. (410)

51. placebo$.tw. (207,217)

52. prospective study/ (261,026)

53. OR/35-52 (1,401,857)

54. case study/ (27,762)

55. case report.tw. (273,139)

56. abstract report/ or letter/ (919,743)

57. OR/54-56 (1,214,831)

58. 53 not 57 (1,363,404)

59. OR/1-12 (180,087)

60. OR/13-34 (72,274)

61. 58 and 59 and 60 (5093)

62. limit 61 to (English language and yr="1990 -Current") (4598)

Ovid MEDLINE and in-process and other nonindexed citations and ovid MEDLINE (1946–9/9/2014)

RCT search filter used: SIGN filter for RCTs 2013

1. exp rheumatoid arthritis/ (94,126)
2. *Caplan Syndrome/ (96)
3. *Felty Syndrome/ (454)
4. *Rheumatoid Nodule/ (555)
5. *Sjogren's Syndrome/ (8011)
6. *Still's Disease, Adult-Onset/ (872)
7. (felty$ adj2 syndrome).tw. (683)
8. (caplan$ adj2 syndrome).tw. (116)
9. (rheumatoid adj nodule).tw. (239)
10. (sjogren$ adj2 syndrome).tw. (11,591)
11. still$ disease.tw. (1677)
12. (arthritis adj2 rheumat$).tw. (80,809)
13. methotrexate.tw. (31,816)
14. mexate.tw. (1)
15. amethopterin$.tw. (386)
16. trexall.tw. (0)
17. rheumatrex.tw. (3)
18. adalimumab.tw. (3111)
19. humira.tw. (122)
20. infliximab.tw. (7673)
21. remicade.tw. (213)
22. etanercept.tw. (4460)

23. enbrel.tw. (207)

24. certolizumab.tw (424)

25. cimzia.tw (19)

26. golimumab.tw (326)

27. simponi.tw (11)

28. sulfasalazine.tw. (2498)

29. salazosulfapyridine.tw. (213)

30. azulfidine.tw. (73)

31. sulfazine.tw. (2)

32. salazopyrin.tw. (146)

33. hydroxychloroquine.tw. (2193)

34. plaquenil.tw. (96)

35. Randomized Controlled Trials as Topic/ (96,153)

36. randomized controlled trial/ (387,879)

37. Random Allocation/ (82,080)

38. Double Blind Method/ (129,323)

39. Single Blind Method/ (19,929)

40. clinical trial/ (495,500)

41. clinical trial, phase i.pt. (14,789)

42. clinical trial, phase ii.pt. (23,840)

43. clinical trial, phase iii.pt. (9663)

44. clinical trial, phase iv.pt. (982)

45. controlled clinical trial.pt. (89,783)

46. randomized controlled trial.pt. (387,879)

47. multicenter study.pt. (180,651)

48. clinical trial.pt. (495,500)

49. exp Clinical Trials as topic/ (287,110)

50. OR/35-49 (1,059,681)

51. (clinical adj trial$).tw. (226,257)

52. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw. (133,848)

53. placebos/ (33,348)

54. placebo$.tw. (164,662)

55. randomly allocated.tw. (17,871)

56. (allocated adj2 random$).tw. (20,512)

57. OR/51-56 (438,173)

58. 50 OR 57 (1,214,438)

59. case report.tw. (212,055)

60. letter/ (857,005)

61. historical article/ (306,577)

62. 59 OR 60 OR 61 (1,363,849)

63. 58 not 62 (1,184,052)

64. OR/1-12 (121,501)

65. OR/13-34 (46,137)

66. 63 and 64 and 65 (2739)

67. limit 66 to (English language and yr="1990 -Current") (2417)

Cochrane library search (only for CENTRAL)

9/9/2014

1. MeSH descriptor: [Arthritis, Rheumatoid] explode all trees (4124)
2. MeSH descriptor: [Rheumatoid Nodule] this term only (11)
3. Rheumatoid arthritis: ti,ab,kw (5808)
4. Methotrexate:ti,ab,kw (4976)
5. Mexate:ti,ab,kw (0)
6. Amethopterin:ti,ab,kw (12)
7. Trexall:ti,ab,kw (0)
8. Rheumatrex:ti,ab,kw (0)
9. Adalimumab:ti,ab,kw (447)
10. Humira:ti,ab,kw (25)
11. Infliximab:ti,ab,kw (763)
12. Remicade:ti,ab,kw (29)
13. Etanercept:ti,ab,kw (667)
14. Enbrel:ti,ab,kw (36)
15. Certolizumab:ti,ab,kw (66)
16. Cimzia:ti,ab,kw (5)
17. Golimumab:ti,ab,kw (98)
18. Simponi:ti,ab,kw (3)
19. Sulfasalazine: ti,ab,kw (523)
20. Salazosulfapyridine:ti,ab,kw (136)
21. Azulfidine:ti,ab,kw (15)
22. Sulfazine:ti,ab, kw (0)
23. Salazopyrin:ti,ab,kw (26)

24. Hydroxychloroquine:ti,b,kw (284)

25. Plaquenil:ti,ab,kw (8)

26. 1 OR 2 OR 3 (6433)

27. OR/4-25 (6765)

28. 26 AND 27 Publication Year from 1990 to 2014, in Trials (1307)

Source	**No.**
EMBASE	4598
MEDLINE	2417
Cochrane	1307
Total	8322
Duplicates	1762
Total deduplicated	**6560**

Table 1 shows the full list of endpoints considered for inclusion in the network meta-analysis (NMA).

Table 1. Endpoints for Inclusion in the Study

Clinical Efficacy Endpoints • ACR70 • EULAR good response • ACR20 • ACR50 • CDAI • CDAI low disease activity • CDAI remission • Change in DAS28 calculated with ESR (DAS28-ESR) or CRP (DAS28-CRP) • DAS28-ESR low disease activity • DAS28-ESR remission • SDAI • SDAI low disease activity • SDAI remission • Boolean-based remission (TJC ≤1, SJC ≤1, CRP≤1 mg/dL, PGA ≤1 [on a 0–10 scale]) • Percentage of dropouts at the end of study • Survival curve on number of study participants
Radiographic Endpoints • vdHmTSS • Joint space narrowing • Probability plots of radiographic progression • Percentage with no radiographic progression (all definitions of “no radiographic progression,” eg, 0, ≤0.5, ≤5 in vdHmTSS
Patient-Reported Outcomes • HAQ-DI score • SF-36; PCS and MCS • EQ-5D (VAS and utility scores) • Fatigue • Pain • PGA • WPAI
Safety Endpoints • Overall AEs • AEs leading to dropouts • LFT elevation (the appropriate cutoff will be further determined based on data availability) • Neutropenia (defined by CTCAE) • Overall infection rate • Serious AEs • Overall • GI-related AEs • Infections • Malignancies

ACR=American College of Rheumatology; ACR20=20% improvement in ACR criteria; ACR50=50% improvement in ACR criteria; ACR70=70% improvement in ACR criteria; AE=adverse event; CDAI=change in Clinical Disease Activity Index; CRP=C-reactive protein; CTCAE=Common Terminology Criteria for Adverse Events; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; GI=gastrointestinal; HAQ-DI=Health Assessment Questionnaire–Disability Index; LFT=liver function test; MCS=Mental Component Summary; PCS=Physical Component Summary; PGA=patient global assessment; SDAI=change in Simplified Disease Activity Index; SF-36=36-Item Short Form Survey; SJC=swollen joint count; TJC=total joint count; VAS=visual analog scale; vdHmTSS=ven der Heijde modified total Sharp score; WPAI=Work Productivity and Activity Impairment.

Risk of Bias Assessment

One reviewer individually extracted data and assessed study quality (using the *Cochrane Collaboration Risk of Bias tool for RCTs*). See **Table 2** below for summarizing study-level risk of bias across domains and the criteria used to judge risk of bias.

Table 2. The Cochrane Collaboration's Tool for Assessing Risk of Bias

Domain	Description	Review Authors' Judgment
Sequence generation	Describe the method used to generate the allocation sequence in sufficient detail to allow an assessment of whether it should produce comparable groups	Was the allocation sequence adequately generated?
Allocation concealment	Describe the method used to conceal the allocation sequence in sufficient detail to determine whether intervention allocations could have been foreseen in advance of, or during, enrollment	Was allocation adequately concealed?
Blinding of participants, personnel, and outcome assessors; assessments should be made for each main outcome (or class of outcomes)	Describe all measures used, if any, to blind study participants and personnel from knowledge of which intervention a participant received; provide any information relating to whether the intended blinding was effective	Was knowledge of the allocated intervention adequately prevented during the study?

Domain	Description	Review Authors' Judgment
Incomplete outcome data; assessments should be made for each main outcome (or class of outcomes)	Describe the completeness of outcome data for each main outcome, including attrition and exclusions from the analysis; state whether attrition and exclusions were reported, the numbers in each intervention group (compared with total randomized participants), reasons for attrition/exclusions where reported, and any reinclusions in analyses performed by the review authors	Were incomplete outcomes data adequately addressed?
Selective outcomes reporting	State how the possibility of selective outcomes reporting was examined by the review authors and what was found	Are reports of the study free of suggestion of selective outcomes reporting?
Other sources of bias	State any important concerns about bias not addressed in the other domains in the tool; if particular questions/entries were prespecified in the review's protocol, responses should be provided for each question/entry	Was the study apparently free of other problems that could put it at a high risk of bias?

Analysis

Classical Meta-analysis

For the classical meta-analysis, data collected on study endpoints for the comparison of triple therapy (TT) versus tumor necrosis factor inhibitor–methotrexate (TNFi-MTX) were analyzed using appropriate effect measures (odds ratio for dichotomous endpoints and weighted mean difference between treatments at follow-up for continuous endpoints), where multiple studies were available for this particular comparison. Both fixed- and random-effects models were run for each endpoint where possible. When there was a single study available, an odds ratio of the comparison was calculated using the data from the single study.

Network Meta-analysis

NMAs were conducted using WinBUGs, a software program commonly used to run Bayesian analyses. Both fixed- and random-effects models were run for each network of evidence. The fixed-effects model assumes that all studies are estimating the same underlying effect size. The difference between individual studies is due only to random (sampling) error within studies and does not account for between-study variance. The weight assigned to each individual study is simply the inverse of the variance (or proportional to its precision) estimates. The combined effect is the estimate of this common (homogeneous) effect size. The random-effects model assumes that the studies are estimating different effect sizes and incorporates the additional variation due to this assumption. The approach employed within a random-effects model is to apportion the observed variance into the two elements: the within- and between-study variance. Both elements are then used to estimate the subsequent weights applied when combining the individual study results. Within the fixed-effects model, the weights attached to each individual study were inversely proportional to the observed variance in each study. Within the random-effects model, these weights are inversely proportional to the sum of the within- and between-

study variances. These were run for each of the four time points of interest: 13 weeks, 26 weeks, 1 year, and 2 years of follow-up.

For the dichotomous endpoints, a logit model to estimate the odds of attaining an endpoint was used. This model was applied to the following endpoints *if feasible*:

- Efficacy Endpoints
    - 70% improvement in American College of Rheumatology criteria (ACR70) (prespecified primary endpoint)
    - ACR20
    - ACR50
    - Change in Clinical Disease Activity Index (CDAI) low disease activity (LDA)
    - CDAI remission
    - Disease Activity Score including 28-joint count–erythrocyte sedimentation rate (DAS28-ESR) LDA
    - DAS28-ESR remission
    - Change in Simplified Disease Activity Index (SDAI) LDA
    - SDAI remission
    - European League Against Rheumatism (EULAR) good response
    - Boolean-defined remission
- Radiographic endpoints
    - % no radiographic progression
- Safety endpoints
    - Overall AEs
    - AEs leading to discontinuation
    - Liver function test (LFT) elevation

        - Aspartate aminotransferase (AST) elevation
        - Alanine aminotransferase elevation
    - Neutropenia
    - Overall infection rate
    - Serious adverse events (AEs)
        - Overall
        - Gastrointestinal-related AEs
        - Infections
        - Malignancies

For continuous endpoints, a weighted mean difference between mean changes from baseline for treatments at follow-up was estimated using end-of-trial mean scores or change in mean score from baseline. This model was applied to the following endpoints, if feasible:

- Efficacy endpoints
    - Mean CDAI
    - Mean DAS28-ESR/DAS28-C-reactive protein (CRP)
    - Mean SDAI
- Radiographic endpoints
    - ven der Heijde modified total Sharp score
    - Joint erosions
    - Joint space narrowing
- Patient-Reported Outcomes endpoints
    - Health Assessment Questionnaire–Disability Index (HAQ-DI) score
    - 36-Item Short Form Survey Physical Component Summary and Mental Component Summary

- EQ-5D (visual analog scale and utility scores)
- Fatigue
- Pain
- Patient global assessment (PGA)
- Work Productivity and Activity Impairment

Model selection, choice of priors, and methods of assessing model fit and consistency

As noted by the International Society for Pharmacoeconomics and Outcomes Research Task Force on Indirect Treatment Comparisons Good Research Practice,[2] one important component of Bayesian methodology is the choice of a prior probability distribution, which reflects a prior belief of the possible values of a model parameter of interest to obtain a corresponding posterior distribution. Vague ("flat") distributions were used such that any parameter value was equally likely. This conservative approach assigns more weight in assuming the therapies are equivalent compared with applying informed prior or traditional frequentist approaches and provides greater confidence when a statistical difference is found.

Fixed- and random-effects models were fitted with preferred model fit determined by the deviance information criterion (DIC). A model with a lower DIC score was considered a better fit. Model fit was also assessed by comparing the residual deviance with the total number of data points. A model with a residual deviance closer to the number of data points was considered a better fit.[3, 4]

Simulation convergence was evaluated by visual inspection of trace from a burn-in of 40,000 iterations. History, trace plots, and Brooks-Gelman-Rubin (BGR; Gelman Rubin convergence statistics) diagnostics were examined to ensure model convergence. Three chains were run, and simulated values from different chains are compared to identify when they become similar. In history and trace plots, each chain is a different color, and model convergence was deemed

to have occurred when all three chains overlap. In the BGR diagnostic plots, three colored lines, green (measure of between-chain variability), blue (measure of within-chain variability), and red (ratio of between- and within-chain variability) were plotted. Model convergence was deemed to have occurred if the green and the blue lines are converging together and the red line is close to one. Furthermore, autocorrelation plots were also assessed to check for slow convergence. Autocorrelations between sampled values were expected to drop off with increasing lag (specified number of iterations apart), and this was examined in these plots. Additional iterations were run if convergence had not been achieved. Model convergence is necessary to ensure that the iterative process is able to obtain appropriate solutions and the coefficient is meaningful.[3, 4] An assessment of consistency was performed by comparing indirect comparison-relative treatment effects estimated via the NMA against the pairwise direct comparison results, when such direct evidence was available. When the point estimates of the treatment effects from the NMA fell between the 95% confidence interval of the pairwise direct comparison, the results were considered consistent.

RESULTS

Characteristics of studies included in the analysis

The search yielded a total of 6560 abstracts and citations from EMBASE, MEDLINE, and Cochrane Library (CENTRAL). After deduplication, 5747 abstracts were screened at the abstract level.

During the first-level screening of abstracts, 5437 citations were excluded, yielding 310 articles suitable for full-text review.

During the second-level screening of the 310 full texts, 175 full-text articles were excluded for the following reasons:

- 52 were case reports, comments, letters, editorials, and reviews
- 1 was full text not in English
- 39 had no treatment of interest in one arm of the trial
- 7 had patients taking treatments of interest for other indications
- 9 had no endpoint of interest
- 28 had no results at time point of interest
- 19 were abstract-only studies
- 17 were duplicates
- 3 had patient population not of interest

Therefore, 60 full-text studies were identified for inclusion and data extraction from EMBASE/MEDLINE/Cochrane Library (CENTRAL) search. EMBASE search results included conference abstracts from ACR Annual Meeting and Annual European Congress of Rheumatology for 2012, 2013, and 2014.

In addition to the database searches, a manual bibliography search was performed using identified relevant systematic reviews, Cochrane reviews, and meta-analysis [6-18]. One study was identified and included through this process.[19]

In summary, 136 records were included from all sources as described above. After grouping the publications from the same primary studies together, there were 60 primary clinical studies included in this review. Of the 60 studies, 39 [40-78] studies were in MTX–inadequate response (IR) patients, and the remaining 21 [19-39] were in methotrexate (MTX)-naive patients.

Study Characteristics: Definitions

Table 3 shows the patient characteristics for each study considered for the analysis.

Table 3. Study and Patient Baseline Characteristics for Patients Who Had Inadequate Response to Methotrexate or Were Methotrexate-Naive for All Studies Considered for the Analysis

Study	Interventions	Study Duration, wk	Patients, n	Mean Age, y	Women, %	Mean Disease Duration, y	RF+, %	Mean DAS28-ESR/CRP	Mean Joint Erosion	Mean Joint Space Narrowing
Patients with inadequate response to methotrexate										
Chen et al, 2009 [40] (Low risk of bias)	ADA 40 mg EOW + MTX	16	35	53*	74	6.2	86	6.4/NR	NR	NR
	MTX	16	12	53*	92	8.3	92	6.5/NR	NR	NR
Abe et al, 2006 [41] (Low risk of bias)	IFX 10 mg/kg + MTX	14	51	57	78	7.1	NR	NR	NR	NR
	IFX 3 mg/kg + MTX	14	49	55	82	9.1	NR	NR	NR	NR
	MTX	14	47	55	75	7.5	NR	NR	NR	NR
Choy et al, 2012 [42] (Low risk of bias)	CZP Q4W + MTX	24	126	53	72	9.4	74	6.2†/NR	NR	NR
	MTX	24	121	56	66	9.9	79	6.3†/NR	NR	NR
Durez et al, 2004 [43] (High risk of bias)	IFX 3 mg/kg + MTX	14	12	48*	100	10*	67	NR	NR	NR
	MP 1 g + MTX	14	15	56*	73	12*	87	NR	NR	NR
Furst et al, 2007 [44] (Unclear risk of bias)	IFX 3 mg/kg + MTX	14	14	45	85	10	100	NR	19	14
Kameda et al, 2010 [45, 112] (Unclear risk of bias)	ETN 25 mg BIW + MTX	25	77	NR	80	NR	87	NR	57*	57*
	ETN 25 mg BIW	25	74	NR	87	NR	92	NR	56*	59*
Kay et al, 2008	GOL 50 mg	16	34	48*	67	8.2*	NR	NR	NR	NR

[46] (Low risk of bias)	Q2W + MTX									
	GOL 50 mg Q4W + MTX	16	35	57*	86	8.2*	NR	NR	NR	NR
	GOL 100 mg Q4W + MTX	16	34	58*	77	6.3*	NR	NR	NR	NR
	GOL 100 mg Q2W + MTX	16	34	54*	80	9*	NR	NR	NR	NR
	MTX	16	35	52*	74	5.6*	NR	NR	NR	NR
Kavanaugh et al, 2000 [47] (Low risk of bias)	IFX 5 mg/kg + MTX	12	7	47	71	7.4	86	NR	NR	NR
	IFX 10 mg/kg + MTX	12	7	53	86	7.5	100	NR	NR	NR
	IFX 20 mg/kg + MTX	12	7	37	100	4.9	71	NR	NR	NR
	MTX	12	7	45	86	4.9	71	NR	NR	NR
Keystone et al, 2008 [48, 113-115] (Low risk of bias)	CZP (initial 400 mg given at wk 0, 2, and 4, then 400 mg EOW) + MTX	12	390	52	86	6.2	84	6.9*/NR	NR	NR
	CZP (initial 400 mg given at wk 0, 2, and 4, then 200 mg EOW) + MTX	12	393	51	82	6.1	80	6.9*/NR	NR	NR
	MTX	12	199	52	84	6.2	83	7*/NR	NR	NR
Keystone et al, 2009 [49, 116-121] (Low risk of bias)	MTX	4-wk run-in, 52-wk double-blind, 5-y follow-up	133	52*	82	6.5*	81	6.1*/4.9*	NR	NR
	GOL 100 mg	4-wk run-in, 52-wk double-blind,	133	51*	79	5.9*	84	6.0*/4.8*	NR	NR

		5-y follow-up								
	GOL 50 mg + MTX	4-wk run-in, 52-wk double-blind, 5-y follow-up	89	52*	81	4.5*	87	6.1*/5.1*	NR	NR
	GOL 100 mg + MTX	4-wk run-in, 52-wk double-blind, 5-y follow-up	89	50*	81	6.7*	84	5.9*/4.9*	NR	NR
Keystone et al, 2004 [50] (Low risk of bias)	ADA 40 mg EOW + MTX	52	207	56	76	11	82	NR	41	31
	ADA 20 mg/wk + MTX	52	212	57	76	11	81	NR	37	30
	MTX	52	200	56	73	10.9	90	NR	37	29
Kim et al, 2012 [51, 122] (Low risk of bias)	ETN 25 mg BIW + MTX	16	197	48	91	6.5	NR	6.1/5.2	NR	NR
	SSZ/HCQ/LEF + MTX	16	103	49	88	6.9	NR	6.1/5.3	NR	NR
Kim et al, 2007 [52] (Low risk of bias)	ADA 40 mg EOW + MTX	24	65	49	95	6.8	77	NR	NR	NR
	MTX	24	63	50	86	6.9	83	NR	NR	NR
Kim et al, 2013 [53] (Unclear risk of bias)	IFX 3 mg/kg + MTX	30	71	49	90	7.4*	NR	NR	NR	NR
	MTX	30	72	51	89	9.8*	NR	NR	NR	NR
Kremer et al, 2010 [54, 123-125] (Low risk of bias)	MTX	48	129	50	80	7.4	NR	NR	NR	NR
	GOL 2 mg/kg Q12W + MTX	48	129	50	77	8.1	NR	NR	NR	NR
	GOL 2 mg/kg Q12W	48	128	50	84	7.4	NR	NR	NR	NR
	GOL 4 mg/kg Q12W + MTX	48	128	50	81	9.4	NR	NR	NR	NR

	GOL 4 mg/kg Q12W	48	129	48	81	8.4	NR	NR	NR	NR
Lan et al, 2004 [55] (Unclear risk of bias)	ETN 25 mg BIW + MTX	12	29	48	83	NR	NR	NR	NR	NR
	MTX	12	29	51	90	NR	NR	NR	NR	NR
Machado et al, 2014 [56] (Unclear risk of bias)	ETN 50 mg/wk + MTX	24	284	48	88	7.9	86	6.6/NR	0	0
	SSZ/HCQ/LEF + MTX	24	145	49	90	9	84	6.7/NR	1	0
Maini et al, 1999 [57, 126-128] (Low risk of bias)	MTX	30	88	51*	80	8.9	77	NR	NR	NR
	IFX 3 mg/kg Q8W + MTX	30	86	56*	81	8.4	84	NR	NR	NR
	IFX 3 mg/kg Q4W + MTX	30	86	51*	77	7.2	80	NR	NR	NR
	IFX 10 mg/kg Q8W + MTX	30	87	55*	77	9	82	NR	NR	NR
	IFX 10 mg/kg Q4W + MTX	30	81	52*	73	8.7	73	NR	NR	NR
Maini et al, 1998 [58] (Unclear risk of bias)	MTX	26	14	49	71	7.6	77	NR	NR	NR
	IFX 1 mg/kg + MTX	26	14	54	71	14.3	71	NR	NR	NR
	IFX 1 mg/kg	26	15	49	73	7.6	93	NR	NR	NR
	IFX 3 mg/kg + MTX	26	15	59	67	12.1	67	NR	NR	NR
	IFX 3 mg/kg	26	14	47	86	7.8	86	NR	NR	NR
	IFX 10 mg/kg + MTX	26	14	50	79	11.1	79	NR	NR	NR
	IFX 10 mg/kg	26	15	56	67	9.7	93	NR	NR	NR
O'Dell et al, 2013 [59] (Low risk of bias)	TT	48	178	58	43	5.5	66	5.8/NR	NR	NR
	ETN 50 mg/wk +	48	175	56	49	4.9	67	5.9/NR	NR	NR

	MTX									
Schiff et al, 2008 [60] (Low risk of bias)	MTX	52	110	49	87	8.4	77	6.8/NR	NR	NR
	IFX 3 mg/kg + MTX	52	165	49	82	7.3	85	6.8/NR	NR	NR
Smolen et al, 2009 [61, 129] (Unclear risk of bias)	MTX	24	127	52	84	5.6	78	6.8/NR	23	23
	CZP (initial 400 mg given at wk 0, 2, and 4, then 200 mg EOW) + MTX	24	246	52	84	6.1	78	6.9/NR	19	21
	CZP (initial 400 mg given at wk 0, 2, and 4, then 400 mg EOW) + MTX	24	246	52	78	6.5	76	6.8/NR	22	25
Tam et al, 2012 [62] (Unclear risk of bias)	IFX 3 mg/kg + MTX	26	20	53*	95	4.2 mo*	70	5.1/NR	2	NR
	MTX	26	20	53*	75	5.8 mo*	90	4.6/NR	4	NR
Tanaka et al, 2012 [63] (Unclear risk of bias)	ADA 40 mg EOW	105	37	59*	76	10.5	86	5.6/4.3	NR	NR
	ADA 40 mg EOW + MTX	105	134	56*	86	8.5	85	5.2/4.5	NR	NR
	ADA 40 mg EOW + MTX + other DMARDs	105	23	60*	65	10.3	85	5.3/4.6	NR	NR
	ADA 40 mg EOW + other DMARDs	105	22	61*	82	9	87	5.6/4.7	NR	NR
Tanaka et al, 2012 [64, 130, 131] (Unclear risk of bias)	MTX	16	90	51*	83	8.7	NR	5.6/NR	31	23
	GOL 50 mg + MTX	16	89	52*	85	8.8	NR	5.5/NR	32	26
	GOL 100 mg +	16	90	52*	90	8.1	NR	5.5/NR	29	24

	MTX									
Taylor et al, 2004 [65, 132] (Unclear risk of bias)	MTX	110	12	51	NR	1.64	NR	5.2 (Unclear ESR/CRP)	NR	NR
	IFX 5 mg/kg + MTX	110	12	55	NR	1.33	NR	5.4/NR	NR	NR
van Riel et al, 2006 [66, 133] (Unclear risk of bias)	ETN 25 mg BIW	16	160	53*	79	10	71	6.2 (Unclear ESR/CRP)	NR	NR
	ETN 25 mg BIW + MTX	16	155	54*	77	9.8	70	6.3 (Unclear ESR/CRP)	NR	NR
van Vollenhoven et al, 2012 [67, 134] (Unclear risk of bias)	MTX (until 6 mo)	52	56	56*	77	6.9	71	6.6/5.6	NR	NR
	MTX (until 6 mo)	52	52	52*	75	9	61	6.3/5.3	NR	NR
	ADA 40 mg EOW + MTX	52	204	53*	79	8.1	68	6.4/5.3	NR	NR
Weinblatt et al, 2013 [71, 91, 135-140] (Unclear risk of bias)	MTX	24	197	52*	80	7	NR	NR/5.9	26	25
	GOL 2 mg/kg + MTX	24	395	53*	83	6.9	NR	NR/6.0	24	24
Weinblatt et al, 2003 [68] (Unclear risk of bias)	MTX	24	62	56	82	11.1	NR	NR	NR	NR
	ADA 20 mg EOW + MTX	24	69	54	75	13.1	NR	NR	NR	NR
	ADA 40 mg EOW + MTX	24	67	57	75	12.2	NR	NR	NR	NR
	ADA 80 mg EOW + MTX	24	73	56	75	12.8	NR	NR	NR	NR
Weinblatt et al, 2013 [70, 141] (Unclear risk of bias)	ABA 125 mg QW + MTX	52	318	51	81	1.9	76	NR/5.5	NR	NR
	ADA 40 mg EOW + MTX	52	328	51	82	1.7	77	NR/5.5	NR	NR
Weinblatt et al, 1999 [72] (Unclear risk of bias)	MTX	24	30	53	73	13	90	NR	NR	NR
	ETN 25 mg BIW + MTX	24	59	48	90	13	84	NR	NR	NR

Weinblatt, 2008 [69] (Unclear risk of bias)	ETN 50 mg BIW + MTX	12	160	53	84	10	61	5.8/5.2	NR	NR
	ETN 50 mg QW + MTX	12	40	51	70	10.1	73	5.5/5.0	NR	NR
Yamamoto et al, 2014 [73, 142-144] (Low risk of bias)	CZP 100 mg Q2W + MTX	12	72	54	81	6	90	6.3/NR	29	25
	CZP 200 mg Q2W + MTX	12	82	51	84	5.6	87	6.2/NR	26	25
	CZP 400 mg Q2W + MTX	12	85	55	81	6	89	6.3/NR	26	24
	MTX	12	77	52	86	5.8	86	6.5/NR	28	25
Yoo et al, 2013 [74, 145-147] (Unclear risk of bias)	CT-P13 3 mg/kg + MTX	30	302	50*	81	NR	NR	NR/5.9	NR	NR
	IFX 3 mg/kg + MTX	30	304	50*	84	NR	NR	NR/5.8	NR	NR
Zhang et al, 2006 [75] (Unclear risk of bias)	IFX 3 mg/kg + MTX	18	87	48*	85	7.1	NR	NR	NR	NR
	MTX	18	86	49*	85	8	NR	NR	NR	NR
van Vollenhoven et al, 2009 [76, 148-150] (Unclear risk of bias)	TT	52	130	53*	78	6.3	65	6.0	2	3
	IFX 3 mg/kg + MTX	52	128	51*	76	6.2	69	5.9	2	3
Takeuchi et al, 2009 [77] (Unclear risk of bias)	IFX 3 mg/kg + MTX	54	99	50*	79	8.3	NR	6.2 (Unclear ESR/CRP)	NR	NR
	IFX 6 mg/kg + MTX	54	104	49*	83	7.2	NR	6.2 (Unclear ESR/CRP)	NR	NR
	IFX 10 mg/kg + MTX	54	104	50*	86	8.4	NR	6.2 (Unclear ESR/CRP)	NR	NR
Westhovens et al, 2006 [78] (Unclear risk of	IFX 3 mg/kg + MTX	22	360	53*	80	7.8	83	NR	NR	NR
	IFX 10 mg/kg +	22	361	52*	78	6.3	77	NR	NR	NR

bias)	MTX									
	MTX	22	363	52*	83	8.4	81	NR	NR	NR
Methotrexate-naive patients										
Takeuchi et al, 2014 [20] (Unclear risk of bias)	ADA 40 mg EOW + MTX	30	171	54	84	0.3	85	6.6/5.8	8	6
	MTX	30	163	54	79	0.3	83	6.6/5.9	7	6
Horslev-Peterson et al, 2014 [21, 80-83] (Unclear risk of bias)	ADA 40 mg EOW + MTX	52	89	56*	63	0.2*	70	NR/5.5	NR	NR
	MTX	52	91	54*	70	0.2*	74	NR/5.6	NR	NR
Burmester et al, 2013 [19, 84-86] (Unclear risk of bias)	ADA 40 mg EOW + MTX	26	98	52	71	0.4	87	NR/6.1	NR	NR
	ADA 40 mg EOW + MTX	26	100	50	78	0.3	83	NR/6.2	NR	NR
	ADA 40 mg EOW + MTX	26	99	52	79	0.3	83	NR/5.9	NR	NR
	ADA 40 mg EOW + MTX	26	98	54	76	0.3	82	NR/5.9	NR	NR
Detert et al, 2013 [22, 87, 88] (Low risk of bias)	ADA 40 mg EOW + MTX	48	76	47	70	0.2	63	6.2/NR	2	4
	MTX	48	57	53	67	0.1	69	6.3/NR	4	7
Kavanaugh et al, 2013 [23, 89-94] (Low risk of bias)	ADA 40 mg EOW + MTX	26	515	51*	74	0.3	87	NR/6.0	5	6
	MTX	26	517	50*	74	0.4	89	NR/6.0	5	6
Soubrier et al, 2009 [24] (Unclear risk of bias)	ADA 40 mg EOW + MTX	52	33	46*	79	0.4*	70	6.3/5.8	1	1
	MTX	52	32	49*	81	0.4*	77	6.2/5.9	4	4
Bejarano et al,	ADA 40 mg	60	75	47	58	0.8	96	5.9/NR	NR	NR

2008 [25] (Low risk of bias)	EOW + MTX assumed 40 mg									
	MTX	60	73	47	53	0.7	95	6.0/NR	NR	NR
Breedveld et al, 2006 [26, 95, 96] (Unclear risk of bias)	ADA 40 mg EOW + MTX	104	268	52	72	0.7	NR	6.3/NR	11	7
	ADA 40 mg EOW	104	274	52	77	0.7	NR	6.4/NR	11	8
	MTX	104	257	52	74	0.8	NR	6.3/NR	14	8
Iannone et al, 2014 [27] (Unclear risk of bias)	MTX	54	9	55	73	6.2	86	NR	NR	NR
	ETN 50 mg/wk	54	13	55	73	6.2	86	NR	NR	NR
	ETN 50 mg/wk + MTX	54	7	55	73	6.2	86	NR	NR	NR
Emery et al, 2008 [28, 97-99] (Low risk of bias)	MTX	52	263	52*	73	0.8	NR	6.5/NR	NR	NR
	ETN 50 mg/wk + MTX	52	265	51*	74	0.7	NR	6.5/NR	NR	NR
Klareskog et al, 2004 [39, 100-102] (Low risk of bias)	MTX	52	228	53*	79	6.8	71	NR	12*	13*
	ETN 25 mg BIW	52	223	53*	77	6.3	75	NR	8*	12*
	ETN 25 mg BIW + MTX	52	231	53*	74	6.8	76	NR	10*	10*
Emery et al, 2009 [29, 103-105] (Low risk of bias)	MTX	52	160	49	84	2.9	82	6.2/5.0	NR	NR
	GOL 100 mg Q4W	52	159	48	84	4.1	81	6.3/5.2	NR	NR
	GOL 50 mg Q4W + MTX	52	159	51	85	3.5	76	6.3/5.1	NR	NR
	GOL 100 mg Q4W + MTX	52	159	50	79	3.6	80	6.3/5.1	NR	NR
	GOL 100 mg Q4W + MTX	52	159	50	79	3.6	80	6.3/5.1	NR	NR

Nam, 2014 [30] (Low risk of bias)	MP 250 mg wk 0 + MTX	26	57	53	72	0.1*	61	NR	4	6
	IFX 3 mg/kg + MTX	26	55	54	66	0.1*	49	NR	1	5
Durez et al, 2007 [31] (Unclear risk of bias)	MTX	46	14	54	71	0.5	64	NR/5.2	NR	NR
	IFX 3 mg/kg + MTX	46	15	50	67	0.4	67	NR/5.3	NR	NR
	MP 1 g + MTX	46	15	50	60	0.3	100	NR/5.3	NR	NR
Quinn et al, 2005 [32, 106] (Low risk of bias)	IFX 3 mg/kg + MTX	54	10	51	60	0.6	70	6.3*/NR	1*	NR
	MTX	54	10	53	70	0.5	60	7.0*/NR	1*	NR
St. Clair et al, 2004 [33] (Low risk of bias)	MTX	46	282	50	75	0.9	71	6.7/NR	8	3
	IFX 3 mg/kg + MTX	46	359	51	71	0.8	71	6.6/NR	9	3
	IFX 6 mg/kg + MTX	46	363	50	68	0.9	73	6.7/NR	8	3
Leirisalo-Repo et al, 2013 [38, 107] (Low risk of bias)	MTX + SSZ 1–2 g/d + HCQ 35 mg/kg/wk	104	49	46*	63	0.3*	73	5.6/NR	2	0
	MTX + SSZ 1–2 g/d + HCQ 35 mg/kg/wk + IFX 3 mg/kg	104	50	47*	70	0.3*	78	5.5/NR	2	0
Saunders et al, 2008 [34] (Low risk of bias)	SSZ 40 mg/kg/d + add MTX at 3 mo if inadequate response + add HCQ 400 mg/d if inadequate response	52	47	55	79	1.1	72	6.9/NR	NR	NR
	MTX + SSZ	52	49	55	76	0.8	69	6.8/NR	NR	NR

	500 mg BID + HCQ 200 mg/d									
O'Dell et al, 1996 [35] (Low risk of bias)	MTX	104	36	50	69	10.0	89	NR	NR	NR
	HCQ 200 mg BID + SSZ 500 mg BID	104	35	49	74	6.0	85	NR	NR	NR
	MTX + HCQ 200 mg BID + SSZ 500 mg BID	104	31	50	65	10.0	84	NR	NR	NR
Moreland et al, 2012 [36, 108, 109] (Low risk of bias)	ETN 50 mg/wk + MTX	102	244	51	74	0.3	89	5.8/NR	3	4
	MTX + SSZ 500–1000 mg BID + HCQ 200 mg BID	102	132	49	77	0.3	92	5.8/NR	3	4
	MTX + if insufficient response add ETN 50 mg/wk	102	255	49	69	0.2	91	5.8/NR	3	2
	MTX + if insufficient response add SSZ 500–1000 mg BID + HCQ 200 mg BID	102	124	49	70	0.4	87	5.8/NR	4	4
Goekoop-Ruiterman et al, 2008 [37, 110, 111] (Low risk of bias)	MTX	52	126	54	68	0.4*	67	NR	4	3
	MTX + if insufficient response add SSZ + add HCQ + followed by prednisone	52	121	54	71	0.5*	64	NR	4	3

MTX + SSZ 2000 mg/d + prednisone 60 mg/d (tapered to 7.5 mg/d)	52	133	55	65	0.4*	65	NR	3	3
IFX 3 mg/kg + MTX	52	128	54	66	0.4*	64	NR	4	3

ABA=abatacept; ADA=adalimumab; BID=twice a day; BIW=twice a week; CRP=C-reactive protein; CT-P13=infliximab biosimilar; CZP=certolizumab; DAS28=disease activity score including 28-joint count with four components; DMARD=disease-modifying antirheumatic drug; EOW=every other week; ESR=erythrocyte sedimentation rate; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; LEF=leflunomide; MP=methylprednisone; MTX=methotrexate; NR=not reported; QW=every week; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; Q12W=every 12 weeks; RF+=rheumatoid factor positive; SSZ=sulfasalazine; TT=triple therapy.

*Median; †Disease activity score including 28-joint count with three components.

NMA Feasibility Assessment

Patients With Inadequate Response to MTX

The literature review found 39 RCTs in the MTX-IR population. These studies were assessed for comparability of the following patient baseline characteristics: mean age, proportion of female enrollment, proportion of RF+ patients, mean disease duration in years, baseline mean DAS28 (ESR and CRP separately), baseline mean mTSS, baseline mean joint erosion, baseline mean baseline joint space narrowing, proportion of patients receiving concomitant NSAIDs, proportion of patients receiving concomitant prednisone, and baseline mean HAQ-DI. The distributions of these baseline characteristics are represented in the figures below (**Figures 1–14**). Overall, there were no clinically meaningful differences seen in treatment cohorts across the studies as determined by coauthors who are practicing rheumatologists.

Figure 1. Distribution of mean (SD) age in years at baseline across all trials. Mean age was largely distributed between 45 and 55 years of age. The minimum mean age, 37 years, was observed in a trial that evaluated IFX.[47] The maximum mean age was 61 years and was observed in an ADA trial.[63] ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

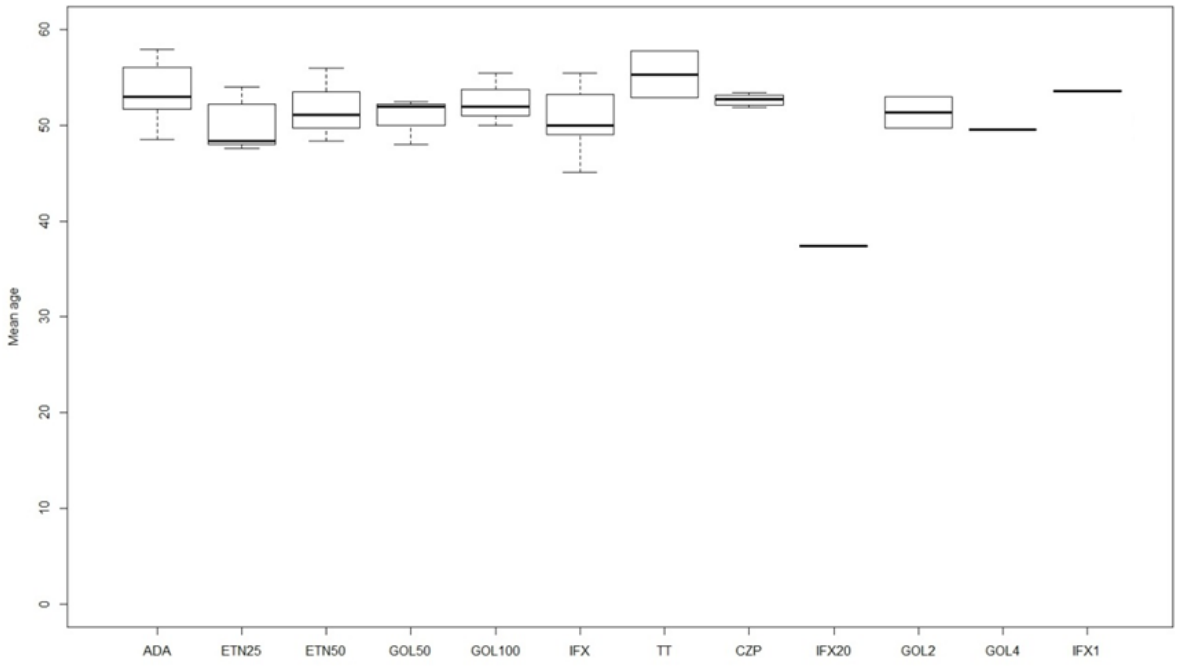


Figure 2. Distribution of mean (SD) proportion (expressed as percentage) of female participants enrolled at baseline. Percentage of women in each study receiving prednisone at baseline ranged from 43% to 100%. Three trials included a higher proportion of women; an ADA study enrolled 95% women, and two IFX studies enrolled more than 95% women. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

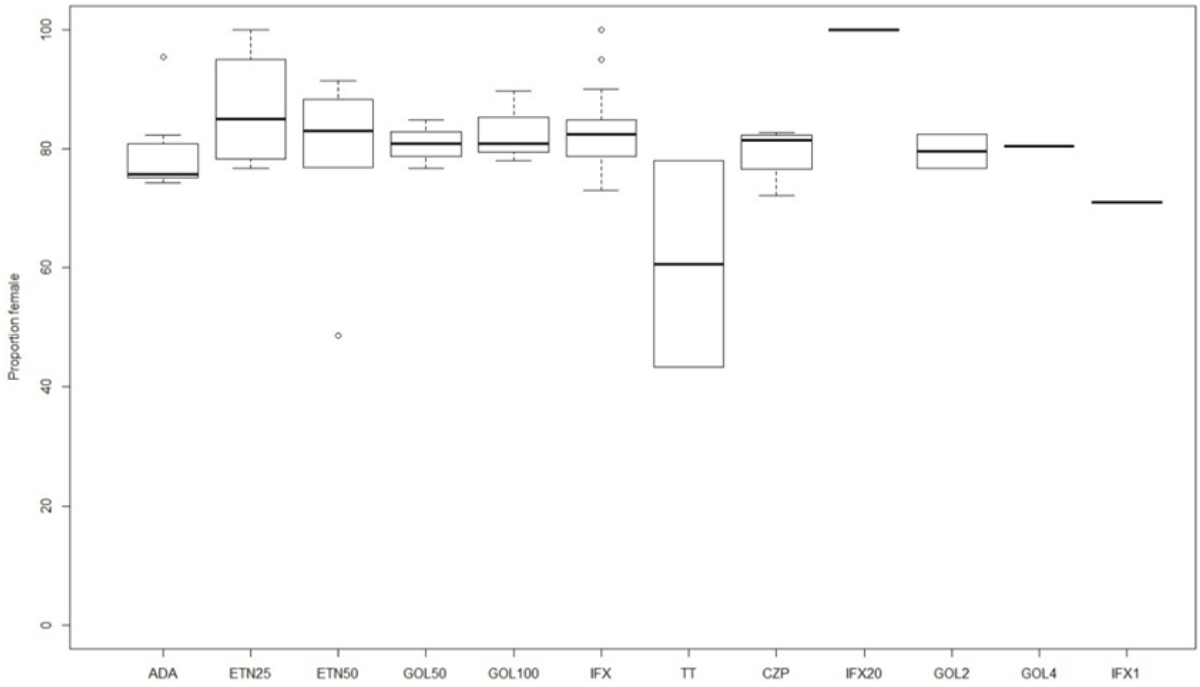


Figure 3. Distribution of mean (SD) proportion of participants (expressed as percentage) who were RF+ at baseline. Percentage of RF+ participants ranged from 65% to 100%. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; RF+=rheumatoid factor–positive; TT=triple therapy. Numbers represent dose in mg.

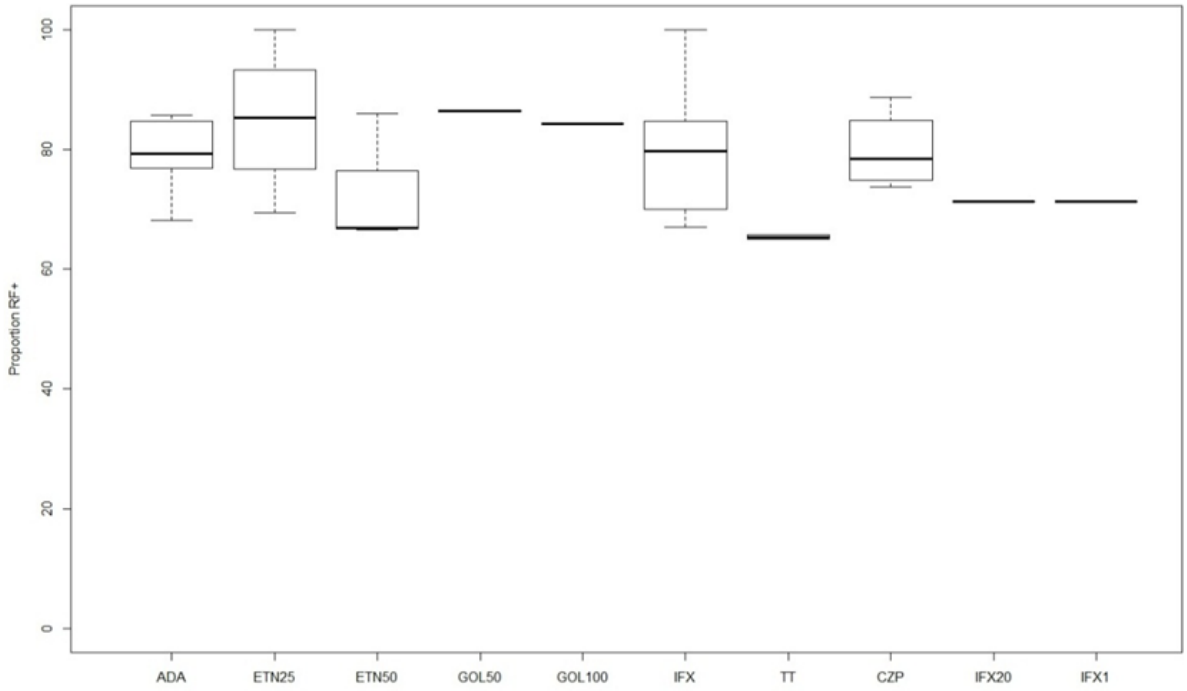


Figure 4. Distribution of mean (SD) baseline disease duration in years as reported by studies. Mean disease duration varied across trials; on average participants had RA for more than 5 years. Duration of disease ranged from <1 year to 14 years. Greatest variation in disease duration was observed within ADA and IFX trials. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; RA=rheumatoid arthritis; TT=triple therapy. Numbers represent dose in mg.

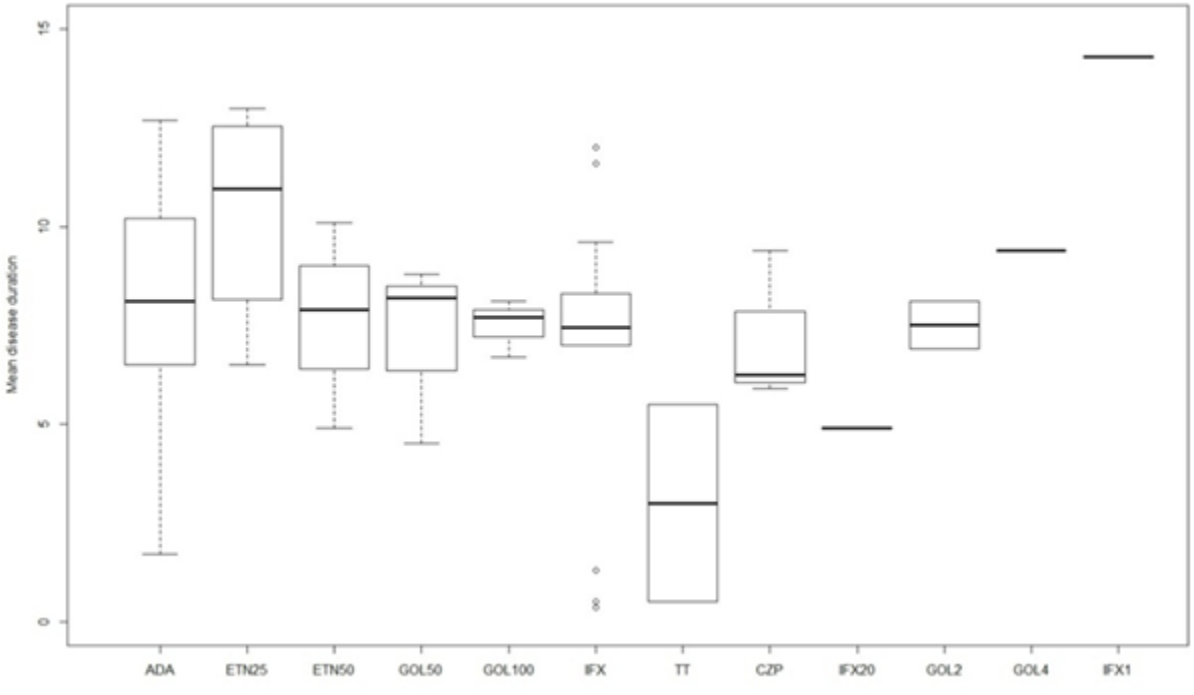


Figure 5. Distribution of mean (SD) DAS28 (CRP) at baseline. Mean DAS28 (CRP) was uniformly distributed across trials, largely between 4.5 and 5.5. ADA=adalimumab; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; ETN=etanercept; GOL=golimumab; IFX=infliximab. Numbers represent dose in mg.

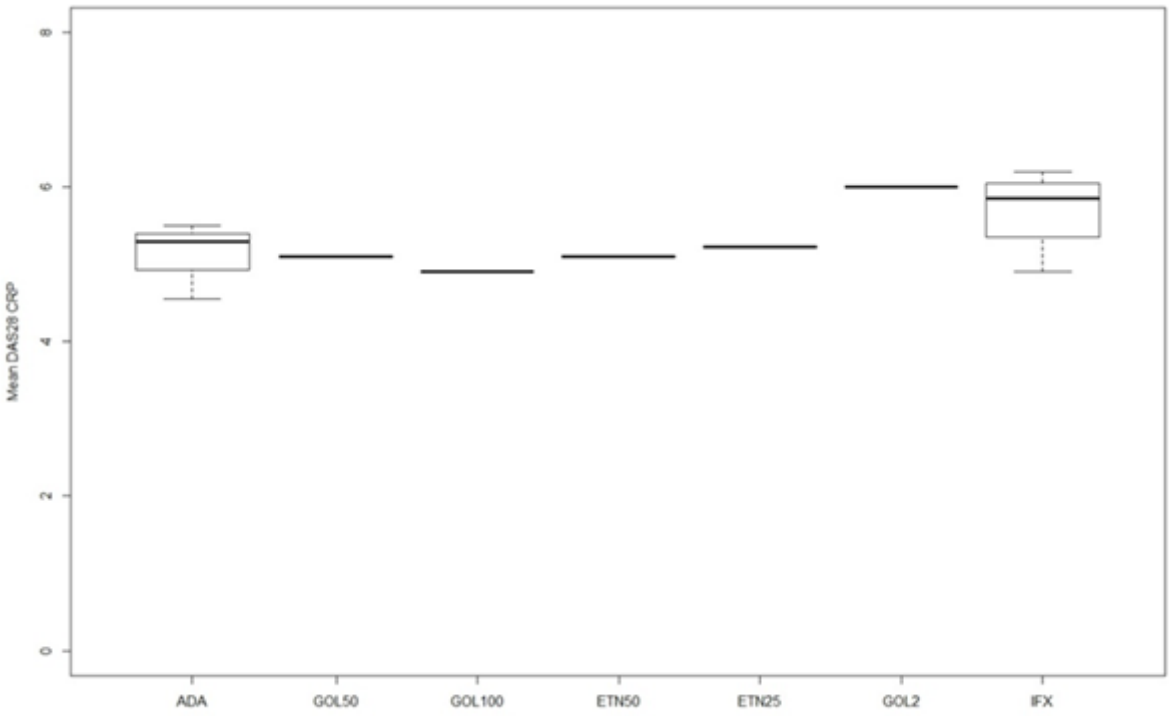


Figure 6. Distribution of mean (SD) DAS28 (ESR) at baseline. Mean DAS28 (ESR) ranged from 5.1 to 6.9. ADA=adalimumab; DAS28=Disease Activity Score including 28-joint count; CZP=certolizumab; ESR=erythrocyte sedimentation rate; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

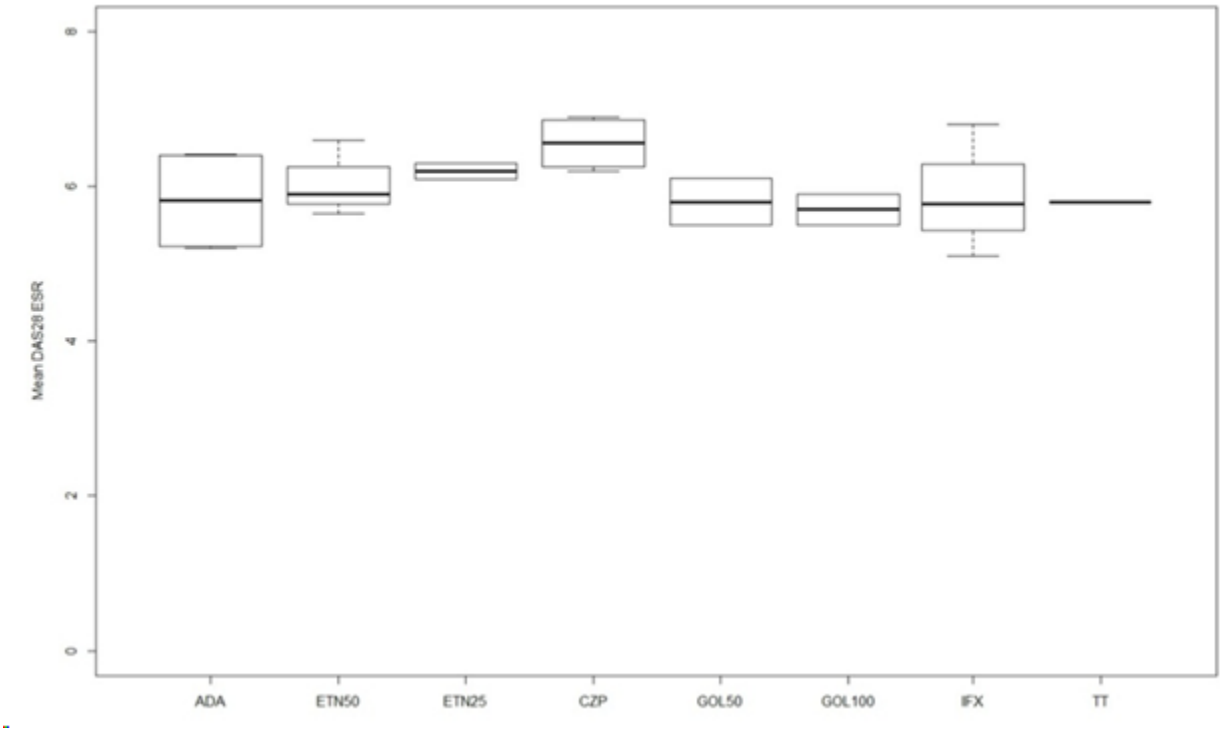


Figure 7. Distribution of mean (SD) CDAI at baseline. Four studies reported mean CDAI; scores ranged from 36 to 40. CDAI=change in Clinical Disease Activity Index; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

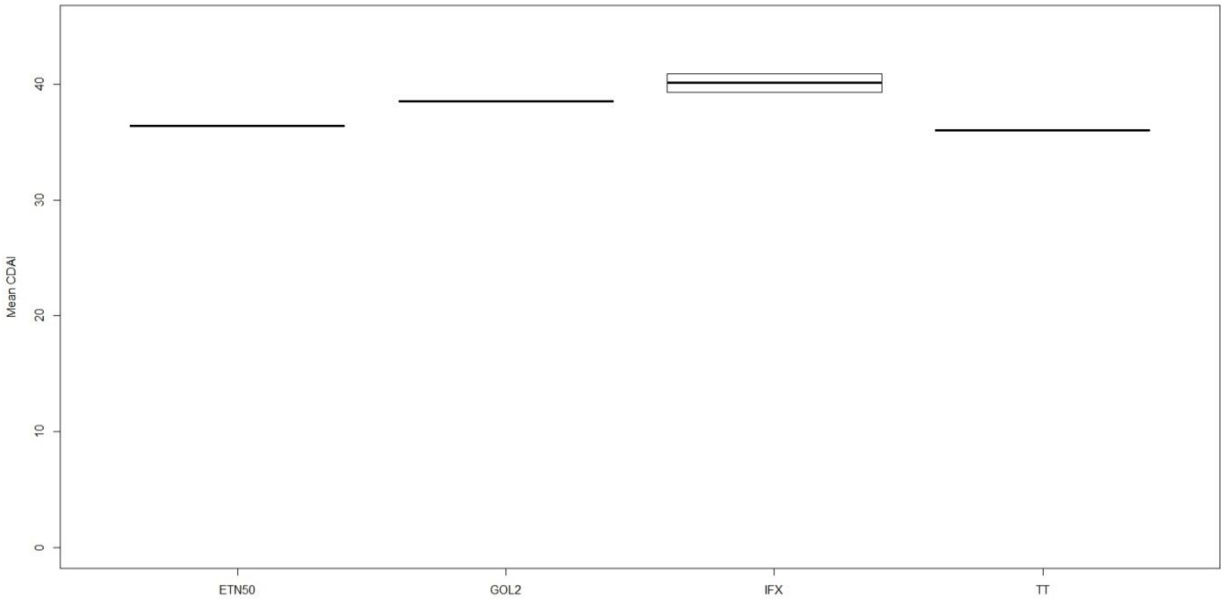


Figure 8. Distribution of mean (SD) SDAI at baseline. Scores were similar for the two trials that reported mean SDAI. GOL=golimumab; IFX=infliximab; SDAI=change in Simplified Disease Activity Index. Numbers represent dose in mg.

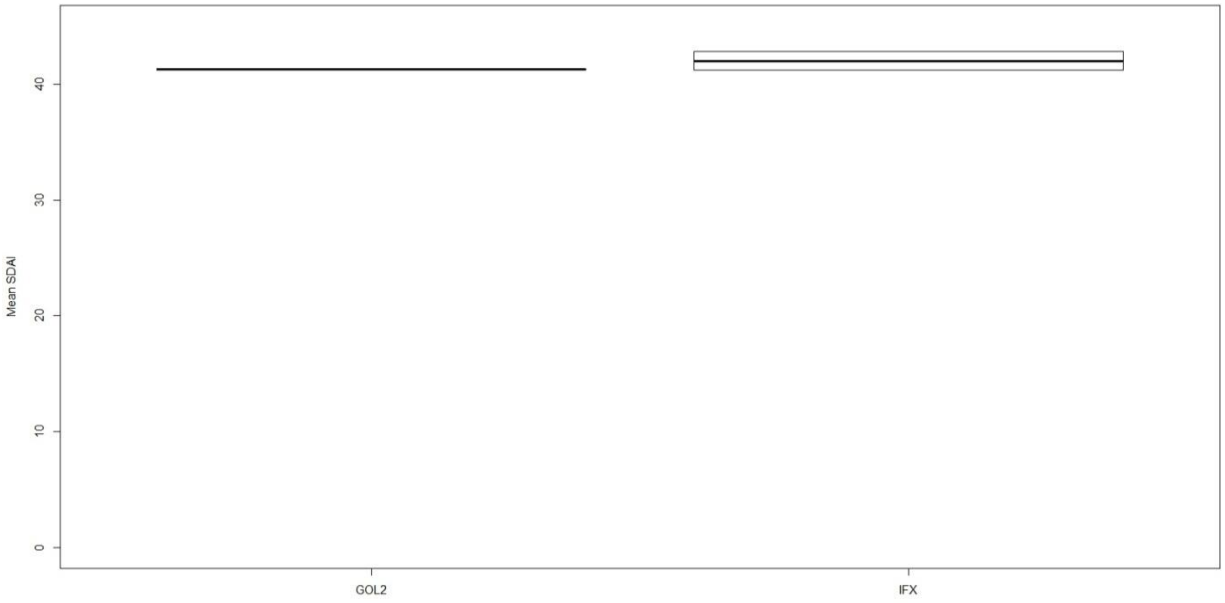


Figure 9. Distribution of mean (SD) mTSSs at baseline. Mean mTSS was reported inconsistently across trials. Greatest variation was observed within IFX trials. CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; mTSS=modified total Sharp score; TT=triple therapy. Numbers represent dose in mg.

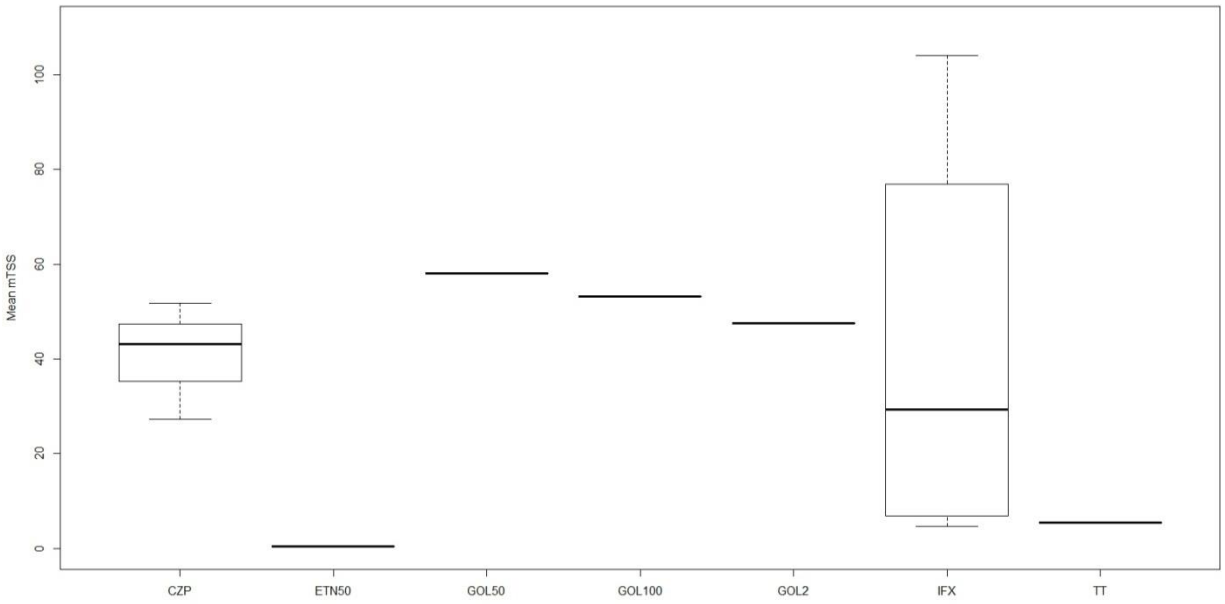


Figure 10. Distribution of mean (SD) joint erosion scores at baseline. Mean joint erosion ranged from 2 to 56. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

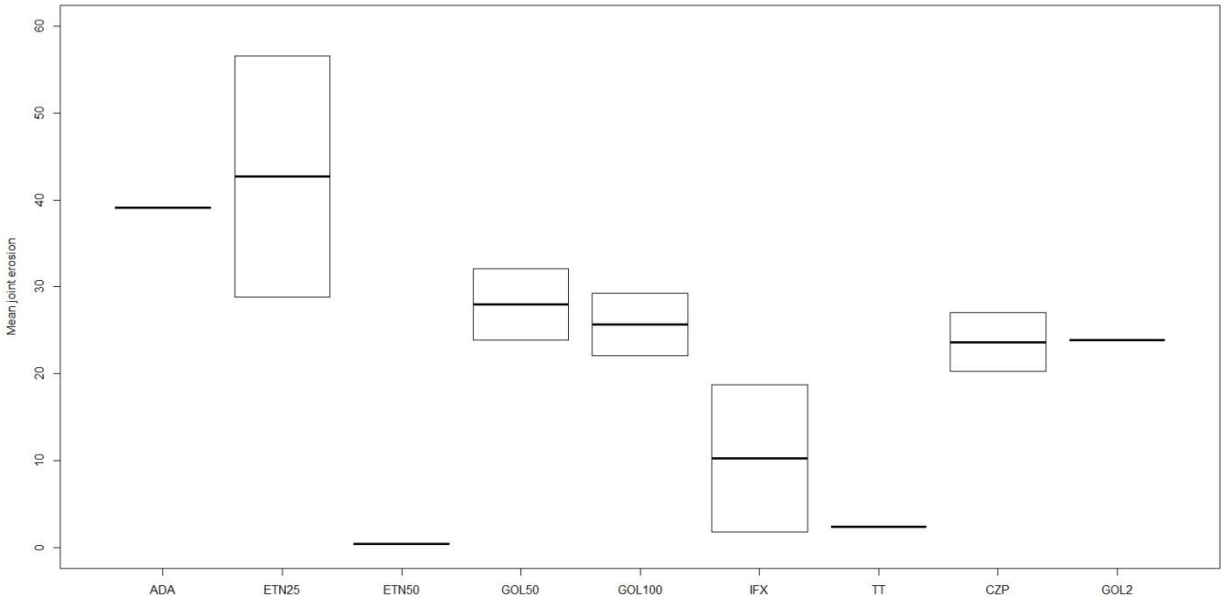


Figure 11. Distribution of mean (SD) joint space narrowing scores at baseline. As with mTSS and joint erosion score, joint space narrowing was infrequently reported at baseline. Mean joint space narrowing ranged from 0 to 56. Most studies reported a mean joint space narrowing score between 20 and 25. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; mTSS=modified total Sharp score; TT=triple therapy. Numbers represent dose in mg.

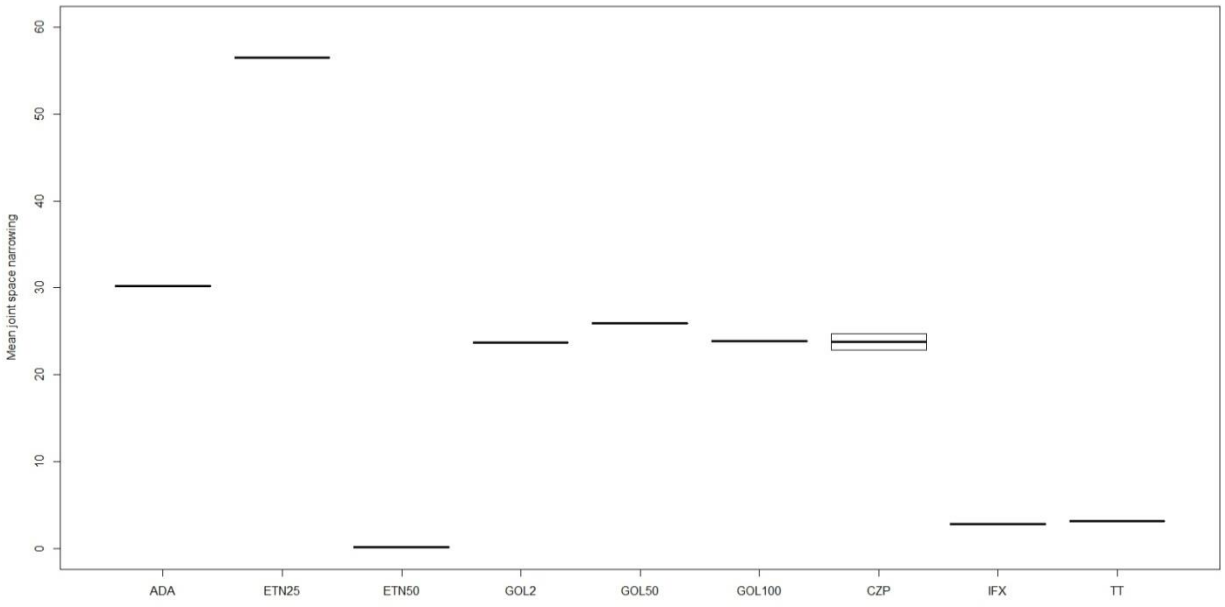


Figure 12. Distribution of mean (SD) proportion of participants (expressed as percentage) who received concomitant NSAIDs at baseline. Percentage of patients taking NSAIDs upon study enrollment ranged from 0% to 95% NSAID use. The bulk of trials reported 55% of study participants using NSAIDs during the trial. ETN=etanercept; GOL=golimumab; IFX=infliximab; NSAID=nonsteroidal anti-inflammatory drug.

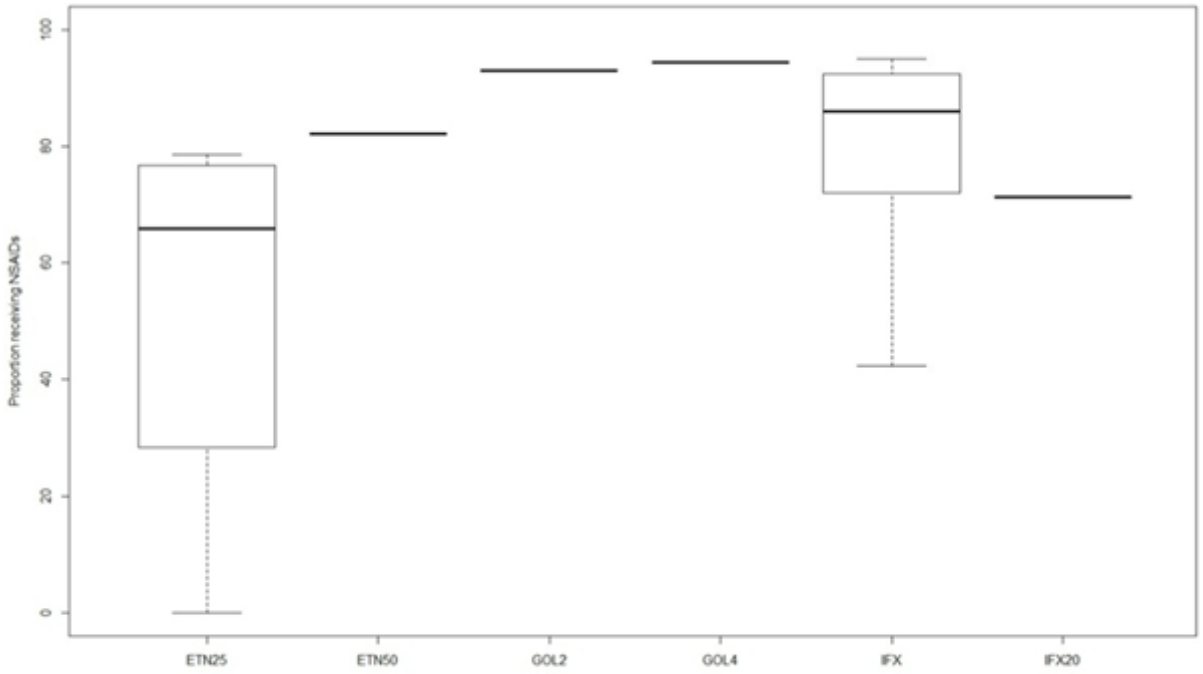


Figure 13 Distribution of mean (SD) proportion of participants who received concomitant prednisone at baseline. Percentage of patients taking prednisone upon study enrollment ranged from 0% to 89% prednisone use. On average, the proportion of patients who used prednisone during each trial was 50% to 70%. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

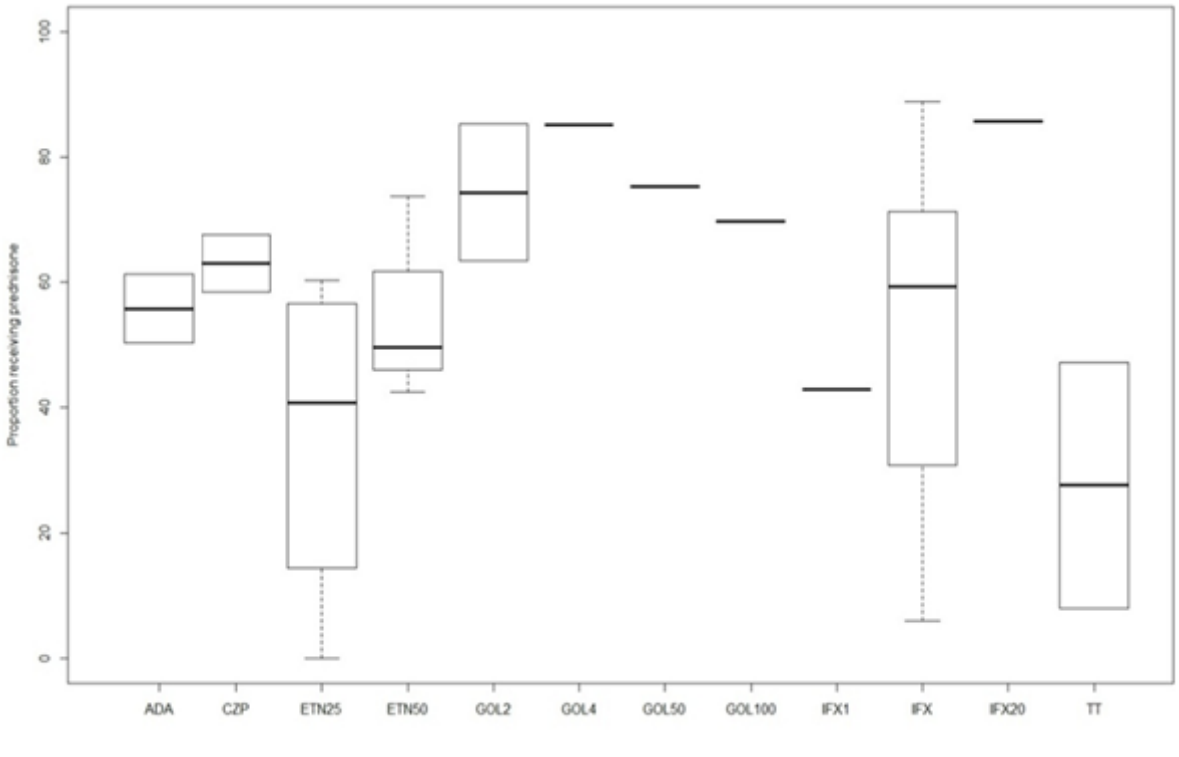


Figure 14. Distribution of mean (SD) HAQ-DI at baseline. Mean HAQ-DI was approximately 1.5 for most studies. Overall mean HAQ-DI ranged from 0.5 to 2. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; HAQ-DI=Health Assessment Questionnaire–Disability Index; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

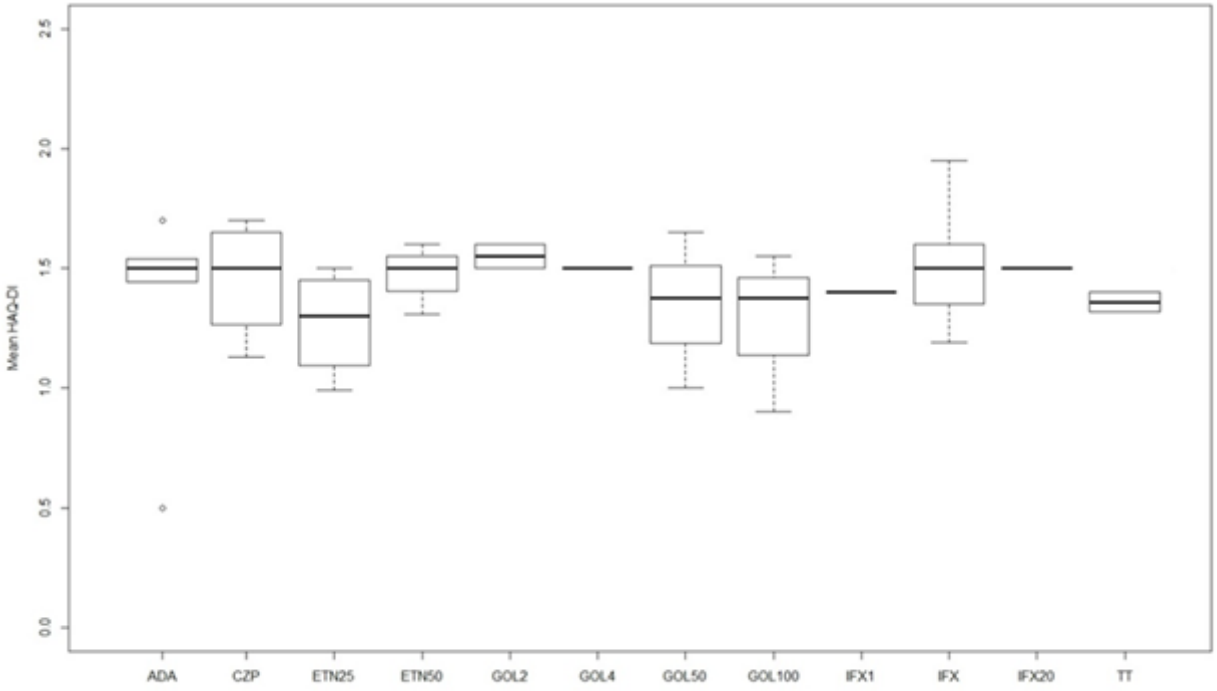


Table 4. Studies of Patients With Inadequate Response to Methotrexate With Special Considerations for the Analysis

Study	Consideration
Yoo et al, 2013 [74, 145-147]	IFX+MTX vs IFX biosimilar + MTX; collapsed into one arm (TNFi-MTX) and could not be used in analyses
Furst et al, 2007 [44]	IFX+MTX vs ETN+MTX; collapsed into one arm (TNFi-MTX) and could not be used in analyses
Weinblatt et al, 2008 [69]	ETN EOW + MTX vs ETN+MTX; collapsed into one arm (TNFi-MTX) and could not be used in analyses
Takeuchi et al, 2009 [77]	Each arm received different dose of IFX in combination with MTX; collapsed into one arm (TNFi-MTX) and could not be used in analyses
Zhang et al, 2006 [75]	Reported endpoints at wk 2 and 18 only; no data time point of interest
Kay et al, 2008 [46]	GOL 50 mg Q2W and GOL 100 mg Q4W not approved for RA treatment; these arms were excluded
Kremer et al, 2010 [54, 123-125]	GOL 2 mg Q12W and GOL 4 mg Q12W not approved for RA treatment; trial was excluded
Tanaka et al, 2012 [64, 130, 131]	GOL 100 mg Q4W not approved for RA treatment; this arm was excluded
Weinblatt et al, 2003 [71]	ADA 20 mg EOW and ADA 80 mg EOW not approved for RA treatment; these arms were excluded
Yamamoto et al, 2014 [73, 142-144]	CZP 100 mg EOW and CZP 200 mg EOW not approved for RA treatment; these arms were excluded
Kavanaugh et al, 2000 [47]	IFX 20 mg not approved for RA treatment; this arm was excluded
O'Dell et al, 2013 [59]	After 6 mo, all patients were allowed to cross over; used up to and including 6 mo data
Keystone et al, 2009 [49, 116-121]	After 6 mo, all patients were allowed GOL; used up to and including 6 mo data
Tam et al, 2012 [62]	After 6 mo, all patients were allowed IFX; used up to and including 6 mo data
Taylor et al, 2004 [65, 132]	After 1 y, all patients were allowed IFX; used up to and

Study	Consideration
	including 1 y data
Weinblatt et al, 2013 [71, 91, 135-140]	After 6 mo, all patients allowed GOL; used up to and including 6 mo data

ADA=adalimumab; CZP=certolizumab; EOW=every other week; ETN=etanercept; GOL=golimumab; IFX=infliximab; MTX=methotrexate; Q2W=every 2 weeks; Q4W=every 4 weeks; Q12W=every 12 weeks; RA=rheumatoid arthritis; TNFi=tumor necrosis factor inhibitor.

Table 5 below highlights the studies available for NMA in the MTX-IR group and the endpoints analyzed in each study. In this group, the following were available for analyses: five studies comparing ADA plus MTX to MTX; nine studies comparing IFX plus MTX to MTX; four studies comparing certolizumab (CZP) plus MTX to MTX; one study comparing MP plus MTX to IFX plus MTX; two studies comparing ETN plus MTX to ETN; three studies comparing subcutaneous GOL plus MTX to MTX; two studies comparing ETN plus MTX to a combination of DMARDs; two studies comparing ETN plus MTX to MTX; one study comparing TT to ETN plus MTX; one study comparing abatacept (ABA) plus MTX to MTX; one study comparing ABA plus MTX to IFX plus MTX; one study comparing ADA plus MTX to ADA; one study comparing tofacitinib (TFC) to MTX; one study comparing ADA plus MTX to TFC; one study comparing intravenous GOL plus MTX to MTX; one study comparing ADA plus MTX to ABA plus MTX; and one study comparing TT to IFX plus MTX. Network of evidence available per endpoint of interest was plotted and is presented along with the NMA results.

For MTX-IR studies, the following endpoints were feasible for analyses:

- Efficacy Endpoints
    - ACR20 3 months
    - ACR20 6 months
    - ACR20 1 year

- ACR20 2 years
- ACR50 3 months
- ACR50 6 months
- ACR50 1 year
- ACR50 2 years
- ACR70 3 months
- ACR70 6 months
- ACR70 1 year
- ACR70 2 years
- EULAR good response 3 months
- EULAR good response 6 months
- EULAR good response 1 year
- EULAR good/moderate response 3 months
- EULAR good/moderate response 6 months
- DAS28 ESR mean change from baseline 6 months
- DAS28 ESR remission 6 months
- DAS28 ESR LDA 6 months
- DAS28 ESR/CRP mean change from baseline 6 months
- DAS28 ESR/CRP mean change from remission 6 months
- DAS28 ESR/CRP LDA 6 months

o Radiographic Endpoints

- mTSS mean change from baseline 6 months
- mTSS mean change from baseline 1 year
- mTSS mean change from baseline 2 years

- Joint erosion (JE) mean change from baseline 6 months
- JE mean change from baseline 1 year
- JE mean change from baseline 2 years
- Joint space narrowing (JSN) mean change from baseline 6 months
- JSN mean change from baseline 1 year
- JSN mean change from baseline 2 years

- Safety Endpoints
  - Discontinuation due to AEs
  - Overall infections
  - Serious overall AEs
  - Overall AEs
  - Malignancies
- PRO Endpoints
  - HAQ-DI mean change from baseline at 6 months
  - PGA mean change from baseline at 6 months

Pain mean change from baseline at 6 months

Table 5. Studies in Patients with Inadequate Response to Methotrexate Available for Analyses

Study	Interventions	Endpoints Analyzed
Chen et al, 2009 [40]	ADA 40 mg EOW + MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR70 3 mo; discontinuation due to AEs; serious overall AEs; overall AEs; malignancies
	MTX	
Abe et al, 2006 [41]	IFX 10 mg/kg + MTX	ACR20 3 mo; ACR50 3 mo; ACR70 3 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs
	IFX 3 mg/kg + MTX	
	MTX	
Choy et al, 2012 [42]	CZP Q4W + MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	MTX	
Durez et al, 2004 [43]	IFX 3 mg/kg + MTX	ACR20 3 mo; ACR50 3 mo; ACR70 3 mo; overall infections; serious overall AEs; overall AEs
	MP 1 g + MTX	
Kameda et al, 2010 [45, 112]	ETN 25 mg BIW + MTX	ACR20 6 mo; ACR20 1 y; ACR50 6 mo; ACR50 1 y; ACR70 6 mo; ACR70 1 y; EULAR good response 3 mo; EULAR good/moderate response 3 mo; EULAR good/moderate response 6 mo; EULAR good response 6 mo; EULAR good/moderate response 1 y; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP LDA 6 mo; DAS28-ESR LDA 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; mTSS 6 mo; mTSS 1 y; JSN 6 mo; JSN 1 y; JE 6 mo; JE 1 y; HAQ-DI 6 mo; PGA 6 mo; discontinuation due to AEs; serious overall AEs
	ETN 25 mg BIW	

Study	Interventions	Endpoints Analyzed
Kay et al, 2008 [46]	GOL 50 mg Q2W + MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	GOL 50 mg Q4W + MTX	
	GOL 100 mg Q4W + MTX	
	GOL 100 mg Q2W + MTX	
	MTX	
Kavanaugh et al, 2000 [47]	IFX 5 mg/kg x 1 + MTX	ACR20 3 mo; ACR50 3 mo; discontinuation due to AEs; overall infections
	IFX 10 mg/kg x 1+ MTX	
	IFX 20 mg/kg x 1+ MTX	
	MTX	
Keystone et al, 2008 [48, 113-115]	CZP (initial 400 mg given at wk 0, 2, and 4, then 400 mg EOW) + MTX	ACR20 3 mo; ACR20 6 mo; ACR20 1 y; ACR50 3 mo; ACR50 6 mo; ACR50 1 y; ACR70 3 mo; ACR70 6 mo; ACR70 1 y; mTSS 6 mo; mTSS 1 y; JSN 6 mo; JSN 1 y; JE 6 mo; JE 1 y; pain 6 mo; discontinuation due to AEs; serious overall AEs
	CZP (initial 400 mg given at wk 0, 2, and 4, then 200 mg EOW) + MTX	

Study	Interventions	Endpoints Analyzed
	MTX	
Keystone et al, 2009 [49, 116-121]	MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; EULAR good/moderate response 3 mo; EULAR good/moderate response 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; HAQ-DI 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	GOL 100 mg	
	GOL 50 mg + MTX	
	GOL 100 mg + MTX	
Keystone et al, 2004 [50]	ADA 40 mg EOW + MTX	ACR20 3 mo; ACR20 6 mo; ACR20 1 y; ACR50 3 mo; ACR50 6 mo; ACR50 1 y; ACR70 3 mo; ACR70 6 mo; ACR70 1 y; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs
	ADA 20 mg QW + MTX	
	MTX	
Kim et al, 2012 [51, 122]	ETN 25 mg BIW + MTX	ACR20 3 mo; ACR50 3 mo; ACR70 3 mo; EULAR good/moderate response 3 mo; discontinuation due to AEs; serious overall AEs; overall AEs
	SSZ/HCQ/LEF+MTX	
Kim et al, 2007 [52]	ADA 40 mg EOW + MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	MTX	
Kim et al, 2013 [53]	IFX 3 mg/kg + MTX	ACR20 6 mo

Study	Interventions	Endpoints Analyzed
	MTX	
Lan et al, 2004 [55]	ETN 25 mg BIW + MTX	ACR20 3 mo; ACR50 3 mo; ACR70 3 mo; discontinuation due to AEs
	MTX	
Machado et al, 2014 [56]	ETN 50 mg/wk + MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; EULAR good/moderate response 6 mo; EULAR good response 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP LDA 6 mo; DAS28-ESR LDA 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; mTSS 6 mo; JSN 6 mo; JE 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; serious overall AEs; overall AEs
	SSZ/HCQ/LEF+MTX	
Maini et al, 1999 [57, 126-128]	MTX	ACR20 3 mo; ACR20 6 mo; ACR20 1 y; ACR20 2 y; ACR50 6 mo; ACR50 1 y; ACR50 2 y; ACR70 6 mo; ACR70 1 y; ACR70 2 y; mTSS 1 y; mTSS 2 y; JSN 1 y; JSN 2 y; JE 1 y; JE 2 y; serious overall AEs; malignancies
	IFX 3 mg/kg Q8W + MTX	
	IFX 3 mg/kg Q4W + MTX	
	IFX 10 mg/kg Q8W + MTX	
	IFX 10 mg/kg Q4W + MTX	
Maini et al, 1998 [58]	MTX	Discontinuation due to AEs
	IFX 1 mg/kg + MTX	

Study	Interventions	Endpoints Analyzed
	IFX 1 mg/kg	
	IFX 3 mg/kg + MTX	
	IFX 3 mg/kg	
	IFX 10 mg/kg + MTX	
	IFX 10 mg/kg	
O'Dell et al, 2013 [59]	TT	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP LDA 6 mo; DAS28-ESR LDA 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; mTSS 6 mo; JSN 6 mo; JE 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo
	ETN 50 mg QW + MTX	
Schiff et al, 2008 [60]	MTX	ACR20 3 mo; ACR20 6 mo; ACR20 1 y; ACR50 3 mo; ACR50 6 mo; ACR50 1 y; ACR70 3 mo; ACR70 6 mo; ACR70 1 y; EULAR good/moderate response 6 mo; EULAR good response 6 mo; EULAR good/moderate response 1 y; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP LDA 6 mo; DAS28-ESR LDA 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; discontinuation due to AEs; serious overall AEs; overall AEs; malignancies
	IFX 3 mg/kg + MTX	
Smolen et al, 2009 [61, 129]	MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; mTSS 6 mo; JSN 6 mo; JE 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies

Study	Interventions	Endpoints Analyzed
	CZP (initial 400 mg given at wk 0, 2, and 4, then 200 mg EOW) + MTX	
	CZP (initial 400 mg given at wk 0, 2, and 4, then 400 mg EOW) + MTX	
Tam et al, 2012 [62]	IFX 3 mg/kg + MTX	DAS28-ESR/CRP remission 6 mo; DAS28-ESR/CRP 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; overall infections
	MTX	
Tanaka et al, 2012 [63]	ADA 40 mg EOW	DAS28-ESR/CRP remission 6 mo; DAS28-ESR/CRP LDA 6 mo; DAS28-ESR/CRP 6 mo; HAQ-DI 6 mo
	ADA 40 mg EOW + MTX	
	ADA 40 mg EOW + MTX + other DMARDs	
	ADA 40 mg EOW + other DMARDs	
Tanaka et al, 2012 [64, 130, 131]	MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; mTSS 6 mo; JSN 6 mo; JE 6 mo; HAQ-DI 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	GOL 50 mg + MTX	

Study	Interventions	Endpoints Analyzed
	GOL 100 mg + MTX	
Taylor et al, 2004 [65, 132]	MTX	ACR20 1 y; ACR50 1 y; EULAR good/moderate response 1 y; mTSS 1 y
	IFX 5 mg/kg + MTX	
van Riel et al, 2006 [66, 133]	ETN 25 mg BIW	ACR20 3 mo; ACR50 3 mo; ACR70 3 mo; EULAR good response 3 mo; EULAR good/moderate response 3 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs
	ETN 25 mg BIW + MTX	
van Vollenhoven et al, 2012 [67, 134]	MTX (until 6 mo)	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; serious overall AEs; overall AEs
	MTX (until 6 mo)	
	ADA 40 mg EOW + MTX	
Weinblatt et al, 2013 [71, 91, 135-140]	MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; EULAR good/moderate response 3 mo; EULAR good/moderate response 6 mo; mTSS 6 mo; JSN 6 mo; JE 6 mo; HAQ-DI 6 mo; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs
	GOL 2 mg/ kg + MTX	
Weinblatt et al, 2003 [68]	MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs

Study	Interventions	Endpoints Analyzed
	ADA 20 mg EOW + MTX	
	ADA 40 mg EOW + MTX	
	ADA 80 mg EOW + MTX	
Weinblatt et al, 2013 [70, 141]	ABA 125 mg QW + MTX	ACR20 3 mo; ACR20 6 mo; ACR20 1 y; ACR20 2 y; ACR50 3 mo; ACR50 6 mo; ACR50 1 y; ACR50 2 y; ACR70 3 mo; ACR70 6 mo; ACR70 1 y; ACR70 2 y; DAS28-ESR/CRP 6 mo; mTSS 1 y; mTSS 2 y; JSN 1 y; JSN 2 y; JE 1 y; JE 2 y; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	ADA 40 mg EOW + MTX	
Weinblatt et al, 1999 [72]	MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; overall infections
	ETN 25 mg BIW + MTX	
Yamamoto et al, 2014 [73, 142, 143, 153]	CZP 100 mg Q2W + MTX	ACR20 3 mo; ACR20 6 mo; ACR50 3 mo; ACR50 6 mo; ACR70 3 mo; ACR70 6 mo; EULAR good/moderate response 3 mo; EULAR good/moderate response 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR remission 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 6 mo; mTSS 6 mo; JSN 6 mo; JE 6 mo; HAQ-DI 6 mo; PGA 6 mo; pain 6 mo; discontinuation due to AEs; serious overall AEs; overall AEs; malignancies
	CZP 200 mg Q2W + MTX	

Study	Interventions	Endpoints Analyzed
	CZP 400 mg Q2W + MTX	
	MTX	
van Vollenhoven et al, 2009 [76, 148-150]	TT	ACR20 3 mo; ACR20 6 mo; ACR20 1 y; ACR20 2 y; ACR50 3 mo; ACR50 6 mo; ACR50 1 y; ACR50 2 y; ACR70 3 mo; ACR70 6 mo; ACR70 1 y; ACR70 2 y; EULAR good response 3 mo; EULAR good/moderate response 3 mo; EULAR good/moderate response 6 mo; EULAR good response 6 mo; EULAR good/moderate response 1 y; mTSS 1 y; mTSS 2 y; JSN 1 y; JSN 2 y; JE 1 y; JE 2 y; discontinuation due to AEs; overall infections; serious overall AEs; overall AEs; malignancies
	IFX 3 mg/kg + MTX	
Westhovens et al, 2006 [78]	IFX 3 mg/kg + MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; DAS28-ESR/CRP remission 6 mo; DAS28-ESR/CRP 6 mo; discontinuation due to AEs; serious overall AEs; overall AEs
	IFX 10 mg/kg + MTX	
	MTX	

ABA=abatacept; ACR=American College of Rheumatology; ACR20=20% improvement in ACR criteria; ACR50=50% improvement in ACR criteria; ACR70=70% improvement in ACR criteria; ADA=adalimumab; AE=adverse event; BID=twice daily; BIW=twice weekly; CRP=C-reactive protein; CZP=certolizumab; DAS28=Disease Activity Score including 28-joint count; DMARD=disease-modifying antirheumatic drug; EOW=every other week; ESR=erythrocyte sedimentation rate; ESR/CRP=both measures combined; ETN=etanercept; EULAR=European League Against Rheumatism; GOL=golimumab; HAQ-DI=Health Assessment Questionnaire−Disability Index; HCQ=hydroxychloroquine; IFX=infliximab; JE=joint erosion; JSN=joint space narrowing; LDA=low

disease activity; LEF=leflunomide; MP=methylprednisolone; mTSS=modified total Sharp score; MTX=methotrexate; PGA=patient global assessment; QW=once weekly; Q2W=every 2 weeks; Q4W=every 4 weeks; Q8W=every 8 weeks; SSZ=sulfasalazine; TT=triple therapy

Table 6. Number of Studies Used for Each Comparison in the Network Meta-Analysis in Patients With an Inadequate Response to Methotrexate

Endpoint	Studies, n	Model Type	DIC
OR ACR20 3 mo	24	REM	319.531
		FEM	332.857
OR ACR20 6 mo	22	REM	325.138
		FEM	401.254
OR ACR20 1 y	8	REM	111.659
		FEM	120.534
OR ACR20 2 y	3	REM	45.495
		FEM	45.468
OR ACR50 3 mo	23	REM	291.27
		FEM	294.379
OR ACR50 6 mo	21	REM	300.108
		FEM	555.588
OR ACR50 1 y	8	REM	106.531
		FEM	107.518
OR ACR50 2 y	3	REM	43.999
		FEM	43.999
OR ACR70 3 mo	22	REM	240.795
		FEM	247.742
OR ACR70 6 mo	21	REM	262.911
		FEM	262.708
OR ACR70 1 y	7	REM	92.338
		FEM	90.49
OR ACR70 2 y	3	REM	41.115
		FEM	41.08
EULAR good response 3 mo	3	REM	41.332
		FEM	42.114
EULAR good response 6 mo	4	REM	62.736
		FEM	62.719
EULAR good response 1 y	4	REM	51.431
		FEM	51.37
EULAR good/moderate response 3 mo	7	REM	97.88

		FEM	102.453
EULAR good/moderate response 6 mo	7	REM	105.594
		FEM	112.281
OR DAS28-ESR remission 6 mo	9	REM	117.948
		FEM	116.32
OR DAS28-ESR/CRP remission 6 mo	13	REM	157..668
		FEM	161.112
OR DAS28-ESR LDA 6 mo	4	REM	63.258
		FEM	63.229
OR DAS28-ESR//CRP LDA 6 mo	5	REM	75.41
		FEM	75.107
DAS28-ESR mean change from baseline to 6 mo	8	REM	–12.85
		FEM	142.22
DAS28-ESR/CRP mean change from baseline to 6 mo	12	REM	–19.269
		FEM	146.229
mTSS scores mean change from baseline 6 mo	8	REM	22.357
		FEM	21.62
mTSS scores mean change from baseline 1 y	6	REM	35.79
		FEM	42.462
mTSS scores mean change from baseline 2 y	3	REM	19.23
		FEM	19.22
JE mean change from baseline 6 mo	8	REM	6.125
		FEM	10.981
JE mean change from baseline 1 y	5	REM	13.278
		FEM	23.184
JSN mean change from baseline 6 mo	8	REM	–8.44
		FEM	10.44
JSN mean change from baseline 1 y	5	REM	13.79
		FEM	15.79
JSN mean change from baseline 2 y	3	REM	11.67
		FEM	11.60
OR dropout AE	26	REM	251.421
		FEM	249.488
OR overall infection	15	REM	178.917
		FEM	177.347
OR serious overall AE	22	REM	238.18

		FEM	238.388
OR overall AE	19	REM	254.975
		FEM	254.885
OR malignancy	12	REM	78.644
		FEM	76.795
HAQ-DI mean change from baseline 6 mo	16	REM	90.476
		FEM	71.242
PGA mean change from baseline 6 mo	12	REM	138.561
		FEM	150.943
Pain mean change from baseline 6 mo	12	REM	129.802
		FEM	129.06

ACR70/50/20=American College of Rheumatology 70%/50%/20% response criteria; AE=adverse event; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; DIC= deviance information criterion; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; FEM=fixed effects model; HAQ-DI=Health Assessment Questionnaire-Disease Index; JE=joint erosion; JSN=joint space narrowing; mTSS=modified total Sharp score; OR=odds ratio; PGA=patient general assessment; REM=random effects model.

Full results of the NMA, including the direct pairwise “classical” meta-analysis are shown in **Tables 7–8.**

Table 7. Full Results of the Network Meta-Analysis for Patients With Inadequate Response to Methotrexate—Efficacy and Patient-Reported Outcomes for Triple Therapy vs TNFi-methotrexate

	3 mo			6 mo			1 y			2 y		
	NMA RE	**NMA FE**	**Direct Pairwise**	**NMA RE**	**NMA FE**	**Direct Pairwise**	**NMA RE**	**NMA FE**	**Direct Pairwise**	**NMA RE**	**NMA FE**	**Direct Pairwise**
ACR20*	0.90 (0.33, 2.50)	0.90 (0.52, 1.57)	0.9 (0.52, 1.56)	0.75 (0.22, 2.52)	0.81 (0.57, 1.15)	0.81 (0.57, 1.14)	0.54 (0.08, 3.46)	0.5436 (0.32, 0.91)	0.55 (0.32, 0.92)	0.75 (0.00, 405.10)	0.75 (0.44, 1.24)	0.75 (0.45, 1.24)
ACR50*	0.55 (0.18, 1.61)	0.55 (0.27, 1.08)	0.55 (0.28, 1.10)	0.60 (0.13, 2.83)	0.61 (0.41, 0.90)	0.61 (0.41, 0.90)	0.50 (0.07, 3.61)	0.51 (0.27, 0.96)	0.51 (0.27, 0.96)	0.65 (0.00, 347.70)	0.65 (0.37, 1.14)	0.65 (0.37, 1.14)
ACR70*	1.30 (0.17, 10.10)	1.27 (0.42, 4.10)	1.25 (0.42, 3.73)	0.36 (0.16, 0.80)	0.35 (0.19, 0.64)	0.36 (0.20, 0.66)	0.56 (0.13, 2.27)	0.55 (0.22, 1.31)	0.56 (0.24, 1.33)	0.81 (0.00, 428.20)	0.82 (0.41, 1.63)	0.82 (0.41, 1.62)
EULAR good response*	0.94 (0.01, 148.70)	0.94 (0.54, 1.63)	0.94 (0.54, 1.63)	0.62 (0.00, 353.30)	0.61 (0.35, 1.07)	0.612 (0.36, 1.07)	0. 50 (0.00, 249.20)	0.51 (0.29, 0.86)	0.51 (0.30, 0.87)	NA	NA	NA
EULAR good/moderate response*	0.94 (0.07, 13.54)	0.94 (0.54, 1.63)	0.94 (0.54, 1.63)	0.62 (0.03, 14.41)	0.62 (0.35, 1.06)	0.62 (0.36, 1.07)	NA	NA	NA	NA	NA	NA
DAS28-ESR remission*	NA	NA	NA	0.52 (0.05, 5.18)	0.5213 (0.28, 0.94)	0.53 (0.29, 0.96)	NA	NA	NA	NA	NA	NA
DAS28-ESR/CRP remission*	NA	NA	NA	0.52 (0.11, 2.56)	0.52 (0.28, 0.95)	0.53 (0.29, 0.96)	NA	NA	NA	NA	NA	NA

	3 mo			6 mo			1 y			2 y		
DAS28-ESR LDA*	NA	NA	NA	0.62 (0.00, 383.20)	0.62 (0.38, 1.01)	0.62 (0.38, 1.00)	NA	NA	NA	NA	NA	NA
DAS28-ESR/CRP LDA*	NA	NA	NA	0.62 (0.00, 89.95)	0.62 (0.38, 0.99)	0.62 (0.38, 1.01)	NA	NA	NA	NA	NA	NA
ΔDAS28-ESR†	NA	NA	NA	0.28 (−2.30, 2.81)	0.27 (−0.02, 0.56)	0.27 (−0.01, 0.55)	NA	NA	NA	NA	NA	NA
ΔDAS28-ESR/CRP†	NA	NA	NA	0.27 (−1.10, 1.65)	0.27 (−0.02, 0.56)	0.27 (−0.01, 0.55)	NA	NA	NA	NA	NA	NA
ΔmTSS†	NA	NA	NA	0.42 (−1.37, 2.18)	0.42 (−0.22, 1.06)	0.42 (−0.22, 1.05)	2.08 (−4.79, 8.90)	2.09 (−0.09, 4.26)	2.09 (−0.07, 4.25)	3.22 (−3.50, 10.00)	3.23 (0.39, 6.10)	3.23 (0.37, 6.09)
ΔJoint erosion†	NA	NA	NA	0.26 (−1.60, 2.17)	0.26 (−0.04, 0.56)	0.26 (−0.04, 0.56)	0.92 (−5.50, 7.33)	0.90 (−0.16, 1.98)	0.91 (−0.15, 1.97)	1.54 (−4.90, 7.96)	1.53 (0.05, 2.96)	1.53 (0.08, 2.98)
ΔJoint space narrowing†	NA	NA	NA	0.16 (−0.48, 0.81)	0.16 (−0.27, 0.59)	0.16 (−0.27, 0.59)	1.25 (−4.35, 6.86)	1.29 (0.04, 2.53)	1.28 (0.03, 2.53)	1.66 (−4.82, 8.10)	1.66 (−0.00, 3.34)	1.66 (−0.01, 3.33)
ΔHAQ-DI†	NA	NA	NA	0.07 (−0.17, 0.31)	0.07 (−0.11, 0.25)	0.07 (−0.10, 0.24)	NA	NA	NA	NA	NA	NA
ΔPGA†	NA	NA	NA	5.29 (−3.66, 14.21)	5.28 (0.77, 9.83)	5.30 (0.80, 9.80)	NA	NA	NA	NA	NA	NA
ΔPain†	NA	NA	NA	3.15 (−3.49, 9.78)	3.2 (−1.56, 7.96)	3.2 (−1.57, 7.97)	NA	NA	NA	NA	NA	NA

ACR=American College of Rheumatology; ACR20=20% improvement in ACR criteria; ACR50=50% improvement in ACR criteria; ACR70=70% improvement in ACR criteria; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; EULAR=European League Against Rheumatism; FE=fixed effects; HAQ-DI=Health Assessment Questionnaire−Disability Index; LDA=low disease activity; mTSS=modified total Sharp score; NA=not applicable; NMA=network meta-analysis; PGA=patient global assessment; RE=random effects; TNFi-MTX=tumor necrosis factor inhibitor–methotrexate; TT=triple therapy.

*Odds ratio and 95% credible interval of TT vs TNFi-MTX, with value <1 indicating a better performance for TNFi-MTX.

†Difference in mean change from baseline of TT vs TNFi-MTX with positive value indicating better performance for TNFi-MTX.

Table 8. Full Results of NMA for Patients With Inadequate Response to Methotrexate—Safety for Triple Therapy vs TNFi-methotrexate

Endpoints	NMA RE	NMA FE	Direct Pairwise
Discontinuation due to AEs*	1.17 (0.47–2.98)	1.17 (0.60–2.31)	1.17 (0.60–2.28)
Overall infections*	0.08 (0.00–0.57)	0.08 (0.00–0.55)	0.11 (0.01–0.94)
Overall serious AEs*	0.38 (0.01–6.26)	0.40 (0.01–5.16)	0.49 (0.04–5.45)
Overall AEs*	1.30 (0.63–2.65)	1.30 (0.79–2.15)	1.30 (0.79–2.13)
Malignancies*	0.97 (0.00–603.4)	1.00 (0.00–667.40)	0.98 (0.02–50.00)

AE=adverse event; FE=fixed effects; NMA=network meta-analysis; RE=random effects; TNFi-MTX=tumor necrosis factor inhibitor–methotrexate; TT=triple therapy.

*Odds ratio and 95% credible interval of TT vs TNFi-MTX with value >1 indicating a better performance for TNFi-MTX.

MTX-Naive

The literature review found 21 RCTs for the MTX-naive RA population. These studies were assessed for comparability of the following patient baseline characteristics: mean age, proportion of female enrollment, proportion of rheumatoid factor–positive (RF+) patients, mean disease duration in years, baseline mean DAS28 (ESR and CRP separately), baseline mean modified total Sharp score (mTSS), baseline mean joint erosion, baseline mean joint space narrowing, proportion of patients receiving concomitant nonsteroidal anti-inflammatory drugs (NSAIDs), proportion of patients receiving concomitant prednisone, and mean HAQ-DI. The distributions of these baseline characteristics are represented in the figures below (**Figures 15–29**). Overall, there were no clinically meaningful differences seen in treatment cohorts across the studies as determined by coauthors who are practicing rheumatologists.

Figure 15. Distribution of baseline mean (SD) age in years within studies by intervention. Mean age was uniform across trials, with participants averaging 52 years of age. ADA=adalimumab; CZP=certolizumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers indicate dose in mg.

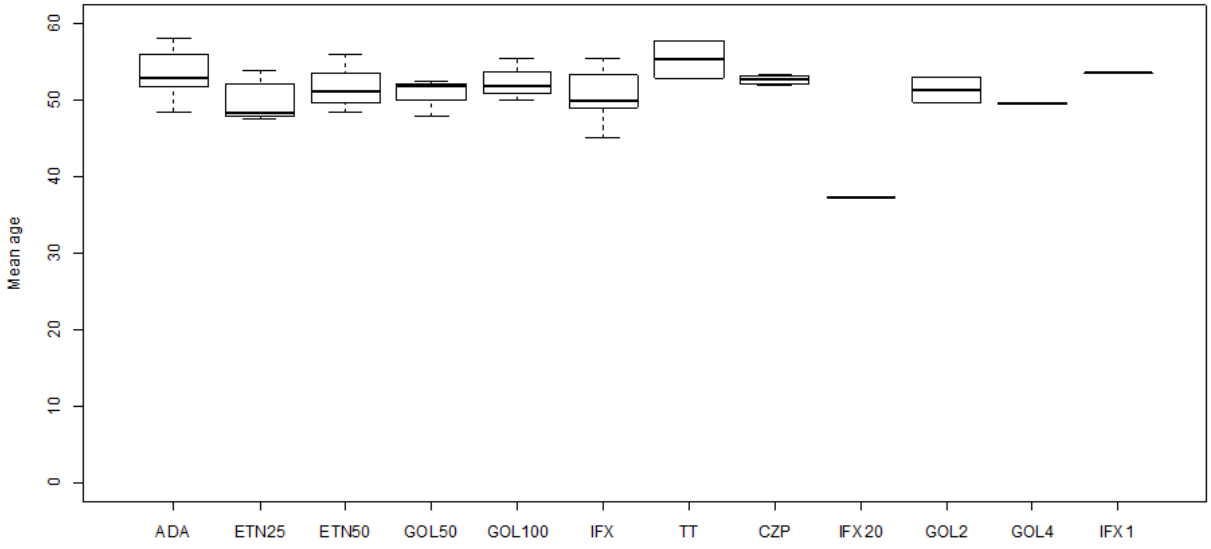


Figure 16. Distribution of mean (SD) proportion of women (expressed as percentage) enrolled at baseline (ranged from 70% to 80%). ADA=adalimumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

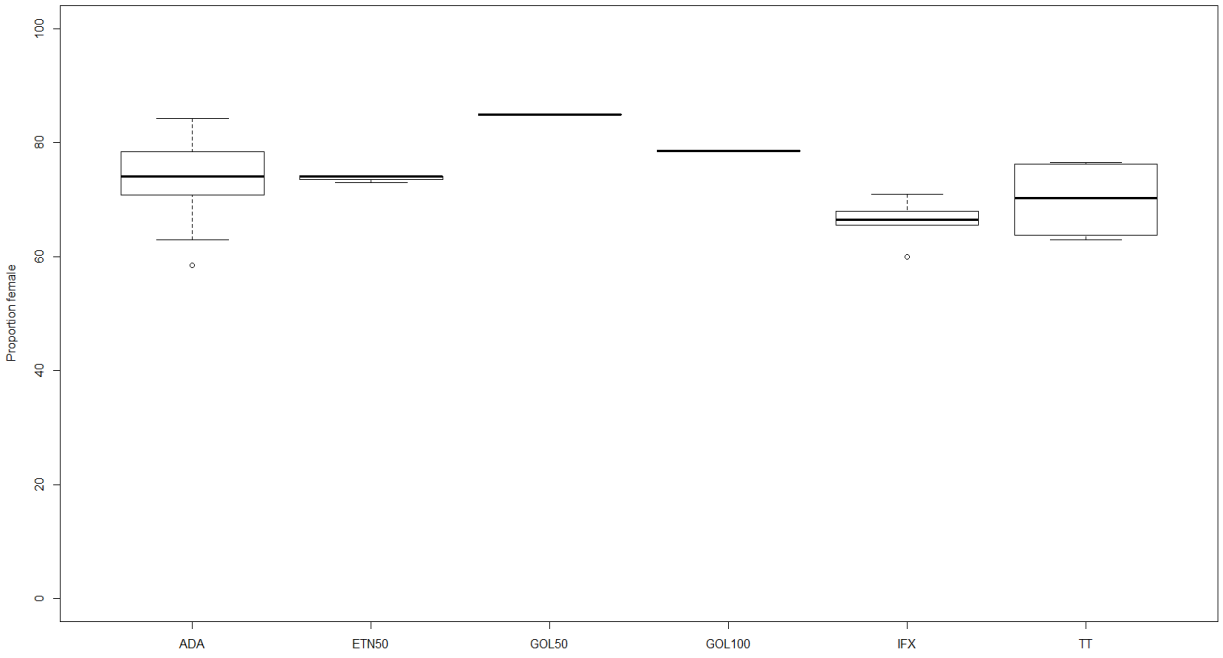


Figure 17. Distribution of mean proportion of participants enrolled at baseline who were RF+ (ranged from 70% to 85%). One study enrolled as low as 49% RF+ participants, whereas another study enrolled as high as 100% RF+ participants. ADA=adalimumab; ETN=etanercept; RF+=rheumatoid factor–positive; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

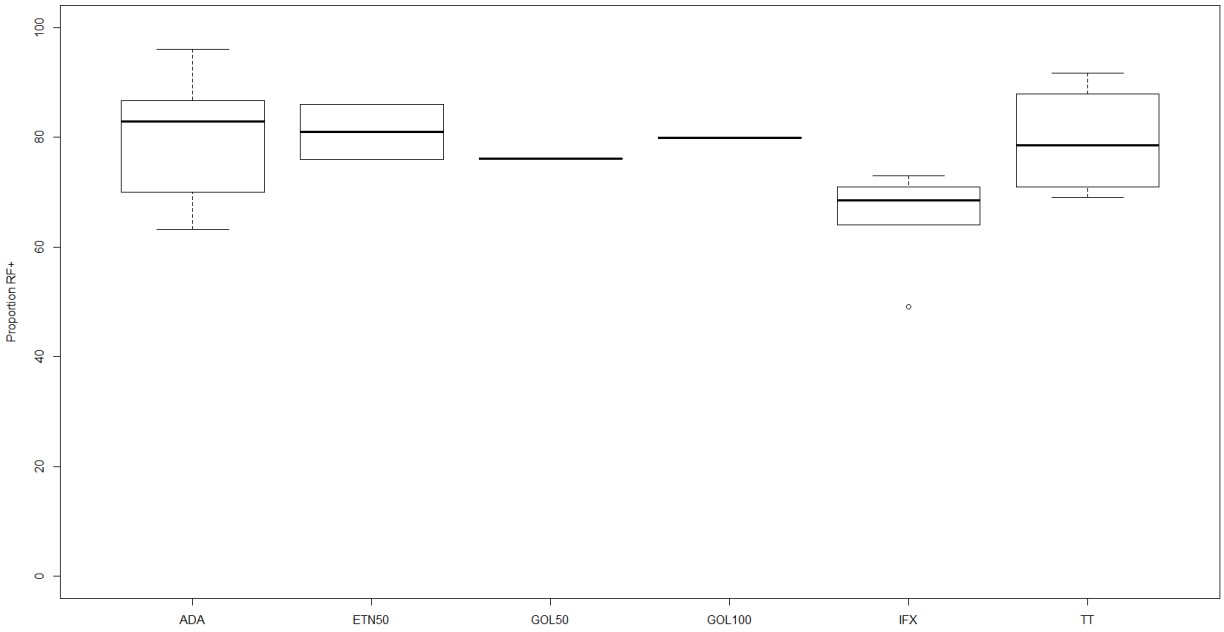


Figure 18. Distribution of mean (SD) baseline disease duration in years as reported by studies. Mean disease duration varied across trials. On average, participants had experienced <1 year of disease. Duration of disease ranged from 0.1 to 10 years, with most studies averaging 0.3 years. ADA=adalimumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

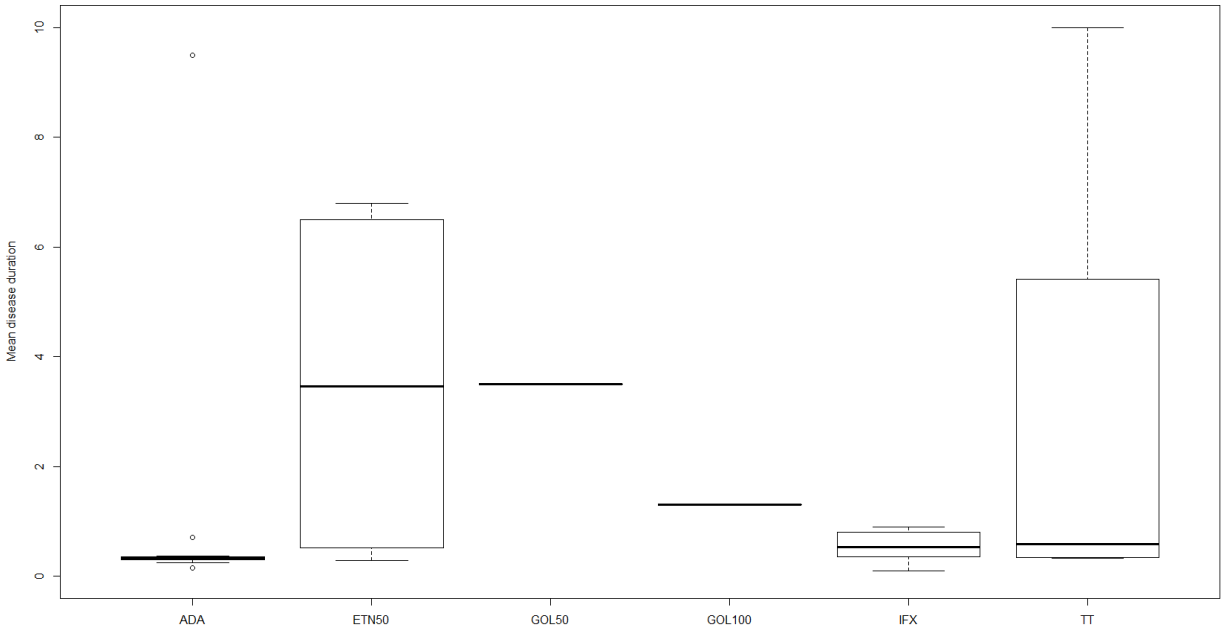


Figure 19. Distribution of mean (SD) DAS28 (ESR) at baseline within studies by intervention. This variable was distributed uniformly across trials, with participants averaging DAS28 (ESR) of 6.3 to 6.6. ADA=adalimumab; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

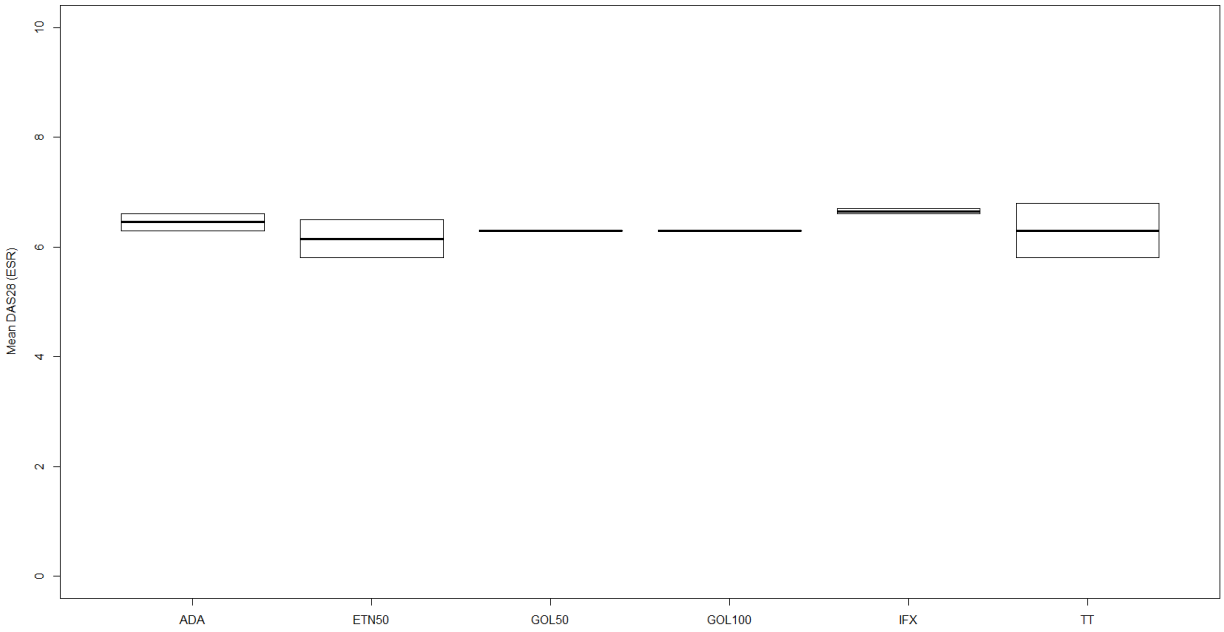


Figure 20. Distribution of mean DAS28 (CRP) at baseline within studies by intervention. DAS28 (CRP) was reported less frequently than DAS28 (ESR) within the MTX-naive group of trials. Trials reported an average DAS28 (CRP) between 5.1 and 5.8. ADA=adalimumab; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; GOL=golimumab; IFX=infliximab, TT=triple therapy. Numbers represent dose in mg.

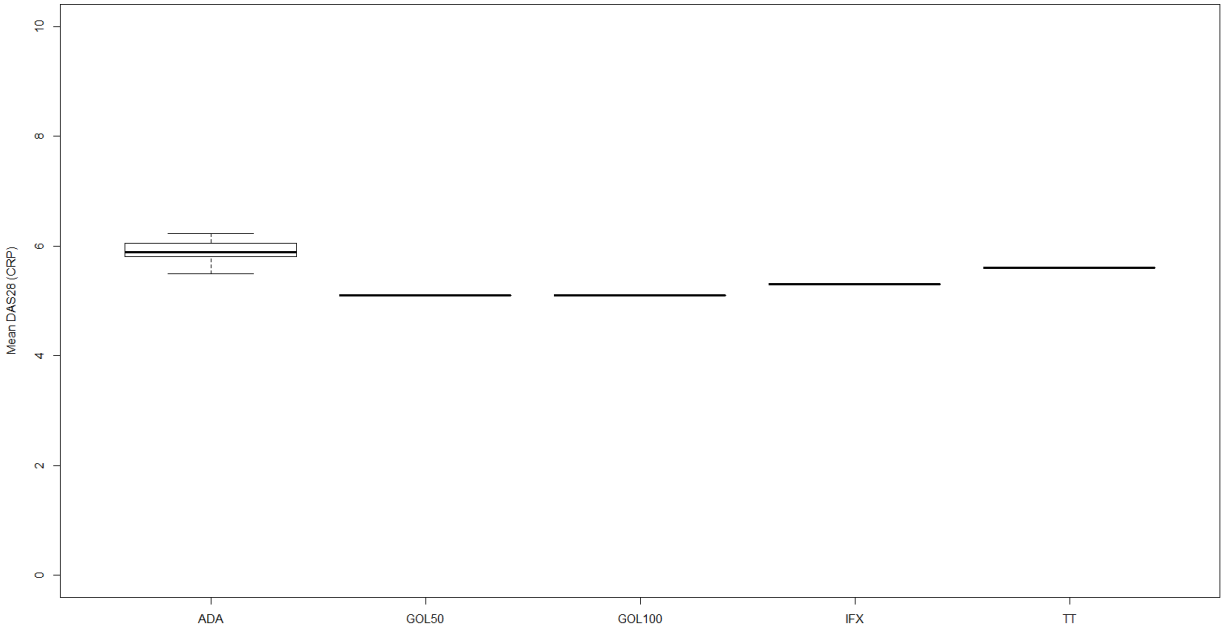


Figure 21. Distribution of mean (SD) mTSS score at baseline. Mean mTSS varied, ranging from 2 and 22; however, this was deemed a minor difference clinically by the investigators. ADA=adalimumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; mTSS=modified total Sharp score; TT=triple therapy. Numbers represent dose in mg.

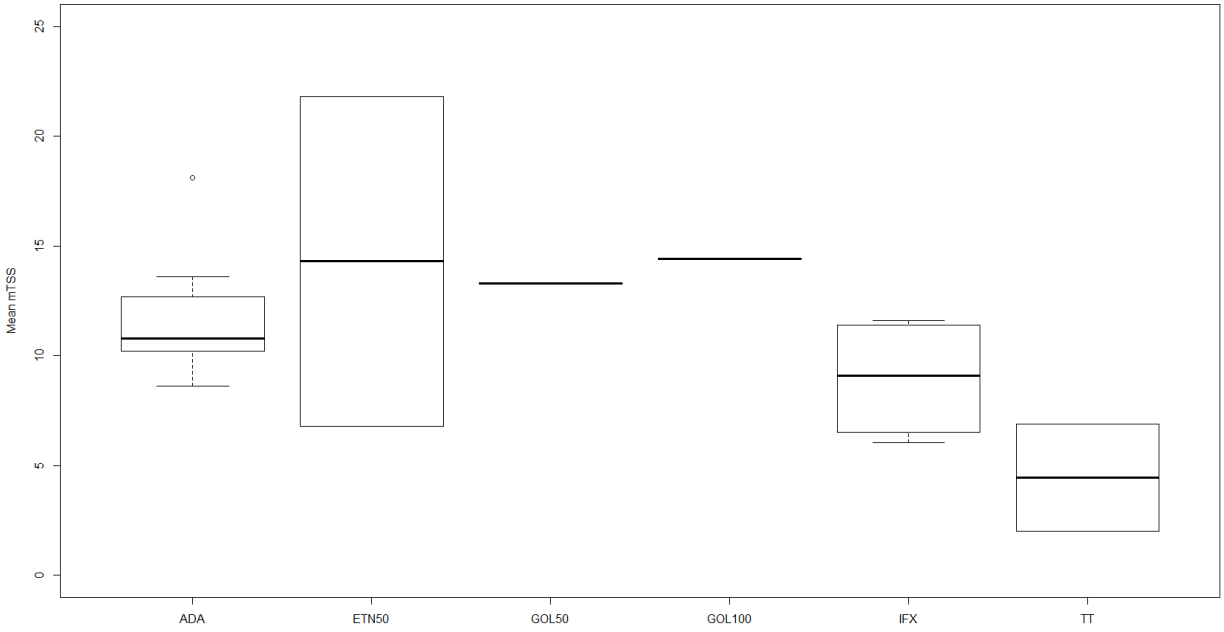


Figure 22. Distribution of mean (SD) joint erosion score at baseline within studies by intervention. Mean joint erosion score ranged between 1 and 12, with most studies distributed between 4 and 6. ADA=adalimumab; ETN=etanercept; IFX=infliximab, TT=triple therapy. Numbers represent dose in mg.

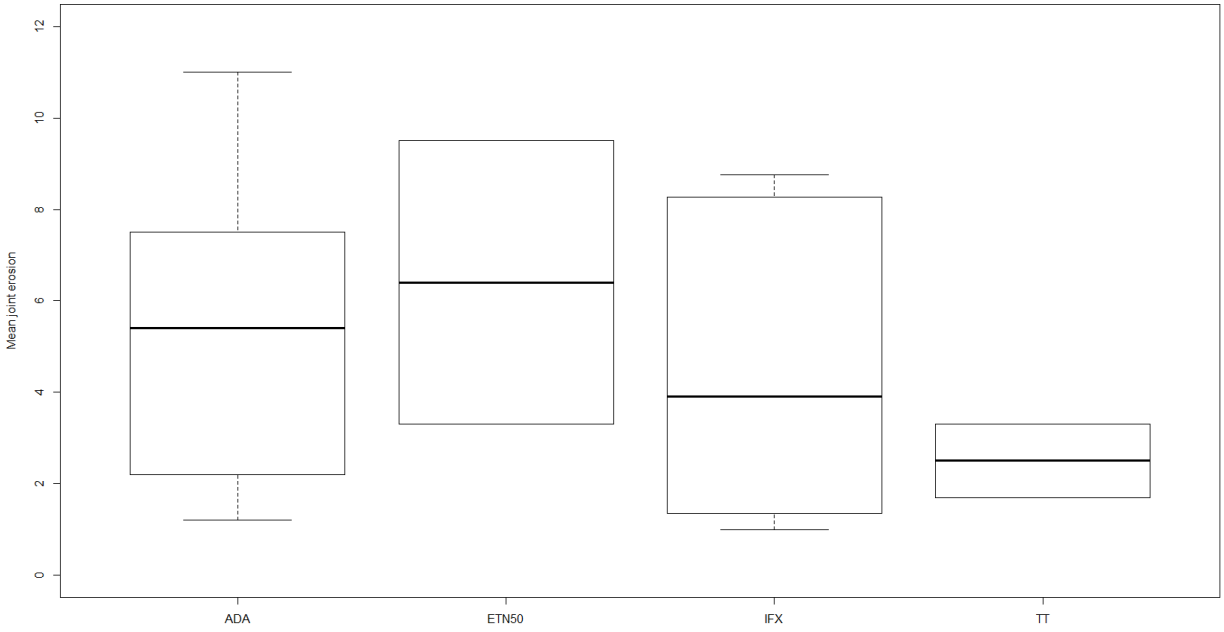


Figure 23. Distribution of mean (SD) joint space narrowing score at baseline within studies by intervention. Mean joint space narrowing score ranged from 0 to 13, with most studies reporting joint space narrowing scores of approximately 5. ADA=adalimumab; ETN=etanercept; IFX=infliximab; TT=triple therapy. Number represents dose in mg.

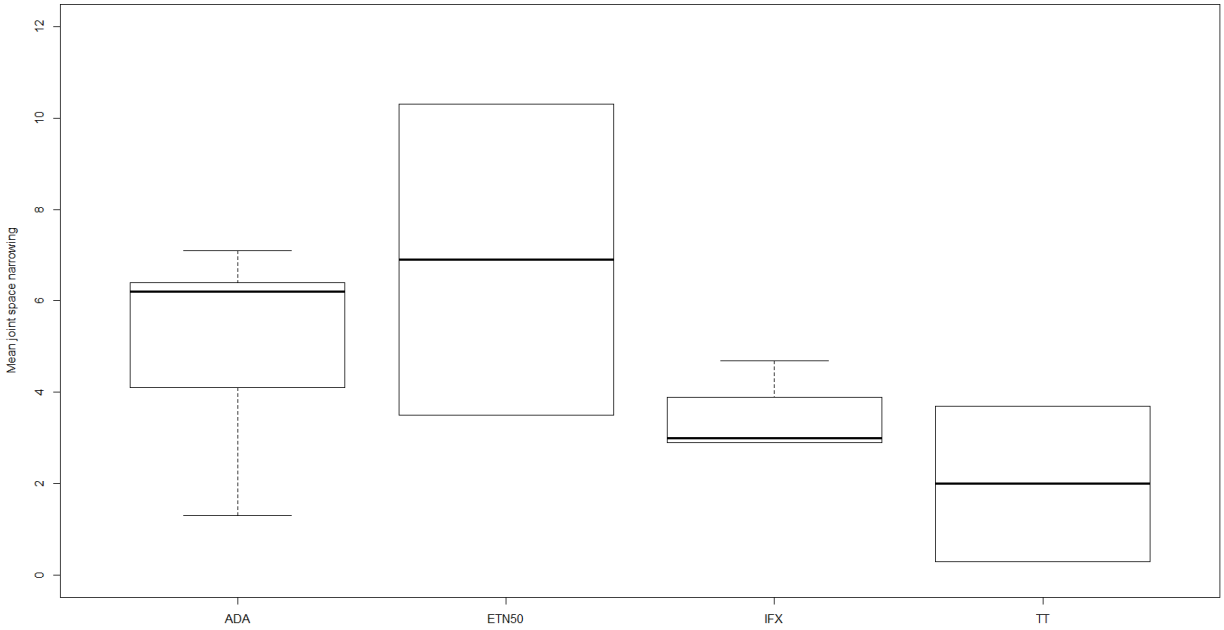


Figure 24. Distribution of mean (SD) proportion of participants enrolled at baseline who received concomitant NSAIDs, expressed in percentages. This variable was distributed largely between 70% and 85%. The highest proportion, 98%, was observed in one study. ADA=adalimumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; NSAID=nonsteroidal anti-inflammatory drug. Numbers represent dose in mg.

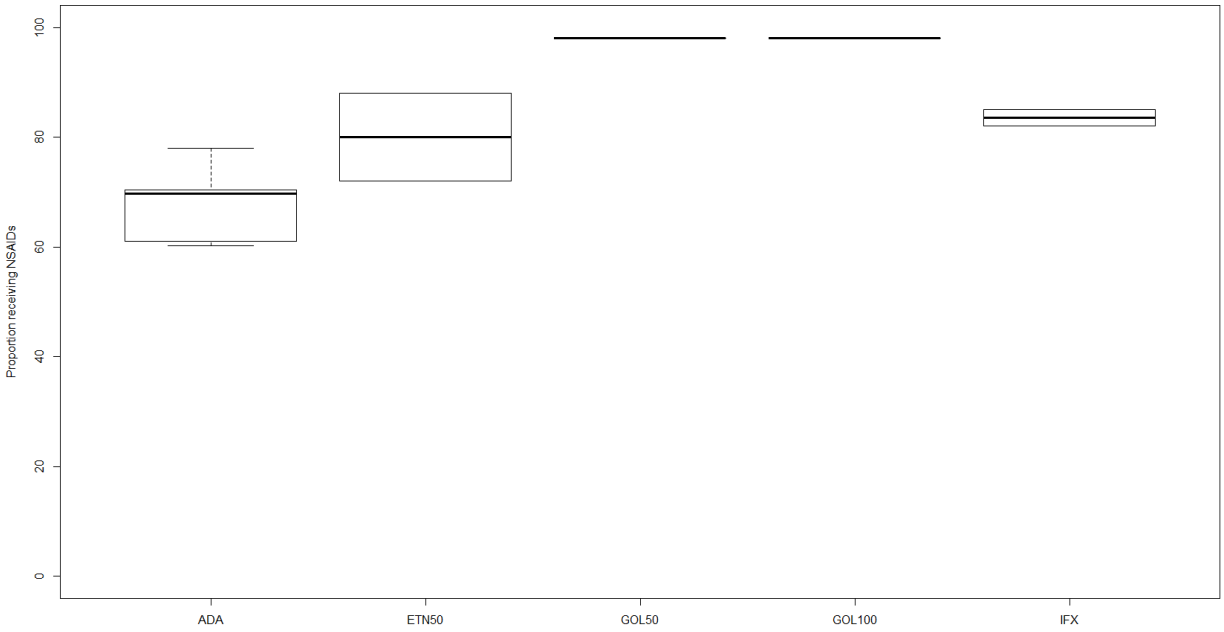


Figure 25. Distribution of mean (SD) proportion (expressed in percentage) of participants enrolled at baseline who received concomitant prednisone. Percentage of patients in each study receiving prednisone at baseline ranged from 17% to 70%. ADA=adalimumab; ETN=etanercept; GOL=golimumab; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

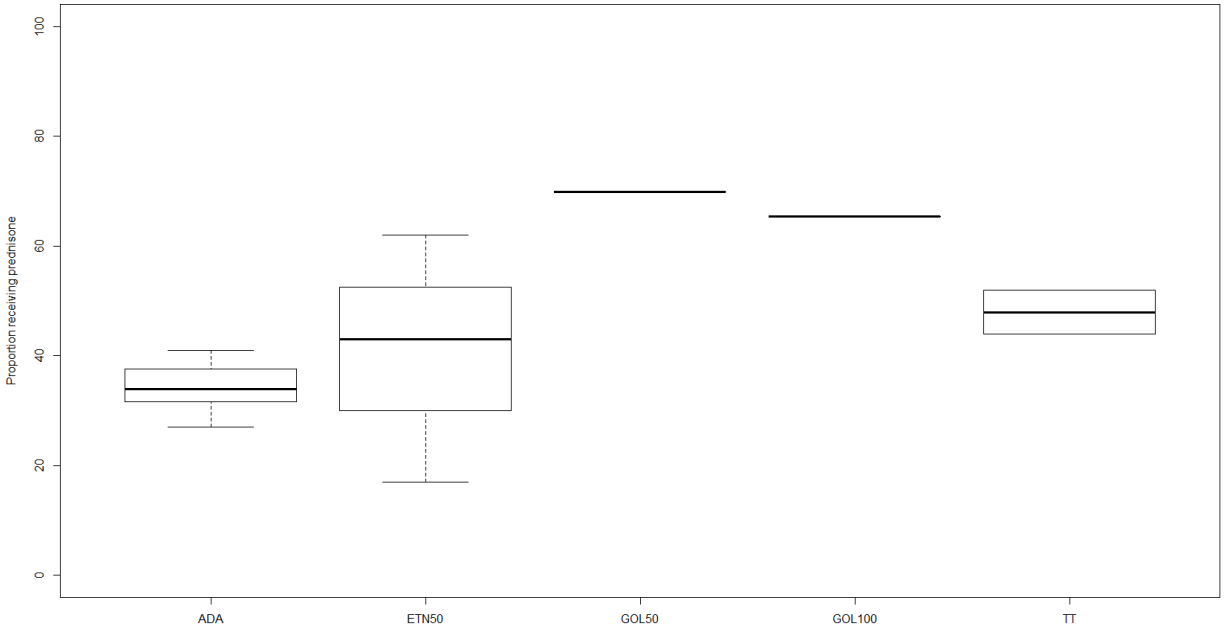


Figure 26. Distribution of mean (SD) HAQ-DI of participants in each study arm at baseline by intervention of interest. Mean HAQ-DI was distributed uniformly across studies with approximate score of 1.5. ADA=adalimumab; ETN=etanercept; GOL=golimumab; HAQ-DI= Health Assessment Questionnaire–Disability Index; IFX=infliximab; TT=triple therapy. Numbers represent dose in mg.

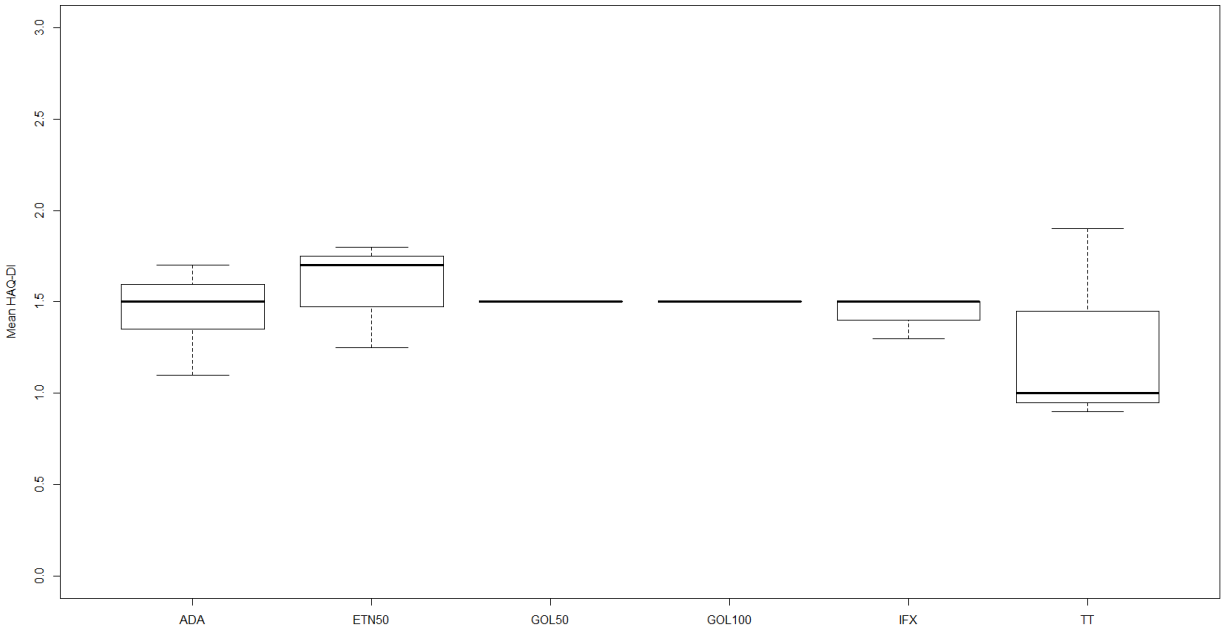


Table 9. Studies Including MTX-Naive Patients With Special Consideration for the Analysis

Study	Considerations
Kavanaugh et al, 2013 (OPTIMA) [23, 89, 90, 92-94, 151]	After 6 mo patients were rerandomized based on level of disease activity (DAS28 <3.2); data available only up to 6 mo
Goekoop-Ruiterman et al, 2008 (BeST) [37, 111, 152]	After 3 mo >20% of patients received additional DMARDs in addition to MTX and IFX+MTX; data available only up to 3 mo
Emery et al, 2009 (GO-BEFORE) [28, 103-105]	After 1 y >20% crossover in each arm; data available only up to 1 y; one arm with GOL 100 mg was not included because this was a nonapproved dose
Moreland et al, 2012 (TEAR) [36, 108, 109]	Two arms randomized to initial MTX monotherapy with stipulation if insufficient response, ETN or HCQ+SSZ added after 6 mo; these two arms were collapsed as MTX monotherapy arm up to and including 6 mo

Study	Considerations
Emery et al, 2008 (COMET) [28, 97-99]	Patients randomized into two arms in phase 1 of the study (1 y): ETN+MTX; MTX monotherapy In year 2, these arms were split into four arms: 1. ETN+MTX treatment in year 1 followed by continued combination ETN+MTX treatment in year 2 2. ETN+MTX combination treatment in year 1 followed by ETN monotherapy in year 2 3. MTX monotherapy in year 1 followed by ETN+MTX combination treatment in year 2 4. MTX monotherapy in year 1 followed by continued MTX monotherapy in year 2 Data available up to 2 y; COMET follow-up at 1 y for DAS28-ESR mean score was taken from Emery et al, 2010; ETN+MTX/ETN+MTX and ETN+MTX/ETN (N=216) were pooled in analysis at the 1-y time point only with the assumption that treatment effect could be attributed to the initial treatment in patients who stepped down from ETN+MTX to ETN at 1 y; patients who stepped up to ETN+MTX from MTX monotherapy were pooled with MTX/MTX (N=182) for analysis purposes; weighted mean average of mean DAS28-ESR score was analyzed

Study	Considerations
Burmester et al, 2014 (CONCERTO) [19, 84-86]	Each arm received different doses of ADA in combination with MTX; this study could not be included in the analyses because all arms collapsed into one arm for the purpose of the analyses (TNFi-MTX)

ADA=adalimumab; DAS28=Disease Activity Score including 28-joint count; DMARD=disease-modifying antirheumatic drug; ESR=erythrocyte sedimentation rate; ETN=etanercept; GOL=golimumab; HCQ=hydroxychloroquine; IFX=infliximab; MTX=methotrexate; SSZ=sulfasalazine; TNFi=tumor necrosis factor inhibitor.

TableError! Reference source not found.**10** below highlights the studies that were available for NMA in the MTX-naive group. The following studies were available for analyses in this group: seven studies comparing adalimumab (ADA) plus MTX to MTX; three studies comparing ETN plus MTX to MTX; one study comparing golimumab (GOL) plus MTX to MTX; five studies comparing infliximab (IFX) plus MTX to MTX; one study comparing TT to TT plus IFX; one study comparing TT to step-up from MTX to TT; one study comparing TT to MTX; one study comparing TT to step-up from MTX to MTX plus ETN; one study comparing TT to HCQ plus SSZ; and two studies comparing methylprednisolone (MP) plus MTX to IFX plus MTX. Network of evidence available per endpoint of outcome was plotted and is presented along with the NMA results. For studies including MTX-naive patients, the following endpoints were feasible for analyses:

- Efficacy Endpoints
    - ACR20 at 6 months
    - ACR20 at 2 years
    - ACR50 at 6 months
    - ACR50 at 2 years
    - ACR70 at 6 months
    - ACR70 at 2 years
    - DAS28-ESR remission at 2 years
    - DAS28-ESR mean change from baseline at 3 months
    - DAS28-ESR mean change from baseline at 6 months
    - DAS28-ESR mean change from baseline at 1 year
    - DAS28-ESR mean change from baseline at 2 years
    - DAS28-ESR + DAS28-CRP mean change from baseline at 3 months
    - DAS28-ESR + DAS28-CRP mean change from baseline at 6 months

- DAS28-ESR + DAS28-CRP mean change from baseline at 1 year
- DAS28-ESR + DAS28-CRP mean change from baseline at 2 years

- Radiographic Endpoints
  - No radiographic progression at 2 years
  - mTSS mean change from baseline at 2 years
  - Joint space narrowing mean change from baseline at 2 years
  - Joint erosion mean change from baseline at 2 years
- Safety Endpoints
- Patient-Reported Outcome (PRO) Endpoints
  - Discontinuation due to AEs
  - Overall serious AEs
  - Overall AEs
  - Serious AEs
  - LFT (AST) elevation
- PRO Endpoints
  - HAQ-DI mean change from baseline at 2 years
  - PGA mean change from baseline at 2 years

Table 10. Studies Including MTX-Naive Patients Available for Analyses

Study	Interventions	Endpoint Analyzed
Takeuchi et al, 2014 [20]	ADA 40 mg EOW + MTX MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; DAS28-ESR 3 mo; DAS28-ESR/CRP 3 mo; DAS28-ESR 6 mo; DAS28-ESR/CRP 6 mo; discontinuation due to AEs; overall serious AEs; overall AEs; serious infections
Horslev-Peterson et al, 2014 [21, 80-83]	ADA 40 mg EOW + MTX MTX	DAS28-ESR/CRP 3 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR/CRP 1 y; DAS28-ESR/CRP 2 y; discontinuation due to AEs; overall serious AEs; serious infections
Detert et al, 2013 [22, 87, 88]	ADA 40 mg EOW + MTX MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; DAS28-ESR 3 mo; DAS28-ESR/CRP 3 mo; DAS28-ESR 6 mo; DAS28-ESR/CRP 6 mo; discontinuation due to AEs
Kavanaugh et al, 2013 [23, 89, 90, 92-94]	ADA 40 mg EOW + MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; DAS28-ESR/CRP 3 mo; DAS28-ESR/CRP 6 mo; discontinuation due to AEs; overall serious AEs; overall AEs; serious infections

Study	Interventions	Endpoint Analyzed
	MTX	
Soubrier et al, 2009 [24]	ADA 40 mg EOW + MTX	DAS28-ESR 3 mo; DAS28-ESR/CRP 3 mo
	MTX	
Bejarano et al, 2008 [25]	ADA 40 mg* EOW + MTX; *assumed 40 mg	DAS28-ESR 1 y; DAS28-ESR/CRP 1 y; discontinuation due to AEs; overall serious AEs; overall AEs; serious infections; LFT (AST) elevation
	MTX	
Breedveld et al, 2006 [26, 95, 96]	ADA 40 mg EOW + MTX	ACR20 2 y; ACR50 2 y; ACR70 2 y; DAS28-ESR remission 2 y; no radiographic progression 2 y; mTSS 2 y; JE 2 y; JSN 2 y; PGA 2 y; HAQ-DI 2 y; discontinuation due to AEs; overall AEs; serious infections
	ADA 40 mg EOW	
	MTX	
Iannone et al, 2014 [27]	MTX	Discontinuation due to AEs; overall serious AEs
	ETN 50 mg weekly	

Study	Interventions	Endpoint Analyzed
	ETN 50 mg weekly + MTX	
Emery et al, 2008 [28, 97-99]	MTX	ACR20 2 y; ACR50 2 y; ACR70 2 y; DAS28-ESR remission 2 y; DAS28-ESR 1 y; DAS28-ESR/CRP 1 y; DAS28-ESR 2 y; DAS28-ESR/CRP 2 y; no radiographic progression 2 y; discontinuation due to AEs; overall serious AEs; overall AEs; serious infections
	ETN 50 mg weekly + MTX	
Klareskog et al, 2004 [39, 100-102]	MTX	ACR20 6 mo; ACR20 2 y; ACR50 6 mo; ACR50 2 y; ACR70 6 mo; ACR70 2 y; DAS28-ESR remission 2 y; no radiographic progression 2 y; mTSS 2 y; JE 2 y; JSN 2 y; PGA 2 y; HAQ-DI 2 y; discontinuation due to AEs; overall AEs; serious infections
	ETN 25 mg BIW	
	ETN 25 mg BIW + MTX	
Emery et al, 2009 [29, 103-105]	MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; discontinuation due

Study	Interventions	Endpoint Analyzed
		to AEs; overall serious AEs; overall AEs; serious infections; LFT (AST) elevation
	GOL 100 mg Q4W	
	GOL 50 mg Q4W + MTX	
	GOL 100 mg Q4W + MTX	
Nam et al, 2014 [30]	MP 250 mg week 0 + MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo
	IFX 3 mg/kg + MTX	
Durez et al, 2007 [31]	MTX	ACR20 6 mo; ACR50 6 mo; ACR70 6 mo; DAS28-ESR/CRP 1 y; serious infections
	IFX 3 mg/kg + MTX	
	MP 1 g + MTX	
Quinn et al, 2005 [32, 106]	IFX 3 mg/kg + MTX	Discontinuation due to AEs

Study	Interventions	Endpoint Analyzed
	MTX	
St Clair et al, 2004 [33]	MTX	DAS28-ESR 1 y; DAS28-ESR/CRP 1 y; discontinuation due to AEs; overall serious AEs; serious infection
	IFX 3 mg/kg + MTX	
	IFX 6 mg/kg + MTX	
Leirisalo-Repo et al, 2013 [38, 107]	MTX + SSZ 1–2 g/d + HCQ 35 mg/kg/wk	ACR50 2 y; ACR70 2 y; DAS28-ESR remission 2 y; no radiographic progression 2 y; mTSS 2 y; JE 2 y; JSN 2 y; HAQ-DI 2 y; overall serious AEs; overall AE
	MTX + SSZ 1–2 g/d + HCQ 35 mg/kg/wk + IFX 3 mg/kg	
Saunders et al, 2008 [34]	MTX + SSZ 40 mg/kg/d + if inadequate response HCQ 400 mg/d	DAS28-ESR 3 mo; DAS28-ESR/CRP 3 mo; DAS28-ESR 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 1 y; DAS28-ESR/CRP 1 y
	MTX + SSZ 500 mg BID	

Study	Interventions	Endpoint Analyzed
	+ HCQ 200 mg daily	
O'Dell et al, 1996 [35]	MTX	PGA 2 y; discontinuation due to AEs; LFT (AST) elevation
	HCQ 200 mg BID + SSZ 500 mg BID	
	MTX + HCQ 200 mg BID + SSZ 500 mg BID	
Moreland et al, 2012 [36, 108, 109]	ETN 50 mg/wk + MTX	ACR20 6 mo; ACR20 2 y; ACR50 6 mo; ACR50 2 y; ACR70 6 mo; ACR70 2 y; DAS28-ESR remission 2 y; DAS28-ESR 3 mo; DAS28-ESR/CRP 3 mo; DAS28-ESR 6 mo; DAS28-ESR/CRP 6 mo; DAS28-ESR 1 y; DAS28-ESR/CRP 1 y; DAS28-ESR 2 y; DAS28-ESR/CRP 2 y; no radiographic progression 2 y; mTSS 2 y; JE 2 y; JSN 2 y; PGA 2 y; HAQ-DI 2 y; discontinuation due to AEs; overall serious AEs; overall AEs; serious infections
	MTX + SSZ 500–1000 mg BID + HCQ 200 mg	

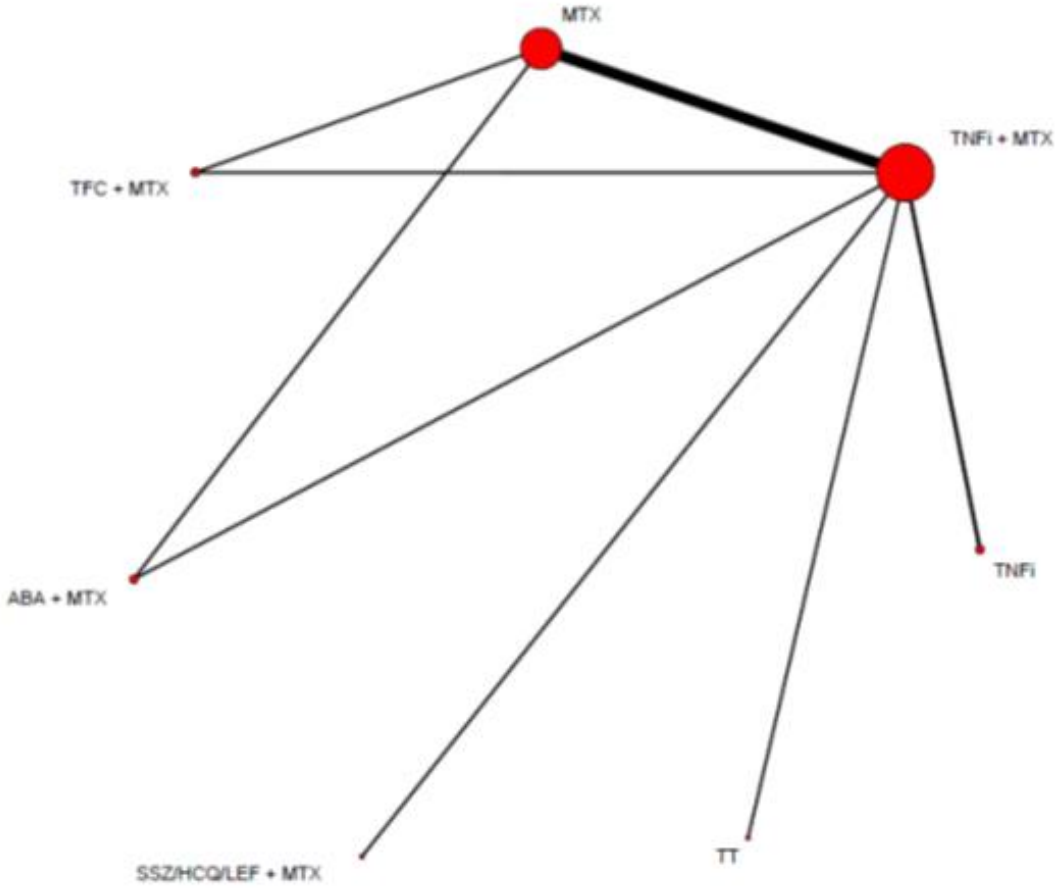
Study	Interventions	Endpoint Analyzed
	BID MTX + ETN 50 mg/wk if insufficient response MTX + SSZ 500–1000 mg BID + HCQ 200 mg BID if insufficient response	

ACR=American College of Rheumatology; ACR20=20% improvement in ACR criteria; ACR50=50% improvement in ACR criteria; ACR70=70% improvement in ACR criteria; ADA=adalimumab; AE=adverse event; AST=aspartate aminotransferase; BID=twice daily; BIW=twice weekly; CRP=C-reactive protein; DAS28= Disease Activity Score including 28-joint count; EOW=every other week; ESR=erythrocyte sedimentation rate; ESR/CRP=both measures combined; ETN=etanercept; GOL=golimumab; HAQ-DI=Health Assessment Questionnaire–Disability Index; IFX=infliximab; JE=joint erosion; JSN=joint space narrowing; LFT=liver function test; MP methylprednisolone; mTSS=modified total Sharp score; MTX=methotrexate; PGA=patient global assessment; SSZ=sulfasalazine

Patients With Inadequate Response to MTX

The networks used for the NMA of the primary endpoint for patients with inadequate response to MTX is shown in **Figure 27.**

Figure 27. Network used in the NMA for the odds ratio of ACR70 at 6 months in patients with inadequate response to MTX. ACR70=70% improvement in American College of Rheumatology criteria; HCQ=hydroxychloroquine; LEF=leflunomide; MTX=methotrexate; NMA= network meta-analysis; SSZ= sulfasalazine; TNFi=tumor necrosis factor inhibitor; TT=triple therapy.

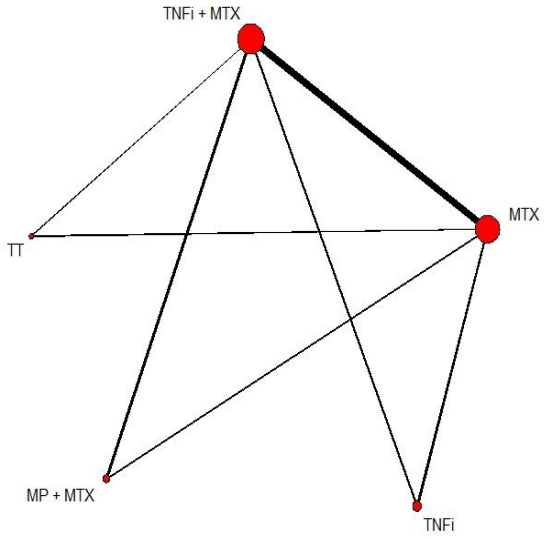


MTX v TNFi-MT
MTX v tofacitini
MTX v abatacep
TNFi-MTX v TN
TNFi-MTX v TT
TNFi-MTX v tofa
TNFi-MTX v aba
TNFi-MTX v HC

MTX-Naive Patients

The networks used for the NMA of the primary endpoint for methotrexate naive patients is shown in **Figure 28**.

Figure 28. Network used in the NMA for the odds ratio of ACR70 at 6 months in MTX-naive patients. ACR70=70% improvement in American College of Rheumatology criteria; TNFi=tumor necrosis factor inhibitor; MP=methylprednisolone; MTX=methotrexate; TT=triple therapy.



TT vs TNFi-MTX= 1

TT vs MTX= 1

MP + MTX vs TNFi-MTX= 2

TNFi vs TNFi-MTX=2

TNFi vs MTX= 2

MTX vs TNFi-MTX=7

MP + MTX vs MTX= 1

Table 11. Number of Studies Used for Each Comparison in the Network Meta-Analysis in Methotrexate-Naive Patients

Endpoint	Studies, n	Model Type	DIC
Primary Analysis			
OR ACR20 6 mo	8	REM	130.649
		FEM	128.879
OR ACR20 2 y	4	REM	103.39
		FEM	104.21
OR ACR50 6 mo	8	REM	130.766
		FEM	128.967
OR ACR50 2 y	5	REM	114.48
		FEM	117.64
OR ACR70 6 mo	8	REM	121.51
		FEM	119.993
OR ACR70 2 y	5	REM	112.52
		FEM	111.05
OR DAS28-ESR remission 2 y LOCF*	5	REM	113.527
		FEM	111.409
DAS28-ESR mean change from baseline to 3 mo LOCF*	5	REM	–4.98
		FEM	–0.942
DAS28-ESR mean change from baseline to 6 mo LOCF*	4	REM	–6.092
		FEM	6.043
DAS28-ESR mean change from baseline to 1 y LOCF*	5	REM	–6.267
		FEM	–8.274
DAS28-ESR mean change from baseline to 2 y completer	2	REM	–2.422
		FEM	–2.413
DAS28-ESR/CRP mean change from baseline to 3 mo	7	REM	–4.692
		FEM	3.668
DAS28-ESR/CRP mean change from baseline to 6 mo	6	REM	–5.632
		FEM	3.974
DAS28-ESR/CRP mean change from baseline to 1 y	7	REM	2.18
		FEM	0.341
DAS28-ESR/CRP mean change from baseline to 2 y	3	REM	3.853
		FEM	3.013
OR no radiographic progression 2 y	5	REM	110.095
		FEM	108.378

mTSS scores mean change from baseline 2 y	4	REM FEM	33.45 44.22
Joint erosion mean change from baseline 2 y	4	REM FEM	20.316 25.449
Joint space narrowing mean change from baseline to 2 y	4	REM FEM	19.04 18.67
OR dropout due to AE	14	REM FEM	183.388 189.908
OR overall serious AE	10	REM FEM	127.744 125.88
OR overall AE	9	REM FEM	144.821 143.863
OR serious infection	11	REM FEM	131.014 130.274
OR LFT (AST) elevation	3	REM FEM	25.267 25.007
HAQ-DI mean change from baseline 2 y	4	REM FEM	30.208 7.038
PGA mean change from baseline 2 y	4	REM FEM	6.882 6.201
Sensitivity Analysis			
OR DAS28-ESR remission 2 y NRI*	5	REM FEM	113.747 111.846
DAS28-ESR mean change from baseline to 3 mo NRI*	5	REM FEM	–5.34 –2.616
DAS28-ESR mean change from baseline to 3 mo completer*	5	REM FEM	–3.963 –4.735
DAS28-ESR mean change from baseline to 6 mo NRI*	4	REM FEM	–6.178 26.96
DAS28-ESR mean change from baseline to 6 mo completer*	4	REM FEM	–3.909 4.153
DAS28-ESR mean change from baseline to 1 y NRI*	5	REM FEM	–6.711 –8.633
DAS28-ESR mean change from baseline to 1 y completer*	5	REM FEM	–3.746 –5.677
DAS28-ESR mean change from baseline to 2 y LOCF*	2	REM	–4.308

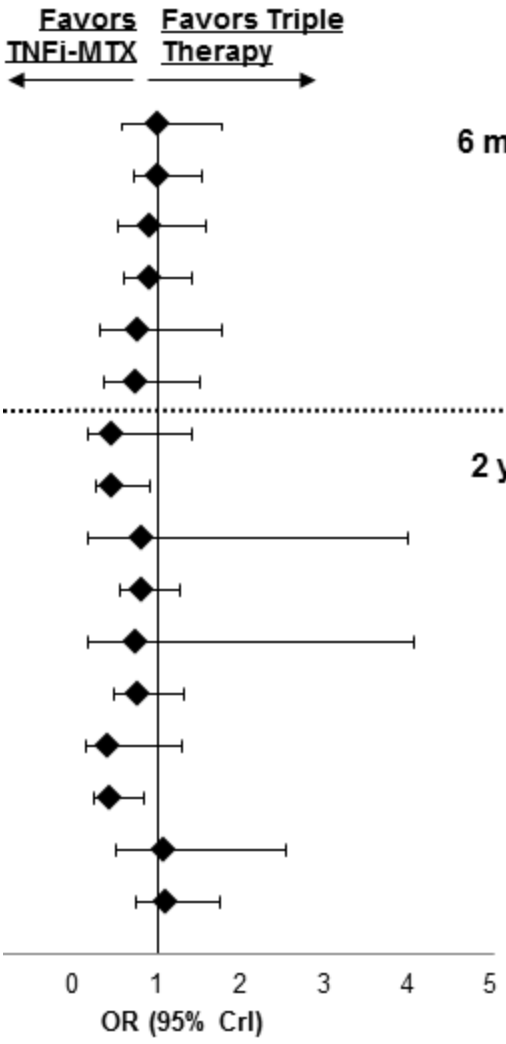
DAS28-ESR mean change from baseline to 2 y NRI*	2	FEM	–4.338
		REM	–4.324
		FEM	–4.342

*Based on Treatment of Early Aggressive Rheumatoid Arthritis trial data.

ACR70/50/20=American College of Rheumatology 70%/50%/20% response criteria; AE=adverse event; AST=aspartate aminotransferase; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; DIC=deviance information criterion; ESR=erythrocyte sedimentation rate; FEM=fixed effects model; HAQ-DI=Health Assessment Questionnaire-Disease Index; LFT=liver function test; LOCF=last observation carried forward; mTSS=modified total Sharpe score; NRI=nonresponder imputation; OR=odds ratio; PGA=patient general assessment; REM=random effects model.

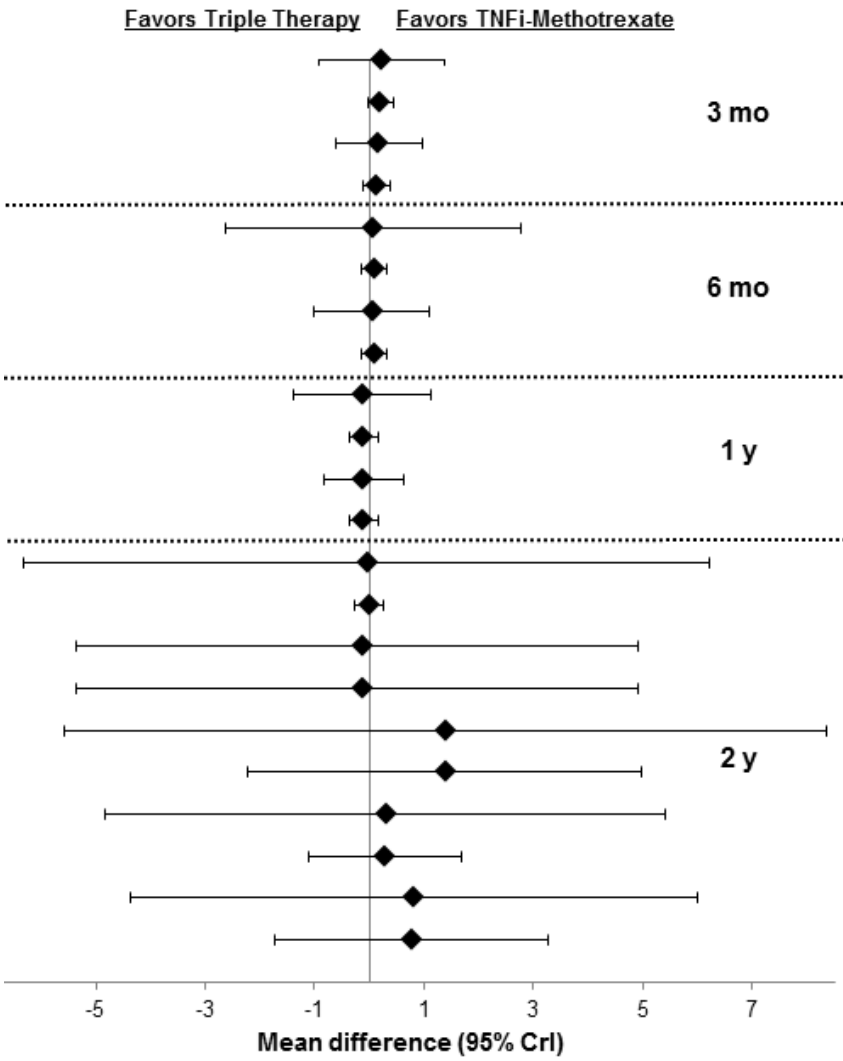
Figure 29. Relative treatment effects concerning efficacy endpoints in patients who were MTX-naive for triple therapy vs TNFi-methotrexate. ACR70/50/20=American College of Rheumatology 70%/50%/20% response criteria; CrI=credible interval; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; FEM=fixed effects model; MTX=methotrexate; OR=odds ratio; REM=random effects model; TNFi=tumor necrosis factor inhibitor.

*ACR70 at 6 months was a prespecified primary endpoint.



Endpoint	Odds ratio (95% CrI)
ACR20 (REM)	1.02 (0.56–1.77)
ACR20 (FEM)	1.03 (0.70–1.52)
ACR50 (REM)	0.92 (0.52–1.58)
ACR50 (FEM)	0.92 (0.60–1.40)
ACR70* (REM)	0.77 (0.31–1.76)
ACR70* (FEM)	0.76 (0.36–1.50)
No radiographic progression (REM)	0.47 (0.15–1.41)
No radiographic progression (FEM)	0.48 (0.25–0.90)
ACR20 (REM)	0.82 (0.16–3.99)
ACR20 (FEM)	0.82 (0.53–1.25)
ACR50 (REM)	0.76 (0.15–4.05)
ACR50 (FEM)	0.79 (0.48–1.31)
ACR20 (REM)	0.43 (0.14–1.28)
ACR20 (FEM)	0.44 (0.22–0.82)
DAS28-ESR remission (REM)	1.10 (0.50–2.52)
DAS28-ESR remission (FEM)	1.12 (0.73–1.73)

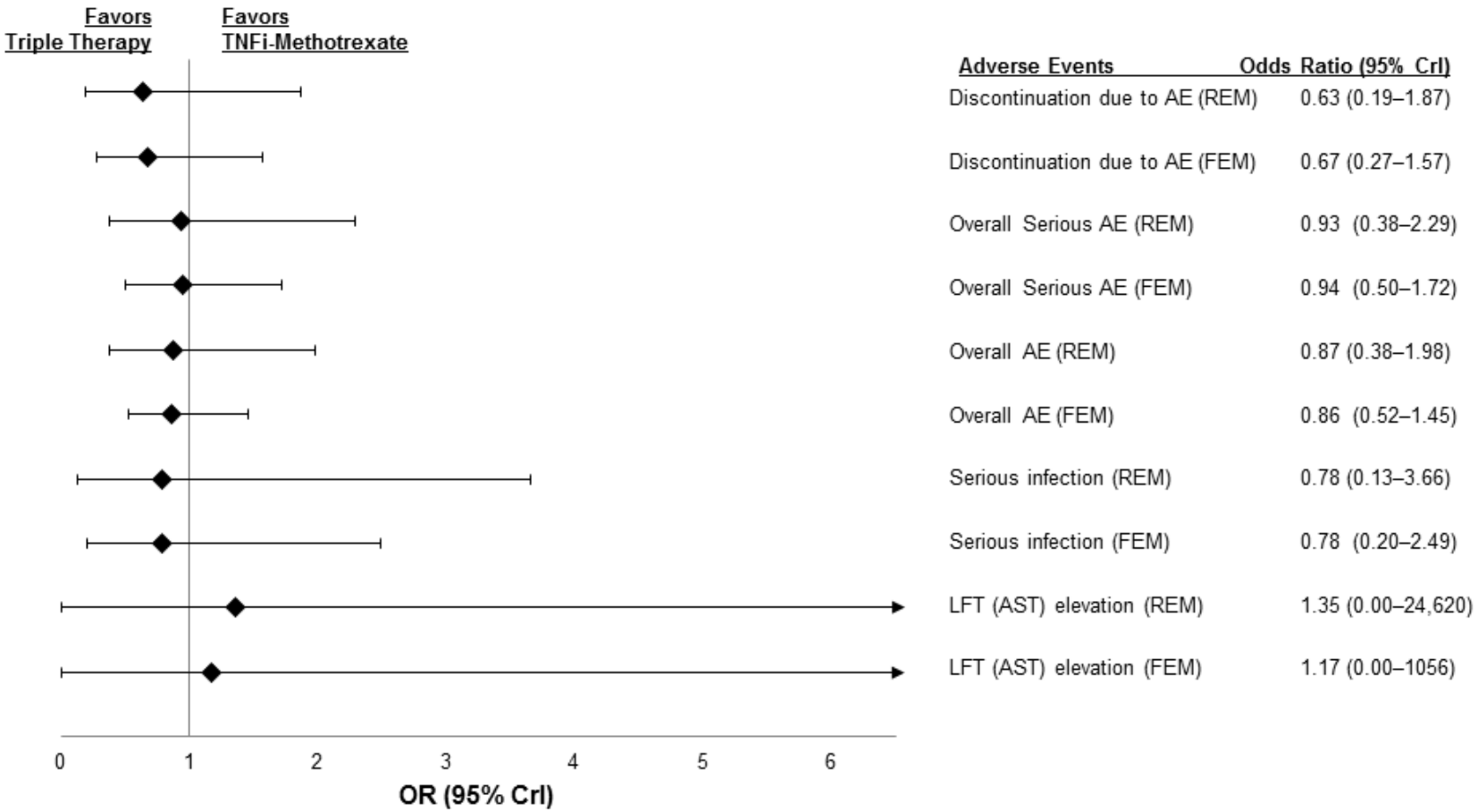
Figure 30. Mean differences in efficacy and radiographic outcomes between triple therapy vs TNFi-methotrexate in patients who were methotrexate-naive. CrI=credible interval; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; FEM=fixed effects model; mTSS=modified total Sharp score; REM=random effects model; TNFi=tumor necrosis factor inhibitor**.**



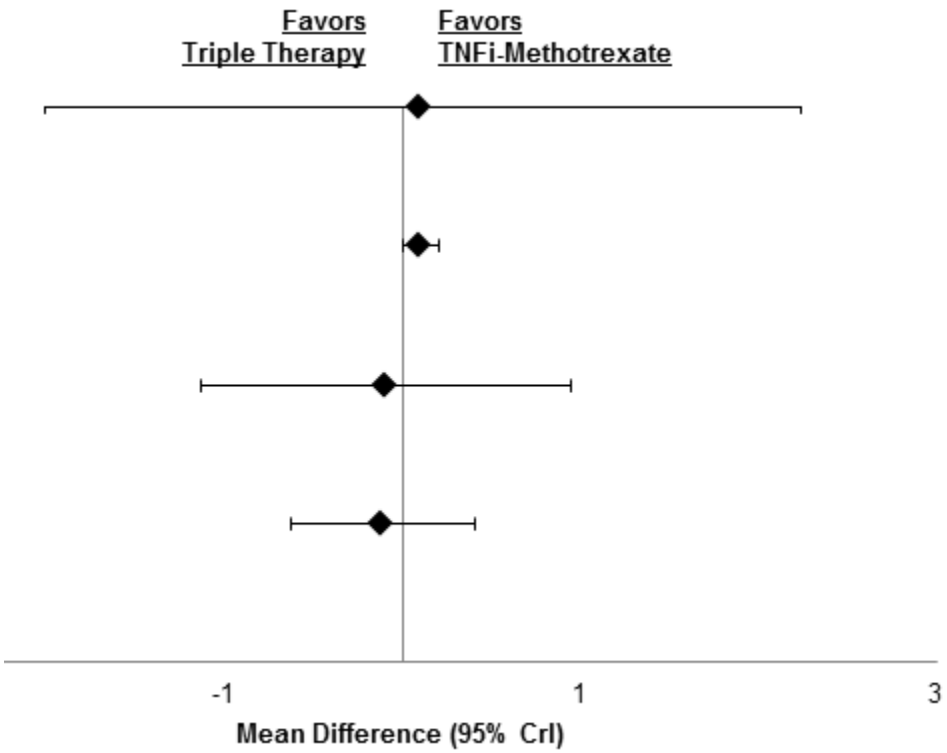
Endpoint	Mean Difference (95% CI)
ΔDAS28-ESR (REM)	0.23 (–0.91 to 1.39)
ΔDAS28-ESR (FEM)	0.21 (–0.03 to 0.46)
ΔDAS28-ESR/CRP (REM)	0.18 (–0.61 to 0.98)
ΔDAS28-ESR/CRP (FEM)	0.14 (–0.10 to 0.37)
ΔDAS28-ESR (REM)	0.07 (–2.62 to 2.76)
ΔDAS28-ESR (FEM)	0.10 (–0.14 to 0.33)
ΔDAS28-ESR/CRP (REM)	0.07 (–1.00 to 1.10)
ΔDAS28-ESR/CRP (FEM)	0.09 (–0.15 to 0.33)
ΔDAS28-ESR (REM)	–0.11 (–1.40 to 1.12)
ΔDAS28-ESR (FEM))	–0.10 (–0.37 to 0.17)
ΔDAS28-ESR/CRP (REM)	–0.10 (–0.82 to 0.62)
ΔDAS28-ESR/CRP (FEM)	–0.10 (–0.37 to 0.17)
ΔDAS28-ESR (REM)	–0.02 (–6.31 to 6.22)
ΔDAS28-ESR (FEM)	–0.002 (–0.28 to 0.27)
ΔDAS28-ESR/CRP (REM)	–0.11 (–5.35 to 4.91)
ΔDAS28-ESR/CRP (FEM)	–0.11 (–5.35 to 4.91)
ΔmTSS (REM)	1.42 (–5.58 to 8.35)
ΔmTSS (FEM)	1.40 (–2.23 to 4.97)
ΔJoint erosion (REM)	0.31 (–4.82 to 5.41)
ΔJoint erosion (FEM)	0.30 (–1.01 to 1.17)
ΔJoint space narrowing (REM)	0.82 (–4.36 to 6.01)
ΔJoint space narrowing (FEM)	0.79 (–1.72 to 3.27)

Figure 31. (A) Odds ratios comparing safety outcomes and (B) mean differences in patient-reported outcome endpoints in patients treated with triple therapy vs TNFi-methotrexate in patients who were methotrexate-naive. AE=adverse event; AST=aspartate aminotransferase; CrI=credible interval; FEM=fixed effects model; HAQ-DI=Health Assessment Questionnaire-Disease Index; LFT=liver function test; OR=odds ratio; PGA=patient general assessment; REM=random effects model; TNFi=tumor necrosis factor inhibitor.

A



B



Endpoint	Mean Difference (95% CI)
ΔHAQ-DI (FEM)	0.1 (–2.03 to 2.21)
ΔHAQ-DI (REM)	0.099 (0.00–0.20)
ΔPGA (FEM)	–0.09 (–1.12 to 0.96)
ΔPGA (REM)	–0.11 (–0.62 to 0.41)

Table 12. Full Results of the NMA in Methotrexate-Naive Patients—Efficacy and Patient-Reported Outcomes for Triple Therapy vs TNFi-methotrexate

Endpoints	3 mo			6 mo			1 y			2 y		
	NMA RE	NMA FE	Direct Pairwise	NMA RE	NMA FE	Direct Pairwise	NMA RE	NMA FE	Direct Pairwise	NMA RE	NMA FE	Direct Pairwise
ACR20*	NA	NA	NA	1.02 (0.56, 1.77)	1.03 (0.70, 1.52)	1.00 (0.65, 1.53)	NA	NA	NA	0.82 (0.16, 3.99)	0.82 (0.53, 1.25)	0.81 (0.54, 1.25)
ACR50*	NA	NA	NA	0.92 (0.52, 1.58)	0.924 (0.60, 1.40)	0.94 (0.60, 1.49)	NA	NA	NA	0.76 (0.15, 4.05)	0.79 (0.48, 1.31)	0.75 (0.48, 1.19)
ACR70*	NA	NA	NA	0.77 (0.31, 1.76)	0.76 (0.36, 1.50)	0.67 (0.33, 1.40)	NA	NA	NA	0.43 (0.14, 1.28)	0.44 (0.22, 0.82)	0.45 (0.24, 0.85)
DAS28-ESR remission*	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.10 (0.50, 2.52)	1.12 (0.73, 1.73)	1.11 (0.72, 1.70)
ΔDAS28-ESR†	0.23 (−0.91, 1.39)	0.21 (−0.03, 0.46)	0.1 (−0.18, 0.38)	0.07 (−2.62, 2.76)	0.10 (−0.14, 0.33)	0.0 (−0.28, 0.28)	−0.11 (−1.40, 1.12)	−0.10 (−0.37, 0.17)	−0.1 (−0.37, 0.17)	−0.02 (−6.31, 6.22)	−0.002 (−0.28, 0.27)	−0.1 (−0.5, 0.3)
ΔDAS28-ESR/CRP†	0.18 (−0.61, 0.98)	0.14 (−0.10, 0.37)	0.1 (−0.18, 0.38)	0.07 (−1.00, 1.10)	0.09 (−0.15, 0.33)	0.0 (−0.28, 0.28)	−0.10 (−0.82, 0.62)	−0.10 (−0.37, 0.17)	−0.1 (−0.37, 0.17)	−0.11 (−5.35, 4.91)	−0.11 (−5.35, 4.91)	−0.1 (−0.5, 0.3)
No radiographic progression*	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.47 (0.15, 1.41)	0.48 (0.25, 0.90)	0.48 (0.26, 0.90)

Endpoints		3 mo			6 mo			1 y			2 y	
ΔmTSS†	NA	NA	NA	NA	NA	NA	NA	NA	NA	1.42 (−5.58, 8.35)	1.4 (−2.23, 4.97)	1.4 (−2.16, 4.96)
ΔJoint erosion†	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.31 (−4.82, 5.41)	0.30 (−1.10, 1.70)	0.30 (−1.09, 1.69)
ΔJoint space narrowing†	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.82 (−4.36, 6.01)	0.79 (−1.72, 3.27)	0.8 (−1.66, 3.26)
ΔHAQ-DI†	NA	NA	NA	NA	NA	NA	NA	NA	NA	0.10 (−2.03, 2.21)	0.099 (0.00, 0.20)	0.1 (0.0, 0.2)
ΔPGA†	NA	NA	NA	NA	NA	NA	NA	NA	NA	−0.09 (−1.12, 0.96)	−0.11 (−0.62, 0.41)	0.1 (−0.69, 0.49)

ACR=American College of Rheumatology; ACR20=20% improvement in ACR criteria; ACR50=50% improvement in ACR criteria; ACR70=70% improvement in ACR criteria; CRP=C-reactive protein; DAS28=Disease Activity Score including 28-joint count; ESR=erythrocyte sedimentation rate; FE=fixed effects; HAQ-DI=Health Assessment Questionnaire−Disability Index; mTSS=modified total Sharp score; NA=not applicable; NMA=network meta-analysis; PGA=patient global assessment; RE=random effects; TNFi-MTX=tumor necrosis factor inhibitor–methotrexate; TT=triple therapy.

*Odds ratio and 95% credible interval of TT vs TNFi-MTX, with value <1 indicating a better performance for TNFi-MTX.

†Difference in mean change from baseline of TT vs TNFi-MTX with positive value indicating better performance for TNFi-MTX.

Table 13. Full Results of NMA in Methotrexate-Naive Patients—Safety for Triple Therapy vs TNFi-methotrexate

Endpoints	NMA RE	NMA FE	Direct Pairwise
Discontinuation due to AEs*	0.63 (0.19, 1.87)	0.67 (0.27, 1.57)	1.01 (0.36, 2.79)
Overall serious AEs*	0.93 (0.38, 2.29)	0.94 (0.50, 1.72)	0.94 (0.51, 1.74)
Overall AEs*	0.87 (0.38, 1.98)	0.86 (0.52, 1.45)	0.86 (0.52, 1.43)
Serious infections*	0.78 (0.13, 3.66)	0.78 (0.20, 2.49)	0.82 (0.25, 2.70)
LFT (AST) elevation*	1.35 (0.00, 24,620.00)	1.17 (0.00, 1056.00)	NA

AE=adverse event; AST=aspartate aminotransferase; FE=fixed effects; LFT=liver function test; NA=not applicable; NMA=network meta-analysis; RE=random effects; TNFi-MTX=tumor necrosis factor inhibitor–methotrexate; TT=triple therapy.

*Odds ratio and 95% credible interval of TT vs TNFi-MTX with value >1 indicating a better performance for TNFi-MTX.

Table 14. PRISMA Checklist for Reporting of Meta-Analyses

Section/Topic	#	Checklist Item	Reported
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Yes
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	Yes
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	Yes
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	Yes
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (eg, web address), and, if available, provide registration information including registration number.	Yes
Eligibility criteria	6	Specify study characteristics (eg, PICOS, length of follow-up) and report characteristics (eg, years considered, language, publication status) used as criteria for eligibility, giving rationale.	Yes
Information sources	7	Describe all information sources (eg, databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	Yes
Search	8	Present full electronic search strategy for at least 1 database, including any limits used, such that it could be repeated.	Yes
Study selection	9	State the process for selecting studies (ie, screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	Yes

Data collection process	10	Describe method of data extraction from reports (eg, piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	Yes
Data items	11	List and define all variables for which data were sought (eg, PICOS, funding sources) and any assumptions and simplifications made.	Yes
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	Yes
Summary measures	13	State the principal summary measures (eg, risk ratio, difference in means).	Yes
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (eg, I^2 for each meta-analysis).	Yes
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (eg, publication bias, selective reporting within studies).	No
Additional analyses	16	Describe methods of additional analyses (eg, sensitivity or subgroup analyses, meta-regression), if done, indicating which were prespecified.	Yes
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Yes
Study characteristics	18	For each study, present characteristics for which data were extracted (eg, study size, PICOS, follow-up period) and provide the citations.	Yes
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Yes
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	Yes
Synthesis of results	21	Present results of each meta-analysis, including confidence intervals and measures of consistency.	Yes
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see item 15).	No
Additional analysis	23	Give results of additional analyses, if done (eg, sensitivity or subgroup analyses, meta-regression [see item 16]).	Yes

DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (eg, healthcare providers, users, and policy makers).	Yes
Limitations	25	Discuss limitations at study and outcome level (eg, risk of bias), and at review level (eg, incomplete retrieval of identified research, reporting bias).	Yes
Conclusions	26	Provide a general interpretation of the results in the context of other evidence and implications for future research.	Yes
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (eg, supply of data); role of funders for the systematic review.	Yes

PRISMA=Preferred Reporting Items for Systematic Reviews and Meta-Analyses

References

1 Hoaglin DC, Hawkins N, Jansen JP, et al. Conducting indirect-treatment-comparison and network-meta-analysis studies: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 2. *Value Health* 2011;14(4):429-437.

2 Jansen JP, Fleurence R, Devine B, et al. Interpreting indirect treatment comparisons and network meta-analysis for health-care decision making: report of the ISPOR Task Force on Indirect Treatment Comparisons Good Research Practices: part 1. *Value Health* 2011;14(4):417-428.

3 Lunn DJ, Thomas A, Best N, et al. WinBUGS -- a Bayesian modelling framework: concepts, structure, and extensibility. *Stat Comput* 2000;10:325-337.

4 Welton NJ, Sutton AJ, Cooper N, et al. Evidence Synthesis for Decision Making in Healthcare. West Sussex, UK: John Wiley & Sons, Ltd, 2012.

5 The Cochrane Collaborations. Cochrane Handbook for Systematic Reviews of Interventions. Available at: http://handbook.cochrane.org/front_page.htm. Accessed September 23, 2015.

6 Aaltonen KJ, Virkki LM, Malmivaara A, et al. Systematic review and meta-analysis of the efficacy and safety of existing TNF blocking agents in treatment of rheumatoid arthritis. *PLoS ONE* 2012;7(1):e30275.

7 Alonso-Ruiz A, Pijoan JI, Ansuategui E, et al. Tumor necrosis factor alpha drugs in rheumatoid arthritis: systematic review and metaanalysis of efficacy and safety. *BMC Musculoskelet Disord* 2008;9:52.

8 Baji P, Pentek M, Czirjak L, et al. Efficacy and safety of infliximab-biosimilar compared to other biological drugs in rheumatoid arthritis: a mixed treatment comparison. *Eur J Health Econ* 2014;15(suppl 1):S53-64.

9 Bongartz T, Sutton AJ, Sweeting MJ, et al. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. *JAMA* 2006;295(19):2275-2285.

10 Choy EH, Smith C, Dore CJ, et al. A meta-analysis of the efficacy and toxicity of combining disease-modifying anti-rheumatic drugs in rheumatoid arthritis based on patient withdrawal. *Rheumatology (Oxford)* 2005;44(11):1414-1421.

11 Gaujoux-Viala C, Nam J, Ramiro S, et al. Efficacy of conventional synthetic disease-modifying antirheumatic drugs, glucocorticoids and tofacitinib: a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73(3):510-515.

12 Jansen JP, Buckley F, Dejonckheere F, et al. Comparative efficacy of biologics as monotherapy and in combination with methotrexate on patient reported outcomes (PROs) in rheumatoid arthritis patients with an inadequate response to conventional DMARDs--a systematic review and network meta-analysis. *Health Qual Life Outcomes* 2014;12:102.

13 Katchamart W, Trudeau J, Phumethum V, et al. Efficacy and toxicity of methotrexate (MTX) monotherapy versus MTX combination therapy with non-biological disease-modifying antirheumatic drugs in rheumatoid arthritis: a systematic review and meta-analysis. *Ann Rheum Dis* 2009;68(7):1105-1112.

14 Launois R, Avouac B, Berenbaum F, et al. Comparison of certolizumab pegol with other anticytokine agents for treatment of rheumatoid arthritis: a multiple-treatment Bayesian metaanalysis. *J Rheumatol* 2011;38(5):835-845.

15 Lethaby A, Lopez-Olivo MA, Maxwell L, et al. Etanercept for the treatment of rheumatoid arthritis. *Cochrane Database Syst Rev* 2013;5:CD004525.

16 Navarro-Sarabia F, Ariza-Ariza R, Hernandez-Cruz B, et al. Adalimumab for treating rheumatoid arthritis. *J Rheumatol* 2006;33(6):1075-1081.

17 Singh JA, Christensen R, Wells GA, et al. A network meta-analysis of randomized controlled trials of biologics for rheumatoid arthritis: a Cochrane overview. *CMAJ* 2009;181(11):787-796.

18 Singh JA, Noorbaloochi S, Singh G. Golimumab for rheumatoid arthritis: a systematic review. *J Rheumatol* 2010;37(6):1096-1104.

19 Burmester G, Kivitz A, Kupper H, et al. Efficacy, pharmacokinetics, and safety of different doses of methotrexate in combination with adalimumab: results from the CONCERTO trial [abstract]. *Ann Rheum Dis* 2013;72(suppl 1):A72-A73.

20 Takeuchi T, Yamanaka H, Ishiguro N, et al. Adalimumab, a human anti-TNF monoclonal antibody, outcome study for the prevention of joint damage in Japanese patients with early rheumatoid arthritis: the HOPEFUL 1 study. *Ann Rheum Dis* 2014;73(3):536-543.

21 Horslev-Petersen K, Hetland ML, Junker P, et al. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. *Ann Rheum Dis* 2014;73(4):654-661.

22 Detert J, Bastian H, Listing J, et al. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72(6):844-850.

23 Kavanaugh A, Fleischmann R, Emery P, et al. Efficacy of addition, or continuation, of adalimumab in patients who did not achieve stable low disease activity with methotrexate or adalimumab plus methotrexate in the optima study. *Ann Rheum Dis* 2013;71:511-512.

24 Soubrier M, Puechal X, Sibilia J, et al. Evaluation of two strategies (initial methotrexate monotherapy vs its combination with adalimumab) in management of early active rheumatoid arthritis: data from the GUEPARD trial. *Rheumatology (Oxford)* 2009;48(11):1429-1434.

25 Bejarano V, Quinn M, Conaghan PG, et al. Effect of the early use of the anti-tumor necrosis factor adalimumab on the prevention of job loss in patients with early rheumatoid arthritis. *Arthritis Rheum* 2008;59(10):1467-1474.

26 Breedveld FC, Weisman MH, Kavanaugh AF, 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.

27 Iannone F, La Montagna G, Bagnato G, et al. 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):286-292.

28 Emery P, Breedveld FC, Hall S, et al. Comparison of methotrexate monotherapy with a combination of methotrexate and etanercept in active, early, moderate to severe rheumatoid arthritis (COMET): a randomised, double-blind, parallel treatment trial. *Lancet* 2008;372(9636):375-382.

29 Emery P, Fleischmann RM, Moreland LW, 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):2272-2283.

30 Nam JL, Villeneuve E, Hensor EMA, 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(1):75-85.

31 Durez P, Malghem J, Toukap AN, et al. Treatment of early rheumatoid arthritis: a randomized magnetic resonance imaging study comparing the effects of methotrexate alone, methotrexate in combination with infliximab, and methotrexate in combination with intravenous pulse methylprednisolone. *Arthritis Rheum* 2007;56(12):3919-3927.

32 Quinn MA, Conaghan PG, O'Connor PJ, et al. Very early treatment with infliximab in addition to methotrexate in early, poor-prognosis rheumatoid arthritis reduces magnetic resonance imaging evidence of synovitis and damage, with sustained benefit after infliximab withdrawal: results from a twelve-month randomized, double-blind, placebo-controlled trial. *Arthritis Rheum* 2005;52(1):27-35.

33 St Clair EW, van der Heijde DM, Smolen JS, et al. Combination of infliximab and methotrexate therapy for early rheumatoid arthritis: a randomized, controlled trial. *Arthritis Rheum* 2004;50(11):3432-3443.

34 Saunders SA, Capell HA, Stirling A, et al. Triple therapy in early active rheumatoid arthritis: a randomized, single-blind, controlled trial comparing step-up and parallel treatment strategies. *Arthritis Rheum* 2008;58(5):1310-1317.

35 O'Dell JR, Haire CE, Erikson N, et al. Treatment of rheumatoid arthritis with methotrexate alone, sulfasalazine and hydroxychloroquine, or a combination of all three medications. *N Engl J Med* 1996;334(20):1287-1291.

36 Moreland LW, O'Dell JR, Paulus HE, et al. 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(9):2824-2835.

37 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, 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* 2008;58(2 suppl):S126-135.

38 Leirisalo-Repo M, Kautiainen H, Laasonen L, et al. 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(6):851-857.

39 Klareskog L, van der Heijde D, de Jager JP, 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):675-681.

40 Chen DY, Chou SJ, Hsieh TY, et al. Randomized, double-blind, placebo-controlled, comparative study of human anti-TNF antibody adalimumab in combination with methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis. *J Formos Med Assoc* 2009;108(4):310-319.

41 Abe T, Takeuchi T, Miyasaka N, et al. A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol* 2006;33(1):37-44.

42 Choy E, McKenna F, Vencovsky J, et al. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology (Oxford)* 2012;51(7):1226-1234.

43 Durez P, Nzeusseu Toukap A, Lauwerys BR, et al. A randomised comparative study of the short term clinical and biological effects of intravenous pulse methylprednisolone and infliximab in patients with active rheumatoid arthritis despite methotrexate treatment. *Ann Rheum Dis* 2004;63(9):1069-1074.

44 Furst DE, Gaylis N, Bray V, et al. Open-label, pilot protocol of patients with rheumatoid arthritis who switch to infliximab after an incomplete response to etanercept: the opposite study. *Ann Rheum Dis* 2007;66(7):893-899.

45 Kameda H, Ueki Y, Saito K, 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):531-538.

46 Kay J, Matteson EL, Dasgupta B, et al. Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008;58(4):964-975.

47 Kavanaugh A, St. Clair EW, McCune WJ, et al. Chimeric anti-tumor necrosis factor-alpha monoclonal antibody treatment of patients with rheumatoid arthritis receiving methotrexate therapy. *J Rheumatol* 2000;27(4):841-850.

48 Keystone E, Heijde DV, Mason D, Jr., et al. Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008;58(11):3319-3329.

49 Keystone EC, Genovese MC, Klareskog L, 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):789-796.

50 Keystone EC, Kavanaugh AF, Sharp JT, et al. Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004;50(5):1400-1411.

51 Kim HY, Hsu PN, Barba M, 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(2):188-196.

52 Kim HY, Lee SK, Song YW, et al. A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR J Rheumatol* 2007;10(1):9-16.

53 Kim J, Ryu H, Yoo DH, et al. A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. *J Korean Med Sci* 2013;28(12):1716-1722.

54 Kremer J, Ritchlin C, Mendelsohn A, 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):917-928.

55 Lan JL, Chou SJ, Chen DY, et al. A comparative study of etanercept plus methotrexate and methotrexate alone in Taiwanese patients with active rheumatoid arthritis: a 12-week, double-blind, randomized, placebo-controlled study. *J Formos Med Assoc* 2004;103(8):618-623.

56 Machado DA, Guzman RM, Xavier RM, 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(1):25-33.

57 Maini R, St. Clair EW, Breedveld F, et al. Infliximab (chimeric anti-tumour necrosis factor alpha monoclonal antibody) versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a randomised phase III trial. ATTRACT Study Group. *Lancet* 1999;354(9194):1932-1939.

58 Maini RN, Breedveld FC, Kalden JR, 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):1552-1563.

59 O'Dell JR, Mikuls TR, Taylor TH, et al. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013;369(4):307-318.

60 Schiff M, Keiserman M, Codding C, et al. Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multi-centre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008;67(8):1096-1103.

61 Smolen J, Landewe RB, Mease P, et al. Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009;68(6):797-804.

62 Tam LS, Shang Q, Li EK, et al. Infliximab is associated with improvement in arterial stiffness in patients with early rheumatoid arthritis - a randomized trial. *J Rheumatol* 2012;39(12):2267-2275.

63 Tanaka C, Shiozawa K, Hashiramoto A, et al. A study on the selection of DMARDs for the combination therapy with adalimumab. *Kobe J Med Sci* 2012;58(2):E41-50.

64 Tanaka Y, Harigai M, Takeuchi T, et al. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. *Ann Rheum Dis* 2012;71(6):817-824.

65 Taylor PC, Steuer A, Gruber J, et al. Comparison of ultrasonographic assessment of synovitis and joint vascularity with radiographic evaluation in a randomized, placebo-controlled study of infliximab therapy in early rheumatoid arthritis. *Arthritis Rheum* 2004;50(4):1107-1116.

66 Van Riel PL, Taggart AJ, Sany J, 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):1478-1483.

67 Van Vollenhoven RF, Fleischmann R, Cohen S, et al. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367(6):508-519.

68 Weinblatt ME, Keystone EC, Furst DE, et al. Adalimumab, a fully human anti-tumor necrosis factor alpha monoclonal antibody, for the treatment of rheumatoid arthritis in patients taking concomitant methotrexate: the ARMADA trial. *Arthritis Rheum* 2003;48(1):35-45.

69 Weinblatt ME, Schiff MH, Ruderman EM, et al. Efficacy and safety of etanercept 50 mg twice a week in patients with rheumatoid arthritis who had a suboptimal response to etanercept 50 mg once a week: results of a multicenter, randomized, double-blind, active drug-controlled study. *Arthritis Rheum* 2008;58(7):1921-1930.

70 Weinblatt ME, Schiff M, Valente R, 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(1):28-38.

71 Weinblatt ME, Bingham COr, Mendelsohn AM, et al. Intravenous golimumab is effective in patients with active rheumatoid arthritis despite methotrexate therapy with responses as early as week 2: results of the phase 3, randomised, multicentre, double-blind, placebo-controlled GO-FURTHER trial. *Ann Rheum Dis* 2013;72(3):381-389.

72 Weinblatt ME, Kremer JM, Bankhurst AD, et al. A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999;340(4):253-259.

73 Yamamoto K, Takeuchi T, Yamanaka H, et al. Efficacy and safety of certolizumab pegol without methotrexate co-administration in Japanese patients with active rheumatoid arthritis: the HIKARI randomized, placebo-controlled trial. *Mod Rheumatol* 2014;24(4):552-560.

74 Yoo DH, Hrycaj P, Miranda P, et al. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013;72(10):1613-1620.

75 Zhang FC, Hou Y, Huang F, et al. Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. *APLAR J Rheumatol* 2006;9(2):127-130.

76 van Vollenhoven RF, Ernestam S, Geborek P, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early

rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* 2009;374(9688):459-466.

77 Takeuchi T, Miyasaka N, Inoue K, et al. Impact of trough serum level on radiographic and clinical response to infliximab plus methotrexate in patients with rheumatoid arthritis: results from the RISING study. *Mod Rheumatol* 2009;19(5):478-487.

78 Westhovens R, Yocum D, Han J, et al. The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum* 2006;54(4):1075-1086.

79 Klareskog L, van der Heijde D, De Jager J, et al. Clinical outcomes of a double-blind study of etanercept and methotrexate, alone and combined, in patients with active rheumatoid arthritis (TEMPO trial), year 2 results. *Ann Rheum Dis* 2004;63:OP0003.

80 Horslev-Petersen K, Hetland ML, Junker P, et al. Remission rates increase substantially by adding adalimumab to methotrexate and intra-articular glucocorticoid in patients with early rheumatoid arthritis: 1-year results of the investigator-initiated, double-blinded randomized clinical trial (OPERA). *Scand J Rheumatol* 2012;41:17-18.

81 Horslev-Petersen K, Hetland ML, Junker P, et al. Adalimumab added to methotrexate and intra-articular glucocorticoid increases remission rates at one year in early, DMARD-naive patients with rheumatoid arthritis: an investigator-initiated randomized, controlled, double-blinded study [abstract]. *Arthritis Rheum* 2011;65(suppl 10):394.

82 Horslev-Petersen K, Hetland ML, Junker P, et al. Very high remission rates are achieved by methotrexate and intraarticular glucocorticoids independent of induction therapy with adalimumab; year 2 clinical results of an investigator-initiated randomised, controlled clinical trial of early, rheumatoid arthritis (OPERA). *Arthritis Rheum* 2013;65(suppl 10):S1148.

83 Horslev-Petersen K, Hetland ML, Junker P, et al. Improved remission rates acquired by adding adalimumab to methotrexate and intraarticular glucocorticoid cannot be maintained after withdrawal of adalimumab. A 2-year investigator initiated randomised, controlled study on early rheumatoid arthritis [abstract]. *Ann Rheum Dis* 2013;72(suppl 3):A236.

84 Burmester G, Kivitz AJ, Van Vollenhoven RF, et al. Methotrexate dose has minimal effects on methotrexate-related toxicity in patients with early rheumatoid arthritis treated in combination with adalimumab-results of CONCERTO trial [abstract]. *Ann Rheum Dis* 2013;72(suppl 3):A246.

85 Burmester GR, Weinblatt ME, McInnes IB, et al. Efficacy and safety of mavrilimumab in subjects with rheumatoid arthritis. *Ann Rheum Dis* 2013;72(9):1445-1452.

86 Fleischmann RM, Kivitz A, Van Vollenhoven RF, et al. No differences in patient-reported outcomes by methotrexate dose among early rheumatoid arthritis patients treated concomitantly with adalimumab: results from the CONCERTO trial [abstract]. *Arthritis Rheum* 2013;65:S574-S575.

87 Detert J, Bastian H, Listing J, et al. Efficacy of an induction therapy with adalimumab plus methotrexate versus methotrexate monotherapy in recent onset rheumatoid arthritis – an investigator initiated randomized controlled trial [abstract]. *Arthritis Rheum* 2011;63(suppl 10):1697.

88 Detert J, Bastian H, Listing J, et al. Induction therapy with adalimumab plus methotrexate versus methotrexate monotherapy in recent onset rheumatoid arthritis (RA)-an investigator initiated randomized controlled trial. *Ann Rheum Dis* 2013;71:102-103.

89 Kavanaugh A, Emery P, Fleischmann R, et al. Withdrawal of adalimumab in early rheumatoid arthritis patients who attained stable low disease activity with adalimumab plus methotrexate: results of a phase 4, double-blind, placebo-controlled trial. *Arthritis Rheum* 2011;63(suppl 10):1699.

90 Kavanaugh A, Fleischmann R, Emery P, et al. Clinical and functional improvements in early RA following treatment with adalimumab plus methotrexate compared with methotrexate monotherapy: 26-week results of the Optima trial. *Arthritis Rheum* 2010;62:1791.

91 Bingham III CO, Weinblatt M, Mendelsohn A, et al. Predictors of significant disease activity score-28 (using C-reactive protein) remission achieved with intravenous golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results of the phase 3, multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2012;64:S558.

92 Kavanaugh A, Fleischmann RM, Emery P, et al. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72(1):64-71.

93 Smolen JS, Fleischmann RM, Emery P, et al. Treating rheumatoid arthritis to target: outcomes and predictors in early rheumatoid arthritis patients treated with adalimumab plus methotrexate, methotrexate alone or methotrexate plus subsequent adalimumab. *Rheumatology (Oxford)* 2012;51:iii114-iii115.

94 Emery P, Kavanaugh AF, Smolen J, et al. Combination therapy with adalimumab-methotrexate significantly improved work ability, physical function, fatigue, and other patient-reported outcomes in early rheumatoid arthritis: results from a 26-week analysis. *Arthritis Rheum* 2011;63(suppl 10):2189.

95 Kimel M, Cifaldi M, Chen N, et al. Adalimumab plus methotrexate improved SF-36 scores and reduced the effect of rheumatoid arthritis (RA) on work activity for patients with early RA. *J Rheumatol* 2008;35(2):206-215.

96 Strand V, Rentz AM, Cifaldi MA, et al. Health-related quality of life outcomes of adalimumab for patients with early rheumatoid arthritis: results from a randomized multicenter study. *J Rheumatol* 2012;39(1):63-72.

97 Emery P, Breedveld F, Van Der Heijde D, et al. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: a two-year, double-blind, randomized study. *Arthritis Rheum* 2010;62(3):674-682.

98 Kekow J, Moots RJ, Emery P, et al. Patient-reported outcomes improve with etanercept plus methotrexate in active early rheumatoid arthritis and the improvement is strongly associated with remission: the COMET trial. *Ann Rheum Dis* 2010;69(1):222-225.

99 Anis A, Zhang W, Emery P, et al. The effect of etanercept on work productivity in patients with early active rheumatoid arthritis: results from the COMET study. *Rheumatology (Oxford)* 2009;48(10):1283-1289.

100 Heijde D, Klareskog L, Boers M, et al. Comparison of different definitions to classify remission and sustained remission: 1 year TEMPO results. *Ann Rheum Dis* 2005;64(11):1582-1587.

101 Heijde D, Klareskog L, Rodriguez-Valverde V, et al. Comparison of etanercept and methotrexate, alone and combined, in the treatment of rheumatoid arthritis: two-year clinical and radiographic results from the TEMPO study, a double-blind, randomized trial. *Arthritis Rheum* 2006;54(4):1063-1074.

102 Heijde D, Klareskog L, Singh A, et al. Patient reported outcomes in a trial of combination therapy with etanercept and methotrexate for rheumatoid arthritis: the TEMPO trial. *Ann Rheum Dis* 2006;65(3):328-334.

103 Emery P, Fleischmann RM, Doyle MK, et al. Golimumab, a human anti-tumor necrosis factor monoclonal antibody, injected subcutaneously every 4 weeks in patients with active rheumatoid arthritis who had never taken methotrexate: 1-year and 2-year clinical, radiologic, and physical function findings of a phase III, multicenter, randomized, double-blind, placebo-controlled study. *Arthritis Care Res* 2013;65(11):1732-1742.

104 Emery P, Fleischmann RM, Moreland LW, et al. Golimumab, a new human anti-TNF-alpha monoclonal antibody, in methotrexate-naive active rheumatoid arthritis (Go-Before study). *Rheumatology (Oxford)* 2009;48:i93.

105 Ostergaard M, Emery P, Conaghan PG, et al. Significant improvement in synovitis, osteitis, and bone erosion following golimumab and methotrexate combination therapy as compared with methotrexate alone: a magnetic resonance imaging study of 318 methotrexate-naive rheumatoid arthritis patients. *Arthritis Rheum* 2011;63(12):3712-3722.

106 Haugeberg G, Conaghan PG, Quinn M, et al. Bone loss in patients with active early rheumatoid arthritis: infliximab and methotrexate compared with methotrexate treatment alone. Explorative analysis from a 12-month randomised, double-blind, placebo-controlled study. *Ann Rheum Dis* 2009;68(12):1898-1901.

107 Valleala H, Kautiainen H, Mottonen T, et al. Bone mineral density in patients with recent onset, active rheumatoid arthritis: two-year data of the NEO-RACo study. *Arthritis Rheum* 2009;60:1008.

108 Moreland LW, O'Dell JR, Paulus HE, et al. Two-year radiographic results from the TEAR trial. *Arthritis Rheum* 2010;62:1368.

109 O'Dell JR, Curtis JR, Mikuls TR, et al. Validation of the methotrexate-first strategy in patients with early, poor-prognosis rheumatoid arthritis: results from a two-year randomized, double-blind trial. *Arthritis Rheum* 2013;65(8):1985-1994.

110 Goekoop-Ruiterman YP, De Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146(6):406-415.

111 Van Der Kooij SM, De Vries-Bouwstra JK, Goekoop-Ruiterman YPM, et al. Patient-reported outcomes in a randomized trial comparing four different treatment strategies in recent-onset rheumatoid arthritis. *Arthritis Care Res* 2009;61(1):4-12.

112 Kameda H, Kanbe K, Sato E, et al. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-week results from the JESMR study. *J Rheumatol* 2011;38(8):1585-1592.

113 Keystone EC, Combe B, Smolen J, et al. Sustained efficacy of certolizumab pegol added to methotrexate in the treatment of rheumatoid arthritis: 2-year results from the RAPID 1 trial. *Rheumatology (Oxford)* 2012;51(9):1628-1638.

114 Smolen J, Keystone E, Schiff M, et al. Sustained long-term efficacy of certolizumab pegol plus methotrexate in the treatment of rheumatoid arthritis: a 2-year analysis of the Rapid 1 study. *Rheumatology (Oxford)* 2009;48:i85-86.

115 Strand V, Mease P, Burmester GR, et al. Rapid and sustained improvements in health-related quality of life, fatigue, and other patient-reported outcomes in rheumatoid arthritis patients treated with certolizumab pegol plus methotrexate over 1 year: results from the RAPID 1 randomized controlled trial. *Arthritis Res Ther* 2009;11(6):R170.

116 Conaghan PG, Emery P, Ostergaard M, et al. Assessment by MRI of inflammation and damage in rheumatoid arthritis patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. *Ann Rheum Dis* 2011;70(11):1968-1974.

117 Conaghan PG, Emery P, Ostergaard M, et al. Assessment of inflammation and damage by MRI in established RA patients with methotrexate inadequate response receiving golimumab: results of the GO-FORWARD trial. *Arthritis Rheum* 2010;62:1097.

118 Genovese MC, Han C, Keystone EC, et al. Effect of golimumab on patient-reported outcomes in rheumatoid arthritis: results from the GO-FORWARD study. *J Rheumatol* 2012;39(6):1185-1191.

119 Genovese MC, Keystone EC, Hsia EC, et al. Impact of golimumab on physical function, health-related quality of life, productivity and employment in rheumatoid arthritis patients: week 52 results from the GO-FORWARD study. *Int J Rheum Dis* 2010;13:88.

120 Keystone EC, Genovese MC, Hall S, et al. Golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results through 2 years of the Go-Forward study extension. *J Rheumatol* 2013;40(7):1097-1103.

121 Rubbert A, Keystone E, Genovese M, et al. Golimumab administered subcutaneously every 4 weeks in active rheumatoid arthritis despite methotrexate: week 24 results of Go-Forward study. *Rheumatology (Oxford)* 2009;48:i92.

122 Bae SC, Gun SC, Mok CC, et al. Improved health outcomes with etanercept versus usual DMARD therapy in an Asian population with established rheumatoid arthritis. *BMC Musculoskel Disord* 2013;14:13.

123 Kremer J, Taylor P, Mendelsohn A, et al. Subcutaneous golimumab sustains effects of intravenous golimumab in patients with active rheumatoid arthritis: results of the Go-Live long term extension. *Rheumatology (Oxford)* 2011;50:iii115.

124 Kremer JM, Taylor P, Mendelsohn A, et al. Subcutaneous golimumab sustains effects of intravenous golimumab in patients with active rheumatoid arthritis: results of the GO-LIVE long term extension. *Arthritis Rheum* 2010;62:1835.

125 Taylor PC, Ritchlin C, Mendelsohn A, et al. Maintenance of efficacy and safety with subcutaneous golimumab among patients with active rheumatoid arthritis who previously received intravenous golimumab. *J Rheumatol* 2011;38(12):2572-2580.

126 Breedveld FC, Emery P, Keystone E, et al. Infliximab in active early rheumatoid arthritis. *Ann Rheum Dis* 2004;63(2):149-155.

127 Lipsky PE, van der Heijde DM, St Clair EW, et al. Infliximab and methotrexate in the treatment of rheumatoid arthritis. Anti-Tumor Necrosis Factor Trial in Rheumatoid Arthritis with Concomitant Therapy Study Group. *N Engl J Med* 2000;343(22):1594-1602.

128 Maini RN, Breedveld FC, Kalden JR, et al. Sustained improvement over two years in physical function, structural damage, and signs and symptoms among patients with rheumatoid arthritis treated with infliximab and methotrexate. *Arthritis Rheum* 2004;50(4):1051-1065.

129 Strand V, Smolen JS, van Vollenhoven RF, et al. Certolizumab pegol plus methotrexate provides broad relief from the burden of rheumatoid arthritis: analysis of patient-reported outcomes from the RAPID 2 trial. *Ann Rheum Dis* 2011;70(6):996-1002.

130 Tanaka Y, Harigai M, Takeuchi T, et al. 52-week results of clinical, radiographic and pharmacokinetic assessments: golimumab, a human anti-TNF monoclonal antibody, administered subcutaneously every four weeks in patients with active rheumatoid arthritis despite methotrexate therapy. *Ann Rheum Dis* 2013;71(suppl 3):372.

131 Tanaka Y, Harigai M, Takeuchi T, et al. Golimumab administered subcutaneously every four weeks in patients with active rheumatoid arthritis despite methotrexate therapy: long-term clinical, radiographic and safety results, including evaluation of remission using the new ACR/EULAR criteria. *Ann Rheum Dis* 2013;72(suppl 3):A442.

132 Taylor PC, Steuer A, Gruber J, et al. Ultrasonographic and radiographic results from a two-year controlled trial of immediate or one-year-delayed addition of infliximab to ongoing methotrexate therapy in patients with erosive early rheumatoid arthritis. *Arthritis Rheum* 2006;54(1):47-53.

133 Van Riel PL, Freundlich B, MacPeek D, et al. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial. *Ann Rheum Dis* 2008;67(8):1104-1110.

134 Van Vollenhoven RF, Wallenstein G, Lee EB, et al. Effects of tofacitinib (CP-690,550), an oral janus kinase inhibitor, or adalimumab on patient reported outcomes in a phase 3 study of active rheumatoid arthritis. *Ann Rheum Dis* 2013;71(suppl 3):206.

135 Bingham III CO, Weinblatt ME, Mendelsohn A, et al. Predictors of significant disease activity score-28 (using C-reactive protein) remission achieved with intravenous golimumab in patients with active rheumatoid arthritis despite methotrexate therapy: results of the phase III, multicentre, double-blind, placebo-controlled trial. *Rheumatology (Oxford)* 2013;52:i82-i83.

136 Bingham III CO, Weinblatt M, Han C, et al. The effect of intravenous golimumab on health-related quality of life in rheumatoid arthritis: 24-week results of the phase III GO-FURTHER trial. *J Rheumatol* 2014;41(6):1067-1076.

137 Bingham III CO, Westhovens R, Mendelsohn AM, et al. Sustained and consistent clinical benefit with intravenous golimumab therapy in patients with active rheumatoid arthritis despite methotrexate therapy: results through 1-year of a phase 3, randomized, multicenter, double-blind, placebo-controlled trial. *Arthritis Rheum* 2013;65:S374.

138 Weinblatt M, Bingham COr, Mendelsohn A, et al. Intravenous golimumab inhibits radiographic progression and maintains clinical efficacy and safety in patients with active rheumatoid arthritis despite methotrexate therapy: 1-year results of a phase 3 trial. *Arthritis Rheum* 2012;64:S353-S354.

139 Westhovens R, Weinblatt ME, Han C, et al. Intravenously administered golimumab significantly improves health related quality of life and work productivity in patients with rheumatoid arthritis: results of a phase III, placebo-controlled trial. *Value Health* 2012;15(4):A42.

140 Westhovens R, Weinblatt ME, Han C, et al. Health-related quality of life of patients with rheumatoid arthritis achieving DAS28 remission, improvement in physical function and no radiographic progression after treatment with intravenous golimumab [abstract]. *Ann Rheum Dis* 2014;73(suppl 2):479-480.

141 Schiff M, Weinblatt ME, Valente R, et al. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis* 2014;73(1):86-94.

142 Atsumi T, Yamamoto K, Takeuchi T, et al. The first early rheumatoid arthritis, certolizumab pegol, multicenter, double-blind, randomized, parallel-group study: C-Opera, in patients fulfilling the 2010 ACR/EULAR classification criteria, demonstrates inhibition of joint damage progression. *Ann Rheum Dis* 2014;73(suppl 2):484.

143 Tanaka Y, Yamamoto K, Takeuchi T, et al. Long-term efficacy and safety of certolizumab pegol in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: 52-week results from an open-label extension of the J-RAPID study. *Mod Rheumatol* 2014;24(5):734-743.

144 Yamanaka H, Yamamoto K, Takeuchi T, et al. Improved physical function, pain, and health related quality of life with certolizumab pegol in Japanese rheumatoid arthritis patients without methotrexate co-administration: results from the Hikari study. *Ann Rheum Dis* 2013;71(suppl 3):664.

145 Yoo D, Miranda P, Piotrowski M, et al. A randomized, double-blind, phase 3 study demonstrates clinical equivalence of CT-P13 to infliximab when co-administered with methotrexate in patients with active rheumatoid arthritis [abstract]. *Ann Rheum Dis* 2013;71:359.

146 Yoo DH, Park W, Brzosko M, et al. Disease activity assessment using the DAS28, CDAI and SDAI and effect of anti-drug antibody on clinical response in a randomized, double-blind, comparative trial of CT-P13 and innovator infliximab: Planetra study. *Ann Rheum Dis* 2014;73(suppl 2):235.

147 Yoo DH, Racewicz A, Brzezicki J, et al. A phase 3 randomised controlled trial to compare CT-P13 with infliximab in patients with active rheumatoid arthritis: 54 week results from the PLANETRA study. *Ann Rheum Dis* 2013;72(suppl 3):A73.

148 Karlsson JA, Neovius M, Nilsson JA, et al. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. *Ann Rheum Dis* 2013;72(12):1927-1933.

149 Rezaei H, Saevarsdottir S, Geborek P, et al. Evaluation of hand bone loss by digital X-ray radiogrammetry as a complement to clinical and radiographic assessment in early rheumatoid arthritis: results from the SWEFOT trial. *BMC Musculoskel Disord* 2013;14:79.

150 Van Vollenhoven RF, Geborek P, Forslind K, 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(9827):1712-1720.

151 Smolen JS, Emery P, Fleischmann R, et al. Adjustment of therapy in rheumatoid arthritis on the basis of achievement of stable low disease activity with adalimumab plus methotrexate or methotrexate alone: The randomised controlled OPTIMA trial. *Lancet* 2014;383(9914):321-332.

152 Goekoop-Ruiterman YP, de Vries-Bouwstra JK, Allaart CF, et al. Comparison of treatment strategies in early rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2007;146(6):406-415.

153 Yamanaka H, Inoue E, Singh G, et al. Improvement of disease activity of rheumatoid arthritis patients from 2000 to 2006 in a large observational cohort study IORRA in Japan. *Mod Rheumatol* 2007;17(4):283-289.