THE LANCET

Supplementary appendix

This appendix formed part of the original submission and has been peer reviewed. We post it as supplied by the authors.

Supplement to: Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. *Lancet* 2015; published online May 12. http://dx.doi.org/10.1016/S0140-6736(14)61704-9.

SUPPLEMENTARY APPENDIX

Appendix 1 (on line): Search Strategy

Database: Cochrane Library, Issue 2, 2014
Description:

ID	Search
#1	MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#2	MeSH descriptor: [Monokines] explode all trees
#3	MeSH descriptor: [Receptors, Interleukin-1] explode all trees
#4	MeSH descriptor: [Receptors, Interleukin-6] explode all trees
#5	MeSH descriptor: [Immunoglobulin G] explode all trees
#6	MeSH descriptor: [Immunoconjugates] explode all trees
#7	MeSH descriptor: [Polyethylene Glycols] explode all trees
#8	MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees
#9	MeSH descriptor: [T-Lymphocytes] explode all trees
#10	adalimumab:ti,ab
#11	humira:ti,ab
#12	trudexa:ti,ab
#13	abatacept:ti,ab
#14	orencia:ti,ab
#15	anakinra:ti,ab
#16	kineret:ti,ab
#17	Certolizumab:ti,ab
#18	cimzia:ti,ab
#19	Etanercept:ti,ab
#20	enbrel:ti,ab
#21	Golimumab:ti,ab
#22	simponi:ti,ab
#23	rituximab:ti,ab
#24	rituxan:ti,ab
#25	mabthera:ti,ab
#26	Tocilizumab:ti,ab
#27	actemra:ti,ab
#28	RoActemra:ti,ab
#29	infliximab:ti,ab
#30	remicade:ti,ab
#31	(#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30)
#32	rheumatoid:ti,ab
#33	arthritis:ti,ab
#34	felty near/2 syndrome
#35	caplan near/2 syndrome
#36	rheumatoid nodule
#37	sjogren* near/2 syndrome
#38	still* next disease
#39	arthritis near/2 rheumat*

#40 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#41 (#32 or #33 or #34 or #35 or #36 or #37 or #38 or #39 or #40)
#42 #31 and #41

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 2014 February 11>
Search Strategy:

---

1 exp arthritis, rheumatoid/
2 (arthritis adj2 rheumat$).tw.
3 (felty$ adj2 syndrome).tw.
4 (caplan$ adj2 syndrome).tw.
5 rheumatoid nodule.tw.
6 (sjogren$ adj2 syndrome).tw.
7 still$ disease.tw.
8 or/1-7
9 exp antibodies, monoclonal/
10 exp monokines/ (117104)
11 exp receptors, interleukin-1/
12 exp receptors, interleukin-6/
13 exp immunoglobulin g/
14 exp immunoconjugates/
15 exp polyethylene glycols
16 exp immunoglobulin fab fragments/
17 exp t-lymphocytes/
18 Infliximab.tw.
19 remicade.tw.
20 adalimumab.tw.
21 humira.tw.
22 trudexa.tw.
23 abatacept.tw.
24 orencia.tw.
25 anakinra.tw.
26 kineret.tw.
27 Certolizumab.tw.
28 cimzia.tw.
29 Etanercept.tw.
30 enbrel.tw.
31 Golimumab.tw.
32 simponi.tw.
33 rituximab.tw.
34 rituxan.tw.
35 mabthera.tw.
36 Tocilizumab.tw.
37 actemra.tw.
38 RoActemra.tw.
39 or/9-36
40 randomized controlled trial.pt.
41 controlled clinical trial.pt.
42 randomized.ab.

43 placebo.ab.
44 clinical trials as topic.sh.
45 randomly.ab.
46 trial.ti.
47 or/40-46
48 exp animals/ not humans.sh.
49 47 not 48
50 8 and 39 and 49
51 limit 50 to ed=20080101-20130507
52 limit 50 to yr="2008 -Current"
53 18 or 19
54 8 and 39 and 53
55 limit 54 to ed=20060101-20130507
56 limit 54 to yr="2006 -Current"
57 51 or 52
58 55 or 56
59 57 or 58

Database: Embase Classic+Embase <1947 to 2014 February 11>
Search Strategy:

---

1 exp arthritis, rheumatoid/
2 (arthritis adj2 rheumat$).tw.
3 (felty$ adj2 syndrome).tw.
4 (caplan$ adj2 syndrome).tw.
5 rheumatoid nodule.tw.
6 (sjogren$ adj2 syndrome).tw
7 still$ disease.tw.
8 or/1-7
9 exp monoclonal antibody/
10 exp monokine/
11 exp interleukin 1 receptor/
12 exp interleukin 6 receptor/
13 exp antibody conjugate/
14 exp immunoglobulin G/
15 exp macrogol derivative/
16 exp "immunoglobulin F(ab) fragment"/
17 exp T lymphocyte/
18 infliximab.mp. or exp infliximab/
19 remicade.mp.
20 humira.mp. or exp adalimumab/
21 trudexa.mp.
22 abatacept.mp. or exp abatacept/
23 orencia.mp.
24 anakinra.mp. or recombinant interleukin 1 receptor blocking agent/
25 kineret.mp.
26 cimzia.mp. or exp certolizumab pegol/
27 enbrel.mp. or exp etanercept/
28 simponi.mp. or exp golimumab/
29 rituxan.mp. or exp rituximab/

30 mabthera.mp.
31 actemra.mp. or exp tocilizumab/
32 RoActemra.mp.
33 or/9-32
34 8 and 33
35 random:.tw.
36 placebo:.mp.
37 double-blind:.tw.
38 or/35-37
39 34 and 38

Tofacitinib search

Search Name: tofacitinib
Description:

ID Search
#1 (tofacitinib or tasocitinib) in Trials
#2 (cp690550 or "cp-690550" or "cp 690550" or "cp-690,550" or "cp 690,550" or "cp-690 550" or "cp 690 550") in Trials
#3 (#1 or #2)
#4 (rheumat* near/5 arthrit*) in Trials
#5 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#6 (stills or still's or felty* or sjogren* or sicca* or sjoegren* or vasculit* or arthrit* or caplan*) in Trials
#7 (#4 or #5 or #6)
#8 (#3 and #7)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to 2014 February 11>
Search Strategy:
---
1 tofacitinib.mp.
2 tasocitinib.mp.
3 cp690550.mp.
4 "cp 690550".mp.
5 "cp 690 550".mp.
6 or/1-5
7 exp Arthritis, Rheumatoid/
8 (rheumatoid adj5 arthrit*).mp.
9 (stills or still's or felty* or sjogren* or sicca* or sjoegren* or vasculit* or arthrit* or caplan*).mp.
10 or/7-9
11 6 and 10

Database: Embase Classic+Embase <1947 to 2014 February 11>
Search Strategy:

---

1 tofacitinib.mp.
2 tasocitinib.mp.
3 Xeljanz.mp.
4 cp690550.mp.
5 "cp 690550".mp.
6 "cp 690 550".mp.
7 or/1-5
8 exp Arthritis, Rheumatoid/
9 (rheumatoid adj5 arthrit*).mp
10 (stills or still's or felty* or sjogren* or sicca* or sjoegren* or vasculit* or arthrit* or caplan*).mp.
11 or/8-10
12 7 and 11

Appendix 2 (on line): Sensitivity analysis removing tofacitinib treatment nodes from the analysis

Tofacitinib was not pooled with other biologics but treated as a separate treatment node within the analysis (**Figure 2**). We included tofacitinib in the primary analysis as a separate node to improve precision and because we wanted this review to be up-to-date and include all relevant treatment options for the management of rheumatoid arthritis. This is particularly important because we want this review to be dynamic and updated as new information evolves over time, including information on newer treatments such as tofacitinib. However, we opted to not include effect estimates on the risk of serious infection for tofacitinib in the main text at this time because 1) tofacitinib was not the focus of this review; 2) we do not report effect estimates for individual biologics, 3) conclusions regarding tofacitinib and the risk of serious infection may be premature because comparisons for tofacitinib may be underpowered at this time (similar to individual biologics), and 4) we observed some inconsistency for studies which included tofacitinib (**Appendix 10**).

We investigated the impact of including tofacitinib in the analysis as a separate node by running an analysis where we remove tofacitinib studies from the evidence network. Inclusion of tofacitinib in the evidence network had negligible impact on results (Table 1a) but allows us to easily update our analysis as new information become available. Results were nearly identical in analyses with and without tofacitinib, although inclusion of tofacitinib did result in a very small reduction in the between study standard deviation (0.1513 vs. 0.1524) and an increase in the number of studies (106 vs.98), patients (42,330 vs. 38,527), and patients who had a serious infection (965 vs. 934).

Appendix 2a – Comparison of effect estimates from Primary analysis and analysis removing tofacitinib from the evidence network

Comparison	Primary Analysis	Sensitivity analysis removing tofacitinib
Combination or triple traditional DMARD therapy vs Traditional DMARD monotherapy	0.84(0.48,1.48)	0.85(0.49,1.51)
SD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	**1.31(1.09,1.58)**	**1.31(1.10,1.59)**
LD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	0.93(0.65,1.33)	0.94(0.64,1.33)
HD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	**1.9(1.50,2.39)**	**1.89(1.50,2.38)**
Combination Biologic vs Traditional DMARD monotherapy	**4.14(1.87,9.05)**	**4.17(1.90,9.16)**
Placebo vs SD Biologic +/- Traditional DMARD	0.57(0.19,1.28)	0.37(0.10,1.03)
Number of trials	106	98
No. of patients in trials	42,330	38,527
No. of patients with serious infection	965	934
Residual deviance	**225.6 vs 265**	**207.3 vs 237**
DIC	**1040.87**	**953.69**
Between study standard deviation	**0.1513**	**0.1524**

Appendix 3 (on line): Methods Supplement

Data Extraction – Patient and study characteristics

The following patient and study characteristics were extracted**:** Patient characteristics (age, RA duration); prior DMARD/biologic treatment (MTX naïve, MTX-experienced, non-MTX traditional DMARD experienced, or TNF-experienced); study characteristics (year and month of publication, length of follow-up, adaptive design); risk of bias in individual RCTs using the risk of bias tool as recommended by the Cochrane Collaboration (sequence generation, allocation concealment, blinding, incomplete outcome data, and selective outcome reporting), rating each item with (low, high or unclear bias) and each trial with an overall risk of bias in terms of low risk (low for all key domains), high risk (high for ≥1 key domains), and unclear risk (unclear for ≥1 key domains); intervention (type, dose and duration, concomitant MTX therapy and dose, monotherapy versus combination therapy; and comparator characteristics (placebo or active comparator with details on type, dose, concomitant methotrexate therapy, monotherapy versus combination therapy. The dose classification of each biologic is provided below. Doses above these doses were classified as high dose biologics and those below were classified as low dose biologics.

Appendix 3a. Dose classification of each biologic

Drug	Standard approved U.S. dose
Infliximab	3mg/kg intravenous every 8 weeks after initial dosing at 0, 2 and 6 weeks
Etanercept	25 mg subcutaneous twice weekly
Adalimumab	40 mg subcutaneous every 2 weeks
Golimumab	SQ: 50 mg subcutaneous every 4 weeks IV: 2 mg/kg given as an intravenous infusion at weeks 0 and 4, then every 8 weeks
Certolizumab	400 mg (given as two subcutaneous injections of 200 mg) initially and at Weeks 2 and 4, followed by 200 mg every other week. For maintenance dosing, 400 mg every 4 weeks can be considered.
Anakinra	100 mg subcutaneous every day
Abatacept	IV: (10 mg/kg every 4 weeks): every 4 weeks intravenously at 500 mg dose in patients <60 kg, 750 mg in patients 60-100 kg and 1000 mg in patients >100 kg, after the initial dosing regimen of baseline, 2 and 4-week infusions; SQ: After a single intravenous infusion as a loading dose (as per body weight categories above), 125 mg administered by a subcutaneous injection should be given within a day, followed by 125 mg subcutaneously once a week.
Tocilizumab	4 mg/kg intravenously every 4 weeks followed by an increase to 8 mg/kg based on clinical response
Rituximab	Two 1000 mg IV doses 2 weeks apart
Tofacitinib	5 mg bid PO

Assessment of model fit, convergence and inconsistency

Assessment of model fit was based on deviance information criterion (DIC) and comparison of residual deviance.[1] To ensure convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed.[1] Three chains were fit in WinBUGS for each analysis, with at least 40,000 iterations, and a burn-in of at least 40,000 iterations.[1] To assess consistency (there is no conflict between direct and indirect evidence),[2] we compared deviance and DIC statistics in fitted consistency and inconsistency models.[2] We also plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to identify where inconsistency is present.

Assessment of Publication Bias

We assessed the publication bias for standard dose biologic versus non-biologic treatments by evaluating a funnel plot of the trial mean differences for asymmetry. The symmetry of such 'funnel plots' was assessed both visually, and formally with Egger's test.

Pre-specified sub-group and sensitivity analyses

We also pre-specified the following analyses: (1) MTX-naïve, MTX experienced (inadequate responders/failures) and TNF-experienced populations; (2) Anti-TNF biologics vs. other biologic; (3) individual biologics; (4) treatment duration with biologics: short (<6 months), intermediate duration (6 to 12 months) or long-duration (>1 year); (5) RA disease duration: categorized as early RA defined as duration of less than 2 years[3] vs. established RA, duration 2 to 10 years vs. late RA defined as >10 years.[4] Finally, we conducted detailed statistical analyses to ensure that findings were robust to type of analysis performed and assumptions around how to handle cells with zero events.

Handling Zero Cells

We also conducted numerous sensitivity analyses related to methods for handling zero cells.[5, 6] We conducted numerous analyses to ensure robustness of results irrespective of how zeroes were handled (**Appendix 6**). We also did not exclude double/multiple zeroes cells to provide analytic consistency and because exclusion may cause an artificial small increase the effect size of serious infection.[5] Finally, since treatment arms within some studies have differential sample size, we did not apply a constant 0.5 continuity correction which would have biased estimates but instead applied an adjusted continuity correction factor centered around 0.5 and accounting for differential sample sizes among the arms.[6]

Role of Funding

This research was supported through grants from Rheumatology division at the University of Alabama at Birmingham. The funding agency played no role in study design, collection, analysis, interpretation of data, writing of the manuscript, or in the decision to submit the paper for publication. They accept no responsibility for the contents.

References

1. Spiegelhalter, D., Thomas, A. & Best, N. WinBUGS user manual. MRC Biostat. Unit 2, (2004).

2. Dias, S., Welton, N.J., Sutton, A.J., et al. NICE Technical Support Document 4: Inconsistency in Networks of Evidence Based on Randomised Controlled Trials. 1–39 (2011). at www.nicedsu.org.uk

3. Boers M. Rheumatoid arthritis. Treatment of early disease. Rheumatic diseases clinics of North America 2001;27:405-14.

4. Singh JA, Christensen R, Wells GA, et al. Biologics for rheumatoid arthritis: an overview of Cochrane reviews (Protocol). Cochrane Database of Systematic Reviews 2009.

5. Bradburn MJ, Deeks JJ, Berlin JA, Russell Localio A. Much ado about nothing: a comparison of the performance of meta-analytical methods with rare events. *Statistics in medicine* 2007; **26**(1): 53-77.

6. Friedrich JO, Adhikari NK, Beyene J. Inclusion of zero total event trials in meta-analyses maintains analytic consistency and incorporates all available data. *BMC medical research methodology* 2007; **7**: 5.

Appendix 4 (on line): Summary of Included Trials

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Abe 2006	147	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.9	yes	no	yes	3 months	3 months
Bathon (ERA) 2000	632	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	1	no	no	yes	24 months	24 months
Bejarano 2008	148	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.7	yes	no	yes	13 months	13 months
Breedveld 2006	799	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.8	yes	no	yes	24 months	24 months
Bresnihan 1998	472	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	n/a	3.9	yes	no	yes	6 months	6 months
Burmester 2013	399	TNF experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	7.5-30	12.3	no	no	yes	6 months	6 months
Chen 2009	47	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6	no	no	yes	3 months	3 months
Choy 2012	247	MTX experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	9.7	no?	no	yes	6 months	6 months
Cohen 2004	501	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	11.5	yes	no	yes	6 months	12 months
Cohen 2002	137	MTX	Traditional	LD Biologic	NA	NA	NA	7.5-30	7.4	yes	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD										
Cohen 2006	520	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	12.1	no	no	yes	6 months	24 months
Combe 2009	254	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	5.6	no	no	yes	24 months	24 months
Conaghan 2013	50	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	2.2	0	0	yes	4 months	12 months
de Jong 2013	179	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditional DMARD therapy	NA	NA	NA	7.5-30	0.4	no	no	yes	3 months	3 months
Detert 2013	172	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.14	yes	yes	yes	6 months	11 months
Dougados 1999	137	MTX naïve	Traditional DMARD monotherapy	MTX + non-MTX traditional DMARD	NA	NA	NA	7.5-30	0.2	no	no	yes	12 months	12 months
Durez 2007	29	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.4	no	no	yes	12 months	12 months
Edwards 2004	120	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-31	10.4	yes	no	yes	6 months	12 months
Emery (RADIATE) 2008a	498	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	12.6	no	no	yes	4 months	6 months
Emery (COMET) 2008	542	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.7	yes	no	yes	12 months	24 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Emery (DANCER) 2006	483	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	10.8	no	no	yes	6 months	6 months
Emery (GO-BEFORE) 2009	637	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	3.5	no	no	yes	6 months	12 months
EMERY (SERENE) 2010a	512	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.1	yes	no	yes	6 months	11 months
Fleischman 2003	1399	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	10.2	yes	no	yes	6 months	6 months
Fleischman_March 2012	331	DMARD experienced	SD Tofacitinib +/- Traditional DMARD	LD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	Placebo	NA	7.5-30	8.1	no?	no	no	3 months	6 months
Fleischmann (FAST4WARD) 2009	220	DMARD experienced	SD Biologic +/- Traditional DMARD	Placebo	NA	NA	NA	n/a	8.7	no	no	yes	6 months	6 months
Fleischmann _ August 2012	610	DMARD experienced	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	Placebo	NA	NA	7.5-30	8.1	no?	no	yes	3 months	6 months
Furst 2003	636	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	9.3	yes	no	yes	6 months	6 months
Gabay (ADACTA) 2013	326	MTX experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	6.8	yes	no	yes	6 months	6 months
Genovese (TOWARD) 2008	1220	DMARD experienced	Traditional DMARD	HD Biologic +/- Traditional	NA	NA	NA	7.5-30	9.8	yes	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD										
Genovese 2004	241	MTX experienced	Traditional DMARD monotherapy	Combination Biologic	NA	NA	NA	7.5-30	9.9	no	no	no	6 months	6 months
Genovese 2005	391	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	no	12.2	no	no	yes	6 months	6 months
Greenwald 2011*	54	TNF experienced	Traditional DMARD monotherapy	Combination Biologic	NA	NA	NA	7.5-30	10.4	no	no	no	6 months	6 months
Haagsma 1994	40	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	5	no	no	yes	5.5 months	5.5 months
Haagsma 1997	71	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.3	no	no	yes	12 months	12 months
Hanyu 1999	37	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	13.5	no	no	yes	60 months	60 months
Heijde (TEMPO Pt reported outcomes) 2007	682	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.4	yes	no	yes	36 months	36 months
Hetland 2006	160	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.3	no	no	yes	12 months	12 months
Ichikawa 2005	47	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD	NA	NA	NA	7.5-30	0.8	no	no	yes	22 months	22 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
				therapy										
Jones 2010	572	TNF experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.4	yes	no	yes	6 months	6 months
Kaine 2011	120	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	6.6	no	no	yes	4 months	9 months
Kavanaugh (OPTIMA) 2013	1032	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.3	yes	no	yes	6 months	6 months
Kay 2008	104	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.8	no	no	yes	4 months	11 months
Keystone (GO-FORWARD) 2010	444	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-31	5.9	no	no	yes	4 months	12 months
Keystone 2004	619	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	11	yes	no	yes	12 months	12 months
Keystone 2004	420	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	8.9	no	no	yes	4 months	4 months
Keystone 2008	982	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	6.2	no	no	no	6 months	12 months
Kim 2007	128	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.8	yes	no	yes	6 months	6 months
Kim 2012	300	MTX experienced	Combination or triple traditional DMARD	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	6.7	yes	no	yes	4 months	4 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			therapy											
Kremer 2002	263	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditional DMARD therapy	NA	NA	NA	7.5-30	11.6	no	no	yes	5.5 months	5.5 months
Kremer 2005	339	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	9.7	no	no	yes	6 months	12 months
Kremer 2006	652	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	8.7	no	no	yes	12 months	12 months
Kremer 2009	195	TNF experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	n/a	8.7	no	no	yes	2 months	3 months
Kremer 2010	645	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.9	no	no	yes	4 months	11 months
Kremer 2010	1190	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	9.2	no	no	yes	12 months	24 months
Kremer 2012	442	MTX experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	LD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	7.5-30	9.6	no	no	yes	3 months	6 months
Kremer 2013	795	DMARD Experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	n/a	8.9	no	no	yes	3 months	12 months
Lan 2004	58	MTX	Traditional DMARD	SD Biologic +/- Traditional	NA	NA	NA	7.5-30	8.5	no	no	yes	3 months	3 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
		experienced	monotherapy	DMARD										
Lipsky 2000	261	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	10	yes	no	yes	12 months	12 months
Maini (CHARISMA) 2006	359	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	7.5-30	9.6	no	no	yes	5 months	5 months
Maini 1998	101	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	7.5-30	10	yes	no	yes	6 months	6 months
Marchesoni 2003	58	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.9	no	no	yes	12 months	12 months
Miyasaka (CHANGE) 2008	352	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	n/a	9.9	yes	no	yes	6 months	6 months
Moreland (TEAR) 2012	500	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	7.5-30	0.3	yes	yes	yes	6 months	6 months
Nishimoto (SAMURAI) 2007	306	DMARD experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	2.4	no	no	yes	12 months	12 months
Nishimoto (SATORI) 2009	127	MTX experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	8.6	yes	no	yes	6 months	6 months
O'Dell 1996	102	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD	NA	NA	NA	7.5-30	8.6	no	no	yes	24 months	24 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
				therapy										
O'Dell 2006	48	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.4	no	no	yes	24 months	24 months
O'Dell 2013	441	MTX experienced	Combination or triple traditionall DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	5.2	yes	no	yes	6 months	12 months
Ogrendik 2007	76	MTX experienced	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	12	no	no	yes	6 months	6 months
Pavelka 2009	141	MTX experienced	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	13	no	no	yes	12 months	12 months
Quinn 2005	20	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.5	yes	yes	yes	12 months	24 months
Rau 2004	54	MTX experienced	Traditional DMARD monotherapy	LD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	11.1	no	no	yes	1 month	1 month
Rubbert-Roth 2010	378	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	8.8	yes	no	yes	11 months	11 months
Schiff 2008	431	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	7	yes	no	yes	6 months	12 months
Smolen (GO-AFTER) 2009a	461	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional	NA	NA	n/a	9.4	no	no	yes	6 months	6 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
					DMARD									
Smolen (RAPID 2) 2008	619	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	6	no	no	yes	6 months	12 months
Smolen 2008 (OPTION)	623	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.6	no	no	yes	4 months	8 months
Smolen 2013	604	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	6.9	yes	no	yes	22 months	22 months
St. Clair (ASPIRE) 2004	1040	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	0.8	yes	no	yes	12 months	12 months
Taciolglu 2003	55	MTX naïve	Traditional DMARD monotherapy	Combination or triple traditionall DMARD therapy	NA	NA	NA	7.5-30	0.6	no	no	yes	12 months	12 months
Tada (PRECEPT) 2012	70	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	9	no	no	yes	12 months	12 monthss
Tak 2012	748	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	NA	NA	7.5-30	0.9	yes	yes	yes	24 months	24 months
Takeuchi 2013	316	DMARD Experienced	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	NA	n/a	8.9	no?	no	yes	4 months	6 months
Takeuchi 2013b	548	DMARD Experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional	NA	NA	<=10	3	yes?	no	yes	12 months	12 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
					DMARD									
Takeuchi 2014	334	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	<=10	0.3	yes	yes	yes	6 months	6 months
Tanaka (GO-FORTH) 2012	269	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	<=10	8.6	yes	no	yes	3 months	6 months
Tanaka 2011	112	MTX experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	LD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	<=10	7.6	no	no	yes	3 months	3 months
Tugwell 1995	148	MTX experienced	Traditional DMARD monotherapy	MTX + non-MTX traditional DMARD	NA	NA	NA	7.5-30	10.3	no	no	yes	6 months	6 months
van de Putte 2003	284	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	no	10	yes	no	yes	3 months	3 months
Van de Putte 2004	544	DMARD experienced	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	Placebo	NA	n/a	10.6	yes	no	yes	6 months	6 months
van der Heijde 2013	718	MTX experienced	Traditional DMARD monotherapy	SD Tofacitinib +/- Traditional DMARD	HD Tofacitinib +/- Traditional DMARD	NA	NA	7.5-30	9.1	no	no	yes	12 months	12 months
Vollenhoven (SWEFOT) 2012	258	MTX naïve	Combination or riple traditional DMARD therapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.5	no	yes	yes	24 months	24 months
Vollenhoven 2012a	717	MTX experienced	Traditional DMARD	SD Biologic +/- Traditional	HD Tofacitinib +/-	NA	NA	7.5-30	7.8	no	no	yes	3 months	12 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
			monotherapy	DMARD	Traditional DMARD									
Weinblatt (Go FURTHER)	592	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	7	yes	no	yes	6 months	6 months
Weinblatt 1999	89	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	13	yes	no	yes	6 months	6 months
Weinblatt 2003	271	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	LD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	7.5-30	12.2	yes	no	yes	6 months	6 months
Weinblatt 2006	121	TNF experienced	SD Biologic +/- Traditional DMARD	Combination Biologic	NA	NA	NA	n/a	12.9	no	no	no	12 months	12 months
Weinblatt 2006	1377	TNF experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	Combination Biologic	NA	NA	7.5-30	11.3	no	no	yes	12 months	12 months
Weinblatt 2008	200	TNF experienced	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	10	no	no	yes	3 months	3 months
Weinblatt 2012	1063	DMARD Experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	8.7	no?	no	yes	3 months	3 months
Weisman 2007	535	DMARD experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	10.1	yes	no	yes	4 months	4 months
Westhovens (START) 2006	1084	MTX experienced	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	HD Biologic +/- Traditional DMARD	NA	NA	7.5-30	7.5	yes	no	yes	5 months	24 months
Westhovens 2009a	509	MTX naïve	Traditional DMARD monotherapy	SD Biologic +/- Traditional DMARD	NA	NA	NA	7.5-30	0.5	no	no	yes	12 months	24 months

Author and Year	N	Patient Population	Treatment 1	Treatment 2	Treatment 3	Treatment 4	Treatment 5	MTX	Duration of RA	Biologic-naive	DMARD-naive	Mono-Biologic	TIME of Outcome abstracted	Trial Duration
Williams 1992	220	MTX naïve	Traditional DMARD monotherapy	MTX + non-MTX traditional DMARD	NA	NA	NA	7.5-30	0.9	no	no	yes	6 months	6 months
Yazici 2012	619	DMARD experienced	Traditional DMARD monotherapy	HD Biologic +/- Traditional DMARD	NA	NA	NA	n/a	8.5	no	no	yes	4 months	6 months

Appendix 5 (on line): Risk of Bias assessment; + = low risk of bias; - = high risk of bias; ? = unclear risk of bias

	Random sequence generation	Allocation concealment	Blinding of assessor	Blinding of participants	Incomplete outcome data	Selective reporting	Major baseline imbalance	Funding source	Risk of Bias
Abe 2006	?	?	?	?	+	+	+	?	Unclear
Bathon 2000	?	-	-	-	-	?	+	+	High
Breedveld 2006	?	?	+	+	-	?	+	-	Low
Burmester 2013	+	+	?	?	-	?	+	-	Low
Chen 2009	?	?	?	?	-	?	+	?	Unclear
Combe 2009	?	?	?	?	-	+	-	-	Unclear
Durez 2007	?	?	+	?	+	+	+	?	Unclear
Emery 2006	?	?	?	?	-	-	+	-	Unclear
Emery 2008a	?	?	?	?	-	+	+	-	Unclear
Emery 2009	+	+	+	+	+	?	+	?	Low
Fleischmann 2009	+	?	+	?	-	+	+	-	Unclear
Gabay 2013	+	+	?	?	-	?	+	-	Low
Genovese 2008	?	?	+	?	-	?	+	-	Unclear
Greenwald 2011	?	?	?	?	-	?	+	-	Unclear
Jones 2010	?	?	?	?	-	?	+	-	Unclear
Kavanaugh 2013	+	+	?	?	-	?	+	-	Low
Kay 2008	?	?	+	+	-	?	+	-	Low
Keystone 2004a	?	?	+	+	-	?	+	-	Low

Keystone 2008	?	?	+	?	+	+	+	-	Unclear
Keystone 2009	+	+	+	+	-	+	+	-	Low
Kim 2012	?	?	-	-	-	?	+	-	High
Kremer 2005	+	+	?	?	-	+	+	-	Low
Kremer 2010	+	+	?	+	-	?	+	-	Low
Lan 2004	?	?	?	?	-	-	+	-	Unclear
Maini 1999	+	+	?	?	-	+	+	-	Low
Maini 2006	+	+	+	+	-	+	+	-	Low
Nishimoto 2007	+	+	-	-	-	?	+	-	High
Nishimoto 2009	?	?	?	?	-	?	+	-	Unclear
Pavelka 2009	?	?	?	?	-	?	+	+	Unclear
Putte 2003	?	?	?	?	-	?	+	-	Unclear
Rubbert-Roth 2010	+	+	?	?	-	?	+	-	Low
Smolen 2008	+	+	+	?	-	?	+	-	Low
Smolen 2009	?	?	-	-	?	+	+	-	High
Smolen 2009a	+	+	+	+	-	?	+	-	Low
Smolen 2013	+	+	-	-	-	?	+	-	High
St. Clair 2004	+	+	-	-	-	+	+	-	High
Tada 2012	+	+	-	-	?	?	+	-	High
Tak 2012	?	?	?	?	-	?	+	-	Unclear
Tanaka 2011	?	?	?	?	-	?	+	-	Unclear
Tanaka 2012	?	?	?	?	-	?	+	-	Unclear

Vollenhoven 2012	+	+	-	-	+	?	+	-	High
Vollenhoven 2012a	+	+	?	?	-	?	+	-	Low
Weinblatt 2008	?	?	?	?	-	?	+	-	Unclear
Weinblatt 2013	+	+	?	?	-	?	+	-	Low
Weisman 2007	?	?	?	?	-	?	+	-	Unclear
Westhovens 2006	+	?	+	+	-	+	+	-	Low
Westhovens 2009a	?	?	?	?	-	+	+	-	Unclear
Yazici 2012	?	?	?	?	-	?	+	-	Unclear
Dougados 1999	?	?	+	?	+	?	+	-	Unclear
Haagsma 1997	+	?	?	+	+	?	-	-	Unclear
Hetland 2006	+	+	+	+	+	?	-	-	Low
Ichikawa 2005	?	?	?	+	+	?	+	-	Unclear
Marchesoni 2003	+	?	?	-	+	?	+	+	High
O'Dell 2006	+	+	?	?	-	?	+	?	Low
Taciolglu 2003	?	-	?	-	-	?	+	?	High
Williams 1992	+	?	?	+	?	?	+	+	Unclear
Moreland 2012	+	+	+	+	+	?	-	-	Low
de Jong 2013	+	?	+	-	+	?	-	-	High
Keystone (GO-FORWARD) 2010	+	+	+	+	+	?	?	-	Low
Lipsky 2000	?	?	+	-	-	?	+	-	High
Emery (SERENE)	?	?	?	?	+	?	+	-	Unclear

2010a									
van der Heijde 2013	+	?	+	+	+	?	+	-	Low
Rau 2004	?	?	?	?	+	?	+	-	Unclear
Kremer 2012	?	?	?	+	+	?	+	-	Unclear
Kremer 2010	?	?	+	+	+	?	+	-	Low
O'Dell 2013	?	?	+	?	-	?	+	-	Unclear
Haagsma 1994	?	?	-	-	+	?	+	?	High
Kremer 2002	+	+	+	+	+	?	+	-	Low
Hanyu 1999	?	?	-	-	-	?	+	?	High
Ogrendik 2007	?	?	?	?	+	?	+	?	Unclear
Tugwell 1995	?	?	+	+	+	?	+	-	Low
O'Dell 1996	+	+	+	+	-	?	+	-	Low
Weinblatt (Aug.) 2006	+	+	+	+	-	?	+	-	Low
Cohen 2006	?	?	+	+	-	+	+	-	Low
Weinblatt (Sept.) 2006	?	?	?	?	?	?	-	-	Unclear
Kremer 2009	?	?	?	?	+	?	+	-	Unclear
Heijde (TEMPO) 2007	?	?	+	+	-	-	+	-	Low
Flesichmann (Aug.) 2012	+	+	?	?	?	?	-	-	Low
Bresnihan 1998	?	?	+	+	+	?	+	-	Low
Flesichmann	?	?	?	+	+	?	+	-	Unclear

(March) 2012									
Weinblatt 2012	+	?	?	?	+	?	+	-	Unclear
Choy 2012	+	?	+	+	-	?	+	-	Low
Kaine 2011	?	?	?	+	+	?	+	-	Unclear
Kremer 2013	?	?	?	?	+	?	-	-	Unclear
Takeuchi 2013	?	?	+	+	-	?	+	-	Low
Takeuchi 2013b	+	+	+	+	+	?	+	-	Low
Takeuchi 2014	?	?	+	+	+	?	+	-	Low
Conaghan 2013	+	+	+	+	+	?	+	-	Low
Detert 2013	?	?	+	+	+	?	+	-	Low
Bejarano 2008	+	+	+	+	+	?	+	-	Low
Quinn 2005	+	+	?	+	?	?	-	-	Low
Cohen 2004	?	?	+	?	+	?	+	-	Unclear
Edwards 2004	?	?	?	+	+	-	+	-	Unclear
Schiff 2008	?	?	+	+	+	?	+	-	Low
Emery 2008 (COMET)	+	+	+	+	-	?	+	-	Low
Kremer 2006	+	+	?	+	+	?	+	-	Low
Cohen 2002	?	?	+	?	?	?	+	-	Unclear
Genovese 2004	?	?	+	+	+	?	+	-	Low
Weinblatt 1999	?	?	+	?	+	?	+	-	Unclear
Genovese 2005	?	?	?	+	+	?	+	-	Unclear
Furst 2003	?	?	+	?	+	?	+	-	Unclear

Miyasaka 2008	?	?	?	?	+	+	?	-	Unclear
Van De Putte 2004	+	?	?	?	-	+	+	-	Unclear
Flesichmann 2003	?	?	+	+	+	+	+	-	Low
Kim 2007	?	?	?	?	-	-	+	-	Unclear
Weinblatt 2003	?	?	?	+	+	+	+	-	Unclear

+ = low risk of bias
- = high risk of bias
? = unclear risk of bias

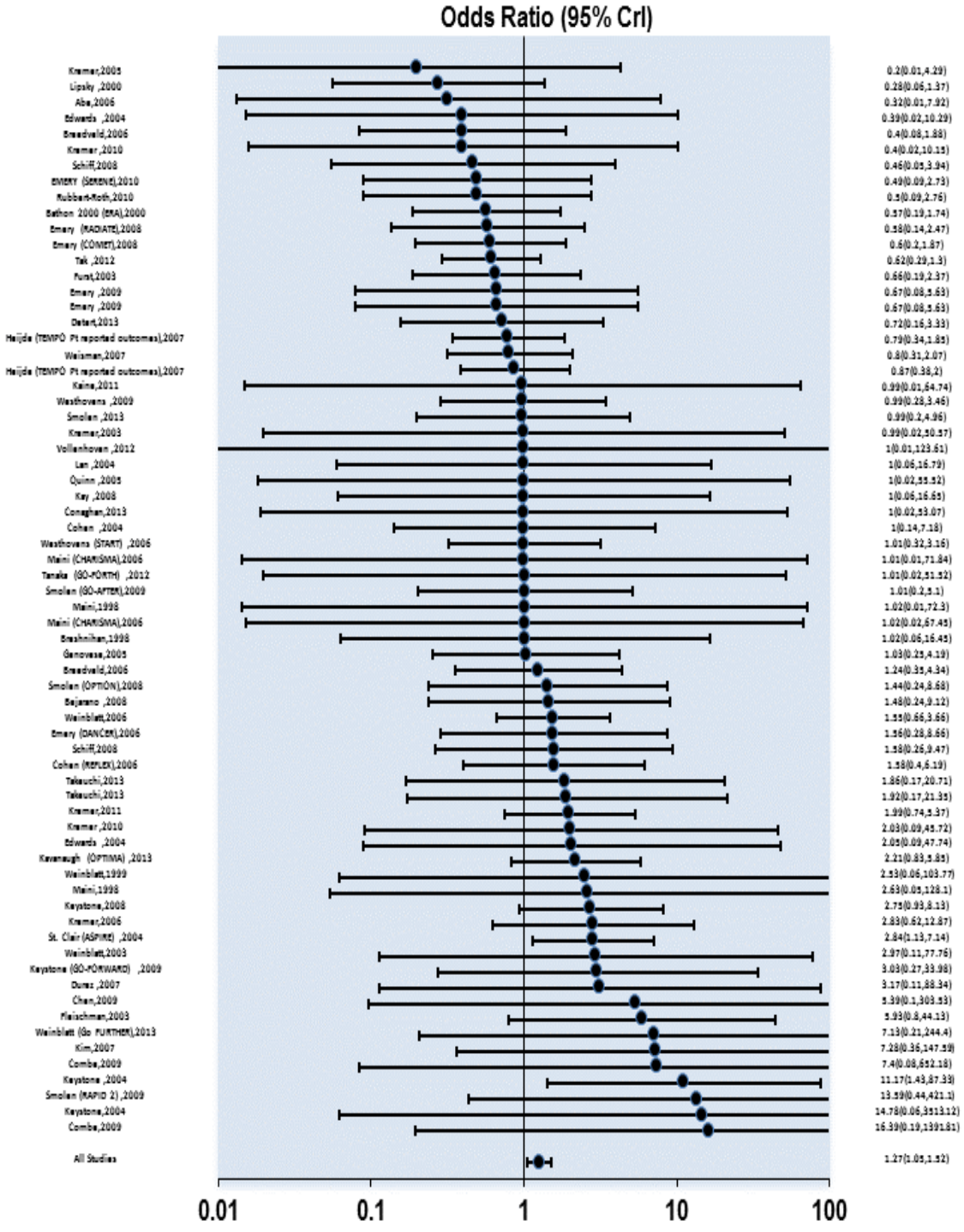
Appendix 6 (on line): Summary of findings from traditional meta-analyses on risk of serious infection for standard dose biologics (Odds ratios (95% CI)) in rheumatoid arthritis

	All Populations	Traditional DMARD naïve	Traditional DMARD experienced	TNF Experienced
All standard dose biologics	1.27(1.05,1.52)	1.05(0.76,1.45)	1.43(1.11,1.83)	1.21(0.71,2.08)
Biologic +/- traditional DMARD				
Abatacept	1.26(0.75,2.11)	0.99(0.28,3.46)	1.19(0.47,3.05)	1.41(0.67,2.90)
Adalimumab	1.86(1.15,3.01)	1.52(0.82,2.80)	2.55(1.16,5.66)	NA
Anakinra	2.71(0.86,8.57)	NA	2.71(0.86,8.57)	NA
Certolizumab	3.61(1.31,9.99)	NA	3.61(1.31,9.99)	NA
Etanercept	0.97(0.60,1.57)	0.60(0.2,1.80)	1.08(0.64,1.85)	NA
Golimumab	1.14(0.41,3.11)	0.67(0.08,5.63)	1.71(0.34,8.67)	1.01(0.2,5.10)
Infliximab	1.33(0.78,2.28)	2.71(1.11,6.62)	0.76(0.37,1.57)	NA
Rituximab	0.75(0.44,1.26)	0.62(0.29,1.30)	0.70(0.28,1.73)	1.58(0.40,6.19)
Tocilizumab	1.35(0.66,2.75)	NA	1.81(0.77,4.22)	0.58(0.14,2.47)
Anti-TNF vs non-TNF biologic				
Anti-TNF biologic	1.34(1.06,1.69)	1.21(0.83,1.77)	1.44(1.07,1.94)	1.01(0.2,5.10)
Non-TNF biologic	1.15(0.85,1.56)	0.7(0.37,1.32)	1.40(0.89,2.18)	1.24(0.70,2.20)
Duration of follow-up				
Less than 6 months	1.07(0.66,1.73)	NA	1.16(0.69,1.94)	0.58(0.14,2.47)
6 to 12 months	1.59(1.15,2.19)	1.37(0.70,2.71)	1.77(1.18,2.67)	1.21(0.53,2.79)
Greater than or equal to 12 months	1.14(0.88,1.47)	0.97(0.67,1.40)	1.28(0.86,1.92)	1.55(0.66,3.66)
Duration of Rheumatoid arthritis				
Early RA - less than 2 years	1.07(0.77,1.48)	1.07(0.77,1.49)	1.00(0.06,16.79)	NA
Established RA - 2 to 10 years	1.35(1.02,1.77)	0.67(0.15,3.02)	1.39(1.05,1.85)	1.01(0.2,5.10)
Late RA - greater than 10 years	1.418(0.96,2.07)	NA	1.57(0.93,2.63)	1.24(0.70,2.20)
Biologic Monotherapy				
Biologic used in combination with Traditional DMARD	1.34(1.09,1.69)	1.17(0.82,1.67)	1.47(1.12,1.92)	1.21(0.71,2.083)
Biologic not used in combination with Traditional DMARD	0.89(0.54,1.48)	0.61(0.27,1.34)	1.18(0.60,2.34)	NA
Traditional DMARD monotherapy vs. combination therapy				
Traditional DMARD monotherapy	1.27(1.05,1.52)	1.05(0.76,1.45)	1.43 (1.11,1.84)	1.21(0.71,2.08)
Traditional DMARD combination or triple therapy*	1.85(0.85,4.10)	1.21(0.38,3.79)	2.68(0.88,8.23)	NA
Year of study				
1995-1999	1.59(0.29,8.79)	NA	1.59(0.29,8.79)	NA
2000-2004	1.63(1.07,2.48)	1.54(0.80,2.96)	1.69(0.98,2.93)	NA

2005-2009	1.22(0.95,1.56)	0.85(0.50,1.45)	1.39(1.002,1.93)	1.21(0.71,2.08)
2010-2014	1.11(0.76,1.62)	1.00(0.60,1.67)	1.25(0.71,2.20)	NA
Risk of Bias				
Studies with low risk of bias	1.31(1.02,1.69)	1.05(0.66,1.67)	1.43(1.01,2.03)	1.46(0.75,2.81)
Studies with high risk of bias	1.34(0.80,2.25)	1.54(0.80,2.96)	1.50(1.02,2.22)	NA
Studies with unclear risk of bias	1.18(0.87,1.61)	0.74(0.40,1.38)	1.05(0.45,2.48)	0.78(0.29,2.09)
Use of corticosteroids				
Remove RCTs, with greater than 5% difference in proportion of patients using corticosteroids between arms or do not report data	1.44(1.12,1.85)	1.20(0.82,1.77)	1.65(1.13,2.40)	1.56 (0.75,3.22)
Remove RCTs with greater than 10% difference in proportion of patients using corticosteroids between arms or do not report data	1.27(1.01,1.61)	1.20(0.82,1.77)	1.34(0.96,1.87)	1.24(0.70,2.20)

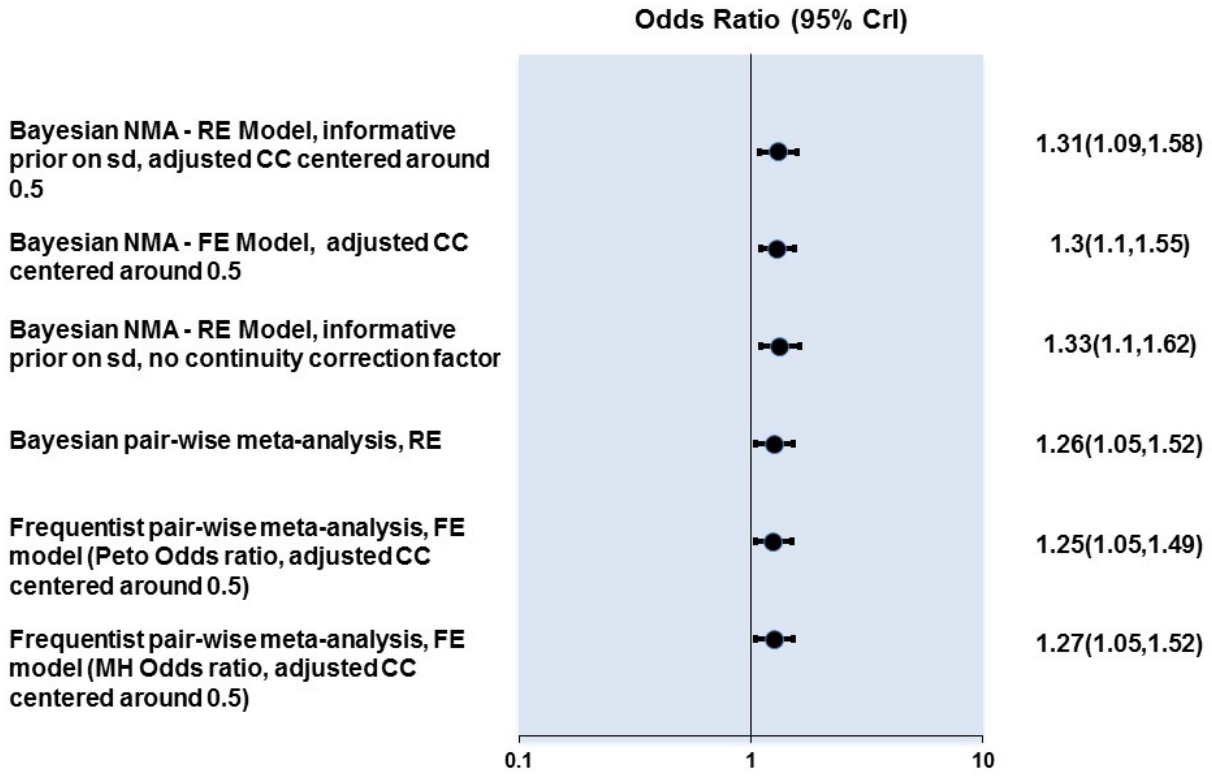
* Studies using Traditional DMARD combination or triple therapy are not included in other calculations because they are treated as separate nodes in evidence network CI= confidence interval; DMARD= disease-modifying antirheumatic drugs; MTX=methotrexate; TNF= Tumor necrosis factors; NA=not available

Appendix 6a. Forest plot for traditional meta-analyses on risk of serious infection for stanc
dose biologics (Odds ratios (95% CI)) in rheumatoid arthritis



Appendix 7 (on line): Summary of sensitivity analyses for Bayesian network meta-analysis (95% Credible interval)

We did not exclude double/multiple zeroes cells from the Primary analysis to provide analytic consistency and because exclusion may cause an artificial small increase the effect size of serious infection.[2] Since treatment arms within some studies have differential sample size, we did not apply a constant 0.5 continuity correction, which would have biased estimates but instead applied an adjusted continuity correction factor centered around 0.5 and accounting for differential sample sizes among the arms.[1] Further, we conducted numerous analyses to ensure robustness of results irrespective of how zeroes were handled.[1] Results were similar using a variety of statistical methods:



CC= continuity correction; FE= fixed-effects; MH= Mantel–Haenszel; NMA= network meta-analysis; RE= random-effects; sd= standard deviation

Appendix 8 (on line): Comparison of fixed versus random-effects model of therapies compared to traditional DMARD therapy, using Bayesian network meta-analysis (95% Credible interval)

	Fixed-effects model	Random-Effects model
Combination or triple traditional DMARD therapy vs. Traditional DMARD monotherapy	0.85 (0.48,1.47)	0.84 (0.48,1.48)
SD Biologic +/- Traditional DMARD vs. Traditional DMARD monotherapy	1.3 (1.1,1.55)	1.31 (1.09,1.58)
LD Biologic +/- Traditional DMARD vs. Traditional DMARD monotherapy	0.94 (0.66,1.33)	0.93 (0.65,1.33)
HD Biologic +/- Traditional DMARD vs. Traditional DMARD monotherapy	1.88 (1.51,2.34)	1.9 (1.5,2.39)
Combination Biologic vs. Traditional DMARD monotherapy	4.05 (1.89,8.42)	4.14 (1.87,9.05)

DMARD= disease-modifying antirheumatic drugs; HD= high dose; LD= low dose; SD= standard dose; DIC, deviance information criterion

* Model includes double zero cells rather than excluding double zeroes, which may inflate serious infection risk estimates. However, inclusion of double zeroes also artificially improves the model fit statistics

Appendix 9 (on line): Summary of findings from Bayesian network meta-analyses (NMA) on the risk of serious infection (Odds ratios (95% CrI) for all doses of biologics in rheumatoid arthritis*

	All Populations (106 Studies; N=42,330)	MTX naïve (24 Studies; N=8,775)	MTX experienced (71 Studies; N=29,167)	TNF Experienced (11 Studies; N=4,788)
Compared to traditional DMARD monotherapy				
MTX + non-MTX traditional DMARD	0.84(0.48,1.48)	0.99(0.44,2.14)	0.73(0.3,1.69)	NA
SD Biologic +/- Traditional DMARD	**1.31(1.09,1.58)**	1.08(0.75,1.53)	**1.48(1.17,1.9)**	1.17(0.65,2.18)
LD Biologic +/- Traditional DMARD	0.93(0.65,1.33)	0.93(0.47,1.8)	0.99(0.61,1.58)	NA
HD Biologic +/- Traditional DMARD	**1.9(1.5,2.39)**	1.73(0.89,3.52)	**2.07(1.57,2.74)**	1.53(0.68,3.51)
Combination Biologic	**4.14(1.87,9.05)**	NA	**69.52(2.89,580200)**	**3.08(1.09,8.51)**
Placebo	0.57(0.19,1.28)	NA	0.64(0.23,1.47)	NA
Compared to combination or triple traditional DMARD therapy				
SD Biologic +/- Traditional DMARD	1.56(0.9,2.73)	1.08(0.5,2.54)	2.04(0.89,4.94)	NA
LD Biologic +/- Traditional DMARD	1.11(0.59,2.14)	0.94(0.34,2.62	1.36(0.53,3.58)	NA
HD Biologic +/- Traditional DMARD	**2.26(1.26,4.07)**	1.73(0.66,5.09	**2.83(1.2,7.01)**	NA
Combination Biologic	**4.94(1.88,12.77)**	NA	**97.06(3.57,836800)**	NA
Placebo	0.67(0.2,1.74)	NA	0.87(0.23,2.92)	NA
Compared to SD Biologic +/- traditional DMARD				
LD Biologic +/- Traditional DMARD	0.71(0.5,1.01)	0.86(0.43,1.66)	0.67(0.42,1.03)	NA
HD Biologic +/- Traditional DMARD	**1.45(1.16,1.81)**	1.59(0.84,3.2)	**1.4(1.06,1.8)**	1.31(0.57,3)
Combination Biologic	**3.15(1.45,6.92)**	NA	**46.43(2,387900)**	2.63(0.99,6.62)
Placebo	0.44(0.15,0.96)	NA	0.43(0.16,0.96)	NA
Compared to LD Biologic +/- traditional DMARD				
HD Biologic +/- Traditional DMARD	**2.03(1.38,3.02)**	1.86(0.76,4.81)	**2.09(1.31,3.43)**	NA
Combination Biologic	**4.44(1.9,10.45)**	NA	**70.91(2.88,562000)**	NA
Placebo	0.61(0.2,1.45)	NA	0.64(0.23,1.54)	NA
Compared to HD Biologic +/- traditional DMARD				
Combination Biologic	2.18(0.96,4.92)	NA	**33.67(1.42,287000)**	2(0.59,6.6)
Placebo	**0.3(0.1,0.67)**	NA	**0.31(0.11,0.7)**	NA
Compared to Combination Biologic				
Placebo	**0.14(0.04,0.43)**	NA	**0.01(0,0.25)**	NA

CrI= credible interval; DMARD= disease-modifying antirheumatic drugs; TNF= Tumor necrosis factors; NA=not available

* Tofacitinib was included in the network to enhance precision of biologic effect estimates.

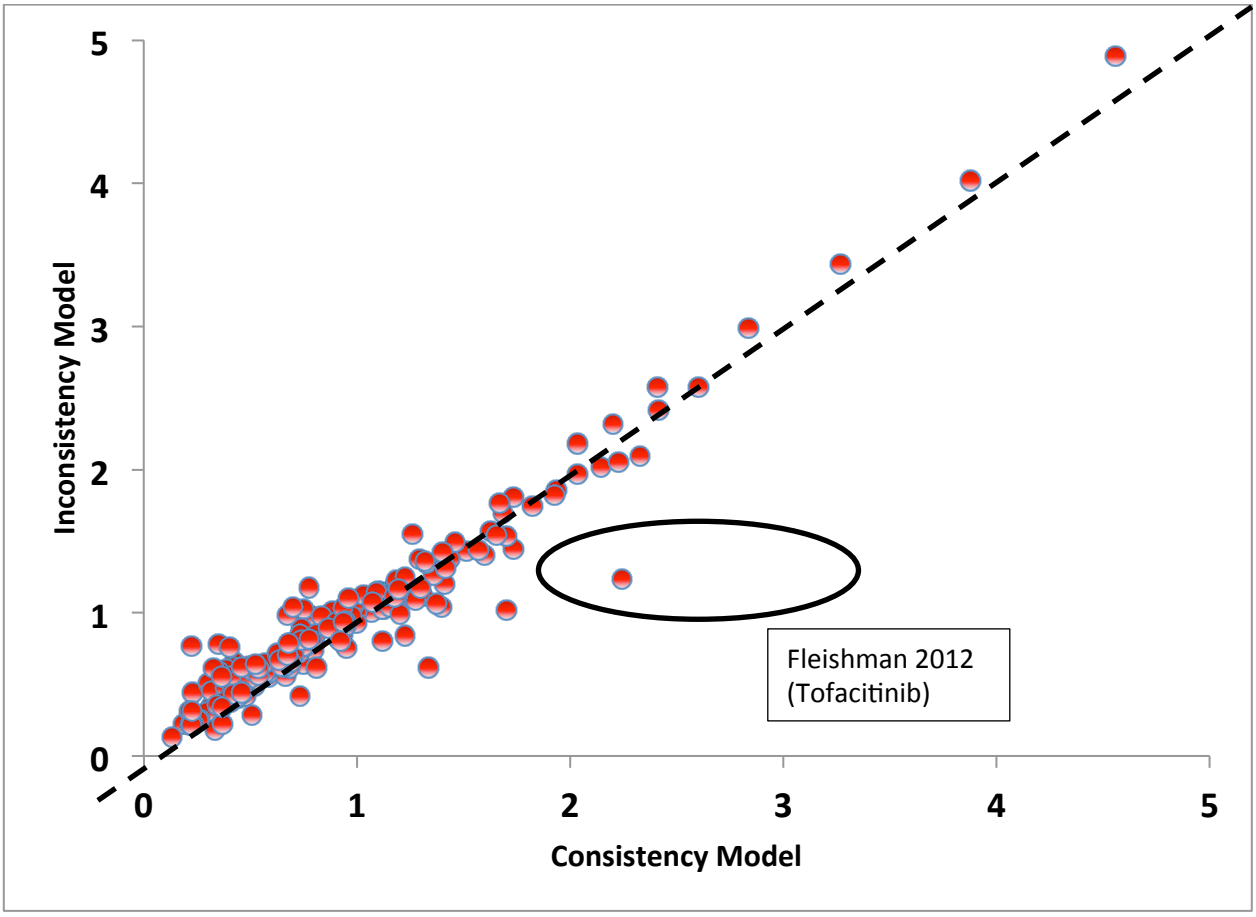
Appendix 9a. Summary of findings from Bayesian network meta-analyses on risk of serious infection (Odds ratios (95% CrI)) - All populations. Odds ratios for serious infections are calculated based on row-defining treatment versus column-defining treatment. To obtain ORs for comparisons in the opposite direction, reciprocals should be taken. Significant results are in bold.

Traditional DMARD monotherapy						
0.84 (0.48,1.48)	Combination or triple DMARD therapy					
1.31 (1.09,1.58)	1.56 (0.9,2.73)	SD Biologic +/- Traditional DMARD				
0.93 (0.65,1.33)	1.11 (0.59,2.14)	0.71 (0.5,1.01)	LD Biologic +/- Traditional DMARD			
1.9 (1.5,2.39)	**2.26 (1.26,4.07)**	**1.45 (1.16,1.81)**	**2.03 (1.38,3.02)**	HD Biologic +/- Traditional DMARD		
4.14 (1.87,9.05)	**4.94 (1.88,12.77)**	**3.15 (1.45,6.92)**	**4.44 (1.9,10.45)**	2.18 (0.96,4.92)	Combination Biologic	
0.57 (0.19,1.28)	0.67 (0.2,1.74)	**0.44 (0.15,0.96)**	0.61 (0.2,1.45)	**0.3 (0.1,0.67)**	**0.14 (0.04,0.43)**	Placebo

Appendix 10 (on line): Assessment of inconsistency

We plotted the posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model to help identify loops where inconsistency is present. In our analysis, the posterior mean deviance contributions are very similar and close to 1, for both models. The consistency model has a lower posterior mean of the residual deviance (225.6 vs. 229.1 each versus 265) and DIC (1040.87 vs. 1048.45) and hence is a better fit. One point shows a lower value of the posterior mean deviance in the inconsistency model but these values are not too far from 1. This point is from the Fleishman 2012 study that compares different doses of tofacitinib with placebo.

Appendix 10a- Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



The effect estimates for Combination or triple traditional DMARD therapy vs Traditional DMARD monotherapy, SD Tofacitinib +/- Traditional DMARD vs Traditional DMARD monotherapy, HD Biologic +/- Traditional DMARD vs SD Biologic +/- Traditional DMARD, and Placebo vs SD Tofacitinib +/- Traditional DMARD are also on different sides of unity.

Appendix 10b - Comparison of effect estimates from consistency and inconsistency models where there were data available for comparison

Comparison	Consistency Model	Inconsistency Model
Combination or triple traditional DMARD therapy vs Traditional DMARD monotherapy	0.84(0.48,1.48)	1.07(0.53,2.13)
SD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	**1.31(1.09,1.58)**	**1.26(1.05,1.52)**
LD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	0.93(0.65,1.33)	0.87(0.59,1.29)
HD Biologic +/- Traditional DMARD vs Traditional DMARD monotherapy	**1.9(1.5,2.39)**	**1.95(1.51,2.49)**
Combination Biologic vs Traditional DMARD monotherapy	**4.14(1.87,9.05)**	**3.06(1.02,7.81)**
SD Biologic +/- Traditional DMARD vs Combination or triple traditional DMARD therapy	1.56(0.90,2.73)	2.98(1.04,9.14)
LD Biologic +/- Traditional DMARD vs SD Biologic +/- Traditional DMARD	0.71(0.50,1.01)	0.7(0.27,1.68)
HD Biologic +/- Traditional DMARD vs SD Biologic +/- Traditional DMARD	**1.45(1.16,1.81)**	1(0.54,1.82)
Combination Biologic vs SD Biologic +/- Traditional DMARD	**3.15(1.45,6.92)**	**12.42(1.98,378.8)**
Placebo vs SD Biologic +/- Traditional DMARD	0.44(0.15,0.96)	0.26(0.07,0.74)

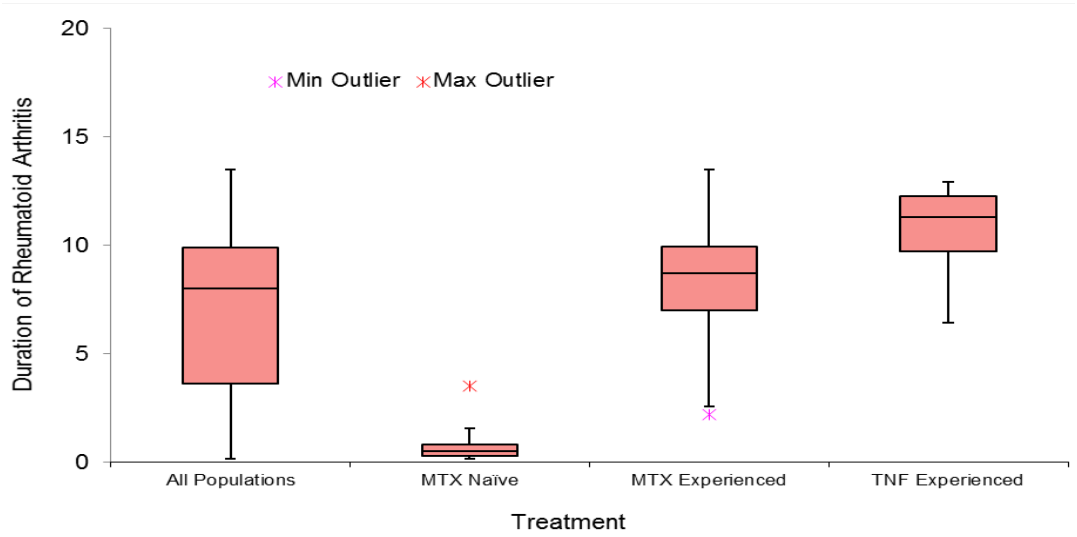
Appendix 11(on line): Summary of published meta-analyses assessing the risk of serious infection in patients with rheumatoid arthritis

Study	No. of RCTs	No. of patients	Biologics considered in Study	Search dates	Population Considered			Conclusion
					MTX naïve	MTX experienced	TNF experienced	
Bongartz 2006	9	5,005	Infliximab, adalimumab	Up to December 2005	Yes	Yes	No	Increased risk of serious infections in patients with rheumatoid arthritis treated with anti-TNF antibody therapy
Salliot et al 2009	12	6,879	rituximab, abatacept, anakinra	Up to October 2007	Yes	Yes	Yes	No increased risk of serious infections in patients with rheumatoid arthritis treated with biologics
Leombruno 2008	18	8,808	Infliximab, adalimumab, etanercept	Up to December 2007	Yes	Yes	Yes	No increased risk of serious infections in patients with rheumatoid arthritis treated with biologics
Thompson et al 2012	6	3,419	Infliximab, adalimumab, etanercept	Up to August 2009	Yes	No	No	No increased risk of serious infections in patients with rheumatoid arthritis treated with biologics

MTX=methotrexate; No= Number; RCT= randomized controlled trial; No= Number; TNF= tumor necrosis factor alpha

Appendix 12 (on line): Box-plots comparing characteristics of populations

Duration of rheumatoid arthritis



Duration of follow-up