Supplementary Materials

Efficacy of Monotherapy With Biologics and JAK Inhibitors for the Treatment of Rheumatoid Arthritis: A Systematic Review

Biodrugs

Paul Emery · Janet E. Pope · Klaus Kruger · Ralph Lippe · Ryan DeMasi · Sadiq Lula · Blerina Kola

Corresponding Author: Professor Paul Emery, Leeds Musculoskeletal Biomedical Research Unit, LTHT and Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Leeds, LS7 4SA, UK.

Email: p.emery@leeds.ac.uk

Supplementary Table 1 Electronic literature sources utilized for search

MEDLINE®/Medline In process & other non-indexed citations via Ovid
Embase® via Ovid
Cochrane Central Trials Register and Database of Systematic Reviews and other Cochrane Library assets

Supplementary Table 2 Electronic database search strategies: Ovid MEDLINE® in-process & other non-indexed citations and Ovid MEDLINE® 1946 to 11 April 2017

S/N	Search terms	Parameter
1	exp rheumatoid arthritis/	Disease
2	rheumatoid arthritis.tw.	
3	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.	
4	(felty$ adj2 syndrome).tw.	
5	(caplan$ adj2 syndrome).tw.	
6	(sjogren$ adj2 syndrome).tw.	
7	(sicca adj2 syndrome).tw.	
8	still$ disease.tw.	
9	or/1-8	
10	(Etanercept or Enbrel or TNR001 or "TNR 001" or ETA or ETN).mp.	Intervention
11	(certolizumab or CDP870 or CDP 870 or PHA738144 or PHA 738144 or Cimzia).mp.	
12	(certolizumab adj2 pegol).mp.	
13	(Tocilizumab or actemra or atlizumab).mp.	
14	(Adalimumab or humira or hum?ra or trudexa).mp.	
15	(Abatacept or orencia or nulojix or belatacept or LEA29Y or BMS-224818 or BMS 188667).mp.	
16	(anakinra or kineret or interleukin-1 or IL-1).mp.	
17	(Tofacitinib or tasocitinib or jakvinus or xeljanz or cp690550 or cp 690550 or cp 690 550).mp	
18	(baracitinib or olumiant or LY3009104 or LY 3009104 or INCB028050 or INCB 028050).mp	
19	sarilumab.mp	
20	(Sirukumab or CNTO136 or CNTO 136).mp	
21	or/10-20	
22	9 and 21	
23	randomized controlled trial.pt.	Study design
24	controlled clinical trial.pt.	
25	randomi?ed.ab.	

26	placebo.tw.	
27	drug therapy.fs.	
28	clinical trials as topic.sh.	
29	randomly.ab.	
30	trial.ab.	
31	groups.ab.	
32	(crossover or cross-over or cross over).tw.	
33	((singl$ or double$ or triple$ or treble$) and (blind$ or mask$)).tw,sh.	
34	(case control or case-control).ti,ab.	
35	or/23-34	
36	(animals not (humans and animals)).sh.	
37	22 and 35	
38	37 not 36	
39	limit 38 to English language	

Supplementary Table 3 Electronic database search strategies: Embase® 1974 to 2017 week 15

S/N	Search terms	Parameter
1	exp rheumatoid arthritis/	Disease
2	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat$ or reumat$ or revmarthrit$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.	
3	(felty$ adj2 syndrome).tw.	
4	(caplan$ adj2 syndrome).tw.	
5	(sjogren$ adj2 syndrome).tw	
6	(sicca adj2 syndrome).tw.	
7	still$ disease.tw	
8	or/1-7	
9	(Adalimumab or Humira or Hum?ra or Trudexa).mp.	Intervention
10	(certolizumab or CDP870 or CDP 870 or PHA738144 or PHA 738144 or Cimzia).mp.	
11	(certolizumab adj2 pegol).mp.	
12	(Etanercept or Enbrel or TNR001 or "TNR 001" or ETA or ETN).mp.	
13	(Tocilizumab or actemra or atlizumab).mp.	
14	(Abatacept or orencia or nulojix or belatacept or LEA29Y or BMS-224818 or BMS 188667).mp.	
15	(anakinra or kineret or interleukin-1 or IL-1).mp.	
16	(Tofacitinib or tasocitinib or jakvinus or xeljanz or cp690550 or cp 690550 or cp 690 550).mp	
17	(baracitinib or olumiant or LY3009104 or LY 3009104 or INCB028050 or INCB 028050).mp	
18	sarilumab.mp	
19	(Sirukumab or CNTO136 or CNTO 136).mp	
20	or/9-19	
21	8 and 20	
22	(random$ or placebo$).ti,ab	
23	clinical trial/	Study design
24	random$.tw.	
25	randomized controlled trial/	

26	trial$.tw.	
27	controlled study/	
28	double blind procedure/	
29	placebo$.tw.	
30	(singl$ adj (blind$ or mask$)).tw.	
31	(crossover$ or cross-over$).ti,ab.	
32	(double$ adj (blind$ or mask$)).tw.	
33	Crossover Procedure/	
34	Single Blind Procedure/	
35	((triple$ or treble$) adj (blind$ or mask$)).tw.	
36	(case control or case-control).ti,ab.	
37	or/22-36	
38	(animal$ not human$).sh,hw.	
39	21 and 37	
40	39 not 38	
41	Limit 40 to English language	

Supplementary Table 4 Electronic database search strategies: Cochrane Library (Run 11 April 2017)

S/N	Search terms	Parameter
1	MeSH descriptor: [Arthritis, Rheumatoid] explode all trees	Disease
2	rheumatoid arthritis:ti,ab,kw	
3	((rheumatoid or reumatoid or revmatoid or rheumatic or reumatic or revmatic or rheumat* or reumat* or revmarthrit*) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab,kw	
4	(felty* near/2 syndrome):ti,ab,kw	
5	(caplan* near/2 syndrome). ti,ab,kw	
6	(sjogren* near/2 syndrome). ti,ab,kw	
7	(sicca near/2 syndrome). ti,ab,kw	
8	still* disease. ti,ab,kw	
9	#1 or #2 or #3 or #4 or #5 or #6 or #7 or #8	
10	(Etanercept or Enbrel or TNR001 or "TNR 001" or ETA or ETN):ti,ab,kw	Intervention
11	(certolizumab or CDP870 or CDP 870 or PHA738144 or PHA 738144 or Cimzia):ti,ab,kw	
12	(certolizumab near/2 pegol):ti,ab,kw	
13	(adalimumab or humira or hum?ra or trudexa):ti,ab,kw	
14	(Tocilizumab or actemra or atlizumab):ti,ab,kw	
15	(Abatacept or orencia or nulojix or belatacept or LEA29Y or BMS-224818 or BMS 188667):ti,ab,kw	
16	(anakinra or kineret or interleukin-1 or IL-1):ti,ab,kw	
17	(Tofacitinib or tasocitinib or jakvinus or xeljanz or cp690550 or cp 690550 or cp 690 550):ti, ab, kw	
18	(baracitinib or olumiant or LY3009104 or LY 3009104 or INCB028050 or INCB 028050):ti,ab,kw	
19	Sarilumab:ti,ab.kw	
20	(Sirukumab or CNTO136 or CNTO 136):ti,ab,kw	
21	#10 or #11 or #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or#20	
22	#9 and #21	

Supplementary Table 5 Quality assessment of full-length publications

First Author, Date	Randomization	Concealment	Baseline characteristics	Blinding	Withdrawals	Outcome selection and reporting	Statistical analysis
Aletaha et al, 2017 [1]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Bathon et al, 2000 [2]	Unclear	Unclear	Low risk	Low risk	Low risk	Unclear	Unclear
Breedveld et al, 2006 [3]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Burmester et al, 2016 [4]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Burmester et al, 2017 [5]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Combe et al, 2006 [6]	Low risk	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk
Combe et al, 2009 [7]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Dougados et al, 2013 [8]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Emery et al, 2015 [9]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Fleischmann et al, 2009 [10]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fleischmann et al, 2012 [11]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Fleischmann et al, 2012 [12]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Fleischmann et al, 2016 [13]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Fleischmann et al, 2017 [14]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Gabay et al, 2013 [15]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Genovese et al, 2004 [16]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Hu et al, 2009 [17]	Low risk	Unclear	Low risk	Unclear	Low risk	High risk	Unclear
Johnsen et al, 2006 [18]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Jones et al, 2010 [19]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Kameda et al, 2010 [20]	Low risk	Low risk	Low risk	High risk	Low risk	Low risk	Low risk
Kawashiri et al, 2011 [21]	Low risk	Low risk	Low risk	Unclear	Unclear	Low risk	Low risk
Klareskog et al, 2004 [22]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Kremer et al, 2009 [23]	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk
Mathias et al, 2000 [24]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Miyasaka et al, 2008 [25]	Low risk	Unclear	Low risk	Unclear	Low risk	Low risk	Low risk

Moreland et al, 1999 [26]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
Moreland et al, 2002 [27]	Unclear	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Nishimoto et al, 2004 [28]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Nishimoto et al, 2007 [29]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Nishimoto et al, 2009 [30]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ogata et al, 2014 [31]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Ogata et al, 2015 [32]	Low risk	Low risk	High risk	Low risk	Low risk	Low risk	Low risk
Popa et al, 2005 [33]	Unclear	Unclear	Unclear	Unclear	High risk	High risk	Low risk
Strand et al, 2015 [34]	Low risk	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk
Strand et al, 2016 [35]	Low risk	Low risk	Low risk	Unclear	Low risk	Low risk	Low risk
Takeuchi et al, 2013 [36]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Tanaka et al, 2015 [37]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
van de Putte et al, 2004 [38]	Low risk	Low risk	Low risk	Low risk	High risk	Low risk	Low risk
van der Heijde et al, 2006 [39]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
van der Heijde et al, 2007 [40]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Weinblatt et al, 2007 [41]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Weinblatt et al, 2012 [42]	Low risk	Unclear	Low risk	Low risk	Low risk	Low risk	Low risk
Weinblatt et al, 2013 [43]	Low risk	Unclear	High risk	High risk	Low risk	Low risk	Low risk
Yamamoto et al, 2014 [44]	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Study questions:

Was randomization carried out appropriately?

Was the concealment of treatment allocation adequate?

Were the groups similar at the outset of the study in terms of prognostic factors, for example, severity of disease?

Were the care providers, participants, and outcome assessors blind to treatment allocation? If any of these people were not blinded, what might be the likely impact on the risk of bias (for each outcome)?

Were there any unexpected imbalances in drop-outs between groups? If so, were they explained or adjusted for?

Is there any evidence to suggest that the authors measured more outcomes than they reported?

Did the analysis include an intention-to-treat analysis? If so, was this appropriate and were appropriate methods used to account for missing data?

Supplementary Table 6 Quality scoring of randomized and non-randomized studies from conference proceedings based on simplified Downs and Black

First author, Date	Total score	Reporting				External Validity	Internal validity – bias			Internal validity – confounding			
		1	2	3	4	5	6	7	8	9	10	11	12
Alten et al, 2014 [45]	7	1	1	1	0	0	1	1	1	0	0	1	0
Burmester et al, 2013 [46]	7	1	1	1	0	0	1	1	1	0	0	1	0
Burmester et al, 2014 [47]	7	0	1	1	0	0	1	1	1	0	0	1	1
Burmester et al, 2014 [48]	6	0	1	1	0	0	1	1	1	0	0	1	0
Burmester et al, 2015 [49]	6	0	1	1	1	0	0	1	1	0	0	1	0
Burmester et al, 2016 [50]	9	1	1	1	1	0	1	1	1	0	0	1	1
Charles-Schoeman et al, 2016 [51]	6	0	1	1	0	0	1	1	1	0	0	1	0
Durez et al, 2013 [52]	8	1	1	1	1	0	0	1	1	0	0	1	1
Emery et al, 2014 [53]	6	1	1	1	0	0	0	0	1	0	0	1	1
Fleischmann et al, 2014 [54]	6	0	1	1	0	0	1	1	1	0	0	1	0
Fleischmann et al, 2015 [55]	7	1	1	1	0	0	0	1	1	0	0	1	1
Fleischmann et al, 2015 [56]	5	0	1	1	0	0	0	1	1	0	0	1	0
Fleischmann et al, 2015 [57]	7	1	1	1	0	0	1	1	1	0	0	1	0
Furst et al, 2015 [58]	6	1	1	1	0	0	0	1	1	0	0	1	0
Herold et al, 2015 [59]	6	0	1	1	1	0	0	1	1	0	0	1	0
Kameda et al, 2010 [60]	7	1	1	1	0	0	1	1	1	0	0	1	0
Lee et al, 2012 [61]	7	1	1	1	0	0	1	0	1	0	0	1	1
Ogata et al, 2016 [62]	9	1	1	1	1	0	1	1	1	0	0	1	1
Pablos et al, 2015 [63]	7	0	1	1	1	0	1	1	1	0	0	1	0
Strand et al, 2016 [64]	8	1	1	1	1	0	1	1	1	0	0	1	0
Strand et al, 2016 [65]	5	0	1	1	0	0	0	1	1	0	0	1	0
Takeuchi et al, 2013 [66]	7	1	1	1	1	0	0	1	1	0	0	1	0
Takeuchi et al, 2015 [67]	7	1	1	1	0	0	1	1	1	0	0	1	0
Takeuchi et al, 2016 [68]	7	1	1	1	0	0	1	1	1	0	0	1	0
Tanaka et al, 2011 [69]	7	1	1	1	0	0	1	0	1	0	0	1	1

Taylor et al, 2016 [70]	9	1	1	1	1	0	1	1	1	0	0	1	1
Yazici et al, 2015 [71]	6	1	1	1	0	0	0	1	1	0	0	1	0

Study questions:

1. Is the hypothesis/aim/objective of the study clearly described?

2. Are the interventions of interest clearly described?

3. Are the main findings of the study clearly described?

4. Does the study provide estimates of the random variability in the data for the main outcomes?

5. Were the subjects asked to participate in the study representative of the entire population from which they were recruited?

6. Was an attempt made to blind study subjects to the intervention they have received?

7. Were the statistical tests used to assess the main outcomes appropriate?

8. Were the main outcome measures used accurate (valid and reliable)?

9. Were the patients in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited from the same population?

10. Were study subjects in different intervention groups (trials and cohort studies) or were the cases and controls (case-control studies) recruited over the same period of time?

11. Were study subjects randomized to intervention groups?

12. Were losses of patients to follow-up taken into account?

Yes=1, No=0, Unable to determine=0

References

1. Aletaha D, Bingham CO, 3rd, Tanaka Y, Agarwal P, Kurrasch R, Tak PP et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. Lancet. 2017;389(10075):1206-17. doi: 10.1016/S0140-6736(17)30401-4.
2. Bathon JM, Martin RW, Fleischmann RM, Tesser JR, Schiff MH, Keystone EC et al. A comparison of etanercept and methotrexate in patients with early rheumatoid arthritis. N Engl J Med. 2000;343(22):1586-93. doi: 10.1056/NEJM200011303432201.
3. Breedveld FC, Weisman MH, Kavanaugh AF, Cohen SB, Pavelka K, van Vollenhoven R 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. doi: 10.1002/art.21519 [doi].
4. Burmester GR, Rigby WF, van Vollenhoven RF, Kay J, Rubbert-Roth A, Kelman A et al. Tocilizumab in early progressive rheumatoid arthritis: FUNCTION, a randomised controlled trial. Ann Rheum Dis. 2016;75(6):1081-91. doi: 10.1136/annrheumdis-2015-207628.
5. Burmester GR, Lin Y, Patel R, van Adelsberg J, Mangan EK, Graham NM et al. Efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy for the treatment of patients with active rheumatoid arthritis (MONARCH): a randomised, double-blind, parallel-group phase III trial. Ann Rheum Dis. 2017;76(5):840-7. doi: 10.1136/annrheumdis-2016-210310.
6. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK et al. Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. Ann Rheum Dis. 2006;65(10):1357-62. doi: 10.1136/ard.2005.049650.
7. Combe B, Codreanu C, Fiocco U, Gaubitz M, Geusens PP, Kvien TK et al. Efficacy, safety and patient-reported outcomes of combination etanercept and sulfasalazine versus etanercept alone in patients with rheumatoid arthritis: a double-blind randomised 2-year study. Ann Rheum Dis. 2009;68(7):1146-52. doi: 10.1136/ard.2007.087106.
8. Dougados M, Kissel K, Sheeran T, Tak PP, Conaghan PG, Mola EM et al. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). Ann Rheum Dis. 2013;72(1):43-50. doi: 10.1136/annrheumdis-2011-201282.
9. Emery P, Burmester GR, Bykerk VP, Combe BG, Furst DE, Barre E et al. Evaluating drug-free remission with abatacept in early rheumatoid arthritis: results from the phase 3b, multicentre, randomised, active-controlled AVERT study of 24 months, with a 12-month, double-blind treatment period. Ann Rheum Dis. 2015;74(1):19-26. doi: 10.1136/annrheumdis-2014-206106.
10. Fleischmann R, Vencovsky J, van Vollenhoven RF, Borenstein D, Box J, Coteur G et al. Efficacy and safety of certolizumab pegol monotherapy every 4 weeks in patients with rheumatoid arthritis failing previous disease-modifying antirheumatic therapy: the FAST4WARD study. Ann Rheum Dis. 2009;68(6):805-11. doi: 10.1136/ard.2008.099291.
11. Fleischmann R, Kremer J, Cush J, Schulze-Koops H, Connell CA, Bradley JD et al. Placebo-controlled trial of tofacitinib monotherapy in rheumatoid arthritis. N Engl J Med. 2012;367(6):495-507. doi: 10.1056/NEJMoa1109071.

12. Fleischmann R, Cutolo M, Genovese MC, Lee EB, Kanik KS, Sadis S et al. Phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) or adalimumab monotherapy versus placebo in patients with active rheumatoid arthritis with an inadequate response to disease-modifying antirheumatic drugs. Arthritis Rheum. 2012;64(3):617-29. doi: 10.1002/art.33383.
13. Fleischmann RM, Huizinga TW, Kavanaugh AF, Wilkinson B, Kwok K, DeMasi R et al. Efficacy of tofacitinib monotherapy in methotrexate-naive patients with early or established rheumatoid arthritis. RMD Open. 2016;2(2):e000262. doi: 10.1136/rmdopen-2016-000262.
14. Fleischmann R, Schiff M, van der Heijde D, Ramos-Remus C, Spindler A, Stanislav M et al. Baricitinib, methotrexate, or combination in patients with rheumatoid arthritis and no or limited prior disease-modifying antirheumatic drug treatment. Arthritis Rheumatol. 2017;69(3):506-17. doi: 10.1002/art.39953.
15. Gabay C, Emery P, van Vollenhoven R, Dikranian A, Alten R, Pavelka K et al. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. Lancet. 2013;381(9877):1541-50. doi: 10.1016/S0140-6736(13)60250-0.
16. Genovese MC, Cohen S, Moreland L, Lium D, Robbins S, Newmark R et al. Combination therapy with etanercept and anakinra in the treatment of patients with rheumatoid arthritis who have been treated unsuccessfully with methotrexate. Arthritis Rheum. 2004;50(5):1412-9. doi: 10.1002/art.20221 [doi].
17. Hu D, Bao C, Chen S, Gu J, Li Z, Sun L et al. A comparison study of a recombinant tumor necrosis factor receptor:Fc fusion protein (rhTNFR:Fc) and methotrexate in treatment of patients with active rheumatoid arthritis in China. Rheumatol Int. 2009;29(3):297-303. doi: 10.1007/s00296-008-0681-x.
18. Johnsen AK, Schiff MH, Mease PJ, Moreland LW, Maier AL, Coblyn JS et al. Comparison of 2 doses of etanercept (50 vs 100 mg) in active rheumatoid arthritis: A randomized double blind study. Journal of Rheumatology. 2006;33(4):659-64. doi: 06/13/026 [pii].
19. Jones G. The AMBITION trial: tocilizumab monotherapy for rheumatoid arthritis. Expert Rev Clin Immunol. 2010;6(2):189-95.
20. Kameda H, Ueki Y, Saito K, Nagaoka S, Hidaka T, Atsumi T et al. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: a randomized trial. Mod Rheumatol. 2010;20(6):531-8. doi: 10.1007/s10165-010-0324-4.
21. Kawashiri SY, Kawakami A, Yamasaki S, Imazato T, Iwamoto N, Fujikawa K et al. Effects of the anti-interleukin-6 receptor antibody, tocilizumab, on serum lipid levels in patients with rheumatoid arthritis. Rheumatol Int. 2011;31(4):451-6. doi: 10.1007/s00296-009-1303-y.
22. Klareskog L, van der Heijde D, de Jager JP, Gough A, Kalden J, Malaise M et al. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: Double-blind randomised controlled trial. Lancet. 2004;363(9410):675-81. doi: 10.1016/S0140-6736(04)15640-7 [doi].
23. Kremer JM, Bloom BJ, Breedveld FC, Coombs JH, Fletcher MP, Gruben D et al. The safety and efficacy of a JAK inhibitor in patients with active rheumatoid arthritis: Results of a double-blind, placebo-controlled phase IIa trial of three dosage levels of CP-690,550 versus placebo. Arthritis Rheum. 2009;60(7):1895-905. doi: 10.1002/art.24567.
24. Mathias SD, Colwell HH, Miller DP, Moreland LW, Buatti M, Wanke L. Health-related quality of life and functional status of patients with rheumatoid arthritis randomly assigned to receive etanercept or placebo. Clin Ther. 2000;22(1):128-39. doi: S0149291800879849 [pii].
25. Miyasaka N, Investigators CS. Clinical investigation in highly disease-affected rheumatoid arthritis patients in Japan with adalimumab applying standard and general evaluation: the CHANGE study. Mod Rheumatol. 2008;18(3):252-62. doi: 10.1007/s10165-008-0045-0.

26. Moreland LW, Schiff MH, Baumgartner SW, Tindall EA, Fleischmann RM, Bulpitt KJ et al. Etanercept therapy in rheumatoid arthritis. A randomized, controlled trial. Ann Intern Med. 1999;130(6):478-86. doi: 199903160-00004 [pii].
27. Moreland LW, Alten R, Van den Bosch F, Appelboom T, Leon M, Emery P et al. Costimulatory blockade in patients with rheumatoid arthritis: a pilot, dose-finding, double-blind, placebo-controlled clinical trial evaluating CTLA-4Ig and LEA29Y eighty-five days after the first infusion. Arthritis Rheum. 2002;46(6):1470-9. doi: 10.1002/art.10294.
28. Nishimoto N, Yoshizaki K, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T et al. Treatment of rheumatoid arthritis with humanized anti-interleukin-6 receptor antibody: a multicenter, double-blind, placebo-controlled trial. Arthritis Rheum. 2004;50(6):1761-9. doi: 10.1002/art.20303.
29. Nishimoto N, Hashimoto J, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T et al. Study of active controlled monotherapy used for rheumatoid arthritis, an IL-6 inhibitor (SAMURAI): evidence of clinical and radiographic benefit from an x ray reader-blinded randomised controlled trial of tocilizumab. Ann Rheum Dis. 2007;66(9):1162-7. doi: ard.2006.068064 [pii].
30. Nishimoto N, Miyasaka N, Yamamoto K, Kawai S, Takeuchi T, Azuma J et al. Study of active controlled tocilizumab monotherapy for rheumatoid arthritis patients with an inadequate response to methotrexate (SATORI): significant reduction in disease activity and serum vascular endothelial growth factor by IL-6 receptor inhibition therapy. Mod Rheumatol. 2009;19(1):12-9. doi: 10.1007/s10165-008-0125-1.
31. Ogata A, Tanimura K, Sugimoto T, Inoue H, Urata Y, Matsubara T et al. Phase III study of the efficacy and safety of subcutaneous versus intravenous tocilizumab monotherapy in patients with rheumatoid arthritis. Arthritis Care Res (Hoboken). 2014;66(3):344-54. doi: 10.1002/acr.22110.
32. Ogata A, Amano K, Dobashi H, Inoo M, Ishii T, Kasama T et al. Longterm safety and efficacy of subcutaneous tocilizumab monotherapy: results from the 2-year open-label extension of the MUSASHI study. J Rheumatol. 2015;42(5):799-809. doi: 10.3899/jrheum.140665.
33. Popa C, Netea MG, Radstake T, Van der Meer JW, Stalenhoef AF, van Riel PL et al. Influence of anti-tumour necrosis factor therapy on cardiovascular risk factors in patients with active rheumatoid arthritis. Ann Rheum Dis. 2005;64(2):303-5. doi: 10.1136/ard.2004.023119.
34. Strand V, Kremer J, Wallenstein G, Kanik KS, Connell C, Gruben D et al. Effects of tofacitinib monotherapy on patient-reported outcomes in a randomized phase 3 study of patients with active rheumatoid arthritis and inadequate responses to DMARDs. Arthritis Res Ther. 2015;17:307. doi: 10.1186/s13075-015-0825-9.
35. Strand V, Lee EB, Fleischmann R, Alten RE, Koncz T, Zwillich SH et al. Tofacitinib versus methotrexate in rheumatoid arthritis: patient-reported outcomes from the randomised phase III ORAL Start trial. RMD Open. 2016;2(2):e000308. doi: 10.1136/rmdopen-2016-000308.
36. Takeuchi T, Miyasaka N, Zang C, Alvarez D, Fletcher T, Wajdula J et al. A phase 3 randomized, double-blind, multicenter comparative study evaluating the effect of etanercept versus methotrexate on radiographic outcomes, disease activity, and safety in Japanese subjects with active rheumatoid arthritis. Mod Rheumatol. 2013;23(4):623-33. doi: 10.1007/s10165-012-0742-6.
37. Tanaka Y, Takeuchi T, Yamanaka H, Nakamura H, Toyoizumi S, Zwillich S. Efficacy and safety of tofacitinib as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week, randomized, phase 2 study. Modern Rheumatology. 2015;25(4):514-21. doi: 10.3109/14397595.2014.995875.
38. van de Putte LB, Atkins C, Malaise M, Sany J, Russell AS, van Riel PL et al. Efficacy and safety of adalimumab as monotherapy in patients with rheumatoid arthritis for whom previous disease modifying antirheumatic drug treatment has failed. Ann Rheum Dis. 2004;63(5):508-16. doi: 10.1136/ard.2003.013052 [doi].

39. van der Heijde D, Klareskog L, Rodriguez-Valverde V, Codreanu C, Bolosiu H, Melo-Gomes J 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):1063-74. doi: 10.1002/art.21655.
40. van der Heijde D, Klareskog L, Landewe R, Bruyn GA, Cantagrel A, Durez P et al. Disease remission and sustained halting of radiographic progression with combination etanercept and methotrexate in patients with rheumatoid arthritis. Arthritis Rheum. 2007;56(12):3928-39. doi: 10.1002/art.23141.
41. Weinblatt M, Schiff M, Goldman A, Kremer J, Luggen M, Li T et al. Selective costimulation modulation using abatacept in patients with active rheumatoid arthritis while receiving etanercept: A randomised clinical trial. Ann Rheum Dis. 2007;66(2):228-34. doi: ard.2006.055111 [pii].
42. Weinblatt ME, Fleischmann R, Huizinga TW, Emery P, Pope J, Massarotti EM et al. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: results from the REALISTIC phase IIIb study. Rheumatology (Oxford). 2012;51(12):2204-14. doi: 10.1093/rheumatology/kes150.
43. Weinblatt ME, Kremer J, Cush J, Rigby W, Teng LL, Devenport J et al. Tocilizumab as monotherapy or in combination with nonbiologic disease-modifying antirheumatic drugs: Twenty-four-week results of an open-label, clinical practice study. Arthritis Care Res (Hoboken). 2013;65(3):362-71. doi: 10.1002/acr.21847 [doi].
44. Yamamoto K, Takeuchi T, Yamanaka H, Ishiguro N, Tanaka Y, Eguchi K 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):552-60. doi: 10.3109/14397595.2013.843764.
45. Alten R, Strand V, Fleischmann R, Koncz T, Zwillich S, Bradley J et al. Effects of tofacitinib monotherapy versus methotrexate on patient-reported outcomes in the 2-year Phase 3 oral start trial in methotrexate-naive patients with rheumatoid arthritis [abstract]. Ann Rheum Dis. 2014;73(2):118-9.
46. Burmester GR, Rigby W, van Vollenhoven R, Kay J, Rubbert-Roth A, Kelman A et al. Tocilizumab in combination therapy and monotherapy versus methotrexate in methotrexate-naive patients with early rheumatoid arthritis: Clinical and radiographic outcomes from a randomized, placebo-controlled trial [abstract]. Arthritis Rheum. 2013;65:2767.
47. Burmester G, Furst DE, Combe BG, Huizinga TWJ, Bykerk VP, Wong D et al. Stringent criteria for low Disease activity and remission after 12 months of treatment, and after treatment withdrawal, with abatacept monotherapy, abatacept with methotrexate or methotrexate alone in early rheumatoid arthritis. Arthritis Rheumatol. 2014;66(10):S1076-S.
48. Burmester GR, Rigby W, Ronald F, van Vollenhoven RF, Kay J, Rubbert-Roth A et al. Tocilizumab combination therapy or monotherapy or methotrexate monotherapy in methotrexate-naive patients with early rheumatoid arthritis: 2-year clinical and radiographic results from a randomized, placebo-controlled trial [abstract]. Arthritis Rheumatol. 2014;66(10):S811.
49. Burmester G, Pethö-Schramm A, Keane C, Jones G. Tocilizumab monotherapy in early rheumatoid arthritis: data from two phase 3 randomized controlled trials [abstract]. Arthritis Rheumatol 2015;67(S10):1650.
50. Burmester G, Lin Y, Patel R, van Adelsberg J, Mangan E, van Hoogstraten H et al. Efficacy and safety of sarilumab versus adalimumab in a phase 3, randomized, double-blind, monotherapy study in patients with active rheumatoid arthritis with intolerance or inadequate response to methotrexate. Arthritis Rheumatol. 2016;68(S10):3221.

51. Charles-Schoeman C, van der Heijde D, Burmester G, Nash P, Zerbini CAF, Connell CA et al. Effect of glucocorticoids on clinical and radiographic efficacy outcomes in methotrexate-naive patients with RA receiving tofacitinib or methotrexate monotherapy: analysis of data from a phase 3 trial. Arthritis Rheumatol. 2016;68(S10):2606.
52. Durez P, Depresseux G, Toukap AN, Lauwerys B, de Bellefon LM, Stoenoiu M et al. Rate of remission by tocilizumab or methotrexate induction therapy in early active rheumatoid arthritis: results of the Tomera Trial. Ann Rheum Dis. 2013;72(3):623-.
53. Emery P, Burmester GR, Bykerk VP, Combe B, Furst DE, Barre E et al. Induction of clinical remission followed by drug free withdrawal with abatacept combination and monotherapy in early RA: Results from the AVERT study over 18 months [abstract]. Ann Rheum Dis. 2014;73(2):69.
54. Fleischmann R, Strand V, Wilkinson B, Kwok K, Bananis E. Relationship between different clinical measurements and patient-reported outcomes: results from a phase 3 study of tofacitinib or methotrexate in methotrexate-naïve patients with rheumatoid arthritis [abstract]. Arthritis Rheumatol. 2014;66(10):S1086.
55. Fleischmann R, Takeuchi T, Schlichting DE, Macias WL, Rooney T, Gurbuz S et al. Baricitinib, methotrexate, or baricitinib plus methotrexate in patients with early rheumatoid arthritis who had received limited or no treatment with disease-modifying anti-rheumatic drugs (DMARDs): phase 3 trial results. Arthritis Rheumatol. 2015;67(S10):1045.
56. Fleischmann R, Huizinga TWJ, Kavanaugh A, Wilkinson B, Kwok K, deMasi R et al. An analysis of the efficacy of tofacitinib monotherapy in MTX-naïve patients with early RA compared with patients with established RA [abstract]. Arthritis Rheumatol 2015;67(S10):2741.
57. Fleischmann R, Strand V, Wilkinson B, Kwok K, Bananis E. Relationship between different clinical measurements and patient-reported outcomes: results from a phase 3 study of tofacitinib or methotrexate in methotrexate-naïve patients with rheumatoid arthritis [abstract]. Ann Rheum Dis. 2015;74(S2):259.
58. Furst DE, Bykerk VP, Burmester GR, Combe BG, Huizinga TWJ, Alemao E et al. Treatment effects and minimal clinically important differences in patient-reported outcomes following treatment and withdrawal of abatacept, methotrexate or combination therapy in patients with early rheumatoid arthritis [abstract]. Ann Rheum Dis. 2015;74:1044.
59. Herold M, Fasching P, Graninger W, Lunzer R, Zamani O, Leeb B. Efficacy of tocilizumab monotherapy in patients with RA is not influenced by ACPA positivity. Arthritis Rheumatol. 2015;67(S10):499.
60. Kameda H, Kanbe K, Sato E, Ueki Y, Saitoh K, Nagaoka S et al. Etanercept (ETN) plus methotrexate (MTX) combination therapy resulted in a better radiographic outcome than ETN monotherapy even in patients with active rheumatoid arthritis despite MTX treatment: 104-week results from the JESMR study [abstract]. Arthritis Rheum. 2010;62(10):1812.
61. Lee EB, Fleischmann RM, Hall S, van Vollenhoven RF, Bradley JD, Gruben D et al. Radiographic, clinical and functional comparison of tofacitinib monotherapy versus methotrexate in methotrexate-naive patients with rheumatoid arthritis [abstract]. Arthritis Rheum. 2012;64(10):S1049.
62. Ogata A, Takagi N, Miwa H. A randomized, double-blind, parallel-group, phase III study of shortening the dosing interval of subcutaneous tocilizumab monotherapy in RA patients with an inadequate response to subcutaneous tocilizumab every other week [abstract]. Arthritis Rheumatol 2016;68(S10):1592.
63. Pablos JL, Navarro Sarabia F, Blanco FJ, Román Ivorra JA, Alonso A, Martin Mola E et al. Switch from tocilizumab + methotrexate to tocilizumab monotherapy. maintenance of response in patients with rheumatoid arthritis at low disease activity [abstract]. Arthritis Rheumatol 2015;67:S10.

64. Strand V, Lampl K, Birchwood C, Pei J, Tuckwell K, Finch R et al. Patient-reported outcomes in two randomized, controlled trials (RCTs) in patients with rheumatoid arthritis (RA) treated with tocilizumab (TCZ) monotherapy compared with methotrexate (MTX) or adalimumab (ADA). Arthritis Rheumatol. 2016;68(S10):2515.
65. Strand V, Bergman MJ, Lee EB, Yazici Y, Wilkinson B, Takiya L et al. Long-term clinical, radiographic and patient-reported outcomes based on RAPID3 responses with tofacitinib at 6 months [abstract]. Arthritis Rheumatol 2016;68(S10):1648.
66. Takeuchi T, Kaneko Y, Atsumi T, Tanaka Y, Inoh M, Kobayashi H et al. Adding tocilizumab or switching to tocilizumab monotherapy in RA patients with inadequate response to methotrexate: 24-week results from a randomized controlled study (SURPRISE study) [abstract]. Ann Rheum Dis. 2013;72(3):62.
67. Takeuchi T, Yamanaka H, Harigai M, Tamamura R, Kato Y, Ukyo Y et al. One-year safety of sirukumab monotherapy: results from a randomized, double-blind, parallel-group, multicenter study in Japanese subjects with moderate to severe rheumatoid arthritis [abstract]. Arthritis Rheumatol 2015;67(S10):1672.
68. Takeuchi T, Thorne C, Karpouzas G, Sheng S, Xu W, Rao R et al. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis despite disease-modifying anti-rheumatic drug treatment: results of a randomized, double-blind, placebo-controlled study [abstract]. Ann Rheum Dis. 2016;75(S2):717.
69. Tanaka Y, Takeuchi T, Yamanaka H, Suzuki M, Nakamura H, Toyoizumi S et al. Tofacitinib (CP-690,550), an oral Janus kinase inhibitor, as monotherapy in Japanese patients with active rheumatoid arthritis: a 12-week phase 2b study [abstract]. Arthritis Rheum. 2011;63(10):2192.
70. Taylor PC, Schiff M, Wang Q, Jiang Y, Kurrasch R, Daga S et al. Efficacy and safety of monotherapy with sirukumab, an anti–IL-6 cytokine monoclonal antibody, compared with adalimumab monotherapy in biologic-naive patients with active rheumatoid arthritis: results of a global, randomized, double-blind, parallel-group, phase 3 study [abstract]. Arthritis Rheumatol. 2016;68(S10):3222.
71. Yazici Y, Gandhi KK, Alemao E, Furst DE. Routine Assessment of Patient Index Data 3 (RAPID3) – defined remission is as stringent as ACR/EULAR Boolean-defined remission in a clinical trial of patients with early rheumatoid arthritis treated with abatacept [abstract]. Arthritis Rheumatol. 2015;67(S10):1644.