Supplementary appendix

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Section 1: Search strategy and PICOs

Table S1.1: MEDLINE Search strategy: biological DMARDs

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or rheumat$ or reumat$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. or/1-4
6. exp biological therapy/
7. exp antibodies, monoclonal/
8. exp monokines/
9. exp receptors, interleukin-1/
10. exp receptors, interleukin-6/
11. exp immunoglobulin g/
12. exp immunoconjugates/
13. exp polyethylene glycols/
14. exp immunoglobulin fab fragments/
15. exp t-lymphocytes/
16. biologic$.tw.
17. bDMARD$.tw.
18. biosimilar$.tw.
19. infliximab.tw.
20. remicade.tw.
21. adalimumab.tw.
22. humira.tw.
23. trudexa.tw.
24. abatacept.tw.
25. orencia.tw.
26. anakinra.tw.
27. kineret.tw.
28. Certolizumab.tw.
29. cimzia.tw.
30. Etanercept.tw.
31. enbrel.tw.
32. Golimumab.tw.
33. simponi.tw.
34. rituximab.tw.
35. rituxan.tw.
36. mabthera.tw.
37. Tocilizumab.tw.
38. actemra.tw.
39. RoActemra.tw.
40. Ofatumumab.tw.
41. Arzerra.tw.
42. Sarilumab.tw.

43. Sirukumab.tw.
44. Ocrelizumab.tw.
45. Tabalumab.tw.
46. Olokizumab.tw.
47. Clazakizumab.tw.
48. Pateclizumab.tw.
49. Ixekizumab.tw.
50. Taltz.tw.
51. Brodalumab.tw.
52. Siliq.tw.
53. Guselkumab.tw.
54. Ustekinumab.tw.
55. Stelara.tw.
56. mavrilimumab.tw.
57. or/6-56
58. 5 and 57
59. randomized controlled trial.pt.
60. controlled clinical trial.pt.
61. randomized.ab.
62. placebo.ab.
63. drug therapy.fs.
64. randomly.ab.
65. trial.ab.
66. groups.ab.
67. or/59-66
68. (animals not (humans and animals)).sh.
69. 67 not 68
70. 58 and 69
71. limit 71 to yr="2016 -Current"

Table S1.2: EMBASE Search strategy: biological DMARDs

#68. #67 AND AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND AND (2016:py OR 2017:py OR 2018:py OR 2019:py)
#67. #55 AND #66
#66. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65
#65. random*:ab,ti
#64. 'randomized controlled trial'/exp
#63. trial:ti
#62. allocat*:ab,ti
#61. (doubl* NEAR/2 blind*):ab,ti
#60. placebo*:ab,ti
#59. crossover*:ab,ti OR 'cross over*':ab,ti
#58. 'single-blind procedure'
#57. 'double blind procedure'/de
#56. 'crossover procedure'/de
#55. #5 AND #54
#54. #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 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#53. mavrilimumab:ab,ti
#52. stelara:ab,ti
#51. ustekinumab:ab,ti
#50. guselkumab:ab,ti
#49. brodalumab:ab,ti
#48. brodalumab:ab,ti
#47. taltz:ab,ti
#46. ixekizumab:ti,ab
#45. pateclizumab:ab,ti
#44. clazakizumab:ab,ti
#43. olokizumab:ab,ti
#42. tabalumab:ab,ti
#41. ocrelizumab:ab,ti
#40. sirukumab:ab,ti
#39. sarilumab:ab,ti
#38. arzerra:ab,ti
#37. ofatumumab:ab,ti
#36. ixekizumab:ab,ti
#35. brodalumab:ab,ti
#34. stelara:ab,ti
#33. ustekinumab:ab,ti
#32. cosentyx:ab,ti
#31. secukinumab:ab,ti
#30. roactemra:ab,ti
#29. actemra:ab,
#28. tocilizumab:ab,ti
#27. mabthera:ab,ti
#26. rituxan:ab,ti
#25. rituximab:ab,ti
#24. simponi:ab,ti
#23. golimumab:ab,ti

#22. enbrel:ab,ti
#21. etanercept:ab,ti
#20. 'etanercept'/de
#19. cimzia:ab,ti
#18. certolizumab:ab,ti
#17. kineret:ab,ti
#16. anakinra:ab,ti
#15. orencia:ab,ti
#14. abatacept:ab,ti
#13. trudexa:ab,ti
#12. humira:ab,ti
#11. adalimumab:ab,ti
#10. remicade:ab,ti
#9. 'infliximab':ab,ti
#8. 'monoclonal antibody'/exp
#7. biologic*:ab,ti OR biosimilar*:ab,ti OR bdmard*:ab,ti
#6. 'biological therapy'/exp
#5. #1 OR #2 OR #3 OR #4
#4. (caplan* NEAR/2 syndrome):ab,ti
#3. (felty* NEAR/2 syndrome):ab,ti
#2. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti
#1. 'rheumatoid arthritis'/exp

Table S1.3: Cochrane Library Search strategy: biological DMARDs

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2 ((rheumatoid or reumatoid or rheumat* or reumat*) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab
#3 (felty* near/2 syndrome):ti,ab
#4 (caplan* near/j2 syndrome):ti,ab
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Biological Therapy] explode all trees
#7 MeSH descriptor: [Antibodies, Monoclonal] explode all trees
#8 MeSH descriptor: [Monokines] explode all trees
#9 MeSH descriptor: [Receptors, Interleukin-1] explode all trees
#10 MeSH descriptor: [Receptors, Interleukin-6] explode all trees
#11 MeSH descriptor: [Immunoglobulin G] explode all trees
#12 MeSH descriptor: [Immunoconjugates] explode all trees
#13 MeSH descriptor: [Polyethylene Glycols] explode all trees
#14 MeSH descriptor: [Immunoglobulin Fab Fragments] explode all trees
#15 MeSH descriptor: [T-Lymphocytes] explode all trees
#16 biologic*:ti,ab
#17 biosimilar*:ti,ab
#18 infliximab:ti,ab
#19 remicade:ti,ab
#20 adalimumab:ti,ab
#21 humira:ti,ab
#22 trudexa:ti,ab
#23 abatacept:ti,ab
#24 orencia:ti,ab
#25 anakinra:ti,ab
#26 kineret:ti,ab
#27 Certolizumab:ti,ab
#28 cimzia:ti,ab
#29 Etanercept:ti,ab
#30 enbrel:ti,ab
#31 Golimumab:ti,ab
#32 simponi:ti,ab
#33 rituximab:ti,ab
#34 rituxan:ti,ab
#35 mabthera:ti,ab
#36 Tocilizumab:ti,ab
#37 actemra:ti,ab
#38 RoActemra:ti,ab
#39 Ofatumumab:ti,ab
#40 Arzerra:ti,ab
#41 Sarilumab:ti,ab
#42 Sirukumab:ti,ab
#43 Ocrelizumab:ti,ab
#44 Tabalumab:ti,ab
#45 Olokizumab:ti,ab
#46 Clazakizumab:ti,ab
#47 Pateclizumab:ti,ab
#48 Ixekizumab:ti,ab
#49 Taltz:ti,ab

#50 Brodalumab:ti,ab
#51 Siliq:ti,ab
#52 Guselkumab:ti,ab
#53 Ustekinumab:ti,ab
#54 Stelara:ti,ab
#55 mavrilimumab:ti,ab
#56 #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 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55

#57 #5 AND #56 with Cochrane Library publication date Between Jan 2016 and Dec 2018

Table S1.4: MEDLINE Search strategy: conventional and targeted synthetic DMARDs + Glucocorticoids

1. exp arthritis, rheumatoid/
2. ((rheumatoid or reumatoid or rheumat$ or reumat$) adj3 (arthrit$ or artrit$ or diseas$ or condition$ or nodule$)).tw.
3. (felty$ adj2 syndrome).tw.
4. (caplan$ adj2 syndrome).tw.
5. or/1-4
6. Antirheumatic Agents/
7. Antirheumatic$.tw.
8. (dmard$ or sdmard$).tw.
9. Methotrexate/
10. Methotrexate.tw.
11. (Abitrexate or amet?opterine or Abitrexate or A Met?opterine$ or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Metotrexat$ or mtx or Novatrex or Rheumatrex).tw.
12. exp Isoxazoles/
13. isoxazole$.tw.
14. leflunomide$.tw.
15. (Afiancen or Arabloc or Arava or Artrilab or Artrimod or Filartros or Inmunoartro or Lefluar or Leflucross or Lefno or Lefra or Lefumide or Lisifen or Molagar or Repso or Rumalef).tw.
16. Sulfasalazine/
17. sulfasalazine.tw.
18. (Salazosulfapyridine or sulfasalazine or Sulfosalazine or Sulfasal#zine or Salazopyridin$ or asulfidine or azulf#dine).tw.
19. Hydroxychloroquine/
20. Hydroxychloro$.tw.
21. (Axokineor or Dolquine or Ercoquin or Evoquin or HCQS or HQT or Hydrocad or Hydroquin or Ilinol or Immard or Metirel or Narbon or Oxcq or Oxiklorin or Oxy-Q or Plaquen?l or Polirreuminor or Quensyl or Reuquinol).tw.
22. exp Gold Compounds/
23. exp Organogold Compounds/
24. gold.tw.
25. exp Chloroquine/
26. chloroquine$.tw.
27. (aralen or arechine or arequin or chingamin or chlorochin or khingamin or nivaquine or oxychloroquine or oxychlorochin or plaquinol or plaquinil or quensy or anoclor or arthrabas or avloclor or cidanchin or clopirim or collagenan or daraclor or daramal or dichinalex or difosquin or diroquine or genocin or heliopar or klorokin or malarex or malaviron or mirquin or nivaquine or novo-chloroquine or novochloroquine or paluken or palux or pharmaquinine or plasmoquine or promal or p-roquine or resoquin$ or savarine or syncoquin or weimerquin).tw.
28. Azathioprine/
29. azathioprine.tw.
30. (Aseroprim or Aseroprin or Azaallen or Azadus or Azafalk or Azafor or Azafrine or Azaglax or Azahexal or Aza?mun$ or Azamedac or Azap or Azap?in$ or Azapress or Aza-Q or Azarek or Azasan or Azathiodura or Azathiodura or Azathioregio or Azatrilem or Azimune or Azop?in$ or Azoran or Berkaprine or Colinsan or Glaxoprin or Immunoprin or Imuger or Imunen or Imuprin$ or Imuran or

Imure?or Imuzat or Oprisine or Satedon or Thioprine or Tiosalprin or Transimune or Zaprine or Zytrim).tw.

31. exp Cyclosporins/

32. c?closporin$.tw.

33. (neoral or gengraf or restasis or sandimmun$ or sangcya).tw.

34. exp Penicillamine/

35. Penicillamine.tw.

36. (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin$ or D-Penamine or Gerodyl or Kelatin$ or Mercaptyl or Metalcaptase or Pendramine or Rhumantin or Sufortan$ or Trisorcin or Trolovol).tw.

37. exp Cyclophosphamide/

38. (cyclophosph$ or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109$ or asta z 4942 or cfx or phosphoramide mustard$).tw.

39. Mycophenolic Acid/

40. mycophenolate.tw.

41. (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or Imuxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilet or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin).tw.

42. exp Chlorambucil/

43. chlorambucil.tw.

44. (Amboclorin or Clokeran or Leukeran or Linfolysin or Lympholysin).tw.

45. Minocycline/

46. minocyclin$.tw.

47. (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomycin$ or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or Minac 50 or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab$ or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udima or Vectrin or Yelnac or Zacnan).tw.

48. Pyrroles/

49. tofacitinib.tw.

50. Xeljanz.tw.

51. baricitinib.tw.

52. peficitinib.tw.

53. filgotinib.tw.

54. upadacitinib.tw.

55. fostamatinib.tw.

56. exp Glucocorticoids/

57. glucocorticoid$.tw.

58. (Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone).tw.

59. or/6-58
60. 5 and 59
61. randomized controlled trial.pt.
62. controlled clinical trial.pt.
63. randomized.ab.
64. placebo.ab.
65. drug therapy.fs.
66. randomly.ab.
67. trial.ab.
68. groups.ab.
69. or/61-68
70. (animals not (humans and animals)).sh.
71. 69 not 70
72. 60 and 71
73. limit 72 to yr="2016 -Current"

Table S1.5: EMBASE Search strategy: conventional and targeted synthetic DMARDs + Glucocorticoids

#71. #70 AND (2016:py OR 2017:py OR 2018:py OR 2019:py)
#70. #57 AND #68 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim
#69. #57 AND #68
#68. #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67
#67. random*:ab,ti
#66. 'randomized controlled trial'/exp
#65. trial:ti
#64. allocat*:ab,ti
#63. (doubl* NEAR/2 blind*):ab,ti
#62. placebo*:ab,ti
#61. crossover*:ab,ti OR 'cross over*':ab,ti
#60. 'single-blind procedure'
#59. 'double blind procedure'/de
#58. 'crossover procedure'/de
#57. #5 AND #56
#56. #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 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
#55. beclomethasone:ti,ab OR betamethasone:ti,ab OR budesonide:ti,ab OR clobetasol:ti,ab OR desoximetasone:ti,ab OR dexamethasone:ti,ab OR diflucortolone:ti,ab OR flumethasone:ti,ab OR fluocinonide:ti,ab OR fluocortolone:ti,ab OR fluorometholone:ti,ab OR fluprednisolone:ti,ab OR flurandrenolone:ti,ab OR 'melengestrol acetate':ti,ab OR methylprednisolone:ti,ab OR paramethasone:ti,ab OR prednisolone:ti,ab OR prednisone:ti,ab OR triamcinolone:ti,ab
#54. glucocorticoid*:ti,ab
#53. 'glucocorticoid'/exp
#52. fostamatinib.:ti,ab
#51. upadacitinib.:ti,ab
#50. filgotinib.:ti,ab
#49. peficitinib:ti,ab
#48. baricitinib:ti,ab
#47. xeljanz:ab,ti
#46. tofacitinib:ab,ti
#45. acneclin:ab,ti OR akamin:ab,ti OR aknemin:ab,ti OR 'akne puren':ab,ti OR aknereduct:ab,ti OR 'aknin mino':ab,ti OR 'aknin n':ab,ti OR aknoral:ab,ti OR aknosan:ab,ti OR apominolin:ab,ti OR arestinor:ab,ti OR auramin:ab,ti OR blemix:ab,ti OR borymycin:ab,ti OR cipancin:ab,ti OR cyclimycin:ab,ti OR dentomycin*:ab,ti OR durakne:ab,ti OR dynacin:ab,ti OR enca:ab,ti OR 'icht oralor':ab,ti OR klinoc:ab,ti OR klinomycin:ab,ti OR klinotab:ab,ti OR lederderm:ab,ti OR logryx:ab,ti OR meibi:ab,ti OR mestacine:ab,ti OR micromycin:ab,ti OR 'minac 50':ab,ti OR minakne:ab,ti OR minaxen:ab,ti OR 'mino 50':ab,ti OR minocin:ab,ti OR minoclin:ab,ti OR minodene:ab,ti OR minoderm:ab,ti OR minogalen:ab,ti OR minolis:ab,ti OR minomax:ab,ti OR minomycin:ab,ti OR minoplus:ab,ti OR minosil:ab,ti OR minostad:ab,ti OR minotab*:ab,ti OR minotekor:ab,ti OR minotrex:ab,ti OR minotyrol:ab,ti OR 'mino wolff':ab,ti OR minox:ab,ti OR mynocine:ab,ti OR myrac:ab,ti OR oracyclin:ab,ti OR parocline:ab,ti OR periocline:ab,ti OR peritrol:ab,ti OR ranmino:ab,ti OR romin:ab,ti OR seboclear:ab,ti OR sebomin:ab,ti OR sebren:ab,ti OR skid:ab,ti OR skinocyclin:ab,ti OR solodyn:ab,ti OR spicline:ab,ti OR triomin:ab,ti OR udima:ab,ti OR vectrin:ab,ti OR yelnac:ab,ti OR zacnan:ab,ti
#44. minocyclin*:ab,ti
#43. 'minocycline'/de

#42. amboclorin:ab,ti OR clokeran:ab,ti OR leukeran:ab,ti OR linfolysin:ab,ti OR lympholysin:ab,ti
#41. chlorambucil:ab,ti
#40. 'chlorambucil'/de
#39. arzip:ab,ti OR baxmune:ab,ti OR cellcept:ab,ti OR cellmune:ab,ti OR celprot:ab,ti OR ceptolate:ab,ti OR imulate:ab,ti OR muxgen:ab,ti OR lanfetil:ab,ti OR limfocept:ab,ti OR metocris:ab,ti OR micocept:ab,ti OR mmf:ab,ti OR mofecept:ab,ti OR mofetyl:ab,ti OR mofilet:ab,ti OR mofimutral:ab,ti OR mometil:ab,ti OR mophecen:ab,ti OR munotras:ab,ti OR myaccord:ab,ti OR mycept:ab,ti OR myclausenor:ab,ti OR mycofenor:ab,ti OR mycolat:ab,ti OR mycoldosa:ab,ti OR mycophen:ab,ti OR myfenax:ab,ti AND myfetil:ab,ti OR mygref:ab,ti OR myotec:ab,ti OR mysept:ab,ti OR presumin:ab,ti OR refrat:ab,ti OR renocell:ab,ti OR supresta:ab,ti OR tevacept:ab,ti OR trixin:ab,ti
#38. mycophenolate:ab,ti
#37. 'mycophenolic acid'/de
#36. cyclophosph*:ab,ti OR cytophosphan:ab,ti OR cytoxan:ab,ti OR sendoxan:ab,ti OR endoxan:ab,ti OR neosar:ab,ti OR 'nsc 26271':ab,ti OR procytox:ab,ti OR 'b 518':ab,ti OR ifosfamide:ab,ti OR isophosphamide:ab,ti OR iphosphamide:ab,ti OR isofosfamide:ab,ti OR holoxan:ab,ti OR 'nsc 109':ab,ti OR 'asta z 4942':ab,ti OR cfx:ab,ti OR 'phosphoramide mustard':ab,ti OR 'phosphoramide mustards':ab,ti
#35. 'cyclophosphamide'/de
#34. adalkenor:ab,ti OR artamin:ab,ti OR atamir:ab,ti OR byanodine:ab,ti OR cilamin:ab,ti OR cuprenil:ab,ti OR cuprimine:ab,ti OR cupripen:ab,ti OR depen:ab,ti OR distamin*:ab,ti OR 'd penamine':ab,ti OR gerodyl:ab,ti OR kelatin*:ab,ti OR mercaptyl:ab,ti OR metalcaptase:ab,ti OR pendramine:ab,ti OR rhumantin:ab,ti OR sufortan*:ab,ti OR trisorcin:ab,ti OR trolovol:ab,ti
#33. 'penicillamine'/de
#32. neoral:ab,ti OR gengraf:ab,ti OR restasis:ab,ti OR sandimmun*:ab,ti OR sangcya:ab,ti
#31. cyclosporin*:ab,ti OR ciclosporin*:ab,ti
#30. 'cyclosporin derivative'/de
#29. aseroprim:ab,ti OR aseroprin:ab,ti OR azaallen:ab,ti OR azadus:ab,ti OR azafalk:ab,ti OR azafor:ab,ti OR azafrine:ab,ti OR azaglax:ab,ti OR azahexal:ab,ti OR azamun*:ab,ti OR azaimun:ab,ti OR azamedac:ab,ti OR azap:ab,ti OR azapin*:ab,ti OR azaprine*:ab,ti OR azapress:ab,ti OR 'aza q':ab,ti OR azarek:ab,ti OR azasan:ab,ti OR azathiodura:ab,ti OR azathioregio:ab,ti OR azatrilem:ab,ti OR azimune:ab,ti OR azopin*:ab,ti OR azoran:ab,ti OR berkaprine:ab,ti OR colinsan:ab,ti OR glaxoprin:ab,ti OR immunproprin:ab,ti OR imuger:ab,ti OR imunen:ab,ti OR imuprin*:ab,ti OR imuran:ab,ti OR imure*:ab,ti OR imuzat:ab,ti OR oprisine:ab,ti OR satedon:ab,ti OR thioprine:ab,ti OR tiosalprin:ab,ti OR
transimune:ab,ti OR zaprine:ab,ti OR zytrim:ab,ti
#28. azathioprine:ab,ti
#27. 'azathioprine'/de
#26. aralen:ab,ti OR arechine:ab,ti OR arequin:ab,ti OR chingamin:ab,ti OR chlorochin:ab,ti OR khingamin:ab,ti OR oxychloroquine:ab,ti OR oxychlorochin:ab,ti OR plaquinol:ab,ti OR plaquinil:ab,ti OR quensy:ab,ti OR anoclor:ab,ti OR arthrabas:ab,ti OR avloclor:ab,ti OR cidanchin:ab,ti OR clopirim:ab,ti OR collagenan:ab,ti OR daraclor:ab,ti OR daramal:ab,ti OR dichinalex:ab,ti OR difosquin:ab,ti OR diroquine:ab,ti OR genocin:ab,ti OR heliopar:ab,ti OR klorokin:ab,ti OR malarex:ab,ti OR malaviron:ab,ti OR mirquin:ab,ti OR nivaquine:ab,ti OR 'novo chloroquine':ab,ti OR novochloroquine:ab,ti OR paluken:ab,ti OR palux:ab,ti OR pharmaquinine:ab,ti OR plasmoquine:ab,ti OR promal:ab,ti OR 'p roquine':ab,ti OR resoquin$:ab,ti OR savarine:ab,ti OR syncoquin:ab,ti OR weimerquin:ab,ti
#25. chloroquine*:ab,ti
#24. 'chloroquine'/de
#23. gold:ab,ti
#22. 'gold therapy'/de
#21. axokineor:ab,ti OR dolquine:ab,ti OR ercoquin:ab,ti OR evoquin:ab,ti OR hcqs:ab,ti OR hqt:ab,ti OR hydrocad:ab,ti OR hydroquin:ab,ti OR ilinol:ab,ti OR immard:ab,ti OR metirel:ab,ti OR

narbon:ab,ti OR oxcq:ab,ti OR oxiklorin:ab,ti OR 'oxy q':ab,ti OR plaquenil:ab,ti OR polirreuminor:ab,ti OR quensyl:ab,ti OR reuquinol:ab,ti
#20. hydroxychloro*:ab,ti
#19. 'hydroxychloroquine'/de
#18. salazosulfapyridine:ab,ti OR sulfasalazine:ab,ti OR sulfosalazine:ab,ti OR sulfasazine:ab,ti OR sulfasizine:ab,ti OR salazopyridin*:ab,ti OR asulfidine:ab,ti OR azulfadine:ab,ti OR azulfidine:ab,ti
#17. sulfasalazine:ab,ti
#16. 'salazosulfapyridine'/de
#15. afiancen:ab,ti OR arabloc:ab,ti OR arava:ab,ti OR artrilab:ab,ti OR artrimod:ab,ti OR filartros:ab,ti OR inmunoartro:ab,ti OR lefluar:ab,ti OR leflucross:ab,ti OR lefno:ab,ti OR lefra:ab,ti OR lefumide:ab,ti OR lisifen:ab,ti OR molagar:ab,ti OR repso:ab,ti OR rumalef:ab,ti
#14. isoxazole*:ab,ti
#13. 'isoxazole derivative'/exp
#12. ametopterine:ab,ti OR amethopterine:ab,ti OR abitrexate:ab,ti OR 'a metopterine':ab,ti OR 'a methopterine':ab,ti OR antifolan:ab,ti OR emtexate:ab,ti OR emtrexate:ab,ti OR enthexate:ab,ti OR farmitrexate:ab,ti OR folex:ab,ti OR ledertrexate:ab,ti OR methoblastin:ab,ti OR methohexate:ab,ti OR methotrate:ab,ti OR methylaminopterin:ab,ti OR metotrexat*:ab,ti OR mtx:ab,ti OR novatrex:ab,ti OR rheumatrex:ab,ti
#11. methotrexate:ab,ti
#10. 'methotrexate'/de
#9. 'disease modifying antirheumatic':ab,ti OR 'disease modifying antirheumatics':ab,ti
#8. dmard*:ab,ti OR sdmard*:ti,ab
#7. antirheumatic*:ab,ti
#6. 'disease modifying antirheumatic drug'/de
#5. #1 OR #2 OR #3 OR #4
#4. (caplan* NEAR/2 syndrome):ab,ti
#3. (felty* NEAR/2 syndrome):ab,ti
#2. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti
#1. 'rheumatoid arthritis'/exp

Table S1.6: Cochrane Libary Search strategy: conventional and targeted synthetic DMARDs + Glucocorticoids

#1 MeSH descriptor: [Arthritis, Rheumatoid] explode all trees
#2 ((rheumatoid or reumatoid or rheumat* or reumat*) near/3 (arthrit* or artrit* or diseas* or condition* or nodule*)):ti,ab
#3 (felty* near/2 syndrome):ti,ab
#4 (caplan* near/j2 syndrome):ti,ab
#5 #1 or #2 or #3 or #4
#6 MeSH descriptor: [Antirheumatic Agents] explode all trees
#7 Antirheumatic*:ti,ab
#8 dmard*:ti,ab
#9 MeSH descriptor: [Methotrexate] this term only
#10 Methotrexate:ti,ab
#11 (Abitrexate or amet?opterine or Abitrexate or A Met?opterine* or Antifolan or Emt?exate or Enthexate or Farmitrexate or Folex or Ledertrexate or Methoblastin or Methohexate or Methotrate or Methylaminopterin or Metotrexat$ or mtx or Novatrex or Rheumatrex):ti,ab
#12 MeSH descriptor: [Isoxazoles] explode all trees
#13 isoxazole*:ti,ab
#14 leflunomide*:ti,ab
#15 (Afiancen or Arabloc or Arava or Artrilab or Artrimod or Filartros or Inmunoartro or Lefluar or Leflucross or Lefno or Lefra or Lefumide or Lisifen or Molagar or Repso or Rumalef):ti,ab
#16 MeSH descriptor: [Sulfasalazine] this term only
#17 sulfasalazine:ti,ab
#18 (Salazosulfapyridine or sulfasalazine or Sulfosalazine or Sulfasal?zine or Salazopyridin* or asulfidine or azulf?dine):ti,ab
#19 MeSH descriptor: [Hydroxychloroquine] this term only
#20 Hydroxychloro*:ti,ab
#21 (Axokineor or Dolquine or Ercoquin or Evoquin or HCQS or HQT or Hydrocad or Hydroquin or Ilinol or Immard or Metirel or Narbon or Oxcq or Oxiklorin or Oxy-Q or Plaquen?l or Polirreuminor or Quensyl or Reuquinol):ti,ab
#22 MeSH descriptor: [Gold Compounds] explode all trees
#23 MeSH descriptor: [Organogold Compounds] explode all trees
#24 gold:ti,ab
#25 MeSH descriptor: [Chloroquine] explode all trees
#26 chloroquine*:ti,ab
#27 (aralen or arechine or arequin or chingamin or chlorochin or khingamin or nivaquine or oxychloroquine or oxychlorochin or plaquinol or plaquinil or quensy or anoclor or arthrabas or avloclor or cidanchin or clopirim or collagenan or daraclor or daramal or dichinalex or difosquin or diroquine or genocin or heliopar or klorokin or malarex or malaviron or mirquin or nivaquine or novo-chloroquine or novochloroquine or paluken or palux or pharmaquinine or plasmoquine or promal or p-roquine or resoquin$ or savarine or syncoquin or weimerquin):ti,ab
#28 MeSH descriptor: [Azathioprine] this term only
#29 azathioprine:ti,ab
#30 (Aseroprim or Aseroprin or Azaallen or Azadus or Azafalk or Azafor or Azafrine or Azaglax or Azahexal or Aza?mun* or Azamedac or Azap or Azap?in* or Azapress or Aza-Q or Azarek or Azasan or Azathiodura or Azathiodura or Azathioregio or Azatrilem or Azimune or Azop?in* or Azoran or Berkaprine or Colinsan or Glaxoprin or Immunoprin or Imuger or Imunen or Imuprin$ or Imuran or Imure? or Imuzat or Oprisine or Satedon or Thioprine or Tiosalprin or Transimune or Zaprine or Zytrim):ti,ab
#31 MeSH descriptor: [Cyclosporins] explode all trees
#32 c?closporin*:ti,ab

#33 (neoral or gengraf or restasis or sandimmun* or sangcya):ti,ab
#34 MeSH descriptor: [Penicillamine] explode all trees
#35 Penicillamine:ti,ab
#36 (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin* or D-Penamine or Gerodyl or Kelatin* or Mercaptyl or Metalcaptase or Pendramine or Rhumantin or Sufortan* or Trisorcin or Trolovol):ti,ab
#37 MeSH descriptor: [Cyclophosphamide] explode all trees
#38 (cyclophosph* or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109* or "asta z 4942" or cfx or "phosphoramide mustard*"):ti,ab
#39 MeSH descriptor: [Mycophenolic Acid] this term only
#40 mycophenolate:ti,ab
#41 (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or Imuxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilet or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin):ti,ab
#42 MeSH descriptor: [Chlorambucil] explode all trees
#43 chlorambucil:ti,ab
#44 (Amboclorin or Clokeran or Leukeran or Linfolysin or Lympholysin):ti,ab
#45 MeSH descriptor: [Minocycline] this term only
#46 minocyclin*:ti,ab
#47 (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomycin$ or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or "Minac 50" or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab$ or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udima or Vectrin or Yelnac or Zacnan):ti,ab
#48 MeSH descriptor: [Pyrroles] this term only
#49 tofacitinib:ti,ab
#50 Xeljanz:ti,ab
#51 baricitinib:ti,ab
#52 peficitinib:ti,ab
#53 filgotinib:ti,ab
#54 upadacitinib:ti,ab
#55 fostamatinib:ti,ab
#56 MeSH descriptor: [Glucocorticoids] explode all trees
#57 glucocorticoid*:ti,ab
#58 (Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone):ti,ab
#59 #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 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
#60 #5 AND #59

Table S1.7: Pharmacologic interventions of interest

Biological DMARDs (bDMARDs)	all formulations and duration (biosimilars included): anakinra (ANA), infliximab (INF), etanercept (ETN), adalimumab (ADA), golimumab (GLM), certolizumab pegol (CZP), rituximab (RTX), ofatumumab (OFA), abatacept (ABA), tocilizumab (TCZ), sarilumab (SAR), sirukumab (SKM), ocrelizumab (OKM), tabalumab (TBM), olokizumab (OLO), clazakizumab (CZK), pateclizumab (PZK), ixekizumab (IXE), brodalumab (BLM), guselkumab (GKM), ustekinumab (UKM), mavrilimumab (MVM)
Targeted synthetic DMARDs (tsDMARDs)	Tofacitinib (TOFA), baricitinib (BARI), peficitinib (PEF), filgotinib (FILGO), upadacitinib (UPA), fostamatinib (FOSTA)
Conventional synthetic DMARDs (csDMARDs)	Methotrexate (MTX), leflunomide (LEF), sulfasalazine (SZP), hydroxychloroquine (HCQ), injectable gold (GOLD), chloroquine (CQ)
Systemic glucocorticoids (GC)	
Any combination of the previous	

Table S1.8: Patient population, Intervention, Control (PICO) definition.

See table S7 for specific definition of interventions.

#	Research question	Population	Intervention	Control	Outcome
1	What is the efficacy of each of bDMARDs in combination with MTX ± other csDMARDs?	Adult Patients with RA	bDMARD + MTX ± other csDMARDs	Comparator not receiving a bDMARD (MTX ± other csDMARD)	ACR response criteria / DAS28-CRP / EULAR response / ACR-EULAR remission / CDAI / SDAI / HAQ / mTSS
2	What is the efficacy of bDMARD monotherapy vs. MTX ± other csDMARDs?	As in #1	bDMARD monotherapy	Comparator receiving a csDMARD but not receiving a bDMARD	As in #1
3	What is the efficacy of bDMARDs as monotherapy vs. bDMARD + MTX (or other csDMARD) combination therapy?	As in #1	bDMARD monotherapy	bDMARD + MTX and/or other csDMARD combination therapy	As in #1
4	What is the efficacy of one bDMARD vs. another (i.e. head to head studies)?	As in #1	bDMARD + MTX ± other csDMARDs	Other bDMARD + MTX ± other csDMARDs	As in #1
5	What is the efficacy of switching between the different bDMARDs?	As in #1	bDMARD + MTX ± other csDMARDs	Alternative bDMARDs	As in #1
6	What is the efficacy of bDMARD induction vs bDMARD add-on therapy (strategic studies)	As in #1	bDMARD initiation	bDMARD add-on to csDMARD	As in #1
7	What is the efficacy of bDMARD induction vs csDMARD combination induction (strategic studies)	As in #1	bDMARD initiation	csDMARD combination initiation	As in #1
8	What is the efficacy of step up to bDMARD induction vs step up to csDMARD combination (strategic studies)	As in #1	Step up from csDMARD monotherapy to combination of csDMARD + bDMARD	Step up from csDMARD monotherapy to combination of csDMARDs	As in #1
9	What is the evidence for stopping bDMARDs?	As in #1	bDMARD stopping	bDMARD continuation	As in #1
10	What is the evidence for stopping csDMARDs while on csDMARD + bDMARD combination therapy?	As in #1	csDMARD stopping, bDMARD continuation	csDMARD continuation, bDMARD continuation	As in #1
11	What is the evidence for bDMARD dose reduction or interval increases?	As in #1	bDMARD dose reduction or interval increases	bDMARD continuation with unchanged dosing/interval	As in #1
12	What is the evidence for efficacy of tsDMARDs?	As in #1	tsDMARD ± csDMARDs	Comparator not receiving a tsDMARD ± csDMARD or placebo	As in #1

13	What is the evidence for efficacy of bDMARDs vs. tsDMARDs?	As in #1	tsDMARD ± csDMARDs or placebo	Comparator receiving a bDMARD ± csDMARDs or placebo	As in #1
14	What is the evidence for efficacy of biosimilars?	As in #1	Biosimilar ± other csDMARDs	respective bDMARD originator	As in #1
15	What is the evidence for switching between bDMARDs (originator) and their respective biosimilars?	As in #1	switching to biosimilar	continuing respective bDMARD originator	As in #1
16	What is the efficacy of one csDMARD (or combination with csDMARDs/GCs) vs. another csDMARD (or combination) or placebo	As in #1	csDMARD ± Glucocorticoids	Other csDMARD or placebo ± Glucocorticoids	As in #1

Section 2: Study characteristics of articles and abstracts included.

Table S2.1: Details of articles and abstracts selected for inclusion.

PICO	Study	Treatment	Target	Population
1	Damjanov 2016 [1]	SBI-087	CD20	MTX-IR / TNF-IR
1	Aletaha 2017 (SIRROUND-T) [2-4]	Sirukumab	IL-6	TNF-IR
1	Buckley ACR 2018 [5]	Otilimab	GM-CSF	MTX-IR
1	Gupta ACR 2018 [6]	Otilimab	GM-CSF	DMARD-IR
1	Bi 2018 (RAPID-C) [7]	Certolizumab pegol	TNF	MTX-IR
1	Takeuchi 2016 (RA0083) [8]	Olokizumab	IL-6	TNF-IR
1	Smolen 2017a [9]	Ustekinumab / Guselkumab	IL12/23; IL23	MTX-IR
1	Burmester 2017b (EARTH EXPLORER 1) [10]	Mavrilimumab	GM-CSF	MTX-IR
1	Dorner 2017 [11]	Vobarilizumab	IL-6R	MTX-IR
1	Weinblatt 2017 [12]	Vobarilizumab	IL-6R	MTX-IR
1	Fleischmann 2017 (TARGET) [13]	Sarilumab	IL-6R	TNF-IR
1	Tahir 2017 (REASSURE) [14]	Secukinumab	IL-17	TNF-IR
1	Takeuchi 2017 (SIRROUND-D) [15]	Sirukumab	IL-6	csDMARD-IR
1	Mease 2018 [16]	CNTO6785	IL-17	MTX-IR
1	Tanaka 2018b (KAKEHASI) [17, 18]	Sarilumab	IL6-R	MTX-IR
1	van Vollenhoven 2018 [19]	Tregalizumab	CD4	MTX-IR
1	Dokoupilova 2018 (REASSURE2) [20]	Secukinumab	IL17	TNF-IR
1	Takeuchi 2018a [21]	Sirukumab	IL-6	MTX/SZP-IR
1	Mazurov 2018 [22]	BCD-020	CD-20	bDMARD-IR
1	Matsubara 2018 [23]	Abatacept vs. MTX	CD80/CD86	MTX-IR
4	Porter 2016 (ORBIT) [24]	Rituximab vs. Etanercept/Adalimumab	CD20 vs. TNF	CSDMARD-IR

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4	Burmester 2017 (MONARCH) [25]	Sarilumab vs. Adalimumab	IL-6R vs. TNF	MTX-IR
4	Strand 2018a (MONARCH) [26]	Sarilumab vs. Adalimumab	IL-6R vs. TNF	MTXIR
4	Blanco 2017 (NURTURE 1) [27]	Secukinumab; Abatacept	IL-17; CD80/CD86	TNF-IR
4	Weinblatt 2018 (EARTH EXPLORER 2) [28]	Mavrilimumab; Golimumab	GM-CSF; TNF	csDMARD-IR / TNF-IR
4	Genovese 2018b [29]	ABT-122; Adalimumab	TNF/IL-17A; TNF	MTXIR
4	Taylor 2018 (SIRROUND-H) [30]	Sirukumab vs. Adalimumab	IL-6 vs. TNF	MTXIR
4.5	Smolen 2016 (EXXELERATE) [31]	Certolizumab pegol vs. Adalimumab	TNF vs. TNF	MTXIR
5	Gottenberg 2016 (ROC) [32]	Abatacept; Rituximab; Tocilizumab vs. Adalimumab; Certolizumab; Infliximab; Golimumab; Etanercept	CD80/CD86; CD20; IL-6 vs. TNF	TNFIR
5	Verschueren 2018 (EXTEND) [33]	Sarilumab	IL-6R	TNF-IR; TCZ-R+IR
6	Emery 2017 (C-EARLY) [34]	Certolizumab pegol vs. MTX	TNF	Early RA; csDMARD naïve
6	Emery ACR 2018 (AVERT-2) [35]	Abatacept vs. MTX	CD80/CD86	Early RA; MTX naïve
6	Stamm 2018 (DINORA) [36]	Infliximab vs. MTX	TNF	Early RA
6	Burmester 2016/2017 (FUNCTION) [37, 38]	Tocilizumab vs. MTX	IL-6R	Early RA; MTX naïve
8	Møller-Bisgaard 2019 (IMAGINE-RA) [39]	csDMARD; bDMARD; MRI guided T2T vs. conventional T2T		DAS28-CRP≤3.2 + no swollen joint
8	Mueller 2019 [40]	Certolizumab pegol; csDMARDs; Glucocorticoids; T2T vs. fixed regime		csDMARD-IR
9	Oba 2017 / Tanaka ACR 2018 (RRRR) [41, 42]	Infliximab	TNF	MTX-IR, SDAI remission at week 54
9	Chatzidionysiou 2016 (ADMIRE) [43]	Adalimumab stopping vs. continuation	TNF	ADA+MTX for 6 months + DAS28<2.6 for 3 months
9	Moghadam 2016 (POET) [44, 45]	TNFi stopping vs. TNFi continuation	TNF	TNFi therapy for 1 year + DAS28<3.2 for 6 months or based on

				rheumatologist's impression
9	Emery 2019 (AVERT) [46]	Abatacept withdrawal and re-treatment on flare	CD80/CD86	DAS28CRP<3.2 after 12 months
9	Atsumi 2017 (C-OPERA) [47]	Stopping Certolizumab pegol	TNF	Early RA; MTX naïve; Discontinuation of CZP after week 52.
9	Kaneko 2018 (SURPRISE) [48]	Stopping Tocilizumab	IL-6R	DAS28-ESR<2.6 at week 52
9.11	Weinblatt 2017 (C-EARLY) [49]	Certolizumab tapering/stopping vs. Certolizumab continuation	TNF	Early-RA + sustained DAS28-ESR<3.2 at week 40+52
9.11	Ibrahim 2017 (OPTIRRA) [50]	TNFi continuation vs. tapering	TNF	DAS28≤3.2 + no increase >0.6 in previous 3 months
8,9,10,11	Akdemir 2018 (IMPROVED) [51]	bDMARD step up vs. csDMARD combination; stepwise T2T tapering according to DAS<1.6		Early RA/undiff. Arthritis
9,10,11	El Miedany 2016 [52]	Tapering and stopping bDMARD and/or csDMARD		DAS28-ESR<2.6 + csDMARD and bDMARD therapy
9,10,11	Van Mulligen EULAR 2018 (TARA) [53]	TNF vs. csDMARD tapering		bDMARD + csDMARD; DAS≤2.4 + SJC≤1 for >3 months
10	Kaeley 2016 (MUSICA) [54]	Adalimumab initiation; MTX high vs. low dosage	TNF	MTX-IR
10	Keystone 2016 (CAMEO) [55]	Etanercept; MTX continuation vs. discontinuation	TNF	MTX-IR; Etanercept + MTX for 6 months
10	Pope EULAR 2017 [56]	Certolizumab pegol; csDMARD continuation vs. discontinuation	TNF	DAS28-ESR improvement of ≥1.2 after 3 or 6 months

10	Pope ACR 2018 [57]	Certolizumab pegol; csDMARD continuation vs. discontinuation	TNF	DAS28-ESR improvement of ≥1.2 after 3 or 6 months
10	Burmester ACR 2018 (SEMIRA) [58]	Tocilizumab; Glucocorticoid tapering vs. continuation	IL-6R	TCZ +/– csDMARDs and GC ≥24 weeks; 5mg GC + DAS28-ESR ≤3.2 ≥4 weeks
10	Pablos 2018 (JUST-ACT) [59]	Tocilizumab + MTX; MTX continuation vs. discontinuation	IL-6R	TCZ + MTX; DAS28≤3.2 after 16 weeks
10	Kremer 2018 (COMP-ACT) [60]	Tocilizumab + MTX; MTX stopping	IL-6R	DAS28≤3.2 at wk24
10	Edwards 2018 (ACT-TAPER) [61]	Tocilizumab + MTX; MTX tapering vs. continuation	IL-6R	EULAR good/moderate at wk24
10	Stouten 2018 (CareRA) [62]	Step-down to LEF or MTX monotherapy	csDMARD	COBRA Avant-Garde arm; DAS28-CRP≤3.2 after 40 to 52 weeks
11	Urata EULAR 2016 (r-T4) [63]	ETN/TCZ/ABA: dose reduction T2T (SDAI/SDAI+MMP3)		bDMARD for 3 months; MMP3 normalization + SDAI<3.3
11	Bouman 2017 (DRESS) [64]	TNFi tapering vs. continuation	TNF	DAS28-CRP <3.2
11	l'Ami 2018 [65]	Adalimumab; interval increase vs. continuation	TNF	ADA trough level >8mcg/ml
12	Fleischmann 2015 [66]	Decernotinib	JAK-3	csDMARD-IR / TNF-IR
12	Genovese 2016c [67]	Decernotinib	JAK-3	csDMARD-IR
12	Genovese 2016b [68]	Decernotinib	JAK-3	MTX-IR
12	Takeuchi 2016a [69]	Peficitinib	JAK-1	csDMARD-IR / TNF-IR
12	Genovese 2017c [70]	Peficitinib	JAK-1	minimal csDMARD exposure; MTX naïve
12	Kivitz 2017 [71]	Peficitinib	JAK-1	MTX-IR
12	Tanaka ACR 2018a [72, 73]	Peficitinib	JAK-1	csDMARD-IR
12	Takeuchi ACR 2018 [74, 75]	Peficitinib	JAK-1	MTX-IR
12	Westhovens 2017 (DARWIN 1) [76]	Filgotinib	JAK-1	MTX-IR

12	Kavanaugh 2017 (DARWIN 2) [77]	Filgotinib	JAK-1	MTX-IR
12	van Vollenhoven ACR 2018 (SELECT-EARLY) [78]	Upadacitinib	JAK-1	MTX-naïve
12	Genovese 2018 (DARWIN 1+2) [79]	Filgotinib	JAK-1	MTXIR
12	Kivitz ACR 2018 [80]	GS-9876; Filgotinib	SYK; JAK-1	MTXIR
12	Takeuchi 2019 (RA-BEYOND) [81]	Baricitinib; Tapering to 2mg vs. BARI 4mg continuation	JAK-1/2	BARI 4mg + CDAI<10
12	Tanaka 2019 [82]	Tofacitinib	JAK-1/3	MTX-IR
12	van der Heijde 2019 (ORAL Scan) [83]	Tofacitinib	JAK-1/3	MTX-IR
12	Dougados 2017 (RA-BUILD) [84]	Baricitinib	JAK-1/2	csDMARD-IR
12	Genovese 2017a [85]	Baricitinib	JAK-1/2	csDMARD-IR
12	Fleischmann/Schiff 2017b (RA-BEGIN) [86, 87]	Baricitinib	JAK-1/2	csDMARD naïve
12	Smolen 2017d (RA-BEACON) [88]	Baricitinib	JAK-1/2	bDMARD-IR
12	Tanaka 2018a (SELECT-SUNRISE) [89]	Upadacitinib	JAK-1	csDMARDIR
12	van der Heijde 2018 (RA-BEYOND) [90]	Baricitinib	JAK-1/2	csDMARD-IR
12	Hu 2018 (RA-BALANCE) [91, 92]	Baricitinib	JAK-1/2	MTX-IR
12	Genovese/Strand 2018 (SELECT-BEYOND) [93, 94]	Upadacitinib	JAK-1	bDMARD-IR
12	Burmester 2018 (SELECT-NEXT) [95]	Upadacitinib	JAK-1	csDMARD-IR
12	Smolen EULAR/ACR 2018 (SELECT-MONOTHERAPY) [96-99]	Upadacitinib	JAK-1	MTX-IR
12	Strand 2018 (SELECT-NEXT) [100]	Upadacitinib	JAK-1	csDMARD-IR
13	Taylor 2017 (RA-BEAM) [101]	Baricitinib vs. Adalimumab	JAK-1/2 vs. TNF	MTX-IR
13	Keystone 2017 (RA-BEAM) [102]	Baricitinib vs. Adalimumab	JAK-1/2 vs. TNF	MTX-IR
13	Strand EULAR 2018 (ORAL-Strategy) [103]	Tofacitinib vs. Adalimumab	JAK-1/3 vs. TNF	MTX-IR
13	Fleischmann ACR 2018 (SELECT-COMPARE) [104, 105]	Upadacitinib vs. Adalimumab	JAK-1 vs. TNF	MTX-IR
13	Fleischmann 2017a (ORAL-Strategy) [103, 106]	Tofacitinib vs. Adalimumab	JAK-1/3 vs. TNF	MTX-IR

14	O'Dell EULAR 2016 [107]	ETN vs. CHS-0214	TNF	MTXIR
14	Jani 2016 [108]	Adalimumab vs. ZRC-3197	TNF	MTXIR
14	Denisov EULAR 2018 (LIRA) [109, 110]	Infliximab vs. BCD-055	TNF	NA
14	Wiland ACR 2018 [111]	Adalimumab vs. GP2017	TNF	csDMARDIR
14	Matsuno and Matsubara 2018 [112]	Infliximab vs. NI-071	TNF	MTX-IR
14	Yoo 2016 (PLANETRA) [113]	Infliximab vs CT-P13	TNF	MTXIR
14	Bae 2017 (HERA) [114]	Etanercept vs. HD203	TNF	MTXIR
14	Jamshidi 2017 [115]	Adalimumab + MTX; CinnoRA + MTX	TNF	MTXIR
14	Smolen 2017c [116]	Rituximab + MTX; GP2013 + MTX	TNF	TNFIR
14	Choe 2017 [117]	Infliximab + MTX; SB2 + MTX	TNF	MTXIR
14	Smolen 2017b [118]	Infliximab + MTX; SB2 + MTX	TNF	MTXIR
14	Cohen 2017 [119]	Adalimumab; ABP 501	TNF	MTXIR
14	Alten EULAR 2017 (ARABESC) [120, 121]	Adalimumab; FKB327	TNF	MTXIR
14	Apsangikar 2018 [122]	Adalimumab; AdaliRel	TNF	MTXIR
14	Cohen 2018b [123]	Infliximab; PF-06438179	TNF	MTXIR
14	Haridas 2018 [124]	DRL_RI; RMP; Rituximab	CD-20	MTXIR
14	Matucci-Cerinic 2018 (EQUIRA) [125]	Etanercept; GP2015	TNF	mixed
14	Matsuno 2018 [126]	Etanercept; LBEC0101	TNF	MTXIR
14	Fleischmann 2018 [127]	Adalimumab; PF-06410293	TNF	MTXIR
14	Park 2018 [128]	CT-P10; Rituximab	CD-20	MTXIR
14,15	Weinblatt 2018 [129]	Adalimumab; SB5	TNF	MTXIR
14,15	Nasonov ACR 2016 [130]	Rituximab; BCD-020	CD-20	TNFIR
14,15	Smolen 2018 [131]	Infliximab; SB2	TNF	MTXIR
14,15	Kavanaugh ACR 2018 (EQUIRA) [132, 133]	Etanercept; GP2015	TNF	csDMARD-IR; TNF-IR
14,15	Cohen 2018a (VOLTAIRE) [134]	Adalimumab; BI 695501	TNF	MTX-IR
14,15	Genovese 2017b [135]	Adalimumab; FKB327	TNF	MTXIR
15	Jorgensen 2017 (NOR-SWITCH) [136]	Infliximab; CT-P13	TNF	csDMARDIR

15	O'Dell 2017 [137]	Etanercept; CHS-0214	TNF	MTXIR
15	Song 2018 [138, 139]	Etanercept; LBEC0101	TNF	MTXIR
15	Weinblatt 2018 [140]	Adalimumab; SB5	TNF	MTXIR
16	Shin 2019 [141]	Tacrolimus + MTX vs. Leflunomide + MTX	csDMARD	MTX-IR
16	Register ACR 2016 [142]	MTX + SZP + HCQ vs. LEF + SZP + HCQ vs. LEF monotherapy	csDMARD	csDMARD-IR, Leflunomide naïve
16	Verschueren/Stouten (CareRA) 2017 [143, 144]	MTX + SZP + GC vs. MTX + GC vs. MTX + LEF + GC; MTX tight-step up vs. MTX + GC	csDMARD	Early RA; csDMARD naïve
NA	Stamp 2018 [145]	Folic acid reduction in MTX treated patients	MTX/Folic acid	MTX-IR

Table S2.2: Risk of bias analysis.

Study	Random sequence generation	Allocation concealment	Blinding of participants and personnel	Blinding of outcome assessment	Incomplete outcome data	Selective reporting	Other sources of bias	Summary	Comment
Damjanov 2016 [1]	Unclear	Unclear	Low	Low	Low	High	Low	High	only p values reported, no numerical ACR response rates
Aletaha 2017 (SIRROUND-T) [2-4]	Low	Low	Low	Low	Low	Low	Low	Low	
Buckley ACR 2018 [5]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Gupta ACR 2018 [6]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Bi 2018 (RAPID-C) [7]	Low	High	Unclear	Low	Low	Low	High	High	Potential unblinding during drug administration; High discontinuation numbers
Takeuchi 2016 (RA0083) [8]	Low	Low	Low	Low	Low	Low	Low	Low	
Smolen 2017a [9]	Unclear	Low	Low	Low	Low	Low	Low	Low	
Burmester 2017b (EARTH EXPLORER 1) [10]	Low	Low	Low	Low	Low	Low	Low	Low	
Dorner 2017 [11]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Weinblatt 2017 [12]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Fleischmann 2017 (TARGET) [13]	Low	Low	Low	Low	Low	Low	Low	Low	
Tahir 2017 (REASSURE) [14]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Takeuchi 2017 (SIRROUND-D) [15]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Mease 2018 [16]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	

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Tanaka 2018b (KAKEHASI) [17, 18]	Low	Low	Low	Low	Low	Low	Low	Low	
van Vollenhoven 2018 [19]	Low	Low	Low	Low	Low	Low	Low	Low	
Dokoupilova 2018 (REASSURE2) [20]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Takeuchi 2018a [21]	Low	Low	Low	Low	Low	Low	Low	Low	Dose finding study; no comparator group
Mazurov 2018 [22]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Matsubara 2018 [23]	Unclear	Low	Low	Low	Low	Low	Low	Low	
Porter 2016 (ORBIT) [24]	Low	Low	High	High	Low	Low	Low	Low	
Burmester 2017 (MONARCH) [25]	Low	Low	Low	Low	Low	Low	Low	Low	
Strand 2018a (MONARCH) [26]	Low	Low	Low	Low	Low	Low	Low	Low	
Oba 2017 / Tanaka ACR 2018 (RRRR) [41, 42]	Low	Low	High	Low	Abstract	Abstract	Unclear	High	Methodology reported; Results only as abstract; Open label study
Blanco 2017 (NURTURE 1) [27]	Unclear	Low	Low	Low	Low	Low	Low	Unclear	
Weinblatt 2018 (EARTH EXPLORER 2) [28]	Low	Low	Low	Low	Low	Low	Low	Low	
Genovese 2018b [29]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Taylor 2018 (SIRROUND-H) [30]	Low	Low	Low	Low	Low	Low	Low	Low	
Smolen 2016 (EXXELERATE) [31]	Low	Low	Low/High*	Low	Low	Low	Low	Unclear	unblinding of patients at wk 12
Gottenberg 2016 (ROC) [32]	Unclear	Unclear	High	High	Low	Low	Low	High	
Verschueren 2018 (EXTEND) [33]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Emery 2017 (C-EARLY) [34]	Low	Low	Low	Low	Low	Low	Low	Low	
Emery ACR 2018 (AVERT-2) [35]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	

Stamm 2018 (DINORA) [36]	Low	Low	Low	Low	High	Low	Low	High	146 pts initially planned in sample size calculation, 90 recruited
Burmester 2016/2017 (FUNCTION) [37, 38]	Low	Low	Low	Low	Low	Low	Low	Low	
Møller-Bisgaard 2019 (IMAGINE-RA) [39]	Low	Low	High	Low	Low	Low	High	High	Open label; group inbalances (remission at baseline); one-sided p (<0.05)
Mueller 2019 [40]	Low	Low	High	Unclear	Low	Low	Low	High	Open label; Blinding of outcome assessors not described;
Chatzidionysiou 2016 (ADMIRE) [43]	Unclear	Unclear	High	High	Low	Low	Low	High	open label
Moghadam 2016/2018 (POET) [44, 45]	low	Unclear	High	High	Low	Low	Low	High	open label
Emery 2019 (AVERT) [46]	Low	Low	High	High	Low	Low	Low	High	open label; retreatment of patients with flare
Atsumi 2017 (C-OPERA) [47]	Low	Low	High	Low	Low	Low	High	High	open label
Kaneko 2018 (SURPRISE) [48]	Low	Low	High	High	High	Low	Low	High	lower number randomized as planned
Weinblatt 2017 (C-EARLY) [49]	Low	Low	Low	Low	Low	Low	Low	Low	
Ibrahim 2017 (OPTIRRA) [50]	Low	Low	High	High	High	Low	Low	High	
Kaeley 2016 (MUSICA) [54]	Low	Low	Low	Low	Low	Low	Low	Low	
Keystone 2016 (CAMEO) [55]	Unclear	Unclear	High	High	Low	Low	High	High	many discontinuations because of lack of efficacy in ETN mono arm
Pope 2019 [56, 57, 146]	Low	Low	High	High	Low	Low	Low	High	Open label
Burmester ACR 2018 (SEMIRA) [58]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Pablos 2018 (JUST-ACT) [59]	Low	Low	Low	Low	Low	Low	Low	Low	

Kremer 2018 (COMP-ACT) [60]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Edwards 2018 (ACT-TAPER) [61]	Unclear	Unclear	Low	Low	Unclear	Low	Unclear	Unclear	terminated early due to poor recruitment
Urata EULAR 2016 (r-T4) [63]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Bouman 2017 (DRESS) [64]	Low	Low	High	High	Low	Low	Unclear	High	
L'Ami 2018 [65]	Unclear	Unclear	High	High	Low	Low	Low	High	
Fleischmann 2015 [66]	Low	Low	Low	Low	Low	Low	Low	Low	
Genovese 2016c [67]	Low	Low	Low	Low	Low	Low	Low	Low	
Genovese 2016b [68]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Takeuchi 2016a [69]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Genovese 2017c [70]	Unclear	Low	Low	Low	Low	Low	Unclear	Unclear	protocol changes reported in original article with reference to the supplementary material, no information in suppl. material available
Kivitz 2017 [71]	Unclear	Low	Low	Low	Low	Low	Unclear	Unclear	
Tanaka ACR 2018a [72, 73]	Low	Low	Low	Low	Low	Low	Low	Low	
Takeuchi ACR 2018 [74, 75]	Low	Low	Low	Low	Low	Low	Low	Low	
Westhovens 2017 (DARWIN 1) [76]	Low	Low	Low	Low	Low	Low	Low	Low	
Kavanaugh 2017 (DARWIN 2) [77]	Low	Low	Low	Low	Low	Low	Low	Low	
van Vollenhoven ACR 2018 (SELECT-EARLY) [78]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Genovese 2018 (DARWIN 1+2) [79]	Low	Low	Low	Low	Low	Low	Low	Low	
Kivitz ACR 2018 [80]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Takeuchi 2019 (RA-BEYOND) [81]	Low	Low	Low	Low	Low	Low	Low	Low	

Tanaka 2019 [82]	Low	Low	Low	Unclear	Low	Low	Low	Unclear	
van der Heijde 2019 (ORAL Scan) [83]	Low	Low	Low	Low	Low	Low	Low	Low	
Dougados 2017 (RA-BUILD) [84]	Low	Low	Low	Low	Low	Low	Low	Low	
Genovese 2017a [85]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Fleischmann 2017b (RA-BEGIN) [86]	Low	Low	Low	Low	Low	Low	Low	Low	
Schiff 2017 (RA-BEGIN) [87]	Low	Low	Low	Low	Low	Low	Low	Low	
Smolen 2017d (RA-BEACON) [88]	Low	Low	Low	Low	Low	Low	Unclear	Low	protocol changes after the enrollment of 97 patients: Inclusion criteria was revised to require csDMARD-IR (before treatment-naïve patients could enter the study)
Tanaka 2018a (SELECT-SUNRISE) [89]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Open label
van der Heijde 2018 (RA-BEYOND) [90]	Low	Low	High	Low	Low	Low	Low	High	
Hu 2018 (RA-BALANCE) [91]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Strand 2018 (SELECT-BEYOND) [94]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Yue 2018 (RA-BALANCE) [92]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Genovese 2018a (SELECT-BEYOND) [93]	Low	Low	Low	Low	Low	Low	Low	Low	
Burmester 2018 (SELECT-NEXT) [95, 100]	Low	Low	Low	Low	Low	Low	Low	Low	
Smolen EULAR/ACR 2018 (SELECT-MONOTHERAPY) [96-99]	Low	Low	Low	Low	Low	Low	Low	Low	

Taylor 2017 (RA-BEAM) [101]	Low	Low	Low	Low	Low	Low	Low	Low	
Keystone 2017 (RA-BEAM) [102]	Low	Low	Low	Low	Low	Low	Low	Low	
Fleischmann ACR 2018 (SELECT-COMPARE) [104, 105]	Low	Low	Low	Low	Low	Low	Low	Low	
Fleischmann 2017a (ORAL-Strategy) [103, 106]	Low	Low	Low	Low	Low	Low	Low	Low	
O'Dell EULAR 2016 [107]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Jani 2016 [108]	Low	Low	Low	Low	Low	Low	High	High	
Denisov EULAR 2018 (LIRA) [109, 110]	Low	Low	Low	Low	Low	Low	Low	Low	
Wiland ACR 2018 [111]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Matsuno and Matsubara 2018 [112]	Low	Low	Low	Unclear	Low	Low	Low	Unclear	
Yoo 2016 (PLANETRA) [113]	Low	Low	Low	Low	Low	Low	Low	Low	
Bae 2017 (HERA) [114]	Low	Low	Low	Low	Low	Low	High	Low	
Jamshidi 2017 [115]	Low	Low	Low	Low	Low	Low	Low	Low	
Smolen 2017c [116]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Choe 2017 [117]	Low	Low	Low	Low	Low	Low	Low	Low	
Smolen 2017b [118]	Low	Low	Low	Low	Low	Low	Low	Low	
Cohen 2017 [119]	Low	Low	Low	Low	Low	Low	Low	Low	
Alten EULAR 2017 (ARABESC) [120, 121]	Low	Low	Low	Low	Low	Low	Low	Low	
Apsangikar 2018 [122]	Low	Low	Low	Low	High	Low	High	High	protocol change: requirement of csdmard washout
Cohen 2018b [123]	Unclear	Unclear	Low	Low	Low	Low	High	High	
Haridas 2018 [124]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Matucci-Cerinic 2018 (EQUIRA) [125]	Low	Low	Low	Low	Low	Low	Low	Low	

Park 2018 [128]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Weinblatt 2018 [129]	Low	Low	Low	Low	Low	Low	Low	Low	
Matsuno 2018 [126]	Low	Low	Low	Low	Low	Low	Low	Low	
Nasonov ACR 2016 [130]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Fleischmann 2018 [127]	Unclear	Unclear	Low	Low	Low	Low	Low	Unclear	
Smolen 2018 [131]	Low	Low	Low	Low	Low	Low	Low	Low	
Kavanaugh ACR 2018 (EQUIRA) [132, 133]	Low	Low	Low	Low	Low	Low	Low	Low	
Genovese 2017b [135]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Jorgensen 2017 (NOR-SWITCH) [136]	Low	Low	Low	Low	Low	Low	Low	Low	
O'Dell 2017 [137]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Song 2018 [138, 139]	Low	Low	High	High	Low	Low	Low	High	Open label
Weinblatt 2018 [140]	Low	Low	Low	Low	Low	Low	Low	Low	
Shin 2019 [141]	Low	Unclear	Low	Unclear	Low	Low	Unclear	Unclear	baseline differences between groups
Register ACR 2016 [142]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Verschueren 2017 (CareRA) [143][144][62]{Stouten, 2019 #2147}	Low	Low	High	High	Low	Low	Low	High	
Cohen 2018a (VOLTAIRE) [134]	Low	Low	Low	Low	High	Low	Low	Unclear	Efficacy at week 48 not reported numerically
Akdemir 2018 (IMPROVED) [51]	Low	Low	High	Low	Low	Low	Low	High	single blinded
El Miedany 2016 [52]	Unclear	Unclear	High	High	High	High	Low	High	open label, primary endpoint (pat in sustained DAS28<2.6) not reported
Van Mulligen EULAR 2018 (TARA) [53]	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	Abstract	
Stamp 2018 [145]	Unclear	Low	Low	Low	Low	Low	Unclear	Unclear	Randomization sequence generation not adequately reported;

Table S2.3: Baseline characteristics of trials investigating bDMARDs ± csDMARDs versus placebo.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean HAQ	Mean mTSS
Damjanov 2016 [1]	SBI-087/Pbo/Pbo + MTX	43	56.8	9	5.7	1.5	
	SBI-087/SBI-087/Pbo + MTX	42	53.9	8.9	5.5	1.5	
	SBI-087/Pbo/SBI-087 + MTX	43	52.9	8.9	5.8	1.5	
	SBI-087/SBI-087/SBI-087 + MTX	41	57.9	7.8	5.5	1.4	
	Pbo/Pbo/Pbo + MTX	40	52	7.7	5.5	1.4	
Aletaha 2017 (SIRROUND-T) [2, 3]	Placebo ± csDMARDs	294	55.4	12.25	5.84	1.57	
	SKM 50mg Q4W ± csDMARDs	292	55.8	12.85	5.94	1.65	
	SKM 100mg Q2W ± csDMARDs	292	55	12.27	5.87	1.61	
Buckley ACR 2018 [5, 6]	Placebo + MTX	37	50				
	OTM 22.5mg + MTX	37	48.4				
	OTM 45mg + MTX	37	52.8				
	OTM 90mg + MTX	37	52.7				
	OTM 135mg + MTX	37	47.1				
	OTM 180mg + MTX	37	52.3				
Bi 2018 (RAPID-C) [7]	Placebo + MTX	113	47.1	6.6	6.6		
	CZP + MTX	316	48.2	7	6.7		
Takeuchi 2016 (RA0083) [8]	Placebo + MTX	29	52.6	6.5	5.3	1.13	
	OKZ 60mg Q4W + MTX	32	53.9	7.6	5.5	1.19	

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	OKZ 120mg Q4W + MTX	32	55.7	6.9	5.2	1.25	
	OKZ 240mg Q4W + MTX	36	56.7	6.9	5.3	0.88	
Smolen 2017a [9]	Placebo + MTX	55	51.1	8.5	6.1	1.7	
	UKM 90mg Q8W + MTX	55	50.8	5.6	6	1.8	
	UKM 90mg Q12W + MTX	55	51.4	6.8	6.1	1.7	
	GKM 50mg Q8W + MTX	55	49.9	6.1	6.1	1.7	
	GKM 200mg Q8W + MTX	54	54.6	8.9	6.1	1.8	
Burmester 2017b (EARTH EXPLORER 1) [10]	MVM 150mg Q2W + MTX	79	52.6	8.5	5.7	1.58	
	MVM 100mg Q2W + MTX	85	50.8	7.2	5.9	1.58	
	MVM 30mg Q2W + MTX	81	51.2	7.8	5.7	1.52	
	Placebo + MTX	81	52.8	7.6	5.8	1.63	
Dorner 2017 [11]	VBM 150mg Q4W	62					
	VBM 150mg Q2W	62					
	VBM 225mg Q2W	63					
	(Open-Label) TCZ 162mg Q1W	60					
Weinblatt 2017 [12]	Placebo + MTX	69					
	VBM 75mg Q4W + MTX	69					
	VBM 150mg Q4W + MTX	70					
	VBM 150mg Q2W	68					
	VBM 225mg Q2W	69					
Fleischmann 2017 (TARGET) [13]	Placebo + csDMARDs	181	51.9	12	6.2	1.8	
	SLM 150mg Q2W + csDMARDs	181	54	11.6	6.1	1.7	
	SLM 200mg Q2W + csDMARDs	184	52.9	12.7	6.3	1.8	
Tahir 2017 (REASSURE) [14]	SEC 3x10mg/kg i.v. Q2W /150mg s.c. Q4W ± MTX	213	53.2	9	4.9	1.7	48.1
	SEC 3x10mg/kg i.v. Q2W /75mg s.c. Q4W ± MTX	210	53.3	8.4	4.9	1.7	55
	Placebo ± MTX	214	52.2	7.8	4.8	1.7	57.7
Takeuchi 2017 (SIRROUND-D) [15]	Placebo + csDMARD	556	52.9	8.3	5.9	1.6	41.9
	SKM 50mg Q4W + csDMARD	557	52.9	8.7	5.9	1.5	41.8

	SKM 100mg Q2W + csDMARD	557	53	8.8	5.8	1.5	42.5
Mease 2018 [16]	Placebo + MTX	51	49.8	5.4	4.9	1.6	
	CNTO6785 15mg Q4W + MTX	52	49.5	3.5	4.9	1.4	
	CNTO6785 50mg Q4W + MTX	51	52.3	4.7	4.9	1.5	
	CNTO6785 100mg Q4W + MTX	51	52.3	5.1	5	1.5	
	CNTO6785 200mg Q4W + MTX	52	52.9	5.8	5	1.4	
Tanaka 2018b (KAKEHASI) [17, 18]	Placebo + MTX	82	53.4				
	SLM 150mg Q2W + MTX	81	56.1				
	SLM 200mg Q2W + MTX	80	55.3				
van Vollenhoven 2018 [19]	Placebo + MTX	79	53.9	7.09	6.66	1.65	
	TLM 25mg + MTX	80	53.7	7.08	6.64	1.59	
	TLM 100mg + MTX	78	48.9	7.58	6.46	1.48	
	TLM 200mg + MTX	76	52.8	7.78	6.57	1.53	
Dokoupilova 2018 (REASSURE2) [20]	SEC 150mg + csDMARDs	81	55.1	10.7	5.7	1.6	
	SEC 75mg + csDMARDs	80	53.2	10.8	5.6	1.6	
	Placebo + csDMARDs	81	54.2	10.5	5.7	1.6	
Takeuchi 2018a [21]	SKM 50mg Q4W + csDMARDs	61	55.4	5	5.6	1.4	
	SKM 100mg Q2W + csDMARDs	61	54.7	6.3	5.9	1.1	
Mazurov 2018 [22]	BCD-020 + MTX	107					
	Placebo + MTX	52					
Matsubara 2018 [23]	ABA ± 500mg/750mg/1000mg Q4W + MTX	203	56.6	1.78	4.9	1	11.3
	Placebo + MTX	202	54.8	1.74	4.7	0.9	10.7

Table S2.3: Baseline characteristics of bDMARD Head-to-Head trials.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Porter 2016 (ORBIT) [24]	Anti-CD20 (RTX)	144	57	0.66	6.2		1.7	
	TNFi (ETA/ADA)	151	57	0.56	6.2		1.8	
Burmester 2017 (MONARCH) [25, 26]	ADA 40mg Q2W	185	53.6	6.6	6		1.6	
	SLM 200mg Q2W	184	50.9	8.1	6		1.6	
Blanco 2017 (NURTURE 1) [27]	SEC 10mg/kg i.v. + 150mg s.c. Q4W + csDMARD	137	55.9	9.5	5.9		1.7	
	SEC 10mg/kg i.v. + 75mg s.c. Q4W + csDMARD	138	54.9	10.2	5.7		1.7	
	ABA 500/750/1000mg + csDMARD	138	51.6	10.2	5.7		1.7	
	Placebo + csDMARD	138	55.5	10.3	5.8		1.8	
Weinblatt 2018 (EARTH EXPLORER 2) [28]	MVM 100mg Q2W + MTX	70	50.2	5.8	5.8		1.6	
	GLM 50mg Q4W	68	49.9	7.6	5.7		1.6	
Genovese 2018b [29]	ADA 40mg Q2W + MTX	56	57.6	7.6	5.8			
	ABT-122 60mg Q2W + MTX	55	55.2	7	6			
	ABT-122 120mg Q2W + MTX	56	53.5	9.4	5.6			
	ABT-122 120mg QW + MTX	55	55.6	6.8	5.7			
Taylor 2018 (SIRROUND-H) [30]	ADA 40mg Q2W	186	52.6	4	6.05		1.7	
	SKM 50mg Q4W	186	52.5	4.24	6.12		1.75	
	SKM 100mg Q2W	187	49.8	4.6	6.08		1.62	
Smolen 2016 (EXXELERATE) [31]	CZP 400/200mg Q2W + MTX	454	53.5	6	6.5	38.1	1.5	
	ADA 40mg Q2W + MTX	454	52.9	5.8	6.5	39.2	1.5	

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Table S2.4: Baseline characteristics of trials investigating switching between different bDMARDs.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Gottenberg 2016 (ROC) [32]	Non-TNFi (ABA; RTX; TCZ)	146	58.2	10	4.8		1.3	
	TNFi (ADA; CZP; ETA; GOL; INF)	146	55.9	11	4.7		1.3	
Smolen 2016 (EXXELERATE) [31]	CZP primary non-responders switched to ADA	65	53	6.1	6.5	38.8	1.6	
	ADA primary non-responders switched to CZP	57			6.3	38.0	1.5	
Verschueren 2018 (EXTEND) [33]	TCZ 4mg/kg non-responders; SAR 200mg Q2W + csDMARDs	37						
	TCZ 4mg/kg responders; SAR 200mg Q2W + csDMARDs							
	TCZ 8mg/kg non-responders; SAR 200mg Q2W + csDMARDs	56						
	TCZ 8mg/kg responders; SAR 200mg Q2W + csDMARDs							

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Table S2.5: Baseline characteristics of bDMARD induction vs. csDMARD induction trials in early RA.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean HAQ	Mean mTSS
Emery 2017 (C-EARLY) [34]	Placebo + MTX	213	51.2	0.24	6.8	1.7	8.5
	CZP 200mg Q4W + MTX	655	50.4	0.24	6.7	1.6	7.2
Emery ACR 2018 (AVERT-2) [35]	ABA 125mg QW + MTX	225[a]/451[b]	50[a]	0.11[a]	5.7[a]	1.6[a]	9.8[b]
	Placebo + MTX	150[a]/301[b]	50[a]	0.11[a]	5.6[a]	1.6[a]	13[b]
Stamm 2018 (DINORA) [36]	INF (3mg/kg wk0 , 2, 6; INF 4mg/kg Q8W) + MTX	36	52.1	0.2	5	0.9	2.8
	Placebo + MTX	36	52.9	0.18	4.8	0.9	3
	Placebo	16	54.4	0.19	4.7	0.7	4.6
Burmester 2016 (FUNCTION) [37, 38]	Placebo + MTX	287	49.6	0.4	6.6	1.48	5.66
	TCZ 4mg/kg Q4W + MTX	288	51.2	0.4	6.7	1.62	7.72
	TCZ 8mg/kg Q4W + MTX	290	49.5	0.5	6.7	1.5	6.17
	TCZ 8mg/kg Q4W + Placebo	292	49.9	0.5	6.7	1.58	6.85

[a] week 24; [b] week 52;

Table S2.6: Baseline characteristics studies investigating strategic studies.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Møller-Bisgaard 2019 (IMAGINE-RA) [39]	MRI treat-to-target	100	62.7	9	2		0.44	20
	Conventional treat-to-target	100	60.55	11	1.9		0	15
Mueller 2019 [40]	CZP + treat-to-target csDMARDs/GCs	21	56.3	0.99	5.89		0.84	
	CZP + fixed regimen	22	56.8	0.85	6.16		0.85	

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Table S2.7: Baseline characteristics studies investigating tapering of DMARDs.

If available, characteristics of the timepoint before treatment discontinuation/tapering are shown.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Oba 2017 / Tanaka ACR 2018 (RRRR) [41, 42]	INF 3/8/10mg/kg programmed Q8W	170	58		4.2		1	
	INF standard 3mg/kg Q8W	167	59		4.1		1	
Chatzidionysiou 2016 (ADMIRE)* [43]	ADA + MTX continuation	16	56	7.6	2.13			0.13
	ADA discontinuation; MTX monotherapy	16	64	10.4	1.69			0.38
Moghadam 2016/2018 (POET) [44] [45]	Stopping TNFi	531	60	12	1.98		0.6	
	Continuation of TNFi	286	59.7	11.1	2.05		0.59	
Emery 2019 (AVERT) [46]	ABA + MTX continuation	84	47.1	0.58	5.4			1.4
	ABA monotherapy	66	44.5	0.64	5.4			1.3
	MTX monotherapy	73	49	0.47	5.3			1.3
Atsumi 2017 (C-OPERA) [47]	CZP + MTX continuation	108	48.8	4.4	5.2		1.04	3.8
	Stopping CZP; MTX + PLC	71	48.6	4.4	5.1		0.79	3.2
Kaneko 2018 (SURPRISE) [48]	stopping TCZ; MTX monotherapy	49	57.5	3.6	1.4			0.32
	stopping TCZ; No DMARD	53	54.4	3.5	1.4			0.31
Weinblatt 2017 (C-EARLY) [49]	CZP 200mg Q2W + MTX (standard)	84	49.1	0.21	2	2.2	0.3	3.3
	CZP 200mg Q4W + MTX (reduced frequency)	126	49.2	0.22	2	2.2	0.3	4.5
	Placebo + MTX (CZP stopped)	79	47.6	0.24	1.9	1.6	0.3	5
	Placebo + MTX (MTX responders)	66	51.2	0.26	2.2	2.6	0.4	6.8
Ibrahim 2017 (OPTIRRA) [50]	TNFi 33% tapering	26	59	11.2	2.3		0.75	
	TNFi 66% tapering	21	58	10.6	2.2		0.38	

	Controls	50	56	11.9	2.1		0.5	
Akdemir 2018 (IMPROVED) [51]	Overall IMPROVED study population	610	52	0.34	3.2		1.2	2.1
	Arm 1 (csDMARD + GC Start) at randomization (4 months)	83			2.5		0.85	
	Arm 2 (ADA Start) at randomization (4 months)	78			2.6		0.88	
El Miedany 2016 [52]	bDMARD tapering -50%, csDMARDs unchanged	31			1.97			
	csDMARD + bDMARD -50%	32			2.1			
	stop bDMARD, reduce csDMARD -50%	31			2.1			
	stop bDMARD+csDMARD	31			2.04			
	continue bDMARD+csDMARD	32			2.2			
Van Mulligen EULAR 2018 (TARA) [53]	Tapering csDMARDs	93	55.8	6	1.1[a]		0.52	
	Tapering TNFi	94	57.1	6.2	1[a]		0.47	
Kaeley 2016 (MUSICA) [54]	ADA 40mg Q2W + 7.5 mg MTX	154	55.1	5.9	0.92	40.6	1.45	
	ADA 40mg Q2W + 20 mg MTX	155	54.5	4.7	0.96	41.3	1.47	
Keystone 2016 (CAMEO) [55]	ETA 50mg QW; MTX discontinuation	98	54.3	9	3.44	13	1.3	37.9
	ETA 50mg QW + MTX continuation	107	54.4	9.3	3.55	12.9	1.5	38.2
Pope EULAR 2017/ACR 2018 [56, 57]	CZP + csDMARD continuation	37	58.4		5.4			
	CZP + csDMARD discontinuation	44	54.2		5			
Burmester ACR 2018 (SEMIRA) [58]	TCZ ± csDMARDs; Glucocorticoid tapering	131		9.2	1.9			
	TCZ ± csDMARDs; Glucocorticoid continuation	128		9.2	1.9			
Pablos 2018 (JUST-ACT) [59]	TCZ 8 mg/kg + MTX	82	50.2	5.8	1.8		0.5	
	TCZ 8 mg/kg + PBO	82	51	6.4	2		0.7	
Kremer 2018 (COMP-ACT) [60]	TCZ 162mg s.c. + PLC	147	54.6	6.8	6.2	37.3	1.3	
	TCZ 162mg s.c. + MTX	147	56.4	6.8	6.3	39.1	1.4	

Edwards 2018 (ACT-TAPER) [61]	TCZ 8mg/kg Q4W + PBO	136	54.4	7.9	6.58			
	TCZ 8mg/kg Q4W + MTX	136	56.4	7.2	6.61			
Urata EULAR 2016 (r-T4) [63]	Standard care	56	60.8	4.9		2.2[b]	0	48.4
	SDAI guided tapering	54	65.4	5.5		2.6[b]	0	42.7
	MMP-3 guided tapering	57	64.5	4.2		2.6[b]	0	51.7
	SDAI + MMP-3 guided tapering	56	62.8	3.3		2.4[b]	0	39
Bouman 2017 (DRESS) [64]	TNFi dose reduction extension	115	60.9	11	2.7			
	Usual care extension	57	59.7	12	2.5			
	TNFi dose reduction intervention	115	59	10	2.5			21
	Usual care intervention	57	58	10	2.5			19
L'Ami 2018 [65]	ADA 40mg Q3W ± MTX	27	60	11	2	3.4	0.4	
	ADA 40mg Q2W ± MTX	27	58	11	1.6	3.4	0.5	
Takeuchi 2019 (RA-BEYOND) [76]	Continued BARI 4mg ± csDMARD	281	54.5	9.5	2.03	3.64	0.52	
	BARI Step-down 2mg ± csDMARD	278	53.6	9.3	2.02	3.64	0.53	
Stouten 2018 (CareRA) [62]	COBRA Avant Garde->MTX 15mg/week	32	51.1	0.06	4.7		1	1
	COBRA Avant Garde->LEF 20mg/d	26						
* numbers reported as median; [a] DAS44; [b] SDAI								

Table S2.8: Baseline characteristics studies investigating tsDMARDs ± csDMARDs versus placebo ± csDMARDs.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Fleischmann 2015 [66]	Placebo	41	54.9	10.6	6.0		1.6	
	DEC 25mg BID	41	56.8	9.5	6.2		1.7	
	DEC 50mg BID	41	55.6	11.3	6.2		1.6	
	DEC 100mg BID	40	56.5	8.9	6.0		1.6	
	DEC 150mg BID	41	57	9.3	6.1		1.7	
Genovese 2016c [67]	Placebo + csDMARD	12	52.8	12.3	6.3			
	DEC 100mg BID + csDMARD	11	56.7	6.5	5.4			
	DEC 200mg BID + csDMARD	10	50.5	11.9	5.8			
	DEC 300mg BID + csDMARD	10	54.9	5	6.1			
Genovese 2016b [68]	Placebo + MTX	71	52.7	13.2	7.2		1.7	
	DEC 100mg OD + MTX	71	53.5	11.3	6.5		1.5	
	DEC 150mg OD + MTX	72	50.1	11.8	8.1		1.2	
	DEC 200mg OD + MTX	72	53.2	13.2	7.2		1.5	
	DEC 100mg BID + MTX	72	55.7	12.2	7.7		1.6	
Takeuchi 2016a [69]	Placebo	56	54.2	12.1	5.1		0.9	
	PEF 25mg OD	55	52.9	9.5	5.3		0.9	
	PEF 50mg OD	57	54.2	11.6	5.26		0.9	
	PEF 100mg OD	55	52.1	12.1	5.34		1.0	
	PEF 150mg OD	58	51.6	12.1	5.41		1.0	
Genovese 2017c [70]	Placebo + HCQ/SZP	51	52.7	9.8	5.9	40.8	1.6	
	PEF 25mg + HCQ/SZP	59	52.6	10.4	5.8	40.8	1.4	
	PEF 50mg + HCQ/SZP	57	54.8	10.3	5.9	42	1.6	
	PEF 100mg + HCQ/SZP	58	54.9	11	5.7	40.4	1.4	

	PEF 150mg + HCQ/SZP	64	54.4	10.5	5.9	41.6	1.5	
Kivitz 2017 [71]	Placebo + MTX	72	52.6	7.2	5.4	36	1.4	
	PEF 25mg + MTX	66	52.8	8.1	5.5	37.6	1.4	
	PEF 50mg + MTX	78	52.3	8	5.6	37.8	1.3	
	PEF 100mg + MTX	84	54.5	7.5	5.6	39.4	1.3	
	PEF 150mg + MTX	78	54.2	7.3	5.6	38.8	1.3	
Tanaka ACR 2018a [72, 73]	Placebo ± csDMARDs	101						
	PEF 100mg OD ± csDMARDs	104						
	PEF 150mg OD ± csDMARDs	102						
	ETA 50mg QW ± csDMARDs	200						
Takeuchi ACR 2018 [74, 75]	Placebo + MTX	170						
	PEF 100mg OD + MTX	174						
	PEF 150mg OD + MTX	174						
Westhovens 2017 (DARWIN 1) [76, 79]	Placebo + MTX	86	52	8	5.98	42	1.7	
	FILGO 50mg OD + MTX	82	53	7	6.08	41	1.7	
	FILGO 100mg OD + MTX	85	52	8	6.14	43	1.7	
	FILGO 200mg OD + MTX	86	55	9	6.22	43	1.8	
	FILGO 25mg BID + MTX	86	52	9	6.05	41	1.7	
	FILGO 50mg BID + MTX	85	55	8	6.1	42	1.8	
	FILGO 100mg BID+ MTX	84	54	10	6.14	42	1.8	
Kavanaugh 2017 (DARWIN 2) [77, 79]	Placebo	72	52	10	6.22	42	1.8	
	FILGO 50mg OD	72	52	9	6.03	41	1.8	
	FILGO 100mg OD	70	53	9	6.18	44	1.8	
	FILGO 200mg OD	69	52	9	6.09	42	1.8	
Kivitz ACR 2018 [80]	Placebo + MTX	22	54		5.51		1.5	
	GS-9876 10mg OD + MTX	20	56		5.65		1.5	
	GS-9876 30mg OD + MTX	20	58		5.78		1.4	
Dougados 2017 (RA-BUILD) [84, 85]	Placebo + csDMARD	228	51	7	5.5	36	1.5	19
	BARI 2mg + csDMARD	229	52	8	5.6	37	1.51	26

	BARI 4mg + csDMARD	227	52	8	5.6	36	1.55	24
Schiff/Fleischmann 2017b (RA-BEGIN) [86, 87]	Placebo + MTX	210	51	1.3	5.9	39	1.7	11.8
	BARI 4mg + Placebo	159	51	1.9	5.9	40	1.6	13.3
	BARI 4mg + MTX	215	49	1.3	5.9	40	1.6	11.4
Smolen 2017d (RA-BEACON) [88]	Placebo + csDMARD	176	56	14	5.9	41	1.78	
	BARI 2mg + csDMARD	174	55	14	6	43	1.71	
	BARI 4mg + csDMARD	177	56	14	5.9	40	1.74	
Hu/Yue 2018 (RA-BALANCE) [91, 92]	Placebo + MTX	145	48.9	9.1			1.52	
	BARI 4mg + MTX	145	49.5	10.7			1.59	
Tanaka 2019 [82]	TOFA 11mg modified-release OD + MTX	104	57.1	9.5	5.1		1	
	TOFA 5mg immediate-release BID + MTX	105	58.9	9.4	5		0.9	
van der Heijde 2019 (ORAL Scan) [83]	TOFA 5mg + MTX	321	53.7	8.9	5.22		1.41	31.1
	TOFA 10mg + MTX	316	52	9	5.2		1.39	37.3
	Placebo->TOFA 5mg + MTX	81	53.2	8.8	5.14		1.4	35
	Placebo->TOFA 10mg + MTX	79	52.1	9.5	5.18		1.23	30.1
Tanaka 2018a (SELECT-SUNRISE) [89]	Placebo + csDMARDs	49						
	UPA 7.5mg + csDMARDs	49						
	UPA 15mg + csDMARDs	49						
	UPA 30mg + csDMARDs	50						
Genovese/Strand 2018 (SELECT-BEYOND) [93, 94]	Placebo + csDMARD	169	57.6	14.5	5.8	41	1.6	
	UPA 15mg + csDMARD	164	56.3	12.4	5.9	41.7	1.7	
	UPA 30mg + csDMARD	165	57.3	12.7	5.8	40.1	1.6	
Burmester/Strand 2018 (SELECT-NEXT) [95, 100]	Placebo + csDMARD	221	56	7.2	5.6	37.8	1.4	
	UPA 15mg + csDMARD	221	55.3	7.3	5.7	38.3	1.5	
	UPA 30mg + csDMARD	219	55.8	7.3	5.7	38.6	1.5	
van Vollenhoven ACR 2018 (SELECT-EARLY) [78]	Placebo + MTX	314						
	UPA 15mg + MTX	317						
	UPA 30mg + MTX	314						

Smolen EULAR/ACR 2018 (SELECT-MONOTHERAPY) [96-99]	Continued MTX	216	55.3	5.8	5.6	37.8	1.5	
	UPA 15mg	217	54.5	7.5	5.6	38	1.5	
	UPA 30mg	215	53.1	6.5	5.6	38.4	1.5	

Table S2.9: Baseline characteristics studies investigating Head-to-Head studies between tsDMARDs and bDMARDs.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Taylor/Keystone 2017 (RA-BEAM) [101, 102]	Placebo + MTX	488	53	10	5.7	38	1.55	45
	BARI 4mg + MTX	487	54	10	5.8	38	1.57	43
	ADA 40mg Q2W + MTX	330	53	10	5.8	38	1.59	44
Fleischmann 2017/Strand EULAR 2018 (ORAL-Strategy) [103, 106]	TOFA 5mg BID + PLC	384	49.7	6.1	5.7	38.6	1.6	
	TOFA 5mg BID + MTX	376	50	5.4	5.8	39.7	1.6	
	ADA 40mg Q2W + MTX	386	50.7	6	5.7	38.2	1.6	
Fleischmann ACR 2018 (SELECT-COMPARE) [104, 105]	Placebo + MTX	651						
	UPA 15mg OD + MTX	651						
	ADA 40mg Q2W + MTX	327						

Table S2.10: Baseline characteristics of studies investigating the efficacy of boDMARDs (biooriginators) versus bsDMARDs (biosimilars).

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Jani 2016 [108]	ZRC-3197	60	45	3.3	5.9			
	ADA	60	45	4	6			
Denisov EULAR 2018 (LIRA) [109, 110]	BCD-055	198						
	INF							
Wiland ACR 2018 [111]	GP2017	177						
	ADA	176						
Matsuno and Matsubara 2018 [112]	NI-071	126	54		5.28		0.64	
	INF	116	53.7		5.13		0.54	
Yoo 2016 (PLANETRA) [113]	CT-P13	302	50		5.9	40.9	1.6	
	INF	304	50		5.8	39.3	1.6	
Bae 2017 (HERA) [114]	HD203	115	51	7.19			1.1	
	ETA	118	51.3	8.05			1.1	
Jamshidi 2017 [115]	CinnoRA	68	48.29	5.51			1.25	
	ADA	68	47.59	5.47			1.38	
Smolen 2017c [116]	GP2013	133	54.4	10.5	5.8		1.9	
	RTX-EU	87	52.7	10.8	5.9		1.8	
	RTX-US	92	55	11.0	5.9		1.9	
Choe/Smolen 2017 [117, 118]	SB2	291	51.6	6.3	6.5	38.3	1.5	37.06
	INF	293	52.6	6.6	6.5	38.7	1.5	38.92
Cohen 2017 [119]	ABP 501	264	55.4	9.41	5.66		1.5	
	ADA	262	56.3	9.37	5.68		1.5	

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Alten EULAR 2017 (ARABESC) [120, 121]	FKB327	366	55.3		6.1			
	ADA	362						
Apsangikar 2018 [122]	AdaliRel	85	42.5					
	ADA	21	47.1					
Cohen 2018b [123]	PF-06438179/GP1111	324	52.8	7.3	6.0		1.6	
	INF	326	52.8	6.4	6.0		1.6	
Haridas 2018 [124]	DRL-RI	276						
	RTX-US							
	RTX-EU							
Matucci-Cerinic 2018 (EQUIRA) [125]	GP2015	186	55.2	8.79	5.43		1.45	
	ETN	190	53.1	8.18	5.55		1.44	
Weinblatt 2018 [129]	SB5	271	49.8	5.4	6.5		1.3	
	ADA	273	52.5	5.5	6.5		1.3	
Matsuno 2018 [126]	LBEC0101	185	52.8	7.6	6.13		1.3	
	ETN	187	55.5	7.8	6.26		1.2	
Nasonov ACR 2016 [130]	BCD-020	80						
	RTX	80						
Fleischmann 2018 [127]	PF-06410293	297	51.5	6.8	5.9		1.5	
	ADA	300	53.3	6.8	6.1		1.7	
Park 2018 [128]	CT-P10	161	51.5	10.7	6.7			
	RTX	211	51.8	9.1	6.7			
Cohen 2018a (VOLTAIRE) [134]	BI 695501	324	53.7	7.3	6.6		1.5	
	ADA	321	53.6	7.0	6.6		1.5	
Genovese 2017b [121, 135]	FKB327	366	53	8.5				
	ADA	362	53.6					
O'Dell 2016/2017 [107, 137]	CHS-0214	256			5.45			
	ETN	256			5.42			

Table S2.11: Patient characteristics of studies investigating the efficacy of switching between boDMARDs (biooriginators) and bsDMARDs (biosimilars).

Shown are patient characteristics at baseline/at re-randomization.

Study	Treatment	No. of patients (n)	Timepoint of re-randomization	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ
Smolen 2018 [131]	INF->SB2	94	54	53	6.3	6.5/3.9	38.8/12.5	1.5/1.0
	INF->INF	101		51.5	6.7	6.6/4.1	38.9/14.3	1.5/1.0
	SB2->SB2	201		51.8	6.3	6.4/4.0	37.7/13.8	1.5/1.0
Cohen 2018a (VOLTAIRE) [134]	GP2015	186	24					
	ETN	190						
Jorgensen 2017 (NOR-SWITCH) [136]	INF	39	52	59.9	2.7	5.8		0.3
	CT-P13	39		60.4	2.2	4.1		0.3
O'Dell 2016/2017 [107, 137]	CHS-0214->CHS-0214	224	24		5.45			
	ETN->CHS-0214	220			5.42			
Song 2018 [138, 139]	LBEC0101->LBEC0101	70	52		3.068			
	ETN->LBEC0101	78			3.161			
Weinblatt 2018 [140]	SB5	271	24	49.8	5.4	6.5/3.7		1.3/0.8
	ADA->SB5	125		51.7	5.3	6.5/3.7		1.4/0.9
	ADA->ADA	129		52.8	5.6	6.4/3.8		1.4/0.9

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Table S2.12: Patient characteristics of studies investigating the efficacy of csDMARDs (or combination with csDMARDs/GCs) vs. another csDMARD (or combination) or placebo.

Study	Treatment	No. of patients (n)	Mean age (years)	Mean disease duration (years)	Mean DAS28	Mean CDAI	Mean HAQ	Mean mTSS
Shin 2019 [141]	TAC 1.5mg OD + MTX	37	51.1	6.9	4.88		1	
	LEF 10mg OD + MTX	37	55.8	8.7	4.66		0.92	
Register ACR 2016 [142]	MTX + SSZ + HCQ	69		0.83 to 2	5.7 to 6			
	LEF + SSZ + HCQ							
	LEF							
Verschueren/Stouten 2017; Stouten 2018 (CareRA) [143, 144]	High risk: COBRA Classic	98	53.2	0.03	5		1.2	1.3
	High risk: COBRA Slim	98	51.8	0.05	4.8		1	1.3
	High risk: COBRA Avant Garde	93	51.1	0.06	4.7		1	1
	Low risk: MTX tight step-up	47	51	0.06	4.6		1	0.7
	Low risk: COBRA Slim	43	51.4	0.03	4.5		0.9	0.9
Stamp 2018 [145]	MTX + Folic acid 5mg/week	22	61.9	9.8	3.5			
	MTX + Folic acid 0.8mg/week	18	57.2	9.5	3.8			

Section 3: Efficacy outcomes

Table S3.1: Efficacy outcomes of trials investigating bDMARDs ± csDMARDs versus placebo.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Damjanov 2016 [1]	SBI-087/Pbo/Pbo + MTX	43	16						-0.4	
	SBI-087/SBI-087/Pbo + MTX	42							-0.3	
	SBI-087/Pbo/SBI-087 + MTX	43							-0.2	
	SBI-087/SBI-087/SBI-087 + MTX	41							-0.4	
	Pbo/Pbo/Pbo + MTX	40							-0.3	
Aletaha 2017 (SIRROUND-T) [2, 3]	Placebo ± csDMARDs	294	16	24	9	3	5.8	1	-0.12	
	SKM 50mg Q4W ± csDMARDs	292		40	21	6	17.5	1.7	-0.25	
	SKM 100mg Q2W ± csDMARDs	292		45	22	10	15.8	3.1	-0.32	
Buckley ACR 2018 [5, 6]	Placebo + MTX	37	24	14	11	5	3	0	-0.34	
	OTM 22.5mg + MTX	37		24	11	5	5	0	-0.32	
	OTM 45mg + MTX	37		41	27	14	16	5	-0.41	
	OTM 90mg + MTX	37		57	30	14	19	8	-0.43	
	OTM 135mg + MTX	37		41	24	19	14	8	-0.42	
	OTM 180mg + MTX	37		59	27	19	14	5	-0.54	
Bi 2018 (RAPID-C) [7]	Placebo + MTX	113	24	23.9	7.1	2.7	0		-0.17	
	CZP + MTX	316		54.8	36.5	16.7	11.5		-0.53	
Takeuchi 2016 (RA0083)* [8]	Placebo + MTX	29	12	21.9	8.6	3.8	3.4		0	
	OKZ 60mg Q4W + MTX	32		58.7	35.7	3.6	21.9		-0.4	
	OKZ 120mg Q4W + MTX	32		62.5	42.1	22.5	40.6		-0.4	

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	OKZ 240mg Q4W + MTX	36		73.8	39.1	17.1	53.8		-0.4	
Smolen 2017a [9]	Placebo+MTX	55	28	40	14.5	5.5	43.6		-0.3	
	UKM 90mg Q8W + MTX	55		52.7	22.2	14.8	66.7		-0.4	
	UKM 90mg Q12W + MTX	55		54.5	14.5	5.5	60		-0.5	
	GKM 50mg Q8W + MTX	55		38.2	21.8	5.5	56.4		-0.5	
	GKM 200mg Q8W + MTX	54		44.4	22.2	7.4	59.3		-0.4	
Burmester 2017b (EARTH EXPLORER 1) [10]	MVM 150mg Q2W + MTX	79	12[a]/24[b]	50.6[b]	28.4[b]	12.3[b]	19[a]	1.3[b]	-0.37[b]	
	MVM 100mg Q2W + MTX	85		61.2[b]	25.9[b]	10.6[b]	9.4[a]	1.2[b]	-0.46[b]	
	MVM 30mg Q2W + MTX	81		73.4[b]	40.5[b]	13.9[b]	9.9[a]	3.7[b]	-0.55[b]	
	Placebo + MTX	81		24.7[b]	12.3[b]	3.7[b]	2.5[a]	0[b]	-0.29[b]	
Dörner 2017 [11]	VBM 150mg Q4W	62	12	73	44	16	10			
	VBM 150mg Q2W	62		77	37	24	5			
	VBM 225mg Q2W	63		81	49	21	6			
	(Open-Label) TCZ 162mg Q1W	60		78	45	23	9			
Weinblatt 2017 [12]	Placebo + MTX	69	12	62	28	9	16			
	VBM 75mg Q4W + MTX	69		75						
	VBM 150mg Q4W + MTX	70		81						
	VBM 150mg Q2W	68		78						
	VBM 225mg Q2W	69		72						
Fleischmann 2017 (TARGET) [13]	Placebo + csDMARDs	181	24	33.7	18.2	7.2	7.2		-0.3	
	SLM 150mg Q2W + csDMARDs	181		55.8	37	19.9	24.9		-0.5	
	SLM 200mg Q2W + csDMARDs	184		60.9	40.8	16.3	28.8		-0.6	
Tahir 2017 (REASSURE) [14]	SEC 3x10mg/kg i.v. Q2W /150mg s.c. Q4W ± MTX	213	24	35.2	16	3.8			-0.4	0.59
	SEC 3x10mg/kg i.v. Q2W /75mg s.c. Q4W ± MTX	210		35.2	17.6	8.1			-0.4	0.83
	Placebo ± MTX	214		19.6	6.5	2.3			-0.5	1.73
	Placebo + csDMARD	556	16[c]/24[b]	26.4[c]	10.8[c]	4[c]	5.6[b]		-0.22[b]	1.96[b]

Takeuchi 2017 (SIRROUND-D) [15]	SKM 50mg Q4W + csDMARD	557		54.8[c]	30[c]	13.5[c]	26[b]		-0.43[b]	0.35[b]
	SKM 100mg Q2W + csDMARD	557		53.5[c]	26.2[c]	13.5[c]	25.5[b]		-0.46[b]	0.3[b]
Mease 2018 [16]	Placebo + MTX	51	16	41.2			7.8	3.9		
	CNTO6785 15mg Q4W + MTX	52		51.9			15	4.9		
	CNTO6785 50mg Q4W + MTX	51		47.1						
	CNTO6785 100mg Q4W + MTX	51		37.3						
	CNTO6785 200mg Q4W + MTX	52		40.4						
Tanaka 2018b (KAKEHASI) [17, 18]	Placebo + MTX	82	24	14.8						
	SLM 150mg Q2W + MTX	81		67.9						
	SLM 200mg Q2W + MTX	80		57.5						
van Vollenhoven 2018 [19]	Placebo + MTX	79	12	35.2	9.9	1.4	2.9		-0.22	
	TLM 25mg + MTX	80		42.3	12.7	2.8	0		-0.26	
	TLM 100mg + MTX	78		47	9.1	1.5	0		-0.22	
	TLM 200mg + MTX	76		44.3	12.9	4.3	2.9		-0.15	
Dokoupilova 2018 (REASSURE2) [20]	SEC 150mg + csDMARDs	81	24	38.3	18.5	11.1			-0.39	
	SEC 75mg + csDMARDs	80		37.5	17.5	3.8			-0.42	
	Placebo + csDMARDs	81		27.2	16.6	2.5			-0.13	
Takeuchi 2018a [21]	SKM 50mg Q4W + csDMARDs	61	16	77	47.5	26.2	45.9			
	SKM 100mg Q2W + csDMARDs	61		72.1	57.4	32.8	49.2			
Mazurov 2018 [118]	BCD-020 600mg + MTX	107	24	65.69	28.43	12.75				
	Placebo + MTX	52		29.41	5.88	1.96				
Matsubara 2018 [23]	ABA 500mg/750mg/1000mg Q4W + MTX	203	16/24	75.4	50.7	26.1	46.8			0.84[b]
	Placebo + MTX	202		27.7	11.4	5	16.3			1.26[b]
*numbers reported as median; [a] week 12; [b] week 24; [c] week 16;										

Table S3.2: Efficacy outcomes of trials comparing bDMARD to other bDMARDs.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	CDAI I≤2.8 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Porter 2016 (ORBIT) [24]	Anti-CD20 (RTX)	140	52	66	49	23	23			-0.49	
	TNFi (ETA/ADA)	134		71	45	26	21			-0.38	
Burmester 2017 (MONARCH) [25] [26]	ADA 40mg Q2W	185	24	71.7	45.7	23.4	13	2.7		-0.43	
	SLM 200mg Q2W	184		58.4	29.7	11.9	49	7,1		-0.61	
Blanco 2017 (NURTURE 1) [27]	SEC 10mg/kg i.v. + 150mg s.c. Q4W + csDMARD	137	24	30.7	16.8	10.2				-0.4	
	SEC 10mg/kg i.v. + 75mg s.c. Q4W + csDMARD	138		28.3	11.6	5.1				-0.3	
	ABA 500/750/1000mg + csDMARD	138		42.8	27.5	12.3				-0.6	
	Placebo + csDMARD	138		18.1	9.4	5.1				-0.3	
Weinblatt 2018 (EARTH EXPLORER 2) [28]	MVM 100mg Q2W + MTX	70	24	62	34.8	16.1	17.4	5.7		-0.44	
	GLM 50mg Q4W	68		65.6	43.4	25.9	29	17.6		-0.64	
Genovese 2018b [29]	ADA 40mg Q2W + MTX	56	12	67.9	48.2	21.4	30.4	7.1		-0.6	
	ABT-122 60mg Q2W + MTX	55		61.8	34.5	21.8	21.8	7.3		-0.6	
	ABT-122 120mg Q2W + MTX	56		75	46.4	17.9	37.5	10.7		-0.6	
	ABT-122 120mg QW + MTX	55		80	47.3	36.4	41.8	10.9		-0.9	
Taylor 2018 (SIRROUND-H) [30]	ADA 40mg Q2W	186	24	56.5	31.7	12.9	7.5		3.8	-0.52	
	SKM 50mg Q4W	186		53.8	26.9	11.8	12.9		3.8	-0.51	
	SKM 100mg Q2W	187		58.8	35.3	15.5	20.3		3.7	-0.53	
Smolen 2016 (EXXELERATE) [31]	CZP 400/200mg Q2W + MTX	454	12	69				24.9			
	ADA 40mg Q2W + MTX	454		71				22.2			

Table S3.3: Efficacy outcomes of trials investigating switching of different bDMARDs.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Gottenberg 2016 (ROC) [32]	Non-TNFi (ABA; RTX; TCZ)	146	24				20			
	TNFi (ADA; CZP; ETA; GOL; INF)	146					10			
Smolen 2016 (EXXELERATE) [31]	CZP primary non-responders switched to ADA	65	24	43.9	16.9	7.7	9.2			
	ADA primary non-responders switched to CZP	57		40	22.8	10.5	5.3			
Verschueren 2018 (EXTEND) [33]	TCZ 4mg/kg non-responders; SAR 200mg Q2W + csDMARDs	37	24	75	35	29	41			
	TCZ 4mg/kg responders; SAR 200mg Q2W + csDMARDs			93	88	90	90			
	TCZ 8mg/kg non-responders; SAR 200mg Q2W + csDMARDs	56		60	47	32	46			
	TCZ 8mg/kg responders; SAR 200mg Q2W + csDMARDs			91	79	75	78			

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Table S3.4: Efficacy outcomes of trials investigating bDMARD induction vs. csDMARD induction trials in early RA.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Emery 2017 (C-EARLY) [34]	Placebo + MTX	213	52	61.5	52.6	39.9	15*	20.7	-0.82	1.8
	CZP 200mg Q4W + MTX	655		69	61.8	51.3	28.9*	32.4	-0.98	0.2
Emery ACR 2018 (AVERT-2) [35]	ABA 125mg QW + MTX	225[a]/451[b]	24[a]/52[b]				38.7[a]	21.5[a]		0.5[b]
	Placebo + MTX	150[a]/301[b]					25.3[a]	11.6[a]		2.5[b]
Stamm 2018 (DINORA) [36]	INF (3mg/kg wk0 , 2, 6; INF 4mg/kg Q8W) + MTX	36	54	58	45	37	63	34	-0.57	0.18
	Placebo + MTX	36		61	44	31	36	25	-0.38	0.16
	Placebo	16		19	19	13	19	6	-0.09	0
Burmester 2016 (FUNCTION) [37] [38]	Placebo + MTX	287	24[a]/52[b]	65.2[a]	43.2[a]	25.4[a]	15[a]		-0.71[a]	1.14[b]
	TCZ 4mg/kg Q4W + MTX	288		73.6[a]	47.9[a]	34.7[a]	31.9[a]		-0.92[a]	0.42[b]
	TCZ 8mg/kg Q4W + MTX	290		74.5[a]	56.9[a]	38.6[a]	44.8[a]		-0.91[a]	0.08[b]
	TCZ 8mg/kg Q4W + Placebo	292		70.2[a]	47.6[a]	30.1[a]	38.7[a]		-0.82[a]	0.26[b]
*sustained remission at both weeks 40 + 52; [a] week 24; [b] week 52										

Table S3.5: Efficacy of strategic studies.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	CDAI ≤ 2.8	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Møller-Bisgaard 2019 (IMAGINE-RA) [39]	MRI Treat-to-Target	100	104				85.3	69.7	49.3	-0-05	1
	Conventional Treat-to-Target	100					88.3	64.8	31.9	0.09	1.3
Mueller 2019 [40]	CZP + T2T csDMARDs/GCs	21	24	90.5	76.2	71.4	68.4	78.9	47.4	-0.68	
	CZP + fixed regimen	22		59.1	36.4	27.3	28.6	23.8	19.1	-0.25	

Table S3.6: Efficacy of trials investigating bDMARD and tsDMARD tapering.

Study	Primary / Secondary Outcome	Timepoint (week)	Treatment arm	No. of patients (n)	Result	p
Oba 2017 / Tanaka ACR 2018 (RRRR) [41, 42]	1-year sustained discontinuation rate of INF;	106	INF 3mg/8mg/10mg/kg Q8W based on TNF levels	170	23.5%	0.631
			INF standard 3mg/kg Q8W	167	21.3%	
Chatzidionysiou 2016 (ADMIRE) [43]	DAS28<2.6 at week 28	28	ADA + MTX continuation	16	93.75	0.001
			ADA discontinuation; MTX monotherapy	16	33	
Moghadam 2016/2018 (POET) [44, 45]	% of pat. DAS28≥3.2 + ΔDAS28 >0.6 during 1 year	52	Stopping TNFi	531	51.2	<0.001; HR: 3.50 (95% CI 2.60-4.72)
			Continuation of TNFi	286	18.2	
Atsumi 2017 (C-OPERA) [47]	Mean Progression of mTSS; SDAI≤3.3; Boolean; DAS28-ESR<2.6	104	CZP + MTX continuation	108	0.66; 41.5%; 34.6%; 41.5%	0.001; 0.026; 0.049; 0.132
			Stopping CZP; MTX + PLC	71	3.01; 29.3%; 24.2%; 33.1%	
Kaneko 2018 (SURPRISE) [48]	TCZ free rate; TCZ free DAS28-ESR<2.6; ≤3.2; ΔmTSS	104	stopping TCZ; MTX monotherapy	49	67.3%; 24.4%; 55.1%; 0.37	0.001; 0.29; 0.005; 0.36
			stopping TCZ; No DMARD	53	28.5%; 14.3%; 26.6%; 0.64	
Weinblatt 2017 (C-EARLY) [49]	DAS28-ESR≤3.2 without flares during week 52-104; % of patients with radiographic progession (ΔmTSS>0.5)	104	CZP 200mg Q2W + MTX (standard)	84	48.8%; 9.7%	Reference
			CZP 200mg Q4W + MTX (reduced frequency)	126	53.2%; 15.9%	0.112; NR
			Placebo + MTX (CZP stopped)	79	39.2%; 81.1%	0.041; NR
Ibrahim 2017 (OPTIRRA) [50]	Flare (ΔDAS28≥0.6 + DAS28>3.2 + ΔSJC OR ΔDAS28>1.2 + DAS28>3.2)	24	TNFi 33% tapering; csDMARD	26	12%	0.873; HR: 0.90, 95% CI: 0.23-3.48
			TNFi 66% tapering; csDMARD	21	29%	0.097; HR 2.52, 95% CI 0.85-7.48
			Control; csDMARD continuation	50	16%	Reference

Bouman 2017 (DRESS) [64]	Incidence of major flare (ΔDAS28-CRP>1.2 or ΔDAS28-CRP>0.6+DAS28-CRP≥3.2 for >12 weeks)	144	TNFi dose reduction extension	115	17%	3%, 95% CI -10%-15%
			Usual care extension	57	14%	
l'Ami 2018 [65]	ΔDAS28-ESR, ΔCDAI, ΔSDAI	28	ADA 40mg Q3W ± MTX	27	-0.14; +0.5; +0.4;	0.01; 0.23; 0.36
			ADA 40mg Q2W ± MTX	27	0.3; +1.5; +1.6	
Takeuchi 2019 (RA-BEYOND) [81]	CDAI≤10; CDAI≤2.8	12	Continued BARI 4mg ± csDMARD	281	93; 41	<0.001; NR
			BARI Step-down 2mg ± csDMARD	278	83; 38	

Table S3.7: Efficacy of trials investigating csDMARD or glucocorticoid tapering

Study	Design	Primary / Secondary Outcome	Timepoint (week)	Treatment arm	No. of patients (n)	Result	P / 95% CI
Kaeley 2016 (MUSICA) [54]	NI (15%)	Mean DAS28-CRP	24	ADA 40mg Q2W + 7.5 mg MTX	154	4.12 (95% CI 3.88-4.34)	0.014
				ADA 40mg Q2W + 20 mg MTX	155	3.75 (95% CI 3.52-3.97)	
Keystone 2016 (CAMEO) [55]	NI (<0.6)	Mean ΔDAS28-ESR; mTSS; ΔDAS28; ΔSDAI; ΔCDAI; %DAS28-ESR<2.6	24/104	ETA 50mg QW; MTX discontinuation	98	0.5; 0.4; 0.56; 4.7; 4.1;	0.815
				ETA 50mg QW + MTX continuation	107	0.04; 0.0; 0.08; 0.9; 1.0;	
Pope EULAR 2017/ACR 2018 [56] [57]	NR	ΔDAS28-ESR; DAS28≤3.2; DAS28-ESR<2.6	76	CZP + csDMARD continuation	37	-2.1; 60%; 43.3%	NR
				CZP + csDMARD discontinuation	44	-2.1; 59.4%; 43.8%	
Burmester ACR 2018 (SEMIRA) [58]	NI/S (0.6)	ΔDAS28-ESR; DAS28-ESR ≤3.2 + no flare + no adrenal insufficiency	24	TCZ ± csDMARDs; Glucocorticoid tapering	131	0.538; 64.9%	<0.001; 0.02
				TCZ ± csDMARDs; Glucocorticoid continuation	128	-0.075; 77.3%	
Pablos 2018 (JUST-ACT) [59]	NI (0.6)	ΔDAS28-ESR week 16-week 28; DAS28<2.6; CDAI<2.6; SDAI<3.3	28	TCZ 8 mg/kg + MTX	82	0.007; 82.3%; 40.7%; 35.1%	95% CI -0.40-0.27; 0.328; 0.518; 0.358
				TCZ 8 mg/kg + PBO	82	0.073; 75.9%; 35.8%; 28.2%	
Kremer 2018 (COMP-ACT) [60]	NI (0.6)	ΔDAS28-ESR week 24-week 40; DAS28<2.6;	40	TCZ 162mg s.c. + PLC	147	0.46; 49.7;	95% CI 0.045-0.592
				TCZ 162mg s.c. + MTX	147	0.14; 59.2;	
Edwards 2018 (ACT-TAPER) [61]	NI (10%)	Pat. Maintaining EULAR good/moderate response from week 24-60; DAS28<2.6	60	TCZ 8mg/kg Q4W + PBO	136	76.5%; 51.5%	0.036; 0.342
				TCZ 8mg/kg Q4W + MTX	136	65.4%; 47.1%	
Stouten 2018 (CareRA) [62]	NS	DAS28-CRP<2.6; CDAI≤2.8; SDAI≤3.3; ΔHAQ; ΔmTSS	65	COBRA Avant Garde->MTX 15mg/week	32	93.8;65.6; 62.5;0.3;0.7	0.031; 0.362; 0.506; 0.968; 0.702
				COBRA Avant Garde->LEF 20mg/d	26	73.1;53.8; 53.8;0.3;0.9	

Table S3.8: Efficacy of trials investigating combined bDMARD and/or csDMARD tapering

Study	Primary Outcome	Timepoint (week)	Treatment arm	No. of patients (n)	Result	p / HR / 95% CI
Emery 2019 (AVERT) [46]	DAS28-CRP<2.6 drug free remission	104	ABA + MTX continuation	84	12.3%	NR
			ABA monotherapy	66	14%	
			MTX monotherapy	73	11.3%	
El Miedany 2016 [52]	Sustained DAS28<2.6 (not reported); DAS28>3.2	52	bDMARD tapering -50%, csDMARDs unchanged	31	41.9	<0.01
			csDMARD + bDMARD -50%	32	59.3	<0.01
			stop bDMARD, reduce csDMARD -50%	31	67.7	<0.01
			stop bDMARD+csDMARD	31	77.4	<0.01
			continue bDMARD+csDMARD	32	6.5	Reference
Van Mulligen EULAR 2018 (TARA) [53]	Flare: DAS44 >2.4 and/or SJC>1	52	Tapering csDMARDs	93	32	0.55; HR: 0.91 (95% CI 0.68-1.22)
			Tapering TNFi	94	41	
Urata EULAR 2016 (r-T4) [63]	SDAI<3.3	52	Standard care	56	38.2	Reference
			SDAI guided tapering	54	NR	NR
			MMP-3 guided tapering	57	32.7	-1.8%, 95% CI 3.8%-5.3%
			SDAI + MMP-3 guided tapering	56	40	5.5%, 95% CI 1.9%-5.3%
Akdemir 2018 (IMPROVED) [51]	DAS<1.6; DFR; ACR/EULAR Boolean Remission	260	Overall IMPROVED study population	610	48%; 22%	
			Arm 1 (csDMARD + GC Start) at randomization (4 months)	83	50%; 15%; 13%	0.768; 0.374; 0.186
			Arm 2 (ADA Start) at randomization (4 months)	78	49%; 20%; 22%	

Table S3.9: Efficacy of trials investigating tsDMARDs ± csDMARDs versus Placebo ± csDMARDs.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	CDAI ≤2.8 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Fleischmann 2015 [66]	Placebo	41	12	28	7	2	7.3			-0.12	
	DEC 25mg BID	41		39	17	7				-0.24	
	DEC 50mg BID	41		61	32	12				-0.5	
	DEC 100mg BID	40		65	38	18	35			-0.52	
	DEC 150mg BID	41		66	49	22	36.6			-0.64	
Genovese 2016c [67]	Placebo + csDMARD	12	12	25	8.3	8.3					
	DEC 100mg BID + csDMARD	11		63	27.3	18.2					
	DEC 200mg BID + csDMARD	10		60	30	10					
	DEC 300mg BID + csDMARD	10		60	60	20					
Genovese 2016b [68]	Placebo + MTX	71	24	16.9	7	2.8	5.6			-0.6	
	DEC 100mg OD + MTX	71		60.6	38	16.9	21.1			-0.62	
	DEC 150mg OD + MTX	72		61.1	38.9	18.1	29.2			-0.65	
	DEC 200mg OD + MTX	72		61.1	40.3	15.3	27.8			-0.79	
	DEC 100mg BID + MTX	72		62.5	47.2	25	31.9			-0.75	
Takeuchi 2016a [69]	Placebo	56	12	10.7	5.4	1.8	5.4			0.16	
	PEF 25mg OD	55		23.6	7.3	0	0			0.14	
	PEF 50mg OD	57		31.6	8.8	1.8	7			0.05	
	PEF 100mg OD	55		54.5	30.9	16.4	27.3			-0.17	
	PEF 150mg OD	58		65.5	29.3	12.1	20.7			-0.23	
Genovese 2017c [70]	Placebo + HCQ/SZP	51	12	29.4	9.8	7.8	9.8				
	PEF 25mg + HCQ/SZP	59		22	15.3	6.8	6.8				
	PEF 50mg + HCQ/SZP	57		36.8	24.6	15.8	12.5				
	PEF 100mg + HCQ/SZP	58		48.3	27.6	19	22.8				
	PEF 150mg + HCQ/SZP	64		56.3	28.1	10.9	20.3				

Kivitz 2017 [71]	Placebo + MTX	72	12	44.4	26.4	11.1					
	PEF 25mg + MTX	66		43.9	18.2	9.1					
	PEF 50mg + MTX	78		61.5	33.3	15.4					
	PEF 100mg + MTX	84		46.4	33.3	16.7					
	PEF 150mg + MTX	78		57.7	37.2	19.2					
Tanaka ACR 2018a [72, 73]	Placebo ± csDMARDs	101	12	30.7	8.9	1	5				
	PEF 100mg OD ± csDMARDs	104		57.7	30.8	13.5	24.5				
	PEF 150mg OD ± csDMARDs	102		74.5	42.2	27.5	34.7				
	ETA 50mg QW ± csDMARDs	200		83.5	52.5	30.5	45.5				
Takeuchi ACR 2018 [74, 75]	Placebo + MTXs	170	12[a]/28[b]	21.8[a]	7.6[a]	2.4[a]	7.7[a]				3.37[b]
	PEF 100mg OD + MTXs	174		58.6[a]	29.9[a]	12.1[a]	31.4[a]				1.62[b]
	PEF 150mg OD + MTXs	174		64.4[a]	46[a]	23.6[a]	35.1[a]				1.03[b]
Westhovens 2017 (DARWIN 1) [76, 79]	Placebo + MTX	86	12	44.19	15.12	8.14	6.98	2.33	3.49	-0.38	
	FILGO 50mg OD + MTX	82		56.1	32.93	15.85	12.2	7.32	3.66	-0.58	
	FILGO 100mg OD + MTX	85		63.53	37.65	21.18	22.35	8.24	3.53	-0.65	
	FILGO 200mg OD + MTX	86		68.6	43.02	24.42	22.09	10.47	5.81	-0.75	
	FILGO 25mg BID + MTX	86		56.98	27.91	13.95	15.12	10.47	4.65	-0.59	
	FILGO 50mg BID + MTX	85		60	34.12	18.82	17.65	8.24	4.71	-0.58	
	FILGO 100mg BID+ MTX	84		78.57	54.76	30.95	35.71	17.86	9.52	-0.84	
Kavanaugh 2017 (DARWIN 2) [77, 79]	Placebo	72	12	29.2	11.1	2.8	6.9	2.8	1.4	-0.226	
	FILGO 50mg OD	72		66.7	34.7	8.3	12.5	2.8	1.4	-0.661	
	FILGO 100mg OD	70		65.7	37.1	18.6	14.3	5.7	4.3	-0.677	
	FILGO 200mg OD	69		72.5	43.5	13	17.4	8.7	4.3	-0.739	
Kivitz ACR 2018 [80]	Placebo + MTX	22	12	40.9	22.7	13.6				-0.39	
	GS-9876 10mg OD + MTX	20		25	20	15				-0.18	
	GS-9876 30mg OD + MTX	20		35	20	5				-0.46	
Dougados 2017 (RA-BUILD) [84]	Placebo + csDMARD	228	12/24[a]	39.47	12.72	3.07			0.44	-0.3	0.70[a]
	BARI 2mg + csDMARD	229		65.94	33.62	17.9			6.99	-0.52	0.33[a]
	BARI 4mg + csDMARD	227		61.67	33.48	18.06			6.61	-0.52	0.15[a]

Schiff/Fleischmann 2017b (RA-BEGIN) [86, 87]	Placebo + MTX	210	24	61.9	43.3	21.4	23.8	11		-0.74	0.61
	BARI 4mg + Placebo	159		76.7	59.7	42.1	40.3	21.4		-1.04	0.39
	BARI 4mg + MTX	215		78.1	63.3	39.5	40.5	22.3		-1.03	0.29
Hu/Yue 2018 (RA-BALANCE) [91, 92]	Placebo + MTX	145	12	28.3	8.3	1.4	2.8			-0.35	
	BARI 4mg + MTX	145		58.6	30.3	9.7	11.7			-0.57	
Tanaka 2019 [82]	TOFA 11mg modified-release OD + MTX	104	12	84.5	68	31.1	50.5	18.5	11.7	-0.44	
	TOFA 5mg immediate-release BID + MTX	105		79.8	68.3	46.2	69.2	36.5	29.8	-0.46	
van der Heijde 2019 (ORAL Scan) [83]	TOFA 5mg + MTX	321	96	2.8	2.7	2.2	1.9	1.9	1.7	-0.5	
	TOFA 10mg + MTX	316		2.8	2.8	2.6	2.2	2.3	2	-0.7	
	Placebo->TOFA 5mg + MTX	81		5.5	5.5	4.6	3.3	3.7	3.9	-0.6	
	Placebo->TOFA 10mg + MTX	79		5.7	5.6	5.1	4.5	4.8	4.7	-0.6	
Tanaka 2018a (SELECT-SUNRISE) [89]	Placebo + csDMARDs	49	12	42.9	16.3	2	6.1			-0.1	
	UPA 7.5mg + csDMARDs	49		75.5	40.6	20.4	36.7			-0.41	
	UPA 15mg + csDMARDs	49		83.7	65.3	34.7	57.1			-0.45	
	UPA 30mg + csDMARDs	50		80	58	28	50			-0.49	
Genovese/Strand 2018 (SELECT-BEYOND) [93, 94]	Placebo + csDMARD	169	12	28	34	7				-0.16	
	UPA 15mg + csDMARD	164		65	36	12				-0.41	
	UPA 30mg + csDMARD	165		93	12	23				-0.44	
Burmester/Strand 2018 (SELECT-NEXT) [95, 100]	Placebo + csDMARD	221	12	36	15	6	10	3	4	-0.26	
	UPA 15mg + csDMARD	221		64	38	21	31	9	10	-0.61	
	UPA 30mg + csDMARD	219		66	43	27	28	12	9	-0.55	
van Vollenhoven ACR 2018 (SELECT-EARLY) [78]	Placebo + MTX	314	12/24[a]	54.1	28.3	14	18.5[a]	6.4	6.4	-0.49	0.67[a]
	UPA 15mg + MTX	317		75.7	52.1	32.5	48.3[a]	16.1	12.9	-0.83	0.14[a]
	UPA 30mg + MTX	314		77.1	56.4	36.9	50[a]	21.3	15.3	-0.86	0.07[a]
Smolen EULAR/ACR 2018 (SELECT-MONOTHERAPY) [96-99]	Continued MTX	216	14	41.2	15.3	2.8	8.3	1	0.9	-0.32	
	UPA 15mg	217		67.7	41.9	22.6	28.1	13	9.2	-0.65	
	UPA 30mg	215		71.2	52.1	33	40.5	19	19.1	-0.73	

Table S3.10: Efficacy of Head-to-Head studies comparing tsDMARDs and bDMARDs.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	CDAI ≤2.8 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Taylor/Keystone 2017 (RA-BEAM) [101] [102]	Placebo + MTX	488	12/24[a]	40.2	16.8	4.7	4	2	1	-0.34	0.9[a]
	BARI 4mg + MTX	487		69.6	45	18.9	24	8	7.2	-0.66	0.41[a]
	ADA 40mg Q2W + MTX	330		61.2	34.8	12.7	19	7	5.2	-0.56	0.33[a]
Fleischmann 2017/Strand EULAR 2018 (ORAL-Strategy) [103, 106]	TOFA 5mg BID + PLC	384	24	64.8	38.3	18.2	21.1	10.2	7	-0.52	
	TOFA 5mg BID + MTX	376		73.1	46	25	30.6	13.8	8.2	-0.58	
	ADA 40mg Q2W + MTX	386		71	43.8	20.7	28	13.2	8.8	-0.54	
Fleischmann ACR 2018 (SELECT-COMPARE) [104, 105]	Placebo + MTX	651	12/26[a]	36.4	14.9	4.9	6.1	3.1	2	-0.28	0.92[a]
	UPA 15mg OD + MTX	651		70.5	45.2	24.9	28.7	13.4	9.8	-0.6	0.24[a]
	ADA 40mg Q2W + MTX	327		63	29.1	13.5	18	7.6	4	-0.49	0.1[a]

ADA: Adalimumab; BARI: Baricitinib; TOFA: Tofacitinib; UPA: Upadacitinib; BID: twice daily; OD: once daily; Q2W: every two weeks; MTX: Methotrexate

Table S3.11: Efficacy outcomes of trials investigating biosimilars.

Study	Treatment	No. of patients (n)	Timepoint (weeks)	Non-inferiority margin	Outcome	Result	Estimate of treatment difference	95% CI
Jani 2016 [108]	ZRC-3197	60	12	28.5%	%ACR20	82		-11.99% to 17.5%
	ADA	60				79.25		
Denisov EULAR 2018 (LIRA) [109, 110]	BCD-055	198	14	20%	%ACR20	75.83		-12.9% to 16.18%
	INF					74.19		
Wiland ACR 2018 [111]	GP2017	177	12	0.6	ΔDAS28-CRP	-2.16	0.02	-0.24 to 0.27
	ADA	176				-2.18		
Matsuno and Matsubara 2018 [112]	NI-071	126	14	0.6	ΔDAS28-ESR	-2.15	0.02	-0.280 to 0.328
	INF	116				-2.13		
Yoo 2016 (PLANETRA) [113]	CT-P13	302	54		%ACR20	74.7	0.03	-0.05 to 0.12
	INF	304				71.3		
Bae 2017 (HERA) [114]	HD203	115	24	20%	%ACR20	83.48	2.12	-7.65 to 11.89
	ETA	118				81.36		
Jamshidi 2017 [115]	CinnoRA	68	24	-0.18	%EULAR good/moderate	70.31	NR	-4 to 4
	ADA	68				67.19		
Smolen 2017c [116]	GP2013	133	24	0.6	ΔDAS28-CRP	-2.07	0.04	-0.241 to 0.323
	RTX-EU	87				-2.11		
	RTX-US	92						
Choe 2017 [117]	SB2	291	30	15%	%ACR20	64.1	-1.88	-10.26 to 6.51
	INF	293				66.0		
Smolen 2017 [118]	SB2	291	54	15%	%ACR20	65.3	-3.07	-12.00 to 5.86
	INF	293				69.2		
Cohen 2017 [119]	ABP 501	264	24			74.6	1.039	0.954 to 1.133

	ADA	262		0.738 to 1.355	Risk Ratio ACR20	72.4		
Alten EULAR 2017 (ARABESC) [120, 121]	FKB327	366	24	13%	%ACR20	74.4	NR	-7.6 to 5.0
	ADA	362				75.7		
Apsangikar 2018 [122]	AdaliRel	85	16	NS	%ACR20	90.48	0.91	-23.96 to 25.54
	ADA	21				90		
Cohen 2018b [123]	PF-06438179/GP1111	324	14	±13.5; -12 to 15	%ACR20	61.1	-2.39	-9.92 to 5.11
	INF	326				63.5		
Haridas 2018 [124]	DRL-RI	276	24	NR	%ACR20	NR	Reference	Reference
	RTX-US					NR	2.8	-11.18 to 16.81
	RTX-EU					NR	3.6	-10.54 to 17.73
Matucci-Cerinic 2018 (EQUIRA) [125]	GP2015	186	24	0.6	ΔDAS28-CRP	-1.62	-0.07	-0.26 to 0.12
	ETN	190				-1.67		
Weinblatt 2018 [129]	SB5	271	24	15%	%ACR20	72.4	0.1	-7.83 to 8.13
	ADA	273				72.2		
Matsuno 2018 [126]	LBEC0101	185	24	0.6	ΔDAS28-ESR	-3.01	-0.15	-0.377 to 0.078
	ETN	187				-2.86		
Nasonov ACR 2016 [130]	BCD-020	80	24	NR	%ACR20	84.14	NR	-13.95 to 8.74
	RTX	80				87.01		
Fleischmann 2018 [127]	PF-06410293	297	12	14%	%ACR20	68.4	-2.98	-10.38 to 4.44
	ADA	300				71.3		
Park 2018 [128]	CT-P10	161	24	0.6	ΔDAS28-CRP	-2.13	-0.04	-0.29 to 0.21
	RTX	211				-2.09		
Cohen 2018a (VOLTAIRE) [134]	BI 695501	324	12/24	-12% to 15%/±15%	%ACR20	67.0/69.0	5.9 / 4.5	90% CI: -0.9 to 12.7 / 95% CI: -3.4 to 12.5
	ADA	321				61.1/64.5		
Genovese 2017b [121, 135]	FKB327	366	24	-12% to 15%	%ACR20	72.5		90% CI: -7.3 to 3.6
	ADA	362				74.3		
O'Dell 2016/2017 [107, 137]	CHS-0214	256	24	15%	%ACR20	91		-4.55 to 5.37
	ETN	256				90.6		

Table S3.12: Efficacy outcomes of trials investigating switching between bsDMARDs and their respective boDMARDs.

Study	Treatment	No. of patients (n)	Timepoint of re-randomization (week)	Endpoint after crossover (week)	Non-inferiority margin	Outcome	Result	Estimate	95% CI
Nasonov ACR 2016 [130]	BCD-020->BCD-020	40	24	48	NR	%ACR20/70	77.78/40		
	BCD-020->RTX	40					92.31/39.29		
	RTX->RTX	40					96.00/34.62		
	RTX->BCD-020	40					89.29/40.74		
Smolen 2018 [131]	INF/SB2	94	54	78	NS	%ACR20/50/70	63.5/37.6/22.4		
	INF/INF	101					68.8/47.3/31.2		
	SB2/SB2	201					68.3/40.6/25.6		
Kavanaugh ACR 2018 (EQUIRA) [132, 133]	GP2015	186	24	48	NS	%ACR20	89		
	ETN	190					82		
Cohen 2018a (VOLTAIRE) [134]	BI 695501	324	24	48	NS	%ACR20/50/70	NR		
	ADA	321					NR		
Genovese 2017b [121, 135]	FKB327->FKB327	216	24	30	NS	%ACR20	82.5		
	ADA->ADA	213					84.3		
	FKB327->ADA	108					86.5		
	ADA->FKB327	108					89.1		
Jorgensen 2017 (NOR-SWITCH) [136]	INF	39	0	54	15% (overall population[1])	Risk difference for disease worsening: ΔDAS28≥1.2 + DAS28≥3.2	36.7%	4.5%	-20.3% to 29.3%[1]
	CT-P13	39					30%		
O'Dell 2016/2017 [107, 137]	CHS-0214->CHS-0214	224	24	48	NR	%ACR20/50/70	93.8/75.0/49.6		
	ETN->CHS-0214	220					92.7/73.6/51.4		

Song 2018 [138, 139]	LBEC0101->LBEC0101	70	48	100	NR	%ACR20/50/70	79.7/65.2/44.9		
	ETN->LBEC0101	78					83.3/66.7/42.3		
Weinblatt 2018 [140]	SB5	271	24	52	NR	%ACR20/50/70; ΔmTSS	77.8/50/31.9/0.2		
	ADA->SB5	125					78.8/54.2/26.3/0.3		
	ADA->ADA	129					73.4/50.8/28.2/0.5		

Table S3.13: Efficacy outcomes of trials investigating the efficacy of csDMARDs (or combination with csDMARDs/GCs) vs. another csDMARD (or combination) or placebo.

Study	Treatment	No. of patients (n)	Endpoint (week)	Non-inferiority margin	Outcome	Result	Estimate	95% CI / p
Shin 2019 [141]	TAC 1.5mg OD + MTX	37	24	0.7	ΔDAS28-ESR	3.06	PP: -0.0565 FAS: -0.181	PP: -0.65-0.54 FAS: -0.81-0.44
	LEF 10/20mg OD + MTX	37				3.24		
Register ACR 2016 [142]	MTX + SSZ + HCQ	69	48		%ACR20/50/70	87/57/35		<0.01[a]/<0.001[b]; <0.05[a]/0.06[b]; <0.005[a]/<0.01[b];
	LEF + SSZ + HCQ[a]					46/25/4		
	LEF[b]					36/27/0		
Verschueren 2017/Stouten 2017; Stouten 2018 (CareRA) [143]	High risk: COBRA Classic	98	52		DAS28-CRP<2.6[a]; SDAI≤3.3; Boolean rem.; ΔHAQ; ΔmTSS	64.3;37.8;26.5;0.7;0.3	4.0%[a]	−9.4% to 17.3%
	High risk: COBRA Slim	98				60.2;30.6;17.3;0.5;0.4	Reference (high risk)[a]	
	High risk: COBRA Avant Garde	93				62.4;45.2;30.1;0.6;0.3	1.9%[a]	−11.6% to 15.3%
	Low risk: MTX tight step-up	47				57.4;29.8;21.3;0.5;0.2	−10.0%[a]	−28.6% to 9.8% / p=0.329
	Low risk: COBRA Slim	43				67.4;44.2;37.2;0.6;0.3		
Stouten ACR 2017 (CareRA) [144]	High risk: COBRA Classic	98	104		%ACR20/50/70; DAS28-CRP<2.6; ΔDAS28-CRP	56.1;41.8;65.4;2.6		0.797; 0.835; 0.568; 0.369; 0.966;
	High risk: COBRA Slim	98				60.2;36.7;73.5;2.6		
	High risk: COBRA Avant Garde	93				59.1;44.1;73.1;2.6		
Stamp 2018 [145]	MTX + Folic acid 5mg/week	22	24		ΔDAS28-CRP	-0.13	0.11	-0.73 to 0.95;
	MTX + Folic acid 0.8mg/week	18				-0.25		

Section 4: References

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Section 5: List of abbreviations

Δ	Change from baseline
ABA	Abatacept
ACR	American College of Rheumatology
ADA	Adalimumab
ANA	Anakinra
BARI	Baricitinib
bDMARD	Biological disease-modifying anti-rheumatic drug
BID	Twice daily
BLM	Brodalumab
boDMARD	Biooriginator disease-modifying anti-rheumatic drug
bsDMARD	Biosimilar disease-modifying anti-rheumatic drug
CD	Cluster of differentiation
CDAI	Clinical Disease Activity Index
csDMARD	Conventional synthetic disease-modifying anti-rheumatic drug
CZK	Clazakizumab
CZP	Certolizumab pegol
DAS28	Disease Activity Score of 28 Joints
DEC	Decernotinib
ETN	Etanercept
FILGO	Filgotinib
FOSTA	Fostamatinib
GC	Glucocorticoids
GKM	Guselkumab
GLM	Golimumab
GM-CSF	Granulocyte-macrophage colony-stimulating factor
HAQ	Health Assessment Questionnaire Disability Index
HCQ	Hydroxychloroquine
IL	Interleukin
IR	Insufficient responder
JAK	Janus Kinase
LEF	Leflunomide
MMP-3	Matrix metalloproteinase 3
MMP-3	Matrix metalloproteinase-3
mTSS	Modified total Sharp Score
MTX	Methotrexate
MVM	Mavrilimumab
NR	Not reported
NS	Not significant
OD	Once daily
OKM	Olokizumab
PEF	Peficitinib
QNW	Every N weeks
R	receptor
RA	Rheumatoid Arthritis
RoB	Risk of bias
RTX	Rituximab
SAR	Sarilumab
SDAI	Simplified Disease Activity Index
SEC	Secukinumab

SKM	Sirukumab
SYK	Spleen tyrosine kinase
SZP/SSZ	Sulfasalazine
TBM	Tabalumab
TCZ	Tocilizumab
TLM	Tregalizumab
TNF	Tumor necrosis factor alpha
TOFA	Tofacitinib
tsDMARD	Targeted synthetic disease-modifying anti-rheumatic drug
UKM	Ustekinumab
UPA	Upadacitinib
VBM	Vobarilizumab