Safety of synthetic and biological DMARDs - a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis

Online Supplementary material

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1. SEARCH STRATEGY

1.1. Search strategy for bDMARDs

Medline

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. biosimilar$.tw.

18. infliximab.tw.

19. remicade.tw.

20. adalimumab.tw.

21. humira.tw.

22. trudexa.tw.

23. abatacept.tw.

24. orencia.tw.

25. anakinra.tw.

26. kineret.tw.

27. Certolizumab.tw.

28. cimzia.tw.

29. Etanercept.tw.

30. enbrel.tw.

31. Golimumab.tw.

32. simponi.tw.

33. rituximab.tw.

34. rituxan.tw.

35. mabthera.tw.

36. Tocilizumab.tw.

37. actemra.tw.

38. RoActemra.tw.

39. or/6-38

40. 5 and 39

41. (safe or safety).tw.

42. side effect$.tw.

43. ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).tw.

44. exp product surveillance, postmarketing/

45. exp adverse drug reaction reporting systems/

46. clinical trials, phase iv/

47. Clinical Trials, Phase III/

48. exp poisoning/

49. exp substance-related disorders/

50. exp drug toxicity/

51. exp abnormalities, drug induced/

52. exp drug monitoring/

53. exp drug hypersensitivity/

54. (toxicity or complication$ or noxious or tolerability).tw.

55. exp Postoperative Complications/

56. exp Intraoperative Complications/

57. or/41-56

58. 40 and 57

59. (animals not (humans and animals)).sh.

60. 58 not 59

61. limit 60 to yr="2013 -Current"

EMBASE

1. 'rheumatoid arthritis'/exp

2. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti

3. (felty* NEAR/2 syndrome):ab,ti

4. (caplan* NEAR/2 syndrome):ab,ti

5. #1 OR #2 OR #3 OR #4

6. 'biological therapy'/exp

7. biologic*:ab,ti OR biosimilar*:ab,ti

8. 'monoclonal antibody'/exp

9. 'infliximab':ab,ti

10. remicade:ab,ti

11. adalimumab:ab,ti

12. humira:ab,ti

13. trudexa:ab,ti

15. orencia:ab,ti

16. anakinra:ab,ti

17. kineret:ab,ti

18. certolizumab:ab,ti

19. cimzia:ab,ti

20. 'etanercept'/de

21. etanercept:ab,ti

22. enbrel:ab,ti

23. golimumab:ab,ti

24. simponi:ab,ti

25. rituximab:ab,ti

26. rituxan:ab,ti

27. mabthera:ab,ti

28. tocilizumab:ab,ti

29. actemra:ab,ti

30. roactemra:ab,ti

31. secukinumab:ab,ti

32. cosentyx:ab,ti

33. ustekinumab:ab,ti

34. stelara:ab,ti

35. brodalumab:ab,ti

36. ixekizumab:ab,ti

37. #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

38. #5 AND #37

39. 'adverse drug reaction'/lnk OR 'complication'/lnk OR 'side effect'/lnk

40. safe:ab,ti OR safety:ab,ti

41. 'side effect':ab,ti OR 'side effects':ab,ti

42. ((adverse OR undesirable OR harms* OR serious OR toxic) NEAR/3 (effect* OR reaction* OR event* OR outcome*)):ab,ti

43. 'postmarketing surveillance'/exp

44. 'phase 4 clinical trial (topic)'/de

45. 'intoxication'/exp

46. 'drug toxicity'/exp

47. 'congenital malformation'/exp

48. 'drug monitoring'/de

49. 'drug hypersensitivity'/exp

50. toxicity:ab,ti OR complication*:ab,ti OR noxious:ab,ti OR tolerability:ab,ti

51. 'postoperative complication'/exp

52. 'peroperative complication'/de

53. #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

54. #38 AND #53 AND [humans]/lim AND [embase]/lim AND #38 AND #54 AND [humans]/lim AND [embase]/lim AND AND (2013:py OR 2014:py OR 2015:py OR 2016:py) AND ('article'/it OR 'article in press'/it)

Cochrane Central

#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 #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 or #15 or #16 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

#40 #5 and #39

1.2. Search strategy for sDMARDs

Medline

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$.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. or/6-50

52. (safe or safety).tw.

53. side effect$.tw.

54. ((adverse or undesirable or harms$ or serious or toxic) adj3 (effect$ or reaction$ or event$ or outcome$)).tw.

55. exp product surveillance, postmarketing/

56. exp adverse drug reaction reporting systems/

57. clinical trials, phase iv/

58. Clinical Trials, Phase III/

59. exp poisoning/

60. exp substance-related disorders/

61. exp drug toxicity/

62. exp abnormalities, drug induced/

63. exp drug monitoring/

64. exp drug hypersensitivity/

65. (toxicity or complication$ or noxious or tolerability).tw.

66. exp Postoperative Complications/

67. exp Intraoperative Complications/

68. or/52-67

69. and/5,51,68

EMBASE

1. 'rheumatoid arthritis'/exp

2. ((rheumatoid OR reumatoid OR rheumat* OR reumat*) NEAR/3 (arthrit* OR artrit* OR diseas* OR condition* OR nodule*)):ab,ti

3. (felty* NEAR/2 syndrome):ab,ti

4. (caplan* NEAR/2 syndrome):ab,ti

5. #1 OR #2 OR #3 OR #4

6. 'disease modifying antirheumatic drug'/de

7. antirheumatic*:ab,ti

8. dmard*:ab,ti

9. 'disease modifying antirheumatic':ab,ti OR 'disease modifying antirheumatics':ab,ti

10. 'methotrexate'/de

11. methotrexate:ab,ti

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

13. 'isoxazole derivative'/exp

14. isoxazole*:ab,ti

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

16. 'salazosulfapyridine'/de

17. sulfasalazine:ab,ti

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

19. 'hydroxychloroquine'/de

20. hydroxychloro*:ab,ti

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

22. 'gold therapy'/de

23. gold:ab,ti

24. 'chloroquine'/de

25. chloroquine*:ab,ti

"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

27. 'azathioprine'/de

28. azathioprine:ab,ti

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

30. 'cyclosporin derivative'/de

31. cyclosporin*:ab,ti OR ciclosporin*:ab,ti

32. neoral:ab,ti OR gengraf:ab,ti OR restasis:ab,ti OR sandimmun*:ab,ti OR sangcya:ab,ti

33. 'penicillamine'/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

35. 'cyclophosphamide'/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

37. 'mycophenolic acid'/de

38. mycophenolate:ab,ti

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

40. 'chlorambucil'/de

41. chlorambucil:ab,ti

42. amboclorin:ab,ti OR clokeran:ab,ti OR leukeran:ab,ti OR linfolysin:ab,ti OR lympholysin:ab,ti

43. 'minocycline'/de

44. minocyclin*: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

46. tofacitinib:ab,ti

47. xeljanz:ab,ti

48. #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

49. #5 AND #48

50. 'adverse drug reaction'/lnk OR 'complication'/lnk OR 'side effect'/lnk

51. safe:ab,ti OR safety:ab,ti

52. 'side effect':ab,ti OR 'side effects':ab,ti

53. ((adverse OR undesirable OR harms* OR serious OR toxic) NEAR/3 (effect* OR reaction* OR event* OR outcome*)):ab,ti

54. 'postmarketing surveillance'/exp

55. 'phase 4 clinical trial (topic)'/de

56. 'intoxication'/exp

57. 'drug toxicity'/exp

58. 'congenital malformation'/exp

59. 'drug monitoring'/de

60. 'drug hypersensitivity'/exp

61. toxicity:ab,ti OR complication*:ab,ti OR noxious:ab,ti OR tolerability:ab,ti

62. 'postoperative complication'/exp

63. 'peroperative complication'/de

64. #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63

65. #49 AND #64 AND [humans]/lim AND [embase]/lim AND #38 AND #54 AND [humans]/lim AND [embase]/lim AND #67 AND (2013:py OR 2014:py OR 2015:py OR 2016:py) AND ('article'/it OR 'article in press'/it)

Cochrane Central

#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 #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

#52 #5 and #51

2. Review flow chart

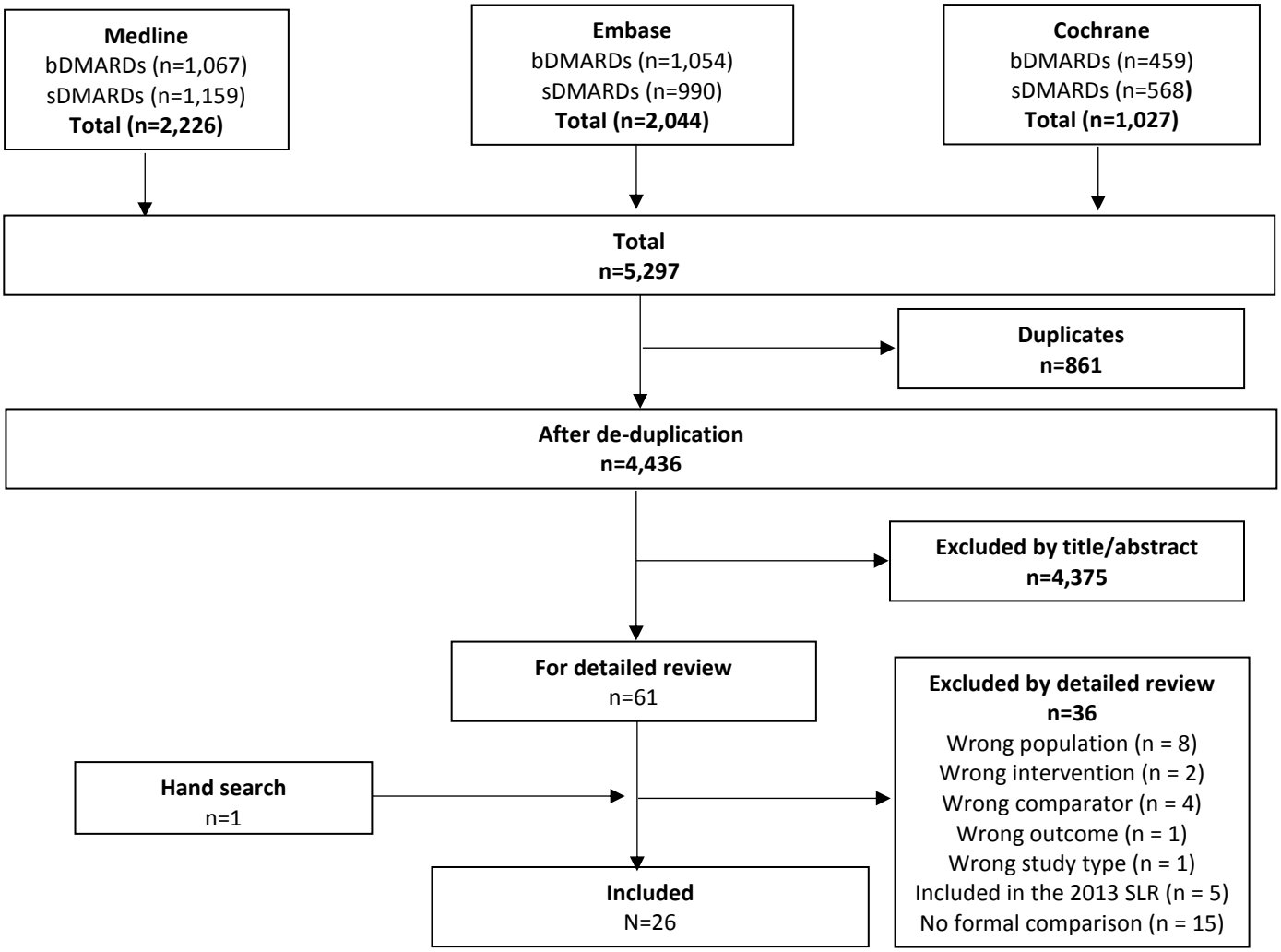

Figure S1. Flowchart for the systematic literature review.

3. SUMMARY OF PUBLICATIONS

Some of the included studies show data pertaining to more than one outcome. Thus, the total number of studies reporting data for each outcome is larger than the total number of included studies.

Table S1. Number of included publications for the different outcomes

Main outcome	Number of studies (n = 26)
Infections	15
Serious infections	11
Herpes zoster	1
Tuberculosis	1 (+3)
Skin infections	1
Non-viral opportunistic infections	1
Cancer	4
Any malignancy	2 (+2)
Solid cancer	1
Head and neck cancer	1
Lymphoma	0 (+1)
Mortality	1 (+1)
Cardiovascular events	4
Major adverse CV events (MI, stroke, CV death)	1
Heart failure	1
Hyperlipidemia	1
Venous thromboembolism	1
Interstitial lung disease	2

4. Details of the studies included in the bDMARDs search

4.1. Infections

4.1.1. Serious infections

Table S2: Included studies (serious infections)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Aaltonen 2015 J Rheum	ROB-FIN + Central Finland Central Hospital	RA, bDMARDs or csDMARDs (bDMARD naive)	None	No	Dec-11
Chiang 2014 Comp Methods	Taiwan's NHIRD (claims dataset)	RA, ETA or ADA	Patients <18 years at cohort entry or who had cancer, a solid organ transplant or HIV infection. Patients without TNFi for 180 days prior to the cohort entry	No	Dec-08
Chiu 2014 Int J Rheum Dis	Taiwan's NHIRD (claims dataset)	RA, holding a catastrophic illness card (be diagnosed with RA ≥2 times), bDMARDs or csDMARDs	Patients <18 years, diagnosis after 1 July 2009, patients who experienced an adverse event before ever receiving treatment with a bDMARD or csDMARD	No	Dec-09
Cobo-Ibanez 2014 Rheumatol Int	BIOBADASER	Adult patients with rheumatic diseases (including RA) on biologics (TNFi, RTX)	NR	Yes	Jul-11
Johnston 2013 Semin Arthr Rheum	Truven Health Analytics (former Thomson Reuters) MartketScan Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits databases (claims dataset)	RA, second line biologic treatment episodes	Alternative indication for biologic treatment during the first course of biologic treatment, NHL, CLL, plaque psoriasis, PsA, JIA, Chron's disease, ulcerative colitis, AS, SLE, HIV, hepatitis B, hepatitis C or demyelinating diseases	No	Dec-10
Lampropoulos 2015 Clin Exp Rheumatol	Files of patients with RA from Laiko University Hospital of Athen's Medical School	RA	<18 years, follow-up <3 months, only receiving steroids	No	2013
Miranda 2014 Rev Colomb Reumatol	Files of patients with RA from a Colombian hospital	RA, 18 years or older, csDMARDs or bDMARDs	Other rheumatic diseases, malignancy, doubtful information in the medical charts	No	2012
Morgan 2014 Rheumatology	BSRBR	Active RA, csDMARDs and bDMARDs, ≥1 consultant follow-up	NR	No	2011
Sakai 2015 AR&T	REAL	RA, csDMARDs or bDMARDs	NR	No	Jan-12
Yun 2016 A&R	Medicare claims dataset	RA (ICD codes, ≥ 2 episodes)	Patients with a claim containing the diagnosis of another rheumatic disease	No	Dec-11
Curtis 2014 AC&R	US Veterans Health Administration (claims dataset)	RA (≥ 2 diagnosis codes or 1 diagnosis code and DMARD prescription)	Active cancer, history of cancer	No	Sep-11

Table S3. Outcome and exposure definition and statistical analysis (serious infections)

Study ID	FolLow-up	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Aaltonen 2015 J Rheum	Variable	Any infection requiring hospitalization (National Hospital Discharge Register) - ICD-10	NS	On drug	Yes	Yes	Poisson regression	Yes
Chiang 2014 Comp Methods	Variable	Serious infection: hospitalization for infection; prescription of an antimicrobial injection; and TB (no cultures available, so algorithm defined) - ICD-9	NS	On drug + ever	No	No	Cox regression adjusted for PS	Yes
Chiu 2014 Int J Rheum Dis	Variable	Serious bacterial infection requiring hospitalization (according to a list of ICD-9 codes)	NS	Up to 90 days	No	No	IRR in a group of patients matched for PS (analysis not further specified)	Yes
Cobo-Ibanez 2014 Rheumatol Int	Variable	Serious infection: any AE that was classified under 'infections and infestations' in MedDra and described as either 'serious' or 'fatal' by the treating physician or leading to hospitalization or death	Rheumatologist + 10% audits	On drug + up to 90 days	No	No	SIR and SMR, compared to general population	Yes
Johnston 2013 Semin Arthr Rheum	Variable	Infection and severe infection (ICD-9 codes). Severe infection: hospitalized infection or an infection requiring outpatient IV anti-infectives	NS	NS (assumed 'on drug')	Yes (all patients were bDMARDs failures)	Yes	Mixed-effects and shared gamma frailty survival models	No
Lampropoulos 2015 Clin Exp Rheumatol	Variable	Serious infection	Rheumatologist	NS (assumed 'on drug')	Yes	Yes	IRR and Cox regression	Yes
Miranda 2014 Rev Colomb Reumatol	1 year	Serious infection: requiring hospitalization, administration of intravenous antibiotics or resulting in death	Rheumatologist	NS (assumed 'on drug')	Yes	Yes	Cox regression	Yes
Morgan 2014 Rheumatology	Variable	Serious infections	Rheumatologist	On drug + up to 90 days	Yes	No	Cox regression	Yes
Sakai 2015 AR&T	1 year	Serious infections	NS	NS (assumed 'on drug')	No	No	Cox regression	NS
Yun 2016 A&R	Variable	Hospitalized infection (incl bacterial, viral and opportunistic infections)	Previous studies with validation of outcome	On drug (with up to 30 days)	Yes (all patients were bDMARDs failures)	Yes	Cox regression	Yes
Curtis 2014 AC&R	Variable	First hospitalization for bacterial infection (ICD-9 codes)	Previous studies with validation of outcome	On drug + up to 90 days (270 days for RTX)	Yes (all patients were bDMARDs failures)	Yes	Cox regression	Yes

Table S4. Population characteristics (serious infections)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up time	Patient-years
Aaltonen 2015 J Rheum	Bio (ETA, IFX, ADA, RTX)	csDMARDs	csDMARDs	1400	0	65 (53-72)	69	9.4 (5.0-13.0)	2.3 (1.2-2.9)	3119
			TNFi	3094	31%	54 (45-61)	75	11 (6.0-19.0)	1.5 (0.57-3.4)	7162
			IFX	642	12%	52 (44-59)	72	11 (5.8-17.0)	1.6 (0.81-3.4)	1700
			ETA	1245	37%	54 (45-61)	76	11 (5.8-19.0)	1.5 (0.50-3.5)	2842
			ADA	1207	36%	55 (47-62)	76	12 (6.4-20.0)	1.3 (0.50-3.4)	2620
			RTX	438	63%	59 (52-67)	77	15 (8.7-23.0)	1.1 (0.50-2.4)	712
Chiang 2014 Comp Methods	ETA	ADA	ETA	1660	0	54.2 (13.1)	81.3	NR	NR	NR
			ADA	484	0	55.5 (12.7)	81	NR	NR	NR
Chiu 2014 Int J Rheum Dis	TNFi (ETA, ADA)	csDMARDs	csDMARDs	8066	0	57.9	82.8	8.0	NR	50380
			TNFi	4033	0	57.8	82.3	8.0	NR	7237
			ETA	1492	0	56.5	82.1	7.0	NR	3028
			ADA	746	0	56.0	81.1	6.9	NR	685
Cobo-Ibanez 2014 Rheumatol Int	TNFi (ADA, ETA, IFX), RTX	General population	TNFi	3050	0	54 (14)	79	8 (4-14)	NR	10242
			RTX	75	0				NR	146
			General population	REF	NR				NR	NR
Johnston 2013 Semin Arthr Rheum	bDMARDs (ABA, ADA, ETA, IFX, RTX)	NA	ABA	870	100	57.0 (12.6)	83.1	NR	330 days	1004
			ADA	1378	100	54.3 (12.0)	80.3	NR	365 days	1772
			ETA	1026	100	54.6 (12.7)	77.2	NR	379 days	1392
			IFX	649	100	54.3 (12.8)	77.8	NR	348 days	789
			RTX	409	100	56.4 (12.0)	77.5	NR	335 days	463
Lampropoulos 2015 Clin Exp Rheumatol	bDMARDs (ADA, ETA, IFX, other)	csDMARDs	csDMARDS	969	0	55.1 (14.8)	80	NR	NR	2557
			bDMARDS	434	40	53.0 (14.1)	78	NR	NR	1371
			ADA	103	NR	52.7 (14.9)	71	NR	NR	NR
			ETA	135	NR	51.6 (14.9)	76	NR	NR	NR
			IFX	129	NR	51.6 (12.9)	82	NR	NR	NR
Miranda 2014 Rev Colomb Reumatol	bDMARDs (ADA, ABA, ETA, RTX, TCZ, IFX)	csDMARDs	csDMARDs	300	0	55 (47-65)	88	5 (3-13)	NR	NR
			bDMARDS	83	39.8	50 (46-59)	85.5	8 (3-15)	NR	NR
Morgan 2014 Rheumatology	ETA	csDMARDs	csDMARDs	2864	NR	59.8 (12.4)	75	9.6 (10.4)	3.9 (2.0) years	11095
			ETA	3529	NR	55.3 (12.1)	77	13.5 (9.4)	4.8 (2.4) years	16919
Sakai 2015 AR&T	TCZ	TNFi (ADA,	TNFi	304	0	57.3 (15.2)	82.8	7.96 (8.70)	NR	231.01

		ETA, IFX)	TCZ	302	0	59.2 (13.0)	82.5	10.20 (8.64)	NR	224.68
Yun 2016 A&R	bDMARDs (ADA, CZP, ETA, GOL, INF, RTX, TCZ, ABA)		ADA	4845	100	61.8 (13.5)	83.9	NR	NR	2171
			CZP	1866	100	64.1 (13.3)	86.3	NR	NR	747
			ETA	3814	100	61.8 (13.3)	85.6	NR	NR	616
			GOL	1394	100	60.4 (13.5)	88.7	NR	NR	1726
			INF	3944	100	65.3 (12.5)	84.9	NR	NR	2178
			RTX	4718	100	65.0 (12.2)	85.0	NR	NR	2898
			TCZ	2016	100	66.4 (11.9)	85.3	NR	NR	863
			ABA	9204	100	66.8 (12.1)	85.5	NR	NR	5377
Curtis 2014 AC&R	Bio (ETA, IFX, ADA, RTX, ABA)		TNFi	3111	100	60.1 (10.6)	12.3	NR	NR	4147
			ABA	451	100	60.3 (10.6)	16.4	NR	NR	498
			RTX	596	100	60.8 (10.6)	12.4	NR	NR	630.2
			ADA	1885	100	60.1 (10.8)	12.0	NR	NR	2534
			ETA	844	100	59.9 (10.7)	11.5	NR	NR	1133.4
			IFX	382	100	57.9 (10.5)	15.2	NR	NR	480.2

Table S5. Effect size intervention and control (non-biologic) and comparison (serious infections)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Aaltonen 2015 J Rheum	csDMARDs	106	34/1000 PY (28-41)	IRR	REF	REF	REF	Age, gender, disease duration, year of cohort inclusion, RF-positive, DAS28, HAQ-DI, prior malignancy, baseline use of MTX, SSZ, HCQ, steroids
	TNFi	198	28/1000 PY (24-32)		0.80 (0.58-1.1)	1.4 (1.0-1.9)	0.9 (0.6-1.4)	
	IFX	53	31/1000 PY (23-41)		0.89 (0.58-1.4)	1.6 (1.1-2.5)	1.2 (0.63-2.3)	
	ETA	68	24/1000 PY (19-30)		0.70 (0.47-1.0)	1.2 (0.82-1.8)	0.84 (0.53-1.3)	
	ADA	77	29/1000 PY (23-37)		0.85 (0.58-1.3)	1.4 (0.96-2.1)	0.98 (0.60-1.6)	
	RTX	37	52/1000 PY (37-72)		1.5 (0.90-2.5)	2.1 (1.3-3.4)	1.1 (0.59-1.9)	
Chiang 2014 Comp Methods	ETA	NR	NR	HR	NR	NR	NR	NR
	ADA	NR	NR		NR	NR	NR	
Chiu 2014 Int J Rheum Dis	csDMARDs	1489	2956/100000 PY (2807-3109)	IRR	REF	NR	NR	Patients were matched for PS and no further adjustment is made. PS: age, COPD/asthma, diabetes, disease duration, number of csDMARDs, sex, steroid exposure
	TNFi	222	3068/100000 PY (2677-3499)		1.04 (0.89-1.19)	NR	NR	
Cobo-Ibanez 2014 Rheumatol Int	TNFi	NA	3.1/100 PY (2.8-3.4)	SIR	M 16 (13-20), W 21 (19-24)	NR	NR	NR
	RTX	NA	11/100 PY (6.7-17.9)		M 32 (1-179), W 186 (106-302)	NR	NR	
	General population		NA		REF	NR	NR	
Johnston 2013 Semin Arthr Rheum	ABA	78	8.2/100 PY	HR	NR	NR	NR	NR
	ADA	110	6.7/100 PY		NR	NR	NR	
	ETA	101	7.9/100 PY		NR	NR	NR	
	IFX	72	10.1/100 PY		NR	NR	NR	
	RTX	35	8.2/100 PY		NR	NR	NR	
Lampropoulos 2015 Clin Exp Rheumatol	csDMARDs	8	0.31/100 PY	IRR	REF		REF	Extra-articular manifestations, comorbidities, initial DAS28, total dose of steroids
	bDMARDS	34	2.48/100 PY		7.93 (3.60-19.83)		6.86 (3.06-15.4)	
Miranda 2014 Rev Colomb Reumatol	csDMARDs	13	NR	HR	REF		REF	MTX, LEF, steroids, diabetes, pulmonary disease, time on DMARDs
	bDMARDS	9	NR		2.56 (1.01-6.01)		2.67 (1.12-6.34)	
Morgan 2014 Rheumatology	csDMARDs	375	36.2/1000 PY	HR	NR	NR	REF	Age, gender, baseline non-RA drugs, baseline steroid, baseline DMARDs, MTX, DAS28, smoking history
	ETA	538	35.1/1000 PY		NR	NR	1.019 (0.831-1.251)	
Sakai 2015 AR&T	TNFi	7	3.03/100 PY (1.35-5.95)	IRR	NR	NR	NR	NR
	TCZ	24	10.68/100 PY (7.02-15.63)		NR	NR	NR	
Yun 2016 A&R	ADA	317	14.6/100 PY (13.1-16.3)	HR	NR	NR	NR	NR

	CZP	106	14.2/100 PY (11.7-17.2)		NR	NR	NR	
	ETA	87	14.1/100 PY (11.5-17.4)		NR	NR	NR	
	GOL	275	15.9/100 PY (14.2-17.9)		NR	NR	NR	
	INF	370	17.0/100 PY (15.3-18.8)		NR	NR	NR	
	RTX	541	18.7/100 PY (17.2-20.3)		NR	NR	NR	
	TCZ	129	14.9/100 PY (12.6-17.8)		NR	NR	NR	
	ABA	705	13.1/100 PY (12.2-14.1)		NR	NR	NR	
Curtis 2014 AC&R	TNFi	123	3.0/100 PY (2.5-3.5)	HR	NR	NR	NR	NR
	ABA	14	2.8/100 PY (1.7-4.7)		NR	NR	NR	
	RTX	28	4.4/100 PY (3.1-6.4)		NR	NR	NR	
	ADA	75	3.0/100 PY (2.4-3.7)		NR	NR	NR	
	ETA	25	2.2/100 PY (1.5-3.3)		NR	NR	NR	
	IFX	23	4.8/100 PY (3.2-7.2)		NR	NR	NR	

Table S6. Comparison across biologics (serious infections)

Study ID	Treatment group	N of events	Type of ratio	uHR I2 vs c2)	Age/gender aHR (i2 vs c2)	aHR (i2 vs c2)	Adjusted for
Aaltonen 2015 J Rheum	TNFi	198	IRR	REF	REF	REF	Age, gender, disease duration, year of cohort inclusion, RF-positive, DAS28, HAQ-DI, prior malignancy, baseline use of MTX, SSZ, HCQ, steroids
	IFX	53		NR	NR	NR	
	ETA	68		NR	NR	NR	
	ADA	77		NR	NR	NR	
	RTX	37		1.9 (1.2-3.1)	1.6 (1.0-2.6)	1.4 (0.78-2.6)	
Chiang 2014 Comp Methods	ETA	NA	HR	1.95 (1.10-3.45)	NR	2.03 (1.14-3.62)	NR
	ADA	NA		REF	NR	REF	
Chiu 2014 Int J Rheum Dis	ETA	82	IRR	REF	NR	NR	Patients were matched for PS and no further adjustment is made. PS: age, COPD/asthma, diabetes, disease duration, number of csDMARDs, sex, steroid exposure
	ADA	34		1.83 (1.19-2.77)	NR	NR	
Cobo-Ibanez 2014 Rheumatol Int	TNFi	NA	SIR	NR	NR	NR	NR
	RTX	NA		NR	NR	NR	
Johnston 2013 Semin Arthr Rheum	ABA	78	HR	NR	NR	1.21 (0.78-)	Age, gender, geographic region, urbanicity, year of

	ADA	110		NR	NR	1.10 (0.72-1.68)	episode start, episode trial, baseline medications, baseline comorbidities, baseline health status
	ETA	101		NR	NR	1.27 (0.83-1.95)	
	IFX	72		NR	NR	1.62 (1.03-2.55)	
	RTX	35		NR	NR	REF	
Lampropoulos 2015 Clin Exp Rheumato	ADA	NA	IRR	1.09 (p=0.826)	NR NR	1.10 (p=0.819)	Extra-articular manifestations, comorbidities, initial DAS28, total dose of steroids
	ETA	NA		0.60 (p=0.332)	NR	0.72 (p=0.559)	
	IFX	NA		REF	NR	REF	
Miranda 2014 Rev Colomb Reumatol	csDMARDs	13	HR	NR	NR	NR	NR
	bDMARDS	9		NR	NR	NR	
Morgan 2014 Rheumatology	csDMARDs	375	HR	NR	NR	NR	NR
	ETA	538		NR	NR	NR	
Sakai 2015 AR&T	TNFi	7	IRR	REF	NR	REF	Age, gender, comorbidity, prednisolone
	TCZ	24		3.53 (1.52-8.18)	NR	2.23 (0.93-5.37)	
Yun 2016 A&R	ADA	317	HR	1.08 (0.95-1.24)	NR	1.08 (0.93-1.25)	Infection risk score decile, number of previous biologic agents used, disability status, glucocorticoid use during baseilne, MTX use during baseline, most recent biologic agent used during baseline, and Medicaid eligibility
	CZP	106		1.04 (0.84-1.27)	NR	1.07 (0.86-1.32)	
	ETA	87		1.05 (0.84-1.31)	NR	1.24 (1.07-1.45)	
	GOL	275		1.19 (1.03-1.36)	NR	1.14 (0.90-1.44)	
	INF	370		1.29 (1.14-147)	NR	1.39 (1.21-1.60)	
	RTX	541		1.41 (1.26-1.58)	NR	1.36 (1.21-1.53)	
	TCZ	129		1.10 (0.91-1.32)	NR	1.10 (0.89-1.34)	
	ABA	705		REF	NR	REF	
Curtis 2014 AC&R	TNFi	123	HR	NR	NR	NR	Age, COPD, BMI, prednisone dose, previous exposure ≥3 biologics, hospitalizations during baseline period, ESR, seropositive RA
	ABA	14		NR	NR	1.1 (0.6-2.1)	
	RTX	28		NR	NR	1.4 (0.8-2.6)	
	ADA	75		NR	NR	1.4 (0.9-2.2)	
	ETA	25		NR	NR	REF	
	IFX	23		NR	NR	2.3 (1.3-4.0)	

Table S7. Additional information on subtypes of the outcome, steroids and additional comments (serious infections)

Study ID	Treatment group	Incidence non-tuberculous mycobacteria	aHR non-tuberculous mycobacteria	Steroids
Sakai 2015 AR&T	TNFi TCZ	NR	NR	aHR prednisolone ≥5mg: 2.26 (1.02-5.01)

Table S8: Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Aaltonen 2015 J Rheum	Low	Moderate	Low	Low	Moderate	Low	Low
Chiang 2014 Comp Methods	Moderate	Moderate	Moderate	Moderate	High	High	High
Chiu 2014 Int J Rheum Dis	Moderate	Moderate	Moderate	Moderate	High	High	High
Cobo-Ibanez 2014 Rheumatol Int	Low	Moderate	Low	Low	High	Low	Moderate
Johnston 2013 Semin Arthr Rheum	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Lampropoulos 2015 Clin Exp Rheumatol	High	High	High	High	High	Moderate	High
Miranda 2014 Rev Colomb Reumatol	High	High	High	High	High	Moderate	High
Morgan 2014 Rheumatology	Low	Low	Low	Low	Moderate	Moderate	Low
Sakai 2015 AR&T	Low	Moderate	Low	Low	Moderate	Moderate	Moderate
Yun 2016 A&R	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Curtis 2014 AC&R	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate

4.1.2. Herpes zoster

Table S9: Included studies (Herpes zoster)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Pappas 2015 AC&R	CORRONA	RA	NA	No	Mar-13

Table S10. Outcome and exposure definition and statistical analysis (Herpes zoster)

Study ID	FolLow-up	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Pappas 2015 AC&R	Variable	Herpes zoster infection	Rheumatologist	On drug	Yes	Yes	Cox regression adjusted for PS	Yes

Table S11. Population characteristics (Herpes zoster)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up time	Patient-years
Pappas 2015 AC&R	bDMARDs (TNFi, non-TNFi); all included	csDMARDs	csDMARDs	1411	23	59.06 (13.22)	76	8.38 (9.21)	1.5 (1.5) years	2100.4
			TNFi	4023	45	56 (12.93)	77.1	9.14 (9.36)	1.9 (1.8) years	7626.2
			non-TNFi	2013	87	57.65 (12.8)	80.6	12.13 (9.52)	1.8 (1.5) years	3667.2

Table S12. Effect size intervention and control and comparison (Herpes zoster)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Pappas 2015 AC&R	csDMARDs	22	10.5/1000 PY (6.9-15.9)	HR	1.552 (0.942-2.557)	NR	1.359 (0.819-2.253)	PS
	TNFi	53	6.9/1000 PY (5.3-9.1)		REF	NR	REF	
	non-TNFi	25	6.8/1000 PY (4.6-10.1)		0.982 (0.609-1.585)	NR	0.834 (0.509-1.367)	

Table S13: Risk of bias assessment (Herpes zoster)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Pappas 2015 AC&R	Low	Low	Low	Low	Low	Low	Low

4.1.3. Tuberculosis

Table S14: Included studies (tuberculosis)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Chiang 2014 Comp Methods	Taiwan's National Health Insurance Research Database (NHIRD) (claims dataset)	RA, ETA or ADA	Patients <18 years at cohort entry or who had cancer, a solid organ transplant or HIV infection. Patients without TNFi for 180 days prior to the cohort entry	No	Dec-08
Chiu 2014 Int J Rheum Dis	Taiwan's National Health Insurance Research Database (NHIRD) (claims dataset)	RA, holding a catastrophic illness card (be diagnosed with RA ≥2 times), bDMARDs or csDMARDs	Patients <18 years, diagnosis after 1 July 2009, patients who experienced an adverse event before ever receiving treatment with a bDMARD or csDMARD	No	Dec-09
Ke 2013 Tuberc Lung Dis	Taiwan's National Health Insurance Research Database (NHIRD) (claims dataset)	RA (ICD-9 codes), holding a catastrophic illness card, bDMARDs or csDMARDs	Patients starting DMARDs <2005, no diagnosis of RA or prescription of DMARDs, age>110 or <18 years, pregnancy, known TB risk factors (history of TB, HIV carrier, organ transplant receiver, cancer patients with chemotherapy, potential drug users, patients on renal replacement therapy and patients with a history of gastrectomy of jejunoileal bypass surgery)	No	Dec-10
Baddley 2014 ARD	4 US insurance datasets (Safety assessment of biologic therapy - SABER Study) (claims dataset)	RA (ICD-9 codes: 1 episode + prescription of DMARD) (also other rheumatic diseases, but not extracted)	NR	Yes	Dec-07

Table S15. Outcome and exposure definition and statistical analysis (tuberculosis)

Study ID	FolLow-up	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Chiang 2014 Comp Methods	Variable	Serious infection: hospitalization for infection; prescription of an antimicrobial injection; and TB (no cultures available, so algorithm defined) - ICD-9	NS	On drug + ever	No	No	Cox regression adjusted for PS	Yes
Chiu 2014 Int J	Variable	Serious bacterial infection requiring hospitalization	NS	Up to 90 days	No	No	IRR in a group of patients	Yes

Rheum Dis		(according to a list of ICD-9 codes)					matched for PS (analysis not further specified)	
Ke 2013 Tuberc Lung Dis	Variable	Tuberculosis (ICD-9 codes) + prescription of ≥2 anti-tuberculosis agents in the following 6 months	Previous studies with validation of outcome	On drug (with up to 30 days)	No	Assume yes (NS)	IRR and Cox regression	Yes
Baddley 2014 ARD	Variable	Non-viral opportunistic infection (ICD-9 codes)	NS	On drug (with up to 30 days)	No	Assume yes (NS)	Cox regression adjusted for PS	Assume yes (NS)

Table S16. Population characteristics (tuberculosis)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up time	Patient-years
Chiang 2014 Comp Methods	ETA	ADA	ETA	1660	0	54.2 (13.1)	81.3	NR	NR	NR
			ADA	484	0	55.5 (12.7)	81	NR	NR	NR
Chiu 2014 Int J Rheum Dis	TNFi (ETA, ADA)	csDMARDs	csDMARDs	8066	0	57.9	82.8	8.0	NR	50380
			TNFi	4033	0	57.8	82.3	8.0	NR	7237
			ETA	1492	0	56.5	82.1	7.0	NR	3028
			ADA	746	0	56.0	81.1	6.9	NR	685
Ke 2013 Tuberc Lung Dis	TNFi (ADA, ETA)	csDMARDs	csDMARDS	5079	0	54.8 (13.7)	76.3	NR	1.6 years	9018.8
			TNFi	829	0	52.8 (12.8)	74.7	NR	2.3 years	942.9
			ETA	NR	NR	NR	NR	NR	NR	NR
			ADA	NR	NR	NR	NR	NR	NR	NR
Baddley 2014 ARD	TNFi (IFX, ADA, ETA)	csDMARDs	csDMARDs	11828	0	58.5 (14.3)	86.3	NR	NR	7188
			TNFi	24384	0	57.7 (14.5)	85.9	NR	NR	22213

Table S17. Effect size intervention and control (non-biologic) and comparison (tuberculosis)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Chiang 2014 Comp Methods	ETA	NR	NR	HR	NR	NR	NR	NR
	ADA	NR	NR		NR	NR	NR	
Chiu 2014 Int J Rheum Dis	csDMARDs	298	546/100000 PY (486-612)	IRR	REF	NR	NR	Patients were matched for PS and no further adjustment is made. PS: age, COPD/asthma, diabetes, disease duration, number of csDMARDs, sex, steroid exposure
	TNFi	108	1458/100000 PY (1196-1761)		2.67 (2.12-3.34)	NR	NR	
Ke 2013 Tuberc Lung Dis	csDMARDS	28	310.5/100000 PY	HR	REF	NR	REF	NR
	TNFi	9	954.5/100000 PY		4.34 (1.95-9.66)	NR	4.87 (2.14-11.06)	
Baddley 2014 ARD	csDMARDs	1	0.1/1000 PY (0.0-1.0)	HR	NR	NR	REF	PS quintile and baseline glucocorticoid use 1 year before time zero *PS: comorbidities, drug use, healthcare utilization (several variables for each of this domains of variables)
	TNFi	8	0.4/1000 PY (0.2-0.7)		NR	NR	4.2 (0.5-33.5)	

Table S18. Comparison across biologics (tuberculosis)

Study ID	Treatment group	N of events	Type of ratio	uHR I2 vs c2)	Age/gender aHR (i2 vs c2)	aHR (i2 vs c2)	Adjusted for
Chiang 2014 Comp Methods	ETA	NR	HR	HR	2.61 (0.34-20.20)	NR	NR
	ADA	NR			REF	NR	
Chiu 2014 Int J Rheum Dis	ETA	38	IRR	REF	NR	NR	Patients were matched for PS and no further adjustment is made. PS: age, COPD/asthma, diabetes, disease duration, number of csDMARDs, sex, steroid exposure
	ADA	20		2.35 (1.29-4.15)	NR	NR	
Ke 2013 Tuberc Lung Dis	csDMARDS	NR	NR	NR	NR	NR	NR
	TNFi	NR		NR	NR	NR	
Baddley 2014 ARD	ADA	NR	HR	NR	NR	1.8 (0.8-4.0)	PS quintile and baseline glucocorticoid use 1 year before time zero *PS: comorbidities, drug use, healthcare utilization (several variables for each of this domains of variables)
	IFX	NR		NR	NR	2.9 (1.5-5.4)	
	ETA	NR		NR	NR	REF	

Table S19. Additional information on subtypes of the outcome, steroids and additional comments (tuberculosis)

Study ID	Treatment group	Incidence non-tuberculous mycobacteria	aHR non-tuberculous mycobacteria	Steroids
Sakai 2015 AR&T	TNFi TCZ	NR	NR	aHR prednisolone ≥5mg: 2.26 (1.02-5.01)
Ke 2013 Tuberc Lung Dis	csDMARDS TNFi	NR	NR	Age, gender, diabetes, hypertension, dyslipidemia, COPD/asthma, lung fibrosis, heart failure, ischaemic heart disease, rhythmic heart disease, hepatitis, liver cirrhosis, concomitant medication (prednisolone, MTX, SSZ, HCQ), TB prevalence in the region, level of hospital certifications
Baddley 2014 ARD	csDMARDs TNFi	0.6/1000 PY (0.2-1.5) 0.4/1000 PY (0.2-0.8)	REF 0.9 (0.3-3.3)	aHR baseline glucocorticoide use in different models: model with ETA in vs csDMARDs: 1.7 (0.7-4.1); model with ADA in vs csDMARDs: 2.8 (0.8-9.9); model with IFX in vs csDMARDs 1.7 (0.9-3.4); model with ADA vs ETA: 2.5 (0.9-7.3); model with IFX vs ETA: 1.6 (0.8-3.1)

Table S20. Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Chiang 2014 Comp Methods	Moderate	Moderate	Moderate	Moderate	High	High	High
Chiu 2014 Int J Rheum Dis	Moderate	Moderate	Moderate	Moderate	High	High	High
Ke 2013 Tuberc Lung Dis	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Baddley 2014 ARD	Moderate	Moderate	Moderate	Moderata	Moderate	Moderate	Moderate

4.1.4. Skin infections

Table S21. Included studies (skin infections)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Wasson 2013 BMC Infect Dis	US Veterans Integrated Service Network (claims dataset)	RA (ICD-9, ≥ 2 episodes AND ≥ 1 prescriptions of DMARD)	NR	No	NR

Table S22. Outcome and exposure definition and statistical analysis (skin infections)

Study ID	FolLow-up	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Wasson 2013 BMC Infect Dis	Variable	Hospitalization due to serious skin and soft tissue infections (ICD-9 codes)	NS	On drug + up to 90 days	Assume yes (NS)	Assume yes (NS)	Logistic regression (case-control study)	Assume yes (NS)

Table S23. Population characteristics (skin infections)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up time	Patient-years
Wasson 2013 BMC Infect Dis	TNFi (ADA, ETA, IFX)	csDMARDs	csDMARDs	291	24	61	11	NR	NR	NR
			TNFi	97	30	63	8	NR	NR	NR

Table S24. Effect size intervention and control and comparison (skin infections)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Adjusted IR	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Wasson 2013 BMC Infect Dis	csDMARDs	53	NA	NR	OR	REF	NR	REF	RA severity, diabetes mellitus, chronic kidney disease, chronic bronchitis, prior history of skin infectio, pneumonia, discharge 3 months prior, prednisone use within 30 days of the index date and antibiotic use 90 days prior to the index
	TNFi	19	NA	NR		1.107 (0.604; NR2.028)	NR	1.107 (0.604; 2.028)	

Table S25. Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Wasson 2013 BMC Infect Dis	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

4.1.5. Non-viral opportunistic infections

Table S26. Included studies (Non-viral opportunistic infections)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Baddley 2014 ARD	4 US insurance datasets (afety assessment of biologic therapy - SABER Study) (claims dataset)	RA (ICD-9 codes: 1 episode + prescription of DMARD) (also other rheumatic diseases, but not extracted)	NR	Yes	Dec-07

Table S27. Outcome and exposure definition and statistical analysis (Non-viral opportunistic infections)

Study ID	FolLow-up	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Baddley 2014 ARD	Variable	Non-viral opportunistic infection (ICD-9 codes)	NS	On drug (with up to 30 days)	No	Assume yes (NS)	Cox regression adjusted for PS	Assume yes (NS)

Table S28. Population characteristics (Non-viral opportunistic infections)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up time	Patient-years
Baddley 2014 ARD	TNFi (IFX, ADA, ETA)	csDMARDs	csDMARDs	11828	0	58.5 (14.3)	86.3	NR	NR	7188
			TNFi	24384	0	57.7 (14.5)	85.9	NR	NR	22213

Table S29. Effect size intervention and control and comparison (Non-viral opportunistic infections)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Baddley 2014 ARD	csDMARDs	13	1.8/1000 PY (1.1-3.1)	HR	NR	NR	REF	PS quintile and baseline glucocorticoid use 1 year before time zero *PS: comorbidities, drug use, healthcare utilization (several variables for each of this domains of variables)
	TNFi	67	3.0/1000 PY (2.4-3.8)		NR	NR	1.6 (0.9-3.1)	
	ADA	15	3.5/1000 PY (2.1-5.8)		NR	NR	1.8 (0.6-5.3)	
	IFX	55	4.1 (3.1-5.3)		NR	NR	2.6 (1.2-5.6)	
	ETA	13	1.5 (0.9-2.6)		NR	NR	0.8 (0.4-1.8)	

Table S30. Comparison across biologics (Non-viral opportunistic infections)

Study ID	Treatment group	N of events	Type of ratio	uHR I2 vs c2)	Age/gender aHR (i2 vs c2)	aHR (i2 vs c2)	Adjusted for
Baddley 2014 ARD	ADA	15	HR	NR	NR	1.8 (0.8-4.0)	PS quintile and baseline glucocorticoid use 1 year before time zero *PS: comorbidities, drug use, healthcare utilization (several variables for each of this domains of variables)
	IFX	55		NR	NR	2.9 (1.5-5.4)	
	ETA	13		NR	NR	REF	

Table S31: Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Baddley 2014 ARD	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate

4.2. Malignancies

Table S32: Included studies (malignancies)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of FU for analysis
Aaltonen 2015 J Rheum	National Register for Biologic Treatment in Finland (ROB-FIN) + Central Finland Central Hospital	RA, bDMARDs or csDMARDs (bDMARD naive)	None	No	Dec-11
Chiu 2014 Int J Rheum Dis	Taiwan's National Health Insurance Research Database (NHIRD) (claims dataset)	RA, hold a catastrophic ilness card (be diagnosed with RA ≥2 times), bDMARDs or csDMARDs	Patients <18 years, diagnosis after 1 July 2009, patients who experienced an adverse event before ever receiving treatment with a bDMARD or csDMARD	No	Dec-09
Morgan 2014 Rheumatology	BSRBR	Active RA, csDMARDs and bDMARDs, ≥1 consultant follow-up	NR	No	2011
Berghen 2015 Clin Rheumatol	Cases from the Leuven University Hospital	RA (1987 ACR criteria)	NR	No	Jan-12
Mercer 2015 ARD	BSRBR	RA, TNFi or (csDMARD if DAS28>4.2)	Prior diagnosis of solid cancer	No	Jan-11
Solomon 2014 Semin Arthr Rheum	CORRONA	NR	Subjects with reports of cancer who had evidence that cancer was prevalent	No	Nov-10
Philips 2015 Plos One	VA dataset (claims dataset)	RA (ICD-9, ≥2 episodes) + DMARD prescription + head and neck cancer (ICD-9)	NR	No	NR

Table S33. Outcome and exposure definition and statistical analysis (malignancies)

Study ID+I1:M26	Follow-up time	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Aaltonen 2015 J Rheum	Variable	Any malignancy	NS	On drug	Yes	Yes	Poisson regression	Yes
Chiu 2014 Int J Rheum Dis	Variable	Lymphoma (not further specified)	NS	Up to 90 days	No	No	IRR in a group of patients matched for PS (analysis not further specified)	Yes
Morgan 2014 Rheumatology	Variable	Malignancies	NHS Information Centre	On drug + up to 90 days	Yes	No	Cox regression	Yes
Berghen 2015 Clin Rheumatol	Variable	Hematologic and solid tumors	Rheumatologist	Assumed on drug (not specified)	No	Yes	Poisson regression and SIR	Yes
Mercer 2015 ARD	Variable up to 5 years	Solid cancer	Questionnaires + patient health diaries+ national cancer agencies. Cancers confirmed with histology report	On drug (with up to 30 days)	No	Yes	Cox regression adjusted for PS	Yes
Solomon 2014 Semin Arthr Rheum	Variable	Malignancies	Rheumatologist + pathology/surgery/oncology reports	NR	Yes	Yes	Cox regression adjusted for PS	Yes
Philips 2015 Plos One	Variable	Head and neck cancer recurrence and/or head and neck cancer attributable death	NS	On drug	Yes	Assume yes (NS)	Cox regression	NR

Table S34. Population characteristics (malignancies)

Study ID	Intervention	Control sDMARDs	Control general population	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	Follow-up times	Patient-years
Aaltonen 2015 J Rheum	bDMARDs (ETA, IFX, ADA, RTX)	csDMARDs	No	csDMARDs	1400	0	65 (53-72)	69	9.4 (5.0-13.0)	2.3 (1.2-2.9)	3119
				TNFi	3094	31%	54 (45-61)	75	11 (6.0-19.0)	1.5 (0.57-3.4)	7162
				IFX	642	12%	52 (44-59)	72	11 (5.8-17.0)	1.6 (0.81-3.4)	1700
				ETA	1245	37%	54 (45-61)	76	11 (5.8-19.0)	1.5 (0.50-3.5)	2842
				ADA	1207	36%	55 (47-62)	76	12 (6.4-20.0)	1.3 (0.50-3.4)	2620
				RTX	438	63%	59 (52-67)	77	15 (8.7-23.0)	1.1 (0.50-2.4)	712
Chiu 2014 Int J Rheum Dis	TNFi (ETA, ADA)	csDMARDs	No	csDMARDs	8066	0	57.9	82.8	8.0	NR	55705
				TNFi	4033	0	57.8	82.3	8.0	NR	7495
				ETA	1492	0	56.5	82.1	7.0	NR	3132
				ADA	746	0	56.0	81.1	6.9	NR	697
Morgan 2014 Rheumatology	ETA	csDMARDs	No	csDMARDs	2864	NR	59.8 (12.4)	75	9.6 (10.4)	3.9 (2.0)	11095
				ETA	3529	NR	55.3 (12.1)	77	13.5 (9.4)	4.8 (2.4)	16919
Berghen 2015 Clin Rheumatol	TNFi (ADA, ETA, IFX)	General population	Yes	General population	365	0	Female: 51.1; Male 54.6	74.2	Female: 10.2 years; Male: 9.15 years	NR	NR
				TNFi	NR	0		NA			
Mercer 2015 ARD	TNFi (ADA, ETA, IFX)	csDMARDs	No	csDMARDs	3249	0	60 (12)	73	6 (1;15)	4.1 (2.3;5.0)	11672
				TNFi	11767	0	56 (12)	76	11 (6;19)	5.0 (4.4; 5.0)	52549
				ETA	NR	NR	NR	NR	NR	4.8 (2.5;5.0)	22146
				IFX	NR	NR	NR	NR	NR	3.9 (1.3; 5.0)	12379
				ADA	NR	NR	NR	NR	NR	3.5 (2.0;4.8)	18027
Solomon 2014 Semin Arthr Rheum	bDMARDs (TNFi - ADA,ETA,IFX-, ABA, RTX), other csDMARDs	MTX	No	MTX	1566	NR	NR	72.3	9.06 (9.9)	NR	2866
				TNFi	3761	NR	NR	77.7	9.84 (9.0)	NR	10293
				other csDMARDs	904	NR	NR	76.9	8.48 (8.9)	NR	1900
				RTX	167	NR	NR	76.7	13.05 (9.4)	NR	247
				ABA	408	NR	NR	84.1	13 (10.2)	NR	589
Philips 2015 Plos One	TNFi (ADA, ETA, IFX)	csDMARDs	No	csDMARDs	149	NR	66.0 (9.1)	1.3	NR	42.4 (32.8) months	NR
				TNFi	31	NR	63.9 (7.8)	0	NR	40.3 (28.2) months	NR

Table S35. Effect size intervention and control and comparison (malignancies)

Study ID	Treatment group	N events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Aaltonen 2015 J Rheum	csDMARDs	39	13/1000 PY (8.9-17)	IRR	REF	REF	REF	Age, gender, disease duration, year of cohort inclusion, RF-positive, DAS28, HAQ-DI, prior malignancy, baseline use of MTX, SSZ, HCQ, steroids
	TNFi	47	6.6/1000 PY (4.8-8.7)		0.52 (0.34-0.80)	0.98 (0.61-1.57)	1.2 (0.63-2.2)	
	IFX	10	5.9/1000 PY (2.8-11)		0.46 (0.23-0.93)	0.91 (0.44-1.9)	1.2 (0.44-3.1)	
	ETA	21	7.4/1000 PY (4.6-11)		0.59 (0.35-1.0)	1.1 (0.63-2.0)	1.3 (0.65-2.6)	
	ADA	16	6.1/1000 PY (3.5-9.9)		0.49 (0.27-0.88)	0.87 (0.47-1.6)	1.1 (0.51-2.2)	
	RTX	6	8.4/1000 PY (3.1-18)		0.68 (0.29-1.6)	1.0 (0.42-2.4)	1.2 (0.49-3.2)	
Chiu 2014 Int J Rheum Dis	csDMARDs	23	41/100000 (26-62)	IRR	REF	NR	NR	Patients were matched for PS and no further adjustment is made. PS: age, COPD/asthma, diabetes, disease duration, number of csDMARDs, sex, steroid exposure
	TNFi	10	133/100000 PY (64-245)		3.24 (1.37-7.06)			
Morgan 2014 Rheumatology	csDMARDs	254	23.9/1000 PY	HR	NR	NR	REF	Age, baseline steroid, smoking history, previous cancer, BMI
	ETA	241	14.7/1000 PY				0.836 (0.683-1.025)	
Berghen 2015 Clin Rheumatol	TNFi	NR	F: 1123.7/100000PY; M: 2179.3/100000PY	SIR	F: 145.5 (137.2-154.3); M: 163.5 (156.8-170.6)	NR	NR	NR
	General population	NR	F: 772.1/100000PY; M: 1332.6/100000PY		REF			
Mercer 2015 ARD	csDMARDs	3249	NR	NA	NR	NR	NR	NR
	TNFi	11767	NR		NR	NR	NR	
	ETA	NR	NR		NR	NR	NR	
	IFX	NR	NR		NR	NR	NR	
	ADA	NR	NR		NR	NR	NR	
Solomon 2014 Semin Arthr Rheum	MTX	30	10.47/1000 PY (5.43-15.51)	HR	NR	NR	REF	PS * Age, gender, race, tobacco, alcohol use, BMI, RA disease duration, serologic status, joint erosions, CDAI, family history of acncer, HAQ, number of past DMARDs used, use of oral glucocorticoids
	TNFi	46	4.46/1000 PY (2.34-6.60)		NR	NR	0.29 (0.14-0.60)	
	other csDMARDs	4	2.11/1000 PY (0-5.09)		NR	NR	0.17 (0.05-0.65)	
	RTX	2	8.1/1000 PY (0-21.69)		NR	NR	0.42 (0.07-2.60)	
	ABA	2	13.58/1000 PY (2.35-24.81)		NR	NR	1.55 (0.40-5.97)	
Philips 2015 Plos One	csDMARDs	44	NR	HR	NR	NR	REF	Age, stage at diagnosis, mean years from RA diagnostic to head and neck cancer diagnosis, smoking, alcohol, comorbidities, radiation, chemotherapy, surgery
	TNFi	5	NR		NR	NR	0.75 (0.31-1.85)	

Table S36. Comparison across biologics (malignancies)

Study ID	Treatment group	N events	Type of ratio	uHR I2 vs c2)	Age/gender aHR (i2 vs c2)	aHR (i2 vs c2)	Adjusted for
Aaltonen 2015 J Rheum	TNFi	47	IRR	REF	REF	REF	Age, gender, disease duration, year of cohort inclusion, RF-positive, DAS28, HAQ-DI, prior malignancy, baseline use of MTX, SSZ, HCQ, steroids
	IFX	10		NR	NR	NR	
	ETA	21		NR	NR	NR	
	ADA	16		NR	NR	NR	
	RTX	6		1.3 (0.56-3.0)	1.0 (0.43-2.4)	1.1 (0.42-2.7)	
Chiu 2014 Int J Rheum Dis	ETA	3	IRR	REF	NR	NR	Patients were matched for PS and no further adjustment is made. PS: age, COPD/asthma, diabetes, disease duration, number of csDMARDs, sex, steroid exposure
	ADA	1		1.49 (0.03-18.66)	NR	NR	
Morgan 2014 Rheumatology	csDMARDs	254	HR	NR	NR	NR	Age, baseline steroid, smoking history, previous cancer, BMI
	ETA	241		NR	NR	NR	
Berghen 2015 Clin Rheumatol	TNFi		SIR	NR	NR	NR	NR
	General population			NR	NR	NR	
Mercer 2015 ARD	csDMARDs	3249	NR	NR	NR	NR	NR
	TNFi	11767		NR	NR	NR	
	ETA	NR		NR	NR	NR	
	IFX	NR		NR	NR	NR	
	ADA	NR		NR	NR	NR	
Solomon 2014 Semin Arthr Rheum	MTX	30	HR	NR	NR	NR	NR
	TNFi	46		NR	NR	NR	
	other csDMARDs	4		NA	NR	NR	
	RTX	2		NR	NR	NR	
	ABA	2		NR	NR	NR	
Philips 2015 Plos One	csDMARDs	44	HR	NR	NR	NR	NR
	TNFi	5		NR	NR	NR	

Table S37.1 Additional information on subtypes of the outcome and additional comments (malignancies)

Study ID	Treatment group	aHR (i vs c) in pts without history of cancer	aHR (i vs c) in pts with history of cancer	aHR cancer without NMSC (i vs c)	aHR NMSC (i vs c)	Age and sex-adjusted death following cancer	uHR lymphoma (i vs c)	aHR lymphoma (i vs c)	aHR lymphoproliferative malign. (i vs c)
Aaltonen 2015 J Rheum	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi								
Chiu 2014 Int J Rheum Dis	csDMARDs	NR	NR	NR	NR	NR	*	NR	NR
	TNFi	NR	NR	NR	NR	NR	*	NR	NR
	ETA	NR	NR	NR	NR	NR	*	NR	NR
	ADA	NR	NR	NR	NR	NR	*	NR	NR
Morgan 2014 Rheumatology	csDMARDs	REF	REF	REF	REF	NR	NR	NR	REF
	ETA	0.804 (0.460-1.430)	0.877 (0.720-1.069)	0.792 (0.636-0.986)	1.016 (0.717-1.441)	NR	NR	NR	0.512 (0.276-0.952)
Berghen 2015 Clin Rheumatol	TNFi	NR	NR	NR	NR	NR	F: 1135.0 (1003.1-1279.5); M 423.6 (361.9-492.8)	NR	F: 450.8 (398.4-508.2); M 473.9 (433.4-517.2)
	General population	NR	NR	NR	NR	NR	REF	NR	REF
Berghen 2015 Clin Rheumatol	TNFi	NR	NR	NR	NR	0.90 (0.70-1.17)	NR	NR	NR
	General population	NR	NR	NR	NR	REF	NR	NR	NR
Mercer 2015 ARD	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi								
Solomon 2014 Semin Arthr Rheum	MTX	NR	NR	NR	REF	NR	NR	REF	NR
	TNFi	NR	NR	NR	0.40 (0.14-1.16)	NR	NR	0.15 (0.01-2.19)	NR
	other csDMARDs	NR	NR	NR	0.11 (0.01-0.91)	NR	NR	NR	NR
	RTX	NR	NR	NR	0.74 (0.04-13.6)	NR	NR	NR	NR
	ABA	NR	NR	NR	15.3 (2.05-114)	NR	NR	NR	NR
Philips 2015 Plos One	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi								

* Reported in tables S35 and S36.

Table S37.2 Additional information on subtypes of the outcome and additional comments (malignancies)

Study ID	Treatment group	Incidence solid tumor	uHR solid tumor	Age,sex-adjusted solid tumor	aHR solid tumor	aHR lung cancer	aHR female breast cancer	aHR colorectal cancer	aHR gastro-oesophageal cancer
Aaltonen 2015 J Rheum	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi	NR	NR	NR	NR	NR	NR	NR	NR
Chiu 2014 Int J Rheum Dis	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi	NR	NR	NR	NR	NR	NR	NR	NR
	ETA	NR	NR	NR	NR	NR	NR	NR	NR
	ADA	NR	NR	NR	NR	NR	NR	NR	NR
Morgan 2014 Rheumatology	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	ETA	NR	NR	NR	NR	NR	NR	NR	NR
Berghen 2015 Clin Rheumatol	TNFi	NR	NR	NR	NR	NR	NR	NR	NR
	General population	NR	NR	NR	NR	NR	NR	NR	NR
Berghen 2015 Clin Rheumatol	TNFi	F: 856.2/100000 PY; M: 1676.4/100000 PY	F: 120.1 (112.2-128.4); M: 136.7 (130.2-143.4)	NR	NR	NR	NR	NR	NR
	General population	F: 712.8/100000 PY; M: 1226.4/100000 PY	REF	NR	NR	NR	NR	NR	NR
Mercer 2015 ARD	csDMARDs	117/10000 PY (98-138)	REF	REF	REF	REF	REF	REF	REF
	TNFi	81/10000 PY (74-89)	0.70 (0.58-0.85)	0.91 (0.75-1.11)	0.83 (0.64-1.07)	0.85 (0.52-1.39)	0.58 (0.32-1.06)	0.51 (0.24-1.06)	0.59 (0.23-1.52)
	ETA	86/10000 PY (74-99)	0.74 (0.59-0.92)	1.00 (0.80-1.25)	0.89 (0.67-1.19)	1.02 (0.58-1.76)	0.56 (0.28-1.10)	0.45 (0.19-1.05)	NR
	IFX	79/10000 PY (64-96)	0.68 (0.53-0.88)	0.87 (0.67-1.12)	0.81 (0.59-1.11)	0.92 (0.50-1.71)	0.59 (0.28-1.24)	0.47 (0.19-1.20)	NR
	ADA	77/10000 PY (65-91)	0.67 (0.53-0.84)	0.81 (0.59-1.11)	0.79 (0.59-1.05)	0.69 (0.39-1.23)	0.59 (0.31-1.15)	0.57 (0.26-1.27)	NR
Solomon 2014 Semin Arthr Rheum	MTX	NR	NR	NR	REF	REF	REF	NR	NR
	TNFi	NR	NR	NR	0.21 (0.07-0.64)	0.05 (0.01-0.58)	0.09 (0.02-0.39)	NR	NR
	other csDMARDs	NR	NR	NR	0.15 (0.02-1.55)	NR	NR	NR	NR
	RTX	NR	NR	NR	0.31 (0.03-3.41)	NR	NR	NR	NR
	ABA	NR	NR	NR	0.39 (0.07-2.22)	NR	0.35 (0.07-2.22)	NR	NR
Philips 2015 Plos One	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi	NR	NR	NR	NR	NR	NR	NR	NR

Table S38. Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Aaltonen 2015 J Rheum	Low	Moderate	Low	Low	Moderate	Low	Low
Chiu 2014 Int J Rheum Dis	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Morgan 2014 Rheumatology	Low	Low	Low	Low	Low	Moderate	Low
Berghen 2015 Clin Rheumatol	Low	Low	Low	Low	High	Moderate	Moderate
Mercer 2015 ARD	Low	Low	Low	Low	Low	Low	Low
Solomon 2014 Semin Arthr Rheum	Low	Low	Low	Low	Low	Low	Low
Philips 2015 Plos One	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

4.3. Mortality

Table S39. Included studies (mortality)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of FU for analysis
Morgan 2014 Rheumatology	BSRBR	Active RA, csDMARDs and bDMARDs, ≥1 consultant follow-up	NR	No	2011
Listing 2015 ARD	RABBIT	Consecutive patients with RA (ACR criteria) and age at onset of RA >15 years, starting csDMARDs and bDMARDs after a failure of at least one DMARD treatment	NR	No	Dec-11

Table S40. Outcome and exposure definition and statistical analysis (mortality)

Study ID	Follow-up time	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Morgan 2014 Rheumatology	Variable	Mortality	NHS Information Centre	On drug + up to 90 days	Yes	No	Cox regression	Yes
Listing 2015 ARD	Variable	Mortality	Rheumatologist, family, local registration office	On drug + 24 months	Yes	Yes	Cox regression	Yes

Table S41. Population characteristics (mortality)

Study ID	Intervention	Control sDMARDs	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	Follow-up times	Patient-years
Morgan 2014 Rheumatology	ETA	csDMARDs	csDMARDs	2864	NA	59.8 (12.4)	75	9.6 (10.4)	3.9 (2.0) years	11095
			ETA	3529	NA	55.3 (12.1)	77	13.5 (9.4)	4.8 (2.4) years	16919
Listing 2015 ARD	TNFi, RTX, other bDMARDs, other csDMARDs	MTX	MTX	2060	NR	56.4 (12.0)	76	7.2 (7.7)	43.9 (32.7) moths	7012
			Other csDMARDs	928	NR	58.5 (12.4)	80.2	8.8 (9.3)	39.4 (31.7) months	3513
			TNFi	4649	NR	54.5 (12.4)	77.1	11.2 (9.3)	46.5 (32.3) months	16843
			RTX	703	NR	58.5 (12.0)	78.5	13.6 (10.2)	28.0 (14.6) months	2599
			other bDMARDs	568	NR	56.4 (12.9)	77.1	12.9 (9.0)	25.4 (23.1) months	1654
			ETA	NR	NR	NR	NR	NR	NR	7226
			IFX	NR	NR	NR	NR	NR	NR	2457
			ADA	NR	NR	NR	NR	NR	NR	7523
			ABA	NR	NR	NR	NR	NR	NR	672
			TCZ	NR	NR	NR	NR	NR	NR	1037

Table S42. Effect size intervention and control and comparison (mortality)

Study ID	Treatment group	N events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Morgan 2014 Rheumatology	csDMARDs	223	20.1/1000 PY	HR			REF	Age, gender, baseline non-RA drugs, baseline steroid, MTX, baseline HAQ, Charlson comorbidity index, smoking history, BMI
	ETA	203	12.0/1000 PY				0.717 (0.537-0.958)	
Listing 2015 ARD	MTX	96	NR	HR	REF	NR	REF	Age, sex, smoking and six groups of comorbid conditions—chronic lung disease, diabetes, coronary heart disease, chronic renal disease, prior malignancy and osteoporosis (as an indicator of a severe course of the disease prior to baseline), mean DAS28 and mean FFbH scores, treatment with glucocorticoids during the last 12 months, exposure to synthetic DMARDs, TNFi, RTX, or other bDMARDs.
	Other csDMARDs	126	NR		2.53 (1.95-3.28)	NR	1.14 (0.86-1.51)	
	TNFi	182	NR		0.77 (0.61-0.98)	NR	0.64 (0.50-0.81)	
	RTX	36	NR		1.01 (0.70-1.46)	NR	0.57 (0.39-0.84)	
	other bDMARDs	25	NR		1.02 (0.68-1.52)	NR	0.64 (0.42-0.99)	
	ETA	93	NR		NR	NR	0.77 (0.58-1.01)	
	IFX	21	NR		NR	NR	0.55 (0.34-0.88)	
	ADA	73	NR		NR	NR	0.60 (0.45-0.81)	
	ABA	8	NR		NR	NR	0.55 (0.26-1.17)	
	TCZ	15	NR		NR	NR	0.83 (0.48-1.47)	

Table S43. Comparison across biologics (mortality)

Study ID	Treatment group	N events	Type of ratio	uHR I2 vs c2)	Age/gender aHR (i2 vs c2)	aHR (i2 vs c2)	Adjusted for
Morgan 2014 Rheumatology	csDMARDs	NA	NA	NA	NA	NA	NA
	ETA	NA		NA	NA	NA	
Listing 2015 ARD	ETA	93	HR	NR	NR	REF	Age, sex, smoking and six groups of comorbid conditions—chronic lung disease, diabetes, coronary heart disease, chronic renal disease, prior malignancy and osteoporosis (as an indicator of a severe course of the disease prior to baseline), mean DAS28 and mean FFbH scores, treatment with glucocorticoids during the last 12 months, exposure to synthetic DMARDs, TNFi, RTX, or other bDMARDs.
	IFX	21		NR	NR	0.69 (0.42-1.13)	
	ADA	73		NR	NR	0.76 (0.56-1.06)	

Table S44. Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Morgan 2014 Rheumatology	Low	Low	Low	Low	Low	Moderate	Low
Listing 2015 ARD	Low	Low	Low	Low	Low	Moderate	Low

4.4. Cardio-vascular events

Table S45. Included studies (CV events)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Ogdie 2015 ARD	The Health Improvement Network (THIN)	R A (and other rheumatic diseases) according to READ codes (standard medical diagnosis codes)	Event of interest prior to the index date	Yes	Sep-10
Solomon 2013 ARD	4 US insurance datasets (safety assessment of biologic therapy - SABER Study) (claims dataset)	RA (ICD-9 codes: 1 episode + previous prescription of MTX)	Other rheumatic diseases	No	Dec-07
Desai 2015 AC&R	US health plans: WellPoint and Healthcare	RA (≥2 episodes with ICD-9 code, <365 days apart + ≥1 DMARD prescription)	DMARD prescription >365 days earlier, in order to focus on early RA; patients with a diagnosis of hyperlipidemia or any lipid-lowering agents, CVD, including MI, angina, heart failure, CVD or other forms of chronic heart disease. Non-TNFi biologics.	No	Sep-12
Kim 2015 Am J Medicine	US health plans: WellPoint and Healthcare	RA (≥2 episodes with ICD-9 code, <365 days apart + ≥1 DMARD prescription)	DMARD prescription >365 days earlier, in order to focus on early RA; malignancies, prior venous thromboembolism or dispensing for an anticoagulant any time before index date	No	Sep-12

Table S46. Outcome and exposure definition and statistical analysis (CV events)

Study ID	FolLow-up time	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Ogdie 2015 ARD	Variable	MI, stroke, CV death (READ and ICD-10 codes), Major adverse CV events (MACE): the first of any of the previous 3	Previous studies with validation of outcome	On drug	Yes	Yes	Cox regression	Yes
Solomon 2013 ARD	Variable	Heart failure hospitalisations and not ischemic heart disease (ICD codes)	Not specified	On drug	Yes	Yes	Cox regression adjusted for PS	Yes
Desai 2015 AC&R	Variable	1) Hyperlipidemia (ICD-9 codes) and a new prescription for lipid-lowering agent; 2) Change in laboratory values of lipid parameters	Not specified	On drug	Assume yes (not specified)	Assume yes (not specified)	Cox regression adjusted for PS	Assume yes (NS)
Kim 2015 AM J Medicine	Variable	Hospitalization for venous thromboembolism, either DVT or pulmonary embolism (ICD-9 codes)	Previous studies with validation of outcome	On drug	Yes	Yes	Cox regression adjusted for PS	Yes

Table S47. Population characteristics (CV events)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up times	Patient-years
Ogdie 2015 ARD	DMARD (bDMARD-ADA,ETA,IFX- and csDMARD)	Unexposed controls	DMARD	23840	NR	59.76 (14.34)	70.1	5.98 (8.78)	NR	NR
			no DMARD	17912	NR	63.48 (16.15)	71.1	8.70 (11.42)	NR	NR
			Unexposed control	81573	NR	49.86 (18.25)	55	NR	NR	NR
Solomon 2013 ARD	TNFi (ADA, ETA, IFX)	csDMARDs	csDMARDs	8656	NR	56.2 (14.3)	85.9	NR	NR	2667
			bDMARDs	11587	NR	55.4 (14.4)	86.5	NR	NR	5548
Desair 2015 AC&R	TNFi (ADA, CZP, ETA, IFX, GOL)	MTX, HCQ, other csDMARDs	MTX	7941	NR	47.8 (12.1)	73.2	NR	NR	6329
			HCQ	6130	NR	45.4 (12.1)	84.1	NR	NR	4770
			other csDMARDs	2064	NR	45.3 (12.1)	67.2	NR	NR	1237
			TNFi	1010	NR	45.1 (13.7)	69.6	NR	NR	1303
Kim 2015 Am J Medicine	bDMARDs (all 8)	MTX, other csDMARDs	MTX	17614	NR	50.7 (11.9)	72	NR	0.7 (0.8) years	NR
			other csDMARDs	16113	NR	49.2 (12.3)	76.4	NR	0.6 (0.7) years	NR
			bDMARDs	5920	NR	48.9 (12.1)	69.5	NR	1.0 (1.1) years	NR

Table S48. Effect size intervention and control and comparison (CV events)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Ogdie 2015 ARD	DMARD	1306	12.1/1000 PY	HR	2.17 (2.02-2.32)	1.62 (1.51-1.74)	1.58 (1.46-1.70)	Age, sex, hypertension, diabetes, hyperlipidemia, smoking status, start year in the cohort
	no DMARD	1198	13.5/1000 PY		2.62 (2.44-2.81)	1.43 (1.33-1.53)	1.39 (1.28-1.50)	
	Unexposed controls	2055	5.0/1000 PY		REF	REF	REF	
Solomon 2013 ARD	csDMARDs	84	3.15/100 PY (2.54-3.90)	HR	NR	NR	REF	PS (demographics, diagnoses, surgical procedures and pharmacy dispensings), prior cumulative oral glucocorticoid dosage, number of heart failure hospitalisations and the use of loop diuretics
	TNFi	111	2.49/100 PY (2.07-3.00)		NR	NR	0.84 (0.62-1.12)	
Desair 2015 AC&R	MTX	183	28.9/1000 PY (24.9-33.4)	HR	REF	NR	REF	Age, gender, cardiovascular risk factors and comorbidities, cardiovascular drug use, pain medications, and health care use in the prior year
	HCQ	96	20.1/1000 PY (16.3-24.6)		0.70 (0.54-0.89)	NR	0.81 (0.63-1.04)	
	other csDMARDs	45	36.4/1000 PY (26.5-48.7)		1.25 (0.90-1.74)	NR	1.33 (0.95-1.84)	
	TNFi	40	30.7/1000 PY (21.9-41.8)		1.08 (0.76-1.52)	NR	1.41 (0.99-2.00)	
Kim 2015 Am J Med	MTX	46	NR	HR	NR	NR	0.78 (0.50-1.21)	PS: age, gender, comorbidities (e.g. Diabetes, obesity, chronic kidney disease, heart failure, CVD, extremity fracture, and surgeries); medications, including oral contraceptives, steroids, and antiplatelet drugs; health care use factors; and index year
	other csDMARDs	47	NR		NR	NR	REF	
	bDMARDs	31	NR		NR	NR	1.83 (0.91-3.66)	

Table S49.1 Additional information on subtypes of the outcome, steroids and additional comments (CV events)

Study ID	Treatment group	uHR MI	Age/gender aHR MI	aHR MI	uHR Stroke	Age/gender aHR Stroke	aHR Stroke	uHR CV death	Age/gender aHR CV death	aHR CV death
Ogdie 2015 ARD	DMARD	2.55 (2.30-2.83)	2.02 (1.82-2.24)	1.96 (1.75-2.19)	1.76 (1.59-1.96)	1.27 (1.14-1.41)	1.24 (1.10-1.39)	2.18 (1.96-2.42)	1.69 (1.53-1.88)	1.66 (1.48-1.86)
	no DMARD	2.20 (1.96-2.48)	1.36 (1.21-1.53)	1.33 (1.17-1.52)	2.54 (2.29-2.81)	1.29 (1.16-1.43)	1.29 (1.15-1.45)	3.29 (2.97-3.63)	1.55 (1.40-1.71)	1.43 (1.28-1.59)
	Unexposed controls	REF	REF	REF	REF	REF	REF	REF	REF	REF
Solomon 2013 ARD	csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi	NR	NR	NR	NR	NR	NR	NR	NR	NR
Desair 2015 AC&R	MTX	NR	NR	NR	NR	NR	NR	NR	NR	NR
	HCQ	NR	NR	NR	NR	NR	NR	NR	NR	NR
	other csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR	NR
	TNFi	NR	NR	NR	NR	NR	NR	NR	NR	NR
Kim 2015 Am J Med	MTX	NR	NR	NR	NR	NR	NR	NR	NR	NR
	other csDMARDs	NR	NR	NR	NR	NR	NR	NR	NR	NR
	bDMARDs	NR	NR	NR	NR	NR	NR	NR	NR	NR

Table S49.2 Additional information on subtypes of the outcome, steroids and additional comments (CV events)

Study ID	Treatment group	aHR heart failure in patients with known HF	aHR heart failure in patients with unknown HF	Post-index mean change in LDL	Post-index mean change in HDL	Post-index mean change in total cholesterol	Post-index mean change in triglycerides
Ogdie 2015 ARD	DMARD	NR	NR	NR	NR	NR	NR
	no DMARD	NR	NR	NR	NR	NR	NR
	Unexposed controls	NR	NR	NR	NR	NR	NR
Solomon 2013 ARD	csDMARDs	REF	REF	NR	NR	NR	NR
	TNFi	0.95 (0.58-1.57)	0.86 (0.58-1.27)	NR	NR	NR	NR
Desair 2015 AC&R	MTX	NR	NR	REF	REF	REF	REF
	HCQ	NR	NR	-8.9 (-15.8; -2.0)	-8.9 (-4.0; 3.3)	-8.9 (-19.8; -4.8)	-8.9 (-38.7; -0.3)
	other csDMARDs	NR	NR	1.1 (-9.3; 11.5)	-4.8 (-10.5; 1.0)	-8.9 ('-20.3; 2.4)	-25.3 (-38-7; -0.3)
	TNFi	NR	NR	2.7 (-8.3; 13.7)	2.7 (-9.1; 2.1)	2.7 (-10; 13.3)	2.7 (-29.6; 29.6)
Kim 2015 Am J Med	MTX	NR	NR	NR	NR	NR	NR
	other csDMARDs	NR	NR	NR	NR	NR	NR
	bDMARDs	NR	NR	NR	NR	NR	NR

Table S50. Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Odgie 2015 ARD	Moderate	Moderate	High	Moderate	Moderate	Moderate	Moderate
Solomon 2013 ARD	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Desai 2015 AC&R	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate
Kim 2015 AM J Med	Moderate	Moderate	Moderate	Moderate	Moderate	Low	Moderate

4.5 Interstitial lung disease

Table S51: Included studies (interstitial lung disease)

Study ID	Registry	Inclusion criteria	Exclusion criteria	Mixed population	End of folLow-up for analysis
Curtis 2015 AR&T	MartketScan Commercial Claims and Encounters (Commercial) and Medicare Supplemental and Coordination of Benefits databases (claims dataset)	RA (ICD-9), ≥18 years old, new biologic agent prescription, discontinuation of bDMARD in the past	History of malignancy, ulcerative colitis, Crohn disease, psoriasis or ankylosing spondylitis in the previous 12 months. History of ILD	No	Not specified
Herrinton 2013 Pharmacoepidemiology and Drug Safety	Kaiser Permanente Northern California (claims dataset)	RA (and other rheumatic diseases) according to ICD-9 codes	Patients with HIV, solid organ transplantation, advanced kidney or liver disease, cancer diagnosis or who were treated with cyclosporine or tacrolimus in the previous 12 months. Patients with a previous diagnosis of ILD	Yes	Dec-07

Table S52. Outcome and exposure definition and statistical analysis (interstitial lung disease)

Study ID	FolLow-up time	Outcome definition	Validation Outcome	Biologic causal attribution	Failures to biologic included at baseline	Failures to biologic included throughout FU	Notes on analysis	Censoring at event
Curtis 2015 AR&T	Variable	ILD (ICD-9) + ILD-diagnostic test (CT thorax or lung biopsy); another more sensitive definition included diagnoses of rheumatoid lung and other specified and unspecified alveolar and parietoalveolar pneumopathies and did not require evidence of an ILD diagnostic test		On drug (with up to 90 days)	Yes (all patients were bDMARD failures)	No	Cox regression	Yes
Herrinton 2013 Pharmacoepidemiology and Drug Safety	Variable	ILD (ICD-9) + x-ray/CT-scan	Pulmonologist	Ever analysis	No	Yes	Cox regression adjusted for PS	Yes

Table S53. Population characteristics (interstitial lung disease)

Study ID	Intervention	Control	Treatment group	N patients	N patients switchers at baseline	Age	% Females	Disease duration	FolLow-up times	Patient-years
Curtis 2015 AR&T	bDMARDs (TNFi, TCZ, RTX, ABA)		TNFi	7951	100	51.7 (12.5)	81.3	NA	NA	5473
			TCZ	1528	100	53.8 (12.0)	82.9	NA	NA	1008
			RTX	1134	100	53.8 (12.1)	82.1	NA	NA	851
			ABA	2683	100	53.9 (12.6)	83.0	NA	NA	1775
			ETA	NR	NR	NR	NR	NR	NR	1012
			ADA	NR	NR	NR	NR	NR	NR	1674
			IFX	NR	NR	NR	NR	NR	NR	735
			CZP	NR	NR	NR	NR	NR	NR	948
			GOL	NR	NR	NR	NR	NR	NR	1104
Herrinton 2013 Pharmacoepidemiology and Drug Safety	TNFi (ETA, ADA, IFX)	csDMARDs	csDMARDs	NR	0	NR	NR	NR	NR	NR
			TNFi	NR	0	NR	NR	NR	NR	NR
			ETA	NR	0	NR	NR	NR	NR	NR
			IFX	NR	0	NR	NR	NR	NR	NR
			ADA	NR	0	NR	NR	NR	NR	NR

Table S54. Effect size intervention and control and comparison (interstitial lung disease)

Study ID	Treatment group	N of events	Incidence rate (95% CI)	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	Adjusted for
Curtis 2015 AR&T	TNFi	9	1.6/1000 PY (0.8-3.1)	HR	NR	NR	REF	Age, gender, recent glucocorticoid or MTX exposure, baseline history of pulmonary condition (COPD, asthma or pneumonia)
	TCZ	1	1/1000 PY (0-5.5)		NR	NR	0.5 (0.06-4.0)	
	RTX	4	4.7/1000 PY (1.3-12.1)		NR	NR	2.2 (0.67-7.25)	
	ABA	2	1.1/1000 PY (0.1-4.1)		NR	NR	0.6 (0.13-2.84)	
	ETA	0	0/1000 PY (0-3)		NR	NR	NR	
	ADA	3	1.8/1000 PY (0.4-5.2)		NR	NR	NR	
	IFX	3	4.1/1000 PY (0.8-12.0)		NR	NR	NR	
	CZP	3	3.2/1000 PY (0.7-9.3)		NR	NR	NR	
	GOL	0	0/1000 PY (0-2.7)		NR	NR	NR	
Herrinton 2013 Pharmacoepidemiology and Drug Safety	csDMARDs	NR	NA	HR	NR	NR	REF	PS*, dose of steroid during the previous 12 months, calendar year, race, gender, age, smoking status, COPD, Charlson comorbidity index, daily dose of steroid * Including >100 variables (not specified) and developed for all rheumatic diseases together, not specific for RA
	TNFi	NR	22		NR	NR	1.03 (0.51-2.07)	

Table S55. Comparison across biologics (interstitial lung disease)

Study ID	Treatment group	N of events	Type of ratio	uHR (i vs c)	Age/gender aHR (i vs c)	aHR (i vs c)	aHR (i vs c)	Adjusted for
Curtis 2015 AR&T	ETA	0	HR	NR	NR	NR	NR	Age, gender, recent glucocorticoid or MTX exposure, baseline history of pulmonary condition (COPD, asthma or pneumonia)
	ADA	3						
	IFX	3						
	CZP	3						
	GOL	0						
Herrinton 2013 Pharmacoepidemiology and Drug Safety	ETA	NR	HR	NR	NR	REF	NR	PS*, dose of steroid during the previous 12 months, calendar year, race, gender, age, smoking status, COPD, Charlson comorbidity index, daily dose of steroid * Including >100 variables (not specified) and developed for all rheumatic diseases together, not specific for RA
	IFX	NR				0.74 (0.30-1.84)	REF	
	ADA	NR				0.54 (0.13-2.21)	1.40 (0.33-5.94)	

Table S56. Additional information on subtypes of the outcome, steroids and additional comments (interstitial lung disease)

Study ID	Treatment group	aHR hospitalization due to ILD (i2 vs c2)	Steroids
Curtis 2015 AR&T	TNFi	REF	aHR steroids: 4.5 (0.59-34.36)
	TCZ	0.5 (0.1-2.1)	
	RTX	1.6 (0.8-3.2)	
	ABA	0.9 (0.4-2.1)	
Herrinton 2013 Pharmacoepidemiology and Drug Safety	csDMARDs	NR	NR
	TNFi		

Table S57. Risk of bias assessment (Hayden tool)

Study ID	Participation	Attrition	Prognostic factor measurement	Outcome measurement	Confounding	Analysis	Overall
Curtis 2015 AR&T	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate
Herrinton 2013 Pharmacoepidemiology and Drug Safety	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate	Moderate

5. References of included studies

5.1. Infections

5.1.1. Serious infections

Aaltonen KJ, Joensuu JT, Virkki L, et al. Rates of serious infections and malignancies among patients with rheumatoid arthritis receiving either tumor necrosis factor inhibitor or rituximab therapy. J Rheumatol 2015;42(3):372-8.

Chiang YC, Kuo LN, Yen YH, et al. Infection risk in patients with rheumatoid arthritis treated with etanercept or adalimumab. Comput Methods Programs Biomed 2014;116(3):319-27.

Chiu YM, Lang HC, Lin HY, et al. Risk of tuberculosis, serious infection and lymphoma with disease-modifying biologic drugs in rheumatoid arthritis patients in Taiwan. Int J Rheum Dis 2014;17 Suppl 3:9-19.

Cobo-Ibáñez T, Descalzo MÁ, Loza-Santamaría E, et al. Serious infections in patients with rheumatoid arthritis and other immune-mediated connective tissue diseases exposed to anti-TNF or rituximab: data from the Spanish registry BIOBADASER 2.0. Rheumatol Int 2014;34(7):953-61.

Johnston SS, Turpcu A, Shi N, et al. Risk of infections in rheumatoid arthritis patients switching from anti-TNF agents to rituximab, abatacept, or another anti-TNF agent, a retrospective administrative claims analysis. Semin Arthritis Rheum 2013;43(1):39-47.

Lampropoulos CE, Orfanos P, Bournia VK, et al. Adverse events and infections in patients with rheumatoid arthritis treated with conventional drugs or biologic agents: a real world study. Clin Exp Rheumatol 2015;33(2):216-24.

Miranda JV, Peñarandab LF, Grajalesb CM, et al. Infecciones en pacientes con artritis reumatoide: medicamentos moduladores de la respuesta biológica versus fármacos modificadores de la enfermedad. Seguimiento a un año. REV COLOMB REUMATOL 2013;21(1):27-34.

Morgan CL, Emery P, Porter D, et al. Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. Rheumatology (Oxford) 2014;53(1):186-94.

Sakai R, Cho SK, Nanki T, et al. Head-to-head comparison of the safety of tocilizumab and tumor necrosis factor inhibitors in rheumatoid arthritis patients (RA) in clinical practice: results from the registry of Japanese RA patients on biologics for long-term safety (REAL) registry. Arthritis Res Ther 2015;17:74.

Yun H, Xie F, Delzell E, et al. Comparative Risk of Hospitalized Infection Associated With Biologic Agents in Rheumatoid Arthritis Patients Enrolled in Medicare. Arthritis Rheumatol 2016;68(1):56-66.

Curtis JR, Yang S, Patkar NM, et al. Risk of hospitalized bacterial infections associated with biologic treatment among US veterans with rheumatoid arthritis. Arthritis Care Res (Hoboken) 2014;66(7):990-7.

5.1.2 Herpes zoster

Pappas DA, Hooper MM, Kremer JM, et al. Herpes Zoster Reactivation in Patients With Rheumatoid Arthritis: Analysis of Disease Characteristics and Disease-Modifying Antirheumatic Drugs. Arthritis Care Res (Hoboken) 2015;67(12):1671-8.

5.1.3 Tuberculosis

(r)Chiang YC, Kuo LN, Yen YH, et al. Infection risk in patients with rheumatoid arthritis treated with etanercept or adalimumab. Comput Methods Programs Biomed 2014;116(3):319-27.

(r)Chiu YM, Lang HC, Lin HY, et al. Risk of tuberculosis, serious infection and lymphoma with disease-modifying biologic drugs in rheumatoid arthritis patients in Taiwan. Int J Rheum Dis 2014;17 Suppl 3:9-19.

Ke WM, Chen LS, Parng IM, et al. Risk of tuberculosis in rheumatoid arthritis patients on tumour necrosis factor-alpha inhibitor treatment in Taiwan. Int J Tuberc Lung Dis 2013;17(12):1590-5.

(r)Baddley JW, Winthrop KL, Chen L, et al. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) study. Ann Rheum Dis 2014;73(11):1942-8.

5.1.4. Skin infections

Wasson NJ, Varley CD, Schwab P, et al. Serious skin & soft tissue infections in rheumatoid arthritis patients taking anti-tumor necrosis factor alpha drugs: a nested case-control study. BMC Infect Dis 2013;13:533.

5.1.5. Non-viral opportunistic infections

Baddley JW, Winthrop KL, Chen L, et al. Non-viral opportunistic infections in new users of tumour necrosis factor inhibitor therapy: results of the SAfety Assessment of Biologic ThERapy (SABER) study. Ann Rheum Dis 2014;73(11):1942-8.

5.2. Malignancies

(r)Aaltonen KJ, Joensuu JT, Virkki L, et al. Rates of serious infections and malignancies among patients with rheumatoid arthritis receiving either tumor necrosis factor inhibitor or rituximab therapy. J Rheumatol 2015;42(3):372-8.

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(r)Morgan CL, Emery P, Porter D, et al. Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. Rheumatology (Oxford) 2014;53(1):186-94.

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Solomon DH, Kremer JM, Fisher M, et al. Comparative cancer risk associated with methotrexate, other non-biologic and biologic disease-modifying anti-rheumatic drugs. Semin Arthritis Rheum 2014;43(4):489-97.

Phillips C, Zeringue AL, McDonald JR, et al. Tumor Necrosis Factor Inhibition and Head and Neck Cancer Recurrence and Death in Rheumatoid Arthritis. PLoS One 2015;10(11):e0143286.

5.3. Mortality

(r)Morgan CL, Emery P, Porter D, et al. Treatment of rheumatoid arthritis with etanercept with reference to disease-modifying anti-rheumatic drugs: long-term safety and survival using prospective, observational data. Rheumatology (Oxford) 2014;53(1):186-94.

Listing J, Kekow J, Manger B, et al. Mortality in rheumatoid arthritis: the impact of disease activity, treatment with glucocorticoids, TNFα inhibitors and rituximab. Ann Rheum Dis 2015;74(2):415-21.

5.4. Cardiovascular events

Ogdie A, Yu Y, Haynes K, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Ann Rheum Dis 2015;74(2):326-32.

Solomon DH, Rassen JA, Kuriya B, et al. Heart failure risk among patients with rheumatoid arthritis starting a TNF antagonist. Ann Rheum Dis 2013;72(11):1813-8.

Desai RJ, Eddings W, Liao KP, et al. Disease-modifying antirheumatic drug use and the risk of incident hyperlipidemia in patients with early rheumatoid arthritis: a retrospective cohort study. Arthritis Care Res (Hoboken) 2015;67(4):457-66.

Kim SC, Solomon DH, Liu J, et al. Risk of venous thromboembolism in patients with rheumatoid arthritis: initiating disease-modifying antirheumatic drugs. Am J Med 2015;128(5):539.e7-17.

5.5. Interstitial lung disease

Curtis JR, Sarsour K, Napalkov P, et al. Incidence and complications of interstitial lung disease in users of tocilizumab, rituximab, abatacept and anti-tumor necrosis factor α agents, a retrospective cohort study. Arthritis Res Ther 2015;17:319.

Herrinton LJ, Harrold LR, Liu L, et al. Association between anti-TNF-α therapy and interstitial lung disease. Pharmacoepidemiol Drug Saf 2013;22(4):394-402.

6. LIST OF ABBREVIATIONS

A&R	arthritis & rheumatology
ABA	abatacept
AC&R	arthritis care & research
ADA	adalimumab
AE	adverse event
aHR	adjusted hazard ratio
Am J Med	The American journal of medicine
AR&T	arthritis research & therapy
ARD	annals of rheumatic diseases
AS	ankylosing spondylitis
bDMARD	biological disease modifying antirheumatic drugs
BMI	body mass index
BSRBR	British society for rheumatology biologics registers
C	control
CDAI	clinical disease activity index
CI	confidence interval
Clin Exp Rheumatol	clinical and experimental rheumatology
CLL	chronic lymphocytic leukemia
Comp Methods	computer methods and programs in biomedicine
COPD	chronic obstructive pulmonary disease
csDMARD	conventional synthetic disease modifying antirheumatic drugs
CT	computerized tomography
CV	cardiovascular
CZP	certolizumab pegol
DAS 28	disease activity score 28
DVT	deep venous thrombosis
ESR	erythrocyte sedimentation rate
ETA	etanercept
F	females
FU	follow-up
GOL	golimumab

HAQ	health assessment questionnaire
HIV	human immunodeficiency virus
HQC	hydroxychloroquine
HR	hazard ratio
I	intervention
ICD	international classification of diseases
ID	identification
IFX	infliximab
ILD	Interstitial lung disease
Int J Rheum Dis	International Journal of Rheumatic Diseases
IRR	incidence rate ratio
IRR	incidence rate ratio
IV	intravenous
J Rheum	journal of rheumatology
JIA	juvenile idiopathic arthritis
LEF	leflunomide
M	males
MI	myocardial infarction
MTX	methotrexate
NA	not applicable
NHL	non-Hodgkin lymphoma
NIHIRD	national health insurance research database
NMSC	non-melanoma skin cancer
NR	not reported
NS	not specified
PBO	placebo
PS	propensity scores
PsA	psoriatic arthritis
PY	patient-years
RA	rheumatoid arthritis
REF	reference group
RF	rheumatoid factor
Rheumatol Int	rheumatology international
RTX	rituximab
Semin Arthr Rheum	seminars in arthritis and rheumatism
SLE	systemic lupus erythematosus
SLR	systematic literature review
SMR	standardized mortality ratio
SSZ	sulfasalazine
TB	tuberculosis
TCZ	tocilizumab

TNFi	tumour necrosis factor inhibitor
Tuberc Lung Dis	international journal of tuberculosis and lung disease
uHR	unadjusted hazard ratio
US	United States
VA	Veterans Affairs