SUPPLEMENTARY

Scoping literature review

Aims

- To identify definitions of difficult-to-treat rheumatoid arthritis (RA)
- To check if these are in accordance with the proposed definition of difficult-to-treat RA

Search

1 PubMed: (resistant[Title/Abstract] OR resistance[Title/Abstract] OR persistent[Title/Abstract] OR persistence[Title/Abstract] OR refractory[Title/Abstract] OR refractoriness[Title/Abstract] OR difficult-to-treat[Title/Abstract] OR “difficult to treat”[Title/Abstract]) AND ("Rheumatoid arthritis"[Title/Abstract] OR "Arthritis, Rheumatoid"[Mesh])

Filter: Human, publication date <5 yr

2 PubMed: (resistant[Title/Abstract] OR resistance[Title/Abstract] OR persistent[Title/Abstract] OR persistence[Title/Abstract] OR refractory[Title/Abstract] OR refractoriness[Title/Abstract] OR difficult-to-treat[Title/Abstract] OR “difficult to treat”[Title/Abstract]) AND ("Rheumatoid arthritis"[Title/Abstract] OR "Arthritis, Rheumatoid"[Mesh])

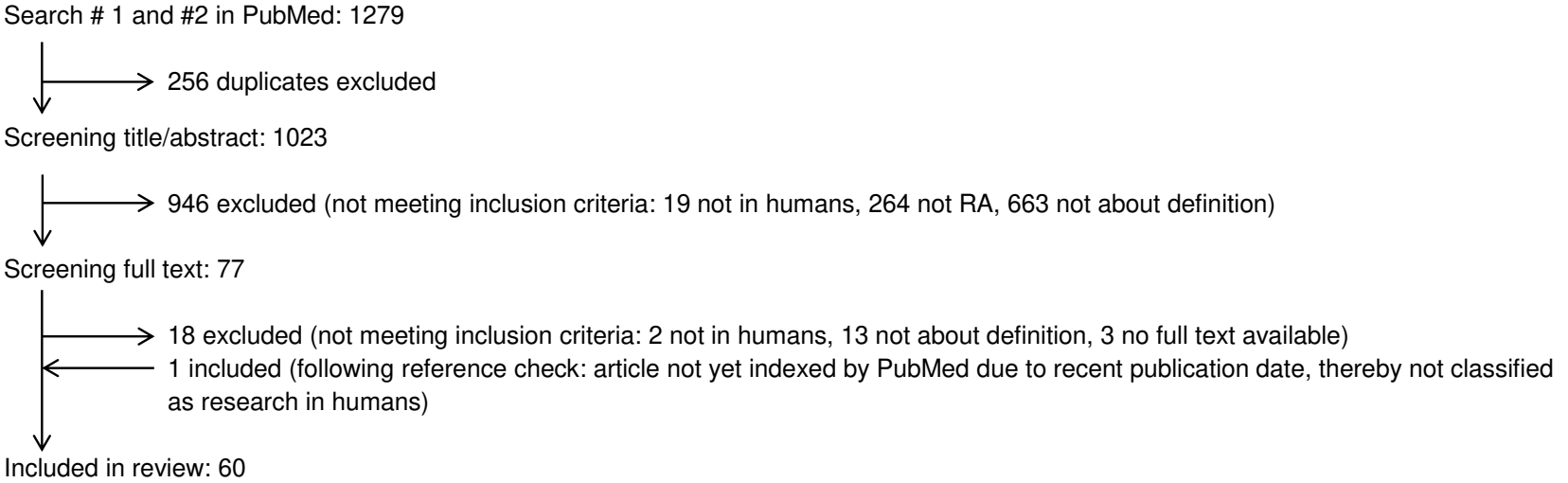
Filter: Review, systematic review, publication date <5 years

Search date: July 3, 2018

Inclusion criteria

- Research in humans
- RA patients
- Defining difficult-to-treat RA

Overview included articles



Conclusion

Out of 1023 unique articles, 60 articles were included in the review. The definition of difficult-to-treat RA (or synonyms) is often not explained. Only three articles used the same number of failed disease-modifying antirheumatic drugs (DMARDs) as used in the proposed definition of difficult-to-treat RA, i.e. ≥2 biological (b-)DMARDs (see Supplementary Table 1, highlighted in green). The study designs of these articles were: one randomised controlled trial, one cohort study, and one editorial. The other 57 articles used a definition that was defined less explicitly (e.g., failure to conventional synthetic (cs-)DMARDs and bDMARDs) or was defined less strictly compared to the proposed definition of difficult-to-treat RA.

Supplementary Table 1. Summary of selected articles

No	Ref	Definition in text	Treatment failure	Study type	Study topic
1	Álvaro-Gracia JM, Jover JA, García-Vicuña R, *et al.* Intravenous administration of expanded allogeneic adipose-derived mesenchymal stem cells in refractory rheumatoid arthritis (Cx611): results of a multicentre, dose escalation, randomised, single-blind, placebo-controlled phase Ib/IIa clinical trial. *Ann Rheum Dis* 2017;**76**:196–202.	refractory RA (failure to at least two biologicals)	≥2bDMARDs	RCT	Efficacy of Cx611 vs placebo
2	Kearsley-Fleet L, Davies R, De Cock D, *et al.* Biologic refractory disease in rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. *Ann Rheum Dis* 2018;**0**:1–8.	bDMARD refractory on the date they started their third class of bDMARD	≥2bDMARDs	Cohort	Quantify frequency and identify associated factors
3	Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis* 2018;:annrheumdis-2017-212862.	failure of at least one anticytokine (TNF and/or IL-6 directed) and one cell-targeted (B cell depletion and/or T cell costimulation blockade) bDMARD	≥2bDMARDs: 1TNFi/IL6, 1B-cell/T-cell	Editorial	Defining refractory RA
4	Genovese MC, Kremer J, Zamani O, *et al.* Baricitinib in Patients with Refractory Rheumatoid Arthritis. *N Engl J Med* 2016;**374**:1243–52. doi:10.1056/NEJMoa1507247	one or more TNF inhibitors and discontinued treatment because of an insufficient response after 3 months or more or because of unacceptable side effects. Patients who had received other biologic DMARDs could also participate	≥1bDMARDs	RCT	Efficacy of baricitinib vs placebo
5	Genovese MC, Kremer JM, Kartman CE, *et al.* Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. Rheumatology (Oxford). 2018;**57**:900–8.	previously received one or more TNF inhibitor and discontinued treatment because of either insufficient response or intolerance	≥1bDMARDs	RCT	Efficacy of baricitinib vs placebo
6	Smolen JS, Kremer JM, Gaich CL, *et al.* Patient-reported outcomes from a randomised phase III study of baricitinib in patients with rheumatoid arthritis and an inadequate response to biological agents (RA-BEACON). Ann. Rheum. Dis. 2017;**76**:694–700.	≥1 tumour necrosis factor inhibitors (TNFis) or other biological disease-modifying antirheumatic drugs (bDMARDs).	≥1bDMARDs	RCT	PROs in patients receiving baricitinib vs placebo
7	Feist E, Burmester GR. Small molecules targeting JAKs--a new approach in the treatment of rheumatoid arthritis. Rheumatology (Oxford). 2013;**52**:1352–7.	patients resistant to biologics	bDMARDs	Review	JAKi as a new treatment option
8	Durez P, Vandepapeliere P, Miranda P, *et al.* Therapeutic vaccination with TNF-Kinoid in TNF antagonist-resistant rheumatoid arthritis: a phase II randomized, controlled clinical trial. PLoS One. 2014;**9**:e113465.	adults with RA who previously experienced secondary failure of TNF antagonists	≥2TNFi	RCT	Efficacy of TNF-Kinoid vaccination
9	Williams JH, Hutmacher MM, Zierhut ML, *et al.* Comparative assessment of clinical response in patients with rheumatoid arthritis between PF-05280586, a	active rheumatoid arthritis refractory to anti-tumour necrosis factor therapy on a	≥1TNFi + MTX	RCT	Efficacy of RTX vs biosimilar RTX

	proposed rituximab biosimilar, and rituximab. Br. J. Clin. Pharmacol. 2016;**82**:1568–79.	background of methotrexate; active RA on a background of methotrexate who had inadequate responses to one or more tumour necrosis factor antagonist therapies			
10	Aletaha D, Bingham CO, Tanaka Y, *et al.* Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. *Lancet* 2017;**389**:1206–17.	refractory or intolerant to previous treatment with at least one anti-TNF drug	≥1TNFi	RCT	Efficacy and safety of sirukumab vs placebo
11	De Keyser F, Hoffman I, Durez P, *et al.* Longterm followup of rituximab therapy in patients with rheumatoid arthritis: results from the Belgian MabThera in Rheumatoid Arthritis registry. J. Rheumatol. 2014;**41**:1761–5.	active rheumatoid arthritis (RA) who failed at least 1 anti-tumor necrosis factor (anti-TNF) treatmen	≥1TNFi	Cohort	Long term followup of RTX treated patients
12	Torrente-Segarra V, Acosta Pereira A, Morla R, *et al.* VARIAR Study: Assessment of short-term efficacy and safety of rituximab compared to an tumor necrosis factor alpha antagonists as second-line drug therapy in patients with rheumatoid arthritis refractory to a first tumor necrosis factor alpha antagonist. Reumatol. Clin. 2016;**12**:319–22.	severe RA refractory to a first anti-TNF agent	≥1TNFi	Cohort	Efficacy and safety of RTX vs TNFi
13	Hirabara S, Takahashi N, Fukaya N, *et al.* Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. *Clin Rheumatol* 2014;**33**:1247–54.	patients with RA who are refractory to anti-TNF monoclonal antibody therapy; patients who do not respond to initial TNFi therapy	≥1TNFi	Cohort, retrospectively	Efficacy of abatacept vs TCZ vs ETA
14	Wells AF, Curtis JR, Betts KA, *et al.* Systematic Literature Review and Meta-analysis of Tumor Necrosis Factor-Alpha Experienced Rheumatoid Arthritis. *Clin Ther* 2017;**39**:1680–1694.e2.	TNF-experienced patients who have rheumatoid arthritis (RA).	1TNFi	SLR + MA	Efficacy of bDMARDs and tsDMARDs for patients who failed TNFi
15	Addimanda O, Possemato N, Macchioni P, *et al.* Efficacy and safety of tocilizumab in refractory rheumatoid arthritis: a real life cohort from a single centre. Clin. Exp. Rheumatol. 2014;**32**:460–4.	refractory to anti-tumour necrosis factor-α	TNFi	Cohort	Efficacy and safety of tocilizumab
16	Avci AB, Feist E, Burmester G-R. Targeting GM-CSF in rheumatoid arthritis. Clin. Exp. Rheumatol. 2016;**34**:39–44.	an alternative agent in TNF inhibitor resistant patients with RA	TNFi	Review	GM-CSF as a treatment target
17	Nakashima Y, Kondo M, Miyahara H, *et al.* Drug delivery options to increase patient adherence and satisfaction in the management of rheumatoid arthritis -- focus on subcutaneous tocilizumab. Drug Des. Devel. Ther. 2014;**8**:913–9.	refractory to tumor necrosis factor inhibitors	TNFi	Review	Efficacy and safety of tocilizumab i.v. vs s.c.

18	Kaneko K, Sugitani M, Goto M, *et al.* Tocilizumab and pregnancy: Four cases of pregnancy in young women with rheumatoid arthritis refractory to anti-TNF biologics with exposure to tocilizumab. *Mod Rheumatol* 2016;**26**:672–5.https://www.ncbi.nlm.nih.gov/pubmed/26872426	active RA refractory to anti-TNF agents	TNFi	Case study	Tocilizumab in pregnancy
19	Gras J. Baricitinib: JAK inhibition for rheumatoid arthritis. *Drugs of Today* 2016;**52**:543.	RA refractory to aggressive standard-of-care treatment (with both conventional DMARDs and bDMARDs)	csDMARDs + bDMARDs	Review	Baricitinib for RA
20	Hidaka T, Hashiba Y, Kubo K, *et al.* Leukocytapheresis in rheumatoid arthritis. Transfus. Apher. Sci. 2017;**56**:698–702.	active RA that was refractory to conventional drug therapy including biological agents; inadequate response to multiple DMARDs	≥2DMARDs	Review	Leukocytapheresis for RA
21	Rakieh C, Conaghan PG. Tofacitinib for treatment of rheumatoid arthritis. Adv. Ther. 2013;**30**:713–26.	a proportion of patients remain resistant or intolerant to multiple conventional and biological DMARDs	≥2DMARDs	Review	Efficacy and safety of tofacitinib
22	Abushouk AI, Ahmed H, Ismail A, *et al.* Safety and efficacy of ocrelizumab in rheumatoid arthritis patients with an inadequate response to methotrexate or tumor necrosis factor inhibitors: a systematic review and meta-analysis. Rheumatol. Int. 2017;**37**:1053–64.	resistance or intolerance to methotrexate or biological therapy	DMARDs	SLR + MA	Efficacy and safety of ocrelizumab + MTX vs placebo + MTX
23	Ahmadzadeh A, Farahmand AN, Gachkar L. Evaluation of safety, efficacy and post-cessation efficacy durability of tocilizumab in patients with active rheumatoid arthritis. *Int J Rheum Dis* 2017;**20**:231–7.	inadequate responses to disease-modifying antirheumatic drugs (DMARDs); receiving at least one DMARD with a constant dose for at least 8 weeks before screening	≥1DMARD	Cohort	Efficacy, safety and post-cessation efficacy of TCZ
24	Azevedo AFB, Petribú KCL de, Lima M de N, *et al.* Quality of life of patients with rheumatoid arthritis under biological therapy. *Rev Assoc Med Bras* 2015;**61**:126–31.	the use of biologic therapy in patients with RA refractory to standard therapies; being a patient with RA refractory to conventional immunosuppressive therapy	csDMARDs	Cohort	QoL of patients undergoing bDMARD therapy
25	Bala S-V, Samuelson K, Hagell P, *et al.* Living with persistent rheumatoid arthritis: a BARFOT study. *J Clin Nurs* 2017;**26**:2646–56.	rheumatoid arthritis live with an ongoing active and symptomatic illness despite access to potent antirheumatic treatment	DMARDs	Cohort, cross sectional	QoL of patients with persistent RA
26	Kalden JR. Emerging Therapies for Rheumatoid Arthritis. *Rheumatol Ther* 2016;**3**:31–42. doi:10.1007/s40744-016-0032-4	which are refractory to currently available treatment options; refractory to the currently available biologics	bDMARDs	Reviews	Novel treatments for RA
27	Berhan A. Efficacy, safety and tolerability of tofacitinib in patients with an inadequate response to disease modifying anti-rheumatic drugs: a meta-analysis of randomized double-blind controlled studies. BMC Musculoskelet. Disord. 2013;**14**:332.h	patients with an inadequate response or intolerance to at least one of the nonbiologic or biologic disease-modifying antirheumatic drugs (DMARDs)	≥1DMARDs	MA	Efficacy and safety of tofacitinib

28	Takeuchi T, Thorne C, Karpouzas G, *et al.* Sirukumab for rheumatoid arthritis: the phase III SIRROUND-D study. *Ann Rheum Dis* 2017;**76**:2001–8.	active RA refractory to disease-modifying antirheumatic drugs; refractory to single-agent or combination DMARD therapy including MTX or sulfasalazine, based on lack of benefit after ≥12week	≥1DMARDs	RCT	Efficacy and safety of sirukumab vs placebo
29	Okano T, Inui K, Tada M, *et al.* Levels of interleukin-1 beta can predict response to tocilizumab therapy in rheumatoid arthritis: the PETITE (predictors of effectiveness of tocilizumab therapy) study. Rheumatol. Int. 2016;**36**:349–57.	resistant to disease-modifying anti-rheumatic drugs and/or other biologics; at least one DMARD including MTX for <6 months or other biologics	≥1DMARD	Cohort	Predicting response to TCZ using levels of IL-1
30	Vastesaeger N, Kutzbach AG, Amital H, *et al.* Prediction of remission and low disease activity in disease-modifying anti-rheumatic drug-refractory patients with rheumatoid arthritis treated with golimumab. *Rheumatology* 2016;**55**:1466–76.	disease-modifying anti-rheumatic drug-refractory patients with rheumatoid arthritis; active RA despite DMARD treatment	DMARDs	Cohort	Matrix tool for prediction of remission in GLM treated patients
31	Furst DE, Kavanaugh A, Florentinus S, *et al.* Final 10-year effectiveness and safety results from study DE020: adalimumab treatment in patients with rheumatoid arthritis and an inadequate response to standard therapy. Rheumatology (Oxford). 2015;**54**:2188–97.	DMARD-refractory RA patients; active disease despite MTX, sulfasalazine (SSZ), and/or hydroxychloroquine (HCQ) therapy	DMARDs	Cohort	Long-term effectiveness and safety of ADA
32	Porter D, van Melckebeke J, Dale J, *et al.* Tumour necrosis factor inhibition versus rituximab for patients with rheumatoid arthritis who require biological treatment (ORBIT): an open-label, randomised controlled, non-inferiority, trial. Lancet (London, England). 2016;**388**:239–47.	inadequate response to synthetic disease modifying anti-rheumatic drugs (DMARDs): failure of treatment with at least two nbDMARDs, including methotrexate	≥2csDMARDs	RCT	Efficacy, safety and cost-effectiveness of TNFi vs RTX
33	Genovese MC, Hsia E, Belkowski SM, *et al.* Results from a Phase IIA Parallel Group Study of JNJ-40346527, an Oral CSF-1R Inhibitor, in Patients with Active Rheumatoid Arthritis despite Disease-modifying Antirheumatic Drug Therapy. J. Rheumatol. 2015;**42**:1752–60.	patients with DMARD-refractory active RA	≥1csDMARD	RCT	Efficacy and safety of CSF-1 vs placebo
34	Funakubo Asanuma Y. Management of rheumatoid arthritis medications and pregnancy. Nihon Rinsho Meneki. Gakkai Kaishi. 2015;**38**:45–56.	active RA resistant to conventional DMARDs	csDMARDs	Review	Management of RA during pregnancy
35	Gavrilă BI, Ciofu C, Stoica V, *et al.* The efficiency of biologic therapy in a group of patients with rheumatoid arthritis. J. Med. Life. 2015;**8**:79–84.	RA refractory to classic remitting treatment administered at least 6 months prior to the initiation of biological therapy	csDMARDs	Cohort, retrospectively	Efficacy of monotherapy of IFX vs ETA vs ADA vs RTX
36	Kopciuch D, Paczkowska A, Leszczynsk P, *et al.* EFFECT OF THERAPY WITH ANTI-TNF α DRUGS AND DMARD ON DISEASE ACTIVITY AND HEALTH RELATED QUALITY OF LIFE AMONG WOMEN WITH RHEUMATOID ARTHRITIS. *Acta Pol Pharm* 2016;**73**:547–54.	refractory to conventional treatment with disease modifying anti-rheumatic drugs	csDMARDs	Cohort, retrospectively	QoL of TNFi treated patients

37	Leroy M, Coiffier G, Pronier C, *et al.* Macrophage activation syndrome with acute hepatitis E during tocilizumab treatment for rheumatoid arthritis. *Joint Bone Spine* 2015;**82**:278–9.	active rheumatoid arthritis (RA) refractory to conventional DMARDs	csDMARDs	Case report	Macrophage activation syndrome during tocilizumab treatment
38	Manzo A, Benaglio F, Vitolo B, *et al.* Power Doppler ultrasonographic assessment of the joint-draining lymph node complex in rheumatoid arthritis: a prospective, proof-of-concept study on treatment with tumor necrosis factor inhibitors. Arthritis Res. Ther. 2016;**18**:242.	patients refractory to conventional synthetic disease-modifying anti-rheumatic drugs; inadequate response to conventional synthetic DMARDs (csDMARDs)	csDMARDs	Post-hoc analysis	Ultrasound analysis of lymph nodes in TNFi treated patients vs healthy controls
39	Markatseli TE, Papagoras C, Nikoli A, *et al.* Certolizumab for rheumatoid arthritis. Clin. Exp. Rheumatol. 2014;**32**:415–23.	patients with rheumatoid arthritis refractory to synthetic disease-modifying anti-rheumatic drugs (DMARDs)	csDMARDs	Review	Certolizumab for RA
40	Motomura H, Matsushita I, Seki E, *et al.* Inhibitory effect of tacrolimus on progression of joint damage in patients with rheumatoid arthritis. *Int J Rheum Dis* 2014;**17**:749–54.	resistant or intolerant to conventional disease-modifying anti-rheumatic drugs	csDMARDs	Cohort, retrospectively	The effect of tacrolimus on radiographic joint damage
41	Sung Y-K, Cho S-K, Kim D, *et al.* Comparative effectiveness of treatment options after conventional DMARDs failure in rheumatoid arthritis. Rheumatol. Int. 2017;**37**:975–82.	refractory to conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs)	csDMARDs	Cohort, retrospectively	Effectiveness of starting TNFi or changing csDMARDs after csDMARD failure
42	Wijesinghe H, Galappatthy P, de Silva R, *et al.* Leflunomide is equally efficacious and safe compared to low dose rituximab in refractory rheumatoid arthritis given in combination with methotrexate: results from a randomized double blind controlled clinical trial. *BMC Musculoskelet Disord* 2017;**18**:310.	active disease despite treatment with non biologic DMARDs containing at least 10 mg of methotrexate per week for more than 6 months	csDMARDs	RCT	Efficacy and safety of RTX + MTX vs leflunomide + MTX
43	Bae S-C, Lee YH. Comparative efficacy and safety of TNF-inhibitor plus methotrexate versus oral triple therapy in patients with active rheumatoid arthritis inadequately responding to methotrexate: A meta-analysis of randomized controlled trials. *Int J Clin Pharmacol Ther* 2018;**56**:263–9.	MTX-resistant RA patients	MTX	MA	Efficacy and safety of TNFi + MTX vs HCQ + SSZ + MTX
44	Bao J, Yue T, Li T, *et al.* Good response to infliximab in rheumatoid arthritis following failure of interleukin-1 receptor antagonist. Int. J. Rheum. Dis. 2016;**19**:370–6.	active RA despite methotrexate (MTX) treatment	MTX	RCT	Efficacy of IFX + MTX vs MTX
45	Choi M, Hyun MK, Choi S, *et al.* Comparative efficacy of biological agents in methotrexate-refractory rheumatoid arthritis patients: a Bayesian mixed treatment comparison. *Korean J Intern Med* 2017;**32**:536–47.	RA patients refractory to methotrexate (MTX)	MTX	Review, MTC	Efficacy of bDMARDS (ADA, ETA, IFX, certolizumab,golimumab) vs csDMARDs

					(HCQ, SSZ, MTX, leflunomide)
46	De Keyser F, De Kock J, Leroi H, *et al.* Ten-year Followup of Infliximab Therapy in Rheumatoid Arthritis Patients with Severe, Longstanding Refractory Disease: A Cohort Study. *J Rheumatol* 2014;**41**:1276–81.	rheumatoid arthritis who were refractory to methotrexate	MTX	Cohort	Long-term followup of IFX therapy
47	Eriksson JK, Karlsson JA, Bratt J, *et al.* Cost-effectiveness of infliximab versus conventional combination treatment in methotrexate-refractory early rheumatoid arthritis: 2-year results of the register-enriched randomised controlled SWEFOT trial. Ann. Rheum. Dis. 2015;**74**:1094–101.	patients with methotrexate-refractory early rheumatoid arthritis	MTX	RCT	Cost-effectiveness of IFX + MTX vs HCQ + SSZ + MTX
48	He Y, Wong AYS, Chan EW, *et al.* Efficacy and safety of tofacitinib in the treatment of rheumatoid arthritis: a systematic review and meta-analysis. BMC Musculoskelet. Disord. 2013;**14**:298.	patients with MTX-resistant RA	MTX	SLR + MA	Efficacy and safety of tofacitinib vs placebo
49	Karlsson JA, Neovius M, Nilsson J-Å, *et al.* Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in early rheumatoid arthritis: 2-year quality-of-life results of the randomised, controlled, SWEFOT trial. Ann. Rheum. Dis. 2013;**72**:1927–33.	early, methotrexate (MTX) refractory rheumatoid arthritis (RA)	MTX	RCT	QoL and QALYs in patients using MTX + IFX vs HCQ + SSZ + MTX
50	Kremer JM, Peterfy C, Russell AS, *et al.* Longterm safety, efficacy, and inhibition of structural damage progression over 5 years of treatment with abatacept in patients with rheumatoid arthritis in the abatacept in inadequate responders to methotrexate trial. J. Rheumatol. 2014;**41**:1077–87.	methotrexate (MTX)-refractory patients	MTX	RCT	Long-term efficacy, safety and inhibiton of structural damage in patients using abatacept vs placebo
51	Kume K, Amano K, Yamada S, *et al.* The effect of tocilizumab on bone mineral density in patients with methotrexate-resistant active rheumatoid arthritis. *Rheumatology (Oxford)* 2014;**53**:900–3.	active RA (indicated by a 28-joint DAS ESR >3.2) despite treatment with MTX	MTX	Cohort	Effect on bone mineral density of TCZ
52	Mori S, Imamura F, Koga Y, *et al.* Pulmonary Mycobacterium abscessus disease in a patient receiving low-dose methotrexate for treatment of early rheumatoid arthritis. *J Infect Chemother* 2013;**19**:1146–51.	methotrexate (MTX)-refractory rheumatoid arthritis (RA)	MTX	Case report	Pulmonary Mycobacterium abcessus disease in RA patient
53	Peres RS, Santos GB, Cecilio NT, *et al.* Lapachol, a compound targeting pyrimidine metabolism, ameliorates experimental autoimmune arthritis. Arthritis Res. Ther. 2017;**19**:47.	MTX resistance	MTX	Cohort	CD39 as a biomarker for resistance to MTX therapy
54	Takeuchi T, Miyasaka N, Inui T, *et al.* High titers of both rheumatoid factor and anti-CCP antibodies at baseline in patients with rheumatoid arthritis are associated with increased circulating baseline TNF level, low drug	Methotrexate-refractory patients with RA	MTX	Post-hoc analysis	Titers of RF and ACPA in IFX treated patients

	levels, and reduced clinical responses: a post hoc analysis of the RISING study. Arthritis Res. Ther. 2017;**19**:194.				
55	Takeuchi T, Miyasaka N, Inui T, *et al.* Prediction of clinical response after 1 year of infliximab therapy in rheumatoid arthritis based on disease activity at 3 months: posthoc analysis of the RISING study. J. Rheumatol. 2015;**42**:599–607.	Methotrexate-refractory patients with RA	MTX	Post-hoc analysis	Prediction of clinical response of IFX treated patients
56	Tan W, Wang F, Guo D, *et al.* High serum level of haptoglobin is associated with the response of 12 weeks methotrexate therapy in recent-onset rheumatoid arthritis patients. *Int J Rheum Dis* 2016;**19**:482–9.	methotrexate (MTX)-resistant rheumatoid arthritis (RA) patients	MTX	Cohort	Level of haptoglobin associated with response to MTX
57	Vital EM, Dass S, Buch MH, *et al.* An extra dose of rituximab improves clinical response in rheumatoid arthritis patients with initial incomplete B cell depletion: a randomised controlled trial. Ann. Rheum. Dis. 2015;**74**:1195–201.	active rheumatoid arthritis despite methotrexate	MTX	RCT	Efficacy of additional infusion (3rd) of RTX vs placebo
58	Yadlapati S, Efthimiou P. Inadequate response or intolerability to oral methotrexate: Is it optimal to switch to subcutaneous methotrexate prior to considering therapy with biologics? Rheumatol. Int. 2016;**36**:627–33.	refractory to low-dose MTX therapy	MTX	Review	Inadequate response or intolerablity to oral MTX
59	Yu MB, Firek A, Langridge WHR. Predicting methotrexate resistance in rheumatoid arthritis patients. Inflammopharmacology. 2018;**26**:699–708.	MTX non-response/resistance in RA patients	MTX	Review	Predicting MTX resistance
60	Pers YM, Jorgensen C. Perspectives of ofatumumab as CD20 targeted therapy in rheumatoid arthritis and other autoimmune diseases. Immunotherapy. 2016;**8**:1091–6.	refractory to rituximab	RTX	Review	Ofatumumab as a new targeted therapy

ACPA: anti-citrullinated protein antibody; ADA: adalimumab; b-: biological; cs-: conventional synthetic; CSF-1: Colony-stimulating factor-1 receptor kinase; DMARDs: disease-modifying antirheumatic drugs; ETA: etanercept; GLM: golimumab; HCQ: hydrochloroquine; IFX: infliximab; JAKi: JAK inhibitor; LEF: leflunomide; MA: meta-analysis; MTC: mixed treatment comparison; MTX: methotrexate; RCT: randomised controlled trial; RF: Rheumatoid factor; RTX: rituximab; SLR: systematic literature review; SSZ: sulfasalazine; TCZ: tocilizumab; TNFi: TNF inhibitor.