Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis

Kerschbaumer, A.; Sepriano, A.; Bergstra, S.A.; Smolen, J.S.; Heijde, D. van der; Caporali, R.; ... ; Landewe, R.B.M.

CLINICAL SCIENCE

Efficacy of synthetic and biological DMARDs: a systematic literature review informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis

Andreas Kerschbaumer ,[1] Alexandre Sepriano ,[2,3] Sytske Anne Bergstra ,[3] Josef S Smolen,[1] Désirée van der Heijde ,[3] Roberto Caporali,[4] Christopher John Edwards,[5] Patrick Verschueren ,[6] Savia de Souza ,[7] Janet E Pope ,[8] Tsutomu Takeuchi ,[9] Kimme L Hyrich ,[10] Kevin L Winthrop ,[11] Daniel Aletaha ,[1] Tanja A Stamm ,[12,13] Jan W Schoones ,[14] Robert B M Landewé [15,16]

Handling editor David S Pisetsky

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/ard-2022-223365).

For numbered affiliations see end of article.

Correspondence to
Dr Andreas Kerschbaumer, Department of Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria; andreas.kerschbaumer@meduniwien.ac.at

Received 15 September 2022
Accepted 10 October 2022
Published Online First 11 November 2022

To cite: Kerschbaumer A, Sepriano A, Bergstra SA, *et al*. *Ann Rheum Dis* 2023;**82**:95–106.

ABSTRACT

Objectives To update the evidence on efficacy of DMARDs (disease-modifying antirheumatic drugs) and inform the taskforce of the 2022 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for management of rheumatoid arthritis (RA).

Methods This systematic literature review (SLR) investigated the efficacy of conventional synthetic (cs), biological (b), biosimilar and targeted synthetic (ts)DMARDs in patients with RA. Medline, EMBASE, Cochrane CENTRAL and Web of Science were used to identify all relevant articles published since the previous update in 2019 to 14 January 2022.

Results Of 8969 search results, 169 articles were selected for detailed review and 47 were finally included. Trials investigated the efficacy of csDMARDs, bDMARDs and tsDMARDs, DMARD switching, tapering and trials investigating different treatment strategies. The compounds investigated were csDMARDs (methotrexate (MTX), leflunomide, sulfasalazine, hydroxychloroquine), bDMARDs (abatacept, adalimumab, certolizumab-pegol, denosumab, etanercept, infliximab, levilimab, olokizumab, opineracept, rituximab, sarilumab, tocilizumab) and tsDMARDs (baricitinib, filgotinib, tofacitinib, upadacitinib). The efficacy of csDMARDs+ short-term glucocorticoids in early RA was confirmed and similar to bDMARD+MTX combination therapy. Interleukin-6 pathway inhibition was effective in trials on olokizumab and levilimab. Janus kinase inhibitor (JAKi) was efficacious in different patient populations. After insufficient response to JAKi, patients could respond to TNFi treatment. Tapering of DMARDs was feasible for a proportion of patients, who were able to taper therapy while remaining in low disease activity or remission.

Conclusion The results of this SLR, together with one SLR on safety of DMARD and one on glucocorticoids, informed the taskforce of the 2022 update of the EULAR recommendations for pharmacological management of RA.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ The 2019 update of the European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of rheumatoid arthritis (RA) provided guidance for the treatment of patients with RA using conventional synthetic, biological and targeted synthetic disease-modifying antirheumatic drugs (DMARDs) and glucocorticoids. To update these recommendations, this systematic literature review (SLR) informed the EULAR task force 2022 with the evolved evidence on the efficacy of DMARD therapies since 2019.

WHAT THIS STUDY ADDS

⇒ In patients with insufficient response to upadacitinib, patients could respond to TNFi treatment after immediate switch to adalimumab.
⇒ Interleukin-6 pathway inhibition was effective in trials investigating olokizumab and levilimab.
⇒ Tapering of DMARDs was feasible for a patients, who were able to taper therapy while remaining in low disease activity or remission.
⇒ Synovial biopsy driven histological stratification to tocilizumab or rituximab treatment did not lead to improved response rates in patients with previous insufficient response to TNFi.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This work, together with two further SLRs, one on safety and one on glucocorticoid treatment informed the 2022 EULAR RA management recommendations task force with the available evidence published since 2019.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic autoimmune disease leading to a symmetric polyarthritis with substantial consequences on quality of life,

daily living and social participation due to joint swelling and pain, stiffness, fatigue and potential long-term joint damage. Pharmacological management of RA aims to relieve these signs and symptoms, preventing structural damage, improving health-related quality of life and normalising physical function.[1] Modern treatment strategies include established pharmacological agents termed disease-modifying antirheumatic drugs (DMARDs), including monoclonal antibodies as well as small molecules targeting specific inflammatory pathways. These are used alongside well known conventional synthetic (cs) DMARDs as well as short-term glucocorticoids.[2] Weighing up efficacy and safety remains a constant challenge as data from clinical trials arise continually since decades, providing new insights into the efficacy of drugs established in routine clinical care, as well as the clinical application of molecules targeting novel treatment targets. The availability of many highly effective therapies, combined with a strategy of treating RA patients to target, facilitates the achievement of clinical remission and/or low disease activity (LDA) in a large proportion of patients. Subsequently, many questions on how to taper established therapies arise: who should be tapered, how should treatment be tapered, which treatment should be tapered first and how quickly should it be withdrawn? Many trials investigating tapering have therefore been conducted in recent years.

To address this stream of constantly evolving evidence, the European Alliance of Associations for Rheumatology (EULAR) management recommendations for pharmacological treatment of RA were updated in 2022.[3] Three systematic literature reviews (SLRs) were conducted covering the areas of (1) efficacy, (2) safety of DMARD treatment and (3) utilisation of glucocorticoids in RA and are published separately.[4 5]

This particular SLR focuses on the evidence for efficacy of the pharmacological interventions of DMARDs, published since the previous update in 2019.[6]

METHODS

This SLR was conducted according to the EULAR standard operating procedures published in 2014 and based on a protocol developed and approved by the task force.[7]

Similar to previous SLRs dealing with efficacy of DMARDs in RA, only randomised controlled trials (RCTs) investigating csDMARD, biological (b) or targeted synthetic (ts) DMARDs in adult patients classified as having RA were eligible for inclusion.[8 9] To further update the previous SLR, articles published between 1 January 2019 and 14 January 2022 with no language restriction were searched by an experienced librarian (JSS) using Medline, EMBASE, The Cochrane CENTRAL Register of Controlled Trials (Central), Web of Science and the EULAR/American College of Rheumatology (ACR) abstract archives as information sources. Studies presented as conference abstracts at the EULAR and ACR annual meetings from 2020 to 2021 were also eligible for inclusion.

All detailed search strategies are provided in online supplemental text S1.1-S1.4.

In total 20 research questions were defined during the first virtual steering committee meeting. The main research questions involved the efficacy of csDMARD, bDMARD and tsDMARDs, efficacy differences between different DMARDs; differences between combination therapy versus monotherapy, switching between bDMARDs and tsDMARDs, evidence on different treatment strategies as well as DMARD dose reduction and treatment discontinuation in patients with ongoing therapy. Patient populations were defined as follows: DMARD-naïve patients, patients with insufficient response (IR) to csDMARD, patients who were bDMARD-IR and/or tsDMARD-IR. Comparator arms were required to include patients, receiving placebo or active therapy. These research questions covered the areas of the efficacy of csDMARDs, csDMARD combination therapies, bDMARDs and tsDMARDs (with and without concomitant csDMARDs), head-to-head comparisons of different bDMARDs and tsDMARDs, DMARD switching as well as DMARD tapering and stopping, and studies on biosimilars. All interventions of interest are listed in online supplemental table 1.5. The detailed research questions and population, intervention, control, outcome are shown in online supplemental table 1.6.

Ten per cent of all titles and abstracts were screened by two separate researchers (AK, SAB) with an agreement of 93%. The remaining studies were screened and assessed by one researcher (AK). Uncertainties were discussed with the senior EULAR methodologist (RBML). After title and abstract screening, selected articles were assessed in detail for eligibility and data of finally eligible articles were extracted using standardised spreadsheet forms. Variables of interest were predefined in the review protocol, including outcomes on signs and symptoms of RA, commonly used composite measures, respective core-set variables, measures of physical function, patient-reported outcomes and outcomes on structural damage. Extensive evidence of the bioequivalence of various biosimilars (bsDMARDs) when compared with their respective biooriginator (boDMARDs) was already shown in a previous SLR, which led to the decision to only include systematic reviews on biosimilars in this SLR. RoB was assessed using the Cochrane Collaborations Risk of Bias tool for RCTs. Conference abstracts were not assessed for RoB. No meta-analytical methods were applied due to the heterogeneity of the available studies; therefore, results are reported descriptively.

RESULTS

In total 8969 search results were obtained, with 5071 unique references (after deduplication) remaining for title and abstract screening. A total of 169 references were selected to be assessed in the detailed article review, resulting in 47 articles describing 38 unique trials were eligible for final inclusion in the SLR. A detailed flow chart is depicted in figure 1. Details of all studies included are shown in online supplemental table 2.1.

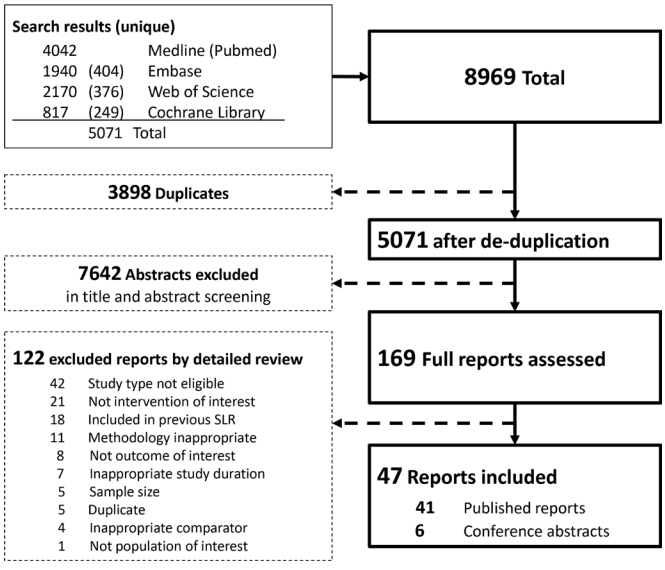

Figure 1 PRISMA flow chart describing the study selection process.

Table 1 Interventions and therapeutic compounds of trials included for review

Intervention	No of articles/abstracts	Therapeutic compound	Target
csDMARDs, csDMARD combination vs other csDMARDs or placebo	3	MTX+SSZ + HCQ vs MTX+LEF + HCQ	Dihydrofolate reductase+purine metabolism; dihydroorotate dehydrogenase
		MTX (+5 mg every 4 wks) vs MTX (+5 mg every 2 wks)	
		MTX+SSZ + GC vs MTX+GC vs MTX+LEF + GC vs MTX	
bDMARD±csDMARDs vs placebo	8	Opineracept	TNF receptor
		Denosumab	RANKL
		Rituximab	CD20
		Olokizumab	IL-6
		Sarilumab	IL-6 receptor
		Levilimab	
tsDMARDs±csDMARDs vs placebo	7	Baricitinib	JAK1,2
		Filgotinib	JAK1
		Upadacitinib	JAK1,2
bDMARDs vs other bDMARDs	4	Rituximab vs Tocilizumab	CD20 vs IL6 receptor
		Olokizumab vs Adalimumab	IL6 receptor vs TNF
		Certolizumab pegol+MTX vs Abatacept+MTX vs. Tocilizumab+MTX	TNF vs CD80/CD86 vs IL6R
tsDMARDs vs bDMARDs	3	Upadacitinib vs Adalimumab	JAK1,2 vs TNF
		Upadacitinib vs Abatacept	JAK1,2 vs CD-80/CD-86
		Filgotinib vs Adalimumab	JAK1 vs TNF
Biosimilars	2	bsDMARDs of infliximab, etanercept, adalimumab	TNF/TNFR
Strategic studies	4		
Switching between tsDMARDs and bDMARDs	1	Upadacitinib <-> Adalimumab	JAK1,2 <-> TNF
csDMARD dose reduction and stopping	3	csDMARDs	
bDMARD dose reduction and stopping	7	Adalimumab	TNF
		Etanercept	TNFR
		Infliximab	TNF
		Tocilizumab	IL6R
		Rituximab	CD20
		Any TNFi	TNF
csDMARD or bDMARD dose reduction or stopping	5	Etanercept/MTX	TNFR
		Abatacept/MTX	CD80/CD86
		Any csDMARD/any bDMARD	
		Any csDMARD/any TNFi	

b, biologic; CD, cluster of differentiation; cs, conventional synthetic; DMARD, disease-modifying antirheumatic drug; HCQ, hydroxychloroquine; IL, interleukin; JAK, Janus Kinase; LEF, leflunomide; MTX, methotrexate; RANKL, receptor activator of nuclear factor kappa-B ligand; SSZ, sulfasalazine; TNF, tumour necrosis factor alpha; TNFi, TNF alpha inhibitor; ts, targeted synthetic; wk, week.

RoB assessment resulted in 17/38 (44.7%) trials rated with a low RoB and 17 of 38 trials (44.7%) had a high RoB, primarily due to open-label or single-blinded trial designs. One trial (1/38, 2.6%) had unclear RoB due to insufficient reporting of randomization sequence generation and allocation concealment methods. Three trials (3/38, 7.9%) were published as conference abstracts only and therefore not assessed for RoB. Detailed RoB results of all studies are provided in online supplemental table 2.2.

A summary of included trials and therapies investigated is shown in table 1. Baseline characteristics of all articles included are presented in online supplemental table 2.3 & online supplemental table 2.4 as well as detailed efficacy results, shown in online supplemental tables 3.1.2.

Efficacy of csDMARDs

CareRA was an open-label trial in csDMARD-naïve RA patients, who were stratified to different csDMARD combination regimens based on factors of poor prognosis (erosive disease, high disease activity, high titres of rheumatoid factor or anti-citrullinated protein antibodies antibodies). High-risk patients received either methotrexate (MTX)+sulfasalazine (SSZ)+60 mg of (protocolised tapered) prednisone or MTX+leflunomide (LEF)+30 mg (tapered protocolised) prednisone or MTX+30 mg prednisone (tapered protocolised) alone. At year 2, no differences in response rates were observed with about 90% of patients achieving LDA (Disease Activity Score 28-C reactive protein (DAS28-CRP) ≤3.2 86/98 (88%) vs 86/98 (88%) vs 85/93 (91%), p=0.65) and about one-fifth achieving ACR-EULAR Boolean remission across

all treatment arms (21/98 (21%), 20/98 (20%), 21/93 (23%), p=1.0). Low-risk patients received either MTX+30 mg of prednisone (step-down) or MTX (with protocolised step-up to 25 mg weekly) alone. Patients with MTX+GC combination therapy showed similar responses in achieving LDA states after 2 years, but MTX+GC treated patients did show faster responses and higher remission rates across several outcomes including Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI) and Boolean remission (CDAI≤2.8: 21/43 (49%) vs 12/47 (28%), p=0.04). Radiographic progression was low and comparable across all treatment arms.[10]

An Indian single-centre open-label RCT (high RoB) investigated the non-inferiority of MTX+LEF+hydroxychloroquine (HCQ) vs MTX+SSZ+HCQ in 136 patients who had an IR (defined as DAS28 ≥3.2) to stable therapy with MTX 25 mg weekly. After 12 weeks, non-inferiority was demonstrated as 40/68 (59%) in the LEF vs 37/68 (54%) in the SSZ arm achieved a EULAR good response (difference 4.4%, 95% CI −12 to 20).[11] Another Indian investigator-blinded trial (high RoB) compared two different MTX dosage escalation strategies in MTX-naïve patients—starting with 15 mg once weekly, MTX was either increased by 5 mg every 2 weeks or by 5 mg every 4 weeks. No efficacy differences in EULAR good response rates were observed at week 16 (22.5% vs 28.1%; p=0.39; for every 2 weeks and every 4 weeks MTX escalation, respectively).[12]

Efficacy of bDMARDs

In total eight trials investigating bDMARDs with or without concomitant csDMARD were included (six with low RoB, one with high RoB, one conference abstract). Primary results are summarised in table 2.[13–21]

Four trials (three with low RoB, one conference abstract) investigated agents targeting the interleukin-6 (IL-6) pathway: olokizumab (OKZ; anti-IL-6 cytokine) in combination with MTX was superior to placebo (+MTX) treatment in CREDO 1 (MTX-IR) and CREDO 3 (TNFi-IR patients)[15 16] levilimab (LEV; human anti-IL-6 receptor)+MTX also showed superior efficacy compared with placebo+MTX at week 12 in patients with previous IR to MTX.[19] HARUKA investigated Japanese patients receiving sarilumab (SAR; anti-IL6 receptor) in combination with non-MTX csDMARDs or sarilumab monotherapy and did show similar response rates across the treatment arms.[18]

Two trials (both with low RoB) investigated the efficacy of denosumab (DEM; receptor activator of nuclear factor kappa-B ligand (RANKL) inhibitor) on structural changes in csDMARD treated patients with presence of erosions at baseline. Patients with or without osteoporosis were eligible for inclusion. Although damage progression was low overall, significant differences between the arms in mean modified total Sharp Scores (mTSS) at 12 months (primary endpoint) were observed in DESIRABLE (placebo: 1.49 (95% CI 0.99 to 1.99) vs DEM 60 mg Q6M: 0.99 (95% CI 0.49 to 1.49; p=0.023) vs DEM 60 mg Q3M: 0.72 (95% CI 0.41 to 1.03; p=0.006)).[20] Another study investigated the effect of DEM on healing of erosions (using peripheral high-resolution CT scans) in patients receiving csDMARD treatment who had stable disease and erosions at the heads of metacarpal bones II–IV. The primary endpoint (healing of erosions at 12 months) was not met (13% vs 18%, p=0.45). However, a higher proportion of patients showed healing of erosions in the DEM group compared with placebo at month 24 (10/50 (20%) vs 3/48 (6%); p=0.045).[21]

AMARA was an RCT investigating rituximab (RTX) combination therapy with LEF in patients who showed IR to LEF alone. Although numerical results were in favour of RTX+LEF, the primary endpoint (ACR 50 response at week 24) was not met (RTX+LEF: 25/68 (27%) vs PBO+LEF: 7/40 (15%); p=0.081).[14]

Efficacy of tsDMARDs (Janus kinase inhibitors)

Seven articles on five different trials (four low RoB, one unclear RoB) investigating Janus kinase inhibitors (JAKi) were included. Key outcomes are also provided in table 2.

Baricitinib (BARI; 4 mg once daily) in combination with MTX was more effective in reducing signs and symptoms of RA and improving health-related quality of life when compared with placebo+MTX in MTX-IR patients from Brazil, Argentina and China (RA-BALANCE, unclear RoB).[22 23]

The efficacy of upadacitinib (UPA; 15 mg or 30 mg once daily) monotherapy was investigated in early patients with RA who had no or limited MTX exposure (SELECT-EARLY, low RoB). UPA was superior to MTX monotherapy regarding clinical, patient-reported and radiographic outcomes.[24 25] In SELECT-SUNRISE (low RoB) UPA (7.5 mg, 15 mg or 30 mg once daily) + csDMARDs demonstrated clinical and functional superiority to placebo+csDMARD treatment in Japanese csDMARD-IR patients.[26]

Filgotinib (FIL; 200 mg once daily and 100 mg once daily) in combination with csDMARDs was superior to placebo in bDMARD-IR patients (FINCH2, low RoB).[27] In early RA patients with limited or no previous exposure to MTX (FINCH3, low RoB), FIL (200 mg once daily and 100 mg once daily) + MTX was superior to MTX monotherapy. However, superiority of FIL 200 mg once daily monotherapy over MTX monotherapy at week 24 was not demonstrated (ACR20: FIL200 OD: 164/210 (78.1%) vs MTX monotherapy: 297/416 (71.4%); p=0.058).[28]

Head-to-head studies

Three bDMARD head-to-head trials were included (two open-label studies with high RoB; one study with low RoB; table 3):

IL-6 cytokine inhibition with OKZ (+MTX) was non-inferior compared with adalimumab (ADA) in combination with MTX in patients with previous IR to MTX in the CREDO-2 study (low RoB).[29 30]

The R4RA open-label trial (high RoB) stratified patients with IR to TNFi to either RTX or tocilizumab (TCZ) treatment based on synovial histology (B-cell poor vs B-cell rich). The hypothesis that TCZ is superior vs RTX in patients with B-cell poor histology was investigated using CDAI50% changes at week 16 as a primary endpoint. The primary endpoint was not met (CDAI50% change: RTX: 17/38 (45%) vs TCZ: 23/41 (56%); p=0.31). In exploratory analyses, RNA sequencing-based stratification (B-cell poor/B-cell rich); however, showed significant differences between the groups and higher response rates for TCZ treated patients in the B-cell poor population (RTX: 12/33 (36%) vs TCZ: 20/32 (63%); p=0.035). No differences were observed in the B-cell rich stratified patient population.[31]

NORD-STAR was a single-blinded head-to-head trial (high RoB) in csDMARD-naïve early RA patients. All patients started MTX (escalated within 4 weeks to 25 mg/week) and received additionally (1) conventional therapy (csDMARD combination: SSZ+HCQ+intraarticular glucocorticoids or 20 mg oral prednisone tapered to 5 mg in 9 weeks); (2) TNFi therapy (certolizumab-pegol (CZP), 200 mg every 2 weeks); 3) CD80/86 inhibition (abatacept (ABA) 125 mg weekly) or 4) anti-IL-6R treatment with TCZ (8 mg/kg iv every 4 weeks or 162 mg s.c. once a week). The primary endpoint was the superiority of CZP+MTX

Table 2 Primary efficacy outcomes of trials comparing biological DMARDs with or without background csDMARD therapy to placebo

Population	Study	Risk of bias	Treatment	n	Week	Primary endpoint	Outcome	P value
bDMARD treatment versus placebo								
MTX-IR	Nasonov 2021 (CREDO 1)[15]	Low	Placebo+MTX	143	12	ACR20	34.3 (49)	Ref.
			OKZ 64 mg Q2W+MTX	143			98 (68.5)	<0.001
			OKZ 64 mg Q4W+MTX	142			101 (71.1)	<0.001
MTX-IR	Mazurov EULAR 2021 (SOLAR)[19]	Conference abstract	Placebo+MTX	50	12	ACR20	20 (40)	Ref.
			LEV 162 mg QW+MTX	99			70 (71)	<0.001
csDMARD-IR	Liang 2020[13]	High	Placebo+csDMARD	33	24	ACR20	10 (30.3)	Ref.
			OPI 25 mg QW+csDMARD	64			49 (76.6)	<0.001
LEF-IR	Behrens 2021 (AMARA)[14]	Low	Placebo+LEF	47	24	ACR50	7 (14.9)	Ref.
			RTX 1000 mg (d1, d15) + LEF	93			25 (26.9)	0.081
TNF-IR	Feist ACR 2021 / Feist 2022 (CREDO 3)[16 17]	Low	Placebo+MTX	69	12	ACR20	28 (40.6)	Ref.
			OKZ Q2W+MTX	138			84 (60.9)	0.003
			OKZ Q4W+MTX	161			96 (59.6)	0.004
tsDMARD treatment versus placebo								
MTX naïve early RA	Van Vollenhoven 2020 (SELECT EARLY)[24 25]	Low	MTX	314	12 24	ACR50 DAS28-CRP<2.6	88 (28) 60 (19)	Ref.
			UPA 15 mg OD	317			165 (52) 152 (48)	<0.001 <0.001
			UPA 30 mg OD	314			176 (56) 157 (50)	<0.001 <0.001
MTX naïve early RA	Westhovens 2021 (FINCH 3)[28]	Low	Placebo+MTX	416	24	ACR20	297 (71.4)	Ref.
			FIL 200 mg OD+MTX	416			337 (81)	<0.001
			FIL 100 mg OD+MTX	207			166 (80.2)	0.017
			FIL 200 mg OD+Placebo	210			164 (78.1)	0.058
MTX-IR	Li 2020 (RA-BALANCE)[22 23]	Unclear	Placebo+MTX	145	12	ACR20	47 (32.4)	Ref.
			BARI 4 mg OD+MTX	145			93 (64.1)	<0.001
csDMARD-IR	Kameda 2020 (SELECT SUNRISE)[26]	Low	Placebo+csDMARD	49	12	ACR20	21 (42.9)	Ref.
			UPA 7.5 mg OD+csDMARD	49			37 (75.5)	<0.001
			UPA 15 mg OD+csDMARD	49			41 (83.7)	<0.001
			UPA 30 mg OD+csDMARD	50			40 (80)	<0.001
bDMARD-IR	Genovese 2019 (FINCH 2)[27]	Low	Placebo+csDMARD	148	12	ACR20	46 (31.1)	Ref.
			FIL 100 mg OD+csDMARD	153			88 (57.5)	<0.001
			FIL 200 mg OD+csDMARD	147			97 (66)	<0.001
RANKL inhibition versus placebo								
≥ 1 erosion+elevated CRP/ESR+RF/ACPA positive	Takeuchi 2019 (DESIRABLE)[20]	Low	Placebo+csDMARD	211	48	ΔmTSS	1.49	Ref.
			DEM 60 mg Q3M+csDMARD	205			0.72	0.006
			DEM 60 mg Q6M+csDMARD	201			0.99	0.024
DAS28-CRP ≤5.1 + 1 erosion in HR-pQCT	So 2021[21]	Low	Placebo+csDMARD	55	48	Healing of erosions in HR-pQCT	13%	Ref.
			DEM 60 mg Q6M+csDMARD	55			18%	0.45

ACPA, anti-citrullinated protein antibodies; ACR, American College of Rheumatology; b, biologic; BARI, baricitinib; CRP, C reactive protein; cs, conventional synthetic; d, day; DAS, Disease Activity Score; DMARD, disease-modifying antirheumatic drug; ESR, erythrocyte sedimentation rate; HR-pQCT, high-resolution peripheral quantitatice CT; IR, insufficient response; LEF, leflunomide; LEV, levilimab; mTSS, modified total Sharp Score; MTX, methotrexate; OD, once daily; OKZ, olokizumab; OPI, opineracept; PBO, placebo; Q3M, every 3 months; Q6M, every 6 months; QW, weekly; Q2W, every 2 weeks; RANKL, receptor activator of nuclear factor kappa-B ligand; Ref, Reference; RF, rheumatoid factor; RTX, rituximab; TNF, tumour necrosis factor alpha; ts, targeted synthetic; UPA, upadacitinib; Δ, change from baseline.

or ABA+MTX or TCZ+MTX vs. conventional therapy with respect to adjusted CDAI ≤2.8 rates at week 24 and radiographic damage progression at week 48. After 24 weeks, no clinically meaningful differences between the treatments were observed. Prespecified non-inferiority (margin 15%) analyses on CDAI remission rates showed that conventional therapy (estimated CDAI remission rate: 42.7%) was non-inferior to CZP+MTX (46.5%) and TCZ+MTX (42.1%), however, not to ABA+MTX (52.0%). ABA+MTX was statistically superior compared with conventional therapy, CZP+MTX and TCZ+MTX were not. No difference in radiographic progression was observed after week 48 between the groups (ΔmTSS from baseline to week 48: conventional therapy: 0.45 vs ABA+MTX 0.62 vs CZP+MTX 0.47 vs TCZ+MTX 0.5).[32 33]

In total four manuscripts on head-to-head trials comparing tsDMARDs to bDMARDs (all with low RoB) were included (table 4).

UPA (15 mg once daily) in combination with MTX showed superiority over ADA (40 mg every 2 weeks) + MTX and over placebo+MTX in MTX-IR patients (SELECT-COMPARE, low RoB). UPA treated patients had significantly less radiographic damage progression compared with placebo, while results were comparable versus ADA at week 26.[34]

In SELECT-CHOICE (high RoB), bDMARD-IR patients were either randomised to ABA (125 mg weekly) or UPA 15 mg once daily (both in combination with csDMARDs). UPA+csDMARDs was superior to ABA+csDMARDs in change from baseline to week 12 in DAS28-CRP. This was mainly driven by changes in

Table 3 Head-to-head studies comparing biological DMARDs to other biological DMARDs

Population	Study	Risk of bias	Treatment	n	Primary endpoint	Result	P / 95% CI	ACR20 (%)	ACR50 (%)	DAS28≤3.2 (%)	DAS28<2.6 (%)	CDAI≤2.8 (%)	ΔHAQ
csDMARD naïve early RA	Hetland 2020 (NORD-STAR)[32]	High (single-blinded)	GC+MTX/ SSZ + HCQ + GC i.a.+MTX	200	Adjusted difference of CDAI ≤2.8 (week 24)	–	Reference				127 (71.3)	84 (47.2)	
			CZP 200 mg Q2W+MTX	203		3.9	−5.5 to 13.2				139 (77.2)	97 (53.9)	
			ABA 125 mg QW+MTX	204		9.4	0.1 to 18.7				142 (74)	107 (55.4)	
			TCZ 8 mg/kg Q4W or TCZ 162 mg QW+MTX	188		−0.6	−10.1 to 8.9				119 (73)	77 (46.7)	
MTX-IR	Feist ACR 2021 / Smolen 2022 (CREDO 2)[29 30]	Low	Placebo+MTX	243	ACR20 (week 12)	108 (44.4)	–	108 (44.4)	55 (22.6)*	31 (12.8)	148 (31.9) *	10 (4.1)*	−0.42*
			OKZ 64 mg Q2W+MTX	464		326 (70.3)	0.034	326 (70.3)	234 (50.4)*	210 (45.3)	168 (35.1) *	52 (11.2)*	−0.64*
			OKZ 64 mg Q4W+MTX	479		342 (71.4)	0.045	342 (71.4)	240 (50.1)*	219 (45.7)	132 (28.6) *	58 (12.1)*	−0.61*
			ADA 40 mg Q2W+MTX	462		309 (66.9)	Reference	309 (66.9)	214 (46.3)*	177 (38.3)	26 (10.7)*	60 (13.0)*	−0.61*
TNF-IR (B-cell poor based on histology)	Humby 2021 (R4RA)[31]	High (open-label)	B-cell poor: RTX 1000 mg (d1, d15) + csDMARDs	38	CDAI50% response (week 16)	17 (45%)	Reference			12 (32%)	7 (18)		−0.3±0.1
			B-cell poor: TCZ 8 mg/kg Q4W+csDMARDs	41		23 (56%)	0.31			19 (46%)	13 (32)		−0.4±0.1

Results of secondary efficacy outcomes are shown at the timepoint of the primary endpoint.
*Week 24.
ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; CDAI, Clinical Disease Activity Index ; csDMARD, conventional synthetic DMARD; CZP, certolizumab-pegol; DMARD, disease-modifying antirheumatic drug; GC, glucocorticoids; HAQ, health assessment questionnaire; HCQ, hydroxychloroquine; i.a., intra-articular; IR, insufficient response; MTX, methotrexate; OKZ, olokizumab; PBO, placebo; QW, weekly; Q2W, every 2 weeks; Q4W, every 4 weeks; RTX, rituximab; SSZ, sulfasalazine; TCZ, tocilizumab; TNF, tumour necrosis factor alpha.

CRP. Numerically higher response rates, but no clinically meaningful difference in outcomes without acute phase reactants (CDAI ≤10, ACR/EULAR Boolean remission) were observed.[35]

Another head-to-head trial (FINCH1, low RoB) investigating FIL 200 mg once daily in combination with MTX demonstrated non-inferiority (NI) in achieving DAS28-CRP≤3.2 responses at week 12 when compared with ADA 40 mg every 2 weeks (+MTX) and superiority when compared with placebo+MTX in MTX-IR patients. NI was not shown for FIL 100 mg OD+MTX.[36]

Biosimilars

Evidence on the bioequivalence of biosimilars was provided through two identified SLRs, both in line with the available evidence from the previous update.[6 37 38] Tanaka *et al* conducted a systematic review on biosimilar treatment to inform the 2020 update of the Japanese College of Rheumatology clinical practice guidelines for the management of RA. In 20 included RCTs on biosimilars of infliximab (INF), etanercept (ETA) and ADA efficacy was similar when comparing the respective bsDMARDs and boDMARDs (risk ratio for ACR50 at week 12: 1.03 (95% CI 0.93 to 1.13); risk ratio for ACR50 at week 24: 1.04 (95% CI 0.98 to 1.10)).[37] Another SLR investigated the bioequivalence as well as switching from (and to) the biooriginator of ADA bsDMARDs (FKB327, ABP 501, BI695501, GP2017, MSB11022, PF-06410293 and SB5), and did not find differences in efficacy.[38]

Strategy trials

In very early patients with RA, the VEDERA trial (open-label; high RoB) did not show statistical superiority of induction therapy with ETA+MTX compared with a treat-to-target strategy using MTX and glucocorticoids in achieving DAS28-CRP<2.6 at week 48 (62/120, 52% vs 46/120, 38%, p=0.211).[39]

Therapeutic drug monitoring (using INF serum drug levels) did not provide benefits compared with fixed INF dosing (3 mg/kg Q8W) in treatment responses of patients with RA included in the NOR-DRUM trial (open-label; high RoB). DAS28-ESR <2.6 rates for therapeutic drug monitoring vs fixed INF dosing were 55.3% vs 50% (adjusted difference: −8.3 (95% CI −30.4 to 13.8)) in the induction phase (week 0 until week 30) and 76.9% vs 73.7% in the maintenance phase (week 30 – week 52). Rates of sustained disease control without disease worsening were numerically higher for patients randomised to therapeutic drug monitoring (69.2% vs 55%, adjusted difference: 13.6 (95% CI −7.4 to 34.6)).[40 41]

A 1-year, open-label trial (high RoB) randomised 108 patients with DAS28-CRP ≤3.2, but subclinical synovitis on ultrasound, to DMARD treatment intensification or maintenance. Relapse rate of patients with intensified therapy was significantly lower than with maintenance of therapy (5/54 (9.1%) vs 13/54 (24.1%); p=0.039)).[42]

Switching from tsDMARDs to bDMARDs (or vice versa)

In SELECT-COMPARE, patients with IR (<20% improvement from baseline in tender or swollen joint counts (SJCs) between week 14 and 22, or CDAI >10 at week 26) to UPA, ADA or placebo received blinded rescue treatment. Patients receiving placebo (305/651; 47%) or ADA (159/327; 49%) were switched to UPA, while patients receiving UPA were switched to ADA (252/651; 39%), all continuing stable background MTX. Three and 6 months after blinded switching, clinical improvements in patients with IR to UPA receiving ADA were observed (CDAI <10 at week 12: 74/242 (30.6%, as observed) and CDAI <10

Table 4 Efficacy outcomes of head-to-head studies comparing JAK inhibitors to biological DMARDs

Population	Study	RoB	Treatment	n	Primary endpoint	P value versus placebo	Head-to-head comparison	P vs active	ACR 20 (%)	ACR 50 (%)	ACR 70 (%)	DAS28<2.6 (%)	DAS28≤3.2 (%)	CDAI≤2.8 (%)	ACR/ EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
MTX-IR	Fleischmann 2019 (SELECT COMPARE)[34]	Low	Placebo+MTX	651	ACR20 DAS28-CRP <2.6 Week 12	Ref.	ACR50 (S) DAS28-CRP ≤3.2 (S) Week 12	–	237 (36.4)	98 (15)	33 (5)	39 (6)	91 (14)	26 (8)	13 (2)	−0.28	0.92*
			UPA 15 mg OD+MTX	651		<0.001 <0.001		<0.001 <0.001	231 (70.5)	147 (45)	82 (25)	95 (29)	293 (45)	20 (3)	33 (10)	−0.6	0.24*
			ADA 40 mg Q2W+MTX	327		<0.001 <0.001		Ref.	410 (63)	189 (29)	85 (13)	117 (18)	95 (29)	85 (13)	26 (4)	−0.49	0.1*
MTX-IR	Combe 2021 (FINCH 1)[36]	Low	Placebo+MTX	475	ACR 20 Week 12	Ref.	DAS28-CRP≤3.2 (NI) Week 12	–	237 (49.9)	94 (19.8)	32 (6.7)	44 (9.3)	111 (23.4)	13 (2.7)	9 (1.9)	−0.42±0.54	0.25 ± 0.09*
			FIL 200 mg OD+MTX	475		<0.001		<0.001	364 (76.6)	224 (47.2)	124 (26.1)	162 (34.1)	236 (49.7)	59 (12.4)	45 (9.5)	−0.69±0.61	0.08 ± 0.08*
			FIL 100 mg OD+MTX	480		<0.001		0.054	335 (69.8)	175 (36.5)	89 (18.5)	114 (23.8)	186 (38.8)	53 (11)	31 (6.5)	−0.56±0.56	0.12 ± 0.08*
			ADA 40 mg Q2W+MTX	325		<0.001		Ref.	229 (70.5)	114 (35.1)	46 (14.2)	77 (23.7)	141 (43.3)	19 (5.8)	17 (5.2)	−0.61±0.56	0.13 ± 0.09*
bDMARD-IR	Rubbert-Roth 2020 (SELECT CHOICE)[35]	High (Outcome)	UPA 15 mg OD+csDMARD	303	ΔDAS28-CRP Week 12		ΔDAS28-CRP Week 12	NI: <0.001 S: <0.001	229 (75.6)	140 (46.2)	113 (37.3)	91 (30)	151 (49.8)	25 (8.3)	19 (6.3)		
			ABA Q4W+csDMARD	309				Ref.	205 (66.3)	106 (34.3)	82 (26.5)	41 (13.3)	89 (28.8)	8 (2.6)	5 (1.6)		

Results of secondary efficacy outcomes are shown at the timepoint of the primary endpoint.
*Week 24.
ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biological DMARD; CRP, C reactive protein; csDMARD, conventional synthetic disease-modifying antirheumatic drug; DAS, disease activity score; FIL, filgotinib; HAQ, Health Assessment Questionnaire; HCQ, hydroxychloroquine; IR, insufficient response; JAKi, Janus kinase inhibitor; mTSS, modified total Sharp Score; MTX, methotrexate; NI, non-inferiority; OD, once daily; Ref, Reference; S, superiority; UPA, upadacitinib.

at week 24: 95/234 (40.6%, as observed)). After switching from ADA to UPA 58/148 (39.2%, as observed) and 77/146 (52.7%, as observed) patients with IR to ADA achieved CDAI LDA at 3 and 6 months, respectively.[43]

Dose reduction and stopping csDMARDs

Open-label randomisation to half-dose versus stable-dose csDMARD therapy in patients with stable csDMARD therapy (≥1 year) in stable remission (DAS44<1.6 + no swollen joint ≥1 year) in ARCTIC REWIND (high RoB) led to higher flare rates (flare defined as: DAS greater than 1.6, an increase in DAS of 0.6 units or more from the previous visit, and at least two swollen joints on examination of 44 joints) during the 1-year follow-up in the half-dose compared with the stable-dose arm (19/77 (25%) vs 5/78 (6%); risk difference 18% (95% CI 7% to 29%); p=0.003); 85% in the half-dose group vs 92% in the stable-dose had a DAS <1.6 after 1 year, and 47/75 (63%) vs 58/73 (79%), respectively, had no radiographic progression.[44]

An open-label non-inferiority trial (high RoB) investigated discontinuation of csDMARD treatment in 125 patients who had CZP added due to inadequate response to csDMARDs. Patients with a change in DAS28 of ≥1.2 after 3 or 6 months of CZP treatment were randomised 1:1 to continue their treatment or discontinue csDMARDs. After 18 months, maintenance of change from baseline in DAS28 ≥1.2 and/or DAS28 LDA achievement was 72%, and 69% for continuation vs discontinuation of csDMARDs. Although clinically comparable, these results were not non-inferior (absolute risk difference 2.6%; upper limit of 90% CI 19.1%; one-sided p=0.402).[45]

ORAL Shift (low RoB) investigated blinded MTX withdrawal of patients achieving CDAI LDA 24 weeks after initiation of tofacitinib (TOFA) modified-release 11 mg once daily treatment: 24 weeks after randomisation, non-inferiority was demonstrated using DAS-28-ESR (difference 0.3, 95% CI 0.12 to 0.48). Numerically better results were consistently obtained for most secondary outcomes (DAS28, CDAI, SDAI, ACR-EULAR Boolean remission) on LDA and remission in patients continuing concomitant MTX.[46]

bDMARD dose reduction and/or stopping with ongoing csDMARD therapy

In the open-label TapERA trial (high RoB) 66 patients on weekly ETA treatment, with or without background csDMARD therapy, and with sustained DAS28-CRP <2.6 were randomised 1:1 to continue ETA weekly or ETA every other week (Q2W). After 6 months, non-inferiority was not met as 26/34 (76%) in the ETA QW arm vs 19/32 (59%) in the ETA Q2W arm maintained DAS28-CRP<2.6 (difference 17%; (95% CI −5% to 41%); NI margin 10%). Although numerically better results were observed in secondary outcomes for ETA QW, after 12 months 78% of patients could maintain SDAI LDA in the ETA EOW arm.[47]

Patients with IR to DMARDs received TCZ 162 mg s.c. weekly for 24 weeks in the ToSpace open-label RCT and those achieving DAS28-ESR <2.6 (at week 20 and week 24) were randomised to continue TCZ 162 mg weekly or switch to TCZ 162 mg every 2 weeks for 24 weeks. Seventy-three per cent of patients switched to TCZ Q2W could maintain DAS28-ESR <2.6 at week 48 vs 90% continuing weekly TCZ treatment (p=0.004).[48]

RTX dose reduction from 1000 mg to 500 mg or 200 mg in patients who previously responded to RTX 1000 mg was investigated in the REDO trial (low RoB). Patients with ongoing RTX treatment and stable disease activity for 6 months (DAS28-CRP <2.9 or DAS28-CRP <3.5 at screening and judgement of LDA by a rheumatologist) were randomised 1:2:2 to receive one infusion of RTX 1000 mg, 500 mg or 200 mg in a double-blind manner. At 3 months, RTX 500 mg and 200 mg had similar response rates compared with 1000 mg (ΔDAS28-CRP: −0.07 (95% CI −0.41 to 0.27) and 0.03 (95% CI −0.32 to 0.38), respectively). At 6 months only RTX 200 mg showed similar responses compared with RTX 1000 mg (ΔDAS28-CRP: −0.02 (95% CI −0.39 to 0.35)), while RTX 500 mg did not (ΔDAS28-CRP: 0.29 (95% CI −0.08 to 0.65)). Due to the predefined hierarchical testing procedure, non-inferiority of RTX 500 mg and 200 mg vs 1000 mg could not be claimed.[49]

ARCTIC REWIND (conference abstract) also investigated TNFi tapering (half-dosage for 4 months) and discontinuation of TNFi therapy (at month 4) compared with TNFi continuation in patients with stable TNFi therapy (≥1 year) being in stable DAS remission (DAS44<1.6 + 0 SJ) for more than 1 year and concomitant csDMARD therapy. Non-inferiority was not demonstrated as 37.2% (tapering/stopping) vs 95.1% (continuation) maintained DAS44 remission (risk difference: 58% (95% CI 43% to 74%)) after 1 year. In the tapering arm 19% of patients experienced radiographic progression of joint damage, compared with 10% in the TNFi continuation arm.[50]

In PREDICTRA (low RoB), double-blind dose reduction of ADA 40 mg (every 2 weeks) to every 3 weeks was compared with treatment discontinuation of ADA while csDMARDs were continued in patients with stable DAS28(CRP)<2.6: 36% of patients in the ADA 40 mg every 3 weeks (dose reduction) arm experienced a flare by week 40, compared with 45% in the ADA discontinuation arm. Baseline MRI inflammation was not predictive for occurrence of flares.[51]

In the RRRR trial (open-label, high RoB), programmed INF dosing Q8W based on TNF-alpha levels vs fixed INF dosing (3 mg/kg) every 8 weeks for 52 weeks followed by withdrawal of INF if patients achieved SDAI remission, did not increase sustained remission rates 1 year after INF withdrawal (22% vs 24%, p=0.631).[52]

One SLR published by Verhoef *et al* was eligible for inclusion. RCTs investigating TNFi dose reduction or withdrawal published until March 2018 were included. Dose reduction of TNFi in patients achieving sustained LDA or remission was comparable to continuation of the standard dosing in sustaining persistent remission (absolute risk difference: 1% (95% CI −13% to 18%)). TNFi discontinuation without disease activity guidance increased the risk for disease activity worsening and flares when compared with continuation ((absolute risk difference: 14% (95% CI 9% to 18%)). However, disease activity-guided tapering was similar to treatment continuation (absolute risk difference for risk of disease worsening: 9%–95% CI −20% to 5%).[53]

Tapering and stopping of csDMARDs or bDMARDs

The single-blinded TARA trial (high RoB) included patients with TNFi and csDMARD combination therapy and controlled disease activity (DAS44 ≤2.4 and SJC ≤1) for more than three consecutive months. Patients were randomised to gradual tapering (and discontinuation) of csDMARDs in year 1, followed by tapering of TNFi treatment in year 2 or vice versa. After 1 year, flare rates (flare defined as DAS >2.4 and/or SJC>1) were numerically higher in the TNFi tapering group compared with the csDMARD tapering group (33% vs 43%; p=0.17).[54] After 2 years of follow-up, the flare rate was similar between the groups: 61% (95% CI 50% to 71%) in the group who tapered csDMARDs first and 62% (95% CI 52% to 72%; p=0.84) in the

group who tapered TNFi first. Mean disease activity, physical function and radiographic progression were similar.[55] A 2-year cost-effectiveness analysis, although formally not included in this SLR, showed similar costs for both tapering strategies: the total costs were €38 833 (±€39 616) for tapering csDMARDs first, and €39 442 (±€47 271) for tapering the TNF-inhibitor first (p=0.88). Healthcare costs were significantly lower if TNFi were tapered first compared with patients who tapered the csDMARD first (€13 616 ± €9162 vs €22 484 ± €8069). However, absenteeism and presenteeism were higher leading to higher productivity costs (€25 826 ± €46 289 vs €16 349 ± €38 277 for tapering TNFi first vs tapering csDMARDs first).[55 56]

A double-blind RCT (SEAM-RA, low RoB) investigated continuation or withdrawal of either ETA 50 mg weekly or MTX in patients with ETA+MTX combination therapy achieving SDAI≤3.3 after a 24-week open-label run-in phase. After a 48-week double-blind period, half of the patients who stopped MTX and continued ETA monotherapy (49.5%) did not experience a worsening of disease, similar to the treatment continuation group (ETA 50 mg weekly+MTX, 52.9%). More patients who stopped MTX and received ETA monotherapy had sustained SDAI remission compared with patients stopping ETA receiving MTX monotherapy (50/101 (49.5%) vs 29/101 (28.7%): p=0.004). Patients who lost a state of SDAI LDA could recapture SDAI LDA/remission (REM) by the end of the study (LDA: 100%, 92% and 96%; REM: 71%, 73% and 81%; for ETA+MTX combination, ETA mono and MTX mono, respectively).[57]

AVERT-2 (conference abstract) investigated early RA patients who received ABA 125 mg weekly+MTX for 52 weeks and achieved SDAI remission (≤3.3) at week 40 and 52. Patients were then randomised to continuation of ABA+MTX; or ABA dose reduction (125 mg Q2W) + MTX for 24 weeks followed by ABA withdrawal (placebo treatment) + MTX for another 24 weeks; or ABA 125 mg weekly and MTX stopping (without withdrawal). In the combination group, SDAI remission was maintained in about 80% of patients. After 24 weeks, the SDAI remission rates were 78% in the ABA QW+MTX continuation group, 74% for ABA EOW+MTX, and 64% for ABA QW+PBO, respectively. After 52 weeks, SDAI remission was maintained in 48% of patients who were able to withdraw ABA (ie, on MTX monotherapy), and in 57% of those who discontinued MTX (ie, who were receiving ABA QW monotherapy).[58]

The open-label RETRO study (high RoB) randomised patients on csDMARD and bDMARD combination therapy, who had a DAS28-ESR <2.6 for 6 months to either continue their treatment regimen, reduce the of csDMARD and bDMARD by 50%, or completely stop b- and csDMARD treatment. Relapse-free DAS28-ESR remission at 12 months was achieved by 83% of patients in the continuation arm, compared with 57% of patients of patients who had their DMARD treatment reduced by 50%, and 45% who stopped DMARD treatment completely.[59]

Primary results of all trials investigating DMARD tapering and/or stopping are shown in table 5.

DISCUSSION

This SLR was conducted to provide an update of the evolving evidence from 2019 to January 2022 on efficacy of DMARDs in RA.

The efficacy of MTX with short-term glucocorticoids in patients with early RA was confirmed. Response rates of patients receiving MTX combined with other csDMARDs and glucocorticoids were similar in the high-risk treatment arm and superior to MTX without glucocorticoids in the low-risk arm in early RA patients in the CareRA trial.[10] Moreover, treatment induction with conventional therapy was similarly efficacious and did not show major differences when compared with induction therapy with bDMARDs (anti-TNF, anti-CD80/86, anti-IL6R) combined with MTX in early RA patients participating in the NORD-STAR trial.[32 33]

Trials on OKZ (anti-IL6 cytokine) and LEV (anti-IL6 receptor) confirmed the efficacy of inhibiting the IL6-pathway in RA. Both molecules showed superior efficacy compared with placebo.[15–17 19] Further, olokizumab treatment was non-inferior to ADA (both in combination with MTX) in MTX-IR patients.[29 30]

Efficacy of different JAKi was further confirmed in trials investigating baricitinib (JAK1/2i),[22 23] UPA (JAK1/2i) and filgotinib (JAK1i).[24–26] Filgotinib monotherapy treatment induction did not show statistically significant differences compared with MTX monotherapy in early RA patients.[28] Head-to-head trials comparing filgotinib and baricitinibto ADA in MTX-IR patients did not show clinically meaningful differences, especially in outcomes not including acute-phase reactants.[34 36] SELECT-COMPARE was the first trial to provide evidence on good treatment responses to TNFi after IR to JAKi.[43]

Several trials in patients with refractory disease were published. SELECT-CHOICE was the first head-to-head trial comparing a JAKi to a non-TNFi bDMARD (ABA) in patients with previous IR to bDMARDs, demonstrating statistical superiority of UPA vs ABA in change of DAS28. Only minor differences between ABA and UPA were observed if outcomes not including acute phase reactants were used.[35]

Trial data do not yet support the use of biopsy driven treatment allocation as a first trial of treatment allocation based on synovial B-cell counts did not result in superior outcomes in patients allocated to either TCZ or RTX although an exploratory analysis hints that an RNAseq based allocation may improve outcomes.[31] No clear benefit for RA patients was observed when comparing therapeutic drug monitoring of INF to standard dosing.[40 41]

Several trials investigated dose reduction and/or discontinuation of csDMARDs, bDMARDs or both. Although endpoints, populations and tapering strategies differed across most trials, the evidence of the feasibility of tapering was confirmed: many patients could lower their DMARD dosage or discontinue treatment without experiencing worsening of disease activity. The TARA trial showed similar flare rates when comparing gradual disease activity-guided tapering of csDMARD or bDMARDs first (or vice versa) in patients on combination therapy. A cost-effectiveness analysis of the trial showed that tapering either the TNFi or the csDMARD first is equally cost-effective—while medication costs were significantly lower in patients who tapered their TNFi first, indirect costs were higher due to more productivity loss.[55 56] Evidence on recapturing LDA or remission after treatment reinduction was also confirmed in patients who experienced a flare.[57] Overall, disease activity-guided tapering appeared beneficial compared with stopping DMARDs abruptly.[53]

The results of this SLR, together with one SLR on the safety of DMARDs and one on glucocorticoids, informed the taskforce of the 2022 update of the EULAR recommendations for pharmacological management of RA.

Author affiliations
[1]Department of Medicine III, Division of Rheumatology, Medical University of Vienna, Vienna, Austria
[2]CHRC Campus Nova Medical School, Universidade Nova de Lisboa, Lisboa, Portugal
[3]Department of Rheumatology, Leiden University Medical Center, Leiden, The Netherlands

Table 5 Primary outcomes of studies investigating DMARD dose reduction and withdrawal

Study	RoB	Primary outcome	Wk	Treatment arm	n	Result	P value/95% CI
csDMARD dose reduction/stopping							
Pope 2020[45]	High	DAS28 LDA+maintenance of ΔDAS28 ≥1.2 NI margin: 0.6	72	CZP 200 mg Q2W+csDMARD (continuation)	43	72%	UL 90% CI: 19.1%; one-sided 0.402 (NI not met)
				CZP 200 mg Q2W monotherapy (csDMARD stopping)	45	69%	
Cohen 2019 (ORAL Shift)[46]	Low	LSM ΔDAS28-4-ESR NI margin: 0.6	24–48	TOFA 11 mg MR OD+MTX (continuation)	266	0.0	95% CI: 0.12 to 0.48 (NI met)
				TOFA 11 mg MR+PBO (MTX stopping)	264	0.3	
Lillegraven 2021 (ARCTIC REWIND)[44]	High	Flare (DAS44>1.6 + ΔDAS44>0.6 + SJ≥2) NI margin 20%	52	csDMARD continuation	78	6%	RD 19%; 95% CI: 8% to 30% (NI not met)
				csDMARD 50% dosage reduction	78	26%	
bDMARD dose reduction and/or stopping with ongoing csDMARD therapy							
Bertrand 2021 (TapERA)[47]	High	Sustained DAS28-ESR<2.6 NI margin: 10%	24	ETA 50 mg QW (continuation)±csDMARD	34	76%	−5% to 41% (NI not met, margin 10%)
				ETA 50 mg EOW (interval increase) ± csDMARD	32	59%	
Sanmarti 2019 (ToSpace)[48]	High	Sustained DAS28-ESR<2.6	48	TCZ 162 mg QW (continuation)±csDMARD	89	90%	0.004
				TCZ 162 mg Q2W (interval increase) ± csDMARD	90	73%	Reference
Verhoef 2019 (REDO)[49]	Low	ΔDAS28-CRP NI margin: 0.6	24	RTX 1000mg±csDMARD (continuation)	28	−0.35	Reference
				RTX 500 mg (dose reduction) ± csDMARD	58	0.05	0.29 95% CI: −0.08 to 0.65 NI not met
				RTX 200 mg (dose reduction) ± csDMARD	54	−0.38	−0.02 95% CI: −0.39 to 0.35
Lillegraven EULAR 2020 (ARCTIC REWIND)[50]	Conference abstract	Flare (DAS44>1.6 + ΔDAS44>0.6 + SJ≥2) NI margin: 20%	52	TNFi (continuation)+csDMARD	41	4.9%	RD 57.9% to 95% CI: 42.0 to 73.8 NI not met
				TNFi (dose reduction+withdrawal) + csDMARD	43	62.8%	
Emery 2020 (PREDICTRA)[51]	Low	Flare rate (DAS28-ESR≥2.6)	40	ADA 40 mg Q3W (interval increase) ± csDMARDs	102	36%	NR
				PBO (stopping)±csDMARDs	20	45%	NR
Tanaka 2020 (RRRR)[52]	High	Sustained treatment discontinuation	54	INF 3 mg/kg Q8W (stopping)+MTX	167	22%	RD 2.2% 95% CI: -6.6% to 11.0% p=0.631
				INF TDM Q8W (stopping)+MTX	170	24%	
Tapering and stopping of csDMARDs or bDMARDs							
Curtis 2021 (SEAM-RA)[57]	Low	Flare rate (SDAI>3.3 or SDAI score of>11 at any time)	48	ETA 50 mg QW+MTX (combination continuation)	51	52.9%	0.006
				ETA 50 mg QW monotherapy+MTX withdrawal	101	49.5%	0.004
				MTX monotherapy+ETA withdrawal	101	28.7%	Reference
Van Mulligen 2019 (TARA)[54]	High	% of flares (DAS>2.4 and/or SJC>1)	0–52	csDMARD withdrawal	94	33%	24% to 43% Reference
				TNFi withdrawal	95	43%	33% to 53% p=0.17
Van Mulligen 2020 (TARA)[55]	High	% of flares (DAS>2.4 and/or SJC>1)	52–104	csDMARD tapering (first year) + TNFi continuation+tapering (second year)	94	61%	50% to 71% Reference
				TNFi tapering (first yr) + csDMARD continuation+tapering (second yr)	95	62%	52% to 72% p=0.84
Emery ACR 2019 (AVERT-2)[54]	Conference abstract	% of patients with SDAI≤3.3	48	ABA 125 mg QW+MTX (continuation)	50	74%	NR
				ABA 125 mg Q2W+MTX ->PBO (ABA withdrawal) + MTX	50	46%	NR
				ABA 125mg+PBO (MTX withdrawal)	47	57%	NR
Tascilar 2021 (RETRO)[59]	High	Relapse-free remission (DAS28-ESR<2.6)	52	Continue DMARDs	93	81%	Reference
				Taper DMARDs	93	57%	HR 3.02 (95% CI: 1.69 to 5.4)
				Stop DMARDs	96	43%	HR 4.34 (95% CI: 2.48 to 7.6)

ABA, abatacept; ADA, adalimumab; bDMARD, biological DMARD; csDMARD, conventional synthetic disease-modifying antirheumatic drug; CZP, certolizumab-pegol; DAS, Disease Activity Score; ESR, erythrocyte sedimentation rate; ETA, etanercept; INF, infliximab; LSM, least squares mean; MR, modified-release; NI, non-inferiority; NR, not reported; OD, once daily; PBO, placebo; QW, every week; Q2W, every 2 weeks; RD, risk difference; RD, risk difference; RoB, risk of bias; RTX, rituximab; SDAI, Simplified Disease Activity Index; SJC, swollen joint count; TCZ, tocilizumab; TDM, therapeutic drug monitoring; TNFi, tumour necrosis factor alpha inhibitor; TOFA, tofacitinib; UL, upper confidence limit; Δ, change from baseline.

[4]Department of Rheumatology, University of Milan, Milan, Italy
[5]NIHR Southampton Clinical Research Facility, University Hospital Southampton NHS Foundation Trust, Southampton, UK
[6]Department of Rheumatology, University Hospitals Leuven and Skeletal Biology and Engineering Research Centre, KU Leuven, Leuven, Belgium
[7]Patient Research Partner Network, European Alliance of Associations for Rheumatology, Zurich, Switzerland
[8]Schulich School of Medicine, University of Western Ontario, London, Ontario, Canada
[9]Division of Rheumatology, Department of Internal Medicine, Keio University School of Medicine, Shinjuku-ku, Japan
[10]Centre for Epidemiology Versus Arthritis, The University of Manchester and NIHR Manchester Biomedical Research Centre, Manchester University NHS Trust, Manchester, UK
[11]School of Public Health, Oregon Health & Science University, Portland, Oregon, USA
[12]Section for Outcomes Research, Centre for Medical Statistics, Informatics, and Intelligent Systems, Medical University of Vienna, Vienna, Austria
[13]Ludwig Boltzmann Institute for Arthritis and Rehabilitation, Vienna, Austria
[14]Walaeus Library, Leiden University Medical Center, Leiden, The Netherlands
[15]Amsterdam Rheumatology Center, AMC, Amsterdam, The Netherlands
[16]Rheumatology, Zuyderland Medical Center, Heerlen, The Netherlands

Twitter Alexandre Sepriano @AlexSepriano and Janet E Pope @Janetbirdope

Contributors All authors contributed and finally approved the current manuscript. AK accepts full responsibility for the work and the conduct of the study, had access to the data, and controlled the decision to publish together with the senior author (RL) and the convenor of the taskforce (JSS).

Funding The European Alliance of Associations for Rheumatology.

Competing interests AK: Speakers bureau, Consultancy: AbbVie, Amgen, Bristol-Myers Squibb, Eli Lilly, Gilead, Janssen, Merck Sharp and Dohme, Novartis, UCB and Pfizer. AS: received speaker/consulting fees from UCB, Novartis and Lilly. SAB: received an ASPIRE grant from Pfizer. JSS received grants from Abbvie, Astra-Zeneca, Janssen, Lilly, Novartis, Roche and honoraria from Abbvie, Amgen, Astra-Zeneca, Astro, BMS, Celgene, Celltrion, Chugai, Gilead, ILTOO, Janssen, Lilly, MSD, Novartis-Sandoz, Pfizer, Roche, Samsung, Sanofi, UCB. DvdH: received consulting fees from AbbVie, Amgen, Astellas, AstraZeneca, BMS, Boehringer Ingelheim, Celgene, Daiichi, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Regeneron, Roche, Sanofi, Takeda, UCB Pharma and is Director of Imaging Rheumatology bv. RC received consulting fees from Abbvie, BMS, Amgen, Celltrion, Eli-Lilly, Fresenius-Kabi, Galapagos, Janssen, MSD, Novartis, Pfizer, UCB Pharma. CJE has received fees from Abbvie, Astra Zeneca, BMS, Celgene, Celltrion, Fresenius Kabi, Gilead, Galapagos, GSK, Janssen, Eli Lilly, Pfizer, Roche, Sanofi for advisory boards, speakers bureau and research support. PV received consulting fees from Abbvie, BMS, Celltrion, Eli Lilly, Galapagos, Gilead, Nordic Pharma, Pfizer, Sidekick Health, UCB and speaker's fees from Eli Lilly, Galapagos, MSD and Roularta and holds the Pfizer Chair Early RA Management at KU Leuven. JEP received research grants from AbbVie, Frensenius Kabi, Mallinckrodt Pharmaceuticals, Pfizer, Seattle Genetics and consulting fees from AbbVie, Amgen, Astra Zeneca, BI, BMS, Celltrion, EMERALD, Frensenius Kabi, Galapagos, GSK, Janssen, Lilly, Mallinckrodt Pharmaceuticals, Medexus, Mitsubishi Tanabe Pharma, Novartis, Pfizer, Roche, Sandoz, Samsung, Sobi, Viatris. TT received grants from AbbVie, Asahikasei, AYUMI, Chugai, Eli Lilly Japan, Mitsubishi-Tanabe, Ono, and honoraria from AbbVie, Asahikasei, Astellas, Bristol-Myers Squibb, Chugai., Daiichi Sankyo., Eisai, Eli Lilly Japan, Gilead Sciences, Janssen K.K., Mitsubishi-Tanabe, Pfizer Japan. KLH received speaker's fees from Abbvie and research grants from Pfizer and BMS. KLW received research grants from Pfizer, BMS, and GSK, and scientific consulting fees from UCB, Abbvie, BMS, Galapagos, Gilead, Lilly, GSK, Roche, and Novartis. DA received grants, speaker fees, or consultancy fees from Abbvie, Amgen, Lilly, Janssen, Merck, Novartis, Pfizer, Roche, Sandoz, Sanofi, and Sobi. TAS has received grant/research support from AbbVie and Roche, has been a consultant for AbbVie and Sanofi Genzyme, and has been a paid speaker for AbbVie, Novartis, Roche, Sanofi, and Takeda. RBML: received consulting fees from AbbVie, BMS, Celgene, Eli-Lilly, Galapagos, Gilead, Glaxo-Smith-Kline, Janssen, Merck, Novartis, Pfizer, Roche, UCB and is Director of Rheumatology Consultancy bv

Patient and public involvement Patients and/or the public were involved in the design, or conduct, or reporting, or dissemination plans of this research. Refer to the Methods section for further details.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available in a public, open access repository. All data relevant to the study are included in the article or uploaded as online supplemental information. Detailed data of all included studies are also available in the public domain.

ORCID iDs
Andreas Kerschbaumer http://orcid.org/0000-0002-6685-8873
Alexandre Sepriano http://orcid.org/0000-0003-1954-0229
Sytske Anne Bergstra http://orcid.org/0000-0002-7136-5248
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Patrick Verschueren http://orcid.org/0000-0002-0340-3580
Savia de Souza http://orcid.org/0000-0003-4953-3257
Janet E Pope http://orcid.org/0000-0003-1479-5302
Tsutomu Takeuchi http://orcid.org/0000-0003-1111-8218
Kimme L Hyrich http://orcid.org/0000-0001-8242-9262
Kevin L Winthrop http://orcid.org/0000-0002-3892-6947
Daniel Aletaha http://orcid.org/0000-0003-2108-0030
Tanja A Stamm http://orcid.org/0000-0003-3073-7284
Jan W Schoones http://orcid.org/0000-0003-1120-4781
Robert B M Landewé http://orcid.org/0000-0002-0577-6620

REFERENCES

1 Smolen JS, Aletaha D, Barton A, *et al*. Rheumatoid arthritis. *Nat Rev Dis Primers* 2018;4:18001.
2 Smolen JS, Landewé RBM, Bijlsma JWJ, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
3 Smolen JS, Landewé RBM, Bergstra SA, *et al*. 2nd Revision eular recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2022 update. *Ann Rheum Dis* 2022;0:1–17.
4 Sepriano A, Kerschbaumer A, Bergstra SA. Safety of synthetic and biological DMARDs: a systematic literature review Informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2023;82:107–18.
5 Bergstra SA, Sepriano A, Kerschbaumer A. Efficacy, duration of use and safety of glucocorticoids: a systematic literature review Informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2023;82:81–4.
6 Kerschbaumer A, Sepriano A, Smolen JS, *et al*. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research Informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020;79:744–59.
7 van der Heijde D, Aletaha D, Carmona L, *et al*. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2015;74:8–13.
8 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League against rheumatism collaborative initiative. *Arthritis Rheum* 2010;62:2569–81.
9 Felson DT, Anderson JJ, Boers M, *et al*. American College of rheumatology. Preliminary definition of improvement in rheumatoid arthritis. *Arthritis Rheum* 1995;38:727–35.
10 Stouten V, Westhovens R, Pazmino S, *et al*. Effectiveness of different combinations of DMARDs and glucocorticoid bridging in early rheumatoid arthritis: two-year results of CareRA. *Rheumatology* 2019;58:2284–94.
11 Belani PJ, Kavadichanda CG, Negi VS. Comparison between leflunomide and sulfasalazine based triple therapy in methotrexate refractory rheumatoid arthritis: an open-label, non-inferiority randomized controlled trial. *Rheumatol Int* 2022;42:771–82.
12 Jain S, Dhir V, Aggarwal A, *et al*. Comparison of two dose escalation strategies of methotrexate in active rheumatoid arthritis: a multicentre, parallel group, randomised controlled trial. *Ann Rheum Dis* 2021;80:1376–84.
13 Liang T-H, Lee C-S, Lee S-S, *et al*. Efficacy and safety of Opinercept tumor necrosis factor inhibitor therapy for Drug-Refractory rheumatoid arthritis: a randomized clinical trial. *Arch Rheumatol* 2020;35:170–9.
14 Behrens F, Koehm M, Rossmanith T, *et al*. Rituximab plus leflunomide in rheumatoid arthritis: a randomized, placebo-controlled, investigator-initiated clinical trial (AMARA study). *Rheumatology* 2021;60:5318–28.
15 Nasonov E, Fatenejad S, Feist E, *et al*. Olokizumab, a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study. *Ann Rheum Dis* 2022;81:469–79.
16 Efficacy and Safety of Olokizumab in a Phase III Trial of Patients with Moderately to Severely Active Rheumatoid Arthritis Inadequately Controlled by TNF-α Inhibitor Therapy - ACR Meeting Abstracts. Available: https://acrabstracts.org/abstract/efficacy-and-safety-of-olokizumab-in-a-phase-iii-trial-of-patients-with-moderately-to-severely-active-rheumatoid-arthritis-inadequately-controlled-by-tnf-%CE%B1-inhibitor-therapy/ [Accessed 9 Mar 2022].
17 Nasonov E, Fatenejad S, Feist E, Feist E, Grishin S, *et al*. Olokizumab, a monoclonal antibody against interleukin 6, in combination with methotrexate in patients with rheumatoid arthritis inadequately controlled by methotrexate: efficacy and safety results of a randomised controlled phase III study. *Ann Rheum Dis* 2022;81:469–79.
18 Kameda H, Wada K, Takahashi Y, *et al*. Sarilumab monotherapy or in combination with non-methotrexate disease-modifying antirheumatic drugs in active rheumatoid arthritis: a Japan phase 3 trial (HARUKA). *Mod Rheumatol* 2020;30:239–48.
19 Mazurov V, Korolev M, Kundzer A, *et al*. POS0624 efficacy and safety of levilimab in combination with methotrexate in subjects with active rheumatoid arthritis: phase iii, double-blind, placebo-controlled, randomized trial. *Ann Rheum Dis* 2021;80:550–1.
20 Takeuchi T, Tanaka Y, Soen S, *et al*. Effects of the anti-RANKL antibody denosumab on joint structural damage in patients with rheumatoid arthritis treated with conventional synthetic disease-modifying antirheumatic drugs (desirable study): a randomised, double-blind, placebo-controlled phase 3 trial. *Ann Rheum Dis* 2019;78:899–907.
21 So H, Cheng IT, Lau S-L, *et al*. Effects of RANKL inhibition on promoting healing of bone erosion in rheumatoid arthritis using HR-pQCT: a 2-year, randomised, double-blind, placebo-controlled trial. *Ann Rheum Dis* 2021;80:981–8.

22 Li Z, Hu J, Bao C, *et al*. Baricitinib in patients with rheumatoid arthritis with inadequate response to methotrexate: results from a phase 3 study. *Clin Exp Rheumatol* 2020;38:732–41.
23 Yang Y, Xu J, Xu J, *et al*. Patient-reported outcomes from a randomized, double-blind, placebo controlled, phase III study of baricitinib *versus* placebo in patients with moderately to severely active rheumatoid arthritis and an inadequate response to methotrexate therapy: results from the RA-BALANCE study. *Ther Adv Musculoskelet Dis* 2021;13:1759720X211006964.
24 van Vollenhoven R, Takeuchi T, Pangan AL, *et al*. Efficacy and safety of Upadacitinib monotherapy in Methotrexate-Naive patients with Moderately-to-Severely active rheumatoid arthritis (SELECT-EARLY): a multicenter, Multi-Country, randomized, double-blind, active Comparator-Controlled trial. *Arthritis Rheumatol* 2020;72:1607–20.
25 Strand V, Tundia N, Wells A, *et al*. Upadacitinib monotherapy improves patient-reported outcomes in rheumatoid arthritis: results from SELECT-EARLY and SELECT-MONOTHERAPY. *Rheumatology* 2021;60:3209–21.
26 Kameda H, Takeuchi T, Yamaoka K, *et al*. Efficacy and safety of upadacitinib in Japanese patients with rheumatoid arthritis (SELECT-SUNRISE): a placebo-controlled phase IIb/III study. *Rheumatology* 2020;59:3303–13.
27 Genovese MC, Kalunian K, Gottenberg J-E, *et al*. Effect of Filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy: the finch 2 randomized clinical trial. *JAMA* 2019;322:315–25.
28 Westhovens R, Rigby WFC, van der Heijde D, *et al*. Filgotinib in combination with methotrexate or as monotherapy versus methotrexate monotherapy in patients with active rheumatoid arthritis and limited or no prior exposure to methotrexate: the phase 3, randomised controlled finch 3 trial. *Ann Rheum Dis* 2021;80:727–38.
29 Efficacy and Safety of Olokizumab in a Phase III Trial of Patients with Moderately to Severely Active Rheumatoid Arthritis Inadequately Controlled by Methotrexate – Placebo and Active Controlled Study - ACR Meeting Abstracts. Available: https://acrabstracts.org/abstract/efficacy-and-safety-of-olokizumab-in-a-phase-iii-trial-of-patients-with-moderately-to-severely-active-rheumatoid-arthritis-inadequately-controlled-by-methotrexate-placebo-and-active-controll/ [Accessed 10 Mar2022].
30 Smolen JS, Feist E, Fatenejad S, *et al*. Olokizumab versus placebo or adalimumab in rheumatoid arthritis. *N Engl J Med* 2022;387:715–26.
31 Humby F, Durez P, Buch MH, *et al*. Rituximab versus tocilizumab in anti-TNF inadequate Responder patients with rheumatoid arthritis (R4RA): 16-week outcomes of a stratified, biopsy-driven, multicentre, open-label, phase 4 randomised controlled trial. *Lancet* 2021;397:305–17.
32 Hetland ML, Haavardsholm EA, Rudin A, *et al*. Active conventional treatment and three different biological treatments in early rheumatoid arthritis: phase IV investigator initiated, randomised, observer blinded clinical trial. *BMJ* 2020;371:m4328.
33 An Investigator-initiated Multicenter Randomized Study in Early Rheumatoid Arthritis of Active Conventional Therapy versus Three Biological Treatments: 48 Week Clinical and Radiographic Results of the NORD-STAR Trial - ACR Meeting Abstracts. Available: https://acrabstracts.org/abstract/an-investigator-initiated-multicenter-randomized-study-in-early-rheumatoid-arthritis-of-active-conventional-therapy-versus-three-biological-treatments-48-week-clinical-and-radiographic-results-of-the/ [Accessed 10 Mar2022].
34 Fleischmann R, Pangan AL, Song I-H, *et al*. Upadacitinib versus placebo or adalimumab in patients with rheumatoid arthritis and an inadequate response to methotrexate: results of a phase III, double-blind, randomized controlled trial. *Arthritis Rheumatol* 2019;71:1788–800.
35 Rubbert-Roth A, Enejosa J, Pangan AL, *et al*. Trial of upadacitinib or abatacept in rheumatoid arthritis. *N Engl J Med* 2020;383:1511–21.
36 Combe B, Kivitz A, Tanaka Y, *et al*. Filgotinib versus placebo or adalimumab in patients with rheumatoid arthritis and inadequate response to methotrexate: a phase III randomised clinical trial. *Ann Rheum Dis* 2021;80:848–58.
37 Tanaka E, Kawahito Y, Kohno M, *et al*. Systematic review and meta-analysis of biosimilar for the treatment of rheumatoid arthritis Informing the 2020 update of the Japan College of rheumatology clinical practice guidelines for the management of rheumatoid arthritis. *Mod Rheumatol* 2022;32:74–86.
38 Huizinga TWJ, Torii Y, Muniz R. Adalimumab biosimilars in the treatment of rheumatoid arthritis: a systematic review of the evidence for Biosimilarity. *Rheumatol Ther* 2021;8:41–61.
39 Emery P, Horton S, Dumitru RB, *et al*. Pragmatic randomised controlled trial of very early etanercept and MTX versus MTX with delayed etanercept in RA: the VEDERA trial. *Ann Rheum Dis* 2020;79:464–71.
40 Syversen SW, Goll GL, Jørgensen KK, *et al*. Effect of therapeutic drug monitoring vs standard therapy during infliximab induction on disease remission in patients with chronic immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA* 2021;325:1744–54.
41 Syversen SW, Jørgensen KK, Goll GL, *et al*. Effect of therapeutic drug monitoring vs standard therapy during maintenance infliximab therapy on disease control in patients with immune-mediated inflammatory diseases: a randomized clinical trial. *JAMA* 2021;326:2375.
42 Zhao J, Wang Y, Geng Y, *et al*. Intensive therapy alleviates subclinical synovitis on ultrasound and disease activity and reduces flare in rheumatoid arthritis patients who have achieved clinical target - a randomized controlled trial. *Semin Arthritis Rheum* 2020;50:673–9.
43 Fleischmann RM, Genovese MC, Enejosa JV, *et al*. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis* 2019;78:1454–62.
44 Lillegraven S, Paulshus Sundlisæter N, Aga A-B, *et al*. Effect of half-dose vs Stable-Dose conventional synthetic disease-modifying antirheumatic drugs on disease flares in patients with rheumatoid arthritis in remission: the Arctic REWIND randomized clinical trial. *JAMA* 2021;325:1755–64.
45 Pope J, Rampakakis E, Vaillancourt J, *et al*. An open-label randomized controlled trial of DMARD withdrawal in RA patients achieving therapeutic response with certolizumab pegol combined with DMARDs. *Rheumatology* 2020;59:1522–8.
46 Cohen SB, Pope J, Haraoui B, *et al*. Methotrexate withdrawal in patients with rheumatoid arthritis who achieve low disease activity with tofacitinib modified-release 11 Mg once daily plus methotrexate (oral shift): a randomised, phase 3b/4, non-inferiority trial. *Lancet Rheumatol* 2019;1:e23–34.
47 Bertrand D, Stouten V, De Cock D, *et al*. Tapering of etanercept is feasible in patients with rheumatoid arthritis in sustained remission: a pragmatic randomized controlled trial. *Scand J Rheumatol* 2021:1–11.
48 Sanmarti R, Veale DJ, Martin-Mola E, *et al*. Reducing or maintaining the dose of subcutaneous tocilizumab in patients with rheumatoid arthritis in clinical remission: a randomized, open-label trial. *Arthritis Rheumatol* 2019;71:1616–25.
49 Verhoef LM, den Broeder N, Thurlings RM, *et al*. Ultra-Low doses of rituximab for continued treatment of rheumatoid arthritis (REDO study): a randomised controlled non-inferiority trial. *Lancet Rheumatol* 2019;1:e145–53.
50 Lillegraven S, Sundlisæter NP, Aga AB, *et al*. OP0019 Stable versus tapered and withdrawn treatment with tumor necrosis factor inhibitor in rheumatoid arthritis remission (arctic rewind): A randomised, open-label, phase 4, non-inferiority trial. *Ann Rheum Dis* 2020;79:14–15.
51 Emery P, Burmester GR, Naredo E, *et al*. Adalimumab dose tapering in patients with rheumatoid arthritis who are in long-standing clinical remission: results of the phase IV PREDICTRA study. *Ann Rheum Dis* 2020;79:1023–30.
52 Tanaka Y, Oba K, Koike T, *et al*. Sustained discontinuation of infliximab with a raising-dose strategy after obtaining remission in patients with rheumatoid arthritis: the RRRR study, a randomised controlled trial. *Ann Rheum Dis* 2020;79:94–102.
53 Verhoef LM, van den Bemt BJ, van der Maas A, *et al*. Down-titration and discontinuation strategies of tumour necrosis factor-blocking agents for rheumatoid arthritis in patients with low disease activity. *Cochrane Database Syst Rev* 2019;5:CD010455.
54 van Mulligen E, de Jong PHP, Kuijper TM, *et al*. Gradual tapering TNF inhibitors versus conventional synthetic DMARDs after achieving controlled disease in patients with rheumatoid arthritis: first-year results of the randomised controlled tara study. *Ann Rheum Dis* 2019;78:746–53.
55 van Mulligen E, Weel AE, Hazes JM, *et al*. Tapering towards DMARD-free remission in established rheumatoid arthritis: 2-year results of the tara trial. *Ann Rheum Dis* 2020;79:1174–81.
56 van Mulligen E, Weel AE, Kuijper TM, *et al*. Two-Year cost effectiveness between two gradual tapering strategies in rheumatoid arthritis: cost-utility analysis of the tara trial. *Ann Rheum Dis* 2020;79:1550–6.
57 Curtis JR, Emery P, Karis E, *et al*. Etanercept or methotrexate withdrawal in rheumatoid arthritis patients in sustained remission. *Arthritis Rheumatol* 2021;73:759–68.
58 Maintenance of Remission Following Dose De-Escalation of Abatacept in Early, MTX-Naïve, ACPA-Positive Patients with RA: Results from a Randomized Phase IIIb Study - ACR Meeting Abstracts. Available: https://acrabstracts.org/abstract/maintenance-of-remission-following-dose-de-escalation-of-abatacept-in-early-mtx-naive-acpa-positive-patients-with-ra-results-from-a-randomized-phase-iiib-study/ [Accessed 14 Mar 2022].
59 Tascilar K, Hagen M, Kleyer A, *et al*. Treatment tapering and stopping in patients with rheumatoid arthritis in stable remission (retro): a multicentre, randomised, controlled, open-label, phase 3 trial. *Lancet Rheumatol* 2021;3:e767–77.