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Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis

Andreas Kerschbaumer ,[1] Alexandre Sepriano ,[2,3] Josef S Smolen,[1] Désirée van der Heijde ,[2] Maxime Dougados,[4] Ronald van Vollenhoven,[5] Iain B McInnes,[6] Johannes W J Bijlsma,[7] Gerd R Burmester,[8] Maarten de Wit ,[9] Louise Falzon,[10] Robert Landewé[5]

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For numbered affiliations see end of article.

Correspondence to
Dr Andreas Kerschbaumer, Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria; andreas.kerschbaumer@meduniwien.ac.at

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ABSTRACT

Objectives To inform the 2019 update of the European League against Rheumatism (EULAR) recommendations for the management of rheumatoid arthritis (RA).

Methods A systematic literature research (SLR) to investigate the efficacy of any disease-modifying antirheumatic drug (DMARD) (conventional synthetic (cs)DMARD, biological (b) and biosimilar DMARD, targeted synthetic (ts)DMARD) or glucocorticoid (GC) therapy in patients with RA was done by searching MEDLINE, Embase and the Cochrane Library for articles published between 2016 and 8 March 2019.

Results 234 abstracts were selected for detailed assessment, with 136 finally included. They comprised the efficacy of bDMARDs versus placebo or other bDMARDs, efficacy of Janus kinase (JAK) inhibitors (JAKi) across different patient populations and head-to-head of different bDMARDs versus JAKi or other bDMARDs. Switching of bDMARDs to other bDMARDs or tsDMARDs, strategic trials and tapering studies of bDMARDs, csDMARDs and JAKi were assessed. The drugs evaluated included abatacept, adalimumab, ABT-122, baricitinib, certolizumab pegol, SBI-087, CNTO6785, decernotinib, etanercept, filgotinib, golimumab, GCs, GS-9876, guselkumab, hydroxychloroquine, infliximab, leflunomide, mavrilimumab, methotrexate, olokizumab, otilimab, peficitinib, rituximab, sarilumab, salazopyrine, secukinumab, sirukumab, tacrolimus, tocilizumab, tofacitinib, tregalizumab, upadacitinib, ustekinumab and vobarilizumab. The efficacy of many bDMARDs and tsDMARDs was shown. Switching to another tumour necrosis factor inhibitor (TNFi) or non-TNFi bDMARDs after TNFi treatment failure is efficacious. Tapering of DMARDs is possible in patients achieving long-standing stringent clinical remission; in patients with residual disease activity (including patients in LDA) the risk of flares is increased during the tapering. Biosimilars are non-inferior to their reference products.

Conclusion This SLR informed the task force regarding the evidence base of various therapeutic regimen for the development of the update of EULAR's RA management recommendation.

Key messages

What is already known about this subject?

- Since the 2016 update of the recommendations for the management of rheumatoid arthritis (RA), the body of evidence has grown vividly. Therefore, this systematic literature research (SLR) was performed to inform the 2019 European League against Rheumatism (EULAR) task force with the summarised evidence on efficacy of conventional and targeted synthetic disease-modifying antirheumatic drugs (DMARDs), biological DMARDs and glucocorticoids.

What does this study add?

- Trials comparing biological DMARDs have shown similar efficacy, regardless of the underlying mode of action.
- Head-to-head trials between Janus kinase (JAK) inhibitors (JAKi) and tumour necrosis factor inhibitor inhibitors did not reveal clinically important differences in efficacy.
- Drug tapering of DMARDs, including JAKi is possible, especially in patients achieving stable remission.
- Treating patients to target using MRI-defined remission does not lead to better outcomes when compared with a conventional clinical treat-to-target strategy.

How might this impact on clinical practice or future developments?

- This SLR, alongside with the safety SLR, provided the 2019 EULAR RA management recommendations task force with the emerged evidence since 2016.

INTRODUCTION

To provide the task force on the 2019 update of the European League against Rheumatism (EULAR) recommendations for the pharmacological management of rheumatoid arthritis (RA) with all available evidence that had emerged since the last update, systematic literature researches (SLRs)

were performed. In 2016, three SLRs were conducted assessing efficacy of biological disease-modifying antirheumatic drugs (bDMARDs),[1] efficacy of glucocorticoids (GCs), conventional synthetic (cs) and targeted synthetic (ts) DMARDs,[2] and safety of pharmacological treatments in RA.[3] The 2019 update was based on two SLRs, one on safety and the present one on efficacy of pharmacological interventions in RA.

The body of evidence has grown vividly in the last 3 years, especially regarding tsDMARDs inhibiting Janus Kinase inhibitor (JAKi), novel bDMARDs targeting new as well as established pathways and trials comparing bDMARDs to other bDMARDs or tsDMARDs, providing important information on the comparative efficacy of these compounds.[4] Further, studies on tapering and stopping treatment broaden the information base for rheumatologists and patients on the question of possible disease flares after tapering or cessation of drugs, once patients have reached the clinical target. Strategic studies on how to optimally treat patients to target,[5] using clinical and imaging targets have also answered important research questions.[6] Finally, a large number of trials compared the efficacy and safety of biosimilars (bs) DMARDs with those of their bio-originators (bo), including switching between boDMARD and respective bsDMARDs.

This SLR was conducted to update the evidence on efficacy of pharmacological interventions in RA. This involves the evidence accrued since the last update of the treatment recommendations for RA, published by EULAR in 2016.[7] Another SLR focusing on safety of pharmacological treatments in RA is published separately.[8]

METHODS

The EULAR updated standard operating procedures were followed,[9] and an SLR protocol was developed and approved by the steering committee.

Studies eligible for inclusion in this SLR were randomised, controlled, double-blind trials investigating csDMARDs, bDMARDs (bo and bsDMARDs), tsDMARDs or GCs in adult patients with RA classified according to the 2010 American College of Rheumatology (ACR)/EULAR or the ACR 1987 criteria. This SLR was considered to further update the available evidence since the previous SLRs, therefore, articles published between 1 January 2016 and 8 March 2019 with no language restriction were searched. Additionally, studies presented as conference abstracts at the EULAR and ACR annual meetings from 2016 to 2018 were also eligible for inclusion. References of original articles published on submission of the manuscript (after the data cut), but with respective conference abstracts included before, were included in the reference list.

The initial literature search was conducted by an experienced librarian (LF) using Medline, Embase, The Cochrane CENTRAL Register of Controlled Trials (Central) and the EULAR/ACR abstract archives as information sources. The detailed search strategy for each database is shown in the online supplementary tables S1.1–S1.6.

The study selection process was conducted independently by two investigators (AK and AS) and discussed until agreement was achieved. A senior methodologist (RL) was consulted in the case of uncertainties. After the initial title and abstract screening for identification of reports of potential interest, a detailed assessment for eligibility of preselected articles was done. Data of eligible studies were extracted based on standardised methods using pivotal forms. Variables of interest were predefined in the review protocol, including signs and symptoms of arthritis and commonly used composite measures, respective core set variables, physical function, patient-reported outcomes and measures of structural damage.

Sixteen research questions were defined according to the Patient population, Intervention, Control, Outcome (PICO) principle with the help of the steering committee. All typical RA study populations were included, methotrexate (MTX)-naïve or generally DMARD-naïve patients, csDMARD insufficient responders (IR), bDMARD-IR or tsDMARD-IR. Adequately defined control groups receiving either placebo or active treatment were mandatory for inclusion in this analysis. These involved the efficacy of bDMARDs with or without csDMARD combination, head-to-head comparisons of bDMARDs and switching between different bDMARDs, tapering and stopping bDMARDs, as well as the efficacy of tsDMARDs and the respective head-to-head comparison to bDMARDs. Other research questions involved biosimilars, switching between bsDMARDs and respective boDMARD, the efficacy of csDMARDs and the efficacy of GC (in combination with csDMARDs). All interventions of interest are shown in online supplementary table S1.7. A detailed description of the PICOs is shown in online supplementary table S1.8.

Risk of bias (RoB) in individual studies was assessed at study level using the Cochrane Collaborations Risk of Bias tool for randomised controlled trials (RCTs). The assessment was done independently by two investigators (AK and AS). Differing assessments were discussed until consensus was reached.

Due to the heterogeneity of the available studies, no meta-analysis was performed, and results will be reported narratively. Descriptive forest plots were created using RevMan V.5.3 (Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

The study selection process involved 15 037 references. After deduplication, 7876 remained for title and abstract screening, of which 234 were selected for full article review and 136 articles finally included. A detailed flow chart is depicted in figure 1. Details of all studies included are shown in online supplementary table S2.1.

RoB was considered as low for most RCTs included. RCTs were rated as having an unclear RoB most commonly due to insufficient reporting of random sequence generation and/or allocation concealment. Due to their unblinded nature, open-label studies were considered as having a high RoB. Trials reported in conference abstracts were not assessed regarding RoB due to limited information. Results of the RoB assessment are shown in online supplementary table S2.2.

Characteristics of each trial for which data were extracted (study size, PICOs), baseline characteristics (online supplementary table S2.3–S2.12), results of studies and summary data for each intervention group (online supplementary table S3.1–S3.13) as well as the respective citations (section 4 in the online supplementary appendix) are shown in the supplement. A summary of included trials and therapies investigated is shown in table 1.

Efficacy of csDMARDs (or combination of csDMARDs) versus other csDMARDs

Five trials (all with unclear or high RoB) investigated the efficacy of csDMARDs alone or in combination versus other csDMARDs (see table 1). Baseline characteristics and detailed results are shown in online supplementary table S2.12 and online supplementary table S3.13, respectively.

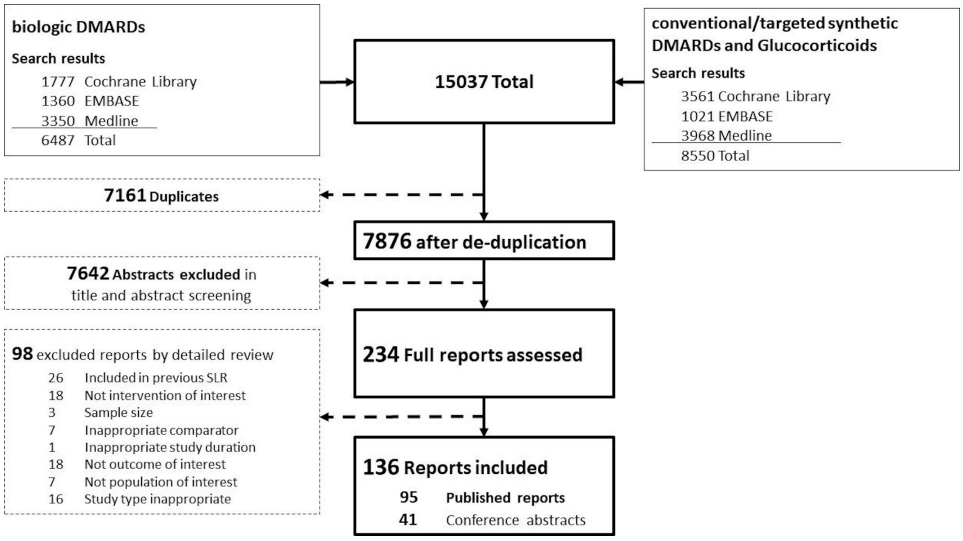

Figure 1 PRISMA flow chart describing the study selection process. DMARDs, disease-modifying antirheumatic drugs; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature research.

The open-label CareRA trial (high RoB) stratified very early, csDMARD naive patients based on their risk factors (presence of erosions, disease activity, rheumatoid factor and anticitrullinated protein antibodies) into high and low risk.[10] High-risk patients were randomised to three different csDMARD regimens (Combination therapy for early Rheumatoid Arthritis (COBRA) classic: methotrexate (MTX)+sulfasalazine (SSZ) + prednisone 60 mg step-down vs COBRA Slim: MTX+prednisone 30 mg step-down vs COBRA Avant Garde: MTX+leflunomide (LEF) + prednisone 60 mg step-down). Low-risk patients were either randomised to MTX tight-step up or COBRA Slim). The treatment arms investigated in high-risk patients showed comparable efficacy in achieving the primary endpoint (Disease Activity Score of 28 joints (DAS28)-C reactive protein (CRP) <2.6) at week 52 for COBRA Classic (64.3%, 63/98).

COBRA Slim (60.2%, 59/98) and COBRA Avant Garde (62.4%, 58/93, p=0.840). In low-risk patients, COBRA-Slim and MTX-tight step up also showed comparable efficacy at week 52 (67.4%, 29/43 vs 57.4%, 27/47, p=0.329). However, the area under the curves for mean DAS28-CRP change from baseline as well as time-to-remission were favouring MTX plus prednisone combination therapy. Radiographic damage was minimal and comparable across all treatment arms. Sustained and comparable efficacy was shown after 2 years of treatment in high-risk patients.[11]

Investigation of LEF plus SSZ plus hydroxychloroquine (HCQ) triple therapy compared with MTX+SSZ+ HCQ triple therapy or LEF alone in a 48-week double-blind RCT was terminated early due to gastrointestinal complications in the LEF +SSZ+ HCQ arm. Conventional triple therapy (MTX+SSZ+ HCQ) was superior to LEF +SSZ+ HCQ and LEF alone (ACR20: 87% vs 46%, p<0.01, 87% vs 36%, p<0.001, respectively), with no apparent efficacy benefit of the LEF triple therapy compared with LEF alone at week 48 (ACR20: 46% vs 36%, p>0.05).[12]

Efficacy of bDMARDs, alone or in combination with csDMARDs, in csDMARD and bDMARD-IR patients with (established) RA

Trials comparing bDMARDs to placebo with or without csDMARD background therapy (21 articles/abstracts, 7 with low RoB) showed effective reduction of signs and symptoms for several different modes of action (see table 1), including molecules targeting B-cells (SBI-087, BCD-020),[13 14] interferon-6 (IL-6) receptor (sarilumab),[15 16] IL-6 cytokine (sirukumab, olokizumab, vobarilizumab),[17–22] GM-CSF receptor (mavrilimumab) and GM-CSF cytokine (otilimab).[23–25] IL-12/23 inhibition (ustekinumab) and IL23i (guselkumab) did not show significant differences from placebo. Molecules targeting IL-17A (secukinumab, CNTO6785),[26–28] and CD4 (tregalizumab) showed no or only minor efficacy compared with placebo (and lower efficacy compared with abatacept (ABA) as active comparator) in different patient populations.[29] Primary efficacy outcomes are summarised in table 2, baseline characteristics are shown in online supplementary table S2.3 and secondary efficacy outcomes in online supplementary table S3.1.

Trials comparing bsDMARDs to boDMARDs

Twenty-four non-inferiority trials (12 with low RoB) investigated the bioequivalence of bsDMARDs to their respective boDMARDs. All showed conclusive comparable results, irrespective of the compound (adalimumab (ADA), etanercept, infliximab and rituximab; for bsDMARD studied see table 1, online supplementary table S2.10 and online supplementary table S3.11).[30–55]

Switching between biosimilars and bio-originators revealed no changes in efficacy in trials of one ADA (SB5, low RoB),[56] three etanercept (two with low RoB: GP2015, LBEC0101; CHS-0214: conference abstract—RoB not assessed),[32 57–59] and two infliximab biosimilars (SB2, CT-P13, both low RoB).[60 61] Detailed characteristics and results of the studies are shown in online supplementary tables S2.11 and S3.11.

Head-to-head studies (bDMARDs)

Seven bDMARD head-to-head studies were included (six with low RoB; one high RoB). Efficacy results are summarised in table 3 (baseline characteristics and detailed efficacy outcomes are shown in online supplementary tables S2.3 and S3.2.).

The Optimal Management of patients with rheumatoid arthritis who Require Biologic Therapy (ORBIT) trial (high RoB), an open-label non-inferiority RCT comparing B-Cell depletion (rituximab) to tumour necrosis factor inhibitor (TNFi) therapy in csDMARD-IR and bDMARD-naïve patients, found

Table 1 Interventions and therapeutic compounds of trials included for review

Intervention	No of articles/ abstracts*	Therapeutic compound	Target
csDMARDs, csDMARD combination, Glucocorticoids versus other csDMARDs or placebo ([10–12 130 131])	5	Tacrolimus +methotrexate (MTX) versus leflunomide+MTX	FKBP12; dihydrofolate reductase +purine metabolism; dihydroorotate dehydrogenase
		MTX+sulfasalazine + glucocorticoids versus MTX +glucocorticoids versus MTX +Leflunomide +Glucocorticoids	
		MTX versus MTX+glucocorticoids	
		MTX+sulfasalazine + Hydroxychloroquine versus leflunomide +sulfasalazine + hydroxychloroquine versus leflunomide monotherapy	
bDMARD ±csDMARDs versus placebo ([13–29 132–136])	21	BCD-020	CD-20
		SBI-087	
		Tregalizumab	CD-4
		Abatacept	CD-80/CD-86
		Certolizumab pegol	TNF
		Olokizumab	IL-6
		Sirukumab	
		Sarilumab	IL-6 receptor
		Vobarilizumab	
		CNTO6785	IL-17
		Secukinumab	
		Otilimab	GM-CSF
		Mavrilimumab	GM-CSF receptor
		Ustekinumab	IL-12/23
		Guselkumab	IL-23
bDMARDs versus other bDMARDs ([4 62–66 137 138])	8	Rituximab versus etanercept/adalimumab	CD-20 versus TNF
		ABT-122 versus adalimumab	TNF/IL-17A versus TNF
		Certolizumab pegol versus adalimumab	TNF
		Sirukumab versus adalimumab	IL-6 versus TNF
		Sarilumab versus adalimumab	IL-6 receptor versus TNF
		Secukinumab versus abatacept	IL-17 versus CD-80/CD-86
		Mavrilimumab versus golimumab	GM-CSF versus TNF
bDMARD induction versus csDMARD induction in early disease ([69–72 139])	5	Certolizumab pegol versus MTX	TNF
		Abatacept versus MTX	CD-80/CD-86
		Infliximab versus MTX	TNF
		Tocilizumab versus MTX	IL-6 receptor
Switching between bDMARDs ([4 67 68])	3	Certolizumab pegol versus adalimumab	TNF
		Abatacept; rituximab; tocilizumab versus adalimumab; certolizumab; infliximab; golimumab; etanercept	CD-80/CD-86; CD-20; IL-6 receptor versus TNF
		Sarilumab	IL-6 receptor
Tapering of bDMARDs/tsDMARDs or csDMARDs ([107–124 126–128 140–145])	25	Abatacept	CD-80/CD-86
		Tocilizumab	IL-6 receptor
		Adalimumab; certolizumab pegol; etanercept; infliximab;	TNF
		csDMARDs	
		Glucocorticoids	
Strategic studies ([6 146])	2		
tsDMARDs±csDMARDs versus placebo ([73–100 125 147–152])	32	Baricitinib	JAK 1/2
		Decernotinib	JAK 3
		Filgotinib	JAK 1
		GS-9876	SYK
		Peficitinib	JAK 1
		Tofacitinib	JAK 1/3
		Upadacitinib	JAK 1
tsDMARDs±csDMARDs versus bDMARDs±csDMARDs ([101–106])	5	Baricitinib versus adalimumab	JAK 1/2 versus TNF
		Tofacitinib versus adalimumab	JAK 1/3 versus TNF
		Upadacitinib versus adalimumab	JAK 1 versus TNF

Continued

Table 1 Continued

Intervention	No of articles/ abstracts*	Therapeutic compound	Target
bsDMARDs versus boDMARDs ([30–34 36–55])	24	Adalimumab: ABP 501, AdaliRel, BI 695501, CinnoRA, FKB327, GP2017, PF-06410293, SB5, ZRC 3197	TNF
		Etanercept: CHS-0214, GP2015, HD203, LBEC0101	TNF
		Infliximab: BCD-055, CT-P13, NI-071, PF-06438179/ GP1111, SB2	TNF
		Rituximab: BCD-020, CT-P10, DRL-RI, GP2013	CD-20
Switching between bsDMARDs and boDMARDs ([32 35 56–61 153])	6	Adalimumab: SB5	TNF
		Etanercept: GP2015, CHS-0214, LBEC0101	TNF
		Infliximab: SB2, CT-P13	TNF

*Studies answering multiple research questions account for mismatch between included articles/abstracts and numbers in this table. References of manuscripts published after the SLRs data cut, with the respective conference abstracts included before, are shown, but were not counted.
bDMARD, biological disease-modifying antirheumatic drug; boDMARD, biooriginator disease-modifying antirheumatic drug; bsDMARD, biosimilar disease-modifying antirheumatic drug; CD, cluster of differentiation; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL, interleukin; JAK, Janus kinase; SYK, spleen tyrosine kinase; TNF, tumour necrosis factor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

that RTX is non-inferior to TNFi over 52 weeks regarding clinical efficacy.[62]

Sarilumab monotherapy showed clinical and functional superiority compared with ADA monotherapy in patients who were intolerant or inadequately responding to MTX.[63]

Mavrilimumab (targeting GM-CSFR) was compared with golimumab in a 24-week phase 2b trial of csDMARD and/or TNFi-IR patients and had similar efficacy.[64]

ABT-122, a bispecific dual variable domain immunoglobulin targeting TNF and IL-17A, exhibited similar efficacy rates in the 120 mg arm as ADA in MTX-IR patients over 12 weeks.[65]

The SIRROUND-H study investigated superiority of sirukumab (IL-6i) monotherapy over ADA monotherapy in MTX-IR, bDMARD naive patients. The study failed to meet one of its coprimary endpoints with no significant differences in ACR50% response rates at week 24; the other primary endpoint (DAS28-ESR mean change from baseline at week 24) was met.[66]

The EXXELERATE study did not show superiority of certolizumab pegol compared with ADA and therefore failed to meet its primary endpoint, showing similar ACR20% response rates at week 12.[4]

Switching between different bDMARDs

Three trials on switching between different bDMARDs were included (see online supplementary table S2.4 and online supplementary table S3.3 for details).

EXXELERATE also studied the efficacy of single-blinded switching to a second TNFi (without washout) in patients with primary non-response to either certolizumab pegol or ADA (unclear RoB). Twelve weeks after switching 58% (ADA to certolizumab pegol) and 62% (certolizumab pegol to ADA) of patients achieved DAS28-ESR≤3.2 or a DAS28-ESR reduction of 1.2 or more.[4]

An exploratory analysis of the EXTEND trial, an open-label extension study of the ASCERTAIN trial, investigated patients switched from tocilizumab (TCZ) to sarilumab (conference abstract). After 12 and 24 weeks about one-third of patients non-responders to TCZ achieved clinical response (Clinical Disease Activity Index (CDAI) ≤10; ACR70) after switching to sarilumab.[67]

The open-label ROC trial (high RoB) investigated patients who failed one TNFi therapy, comparing non-TNFi therapies (ABA, RTX, TCZ) to a second TNFi drug. The primary efficacy endpoint, superiority in EULAR good or moderate response at week 24, was met with higher responses in the non-TNFi group (101/146, 69%) compared with 52% in the second TNFi group (OR 2.12; 95% CI 1.31 to 3.46; p=0.003).[68] bDMARD therapies in early RA patients.

Five reports on induction therapy with bDMARDs in early disease were included (two with low RoB), baseline characteristics are shown in online supplementary table S2.5 and results in online supplementary table S3.4.

In DMARD naïve patients with poor prognostic factors, CZP in combination with dose optimised MTX (C-EARLY) was shown to be superior to placebo +MTX, with 28.9% of patients achieving sustained DAS28 <2.6 at week 40 and week 52 in the combination arm compared with 15% of patients in the MTX arm.[69]

In the AVERT-2 study, ABA+MTX did not show superiority to placebo +MTX regarding SDAI remission (≤3.3) at week 24 (21.3% ABA+MTX vs 16% placebo +MTX), the primary efficacy endpoint.[70]

DINORA compared infliximab +MTX treatment to MTX or placebo treatment only. INF+MTX showed superiority to placebo only, but not to MTX monotherapy, in achieving sustained remission (no swollen joints, ≤2 tender joints and an acute phase within the normal range) after 1 year (32% vs 14% vs 0% for INF+MTX, MTX and placebo, respectively).[71]

TCZ monotherapy as well as combination therapy of TCZ with MTX was clinically superior to MTX therapy in early RA patients. Inhibition of radiographic damage was found to be significantly greater with 8 mg/kg TCZ intravenous +MTX than in the MTX monotherapy arm modified total Sharp score (ΔmTSS 0.08 vs 1.14). TCZ 8 mg/kg intravenous monotherapy showed less radiographic progression than MTX monotherapy (ΔmTSS 0.26 vs 1.14, p value not reported).[72]

Efficacy of tsDMARDs (JAKi)

In total, 32 articles/abstracts on tsDMARDs were included (see table 1); 16 trials were regarded as having low RoB. Baseline characteristics and efficacy outcomes are shown in online supplementary tables S2.8 and S3.9, respectively.

Decernotinib (JAK-3i) and peficitinib (non-selective JAKi) were effective as monotherapy and in combination with csDMARDs or MTX in various populations.[73–82]

Filgotinib (JAK-1 selective JAKi) was effective in reducing signs and symptoms of RA as well as improving physical function and patients quality of life in two phase II studies investigating MTX-IR patients in combination with MTX (DARWIN 1) and as monotherapy (DARWIN 2).[83]

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

Study	Risk of bias	Treatment	N	Time point (weeks)	Primary endpoint	Outcome	P value
Damjanov 2016[13]	High	Pbo/Pbo/Pbo+MTX	40	16	ACR 20 (%)	NR	Reference
		SBI-087/Pbo/Pbo+MTX	43			NR	NS
		SBI-087/SBI-087/Pbo+MTX	42			NR	NS
		SBI-087/Pbo/SBI-087+MTX	43			NR	NS
		SBI-087/SBI-087/SBI-087+MTX	41			NR	0.046
Mazurov 2018[14]	Abstract	Placebo +MTX	52	24	ACR 20 (%)	29	Reference
		BCD-020 600 mg+MTX	107			66	<0.001
Fleischmann 2017 (TARGET)[15]	Low	Placebo +csDMARDs	181	12/24	ACR 20 (%) / ΔHAQ-DI	34/−0.3	Reference
		SLM 150 mg Q2W+csDMARDs	181			56/−0.5	<0.001
		SLM 200 mg Q2W+csDMARDs	184			61/−0.6	<0.001
Tanaka 2018b (KAKEHASI)[16]	Abstract	Placebo +MTX	82	24	ACR 20 (%)	15	Reference
		SLM 150 mg Q2W+MTX	81			68	<0.001
		SLM 200 mg Q2W+MTX	80			58	<0.001
Aletaha 2017 (SIRROUND-T)[17 18]	Low	Placebo±csDMARDs	294	16	ACR 20 (%)	24	Reference
		SKM 50 mg Q4W±csDMARDs	292			40	<0.001
		SKM 100 mg Q2W±csDMARDs	292			45	<0.001
Takeuchi 2017 (SIRROUND-D)[19]	Unclear	Placebo +csDMARD	556	16/52	ACR 20 (%)/ΔmTSS	26/1.96	Reference
		SKM 50 mg Q4W+csDMARD	557			55/0.35	<0.001
		SKM 100 mg Q2W+csDMARD	557			54/0.3	<0.001
Takeuchi 2016 (RA0083)[20]	Low	Placebo +MTX	29	12	ΔDAS28-CRP	−0.64	Reference
		OKZ 60 mg Q4W+MTX	32			−2.18	<0.001
		OKZ 120 mg Q4W+MTX	32			−2.45	<0.001
		OKZ 240 mg Q4W+MTX	36			−2.68	<0.001
Dorner 2017[21]	Abstract	(Open-Label) TCZ 162 mg QW	60	12	ACR 20 (%), no formal comparison	78	NR
		VBM 150 mg Q4W	62			73	
		VBM 150 mg Q2W	62			77	
		VBM 225 mg Q2W	63			81	
Weinblatt 2017[22]	Abstract	Placebo +MTX	69	12	ACR 20 (%)	62	Reference
		VBM 75 mg Q4W+MTX	69			75	NS
		VBM 150 mg Q4W+MTX	70			81	NS
		VBM 150 mg Q2W	68			78	NS
		VBM 225 mg Q2W	69			72	NS
Burmester 2017b (EARTH EXPLORER 1)[23]	Low	Placebo +MTX	81	12/24	ACR 20 (%)/ΔDAS28-CRP	25/−0.68	Reference
		MVM 150 mg Q2W+MTX	79			51/−1.9	<0.001
		MVM 100 mg Q2W+MTX	85			61/−1.64	<0.001
		MVM 30 mg Q2W+MTX	81			73/−1.37	<0.001
Buckley ACR 2018[24 25]	Abstract	Placebo +MTX	37	12	DAS28-CRP <2.6 (%)	3	Reference
		OTM 22.5 mg +MTX	37			5	0.547
		OTM 45 mg+MTX	37			16	0.077
		OTM 90 mg+MTX	37			19	0.053
		OTM 135 mg+MTX	37			14	0.122
		OTM 180 mg+MTX	37			14	0.134
Tahir 2017 (REASSURE)[26]	Unclear	Placebo±MTX	214	24	ACR 20 (%)	19.6	Reference
		SEC 3×10 mg/kg i.v. Q2W/150 mg s.c. Q4W±MTX	213			35	<0.001
		SEC 3×10 mg/kg i.v. Q2W/75 mg s.c. Q4W±MTX	210			35	<0.001
Mease 2018[27]	Unclear	Placebo +MTX	51	16	ACR 20 (%)	41	Reference
		CNTO6785 15 mg Q4W+MTX	52			52	NS
		CNTO6785 50 mg Q4W+MTX	51			47	NS
		CNTO6785 100 mg Q4W+MTX	51			37	NS
		CNTO6785 200 mg Q4W+MTX	52			40	NS
Dokoupilova 2018 (REASSURE2)[28]	Unclear	Placebo +csDMARDs	81	24	ACR 20 (%)	27	Reference
		SEC 150 mg+csDMARDs	81			38	0.157
		SEC 75 mg+csDMARDs	80			38	0.200

Continued

Table 2 Continued

Study	Risk of bias	Treatment	N	Time point (weeks)	Primary endpoint	Outcome	P value
van Vollenhoven 2018[29]	Low	Placebo +MTX	79	12	ACR 20 (%)	35	Reference
		TLM 25 mg+MTX	80			42	0.395
		TLM 100 mg+MTX	78			47	0.165
		TLM 200 mg+MTX	76			44	0.274
Bi 2018 (RAPID-C)[132]	High	Placebo +MTX	113	24	ACR 20 (%)	24	Reference
		CZP +MTX	316			55	<0.001
Smolen 2017a[133]	Low	Placebo +MTX	55	28	ACR 20 (%)	40	Reference
		UKM 90 mg Q8W+MTX	55			53	0.877
		UKM 90 mg Q12W+MTX	55			55	
		GKM 50 mg Q8W+MTX	55			38	0.101
		GKM 200 mg Q8W+MTX	54			44	

Detailed results of risk of bias analyses are shown in online supplementary table S2.2 in the supplementary appendix.
Δ, change from baseline; ACR, American College of Rheumatology response criteria; csDMARD, conventional synthetic disease-modifying antirheumatic drugs; CZP, certolizumab pegol; DAS28-CRP, Disease Activity Score of 28 joints with C-reactive protein; GKM, guselkumab; HAQ-DI, Health Assessment Questionnaire Disability Index; i.v., intravenous; mTSS, modified total Sharp score; MTX, methotrexate; MVM, mavrilimumab; NR, not reported; NS, not significant; OKZ, olokizumab; OTM, Otilimab; Pbo, placebo; s.c., subcutaneous; SEC, secukinumab; SKM, sirukumab; SLM, sarilumab; TCZ, tocilizumab; TLM, tregalizumab; UKM, ustekinumab; VBM, vobarilizumab.

GS-9876, an oral spleen tyrosine kinase inhibitor did not show clinical efficacy compared with placebo.[84]

Baricitinib (BARI) (JAK-1/2i) showed efficacy compared with placebo in csDMARD-IR (RA-BUILD) patients,[85 86] MTX-IR patients,[87 88] and in early RA as monotherapy or in combination with MTX.[89 90]

Upadacitinib proved to be efficacious versus placebo in phase 3 trials of various RA populations, MTX-naive,[91] csDMARD/MTX-IR,[92–98] bDMARD-IR (SELECT-BEYOND)[99 100] and tsDMARD versus bDMARD head-to-head trials.

Five reports on three different head-to-head trials (three with low RoB) comparing tsDMARDs to ADA were included. Baseline characteristics are shown in online supplementary table S2.9 and detailed efficacy results in online supplementary table S3.10.

In RA-BEAM, BARI 4 mg+MTX was shown to be superior to ADA 40 mg Q2W+MTX clinically (ACR20 at week 12: 70% vs 61%, p=0.014; ΔDAS28-CRP at week 12: −2.24 vs −1.95, p<0.001) and functionally (ΔHAQ at week 12: −0.66 vs −0.56, p≤0.01). Regarding structural progression, ADA and BARI were superior compared with placebo (change from baseline in mTSS at week 24: BARI: 0.41 vs ADA: 0.33 vs placebo: 0.9, p vs placebo <0.001).[101 102] Regarding core set variables, the differences related to patient reported outcomes and CRP, but not to swollen joint counts (SJCs).

ORAL strategy investigated the non-inferiority of tofacitinib 5 mg two times per day with or without MTX compared with ADA 40 mg Q2W+MTX. Non-inferiority was demonstrated for tofacitinib +MTX versus ADA +MTX (ACR50 at week 24: 46% vs 44%, difference: 2%; 98.34% CI −6% to 11%), but not for tofacitinib monotherapy versus ADA +MTX (ACR50 at week 24: 38% vs 44%; −6% (−14%–3%)) or versus tofacitinib +MTX (ACR 50 at week 24: 38% vs 46%; −8% (−16%–1%)).[103 104]

Upadacitinib+MTX was shown to be superior to ADA +MTX in SELECT-COMPARE in both coprimary endpoints (ACR20 at week 12: 70.5% vs 63%, p<0.05; DAS28-CRP<2.6 at week 12: 28.7% vs 18%, p<0.001), with radiographic superiority of upadacitinib +MTX vs placebo +MTX (ΔmTSS at week 26: 0.24 vs 0.92, p<0.001) and numerically similar results between upadacitinib +MTX and ADA +MTX (ΔmTSS at week 26: 0.24 vs 0.10).[105 106] Also in this study, the differences related to patient-reported outcomes and CRP, but not to SJCs.

Key outcomes are summarised in table 4. Figure 2 shows descriptive forest plots using ACR 20/50 and 70 response rates. Figure 3 summarises outcomes of trials investigating the efficacy of bDMARDs and tsDMARDs (based on their mode of action) compared with placebo.

Strategy trials

IMAGINE-RA, a non-blinded strategic trial (high RoB) which enrolled patients with stable, controlled disease activity (DAS28-CRP ≤3.2 and no swollen joints), compared an MRI guided with a purely clinical treat-to-target strategy. The trial did not meet its coprimary endpoints at month 24, as no differences in DAS28-CRP<2.6 rates (85% vs 88%, respectively) or differences in the proportion of patients who had no radiographic progression (66% vs 62%) were observed. However, in the MRI-T2T group, more patients needed treatment escalation (73% vs 17%) and initiation of bDMARD therapy (46% vs 2%) accompanied by higher costs and three times more serious adverse events.[6]

Tapering and stopping therapy

In total 25 studies (three with low RoB) investigated tapering and/or stopping csDMARD, bDMARD or tsDMARD therapy. Primary results are shown in table 5, baseline characteristics are shown in online supplementary table S2.7 and secondary outcomes are shown in online supplementary tables S3.6, S3.7 and S3.8

Tapering and stopping csDMARDs or GCs

MUSICA, a double-blind, non-inferiority RCT (low RoB) investigated randomised MTX dosage reduction to 7.5 mg/week compared with continuation of 20 mg/week in MTX-IR patients with open-label ADA initiation. The mean DAS28-CRP was statistically lower in the standard-dose group (3.75 vs 4.12, p=0.014) and non-inferiority of high versus low MTX dosage was therefore not shown (ΔDAS28-CRP 0.37 (95% CI 0.07 to 0.66) at week 24; NI-margin: 15%=0.56).[107] Thus, a mandatory dose reduction from 20 to 7.5 mg MTX weekly seems too low for combination therapy with a TNFi.

A Canadian open-label RCT (high RoB) reported no differences in DAS28-ESR change after patients treated with certolizumab

Table 3 Head-to-head studies comparing bDMARDs to other bDMARDs

Population	Study	Risk of bias	Treatment	N	Primary endpoint	P value	ACR20 (%)	ACR50 (%)	ACR70 (%)	DAS28 <2.6 (%)	CDAI ≤2.8 (%)	ΔHAQ
MTX-IR	Burmester 2017 (MONARCH)[63 137]	Low	ADA 40 mg Q2W	185	ΔDAS28-ESR at week 24	<0.001	58	30	12	7	3	−0.43
			SLM 200 mg Q2W	184			72	46	23	27	7	−0.61
	Smolen 2016 (EXXELERATE)[4]	Low	ADA 40 mg Q2W+MTX	454	ACR 20 (%) at week 12	0.532	71				22	
			CZP 400/200 mg Q2W+MTX	454			69				25	
	Taylor 2018 (SIRROUND-H)[66]	Low	ADA 40 mg Q2W	186	ACR 50 (%) + ΔDAS28-ESR at week 24	Reference	57	32	13	8		−0.52
			SKM 50 mg Q4W	186		0.306/0.013	54	27	12	13		−0.51
			SKM 100 mg Q2W	187		0.464/ <0.001	59	35	16	20		−0.53
	Genovese 2018b[65]	Low	ADA 40 mg Q2W+MTX	56	ACR 20 (%) at week 12	Reference	68	48	21	30	7	−0.6
			ABT-122 60 mg Q2W+MTX	55		0.863	62	35	22	22	7	−0.6
			ABT-122 120 mg Q2W+MTX	56		0.414	75	46	18	38	11	−0.6
			ABT-122 120 mg QW +MTX	55		0.196	80	47	36	42	11	−0.9
csDMARD-IR	Porter 2016 (ORBIT)[62]	High	Anti-CD20 (RTX)	140	ΔDAS28-ESR (non-inferiority) at week 52	0.24	66	49	23	23		−0.49
			TNFi (ETA/ADA)	134			71	45	26	21		−0.38
TNF-IR	Blanco 2017 (NURTURE 1)[138]	Low	Placebo +csDMARD	138	ACR 20 (%) at week 24	Reference	18	9	5			−0.3
			ABA 500/750/1000mg+csDMARD	138		<0.05	43	28	12			−0.6
			SEC 10 mg/kg i.v. +150 mg s.c. Q4W+csDMARD	137		0.031	31	17	10			−0.4
			SEC 10 mg/kg i.v. +75 mg s.c. Q4W+csDMARD	138		0.092	28	12	5			−0.3
Mixed cs/bDMARD-IR	Weinblatt 2018 (EARTH EXPLORER 2)*[64]	Low	GLM 50 mg Q4W	68	ACR 20/50/70%, DAS28-CRP <2.6, ΔHAQ>0.22 at week 24	0.666/0.293/0.156/0.108/0.208	66	43	26	29	18	−0.64
			MVM 100 mg Q2W+MTX	70			62	35	16	17	6	−0.44

Results of secondary efficacy outcomes are shown at the time point of the primary endpoint.
*Study not powered to formally compare the treatments. Detailed results of risk of bias analyses are shown in online supplementary table S2.2 in the supplementary appendix.
Δ, change from baseline; ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; bDMARDs, biological disease-modifying antirheumatic drugs; CDAI, clinical disease activity index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CZP, certolizumab pegol; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; ETA, etanercept; GLM, golimumab; HAQ, Health Assessment Questionnaire; i.v., intravenous; MTX, methotrexate; MVM, mavrilimumab; RTX, rituximab; SEC, secukinumab; SKM, sirukumab; SLM, sarilumab; TNFi, TNF inhibitor; TNF-IR, tumour necrosis factor-insufficient responder.

Table 4 Major efficacy outcomes of head-to-head studies comparing JAK inhibitors to adalimumab

Study	Study design	Risk of bias	Treatment	N	Primary endpoint	P value	ACR20 (%)	ACR 50 (%)	ACR 70 (%)	DAS28 <2.6 (%)	CDAI ≤2.8 (%)	ACR/EULAR Boolean rem. (%)	ΔHAQ	ΔmTSS
Taylor/Keystone 2017 (RA-BEAM)[101 102]	S	Low	Placebo +MTX	488	ACR 20 (%) at week 12	BARI versus PLC:<0.001; BARI versus ADA <0.01	40	17	5	4	2	1	−0.34	0.9*
			BARI 4 mg+MTX	487			70	45	19	24	8	7	−0.66	0.41*
			ADA 40 mg Q2W+MTX	330			61	35	13	19	7	5	−0.56	0.33*
Fleischmann 2017/Strand EULAR 2018 (ORAL-Strategy)[103 104]	NI	Low	ADA 40 mg Q2W+MTX	386	ACR 50 (%) at week 24	Reference	71	44	21	28	13	9	−0.54	NR
			TOFA 5 mg two times per day+PLC	384		0.051	65	38	18	21	10	7	−0.52	NR
			TOFA 5 mg two times per day+MTX	376		<0.001	73	46	25	31	14	8	−0.58	NR
Fleischmann ACR 2018 (SELECT-COMPARE)[105 106]	S	Low	Placebo +MTX	651	ACR 20 (%)+DAS28-CRP<2.6 at week 12	UPA versus PLC:<0.001 / <0.001; UPA versus ADA:<0.05/<0.001	36	15	5	6	3	2	−0.28	0.92†
			ADA 40 mg Q2W+MTX	327			63	29	14	18	8	4	−0.49	0.1†
			UPA 15 mg OD +MTX	651			71	45	25	29	13	9.8	−0.6	0.24†

Results of secondary efficacy outcomes are shown at the time point of the primary endpoint.
*Week 24.
†Week 26.
ADA, adalimumab; BARI, baricitinib; CRP, C-reactive protein; DAS28, Disease Activity Score of 28 joints; EULAR, European League against Rheumatism; HAQ, Health Assessment Questionnaire; JAK, Janus kinase; mTSS, modified total Sharp Score; MTX, methotrexate; MTX, methotrexate; NI, non-inferiority; NR, not reported; OD, once daily; PLC, placebo; S, superiority; TOFA, tofacitinib; UPA, upadacitinib.

plus csDMARD had been randomised to continue combination therapy or discontinue csDMARDs (−2.1 vs −2.1).[108–110]

The SEMIRA trial (conference abstract) investigated patients treated with TCZ ±csDMARD therapy who also had stable GC therapy of 5 mg/day, comparing blinded tapering of GCs with continuation of GCs. A significant increase of disease activity (ΔDAS28-ESR) was seen in the discontinuation group compared with continuation (0.613, 95% CI 0.346 to 0.879, p<0.001). Sixty-six per cent of patients discontinuing remaining in stable DAS28 ≤3.2 without experiencing disease flares, compared with 77% (RR 0.833, 95% CI 0.714 to 0.972, p=0.021) in the stable GC group.[111]

Several trials (one low RoB, one unclear RoB, one high RoB) showed non-inferiority of MTX tapering versus continuation in patients receiving ongoing (long-term) TCZ therapy.[112–114]

A substudy of the CareRA study investigated randomised step-down from COBRA Avant-Garde (MTX+LEF + initial prednisone 30 mg step-down) to either MTX (15 mg/week) or LEF (20 mg/day) monotherapy if they achieved an DAS28-CRP ≤3.2 after treatment induction during period of 40–52 weeks of therapy. After 65 weeks, significantly more patients achieved DAS28-CRP <2.6, CDAI ≤10 or SDAI ≤11 in the MTX arm (30/32, 93.8%; 32/32, 100%; 32/32, 100% respectively) than in the LEF arm (19/26, 73.1%, p=0.031; 21/26, 80.8%, p=0.009; 22/26, 84.6%, p=0.021)[115 116] bDMARD tapering.

The POET study, a large open-label RCT (high RoB) randomised patients in stable low disease activity for 6 months (DAS28-ESR ≤3.2 or based on rheumatologists' impression) to either stop or continue their TNFi therapy, comparing proportions of patients experiencing a disease flare (DAS28-ESR ≥3.2 + DAS28-ESR change from baseline >0.6) during 12 months. About 20% of patients could stop their TNFi therapy without experiencing a flare, but among those who continued TNFi therapy 50% did not experience a flare (TNFi stopping: 18.2% vs TNFi continuation: 51.2%, p<0.001; HR 3.50; 95% CI 2.60 to 4.72).[117 118]

In C-OPERA, Japanese patients discontinued or continued certolizumab pegol after achieving DAS28-ESR ≤3.2 at week 52. At week 104, 29.3% of patients who stopped certolizumab pegol could maintain SDAI remission, compared with 41.5% of patients continuing (p=0.026). Significantly more radiographic progression occurred in patients who stopped certolizumab until week 104 (ΔmTSS at week 104 0.66 vs 3.01, p=0.001).[119]

In C-EARLY, a trial investigating certolizumab +MTX in csDMARD naive patients with early RA, patients who achieved DAS28-ESR≤3.2 at year 1 were either continued on CZP every 2 weeks, increased dosing interval of CZP (to every 4 weeks) or stopped CZP completely. Although the trial failed to meet its primary endpoint (% of patients in DAS28-ESR≤3.2 without flare at week 104), similar results for CZP Q2W versus interval prolongation to CZP every 4 weeks (48.8% vs 53.2%, p=0.112) were seen. Furthermore, 39.2% of patients could stop CZP completely and maintain DAS28-ESR ≤3.2 but the difference compared with continuation was significant (48.8% vs 39.2%, p=0.041).[120]

Further studies investigated the discontinuation of TCZ after combination therapy with MTX (SURPRISE study) and achieving DAS28-ESR <2.6: sustained DAS28-ESR <2.6 and DAS28-ESR ≤3.2 rates were more frequent in patients receiving concomitant MTX compared with TCZ monotherapy after 104 weeks (24% vs 14%, p=0.005; 55% vs 27%, p=0.005).[121] Tapering TNFi dose by 33% in patients with DAS28-ESR ≤3.2 for 3 months did not lead to increased flare rates (12% vs 16%, HR: 0.90, 95% CI 0.23 to 3.48, p=0.873), reducing the TNFi

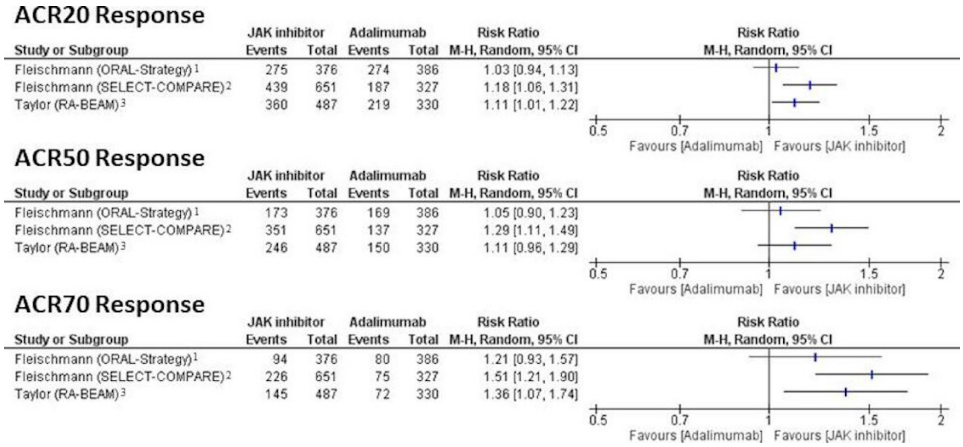

Figure 2 Forest plots showing risk ratios of ACR 20, 50 and 70 responses in trials comparing JAK inhibitors+MTX to adalimumab +MTX in MTX-IR patients. 1, tofacitinib; 2, upadacitinib; 3, baricitinib. ACR, American College of Rheumatology; IR, insufficient responder; M-H, Mantel-Haenszel; MTX, methotrexate; JAK, Janus kinase.

dose by 66% resulted in not statistically significantly different flare rates (DAS28-ESR >3.2 and ΔDAS28-ESR ≥0.6) compared with treatment continuation (29% vs 16%, HR 2.52, 95% CI 0.85 to 7.48, p=0.097).[122]

A novel tapering strategy, using a biomarker, matrix metalloproteinase (MMP-3), or combined SDAI +MMP-3-guided tapering of bDMARDs in patients achieving SDAI ≤3.3 and normalisation of MMP-3 showed non-inferiority at week 52 as compared with just clinically guided maintenance of SDAI ≤3.3.[123] Open-label interval prolongation in patients with high ADA trough levels (defined as >8 µg/mL) did not lead to increased disease activity (using DAS28-ESR, CDAI or SDAI).[124]

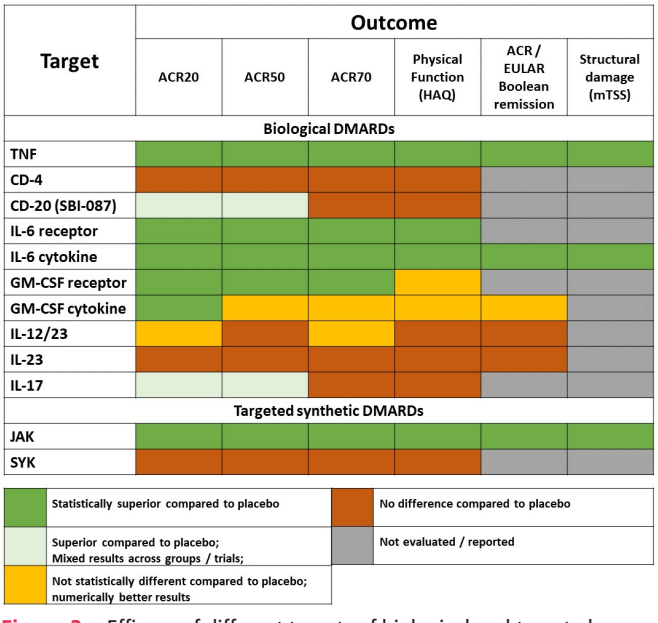

Figure 3 Efficacy of different targets of biological and targeted synthetic disease-modifying drugs compared against placebo, shown across major clinical trial outcomes of randomised controlled trials published from 2016 to 2018. ACR, American College of Rheumatology response criteria; CD, cluster of differentiation; DMARD, disease-modifying antirheumatic drugs; EULAR, European League against Rheumatism; GM-CSF, colony-stimulating factor; HAQ, Health Assessment Questionnaire; IL, interleukin; JAK, Janus kinase; mTSS, modified total Sharp score; Syk, spleen tyrosine kinase; TNF, tumour necrosis factor.

Tapering of tsDMARDs

The RA-BEYOND study randomised patients from four trials of BARI at 4 mg who had achieved stable CDAI ≤10 to either continue BARI 4 mg or reduce dose to 2 mg. While more patients who continued full dose maintained CDAI low disease activity compared with those who reduced the dose (93% vs 83%, p<0.001 at 3 months; 87% vs 75%, p<0.001, at 6 months; 80% vs 67%, p<0.01 at 12 months for BARI 4 mg continuation vs dose reduction to BARI 2 mg, respectively), a majority of patients maintained their good disease state despite dose reduction. Further, in patients being in CDAI ≤2.8 at randomisation, fewer patients lost their disease activity state. Of those who flared after dose reduction, the majority (66.7%) regained their CDAI <10 state within 24 weeks after dose increase to 4 mg. Thirteen of the 16 patients not regaining their CDAI <10 state after 24 weeks were able to do so at a subsequent time point.[125]

Combined bDMARDs and csDMARDs tapering and/or stopping

IMPROVED, a Dutch strategy trial (high RoB) aimed at drug free remission in patients with early RA and undifferentiated arthritis. After 5 years, 15%–20% (p=0.374) of patients could achieve drug-free remission.[126]

Dose reduction (by 50%) or stopping either csDMARDs, bDMARDs or both compared with dose continuation was investigated in a study of patients achieving stable DAS28-ESR <2.6 for at least 6 months (high RoB). In the control group 6.5% of patients flared, while 42%–77% flared after dose reduction or stopping therapy completely.[127]

The TARA study compared csDMARD tapering with bDMARD tapering in patients who had long-standing combination therapy and found no significant differences in the flare (defined as DAS44 >2.4 and/or SJC >1) ratio between both groups (HR 0.91; 95% CI 0.68 to 1.22; p=0.55).[128]

DISCUSSION

This SLR was performed to inform the task force for the 2019 update of the EULAR recommendations for the management of RA on the efficacy of various DMARDs as presented in publications from 2016 to March 2019. These publications covered a total of 32 DMARDs.

The SLR confirmed the high efficacy of csDMARD plus GC combination therapy as well as the efficacy of TNFi, IL-6Ri, ABA

Table 5 Primary outcomes of studies investigating csDMARD, bDMARD and tsDMARD tapering and stopping

Study	Primary outcome	Endpoint (week)	Treatment arm	N	Result	P value
csDMARD tapering						
Kaeley 2016 (MUSICA)[107]	Mean DAS28-CRP	24	ADA 40 mg Q2W+7.5 mg MTX	154	4.12	0.014
			ADA 40 mg Q2W+20 mg MTX	155	3.75	
Keystone 2016 (CAMEO)[144]	ΔDAS28-ESR	24	ETN 50 mg QW; MTX discontinuation	98	0.5	0.815
			ETN 50 mg QW +MTX continuation	107	0.04	
Pope EULAR 2017/ACR 2018/2019[108–110]	ΔDAS28-ESR	76	CZP +csDMARD continuation	37	−2.1	NR
			CZP +csDMARD discontinuation	44	−2.1	
Burmester ACR 2018 (SEMIRA)[111]	ΔDAS28-ESR	24	TCZ ±csDMARDs; GC tapering	131	0.538	<0.001
			TCZ ±csDMARDs; GC continuation	128	−0.075	
Pablos 2018 (JUST-ACT)[112]	ΔDAS28-ESR week 16 week 28	28	TCZ 8 mg/kg+MTX	82	0.007	95% CI −0.40 to 0.27
			TCZ 8 mg/kg+PLC	82	0.073	
Kremer 2018 (COMP-ACT)[113]	ΔDAS28-ESR week 24 week 40	40	TCZ 162 mg s.c. +PLC	147	0.46	95% CI 0.045 to 0.592
			TCZ 162 mg s.c. +MTX	147	0.14	
Edwards 2018 (ACT-TAPER)[114]	Pat. Maintaining EULAR good/moderate response from week 24–60	60	TCZ 8 mg/kg Q4W+PBO	136	77%	0.036
			TCZ 8 mg/kg Q4W+MTX	136	65%	
Stouten 2018 (CareRA)[115 116]	DAS28-CRP <2.6	65	MTX +LEF->MTX 15 mg/week	32	94%	0.031
			MTX+LEF->LEF 20 mg/day	26	73%	
bDMARD tapering						
Oba 2017/Tanaka ACR 2018 (RRRR)[140 141]	1-year sustained discontinuation rate of INF	106	INF 3 mg/8 mg/10 mg/kg Q8W based on TNF levels	170	24%	0.631
			INF standard 3 mg/kg Q8W	167	21%	
Chatzidionysiou 2016 (ADMIRE)[142]	DAS28 <2.6 at week 28	28	ADA +MTX continuation	16	94%	0.001
			ADA discontinuation; MTX monotherapy	16	33%	
Ghiti Moghadam 2016/2018 (POET)[117 118]	% of pat. DAS28 ≥3.2 + ΔDAS28 >0.6 for 1 year	52	Stopping TNFi	531	51%	<0.001
			Continuation of TNFi	286	18%	
Atsumi 2017 (C-OPERA)[119]	ΔmTSS	104	CZP +MTX continuation	108	0.66	0.001
			Stopping CZP; MTX+PLC	71	3.01	
Kaneko 2018 (SURPRISE)[121]	TCZ free rate	104	stopping TCZ; MTX monotherapy	49	67%	0.001
			stopping TCZ; No DMARD	53	29%	
Weinblatt 2017 (C-EARLY)[120]	DAS28-ESR ≤3.2 without flares during week 52–104	104	CZP 200 mg Q2W+MTX (standard)	84	49%	Reference
			CZP 200 mg Q4W+MTX (reduced frequency)	126	53%	0.112
			Placebo +MTX (CZP stopped)	79	39%	0.041
Ibrahim 2017 (OPTIRRA)[122]	Flare rate (ΔDAS28 ≥0.6 + DAS28 >3.2 + ΔSJC OR ΔDAS28 >1.2 + DAS28 >3.2)	24	TNFi 33% tapering; csDMARD	26	12%	0.873
			TNFi 66% tapering; csDMARD	21	29%	0.097
			Control; csDMARD continuation	50	16%	Reference
Bouman 2017 (DRESS)[145]	Incidence of major flare (ΔDAS28-CRP >1.2 or ΔDAS28-CRP >0.6+DAS28-CRP ≥3.2 for >12 weeks)	144	TNFi dose reduction extension	115	17%	3%, 95% CI -10% to 15%
			Usual care extension	57	14%	
l'Ami 2018[124]	ΔDAS28-ESR	28	ADA 40 mg Q3W±MTX	27	−0.14	0.01
			ADA 40 mg Q2W±MTX	27	0.3	
tsDMARD tapering						
Takeuchi 2019 (RA-BEYOND)[125]	CDAI ≤10	12	Continued BARI 4 mg±csDMARD	281	93%	<0.001
			BARI Step-down 2 mg±csDMARD	278	83%	

Δ, change from baseline; ACR, American College of Rheumatology; ADA, adalimumab; BARI, baricitinib; bDMARD, biological disease-modifying antirheumatic drug; CDAI, Clinical Disease Activity Index; CRP, C-reactive protein; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; CZP, certolizumab pegol; DAS28, Disease Activity Score of 28 joints; ESR, erythrocyte sedimentation rate; ETN, etanercept; EULAR, European League against Rheumatism; GC, glucocorticoid; INF, infliximab; LEF, leflunomide; mTSS, modified total Sharp Score; MTX, methotrexate; MTX, methotrexate; PLC, placebo; SJC, swollen joint count; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic DMARD.

and rituximab as well as bsDMARDs in csDMARD (including MTX) IR patients. With respect to bsDMARDs, switch (including multiple switch) studies between bs and boDMARDs confirmed long-term safety and efficacy of biosimilars. Like bDMARDs, JAKi are efficacious in patients with RA. Several trials compared one bDMARD class (usually TNFi agents) with bDMARDs of other classes revealing similarity of response. Likewise, head-to-head trials between JAKi and anti-TNF did not reveal clinically important differences regarding efficacy.

In patients who failed a TNFi or other bDMARDs, tsDMARDs and also bDMARDs of the same or other classes revealed generally similar clinical efficacy[4 99 100] or relatively small differences.[68] Of interest (and part of the previous research agenda), sarilumab, an anti-IL-6R antibody, showed efficacy in patients who had an IR to TCZ, another IL-6Ri,[67] and in a study published after this SLR, TNFi showed efficacy after failure of JAKi.[129]

A strategy trial comparing treatment aimed at clinical remission to therapy aimed at remission by MRI showed no difference in clinical outcomes, but more adverse events and more costs in the imaging group, further confirming that stringent clinical remission is a sufficient treatment target and that imaging remission not only fails to convey better efficacy, but may constitute a potentially dangerous and costly overtreatment.[6]

Tapering studies revealed that dose reduction of JAKi and bDMARDs is feasible and that when starting dose reduction in sustained stringent remission less patients flare when compared with start of tapering just in sustained low disease activity.[125] Importantly, patients who flare can mostly (70%–80%) regain their prior good response.

The results of this SLR were presented to the task force and, together with the safety SLR,[8] formed the basis for the update of the EULAR RA management recommendations.

Author affiliations
[1]Medical University of Vienna, Vienna, Austria
[2]Leiden University Medical Center, Leiden, The Netherlands
[3]NOVA Medical School, Universidade Nova de Lisboa, Lisbon, Portugal
[4]Hospital Cochin, Paris, France
[5]Amsterdam Rheumatology Center, Amsterdam, The Netherlands

[6]University of Glasgow, Glasgow, UK
[7]University Medical Center Utrecht, Utrecht, The Netherlands
[8]Charité – University Medicine Berlin, Berlin, Germany
[9]EULAR Standing Committee, Zurich, Switzerland
[10]Northwell Health, New York, New York, USA

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ORCID iDs
Andreas Kerschbaumer http://orcid.org/0000-0002-6685-8873
Alexandre Sepriano http://orcid.org/0000-0003-1954-0229
Désirée van der Heijde http://orcid.org/0000-0002-5781-158X
Maarten de Wit http://orcid.org/0000-0002-8428-6354

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