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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.

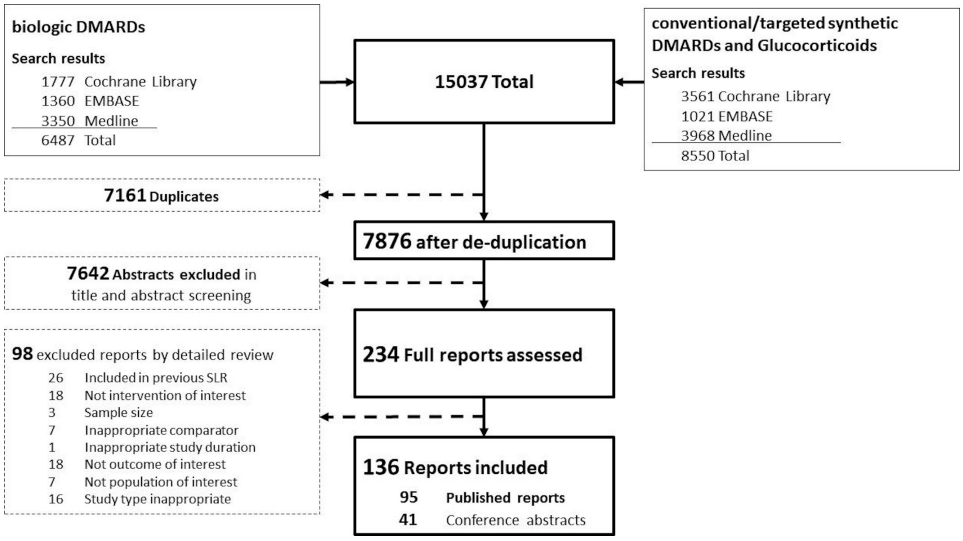

Figure 1 PRISMA flow chart describing the study selection process. DMARDs, disease-modifying antirheumatic drugs; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; SLR, systematic literature research.

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

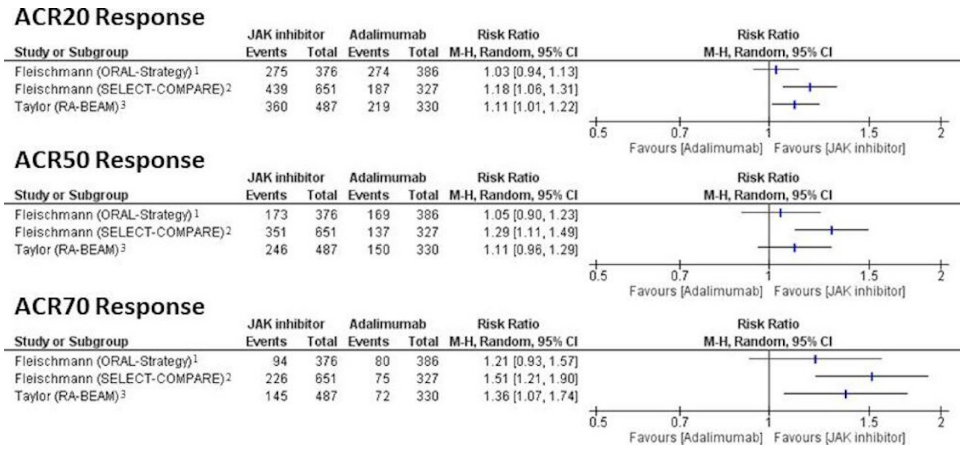

Figure 2 Forest plots showing risk ratios of ACR 20, 50 and 70 responses in trials comparing JAK inhibitors+MTX to adalimumab +MTX in MTX-IR patients. 1, tofacitinib; 2, upadacitinib; 3, baricitinib. ACR, American College of Rheumatology; IR, insufficient responder; M-H, Mantel-Haenszel; MTX, methotrexate;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

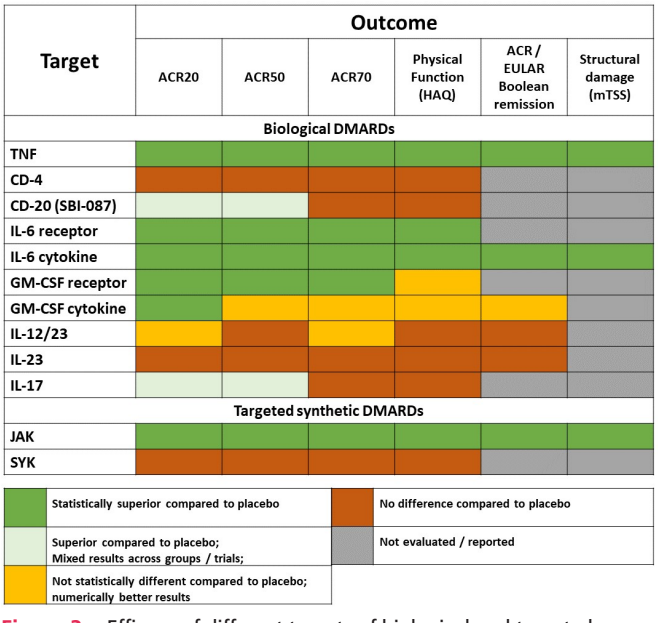

Figure 3 Efficacy of different targets of biological and targeted synthetic disease-modifying drugs compared against placebo, shown across major clinical trial outcomes of randomised controlled trials published from 2016 to 2018. ACR, American College of Rheumatology response criteria; CD, cluster of 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	14	
Edwards 2018 (ACT-TAPER)[114]	Pat. maintaining EULAR good/moderate response from week 24–60	60	TCZ 8 mg/kg Q4W+PBO	136	7%	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 disease inactivity rate of INF	106	INF 3 mg/8 mg/kg Q8W based on TNF levels	110	24%	0.621
			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	38%	
Ghiti Moghadam 2016/2018 (POET)[117]	% of pat. DAS28 >3.2 + ΔDAS28 >0.6 for 1 year	52	Stopping TNFi	531	1%	<0.001
			Continuation of TNFi	86	38%	
Atsumi 2017 (CAPER)[119]	ΔmTSS	104	CZP+MTX continuation	70	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	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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Supplementary appendix

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Section 1: Search strategy and PICOs

Table S1.1: MEDLINE Search strategy: biological DMARDs

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

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

Table S1.2: EMBASE Search strategy: biological DMARDs

#68. #67 AND AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND AND (2016:py OR 2017:py OR 2018:py OR 2019:py)
#67. #55 AND #66
#66. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65
#65. random*:ab,ti
#64. 'randomized controlled trial'/exp
#63. trial:ti
#62. allocat*:ab,ti
#61. (doubl* NEAR/2 blind*):ab,ti
#60. placebo*:ab,ti
#59. crossover*:ab,ti OR 'cross over*':ab,ti
#58. 'single-blind procedure'
#57. 'double blind procedure'/de
#56. 'crossover procedure'/de
#55. #5 AND #54
#54. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#53. mavrilimumab:ab,ti
#52. stelara:ab,ti
#51. ustekinumab:ab,ti
#50. guselkumab:ab,ti
#49. brodalumab:ab,ti
#48. brodalumab:ab,ti
#47. taltz:ab,ti
#46. ixekizumab:ti,ab
#45. pateclizumab:ab,ti
#44. clazakizumab:ab,ti
#43. olokizumab:ab,ti
#42. tabalumab:ab,ti
#41. ocrelizumab:ab,ti
#40. sirukumab:ab,ti
#39. sarilumab:ab,ti
#38. arzerra:ab,ti
#37. ofatumumab:ab,ti
#36. ixekizumab:ab,ti
#35. brodalumab:ab,ti
#34. stelara:ab,ti
#33. ustekinumab:ab,ti
#32. cosentyx:ab,ti
#31. secukinumab:ab,ti
#30. roactemra:ab,ti
#29. actemra:ab,
#28. tocilizumab:ab,ti
#27. mabthera:ab,ti
#26. rituxan:ab,ti
#25. rituximab:ab,ti
#24. simponi:ab,ti
#23. golimumab:ab,ti

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

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

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

#50 Brodalumab:ti,ab
#51 Siliq:ti,ab
#52 Guselkumab:ti,ab
#53 Ustekinumab:ti,ab
#54 Stelara:ti,ab
#55 mavrilimumab:ti,ab
#56 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55

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

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

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

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

31. exp Cyclosporins/

32. c?closporin$.tw.

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

34. exp Penicillamine/

35. Penicillamine.tw.

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

37. exp Cyclophosphamide/

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

39. Mycophenolic Acid/

40. mycophenolate.tw.

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

42. exp Chlorambucil/

43. chlorambucil.tw.

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

45. Minocycline/

46. minocyclin$.tw.

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

48. Pyrroles/

49. tofacitinib.tw.

50. Xeljanz.tw.

51. baricitinib.tw.

52. peficitinib.tw.

53. filgotinib.tw.

54. upadacitinib.tw.

55. fostamatinib.tw.

56. exp Glucocorticoids/

57. glucocorticoid$.tw.

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

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

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

#71. #70 AND (2016:py OR 2017:py OR 2018:py OR 2019:py)
#70. #57 AND #68 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim
#69. #57 AND #68
#68. #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67
#67. random*:ab,ti
#66. 'randomized controlled trial'/exp
#65. trial:ti
#64. allocat*:ab,ti
#63. (doubl* NEAR/2 blind*):ab,ti
#62. placebo*:ab,ti
#61. crossover*:ab,ti OR 'cross over*':ab,ti
#60. 'single-blind procedure'
#59. 'double blind procedure'/de
#58. 'crossover procedure'/de
#57. #5 AND #56
#56. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
#55. beclomethasone:ti,ab OR betamethasone:ti,ab OR budesonide:ti,ab OR clobetasol:ti,ab OR desoximetasone:ti,ab OR dexamethasone:ti,ab OR diflucortolone:ti,ab OR flumethasone:ti,ab OR fluocinonide:ti,ab OR fluocortolone:ti,ab OR fluorometholone:ti,ab OR fluprednisolone:ti,ab OR flurandrenolone:ti,ab OR 'melengestrol acetate':ti,ab OR methylprednisolone:ti,ab OR paramethasone:ti,ab OR prednisolone:ti,ab OR prednisone:ti,ab OR triamcinolone:ti,ab
#54. glucocorticoid*:ti,ab
#53. 'glucocorticoid'/exp
#52. fostamatinib.:ti,ab
#51. upadacitinib.:ti,ab
#50. filgotinib.:ti,ab
#49. peficitinib:ti,ab
#48. baricitinib:ti,ab
#47. xeljanz:ab,ti
#46. tofacitinib:ab,ti
#45. acneclin:ab,ti OR akamin:ab,ti OR aknemin:ab,ti OR 'akne puren':ab,ti OR aknereduct:ab,ti OR 'aknin mino':ab,ti OR 'aknin n':ab,ti OR aknoral:ab,ti OR aknosan:ab,ti OR apominolin:ab,ti OR arestinor:ab,ti OR auramin:ab,ti OR blemix:ab,ti OR borymycin:ab,ti OR cipancin:ab,ti OR cyclimycin:ab,ti OR dentomycin*:ab,ti OR durakne:ab,ti OR dynacin:ab,ti OR enca:ab,ti OR 'icht oralor':ab,ti OR klinoc:ab,ti OR klinomycin:ab,ti OR klinotab:ab,ti OR lederderm:ab,ti OR logryx:ab,ti OR meibi:ab,ti OR mestacine:ab,ti OR micromycin:ab,ti OR 'minac 50':ab,ti OR minakne:ab,ti OR minaxen:ab,ti OR 'mino 50':ab,ti OR minocin:ab,ti OR minoclin:ab,ti OR minodene:ab,ti OR minoderm:ab,ti OR minogalen:ab,ti OR minolis:ab,ti OR minomax:ab,ti OR minomycin:ab,ti OR minoplus:ab,ti OR minosil:ab,ti OR minostad:ab,ti OR minotab*:ab,ti OR minotekor:ab,ti OR minotrex:ab,ti OR minotyrol:ab,ti OR 'mino wolff':ab,ti OR minox:ab,ti OR mynocine:ab,ti OR myrac:ab,ti OR oracyclin:ab,ti OR parocline:ab,ti OR periocline:ab,ti OR peritrol:ab,ti OR ranmino:ab,ti OR romin:ab,ti OR seboclear:ab,ti OR sebomin:ab,ti OR sebren:ab,ti OR skid:ab,ti OR skinocyclin:ab,ti OR solodyn:ab,ti OR spicline:ab,ti OR triomin:ab,ti OR udima:ab,ti OR vectrin:ab,ti OR yelnac:ab,ti OR zacnan:ab,ti
#44. minocyclin*:ab,ti
#43. 'minocycline'/de

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

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

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

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

#33 (neoral or gengraf or restasis or sandimmun* or sangcya):ti,ab
#34 MeSH descriptor: [Penicillamine] explode all trees
#35 Penicillamine:ti,ab
#36 (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin* or D-Penamine or Gerodyl or Kelatin* or Mercaptyl or Metalcaptase or Pendramine or Rhumantin or Sufortan* or Trisorcin or Trolovol):ti,ab
#37 MeSH descriptor: [Cyclophosphamide] explode all trees
#38 (cyclophosph* or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109* or "asta z 4942" or cfx or "phosphoramide mustard*"):ti,ab
#39 MeSH descriptor: [Mycophenolic Acid] this term only
#40 mycophenolate:ti,ab
#41 (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or Imuxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilet or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin):ti,ab
#42 MeSH descriptor: [Chlorambucil] explode all trees
#43 chlorambucil:ti,ab
#44 (Amboclorin or Clokeran or Leukeran or Linfolysin or Lympholysin):ti,ab
#45 MeSH descriptor: [Minocycline] this term only
#46 minocyclin*:ti,ab
#47 (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomycin$ or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or "Minac 50" or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab$ or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udima or Vectrin or Yelnac or Zacnan):ti,ab
#48 MeSH descriptor: [Pyrroles] this term only
#49 tofacitinib:ti,ab
#50 Xeljanz:ti,ab
#51 baricitinib:ti,ab
#52 peficitinib:ti,ab
#53 filgotinib:ti,ab
#54 upadacitinib:ti,ab
#55 fostamatinib:ti,ab
#56 MeSH descriptor: [Glucocorticoids] explode all trees
#57 glucocorticoid*:ti,ab
#58 (Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone):ti,ab
#59 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
#60 #5 AND #59

Table S1.7: Pharmacologic interventions of interest

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

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

See table S7 for specific definition of interventions.

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

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

Section 2: Study characteristics of articles and abstracts included.

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

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

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

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

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

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

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

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

Table S2.2: Risk of bias analysis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Section 3: Efficacy outcomes

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

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

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

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

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

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

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

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

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

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

Table S3.5: Efficacy of strategic studies.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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Section 5: List of abbreviations

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

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

Supplementary appendix

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Section 1: Search strategy and PICOs

Table S1.1: MEDLINE Search strategy: biological DMARDs

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

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

Table S1.2: EMBASE Search strategy: biological DMARDs

#68. #67 AND AND ([article]/lim OR [article in press]/lim) AND [humans]/lim AND AND (2016:py OR 2017:py OR 2018:py OR 2019:py)
#67. #55 AND #66
#66. #56 OR #57 OR #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65
#65. random*:ab,ti
#64. 'randomized controlled trial'/exp
#63. trial:ti
#62. allocat*:ab,ti
#61. (doubl* NEAR/2 blind*):ab,ti
#60. placebo*:ab,ti
#59. crossover*:ab,ti OR 'cross over*':ab,ti
#58. 'single-blind procedure'
#57. 'double blind procedure'/de
#56. 'crossover procedure'/de
#55. #5 AND #54
#54. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53
#53. mavrilimumab:ab,ti
#52. stelara:ab,ti
#51. ustekinumab:ab,ti
#50. guselkumab:ab,ti
#49. brodalumab:ab,ti
#48. brodalumab:ab,ti
#47. taltz:ab,ti
#46. ixekizumab:ti,ab
#45. pateclizumab:ab,ti
#44. clazakizumab:ab,ti
#43. olokizumab:ab,ti
#42. tabalumab:ab,ti
#41. ocrelizumab:ab,ti
#40. sirukumab:ab,ti
#39. sarilumab:ab,ti
#38. arzerra:ab,ti
#37. ofatumumab:ab,ti
#36. ixekizumab:ab,ti
#35. brodalumab:ab,ti
#34. stelara:ab,ti
#33. ustekinumab:ab,ti
#32. cosentyx:ab,ti
#31. secukinumab:ab,ti
#30. roactemra:ab,ti
#29. actemra:ab,
#28. tocilizumab:ab,ti
#27. mabthera:ab,ti
#26. rituxan:ab,ti
#25. rituximab:ab,ti
#24. simponi:ab,ti
#23. golimumab:ab,ti

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

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

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

#50 Brodalumab:ti,ab
#51 Siliq:ti,ab
#52 Guselkumab:ti,ab
#53 Ustekinumab:ti,ab
#54 Stelara:ti,ab
#55 mavrilimumab:ti,ab
#56 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55

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

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

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

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

31. exp Cyclosporins/

32. c?closporin$.tw.

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

34. exp Penicillamine/

35. Penicillamine.tw.

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

37. exp Cyclophosphamide/

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

39. Mycophenolic Acid/

40. mycophenolate.tw.

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

42. exp Chlorambucil/

43. chlorambucil.tw.

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

45. Minocycline/

46. minocyclin$.tw.

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

48. Pyrroles/

49. tofacitinib.tw.

50. Xeljanz.tw.

51. baricitinib.tw.

52. peficitinib.tw.

53. filgotinib.tw.

54. upadacitinib.tw.

55. fostamatinib.tw.

56. exp Glucocorticoids/

57. glucocorticoid$.tw.

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

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

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

#71. #70 AND (2016:py OR 2017:py OR 2018:py OR 2019:py)
#70. #57 AND #68 AND ([article]/lim OR [article in press]/lim) AND [humans]/lim
#69. #57 AND #68
#68. #58 OR #59 OR #60 OR #61 OR #62 OR #63 OR #64 OR #65 OR #66 OR #67
#67. random*:ab,ti
#66. 'randomized controlled trial'/exp
#65. trial:ti
#64. allocat*:ab,ti
#63. (doubl* NEAR/2 blind*):ab,ti
#62. placebo*:ab,ti
#61. crossover*:ab,ti OR 'cross over*':ab,ti
#60. 'single-blind procedure'
#59. 'double blind procedure'/de
#58. 'crossover procedure'/de
#57. #5 AND #56
#56. #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55
#55. beclomethasone:ti,ab OR betamethasone:ti,ab OR budesonide:ti,ab OR clobetasol:ti,ab OR desoximetasone:ti,ab OR dexamethasone:ti,ab OR diflucortolone:ti,ab OR flumethasone:ti,ab OR fluocinonide:ti,ab OR fluocortolone:ti,ab OR fluorometholone:ti,ab OR fluprednisolone:ti,ab OR flurandrenolone:ti,ab OR 'melengestrol acetate':ti,ab OR methylprednisolone:ti,ab OR paramethasone:ti,ab OR prednisolone:ti,ab OR prednisone:ti,ab OR triamcinolone:ti,ab
#54. glucocorticoid*:ti,ab
#53. 'glucocorticoid'/exp
#52. fostamatinib.:ti,ab
#51. upadacitinib.:ti,ab
#50. filgotinib.:ti,ab
#49. peficitinib:ti,ab
#48. baricitinib:ti,ab
#47. xeljanz:ab,ti
#46. tofacitinib:ab,ti
#45. acneclin:ab,ti OR akamin:ab,ti OR aknemin:ab,ti OR 'akne puren':ab,ti OR aknereduct:ab,ti OR 'aknin mino':ab,ti OR 'aknin n':ab,ti OR aknoral:ab,ti OR aknosan:ab,ti OR apominolin:ab,ti OR arestinor:ab,ti OR auramin:ab,ti OR blemix:ab,ti OR borymycin:ab,ti OR cipancin:ab,ti OR cyclimycin:ab,ti OR dentomycin*:ab,ti OR durakne:ab,ti OR dynacin:ab,ti OR enca:ab,ti OR 'icht oralor':ab,ti OR klinoc:ab,ti OR klinomycin:ab,ti OR klinotab:ab,ti OR lederderm:ab,ti OR logryx:ab,ti OR meibi:ab,ti OR mestacine:ab,ti OR micromycin:ab,ti OR 'minac 50':ab,ti OR minakne:ab,ti OR minaxen:ab,ti OR 'mino 50':ab,ti OR minocin:ab,ti OR minoclin:ab,ti OR minodene:ab,ti OR minoderm:ab,ti OR minogalen:ab,ti OR minolis:ab,ti OR minomax:ab,ti OR minomycin:ab,ti OR minoplus:ab,ti OR minosil:ab,ti OR minostad:ab,ti OR minotab*:ab,ti OR minotekor:ab,ti OR minotrex:ab,ti OR minotyrol:ab,ti OR 'mino wolff':ab,ti OR minox:ab,ti OR mynocine:ab,ti OR myrac:ab,ti OR oracyclin:ab,ti OR parocline:ab,ti OR periocline:ab,ti OR peritrol:ab,ti OR ranmino:ab,ti OR romin:ab,ti OR seboclear:ab,ti OR sebomin:ab,ti OR sebren:ab,ti OR skid:ab,ti OR skinocyclin:ab,ti OR solodyn:ab,ti OR spicline:ab,ti OR triomin:ab,ti OR udima:ab,ti OR vectrin:ab,ti OR yelnac:ab,ti OR zacnan:ab,ti
#44. minocyclin*:ab,ti
#43. 'minocycline'/de

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

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

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

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

#33 (neoral or gengraf or restasis or sandimmun* or sangcya):ti,ab
#34 MeSH descriptor: [Penicillamine] explode all trees
#35 Penicillamine:ti,ab
#36 (Adalkenor or Artamin or Atamir or Byanodine or Cilamin or Cuprenil or Cuprimine or Cupripen or Depen or Distamin* or D-Penamine or Gerodyl or Kelatin* or Mercaptyl or Metalcaptase or Pendramine or Rhumantin or Sufortan* or Trisorcin or Trolovol):ti,ab
#37 MeSH descriptor: [Cyclophosphamide] explode all trees
#38 (cyclophosph* or cytophosphan or Cytoxan or sendoxan or endoxan or neosar or nsc-26271 or procytox or b-518 or ifosfamide or isophosphamide or iphosphamide or isofosfamide or holoxan or nsc-109* or "asta z 4942" or cfx or "phosphoramide mustard*"):ti,ab
#39 MeSH descriptor: [Mycophenolic Acid] this term only
#40 mycophenolate:ti,ab
#41 (Arzip or Baxmune or CellCept or Cellmune or Celprot or Ceptolate or Imulate or Imuxgen or Lanfetil or Limfocept or Metocris or Micocept or MMF or Mofecept or Mofetyl or Mofilet or Mofimutral or Mometil or Mophecen or Munotras or Myaccord or Mycept or Myclausenor or Mycofenor or Mycolat or Mycoldosa or Mycophen or Myfenax Myfetil or Mygref or Myotec or Mysept or Presumin or Refrat or Renocell or Supresta or Tevacept or Trixin):ti,ab
#42 MeSH descriptor: [Chlorambucil] explode all trees
#43 chlorambucil:ti,ab
#44 (Amboclorin or Clokeran or Leukeran or Linfolysin or Lympholysin):ti,ab
#45 MeSH descriptor: [Minocycline] this term only
#46 minocyclin*:ti,ab
#47 (Acneclin or Akamin or Aknemin or Akne-Puren or Aknereduct or Aknin-Mino or Aknin-N or Aknoral or Aknosan or Apominolin or Arestinor or Auramin or Blemix or Borymycin or Cipancin or Cyclimycin or Dentomycin$ or durakne or Dynacin or Enca or Icht-Oralor or Klinoc or Klinomycin or Klinotab or Lederderm or Logryx or Meibi or Mestacine or Micromycin or "Minac 50" or Minakne or Minaxen or Mino-50 or Minocin or Minoclin or Minodene or Minoderm or Minogalen or Minolis or Minomax or Minomycin or Minoplus or Minosil or Minostad or Minotab$ or Minotekor or Minotrex or Minotyrol or Mino-Wolff or Minox or Mynocine or Myrac or Oracyclin or Parocline or Periocline or Peritrol or Ranmino or Romin or Seboclear or Sebomin or Sebren or Skid or Skinocyclin or Solodyn or Spicline or Triomin or Udima or Vectrin or Yelnac or Zacnan):ti,ab
#48 MeSH descriptor: [Pyrroles] this term only
#49 tofacitinib:ti,ab
#50 Xeljanz:ti,ab
#51 baricitinib:ti,ab
#52 peficitinib:ti,ab
#53 filgotinib:ti,ab
#54 upadacitinib:ti,ab
#55 fostamatinib:ti,ab
#56 MeSH descriptor: [Glucocorticoids] explode all trees
#57 glucocorticoid*:ti,ab
#58 (Beclomethasone or Betamethasone or Budesonide or Clobetasol or Desoximetasone or Dexamethasone or Diflucortolone or Flumethasone or Fluocinonide or Fluocortolone or Fluorometholone or Fluprednisolone or Flurandrenolone or Melengestrol Acetate or Methylprednisolone or Paramethasone or Prednisolone or Prednisone or Triamcinolone):ti,ab
#59 #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR #19 OR #20 OR #21 OR #22 OR #23 OR #24 OR #25 OR #26 OR #27 OR #28 OR #29 OR #30 OR #31 OR #32 OR #33 OR #34 OR #35 OR #36 OR #37 OR #38 OR #39 OR #40 OR #41 OR #42 OR #43 OR #44 OR #45 OR #46 OR #47 OR #48 OR #49 OR #50 OR #51 OR #52 OR #53 OR #54 OR #55 OR #56 OR #57 OR #58
#60 #5 AND #59

Table S1.7: Pharmacologic interventions of interest

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

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

See table S7 for specific definition of interventions.

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

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

Section 2: Study characteristics of articles and abstracts included.

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

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

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

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

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

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

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

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

Table S2.2: Risk of bias analysis.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Section 3: Efficacy outcomes

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

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

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

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

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

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

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

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

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

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

Table S3.5: Efficacy of strategic studies.

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

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

Section 4: References

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Section 5: List of abbreviations

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

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