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ORIGINAL RESEARCH

Pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis

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ABSTRACT

Objectives To summarise, by a systematic literature review (SLR), the evidence regarding pharmacological and non-pharmacological therapeutic strategies in difficult-to-treat rheumatoid arthritis (D2T RA), informing the EULAR recommendations for the management of D2T RA.

Methods PubMed, Embase and Cochrane databases were searched up to December 2019. Relevant papers were selected and appraised.

Results Two hundred seven (207) papers studied therapeutic strategies. Limited evidence was found on effective and safe disease-modifying antirheumatic drugs (DMARDs) in patients with comorbidities and other contraindications that limit DMARD options (patients with obesity, hepatitis B and C, risk of venous thromboembolisms, pregnancy and lactation). In patients who previously failed biological (b-)DMARDs, all currently used b/targeted synthetic (ts-)DMARDs were found to be more effective than placebo. In patients who previously failed a tumour necrosis factor inhibitor (TNFi), there was a tendency of non-TNFi bDMARDs to be more effective than TNFis. Generally, effectiveness decreased in patients who previously failed a higher number of bDMARDs. Additionally, exercise, psychological, educational and self-management interventions were found to improve non-inflammatory complaints (mainly functional disability, pain, fatigue), education to improve goal setting, and self-management programmes, educational and psychological interventions to improve self-management.
The identified evidence had several limitations: (1) no studies were found in patients with D2T RA specifically, (2) heterogeneous outcome criteria were used and (3) most studies had a moderate or high risk of bias.

Conclusions This SLR underscores the scarcity of high-quality evidence on the pharmacological and non-pharmacological treatment of patients with D2T RA. Effectiveness of b/tsDMARDs decreased in RA patients who had failed a higher number of bDMARDs and a subsequent b/tsDMARD of a previously not targeted mechanism of action was somewhat more effective. Additionally, a beneficial effect of non-pharmacological interventions was found for improvement of non-inflammatory complaints, goal setting and self-management.

Key messages

- This systematic literature review, conducted to inform the Task Force on the EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis (D2T RA), provides an extensive overview of the current literature regarding pharmacological and non-pharmacological therapeutic strategies in D2T RA.
- The identified evidence had several limitations: (1) the evidence is indirect as the study population could not be considered as having D2T RA, (2) heterogeneous outcome criteria were used and (3) most studies had a moderate or high risk of bias.
- Several biological/targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) were found to be effective in RA patients who failed ≥2 bDMARDs, although generally effectiveness decreased with a higher number of previously failed bDMARDs.
- A subsequent b/tsDMARD of a previously not targeted mechanism of action was somewhat more effective in patients who failed ≥1 bDMARD.
- Non-pharmacological interventions, especially education, were found to have an additional beneficial effect for improvement of non-inflammatory complaints, goal setting and self-management.

INTRODUCTION

Therapeutic strategies for patients with rheumatoid arthritis (RA) have significantly improved over the past decades. However,

there is still a substantial proportion of patients that remains symptomatic, even though they have been treated according to the current EULAR recommendations and/or American College of Rheumatology (ACR) guideline for the management of RA.[1 2] This patient group is referred to as having 'difficult-to-treat (D2T) RA'. This disease state is estimated to affect 5% to 20% of all RA patients, depending on the specific definition used.[3–5] D2T RA has recently been defined as failure of at least two biological or targeted synthetic disease-modifying antirheumatic drugs (b/tsDMARDs) with different mechanisms of action (MOA), in patients who are still having complaints which may be indicative of active disease and which is perceived as problematic by patient and/or rheumatologist.[6] An international survey that was conducted among rheumatologists showed the unmet need for this patient population.[7] Consequently, the importance has been acknowledged by EULAR with the approval of a Task Force in charge of the development of management recommendations for D2T RA.

D2T RA is a highly heterogeneous disease state.[4] Patients could be symptomatic due to inflammatory activity: for example, refractory disease (having underlying immunologic disease mechanisms driving multidrug-resistant or 'true' refractory disease), having active disease because they cannot be adequately treated (ie, having limited drug options because of contraindications, such as comorbidities and/or (risk of) adverse events) or having persistent inflammatory activity due to non-adherence. In addition, patients could be symptomatic due to non-inflammatory factors, for example, concomitant osteoarthritis and fibromyalgia.[3 4 8 9] One of the abovementioned factors could be present, although inflammatory activity and non-inflammatory complaints frequently seem to coexist in daily practice.[9]

Furthermore, in patients with D2T RA, a mismatch in goal setting between patients and healthcare professionals, as well as suboptimal self-management, could negatively impact treatment outcomes and illness perception.[10] Patients' management goals could be unrealistic, for example, aiming to return to all normal activities of daily living, while this is not always achievable because of, for instance, the presence of joint damage. To be able to align treatment goals and to optimise self-management, it will be important to identify mismatches in treatment goals and suboptimal self-management to achieve the most optimal effect from available therapeutic strategies.

Currently, RA management recommendations endorse to switch to another b/tsDMARD in symptomatic patients who failed at least one previous b/tsDMARD and could possibly classify as having D2T RA.[1] This therapeutic strategy leads to a trial-and-error approach in patients with D2T RA, as the origin of complaints remains unclear.[4] Furthermore, prioritisation of b/tsDMARDs and non-pharmacological interventions are lacking in the current recommendations. Additionally, no recommendations are currently available for RA patients with limited drug options because of contraindications, those with predominantly non-inflammatory complaints (eg, pain, fatigue, reduced function and quality of life), suboptimal self-management, and for those in whom treatment goals are unclear or do not match with the healthcare professional.

Before switching to yet another DMARD, thorough evaluation of the origin of the complaints is needed to be able to choose the most appropriate treatment option. It will be needed to ascertain the diagnosis of RA and to evaluate alternative or coexisting mimicking diseases. Furthermore, it will be important to assess the presence or absence of inflammatory activity. Optimal diagnostic tests for these diagnostic issues are reviewed in a separate systematic literature review (SLR).[11]

The aim of this SLR was first to explore and summarise pharmacological and non-pharmacological therapeutic strategies in patients with D2T RA that could be used to treat inflammatory activity and non-inflammatory complaints. Furthermore, this SLR focused on the optimisation, and therefore also the identification, of a mismatch in goal setting between patients and healthcare professionals and of suboptimal self-management. This SLR was conducted to inform the EULAR recommendations for the management of D2T RA.

METHODS

Research questions

This SLR was conducted following the EULAR Standardised Operating Procedures (SOP).[12] Seven clinical questions on therapeutic strategies and the identification of suboptimal goal setting and self-management in patients with D2T RA were proposed by the fellow (NMTR), co-methodologist (PMJW) and postdoctoral fellow (MJHdH), and then approved by the steering committee (GN (convenor), JMvL (co-convenor), DvdH (methodologist), MK (fellow)). At the first Task Force meeting, the questions were discussed, amended and then approved by the whole Task Force.

The clinical questions were focused on pharmacological and non-pharmacological therapeutic strategies for (1a) patients with limited DMARD choices because of adverse events, comorbidities or other contraindications, (1b) patients who failed ≥2 b/tsDMARD with different MOA, (1c) patients with predominantly non-inflammatory complaints; and additionally on (2a) the identification and (2b) optimisation of a mismatch in goal setting, and (2c) the identification and (2d) optimisation of suboptimal self-management. The clinical questions were transformed into epidemiological questions using the 'Patients, Intervention (index test for diagnostic question), Comparator (reference test), Outcome (PICO) format' (online supplemental file).[13]

Search strategy

The databases of PubMed, Embase and Cochrane were searched for papers in English until December 2019 for search 1 and December 2018 for search 2. Additionally,

the conference abstracts of EULAR and ACR were screened, from 2017 until 2019 for search 1 and from 2017 until 2018 for search 2. Advice regarding the set-up of the search strategy was provided by two experienced librarians of Utrecht University (FPW and PHW).

The first search focused on the pharmacological and non-pharmacological therapeutic strategies for RA patients with limited DMARD choices, who previously failed b/tsDMARDs or those with predominantly non-inflammatory complaints. In addition to terms for RA and terms related to therapeutic studies, terms were included for difficult-to-treat disease, adverse events, fatigue, pregnancy and comorbidities that may limit DMARD choices (infections: hepatitis B virus (HBV), hepatitis C virus (HCV), HIV, tuberculosis (TBC); malignancies; lung disease: fibrosis, asthma, chronic obstructive pulmonary disease (COPD); cardiovascular (CV) disease: hypertension, cardiomyopathy; hyperlipidaemia; chronic kidney dysfunction; chronic liver dysfunction; liver enzyme elevation; osteoporosis; diabetes mellitus; thrombosis; depression; anxiety; online supplemental file). Furthermore, terms were included for specific DMARDs, glucocorticoids (GCs), non-steroidal- anti-inflammatory drugs (NSAIDs) and non-pharmacological treatment options. A search limit was set to the last 10 year. In addition, the reference lists of selected papers were manually screened. References published in the year 2000 and later were eligible for inclusion. This cut-off was chosen because of the introduction of bDMARDs around this time and, herewith, the beginning of a new therapeutic landscape regarding available treatment strategies in the field of RA. Moreover, as failure of ≥2 b/tsDMARD with different MOA is part of the D2T RA definition, RA patients could not fulfil the definition before this time point.

The second search focused on the identification and optimisation of suboptimal goal setting and self-management. In this search, terms for RA as well as terms for management goals and self-management were included (online supplemental file). No terms for difficult-to-treat patients were included, as studies in other RA patients were also considered to be relevant as indirect evidence for these specific questions, since limited evidence was expected. Additionally, no terms on specific outcomes were included as many outcomes could be of interest and they may be described in many different ways.

Selection of studies

First, titles and abstracts were screened in duplicate by the fellows (first search: NMTR and MK; second search: NMTR and AH) according to a predefined list of selection criteria (online supplemental file) until the percentage of conflicts was below 5%. In case of conflicts or when in doubt, eligibility was discussed with the co-methodologist (PMJW). Second, all full-text versions of the selected papers were screened in duplicate by the fellows (first search: NMTR, and MK or AH; second search: NMTR and AH). Disagreements were discussed with the co-methodologist (PMJW) until consensus was reached.

Following the EULAR SOP, SLRs of sufficient quality could be selected in addition to original studies.[12] The original studies of the selected SLRs were excluded to avoid duplicate evidence. Additionally, the most recent SLR was selected in case of fully overlapping evidence in two or more SLRs.

As evidence for patients with D2T RA specifically was expected to be scarce, for the question on RA patients who previously failed ≥2 b/tsDMARDs with different MOA (1b), it was decided to select papers with patients who failed ≥1 b/tsDMARD. For the question on RA patients with non-inflammatory complaints (1c), papers specifically including patients with active disease, for example, according to composite indices, were excluded and only papers regarding patients with non-inflammatory complaints (reduced function and quality of life, and presence of pain and fatigue) or in unselected populations (ie, not specifically active disease) reporting on these outcomes were selected. Regarding the question on a mismatch in goal setting between patients and healthcare professionals (2a), studies comparing the frequencies of the importance of specific treatment goals between patients and healthcare professionals were also selected, as these may highlight important goals that may not match between patients and healthcare professionals.

Data extraction and quality assessment

Information on study design, patient characteristics, interventions, comparators and outcomes (including relevant descriptive statistics and/or occurrence and association measures) were extracted from the included papers using a predetermined format (online supplemental file).

Risk of bias (RoB) of the original papers was assessed using the Cochrane Collaboration's risk of bias tool,[14] and highest RoB as found was reported here (low, moderate, high). For the questions on the identification of suboptimal goal setting (2a) and self-management (2c), RoB was assessed using the Quality Assessment of Diagnostic Accuracy Studies tool version 2 (QUADAS-2),[15] and highest RoB as found was reported (low, moderate, high). For SLRs, 'A MeaSurement Tool to Assess systematic Reviews version 2' (AMSTAR-2) was used and overall RoB was reported according to the AMSTAR-2 scoring system (low, moderate, high, critically high).[16]

Data extraction and quality assessment were performed in duplicate by the fellows (NMTR and AH) until the number of conflicts was below 5%. Disagreements and remaining doubts were discussed with the co-methodologist (PMJW) until consensus was reached.

Statistical analyses

Extracted data were summarised descriptively regarding the main reported or calculable association measures for the therapeutic questions (eg, odds ratio (OR), mean outcome in intervention and comparator group) and the

diagnostic evaluations (eg, sensitivity, specificity, likelihood ratio).

Pooling of results was performed in case of sufficient clinical and statistical homogeneity as determined by the steering committee. For the questions on therapeutic strategies for RA patients with predominantly non-inflammatory complaints (1c) and optimisation of self-management (2d), effect sizes (using Cohen's d) were calculated or extracted to be able to compare results over different outcomes and scoring methods.

RESULTS

Study characteristics

The first search regarding pharmacological and non-pharmacological strategies resulted in 5885 unique papers. After title and abstract screening, 1165 papers were selected for full-text screening and 121 papers were finally deemed eligible for inclusion. Additionally, 36 papers were selected via reference screening and hand search (figure 1A). Thirty-two papers were selected for ttherapeutic strategies in patients with limited DMARD options,[17–48] 73 for patients who failed ≥1 b/tsDMARD[49–121] and 50 for patients with predominantly non-inflammatory complaints.[122–171]

The second search regarding goal setting and self-management yielded 1385 unique papers. Title and abstract screening resulted in 236 papers, and 38 papers were selected for data extraction. Four additional papers were selected via reference screening (figure 1B). Three[172–174] and four papers[175–178] were selected for the identification and optimisation, respectively, of a mismatch in goal setting between patients and healthcare professionals. Five[173 179–182] and 31 papers[122 125 126 130–132 135 137 144 145 148 152 153 159 160 162 167 183–196] were selected for the identification and optimisation, respectively, of suboptimal self-management.

None of the studies in search 1 or search 2 included patients with D2T RA specifically, resulting in a lower applicability of the results overall. Heterogeneity in study populations, therapeutic strategies, outcome criteria and association measures prohibited pooling the data in an appropriate way. All quantitative information regarding study characteristics, therapeutic strategies and outcomes are summarised in online supplemental tables 1-7.

The overall RoB was moderate or high in the majority of studies. Studies were considered as having a high RoB because of their study design (ie, observational studies), subanalyses of randomised controlled trials (RCTs) were performed (not a priori planned or not based on stratified groups) or blinding of participants was not performed (as in the majority of studies regarding non-pharmacological strategies). Studies were assessed as having a moderate RoB, due to insufficient reporting of the randomisation process and/or allocation concealment. Detailed RoB assessment is shown in online supplemental tables 1-7.

RA patients with limited drug options

Thirty-two papers (6 SLRs, 9 RCTs, 17 observational studies; 1 low RoB, 7 moderate RoB, 24 high RoB) were selected comparing efficacy and/or safety of DMARDs in RA patients with limited DMARD options due to a comorbidity and/or another contraindication: HBV, HCV, hepatic disease, pulmonary disease, CV disease, obesity, osteoporosis/osteopenia, renal disease, extra-articular manifestations, pregnancy, psychological disease (online supplemental table 1).[17–26 28–41 44–48] No evidence was identified comparing the efficacy and/or safety of DMARDs in RA patients with gastrointestinal disease, HIV, (latent) TBC, malignancies or previously experienced adverse events related to the treatment.

Only the efficacy of infliximab in RA patients with obesity was assessed in more than one cohort of RA patients. In both papers (high RoB), infliximab (3 mg/kg) was found to be less effective in patients with a body mass index (BMI) >30 than in those with BMI <30 (Disease Activity Score assessing 28 joints based on erythrocyte sedimentation rate (DAS28-ESR) remission at 12 months: 0% vs 22.4%, p=0.01[28]; change in DAS28 ≥1.2 from baseline (BL) until 16 weeks: 58.1% vs 46.7%, p=0.04).[33] No differences in RA patients with BMI >30 compared with those with BMI <30 were found for treatment with adalimumab, etanercept or rituximab (in single observational studies: DAS28 based on C reactive protein (CRP) <2.6 at 12 months, adalimumab: 14.8% vs 30.1%, p=0.08; DAS28-CRP <2.6 at 12 months, etanercept: 27.6% vs 36.2%, p=0.44; ACR50 response at 24 weeks, rituximab: 55.7% vs 49.1%–53.4%, not significant).[48] In patients with obesity, no studies comparing different treatment options were identified.

Safety of DMARD use in patients with a comorbidity was assessed in an SLR or in more than one cohort of RA patients with HBV, HCV, pregnancy/lactation and in those at risk for venous thromboembolisms (VTEs). In patients with active HBV, a relatively low rate of HBV reactivation was found using bDMARDs in one SLR (of 21 studies, moderate RoB) and two observational studies (high RoB) compared with patients with inactive HBV (tumour necrosis factor inhibitor (TNFi), SLR: 10.7% vs 2.6%; tocilizumab: 0% vs 4.8%; abatacept: 0% vs 0%).[20 22 39] The authors of the SLR concluded that antiviral prophylaxis would be recommended in patients with active HBV infection.[20]

In an observational study (high RoB) in patients with HCV undergoing treatment with TNFi, liver disease developed more frequently compared with patients without HCV (development of liver injury within 1 year: 10% vs 1.23%, p=0.099),[34] a difference that did not reach statistical significance in this relatively small sample size (n=101). The authors of the SLR (of 37 studies, high RoB) concluded that the safety profile of TNFi in the setting of HCV infection seemed to be acceptable.[18]

Evidence regarding safe DMARD use before and during pregnancy and during lactation was found in the 2020 ACR guideline and 2016 EULAR points to consider (of 53

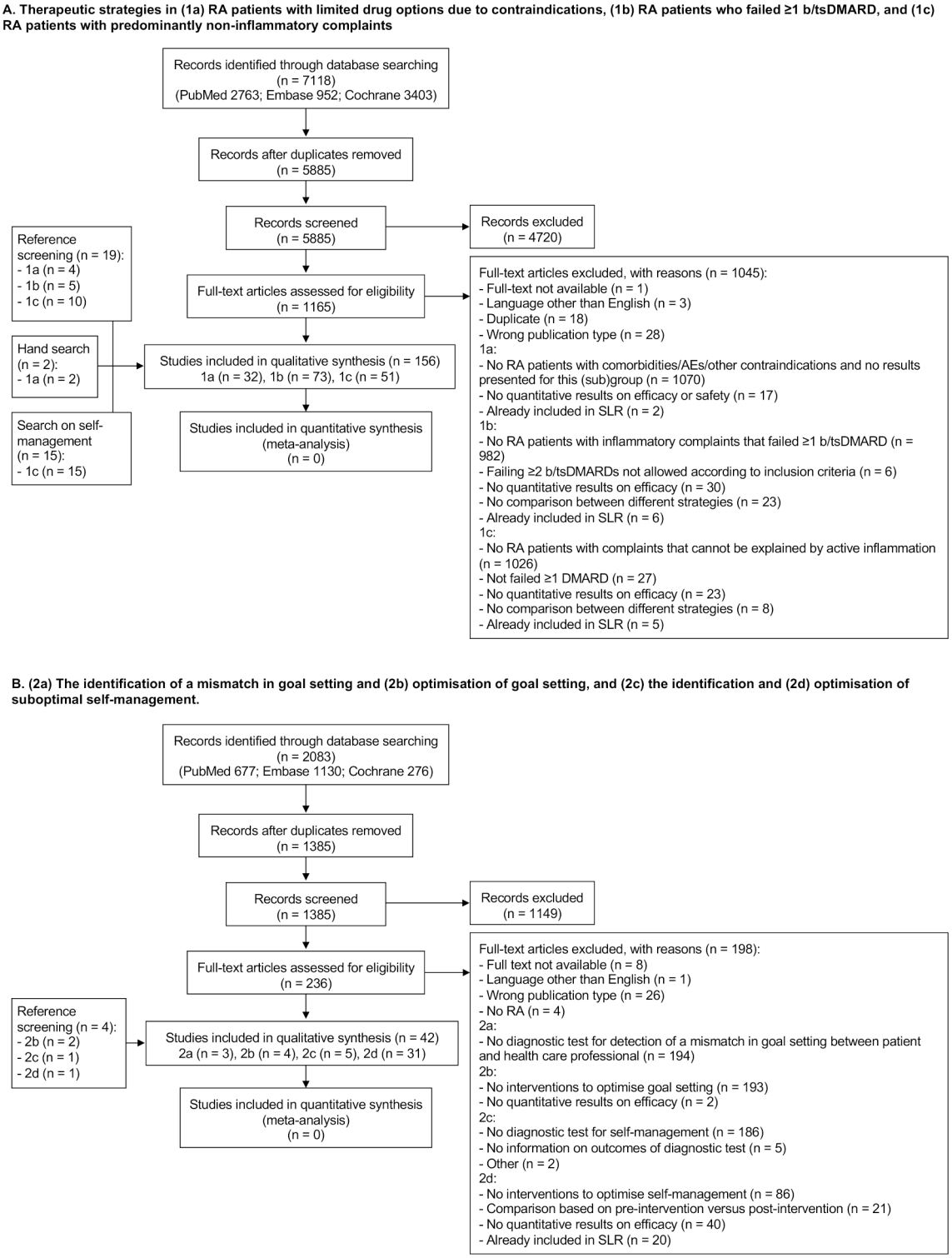

Figure 1 Flow charts of search and selection of papers. AEs, adverse events; n, number of papers; RA, rheumatoid arthritis; SLR, systematic literature review.

and 319 studies, respectively, moderate RoB).[27 42] These recommendations have been based on extensive SLRs and summarise the evidence per DMARD. In patients before and during pregnancy and lactation, no safety issues have been identified for antimalarials, sulfasalazine, azathioprine, ciclosporin, tacrolimus and glucocorticoids. Of bDMARDs, TNFis (especially certolizumab pegol) and rituximab appear without identified safety issues. Three additional papers (1 SLR (of 84 studies, moderate RoB), 2 observational studies (high RoB)) resembled the findings of these recommendations.[23 30 36]

In the SLR (of three studies on this topic, moderate RoB) regarding the safety of DMARDs informing the 2019 EULAR RA management recommendations, the

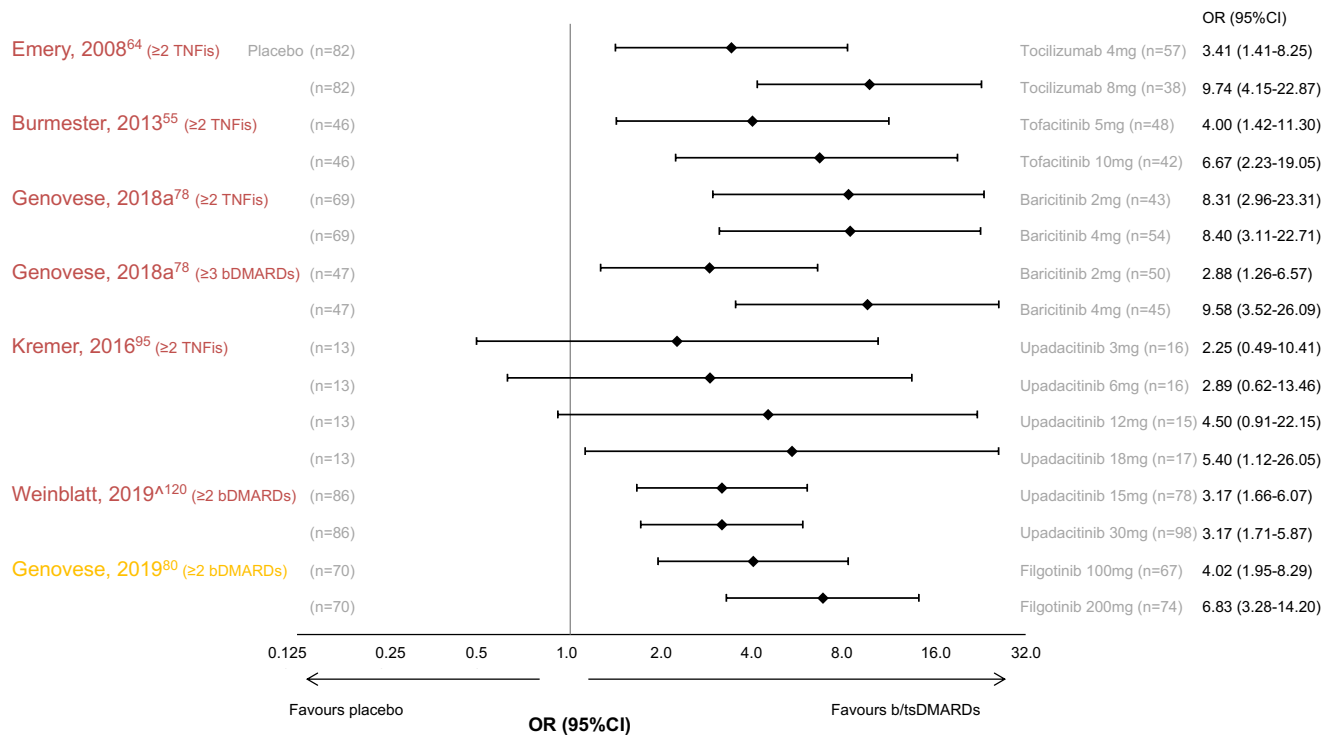

Figure 2 ACR20 response at 12to 24 weeks in RA patients who failed ≥2 bDMARDs. (m)ACR, (modified) American College of Rheumatology; bDMARD, biological synthetic disease-modifying antirheumatic drug; n, number of patients; OR, odds ratio; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor. Colours of author names according to risk of bias: font in yellow: moderate risk of bias; font in red: high risk of bias. ORs are shown as diamonds and whiskers represent 95% CI.

safety of tsDMARDs in RA patients and especially those at risk for VTEs was summarised.[43] In these patients, an increased risk of VTEs was found for tofacitinib and baricitinib, specifically when using the higher doses of 10 and 4 mg, respectively. Evidence on other tsDMARDs is not yet available.

RA patients who failed ≥1 b/tsDMARD

Failure of ≥2 bDMARDs

Nine papers were found regarding the efficacy of b/tsDMARDs in patients who failed ≥2 bDMARDs (7 RCTs (subanalyses), 2 observational studies; 1 moderate RoB, 8 high RoB; online supplemental table 2). In six of these papers, the efficacy of tocilizumab, tofacitinib, baricitinib, upadacitinib and filgotinib, respectively, versus placebo was assessed using ACR20 response at 12 to 24 weeks as an outcome (graphically summarised in figure 2).[55 64 72 80 95 120] ACR20 response favoured therapy with b/tsDMARD in all papers. The other study (high RoB) assessed the efficacy of mavrilimumab versus golimumab in a small population of six patients who previously failed two TNFis excluding golimumab (ACR20 response at 24 weeks 66.7% vs 0%).[119] In two observational studies (high RoB), the efficacy of an alternative TNFi versus rituximab was assessed and rituximab was found to be more effective (DAS28-ESR at 6 months 4.54 vs 3.91, p=0.021; change in DAS28 from BL until 6 months −0.75 vs −1.31, not significant).[53 66]

Failure of ≥1 b/tsDMARD

Thirty-one papers (7 SLRs, 23 RCTs, 1 observational study; 8 low RoB, 16 moderate RoB, 7 high RoB) assessed the efficacy of b/tsDMARDs in patients who failed ≥1 bDMARD versus placebo (online supplemental table 2).[50 52 56 57 61 67 68 70–77 79 80 85 92 94 95 97 98 103 104 108 109 111 113 115 116] A significant higher efficacy was found for the following b/tsDMARDs compared with placebo: alternative TNFi, abatacept, rituximab, tocilizumab, ixekizumab, ocrelizumab, olokizumab, sarilumab, secukinumab, sirukumab, tofacitinib, baricitinib, upadacitinib and filgotinib. No benefit in efficacy was found for other bDMARDs compared with placebo, which are not approved for RA (atacicept, fostamatinib and tabalumab).

Thirty-eight papers (7 SLRs, 6 RCTs, 25 observational studies; 2 low RoB, 7 moderate RoB, 29 high RoB) compared the efficacy of different b/tsDMARDs in patients who failed ≥1 b/tsDMARD (online supplemental table 2).[49 52 54 58–60 62 63 65 69 75 81–84 87–94 96 97 99–101 106 107 110 112 114 115 117–119 121] Only one study (high RoB) explicitly included a mixed population of patients who failed a bDMARD or a tsDMARD, all other papers only included patients who failed ≥1 bDMARD.[69] In 30 of 38 papers, patients explicitly failed a TNFi. Patients failed rituximab in three papers,[62 114 117] tocilizumab in two papers,[49 100] a non-TNFi in one paper,[101] and a mix of TNFis and non-TNFi bDMARDs in two papers.[96 110]

Six papers (4 SLRs (of 9, 24, 6 and 4 papers (partly overlapping)), 1 RCT and 1 observational study; 3 moderate RoB, 3 high RoB) assessed the efficacy of alternative TNFis versus non-TNFi bDMARDs as a group, in patients who failed a TNFi.[52 82 83 94 99 118] Non-TNFi bDMARDs were found to be more effective in two original studies using different outcome criteria (EULAR good/moderate response at 52 weeks 43% vs 60%, p=0.0006 (high RoB)[83]; change in clinical disease activity index (CDAI) from BL until 1 year −4.81 vs −7.54, p=0.037 (high RoB)[118]). Two of four SLRs (of 24 and 6 studies (partly overlapping); moderate RoB) concluded that there was a tendency of non-TNFi bDMARDs to be more effective than TNFis, after failure of a TNFi.[52 82 94 99]

Three papers assessed the efficacy of an alternative TNFi versus abatacept, conflicting results were found regarding the superiority of abatacept in patients who failed a TNFi (1 SLR (of six studies), 1 observational study; 1 moderate RoB, 1 high RoB),[88 94] and some advantage was found for TNFi to be more effective than abatacept in patients who failed tocilizumab (1 observational study; high RoB).[49] There was a numerical advantage of rituximab to be more effective than TNFi in patients who failed a TNFi in 6 of 10 papers (statistically significant in at least one of the response criteria in 5 papers (2 SLRs (of 24 and 6 studies (partly overlapping)), 1 RCT, 7 observational studies; 2 moderate RoB, 8 high RoB).[54 59 65 81 82 86 93 94 107 112] Additionally, there was a numerical advantage of tocilizumab in patients who failed a TNFi in three of four papers (statistically significant in at least one of the response criteria in 3 papers (2 SLRs (of 24 and 6 studies (partly overlapping)), 2 observational studies; 2 moderate RoB, 3 high RoB),[82 90 91 94] a numerical advantage of tocilizumab in patients who failed rituximab in 2 of 2 papers (statistically significant in at least one of the response criteria in 1 paper (2 observational studies; 2 high RoB)[114 117] and no advantage of TNFi nor tocilizumab in patients who failed a bDMARD (not further specified (1 observational study; high RoB).[96] Five of the abovementioned papers reported an (modified) ACR50 response as outcome and are graphically summarised in figure 3.[54 86 88 90 94]

Six papers compared the efficacy of different alternative TNFis in patients who failed a TNFi and concluded that there was insufficient evidence to prioritise (1 SLR (of 9 studies), 1 RCT, 4 observational studies; 1 low RoB, 5 high RoB).[52 58–60 106 121] When directly comparing different non-TNFi bDMARDs, there was a numerical advantage of tocilizumab to be more effective than abatacept in patients who failed a TNFi in six of seven papers (statistically significant in at least one of the response criteria in 3 papers (1 SLR (of 4 studies), 1 RCT, 5 observational studies; 1 moderate RoB, 6 high RoB)).[63 83 84 89 91 97 101] Additionally, there was a numerical advantage of tocilizumab to be more effective than abatacept in patients who failed rituximab in three of three papers (statistically significant in at least one of the response criteria in 2 papers (3 observational studies; 3 high RoB)).[62 114 117] Furthermore, there was some advantage of tocilizumab to be more effective than rituximab in patients who failed a TNFi (4 papers) or a non-TNFi (1 paper) in five of five papers (statistically significant in at least one of the response criteria in all papers (2 SLRs (of 24 and 4 studies (partly overlapping)), 1 RCT, 2 observational studies; 2 moderate RoB, 3 high RoB)).[82–84 97 101] Additionally, a numerical advantage of rituximab to be more effective than abatacept was found in patients who failed a TNFi in three of three papers (statistically significant in at least one of the response criteria in 1 paper (1 SLR (of 4 studies), 1 RCT, 1 observational study; 1 moderate RoB; 2 high RoB)).[54 84 97]

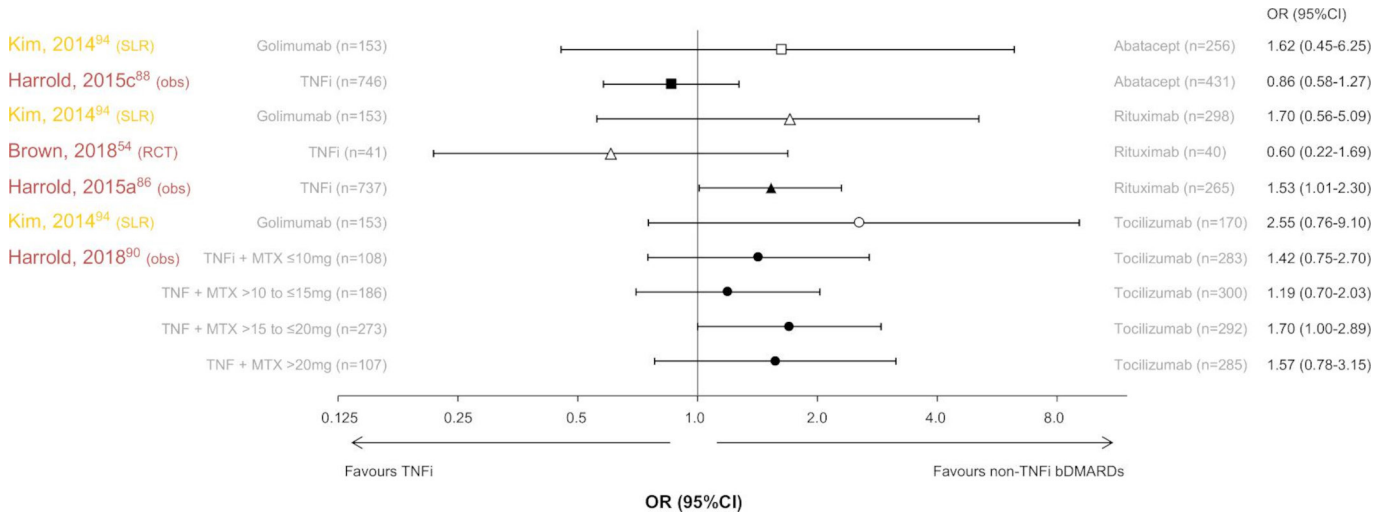

Figure 3 TNFi versus non-TNFi bDMARDs: (m)ACR50 response at 6 to 12 months in patients with rheumatoid arthritis (RA) who failed ≥1 TNFi. (m)ACR, (modified) American College of Rheumatology; bDMARD, biological disease-modifying antirheumatic drug; mg, milligram; MTX, methotrexate; n, number of patients; obs, observational study; TNFi, tumour necrosis factor inhibitor; SLR, systematic literature review. Colours of author names according to risk of bias: font in yellow: moderate risk of bias; font in red: high risk of bias. ORs are shown as ▄, abatacept; ▲, rituximab; ●, tocilizumab. White symbols represent univariate analyses, black symbols multivariate analyses and whiskers 95% CI.

Three papers compared the efficacy between tsDMARDs and different bDMARDs (2 SLRs (of 4 and 5 studies (partly overlapping)), 1 observational study; 2 moderate RoB, 1 high RoB).[69 97 115] There was a numerical advantage of rituximab to be more effective than tofacitinib in patients who failed a TNFi two of two papers, although statistical significance was not reached.[97 115] Conflicting results were found regarding superiority in efficacy of the other bDMARDs assessed (TNFi, abatacept, tocilizumab) versus tofacitinib. No studies comparing bDMARDs versus other tsDMARDs were identified nor studies comparing different tsDMARDs.

Comparison of efficacy of b/tsDMARDs between RA patients who previously failed a different number of bDMARDs

Nine papers compared the efficacy of a b/tsDMARD between patients who previously failed an increasing number of bDMARDs (8 RCTs (subanalyses), 1 observational study; 1 moderate RoB, 8 high RoB; online supplemental table 2).[55 57 64 78 80 86 102 105 120] Seven studies used ACR20 response as an outcome, a graphical summary is shown in figure 4.[55 57 64 78 80 105 120] For golimumab, tocilizumab 4 mg (intravenous), tofacitinib 5 mg and baricitinib 2 mg, the efficacy numerically decreased with an increasing number of previously failed bDMARDs.[55 57 64 78 105] For upadacitinib and filgotinib, this tendency in decreased efficacy was less clear,[80 120] as well as for the higher doses of tocilizumab (intravenous), tofacitinib and baricitinib (figure 4).[55 57 64 78]

Two studies reported other response criteria than the ACR20 response. In these studies, the efficacy of abatacept and rituximab also numerically decreased with an increasing number of previously failed bDMARDs (abatacept: change in DAS28-CRP from BL until 6 months, failure of 1 TNFi vs 3 TNFis: −2.1% vs −1.7%, statistically significant (high RoB)[102]; rituximab: CDAI at 12 months (not corrected for baseline values), failure of 1 TNFi vs ≥2 TNFis: 13.2 vs 18.3, significance not reported (high RoB)[87]).

RA patients with predominantly non-inflammatory complaints

Fifty papers (21 SLRs (on different topics, although partly overlapping), 27 RCTs, 2 observational studies; 12 low RoB, 11 moderate RoB, 27 high RoB) were found regarding RA patients with non-inflammatory complaints (online supplemental table 3).[122–171] Heterogeneous interventions were assessed, while the control intervention was mostly usual care or waiting list. Different outcome criteria were used to assess efficacy. The number of papers with statistically significant benefit of the intervention compared with control per category of intervention and per outcome, including their effect size (if reported or calculable), is shown in table 1.

Only eight papers specifically selected patients with non-inflammatory complaints (pain: 4 (1 SLR (of 11 studies), 3 RCTs; 1 low RoB, 2 moderate RoB, 1 high RoB)[143 151 156 170]; fatigue: 3 (3 RCTs; 3 high RoB)[137 143 146]; psychological problems: 1 (RCT; high RoB)[138]; difficulties in performing daily activities: 1 (RCT; high RoB)[168]). Although patients in these studies were selected on the presence of non-inflammatory complaints, DAS28 still ranged from 2.82 to 5.85 (not reported in 3 studies, online supplemental table 3). Therefore, the presence of inflammatory activity could not be excluded. The results of these papers resembled the findings of the other studies, which enrolled an unselected population of RA patients and reported on outcomes regarding non-inflammatory complaints.

Exercise, education, self-management programmes and intensification of patient care were found to improve function. Dietary, psychological interventions and self-management programmes were found to reduce pain, as well as pharmacological interventions (ketoprofen patch and celecoxib). Psychological and self-management programmes were found to reduce fatigue. No (sufficient) benefit in any of the abovementioned complaints was found for alternative medicine, cryotherapy and balneotherapy.

Identification and optimisation of a mismatch in goal setting between RA patients and healthcare professionals

Identification of a mismatch in goal setting

Three studies (all with a cross-sectional design; two high RoB, one qualitative study) were found regarding the identification of a mismatch in goal setting between patients and healthcare professionals (online supplemental table 4).[172–174] A diagnostic test to identify a mismatch was not identified. All studies compared two different populations regarding the importance of treatment goals: RA patients and clinicians in two studies, and RA patients with high and low disease activity in the other study. In the qualitative study, patients expressed a desire for clinicians to look beyond clinical markers and to consider patient-reported outcomes.[172] In the other study comparing RA patients and clinicians (high RoB), patients and clinicians had the same treatment goals regarding complaints, medication use and daily activity.[173] Most treatment goals, such as reduction in inflammation, pain and fatigue, were more frequently scored as important by clinicians (patients vs clinicians: 50% vs 74%, 67% vs 88% and 46% vs 62%, respectively). Only 'see more/other physicians to help RA management' was more frequently scored as important by RA patients, although the difference was small (13% vs 9%). In the study comparing RA patients with high and those with low disease activity (high RoB), improvement in arthritis was more frequently scored as important by patients with high disease activity.[174] On the other hand, improvement in morning stiffness was more frequently scored as important by patients with low disease activity.

Optimisation of goal setting

Four studies (1 RCT, 3 observational studies; all high RoB) were found regarding the optimisation of goal setting.[175–178] All studies used a web-based education tool as the intervention (online supplemental table

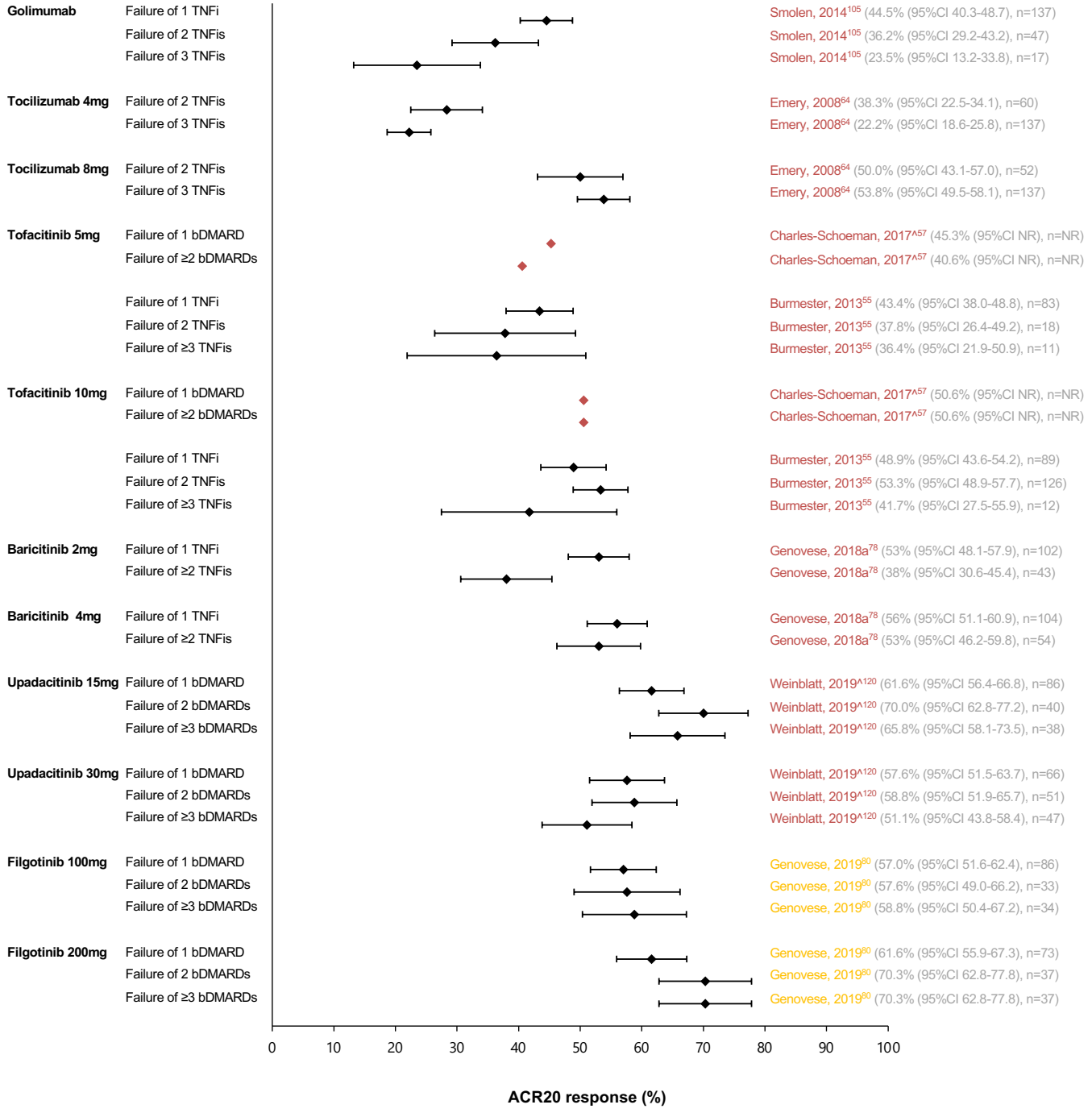

Figure 4 Comparison of ACR20 response at 3 months to 24 weeks in studies comparing RA patients with different numbers of previously failed bDMARDs. ACR, American College of Rheumatology; bDMARD, biological disease-modifying antirheumatic drug; n, number of patients; NR, not reported; RA, rheumatoid arthritis; TNFi, tumour necrosis factor inhibitor; ^Abstract. Colours of author names according to risk of bias: font in yellow: moderate risk of bias; font in red: high risk of bias. Black diamond with whiskers: OR with 95% CI; red diamond: OR, 95% CIs are not reported.

5). Different selections of RA patients were included: patients with active disease, patients who were unsure about starting treatment with methotrexate, patients who were starting b/tsDMARDs or an unselected population. RA knowledge improved statistically significantly using the intervention in all studies. In one study, in an unselected population of RA patients, willingness to try a b/tsDMARD was assessed and improved statistically significantly.[175] In another study, in patients starting b/tsDMARDs, certainty in choosing a DMARD option was assessed and increased statistically significantly.[178]

Identification and optimisation of self-management

Identification of suboptimal self-management

Five papers were found regarding the identification of suboptimal self-management: two assessed the importance

Table 1 Papers on therapeutic strategies for non-inflammatory complaints, including effect sizes

Type of intervention	Outcome	Benefit of intervention compared with control* in *n* of *n* selected papers (if applicable: of which *n* of *n* SLRs)	Effect size for papers with benefit of intervention† (if available)	RoB (n) L	M	H
Exercise[129 136 137 140 147 153 154 157–159 165 166 171]	Function	7/8(4/4)	0.39; 0.46; 0.73; 0.88	2	2	4
	Pain	4/10(2/7)	0.99‡; 1.02	3	3	4
	QoL	2/3(0/1)	0.90	0	1	2
	Fatigue	2/4(1/2)	0.37	0	2	2
	Other:					
	- Aerobic capacity and muscle strength	1/2(1/1)	0.47–0.99‡	1	0	1
	- Range of motion	1/2(1/1)		0	1	1
	- Grip function	0/1(0/1)		1	0	0
	- Global impact of disease	1/1(1/1)		0	1	0
	- Mood	0/1(0/1)		0	1	0
Diet[127 129]	Function	No papers				
	Pain	2/2(2/2)	–	2	0	0
	QoL	No papers				
	Fatigue	No papers				
Psychological interventions[133 134 138 146 162 165]	Function	1/2(1/1)	–	0	1	1
	Pain	3/5(3/3)	0.177‡	1	2	2
	QoL	No papers				
	Fatigue	4/4(2/2)	0.16	1	1	2
	Other:					
	- Overall efficacy	1/1(1/1)	–	0	1	0
	- Negative mood and anxiety	1/1	0.31–0.46	0	0	1
Education[128 129 159]	Function	1/1(1/1)	–	1	0	0
	Pain	0/1	–	0	0	1
	QoL	No papers				
	Fatigue	0/1	–	0	0	1
	Other: Mood	1/1(1/1)	–	0	1	0
Self-management programmes§[122 125 126 132 135 137 144 148 152 160 167]	Function	2/7(2/3)	–	1	2	4
	Pain	3/9(3/4)	–	2	2	5
	QoL	0/2(0/1)		1	0	1
	Fatigue	4/4(3/3)	0.37	1	2	1
Alternative medicine[143 150 155 158]	Function	No papers				
	Pain	2/3(0/1)	1.44–2.00	1	1	1
	QoL	No papers				
	Fatigue	1/1	0.98–1.67	0	0	1
	Other:					
	- Range of motion	1/1	0.49–14.37	0	0	1
	- Morning stiffness	1/1(1/1)		1	0	0
	- Patient global assessment	1/1(1/1)		0	1	0

Continued

Table 1 Continued

Type of intervention	Outcome	Benefit of intervention compared with control* in *n* of *n* selected papers (if applicable: of which *n* of *n* SLRs)	Effect size for papers with benefit of intervention† (if available)	RoB (n)		
				L	M	H
Cryotherapy[142 149]	Function	0/2		0	0	2
	Pain	0/2		0	0	2
	QoL	No papers				
	Fatigue	0/1		0	0	1
Balneotherapy[123 124 164 165]	Function	1/3(0/1)	–	0	1	2
	Pain	1/3(0/1)	0.88	0	1	2
	QoL	0/1		0	0	1
	Fatigue	0/1		0	0	1
	Other: Global impact of disease	0/1(0/1)		0	1	0
Intensification of patient care[130 131 145 161 168 169]	Function	2/4	0.29	0	0	4
	Pain	1/2	–	0	0	2
	QoL	0/3		0	0	3
	Fatigue	1/2(0/1)	–	1	0	1
Pharmacological (non-DMARD)[139 141 151 156 163 170]	Function	0/1(0/1)		1	0	0
	Pain	2/6(1/4)	0.15ketoprofen patch	3	3	0
	QoL	0/2(0/2)		1	1	0
	Fatigue	No papers				
	Other: Patient global assessment	1/1(1/1)	–	1	0	0

*Mostly usual care or wait list.
†Cohen's d, if different outcome measures were used, the range in effect sizes over these measures is reported.
‡Pooled effect size, reported in SLR.
§Combination of non-pharmacological interventions.
H, high (red); L, low (green); M, moderate (yellow); n, number of papers; RA, rheumatoid arthritis; RoB, risk of bias; SLR, systematic literature review.

of factors associated with successful self-management comparing RA patients and clinicians (2 with a cross-sectional design; 1 low RoB, high RoB)[173 181] and three assessed a diagnostic measure (1 SLR (of 15 studies), 2 cross-sectional studies; all moderate RoB; online supplemental table 6).[179 180 182]

In both descriptive studies regarding the importance of factors associated with optimal self-management, most factors were more frequently scored as important by clinicians than by RA patients (eg, a discussion about self-management, more/longer visits, education about psychosocial needs, activities of daily living, sexual concerns).[173 181] Patients expressed a desire for a more important role of pharmacists and nutritionists in arthritis education, and for more education on the disease, diagnostic process and nutrition.[181]

In the SLR regarding diagnostic measures, the Arthritis Self-Efficacy Scale (ASES) and RA Self-Efficacy Scale (RASE) were found to be assessed in more than one cohort of RA patients. Evidence for the RASE suggested that this measure is multidimensional, which is not adequately represented in the scoring. Therefore, ASES was concluded to be the most reliable test, although its methodological weakness was acknowledged by the authors (ie, the content validity and whether it adequately reflects self-efficacy was not explicitly addressed during development).[179] In another study, the Modified Rheumatology Attitude Index correlated with the combined questionnaire for functional impairment and quality of life, pain score, patient global assessment and functional impairment questionnaire.[180] In a study assessing two cohorts of RA patients, the Brief Resilient Coping scale also significantly correlated with different other measures.[182]

Optimisation of self-management

Thirty-one papers (7 SLRs (on different topics, although partly overlapping), 23 RCT, 1 observational study; 5 low Rob, 3 moderate RoB, 23 high RoB) were found regarding the optimisation of self-management (online supplemental table 7). No papers specifically selected patients with suboptimal self-management. Different outcomes were found to describe self-management for which different outcome measures were used and heterogeneous interventions were assessed (table 2). The number of papers with statistically significant benefit of the intervention compared with control (mostly usual care or waiting list) per outcome and per type

Table 2 Papers on the optimisation of self-management, including effect sizes

Outcome	Type of intervention	Benefit of intervention compared with control* in *n* of *n* selected papers (if applicable: of which *n* of *n* SLRs)	Effect size for papers with benefit of intervention† (if available)	RoB (n)		
				L	M	H
Self-efficacy[122 125 126 130–132 137 144 145 148 152 159 160 162 167 183 185–196]	Self-management programmes‡	12/13(4/4)	0.18–0.39; 0.23–0.67; 0.37; 0.43–0.53; 0.49§; 7.52–8.25	2	2	9
	Education	6/6(1/1)	0.05–0.17; 0.22–0.59; 1.23	0	1	5
	Psychological	2/2(1/1)	0.20–0.35; 0.45	1	0	1
	Other:					
	- Exercise	1/1	0.44–1.06	0	0	1
	- Nurse-led follow-up	1/1(1/1)	–	1	0	0
	- Eszopiclone 3 mg	1/1	0.05–0.37	0	1	0
	- Assistive technology (eye drop dispenser)	1/1(1/1)	–	1	0	0
	- Patient-reported outcome-based telehealth follow-up	0/1		0	0	1
	- Direct access to hospital review through helpline	0/1		0	0	1
Anxiety[137 145 162 183 184 187 191–193]	Self-management programs‡	1/1	0.69–0.71	0	0	1
	Education	1/3	0.039	0	0	3
	Psychological	1/2(1/1)	0.17§	1	0	1
	Other:					
	- Relaxation therapy	0/1		0	0	1
	- Direct access to hospital review through helpline	0/1		0	0	1
Depressive symptoms[132 137 145 152 162 183 184 187 191–193]	Self-management programmes‡	0/2		0	0	2
	Education	0/3		0	0	3
	Psychological	3/3(2/2)	0.15–0.33§; 0.65	2	0	1
	Other:					
	- Relaxation therapy	0/1		0	0	1
	- Direct access to hospital review through helpline	0/1		0	0	1
RA knowledge[122 167 183 185 189 193]	Self-management programmes‡	1/1	0.34-0.47	0	0	1
	Education	2/3(1/1)	0.84	0	1	2
	Psychological	No papers				
	Other: Web-based rehabilitation	1/1(1/1)	–	1	0	0

*Mostly usual care or wait list.
†If different outcome measures were used, the range in effect sizes over these measures is reported.
‡Combination of non-pharmacological interventions.
§Pooled effect size, reported in SLR.
H, high (red); L, low (green); M, moderate (yellow); n, number of papers; RA, rheumatoid arthritis; RoB, risk of bias; SLR, systematic literature review.

of intervention, including their effect size (if reported or calculable), is shown in table 2.

Improvement in self-efficacy was found using self-management programmes, educational and psychological interventions, exercise programmes, nurse-led follow-up, eszopiclone 3 mg (in RA patients with insomnia) and assistive technology (eye drop dispenser in RA patients with concomitant Sjögren's syndrome). Psychological interventions were found to reduce anxiety and depression. Education and web-based rehabilitation were found

to improve RA knowledge. Benefit of the interventions was also found for other outcomes: self-management programmes and cognitive behavioural therapy to reduce helplessness; self-management programmes to improve autonomous motivation and self-management behaviour and to reduce psychological distress; and psychological interventions to improve coping.

DISCUSSION

In this SLR, evidence is summarised regarding pharmacological and non-pharmacological therapeutic strategies informing the EULAR Task Force in charge of the development of recommendations for the management of D2T RA. Several limitations were found in the selected available evidence. First, no studies were found evaluating therapeutic strategies in patients who fulfilled the definition of D2T RA.[6] Therefore, typically, evidence regarding pharmacological therapeutic strategies needed to be extrapolated from studies in patients with active disease who failed at least one bDMARD, which was a TNFi in almost all studies, instead of two b/tsDMARDs with a different MOA as in the definition. Additionally, most studies on non-pharmacological strategies were performed in an unselected population of RA patients instead of in patients with D2T RA with predominantly non-inflammatory complaints, in whom the absence of inflammatory activity could not be ascertained. Second, heterogeneity in patient populations, interventions, comparators and outcome criteria hampered pooling of efficacy outcomes. Third, only very few studies with low RoB were found. Considering these limitations, the results should be interpreted cautiously for patients with D2T RA.

Regarding pharmacological interventions for patients with D2T RA, limited evidence (of low to moderate quality) was found on the efficacy and safety of DMARDs for patients with limited DMARD options due to contraindications regarding obesity, HBV, HCV, pregnancy, lactation and those at risk for VTEs. In patients with obesity, infliximab may be less effective compared with patients with a normal BMI, and adalimumab, etanercept and rituximab may be less affected by BMI.[28 33 48] For patients with HBV, TNFi, abatacept and tocilizumab were found to be relatively safe.[20 22 39] For patients with HCV, TNFi was found to be a relatively safe treatment option.[18 34] For patients before and during pregnancy and during lactation, no safety issues have been identified for several DMARDs, which are described in the 2020 ACR guideline and 2016 EULAR points to consider.[27 42] In patients at risk for VTEs, an increased risk of VTEs was found during treatment with tsDMARDs, especially in the higher doses.[43] In these patients, other DMARDs may be preferred.

In patients who failed at least two bDMARDs, several b/tsDMARDs (tocilizumab, tofacitinib, baricitinib, upadacitinib and filgotinib) were found to be more effective than placebo.[55 64 72 80 95 120] In patients who failed at least one bDMARD, a benefit in efficacy compared with placebo was found for all currently used b/tsDMARDs.[52 56 57 67 68 76 77 79 80 85 94 95 97 98 104 108 115 116] Despite this benefit in efficacy compared with placebo, generally, the extent of the beneficial effect of b/tsDMARDs was found to become less when patients failed a higher number of previous bDMARDs.[55 57 64 78 86 102 105] This tendency was less convincing for upadacitinib and filgotinib and for the higher doses of tocilizumab (intravenous), tofacitinib and baricitinib.[55 57 64 78 80 120] Although this may suggest a preference for these b/tsDMARDs (in these higher doses) in patients with D2T RA, it may also be related to the more recent introduction of these drugs with a novel MOA and the timing of their application in therapeutic strategies. If, for instance, a TNFi would have been applied in patients who previously failed increasing numbers of tsDMARDs, the beneficial effect of TNFi may also have been less dependent on the number of previously failed tsDMARDs. However, for tocilizumab, tofacitinib and baricitinib, the tendency of decreasing efficacy with an increasing number of previously failed bDMARDs was not apparent for their higher doses and only for their lower doses.[55 57 64 78] This may indicate that not only their more recent introduction and the novel MOA play a role. Additionally, the studies on tofacitinib, upadacitinib and filgotinib enrolled patients who failed different bDMARDs and not only TNFis.[57 80 120] Nevertheless, future studies should assess to what extent this tendency is related to these specific b/tsDMARDs or to the order of their application in therapeutic strategies. Furthermore, a tendency was found for non-TNFi bDMARDs to be more effective than TNFis in patients who failed at least one TNFi, although insufficient evidence was identified to prioritise different non-TNFi b/tsDMARDs.[49 52 54 59 65 81–83 86 88 90 91 93 94 96 99 107 112 114 117 118] These findings could indicate that non-TNFi bDMARDs and tsDMARDs may be somewhat more effective in comparison to another TNFi in patients with D2T RA. Specifically, if these non-TNFi b/tsDMARDs are of a previously not targeted MOA.

Regarding non-pharmacological interventions for patients with D2T RA, exercise, education, psychological and self-management interventions were found to be of additional benefit to improve non-inflammatory complaints (mainly functional disability, pain and fatigue).[122 125 126 129 132–138 140 144 146–148 152–154 157–160 162 165–167 171] It may be expected that non-pharmacological interventions do not become less effective in patient failing a higher number of previous bDMARDs as much as pharmacological interventions as described above. Therefore, the additional benefit of non-pharmacological interventions might be even higher in patients with D2T RA. However, no formal evidence was found to support this.

Furthermore, education was found to improve goal setting and self-management.[175–178] Additionally, self-management programmes, education and psychological interventions were found to improve different aspects of self-management, namely,

self-efficacy, anxiety, depression and RA knowledge.[122 125 132 137 144 148 152 159 160 162 167 183 185–193 195] Before goal setting between patients and healthcare professionals as well as self-management can be improved, a mismatch in goal setting and suboptimal self-management should be identified. No accurate measures were found to identify a mismatch in goal setting, although patients expressed a desire to take their quality of life goals more explicitly into account.[172] ASES was found to be the most extensively studied tool to identify the level of self-management, although validated cut-offs are not available, hampering its use in clinical practice as a diagnostic instrument.[179 197]

This SLR was aimed to supplement the evidence as summarised for the current EULAR recommendations for the management of RA.[1] In the SLR informing the current RA management recommendations, insufficient evidence was found to prioritise different b/tsDMARDs.[198] In contrast, in our SLR a tendency was found of non-TNFi bDMARDs to be more effective than TNFis in RA patients who failed at least one TNFi. This difference is explained by the inclusion of observational studies and network meta-analyses in our SLR, while these study designs were specifically excluded from the SLR informing the RA management recommendations. However, we felt it was necessary not to exclude this evidence from our SLR, as direct comparisons in RCTs are lacking in patients with D2T RA. By all means, careful interpretation of the outcomes of these types of studies is warranted, also as results need to be extrapolated to the D2T RA patient population.

Although many therapeutic clinical questions were assessed in this SLR, not all therapeutic strategies for all potential factors contributing to D2T RA have been addressed. At the first meeting of the D2T RA Task Force, treatment non-adherence and lifestyle interventions were also discussed as topics of interest. As there are currently two ongoing EULAR projects related to these issues in patients with rheumatic and musculoskeletal diseases, it was decided to refer to the evidence found in their SLRs for the D2T RA recommendations in consultation with the steering committees of these Task Forces. Therefore, these topics are not included in this SLR.

In clinical practice, the heterogeneity of D2T RA should be considered when choosing the optimal therapeutic strategy for the individual patient with D2T RA. As a myriad of factors may contribute to the D2T RA state,[4 9] the therapeutic strategy should be individually tailored and may consist of multiple (pharmacological and non-pharmacological) interventions. Further guidance on this will be provided by the EULAR Task Force on D2T RA in their recommendations for the management of D2T RA, including their interpretation of the clinical implications of the results, which will be published soon.[199] Additionally, the heterogeneity of D2T RA should be considered in future studies as not all therapeutic strategies will be useful for all patients with D2T RA. The EULAR Task Force on D2T RA will also provide a research agenda, in which further guidance on topics of interest will be given.[199]

In addition to the limitations in the evidence that was found, this SLR has some limitations itself. Although an extensive literature search has been performed, relevant papers might have been missed due to the choices that have been made in the search strategy. For the search on pharmacological and non-pharmacological therapeutic strategies, the publication year 2000 was chosen as a cut-off because of the introduction of bDMARDs around this time point. For the subquestion on patients with predominantly non-inflammatory complaints, it was chosen to focus on the often-reported outcomes of function, pain, quality of life and fatigue. For the subquestions on goal setting and self-management, it was chosen to focus on RA patients only, while studies in patients with other chronic diseases may also provide useful information. In our opinion, these choices were mandatory to most efficiently create an overview of the current literature on the most important outcomes in the present therapeutic landscape. Nevertheless, these choices need to be reassessed in case the D2T RA recommendations, and consequently the SLRs, will be updated. Additionally, we chose to report effect sizes to compare results over different outcomes and scoring methods. However, effect sizes were not extractable for all studies, which hampers interpretation and pooling of results. The reported effect sizes varied widely for some outcomes (eg, alternative medicine to improve range of motion: 0.49–14.37), which may indicate publication bias. Although the possibility of publication bias was assessed within the RoB assessment of the SLRs[16] and the level of evidence of the recommendations, interpreting this bias, especially with a limited number of studies, is difficult and, therefore, the effect sizes should be interpreted cautiously.

In conclusion, this SLR underscores the scarcity of (high-quality) evidence on the optimal treatment of patients with D2T RA. As D2T RA is a newly defined disease state, all evidence is to an extent indirect. Limited evidence was found on effective and/or safe DMARDs for patients with limited DMARD options due to contraindications. In patients who previously failed bDMARDs, all currently used b/tsDMARDs were found to be more effective than placebo. However, generally, effectiveness of b/tsDMARDs decreased in patients who had failed a higher number of bDMARDs and subsequent b/tsDMARDs of a previously not targeted MOA appear to be more effective. Furthermore, a beneficial effect of non-pharmacological interventions, specifically education, was found for improvement of non-inflammatory complaints (function, pain, fatigue), goal setting and self-management (self-efficacy, anxiety, depression, RA knowledge).

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REFERENCES

1 Smolen JS, Landewé RBM, Bijlsma JWJ. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. *Ann Rheum Dis* 2020;79:685–99.
2 Singh JA, Saag KG, Bridges SL. American College of rheumatology guideline for the treatment of rheumatoid arthritis. *Arthritis Rheumatol* 2015;2016:1–26.
3 Buch MH. Defining refractory rheumatoid arthritis. *Ann Rheum Dis* 2018;77:966–9.
4 de Hair MJH, Jacobs JWG, Schoneveld JLM. Difficult-to-treat rheumatoid arthritis: an area of unmet clinical need. *Rheumatology* 2017;57:1135–44.
5 Kearsley-Fleet L, Davies R, De Cock D, *et al*. Biologic refractory disease in rheumatoid arthritis: results from the British Society for rheumatology biologics register for rheumatoid arthritis. *Ann Rheum Dis* 2018;77:1405–12.
6 Nagy G, Roodenrijs NMT, Welsing PMJ. EULAR definition of difficult-to-treat rheumatoid arthritis. *Ann Rheum Dis* 2020:annrheumdis-2020-217344.
7 Roodenrijs NMT, de Hair MJH, van der Goes MC, *et al*. Characteristics of difficult-to-treat rheumatoid arthritis: results of an international survey. *Ann Rheum Dis* 2018;77:1705–9.
8 Roodenrijs NMT, de Hair MJH, van der Goes MC, *et al*. Correspondence to viewpoint 'Defining refractory rheumatoid arthritis' by Buch. *Ann Rheum Dis* 2019;78:e105.
9 Roodenrijs NMT, van der Goes MC, Welsing PMJ, *et al*. Difficult-to-treat rheumatoid arthritis: contributing factors and burden of disease. *Rheumatology* 2020. doi:10.1093/rheumatology/keaa860. [Epub ahead of print: 17 Dec 2020].
10 Strand V, Wright GC, Bergman MJ, *et al*. Patient expectations and perceptions of Goal-setting strategies for disease management in rheumatoid arthritis. *J Rheumatol* 2015;42:2046–54.
11 Roodenrijs NMT, Kedves M, Hamar A. Diagnostic issues in difficult-to-treat rheumatoid arthritis: a systematic literature review Informing the 2020 EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. *Manuscript under review*.
12 van der Heijde D, Aletaha D, Carmona L. Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. *Ann Rheum Dis* 2014;2015:8–13.
13 Thompson M, Tiwari A, Fu R. A framework to facilitate the use of systematic reviews and meta-analyses in the design of primary research studies. Rockville, MD agency Healthc. *Res. Qual* 2012 http://www.ncbi.nlm.nih.gov/books/ NBK83621/ (accessed 13 Nov 2019).
14 Higgins JPT, Altman DG, Gøtzsche PC, *et al*. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011;343:d5928.
15 Whiting PF*et al*. Quadas-2: a revised tool for the quality assessment of diagnostic accuracy studies. *Ann Intern Med* 2011;155:529–36.
16 Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
17 Abramkin A, Lisitsyna T, Veltishchev D. THU0127 the dynamics of mental disorders frequency in complex dmards, biologics and antidepressants treatment of rheumatoid arthritis patients. *Ann Rheum Dis* 2017;76::249.1–249.
18 Brunasso AMG, Puntoni M, Gulia A, *et al*. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. *Rheumatology* 2011;50:1700–11.
19 Burmester G, Lin Y, Mangan E. SAT0202 efficacy and safety of sarilumab monotherapy versus adalimumab monotherapy in patients with active rheumatoid arthritis in the phase 3 monarch study, including subpopulations. *Ann Rheum Dis* 2017;76:849.1–849.
20 Cantini F, Boccia S, Goletti D, *et al*. HBV reactivation in patients treated with antitumor necrosis factor-alpha (TNF-α) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. *Int J Rheumatol* 2014;2014:1–9.
21 Chen Y-M, Chen H-H, Chen Y-H, *et al*. A comparison of safety profiles of tumour necrosis factor α inhibitors and rituximab therapy in patients with rheumatoid arthritis and chronic hepatitis C. *Ann Rheum Dis* 2015;74:626–7.
22 Chen L-F, Mo Y-Q, Jing J, *et al*. Short-Course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. *Int J Rheum Dis* 2017;20:859–69.
23 Clowse MEB, Feldman SR, Isaacs JD, *et al*. Pregnancy outcomes in the tofacitinib safety databases for rheumatoid arthritis and psoriasis. *Drug Saf* 2016;39:755–62.
24 Combe B, Balsa A, Sarzi-Puttini P, *et al*. Efficacy and safety data based on historical or pre-existing conditions at baseline for patients with active rheumatoid arthritis who were treated with baricitinib. *Ann Rheum Dis* 2019;78:1135–8.
25 Deodhar A, Bitman B, Yang Y, *et al*. The effect of etanercept on traditional metabolic risk factors for cardiovascular disease in patients with rheumatoid arthritis. *Clin Rheumatol* 2016;35:3045–52.
26 Genovese MC, Burmester GR, Hagino O. SAT0121 effect of sarilumab on glycosylated hemoglobin in patients with rheumatoid arthritis and diabetes. *Ann Rheum Dis* 2019;78:1128–9.

27 Götestam Skorpen C, Hoeltzenbein M, Tincani A, *et al*. The EULAR points to consider for use of antirheumatic drugs before pregnancy, and during pregnancy and lactation. *Ann Rheum Dis* 2016;75:795–810.
28 Gremese E, Carletto A, Padovan M, *et al*. Obesity and reduction of the response rate to anti-tumor necrosis factor α in rheumatoid arthritis: an approach to a personalized medicine. *Arthritis Care Res* 2013;65:94–100.
29 Hang Y, Qin X, Ren T, *et al*. Baicalin reduces blood lipids and inflammation in patients with coronary artery disease and rheumatoid arthritis: a randomized, double-blind, placebo-controlled trial. *Lipids Health Dis* 2018;17:146.
30 Hoeltzenbein M, Beck E, Rajwanshi R, *et al*. Tocilizumab use in pregnancy: analysis of a global safety database including data from clinical trials and post-marketing data. *Semin Arthritis Rheum* 2016;46:238–45.
31 Iannone F, La Montagna G, Bagnato G, *et al*. Safety of etanercept and methotrexate in patients with rheumatoid arthritis and hepatitis C virus infection: a multicenter randomized clinical trial. *J Rheumatol* 2014;41:286–92.
32 Ikonomidis I, Tzortzis S, Andreadou I, *et al*. Increased benefit of interleukin-1 inhibition on vascular function, myocardial deformation, and twisting in patients with coronary artery disease and coexisting rheumatoid arthritis. *Circulation* 2014;7:619–28.
33 Klaasen R, Wijbrandts CA, Gerlag DM, *et al*. Body mass index and clinical response to infliximab in rheumatoid arthritis. *Arthritis & Rheumatism* 2011;63:359–64.
34 Lin K-M, Cheng T-T, Lin J-C, *et al*. Tumor necrosis factor-α antagonist therapy for concomitant rheumatoid arthritis and hepatitis C virus infection: a case series study. *Clin Rheumatol* 2015;34:1039–46.
35 Mori S, Yoshitama T, Hidaka T, *et al*. Effectiveness and safety of tocilizumab therapy for patients with rheumatoid arthritis and renal insufficiency: a real-life registry study in Japan (the ACTRA-RI study). *Ann Rheum Dis* 2015;74:627–30.
36 Mouyis M, Flint JD, Giles IP. Safety of anti-rheumatic drugs in men trying to conceive: a systematic review and analysis of published evidence. *Semin Arthritis Rheum* 2019;48:911–20.
37 Nakamura T, Higashi S-i, Tomoda K, *et al*. Effectiveness of etanercept vs cyclophosphamide as treatment for patients with amyloid A amyloidosis secondary to rheumatoid arthritis. *Rheumatology* 2012;51:2064–9.
38 Nakamura Y, Suzuki T, Yoshida T, *et al*. Vitamin D and calcium are required during denosumab treatment in osteoporosis with rheumatoid arthritis. *Nutrients* 2017;9:E428.
39 Padovan M, Filippini M, Tincani A, *et al*. Safety of abatacept in rheumatoid arthritis with serologic evidence of past or present hepatitis B virus infection. *Arthritis Care Res* 2016;68:738–43.
40 Papalopoulos I, Fanouriakis A, Kougkas N, *et al*. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. *Clin Exp Rheumatol* 2018;36:102–9.
41 Ruscitti P, Masedu F, Alvaro S, *et al*. Anti-Interleukin-1 treatment in patients with rheumatoid arthritis and type 2 diabetes (track): a multicentre, open-label, randomised controlled trial. *PLoS Med* 2019;16:e1002901.
42 Sammaritano LR, Bermas BL, Chakravarty EE. American College of rheumatology guideline for the management of reproductive health in rheumatic and musculoskeletal diseases. *Arthritis Rheumatol* 2020;2020.
43 Sepriano A, Kerschbaumer A, Smolen JS, *et al*. Safety of synthetic and biological DMARDs: a systematic literature review Informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2020:annrheumdis-2019-216653.
44 Shin K, Park S-H, Park W, *et al*. Monthly oral ibandronate reduces bone loss in Korean women with rheumatoid arthritis and osteopenia receiving long-term glucocorticoids: a 48-week double-blinded randomized placebo-controlled investigator-initiated trial. *Clin Ther* 2017;39:268–78.
45 Strand V, Hagino O, Guillonneau S. SAT0207 depressive symptoms in patients with rheumatoid arthritis in sarilumab target and mobility trials and impact of treatment. *Ann Rheum Dis* 2018;77:964.1–964.
46 Suissa S, Hudson M, Dell'Aniello S, *et al*. Comparative safety of abatacept in rheumatoid arthritis with COPD: a real-world population-based observational study. *Semin Arthritis Rheum* 2019;49:366–72.
47 Weinblatt M, Combe B, Covucci A, *et al*. Safety of the selective costimulation modulator abatacept in rheumatoid arthritis patients receiving background biologic and nonbiologic disease-modifying antirheumatic drugs: a one-year randomized, placebo-controlled study. *Arthritis Rheum* 2006;54:2807–16.
48 Yoo D-H, Park W, Suh C-H. Rituximab is effective in the treatment of rheumatoid arthritis irrespective of body mass index; up to 48 weeks results from phase 3 study. *Arthritis Rheumatol*2017;69.
49 Akiyama M, Kaneko Y, Kondo H, *et al*. Comparison of the clinical effectiveness of tumour necrosis factor inhibitors and abatacept after insufficient response to tocilizumab in patients with rheumatoid arthritis. *Clin Rheumatol* 2016;35:2829–34.
50 Aletaha D, Bingham CO, Tanaka Y, *et al*. Efficacy and safety of sirukumab in patients with active rheumatoid arthritis refractory to anti-TNF therapy (SIRROUND-T): a randomised, double-blind, placebo-controlled, parallel-group, multinational, phase 3 study. *The Lancet* 2017;389:1206–17.
51 Al-Gareeb AIA, Gorial FI, Mahmood AS. Niclosamide as an adjuvant to etanercept in treatment patients with active rheumatoid arthritis: an 8-week randomized controlled pilot study. *Clin Rheumatol* 2018;37:2633–41.
52 Alivernini S, Laria A, Gremese E, *et al*. ACR70-disease activity score remission achievement from switches between all the available biological agents in rheumatoid arthritis: a systematic review of the literature. *Arthritis Res Ther* 2009;11:R163.
53 Blom M, Kievit W, Donders ART, *et al*. Effectiveness of a third tumor necrosis factor-α-blocking agent compared with rituximab after failure of 2 TNF-blocking agents in rheumatoid arthritis. *J Rheumatol* 2011;38:2355–61.
54 Brown S, Everett CC, Naraghi K, *et al*. Alternative tumour necrosis factor inhibitors (TNFi) or abatacept or rituximab following failure of initial TNFi in rheumatoid arthritis: the switch RCT. *Health Technol Assess* 2018;22:1–280.
55 Burmester GR, Blanco R, Charles-Schoeman C, *et al*. Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *The Lancet* 2013;381:451–60.
56 Charles-Schoeman C, Burmester G, Nash P, *et al*. Efficacy and safety of tofacitinib following inadequate response to conventional synthetic or biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2016;75:1293–301.
57 Charles-Schoeman C, Kremer J, Krishnaswami S. THU0185 comparison of tofacitinib safety and efficacy in rheumatoid arthritis patients with inadequate response to conventional synthetic dmards, or to one or more biological dmards. *Ann Rheum Dis* 2017;76:271.3–2.
58 Chatzidionysiou K, Askling J, Eriksson J, *et al*. Effectiveness of TNF inhibitor switch in RA: results from the National Swedish register. *Ann Rheum Dis* 2015;74:890–6.
59 Chatzidionysiou K, Vollenhoven RFvan. Rituximab versus anti-TNF in patients who previously failed one TNF inhibitor in an observational cohort. *Scand J Rheumatol* 2013;42:190–5.
60 Cohen G, Courvoisier N, Cohen JD. The efficiency of switching from infliximab to etanercept and vice-versa in patients with rheumatoid arthritis. *Clin Exp Rheumatol* 2015;23:795–800.
61 Cohen S, Tuckwell K, Katsumoto TR. OP0025 Fenebrutinib compared to placebo and adalimumab in patients with inadequate response to either methotrexate therapy or prior TNF therapy: phase 2 study. *Ann Rheum Dis* 2019;78:80–1.
62 Das S, Vital EM, Horton S, *et al*. Abatacept or tocilizumab after rituximab in rheumatoid arthritis? an exploratory study suggests non-response to rituximab is associated with persistently high IL-6 and better clinical response to IL-6 blocking therapy. *Ann Rheum Dis* 2014;73:909–12.
63 Elmedany SH, Mohamed AE, Galil SMA. Efficacy and safety profile of intravenous tocilizumab versus intravenous abatacept in treating female Saudi Arabian patients with active moderate-to-severe rheumatoid arthritis. *Clin Rheumatol* 2019;38:2109–17.
64 Emery P, Keystone E, Tony HP, *et al*. Il-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008;67:1516–23.
65 Emery P, Gottenberg JE, Rubbert-Roth A, *et al*. Rituximab versus an alternative TNF inhibitor in patients with rheumatoid arthritis who failed to respond to a single previous TNF inhibitor: SWITCH-RA, a global, observational, comparative effectiveness study. *Ann Rheum Dis* 2015;74:979–84.
66 Finckh A, Ciurea A, Brulhart L, *et al*. Which subgroup of patients with rheumatoid arthritis benefits from switching to rituximab versus alternative anti-tumour necrosis factor (TNF) agents after previous failure of an anti-TNF agent? *Ann Rheum Dis* 2010;69:387–93.

67 Fleischmann R, Kremer J, Cush J, *et al*. Placebo-Controlled trial of tofacitinib monotherapy in rheumatoid arthritis. *N Engl J Med* 2012;367:495–507.
68 Fleischmann R, van Adelsberg J, Lin Y, *et al*. Sarilumab and Nonbiologic disease-modifying antirheumatic drugs in patients with active rheumatoid arthritis and inadequate response or intolerance to tumor necrosis factor inhibitors. *Arthritis Rheumatol* 2017;69:277–90.
69 Fleischmann RM, Genovese MC, Enejosa JV, *et al*. Safety and effectiveness of upadacitinib or adalimumab plus methotrexate in patients with rheumatoid arthritis over 48 weeks with switch to alternate therapy in patients with insufficient response. *Ann Rheum Dis* 2019;78:1454–62.
70 Genovese MC, Kavanaugh A, Weinblatt ME, *et al*. An oral Syk kinase inhibitor in the treatment of rheumatoid arthritis: a three-month randomized, placebo-controlled, phase II study in patients with active rheumatoid arthritis that did not respond to biologic agents. *Arthritis & Rheumatism* 2011;63:337–45.
71 Genovese MC, Kinnman N, de La Bourdonnaye G, *et al*. Atacicept in patients with rheumatoid arthritis and an inadequate response to tumor necrosis factor antagonist therapy: results of a phase II, randomized, placebo-controlled, dose-finding trial. *Arthritis & Rheumatism* 2011;63:1793–803.
72 Genovese MC, Fleischmann RM, Greenwald M, *et al*. Tabalumab, an anti-BAFF monoclonal antibody, in patients with active rheumatoid arthritis with an inadequate response to TNF inhibitors. *Ann Rheum Dis* 2013;72:1461–8.
73 Genovese MC, Greenwald M, Cho C-S, *et al*. A phase II randomized study of subcutaneous ixekizumab, an anti-interleukin-17 monoclonal antibody, in rheumatoid arthritis patients who were naive to biologic agents or had an inadequate response to tumor necrosis factor inhibitors. *Arthritis Rheumatol* 2014;66:1693–704.
74 Genovese MC, van der Heijde DM, Keystone EC, *et al*. A phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study of 2 dosing regimens of fostamatinib in patients with rheumatoid arthritis with an inadequate response to a tumor necrosis factor-α antagonist. *J Rheumatol* 2014;41:2120–8.
75 Genovese MC, Fleischmann R, Furst D, *et al*. Efficacy and safety of olokizumab in patients with rheumatoid arthritis with an inadequate response to TNF inhibitor therapy: outcomes of a randomised phase IIb study. *Ann Rheum Dis* 2014;73:1607–15.
76 Genovese MC, Kremer J, Zamani O, *et al*. Baricitinib in patients with refractory rheumatoid arthritis. *N Engl J Med Overseas Ed* 2016;374:1243–52.
77 Genovese MC, Mangan EK, Fay J. Improvements in Remission and Low Disease Activity Are Achieved with Ongoing Sarilumab Treatment, in Patients with Rheumatoid Arthritis in 2 Phase 3 Studies - ACR Meeting Abstracts. *Arthritis Rheumatol* 2017;69:Suppl 10.
78 Genovese MC, Kremer JM, Kartman CE, *et al*. Response to baricitinib based on prior biologic use in patients with refractory rheumatoid arthritis. *Rheumatology* 2018;57:900–8.
79 Genovese MC, Fleischmann R, Combe B, *et al*. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. *Lancet* 2018;391:2513–24.
80 Genovese MC, Kalunian K, Gottenberg J-E, *et al*. Effect of Filgotinib vs placebo on clinical response in patients with moderate to severe rheumatoid arthritis refractory to disease-modifying antirheumatic drug therapy. *JAMA* 2019;322:315–25.
81 Gomez-Reino JJ, Maneiro JR, Ruiz J, *et al*. Comparative effectiveness of switching to alternative tumour necrosis factor (TNF) antagonists versus switching to rituximab in patients with rheumatoid arthritis who failed previous TNF antagonists: the MIRAR study. *Ann Rheum Dis* 2012;71:1861–4.
82 González-Vacarezza N, Alemán A, González G, *et al*. Rituximab and tocilizumab for the treatment of rheumatoid arthritis. *Int J Technol Assess Health Care* 2014;30:282–8.
83 Gottenberg J-E, Brocq O, Perdriger A, *et al*. Non–TNF-Targeted biologic vs a second anti-TNF drug to treat rheumatoid arthritis in patients with insufficient response to a first anti-TNF drug. *JAMA* 2016;316:1172–80.
84 Gottenberg J-E, Morel J, Perrodeau E, *et al*. Comparative effectiveness of rituximab, abatacept, and tocilizumab in adults with rheumatoid arthritis and inadequate response to TNF inhibitors: prospective cohort study. *BMJ* 2019;364:l67.
85 Greenwald MW, Shergy WJ, Kaine JL, *et al*. Evaluation of the safety of rituximab in combination with a tumor necrosis factor inhibitor and methotrexate in patients with active rheumatoid arthritis: results from a randomized controlled trial. *Arthritis Rheum* 2011;63:622–32.
86 Harrold LR, Reed GW, Magner R, *et al*. Comparative effectiveness and safety of rituximab versus subsequent anti–tumor necrosis factor therapy in patients with rheumatoid arthritis with prior exposure to anti–tumor necrosis factor therapies in the United States Corrona registry. *Arthritis Res Ther* 2015;17:256.
87 Harrold LR, Reed GW, Shewade A, *et al*. Effectiveness of rituximab for the treatment of rheumatoid arthritis in patients with prior exposure to anti-TNF: results from the CORRONA registry. *J Rheumatol* 2015;42:1090–8.
88 Harrold LR, Reed GW, Kremer JM, *et al*. The comparative effectiveness of abatacept versus anti-tumour necrosis factor switching for rheumatoid arthritis patients previously treated with an anti-tumour necrosis factor. *Ann Rheum Dis* 2015;74:430–6.
89 Harrold LR, Reed GW, Solomon DH, *et al*. Comparative effectiveness of abatacept versus tocilizumab in rheumatoid arthritis patients with prior TNFi exposure in the US Corrona registry. *Arthritis Res Ther* 2016;18:280.
90 Harrold LR, Reed GW, Best J, *et al*. Real-World comparative effectiveness of tocilizumab monotherapy vs. tumor necrosis factor inhibitors with methotrexate in patients with rheumatoid arthritis. *Rheumatol Ther* 2018;5:507–23.
91 Hirabara S, Takahashi N, Fukaya N, *et al*. Clinical efficacy of abatacept, tocilizumab, and etanercept in Japanese rheumatoid arthritis patients with inadequate response to anti-TNF monoclonal antibodies. *Clin Rheumatol* 2014;33:1247–54.
92 Huang Y, Fan Y, Liu Y, *et al*. Efficacy and safety of secukinumab in active rheumatoid arthritis with an inadequate response to tumor necrosis factor inhibitors: a meta-analysis of phase III randomized controlled trials. *Clin Rheumatol* 2019;38:2765–76.
93 Kekow J, Mueller-Ladner U, Schulze-Koops H. Rituximab is more effective than second anti-TNF therapy in rheumatoid arthritis patients and previous TNFα blocker failure. *Biol Targets Ther* 2012;6:191–9.
94 Kim H-L, Lee M-Y, Park S-Y, *et al*. Comparative effectiveness of cycling of tumor necrosis factor-α (TNF-α) inhibitors versus switching to non-TNF biologics in rheumatoid arthritis patients with inadequate response to TNF-α inhibitor using a Bayesian approach. *Arch Pharm Res* 2014;37:662–70.
95 Kremer JM, Emery P, Camp HS, *et al*. A phase IIb study of ABT-494, a selective JAK-1 inhibitor, in patients with rheumatoid arthritis and an inadequate response to anti-tumor necrosis factor therapy. *Arthritis & Rheumatology* 2016;68:2867–77.
96 Lauper K, Nordström DC, Pavelka K, *et al*. Comparative effectiveness of tocilizumab versus TNF inhibitors as monotherapy or in combination with conventional synthetic disease-modifying antirheumatic drugs in patients with rheumatoid arthritis after the use of at least one biologic disease-modifying antirheumatic drug: analyses from the pan-European TOCERRA register collaboration. *Ann Rheum Dis* 2018;77:1276–82.
97 Lee YH, Bae S-C. Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled tri. *Int J Rheum Dis* 2016;19:1103–11.
98 Malottki K, Barton P, Tsourapas A. Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a tumour necrosis factor inhibitor: a systematic review and economic evaluation. *Health Technol Assess* 2011;15:1–300.
99 Nam JL, Takase-Minegishi K, Ramiro S, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review Informing the 2016 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2017;76:1113–36.
100 Ogata A, Tanaka Y, Ishii T, *et al*. A randomized, double-blind, parallel-group, phase III study of shortening the dosing interval of subcutaneous tocilizumab monotherapy in patients with rheumatoid arthritis and an inadequate response to subcutaneous tocilizumab every other week: results of the 12-week double-blind period. *Modern Rheumatology* 2018;28:76–84.
101 Pascart T, Philippe P, Drumez E, *et al*. Comparative efficacy of tocilizumab, abatacept and rituximab after non-TNF inhibitor failure: results from a multicentre study. *Int J Rheum Dis* 2016;19:1093–102.
102 Schiff M, Pritchard C, Huffstutter JE, *et al*. The 6-month safety and efficacy of abatacept in patients with rheumatoid arthritis who underwent a washout after anti-tumour necrosis factor therapy or were directly switched to abatacept: the ARRIVE trial. *Ann Rheum Dis* 2009;68:1708–14.

103 Schiff M, Combe B, Dörner T, *et al*. Efficacy and safety of tabalumab, an anti-BAFF monoclonal antibody, in patients with moderate-to-severe rheumatoid arthritis and inadequate response to TNF inhibitors: results of a randomised, double-blind, placebo-controlled, phase 3 study. *RMD Open* 2015;1:e000037.
104 Singh JA, Hossain A, Tanjong Ghogomu E, *et al*. Biologics or tofacitinib for people with rheumatoid arthritis unsuccessfully treated with biologics: a systematic review and network meta-analysis. *Cochrane Database Syst Rev* 2017;74.
105 Smolen JS, Kay J, Matteson EL, *et al*. Insights into the efficacy of golimumab plus methotrexate in patients with active rheumatoid arthritis who discontinued prior anti-tumour necrosis factor therapy: post-hoc analyses from the GO-AFTER study. *Ann Rheum Dis* 2014;73:1811–8.
106 Smolen JS, Burmester G-R, Combe B, *et al*. Head-To-Head comparison of certolizumab pegol versus adalimumab in rheumatoid arthritis: 2-year efficacy and safety results from the randomised EXXELERATE study. *The Lancet* 2016;388:2763–74.
107 Soliman MM, Hyrich KL, Lunt M, *et al*. Rituximab or a second anti–tumor necrosis factor therapy for rheumatoid arthritis patients who have failed their first anti–tumor necrosis factor therapy? comparative analysis from the British Society for rheumatology biologics register. *Arthritis Care Res* 2012;64:1108–15.
108 Strand V, Burmester GR, Zerbini CAF, *et al*. Tofacitinib with methotrexate in third-line treatment of patients with active rheumatoid arthritis: patient-reported outcomes from a phase III trial. *Arthritis Care Res* 2015;67:475–83.
109 Tak PP, Mease PJ, Genovese MC, *et al*. Safety and efficacy of ocrelizumab in patients with rheumatoid arthritis and an inadequate response to at least one tumor necrosis factor inhibitor: results of a forty-eight-week randomized, double-blind, placebo-controlled, parallel-group phase III trial. *Arthritis Rheum* 2012;64:360–70.
110 Takahashi N, Fujibayashi T, Kida D, *et al*. Concomitant methotrexate and tacrolimus augment the clinical response to abatacept in patients with rheumatoid arthritis with a prior history of biological DMARD use. *Rheumatol Int* 2015;35:1707–16.
111 Takeuchi T, Tanaka Y, Yamanaka H, *et al*. Efficacy and safety of olokizumab in Asian patients with moderate-to-severe rheumatoid arthritis, previously exposed to anti-TNF therapy: results from a randomized phase II trial. *Mod Rheumatol* 2016;26:15–23.
112 Torrente-Segarra V, Acosta Pereira A, Morla R. VARIAR study: assessment of short-term efficacy and safety of rituximab compared to an tumor necrosis factor alpha antagonists as second-line drug therapy in patients with rheumatoid arthritis refractory to a first tumor necrosis factor alpha antagonist. *Reumatol Clínica* 2016;12:319–22.
113 van Vollenhoven RF, Wax S, Li Y, *et al*. Safety and efficacy of Atacicept in combination with rituximab for reducing the signs and symptoms of rheumatoid arthritis: a phase II, randomized, Double-Blind, Placebo-Controlled pilot trial. *Arthritis Rheumatol* 2015;67:2828–36.
114 Vial G, De PA, Scouppe L. FRI0234 choice of biologic therapy following rituximab: influencing factors in a French multicenter cohort of rheumatoid arthritis. *Ann Rheum Dis* 2017;76:573.2–4.
115 Vieira M-C, Zwillich SH, Jansen JP, *et al*. Tofacitinib versus biologic treatments in patients with active rheumatoid arthritis who have had an inadequate response to tumor necrosis factor inhibitors: results from a network meta-analysis. *Clin Ther* 2016;38:2628–41.
116 Vital EM, Dass S, Buch MH, *et al*. An extra dose of rituximab improves clinical response in rheumatoid arthritis patients with initial incomplete B cell depletion: a randomised controlled trial. *Ann Rheum Dis* 2015;74:1195–201.
117 Walker UA, Jaeger VK, Chatzidionysiou K, *et al*. Rituximab done: what's next in rheumatoid arthritis? A European observational longitudinal study assessing the effectiveness of biologics after rituximab treatment in rheumatoid arthritis. *Rheumatology* 2016;55:230–6.
118 Wei W, Knapp K, Wang L, *et al*. Treatment persistence and clinical outcomes of tumor necrosis factor inhibitor cycling or switching to a new mechanism of action therapy: real-world observational study of rheumatoid arthritis patients in the United States with prior tumor necrosis factor inhibitor therapy. *Adv Ther* 2017;34:1936–52.
119 Weinblatt ME, McInnes IB, Kremer JM, *et al*. A Randomized Phase II b Study of Mavrilimumab and Golimumab in Rheumatoid Arthritis. *Arthritis Rheumatol* 2018;70:49–59.
120 Weinblatt M, Thomson G, Chen K. FRI0171 clinical responses in patients with inadequate response to bdmards upon treatment with upadacitinib. *Ann Rheum Dis* 2019;78:759.
121 Zhang F, Ma C. Comparison of the effectiveness on intra-articular and subcutaneous TNF inhibitor in rheumatoid arthritis patients. *Clin Rheumatol* 2018;37:199–204.
122 Albano MG, Giraudet-Le Quintrec J-S, Crozet C, *et al*. Characteristics and development of therapeutic patient education in rheumatoid arthritis: analysis of the 2003–2008 literature. *Joint Bone Spine* 2010;77:405–10.
123 Allam NM, Koura GMR, Alrawaili SM, *et al*. The effect of Siwan therapy in management of patients with rheumatoid arthritis: a single blind randomized controlled trial. *Biomed Res* 2018;29:1400–6.
124 Annegret F, Thomas F. Long-Term benefits of radon spa therapy in rheumatic diseases: results of the randomised, multi-centre IMuRa trial. *Rheumatol Int* 2013;33:2839–50.
125 Anvar N, Matlabi H, Safaiyan A, *et al*. Effectiveness of self-management program on arthritis symptoms among older women: a randomized controlled trial study. *Health Care Women Int* 2018;39:1326–39.
126 Baxter SV, Hale LA, Stebbings S, *et al*. Walking is a feasible physical activity for people with rheumatoid arthritis: a feasibility randomized controlled trial. *Musculoskeletal Care* 2016;14:47–56.
127 Cameron M, Gagnier JJ, Chrubasik S. Herbal therapy for treating rheumatoid arthritis. *Cochrane Database Syst Rev* 2011:CD002948.
128 Carandang K, Pyatak EA, Vigen CLP. Systematic review of educational interventions for rheumatoid arthritis. *Am J Occup Ther* 2016;70:7006290020p1.
129 Christie A, Jamtvedt G, Dahm KT, *et al*. Effectiveness of nonpharmacological and nonsurgical interventions for patients with rheumatoid arthritis: an overview of systematic reviews. *Phys Ther* 2007;87:1697–715.
130 de Thurah A, Esbensen BA, Roelsgaard IK, *et al*. Efficacy of embedded nurse-led versus conventional physician-led follow-up in rheumatoid arthritis: a systematic review and meta-analysis. *RMD Open* 2017;3:e000481.
131 de Thurah A, Stengaard-Pedersen K, Axelsen M, *et al*. Tele-Health followup strategy for tight control of disease activity in rheumatoid arthritis: results of a randomized controlled trial. *Arthritis Care Res* 2018;70:353–60.
132 DiRenzo D, Crespo-Bosque M, Gould N, *et al*. Systematic review and meta-analysis: Mindfulness-Based interventions for rheumatoid arthritis. *Curr Rheumatol Rep* 2018;20:75.
133 Dissanayake RK, Bertouch J V. Psychosocial interventions as adjunct therapy for patients with rheumatoid arthritis: a systematic review. *Int J Rheum Dis* 2010;13:324–34.
134 Dixon KE, Keefe FJ, Scipio CD, *et al*. Psychological interventions for arthritis pain management in adults: a meta-analysis. *Health Psychology* 2007;26:241–50.
135 El Miedany Y, El Gaafary M, El Arousy N. Arthritis education: the integration of patient-reported outcome measures and patient self-management. *Clin Exp Rheumatol* 2012;30:899–904.
136 Eversden L, Maggs F, Nightingale P, *et al*. A pragmatic randomised controlled trial of hydrotherapy and land exercises on overall well being and quality of life in rheumatoid arthritis. *BMC Musculoskelet Disord* 2007;8:23.
137 Feldthusen C, Dean E, Forsblad-d'Elia H, *et al*. Effects of Person-Centered physical therapy on Fatigue-Related variables in persons with rheumatoid arthritis: a randomized controlled trial. *Arch Phys Med Rehabil* 2016;97:26–36.
138 Ferwerda M, van Beugen S, van Middendorp H, *et al*. A tailored-guided Internet-based cognitive-behavioral intervention for patients with rheumatoid arthritis as an adjunct to standard rheumatological care. *Pain* 2017;158:868–78.
139 Fidahic M, Jelicic Kadic A, Radic M, *et al*. Celecoxib for rheumatoid arthritis. *Cochrane Database Syst Rev* 2017;15.
140 Figen A, Geçene M, Gündüz R. Long-Term effects of comprehensive inpatient rehabilitation on function and disease activity in patients with chronic rheumatoid arthritis and ankylosing spondylitis. *Turkish J Rheumatol* 2011;26:135–44.
141 Fitzcharles M-A, Ste-Marie PA, Häuser W, *et al*. Efficacy, tolerability, and safety of cannabinoid treatments in the rheumatic diseases: a systematic review of randomized controlled trials. *Arthritis Care Res* 2016;68:681–8.
142 Gizińska M, Rutkowski R, Romanowski W, *et al*. Effects of whole-body cryotherapy in comparison with other physical modalities used with Kinesitherapy in rheumatoid arthritis. *Biomed Res Int* 2015;2015:1–7.
143 Gok Metin Z, Ozdemir L. The effects of Aromatherapy massage and reflexology on pain and fatigue in patients with rheumatoid arthritis: a randomized controlled trial. *Pain Management Nursing* 2016;17:140–9.
144 Hammond A, Young A, Kidao R. A randomised controlled trial of occupational therapy for people with early rheumatoid arthritis. *Ann Rheum Dis* 2004;63:23–30.

145 Hewlett S, Kirwan J, Pollock J, *et al*. Patient initiated outpatient follow up in rheumatoid arthritis: six year randomised controlled trial. *BMJ* 2005;330:171.
146 Hewlett S, Almeida C, Ambler N, *et al*. Group cognitive–behavioural programme to reduce the impact of rheumatoid arthritis fatigue: the raft RCT with economic and qualitative evaluations. *Health Technol Assess* 2019;23:1–130.
147 Hurkmans E, Van Der Giesen FJ, Vlieland T. Dynamic exercise programs (aerobic capacity and/or muscle strength training) in patients with rheumatoid arthritis. *Cochrane Database Syst Rev* 2009;2009:CD006853.
148 Iversen MD, Hammond A, Betteridge N. Self-Management of rheumatic diseases: state of the art and future perspectives. *Ann Rheum Dis* 2010;69:955–63.
149 Jastrząbek R, Straburzyńska-Lupa A, Rutkowski R, *et al*. Effects of different local cryotherapies on systemic levels of TNF-α, IL-6, and clinical parameters in active rheumatoid arthritis. *Rheumatol Int* 2013;33:2053–60.
150 Jiang G, Wan B, Huang W, *et al*. Influence of acupotomy loosing on IL-6, IL-10 and TNF-α in synovial fluid of rheumatoid arthritis patients with elbow joint stiffness. *World J Acupunct - Moxibustion* 2018;28:91–6.
151 Kawai S, Uchida E, Kondo M, *et al*. Efficacy and safety of ketoprofen patch in patients with rheumatoid arthritis: a randomized, double-blind, placebo-controlled study. *J Clin Pharmacol* 2010;50:1171–9.
152 Knittle K, De Gucht V, Hurkmans E, *et al*. Targeting motivation and self-regulation to increase physical activity among patients with rheumatoid arthritis: a randomised controlled trial. *Clin Rheumatol* 2015;34:231–8.
153 Lau YN, Ng J, Lee SY, *et al*. A brief report on the clinical trial on neural mobilization exercise for joint pain in patients with rheumatoid arthritis. *Z Rheumatol* 2019;78:474–8.
154 Lee MS, Pittler MH, Ernst E. Tai chi for rheumatoid arthritis: systematic review. *Rheumatology* 2007;46:1648–51.
155 Lee JA, Son MJ, Choi J, *et al*. Bee venom acupuncture for rheumatoid arthritis: a systematic review of randomised clinical trials. *BMJ Open* 2014;4:e006140.
156 Lee YC, Massarotti E, Edwards RR, *et al*. Effect of milnacipran on pain in patients with rheumatoid arthritis with widespread pain: a randomized blinded crossover trial. *J Rheumatol* 2016;43:38–45.
157 Macedo AM, Oakley SP, Panayi GS, *et al*. Functional and work outcomes improve in patients with rheumatoid arthritis who receive targeted, comprehensive occupational therapy. *Arthritis Rheum* 2009;61:1522–30.
158 Macfarlane GJ, Paudyal P, Doherty M, *et al*. A systematic review of evidence for the effectiveness of practitioner-based complementary and alternative therapies in the management of rheumatic diseases: rheumatoid arthritis. *Rheumatology* 2012;51:1707–13.
159 Manning VL, Hurley MV, Scott DL, *et al*. Education, self-management, and upper extremity exercise training in people with rheumatoid arthritis: a randomized controlled trial. *Arthritis Care Res* 2014;66:217–27.
160 Mollard E, Michaud K. A mobile APP with optical imaging for the self-management of hand rheumatoid arthritis: pilot study. *JMIR Mhealth Uhealth* 2018;6:e12221.
161 Muñoz-Fernández S, Aguilar MD, Rodríguez A, *et al*. Evaluation of the impact of nursing clinics in the rheumatology services. *Rheumatol Int* 2016;36:1309–17.
162 Prothero L, Barley E, Galloway J, *et al*. The evidence base for psychological interventions for rheumatoid arthritis: a systematic review of reviews. *Int J Nurs Stud* 2018;82:20–9.
163 Richards BL, Whittle SL, Buchbinder R. Antidepressants for pain management in rheumatoid arthritis. *Cochrane Database Syst Rev* 2011.
164 Santos I, Cantista P, Vasconcelos C. Balneotherapy and rheumatoid arthritis: a randomized control trial. *Isr Med Assoc J* 2016;18:474–8.
165 Santos EJF, Duarte C, Marques A, *et al*. Effectiveness of non-pharmacological and non-surgical interventions for rheumatoid arthritis. *JBI database Syst Rev Implement reports* 2019;17:1494–531.
166 Siqueira US, Orsini Valente LG, De Mello MT. Effectiveness of aquatic exercises in women with rheumatoid arthritis: a randomized, controlled, 16-Week Intervention-The Hydra trial. *Am J Phys Med Rehabil* 2017;96:167–75.
167 Srikesavan C, Bryer C, Ali U, *et al*. Web-Based rehabilitation interventions for people with rheumatoid arthritis: a systematic review. *J Telemed Telecare* 2019;25:263–75.
168 Tijhuis GJ, Zwinderman AH, Hazes JMW, *et al*. A randomized comparison of care provided by a clinical nurse specialist, an inpatient team, and a day patient team in rheumatoid arthritis. *Arthritis & Rheumatism* 2002;47:525–31.
169 Wang J, Zou X, Zhou L. Patient satisfaction after nurse-led care in Chinese patients with rheumatoid arthritis: a China study. *Biomed Res* 2017;28:4972–8.
170 Whittle SL, Richards BL, Husni E, *et al*. Opioid therapy for treating rheumatoid arthritis pain. *Cochrane Database Syst Rev* 2011;23.
171 Williams MA, Srikesavan C, Heine PJ, *et al*. Exercise for rheumatoid arthritis of the hand. *Cochrane Database Syst Rev* 2018;32.
172 Barton JL, Hulen E, Schue A, *et al*. Experience and context shape patient and clinician goals for treatment of rheumatoid arthritis: a qualitative study. *Arthritis Care Res* 2018;70:1614–20.
173 Gibofsky A, Galloway J, Kekow J, *et al*. Comparison of patient and physician perspectives in the management of rheumatoid arthritis: results from global physician- and patient-based surveys. *Health Qual Life Outcomes* 2018;16:211.
174 Torikai E, Suzuki D, Matsuyama Y. AB0222 differences of disease impression and treatment expectation in rheumatoid arthritis patients with different disease activity. *Ann Rheum Dis* 2018;77:1295.
175 Fraenkel L, Peters E, Charpentier P. Decision tool to improve the quality of care in rheumatoid arthritis. *Arthritis Care Res* 2012;64:977–85.
176 Fraenkel L, Matzko CK, Webb DE, *et al*. Use of decision support for improved knowledge, values clarification, and informed choice in patients with rheumatoid arthritis. *Arthritis Care Res* 2015;67:1496–502.
177 LC L, Adam PM, Backman CL. Proof-Of-Concept study of a web-based methotrexate decision aid for patients with rheumatoid arthritis. *Arthritis Care Res* 2014;66:1472–81.
178 LC L, Shaw CD, Lacaille D. Effects of a web-based patient decision aid on biologic and small-molecule agents for rheumatoid arthritis: results from a proof-of-concept study. *Arthritis Care Res* 2018;70:343–52.
179 Garratt AM, Løchting I, Smedslund G, *et al*. Measurement properties of instruments assessing self-efficacy in patients with rheumatic diseases. *Rheumatology* 2014;53:1161–71.
180 Palmer D, El Miedany Y. Self-helplessness in arthritis: an important but overlooked index. *Br J Nurs* 2010;19:965–71.
181 Silvers IJ, Hovell MF, Weisman MH, *et al*. Assessing physician/patient perceptions in rheumatoid arthritis. A vital component in patient education. *Arthritis Rheum* 1985;28:300–7.
182 Sinclair VG, Wallston KA. The development and psychometric evaluation of the brief resilient coping scale. *Assessment* 2004;11:94–101.
183 Barlow J, Wright CC. Knowledge in patients with rheumatoid arthritis: a longer term follow- up of a randomized controlled study of patient education leaflets. *Rheumatology* 1998;37:373–6.
184 Barsky AJ, Ahern DK, Orav EJ, *et al*. A randomized trial of three psychosocial treatments for the symptoms of rheumatoid arthritis. *Semin Arthritis Rheum* 2010;40:222–32.
185 Bell MJ, Lineker SC, Wilkins AL. A randomized controlled trial to evaluate the efficacy of community based physical therapy in the treatment of people with rheumatoid arthritis. *J Rheumatol* 1998;25:231–7.
186 Breedland I, van Scheppingen C, Leijsma M, *et al*. Effects of a group-based exercise and educational program on physical performance and disease self-management in rheumatoid arthritis: a randomized controlled study. *Phys Ther* 2011;91:879–93.
187 Hewlett S, Ambler N, Almeida C, *et al*. Self-Management of fatigue in rheumatoid arthritis: a randomised controlled trial of group cognitive-behavioural therapy. *Ann Rheum Dis* 2011;70:1060–7.
188 Hosseini Moghadam M, Jahanbin I, Nazarinia MA. The effect of educational program on self-efficacy of women with rheumatoid arthritis: a randomized controlled clinical trial. *Int J community based Nurs midwifery* 2018;6:12–20.
189 Lineker SC, Bell MJ, Wilkins AL. Improvements following short term home based physical therapy are maintained at one year in people with moderate to severe rheumatoid arthritis. *J Rheumatol* 2001;28:165–8.
190 Lorig KR, Ritter PL, Laurent DD, *et al*. The internet-based arthritis self-management program: a one-year randomized trial for patients with arthritis or fibromyalgia. *Arthritis Rheum* 2008;59:1009–17.
191 Niedermann K, de Bie RA, Kubli R, *et al*. Effectiveness of individual resource-oriented joint protection education in people with rheumatoid arthritis. A randomized controlled trial. *Patient Educ Couns* 2011;82:42–8.
192 Niedermann K, Buchi S, Ciurea A, *et al*. Six and 12 months' effects of individual joint protection education in people with rheumatoid arthritis: A randomized controlled trial. *Scand J Occup Ther* 2012;19:360–9.

193 Riemsma RP, Taal E, Brus HLM, *et al*. Coordinated individual education with an arthritis passport for patients with rheumatoid arthritis. *Arthritis Care Res* 1997;10:238–49.
194 Roth T, Price JM, Amato DA, *et al*. The effect of eszopiclone in patients with insomnia and coexisting rheumatoid arthritis: a pilot study. *Prim Care Companion J Clin Psychiatry* 2009;11:292–301.
195 AMH S, Chui DYY. Evaluation of a community rehabilitation service for people with rheumatoid arthritis. *Patient Educ Couns* 2004;55:62–9.
196 Tuntland H, Kjeken I, Nordheim L. The Cochrane review of assistive technology for rheumatoid arthritis. *Eur J Phys Rehabil Med* 2010;46:261–8.
197 Lorig K, Chastain RL, Ung E, *et al*. Development and evaluation of a scale to measure perceived self-efficacy in people with arthritis. *Arthritis Care Res.* 1989;32:37–44.
198 Kerschbaumer A, Sepriano A, Smolen JS, *et al*. Efficacy of pharmacological treatment in rheumatoid arthritis: a systematic literature research Informing the 2019 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2020:annrheumdis-2019-216656.
199 Nagy G, Roodenrijs NMT, Welsing PMJ. EULAR recommendations for the management of difficult-to-treat rheumatoid arthritis. *Manuscript in preparation*.