ARD Online First, published on January 7, 2014 as 10.1136/annrheumdis-2013-204577

EXTENDED REPORT

Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis

Jackie L Nam,[1] Sofia Ramiro,[2] Cecile Gaujoux-Viala,[3] Kaoru Takase,[1,4] Mario Leon-Garcia,[1,5] Paul Emery,[1] Laure Gossec,[6] Robert Landewe,[7] Josef S Smolen,[8,9] Maya H Buch[1]

▶ Additional material is published online only. To view please visit the journal online (http://dx.doi.org/10.1136/annrheumdis-2013-204577).

For numbered affiliations see end of article.

Correspondence to
Dr Maya H Buch, Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds LS7 4SA, UK; M.Buch@leeds.ac.uk

Received 8 September 2013
Revised 15 October 2013
Accepted 24 October 2013

ABSTRACT

Objectives To update the evidence for the efficacy of biological disease-modifying antirheumatic drugs (bDMARD) in patients with rheumatoid arthritis (RA) to inform the European League Against Rheumatism (EULAR) Task Force treatment recommendations.

Methods Medline, Embase and Cochrane databases were searched for articles published between January 2009 and February 2013 on infliximab, etanercept, adalimumab, certolizumab-pegol, golimumab, anakinra, abatacept, rituximab, tocilizumab and biosimilar DMARDs (bsDMARDs) in phase 3 development. Abstracts from 2011 to 2012 American College of Rheumatology (ACR) and 2011–2013 EULAR conferences were obtained.

Results Fifty-one full papers, and 57 abstracts were identified. The randomised controlled trials (RCT) confirmed the efficacy of bDMARD+conventional synthetic DMARDs (csDMARDs) versus csDMARDs alone (level 1B evidence). There was some additional evidence for the use of bDMARD monotherapy, however bDMARD and MTX combination therapy for all bDMARD classes was more efficacious (1B). Clinical and radiographic responses were high with treat-to-target strategies. Earlier improvement in signs and symptoms were seen with more intensive initial treatment strategies, but outcomes were similar upon addition of bDMARDs in patients with insufficient response to MTX. In general, radiographic progression was lower with bDMARD use, mainly due to initial treatment effects. Although patients may achieve bDMARD- and drug-free remission, maintenance of clinical responses was higher with bDMARD continuation (1B), but bDMARD dose reduction could be applied (1B). There was still no RCT data for bDMARD switching.

Conclusions The systematic literature review confirms efficacy of biological DMARDs in RA. It addresses different treatment strategies with the potential for reduction in therapy, particularly with early disease control, and highlights emerging therapies.

Linked

▶ http://dx.doi.org/10.1136/annrheumdis-2013-204573
▶ http://dx.doi.org/10.1136/annrheumdis-2013-204575
▶ http://dx.doi.org/10.1136/annrheumdis-2013-204588

To cite: Nam JL, Ramiro S, Gaujoux-Viala C, *et al*. *Ann Rheum Dis* Published Online First: [*please include* Day Month Year] doi:10.1136/annrheumdis-2013-204577

INTRODUCTION

Systematic literature reviews (SLR) on biological disease modifying drugs (bDMARDs)[1] and treatment strategies including bDMARDs in rheumatoid arthritis (RA)[2] were performed in 2010 to provide evidence that informed a European League Against Rheumatism (EULAR) Task Force for the development of the 2010 EULAR recommendations for the management of RA with DMARDs.[3] Since then, several additional bDMARD studies have been published, as well as a number of studies evaluating different approaches and strategies, biosimilar DMARDs[4] and tofacitinib, the first of a new class of targeted synthetic DMARDs that inhibit Janus kinase. Some studies have also addressed the use of bDMARDs at the earlier stages of the disease, during the undifferentiated inflammatory arthritis (UA) phase. The aim of this SLR was therefore to provide an update of the available evidence for the 2013 EULAR RA treatment recommendations.[5] Where appropriate, we have used the recently proposed nomenclature for DMARDs that takes into account biosimilars (bsDMARDs) and also differentiates between conventional synthetic (cs) and targeted synthetic (ts) DMARDs.[6]

METHODS

The Steering Group outlined the scope of the literature search on the role of bDMARDs in the treatment of RA, which, once performed, was discussed by a subgroup of the Task Force and subsequently the whole Task Force. Studies evaluating nine bDMARDs: infliximab (IFX), etanercept (ETN), adalimumab (ADA), certolizumab-pegol (CZP), golimumab (GLM), anakinra (ANA), abatacept (ABT), rituximab (RTX) and tocilizumab (TCZ) were included. Information on bsDMARDs in phase 3 development and tsDMARDs in the context of bDMARD therapy was also sought. The previous SLR included studies to 2009.[1] This updated literature search was therefore performed for the period between January 2009 and February 2013 using Medline, Embase and Cochrane databases. Abstracts were also obtained from the 2011–2012 American College of Rheumatology (ACR) and 2011–2013 EULAR conferences. Where full papers of these abstracts were published online until mid-2013, the latter were obtained and used

for data extraction. Relevant articles published after this time-point were also included.

The criteria for study selection were (1) randomised controlled trials (RCT) (double-blind stipulated for RCTs evaluating bDMARDs or bsDMARDs vs a csDMARD; for strategy-type trials and head-to-head studies open-label studies were also included as in the previous SLR[2]); (2) patients with RA (1987 ACR[7] or 2010 ACR/EULAR RA classification criteria[8]) or UA at risk of developing RA; (3) studies evaluating one of the nine bDMARDs mentioned above or bsDMARDs in phase 3 or tsDMARDs in comparison with a bDMARD; (4) trials of ≥6 months' duration; (5) studies with ≥50 patients; (6) publications in English. Published meta-analyses and SLRs were also reviewed and included where relevant.

As in the previous SLR, studies were grouped according to the following patient categories reflecting current clinical practice and trial design: (1) no prior DMARD use (DMARD naive); (2) no prior MTX use (MTX naive); (3) inadequate response to MTX (MTX-IR); (4) incomplete response to any csDMARD, which may not necessarily include MTX (mixed DMARD-IR); (5) inadequate response to tumour necrosis factor-inhibitor (TNFi; TNFi-IR). Levels of evidence were assigned according to the Oxford Centre for Evidence-based Medicine levels of evidence (http://www.cebm.net/index.aspx?o=1025).

Quality of published studies was assessed using the Cochrane risk of bias assessment tool for RevMan 5.1.[9] Efficacy outcomes included those relating to signs and symptoms (ACR and EULAR responses), radiographic outcomes, physical function (Health Assessment Questionnaire Disability Index (HAQ)),[10] quality-of-life measures (using the Physical Component Score and Mental Component Score of the Short Form-36)[11] and fatigue (measured by the FACIT score[12 13] and fatigue visual analogue scale (FAS)).

A meta-analysis of RCTs was performed comparing (1) bDMARD+csDMARDs versus csDMARD (2) bDMARD monotherapy versus csDMARD/placebo and (3) bDMARD+MTX versus bDMARD monotherapy. This was done for all patient populations where more than one new RCT was identified. This was not done for strategy trials due to the heterogeneity of the studies in terms of design, inclusion criteria, target and methodology, or for the individual head-to-head and bsDMARD studies, for which results have been described in tabulated form. Details of the search, the studies included and details of efficacy outcome measures extracted can be found in the online supplementary material.

The heterogeneous nature of the studies introduced significant challenges in the analysis and interpretation of the results; with the increasing number of therapies evaluated as well as treatment strategies adding to this complexity. When drawing conclusions from this initiative, we have acknowledged and taken careful consideration of the inherent biases associated with comparing different patient populations and different compounds, in studies using different statistical plans and powered for different endpoints.

RESULTS

The initial search yielded 10 265 articles for titles and abstracts for screening of which 134 were selected for detailed review. Together with the additional conference, abstracts and full papers obtained from a hand search (including relevant articles found after the main search), 51 full papers and 57 abstracts met the inclusion criteria.

Overall risk of bias for the majority of studies evaluated was low. Several were not blinded and were therefore classed as 'high risk of bias' in terms of 'blinding of participants and personnel'[14–17] and 'blinding of outcome assessment'.[16] In some, under-recruitment was a noted concern, and studies were, therefore, also classed as high risk in the 'incomplete outcome data' category.[16 18 19] Details can be found in the online supplementary section.

The efficacy data are summarised by addressing four main areas of bDMARD use: (1) bDMARD efficacy (in combination therapy with csDMARDs or as monotherapy, head-to-head bDMARD studies and bDMARD switching); (2) treatment strategies including bDMARDs; (3) bDMARD stopping or dose reduction; and (4) studies including bDMARDs and new therapies (bsDMARDs and tsDMARDs).

Biological DMARD efficacy

Outcomes in this group will focus on those relating to signs and symptoms with ACR responses for ACR70 responses shown by way of example. The ACR response, which was used by way of example in the original SLR, remained the most frequently reported measure demonstrating overall efficacy. Of the ACR responses, the ACR70 was chosen as it was felt to be the most clinically meaningful response, most closely representing low disease activity.[20] Details of other efficacy outcomes including measures of low disease activity and remission can be found in the online supplementary section.

Biological DMARD±conventional synthetic DMARD versus conventional synthetic DMARD

Biological DMARD+MTX combination versus conventional synthetic DMARD

While there were no studies fulfilling inclusion criteria for DMARD-naive patients in the previous search, this update identified one study ('HIT HARD'),[21] which confirmed efficacy at 6 months for ADA+MTX versus moderate dose MTX (15 mg weekly) in this group. In the MTX-naive RA group, there was further evidence for efficacy for ADA[22] and TCZ,[23] and new data for RTX from the IMAGE study.[24] In the MTX-IR group, there was data for all nine bDMARDS. Additional studies for this and the mixed DMARD-IR groups have been published for ANA,[25] CZP[26 27] and GLM.[28–31] All confirm enhanced efficacy of a bDMARD+MTX versus placebo+MTX in MTX-naive RA (RR (95% CI) 1.68 (1.54 to 1.84) for ACR 70 responses) (figure 1A), bDMARD+MTX versus placebo+MTX in MTX-IR (RR (95% CI) 4.07 (3.21 to 5.17)) (figure 1B) and bDMARD+csDMARD versus csDMARD in mixed DMARD –IR (RR (95% CI) 4.74 (2.63 to 8.56)) (figure 1C) (level of evidence 1B). In a SLR and meta-analysis of four RCTs in TNFi-IR,[32–35] which were included in our previous SLR,[1] the mean pooled OR for ACR 70 (95% CI) was 7.43 (3.77 to 14.61)[36] (level of evidence 1A). Although there were no new RCTs fulfilling inclusion criteria for this group, the 12-week REALISTIC RCT in which approximately 40% were TNFi-IR and subanalysed accordingly, confirmed clinical efficacy of CZP.[37]

Biological DMARD monotherapy versus conventional synthetic DMARD

Our previous SLR failed to confirm clear efficacy of bDMARD monotherapy versus a csDMARD. Results once again have varied for this group with no clear benefit seen in subassessments of these patients in three more recent GLM RCTs.[28 38–40] In the FUNCTION study, which aimed to assess the efficacy and safety of TCZ±MTX versus MTX in MTX- naive early RA, the TCZ 8 mg/kg monotherapy group met its primary endpoint (DAS28 ESR remission at 6 months: 38.7% vs 15% in the TCZ

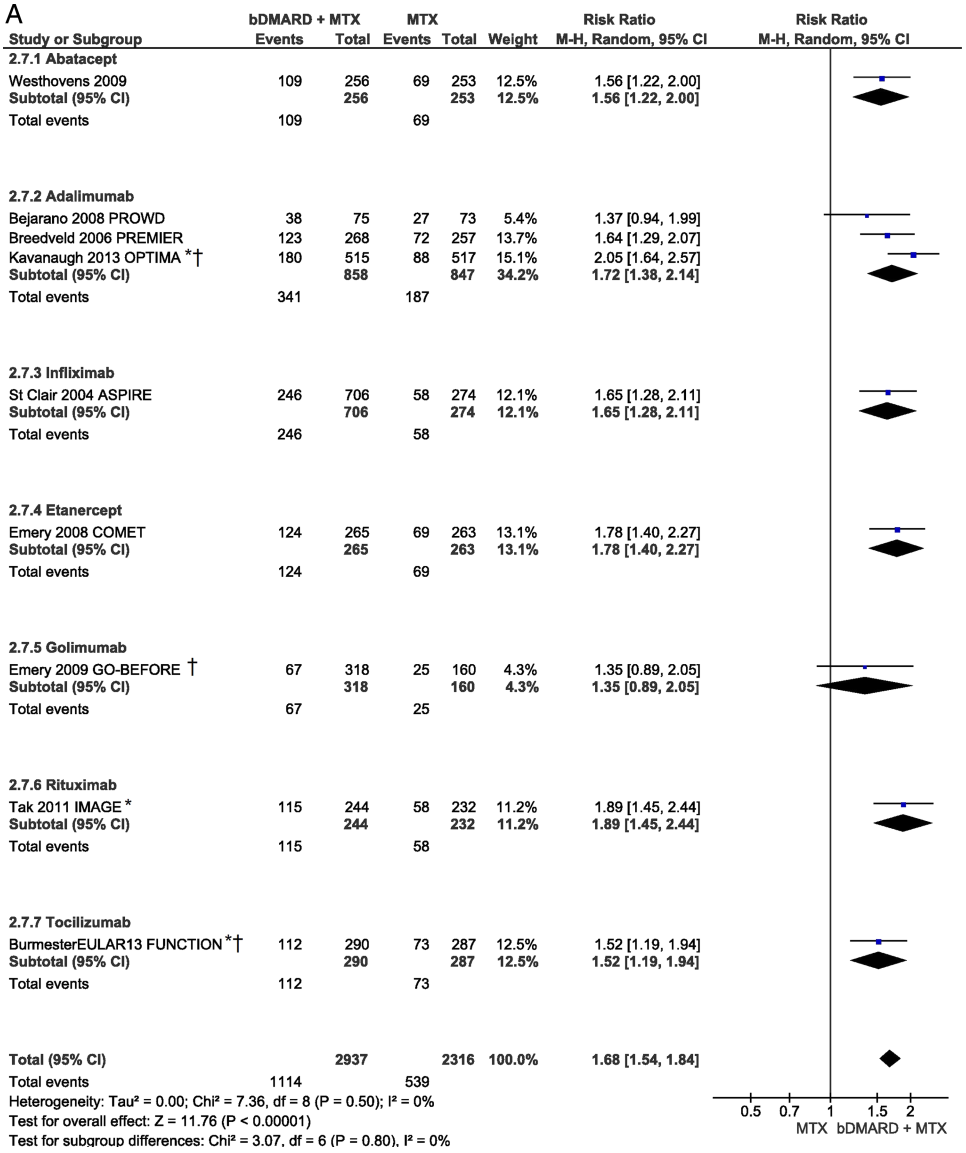

Figure 1 (A) Risk ratios for the ACR 70 responses comparing a biological disease modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus MTX monotherapy in patients with early rheumatoid arthritis who are MTX naive. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review[1]; † ACR 70 responses at 6 months for Kavanaugh 2013 OPTIMA, Emery 2009 GO-BEFORE and Burmester EULAR 2013 FUNCTION; all other ACR 70 responses are at 12 months. (B) Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus MTX monotherapy in patients with rheumatoid arthritis (RA) who are MTX-incomplete responders. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review[1]; †ACR 70 response at 12 months for Kremer 2011 LITHE; all other ACR 70 responses are at 6 months. (C) Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus synthetic disease-modifying antirheumatic drug (csDMARD csDMARD) versus csDMARD monotherapy in patients with rheumatoid arthritis for whom a csDMARD (not necessarily MTX) has failed. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review.[1]; † ACR 70 response at 12 months for Klareskog 2004 TEMPO; all other ACR 70 responses are at 6 months.

8 mg/kg monotherapy vs MTX monotherapy groups, respectively, p≤0.0001). This endpoint, however, favours agents that, like tocilizumab, interfere with the acute-phase response, while ACR response rates (ACR20, ACR 50 and ACR70) and changes in physical function, which do not, were similar between the two groups. Radiographic progression at 12 months was lower in those receiving TCZ than MTX, being lowest in the TCZ 8 mg/kg+MTX combination group.[23]

Biological DMARD+MTX combination versus biological DMARD monotherapy

In several previously published RCTs in which bDMARD monotherapy was compared to MTX, better clinical and radiographic outcomes were seen with bDMARD+MTX than with a bDMARD alone.[41 42] Data from RCTs with MTX-naive patients which include bDMARD+MTX and bDMARD monotherapy groups confirm clinical (and also structural) superiority of combination therapy (figure 2A).[23 43]

A 16-week open-label study in MTX-IR RA, however, showed similar clinical and patient-reported outcomes with ETN+MTX versus ETN monotherapy.[44 45] In this SLR, three studies were found, all in the MTX-IR group, directly comparing starting bDMARD+MTX combination therapy versus bDMARD monotherapy. In the open-label JESMR study, ETN+MTX was superior to ETN monotherapy for clinical outcomes. Although less radiographic progression was seen with combination therapy, the between-group difference was not statistically significant.[14 46] Two studies compared the addition of TCZ with MTX (combination) with switching from MTX to TCZ monotherapy (MTX-withdrawal). In the non-inferiority SURPRISE study[47] and in the ACT-RAY study, similar ACR 70 responses were seen for both groups at 6 months.[48] (figure 2B) By contrast with the 6-month outcomes, however, 12-month data from the ACT-RAY study showed higher proportions of DAS28 remission and radiographic non-progression with combination TCZ+MTX (DAS28 remission 37% vs 46%, p=0.03 and radiographic non-progression 86% vs 92%, p=0.007 in the TCZ monotherapy and TCZ +MTX groups, respectively).[49] (figure 2C)

One study has addressed the possibility of stepping down from bDMARD+MTX to bDMARD monotherapy. In the COMET study, patients were randomised at baseline for a 2-year period to MTX monotherapy for 1 year then continuing or adding ETN, or MTX+ETN for 1 year then continuing or stopping MTX.[50] DAS 28 remission at 2 years in the group continuing MTX+ETN (EM/EM) and the step down to ETN monotherapy (EM/E) were 45% and 37%, respectively.

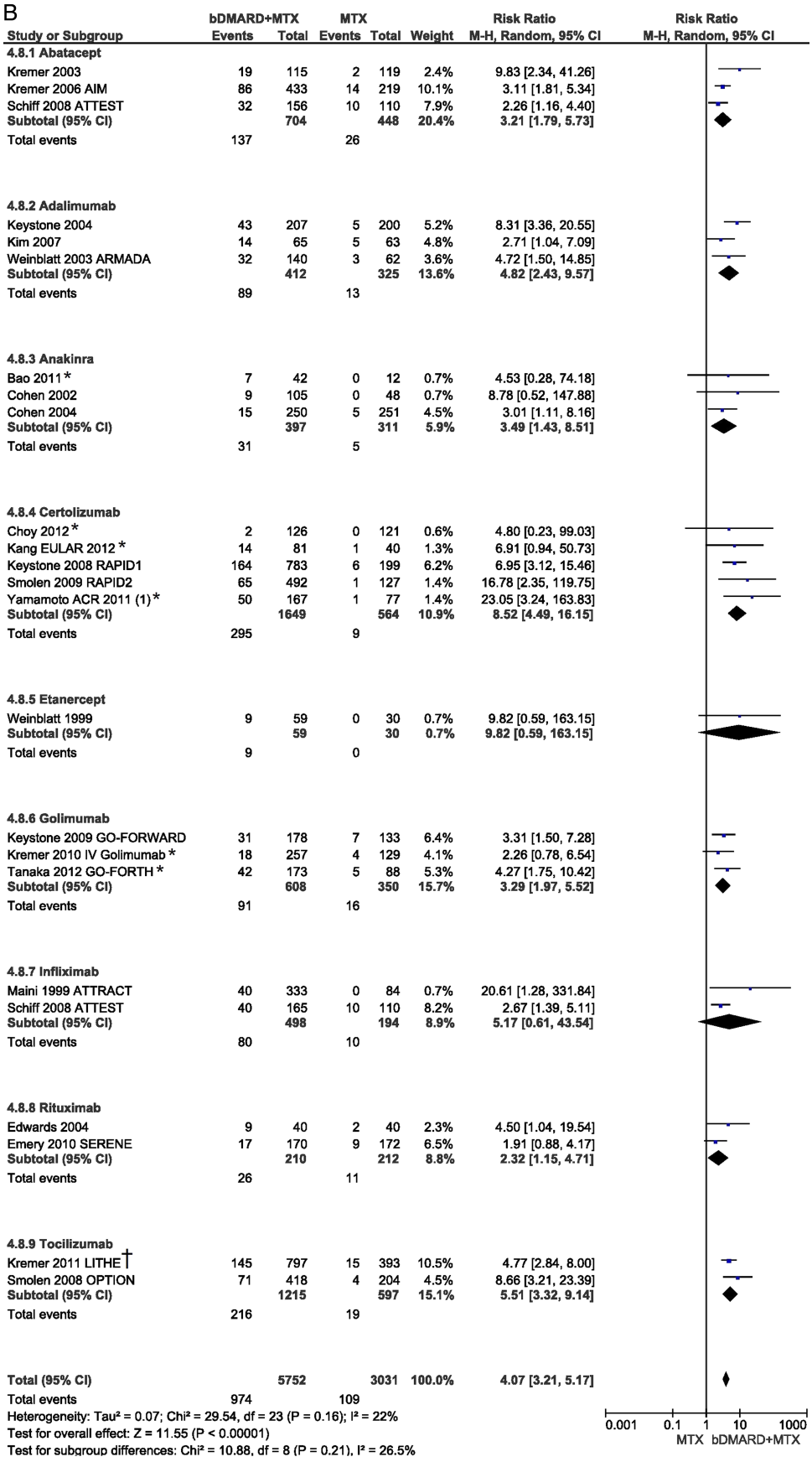

Figure 1. Continued.

Radiographic non-progression was high in both groups, but higher with combination therapy than with monotherapy (EM/EM vs EM/E 90% vs 75%, p 0.008).

Head-to-head biological DMARD studies

Two studies, both in MTX-IR RA, have evaluated two bDMARDs in a direct ('head-to-head') comparison. The AMPLE study

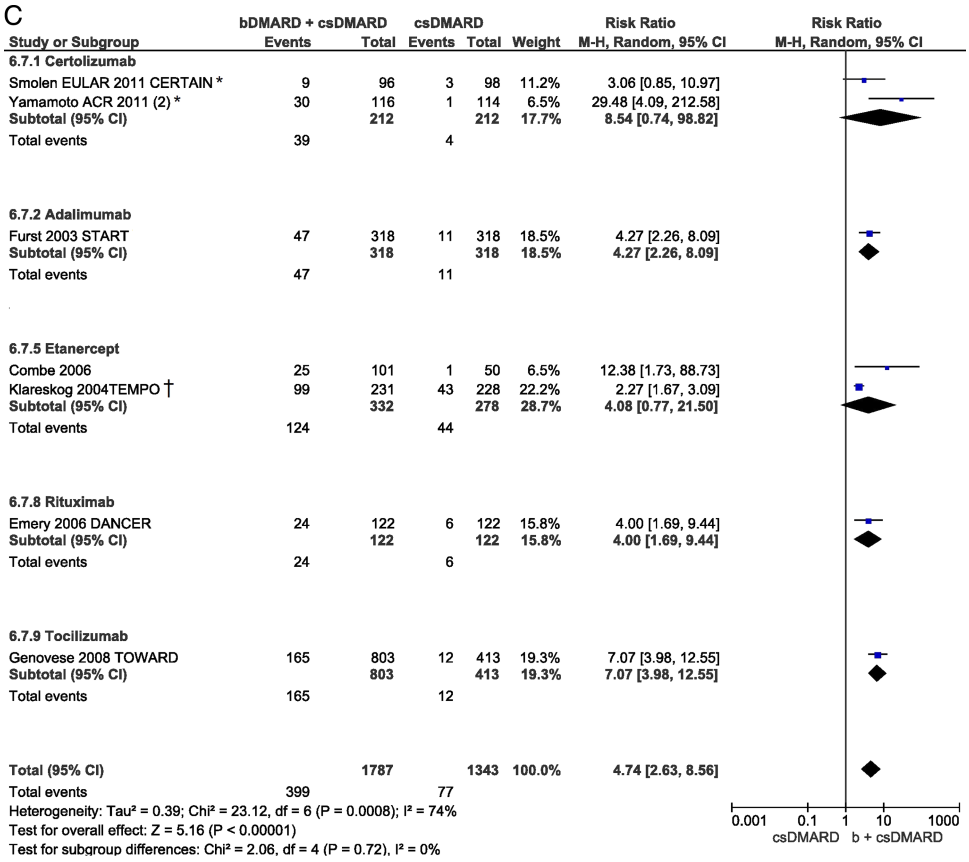

Figure 1. Continued.

compared ABT+MTX versus ADA+MTX combination therapy in an early RA cohort (less than 2 years).[15] In this non-inferiority study, the primary endpoint (ACR20 response at 12 months) was met. Similar results were also seen for the ACR50 and 70 responses (ACR20, 50 and 70 response rates of 65, 46 and 29% vs 63, 46 and 26% in the ABT+MTX and ADA+MTX groups, respectively). The ADACTA study evaluated bDMARD monotherapy, comparing TCZ versus ADA.[51] This superiority study showed a significantly greater change in DAS28 from baseline to 6 months in the TCZ 8 mg/kg monotherapy versus ADA 40 mg SC monotherapy group (difference (95% CI): −1.5 (−1.8 to −1.1), p<0.0001). ACR responses at 6 months were also higher in the TCZ monotherapy group (ACR20, 50 and 70 response rates of 65, 47 and 33% vs 49, 28 and 18% in the TCZ and ADA monotherapy groups, respectively), as were changes in the clinical disease activity index (CDAI) (which does not comprise an acute-phase reactant) (table 1).

Switching between biological DMARDs

There were no RCTs fulfilling inclusion criteria for switching between bDMARDs.

Strategy trials

Several strategy trials have been published since the last EULAR SLR[2] (tables 2 and 3) aiming to address the place of bDMARD therapy in the treatment of RA. These have mainly compared (1) step-up to a bDMARD versus step-up to csDMARD combination therapy after MTX failure (SWEFOT,[16] TEAR,[18] RACAT[19]); (2) bDMARD+MTX versus csDMARD (MTX) monotherapy as induction therapy (HIT HARD,[21] TEAR,[18] OPTIMA,[22] COMET[50]); (3) induction therapy with bDMARDs versus combination csDMARDs (TEAR[18]) and (4) evaluated bDMARD therapy versus csDMARD within a treat-to-target approach, in which patients were seen at regular intervals with treatment changes if a treatment outcome (eg, low disease activity or remission) was not met (Neo-RACo,[52] OPERA,[53] IDEA,[54]). A number of RCTs comparing bDMARD+MTX versus MTX monotherapy have incorporated a cross-over arm from MTX monotherapy to MTX+bDMARD combination therapy, providing further information on therapy with initial bDMARD+MTX versus step-up to bDMARD+MTX therapy ([30 31 39 55]). Several studies have also aimed to look at the use of bDMARD therapy in patients at earlier stages of inflammatory arthritis, presenting as UA or including patients that fulfil the 2010 ACR-EULAR RA,[8] but not all fulfilling the 1987 ACR RA classification criteria[7] (ADJUST,[56] EMPIRE,[57] IMPROVED,[17] STREAM[58]).

In essence, earlier improvement in signs and symptoms was seen with the more intensive strategies, however, outcomes were similar once bDMARDs were added in patients with insufficient response to MTX.[16 18 50 59–61] Studies addressing the use of combination csDMARD therapy with MTX, SSZ+HCQ as step-up therapy in MTX-IR also reported similar clinical efficacy to step up bDMARD therapy.[18 19 60] Low recruitment (and thus possibly insufficient power) was noted in several of these studies. Nevertheless, greater depth of response (higher proportions achieving ACR 70 responses (essentially equivalent to reaching low disease activity[20]) or remission, today's treatment goals) was seen with bDMARD therapy.[52 53 62] Moreover, less radiographic progression and higher proportions of non-progression were noted with combination therapies that included a bDMARD,[50 59 61 63] mainly due to early treatment effects.[50 64] High proportions of clinical response rates and less radiographic progression were seen in studies using treat-to-target strategies, many of which also included glucocorticoids within their treatment strategies.[52–54]

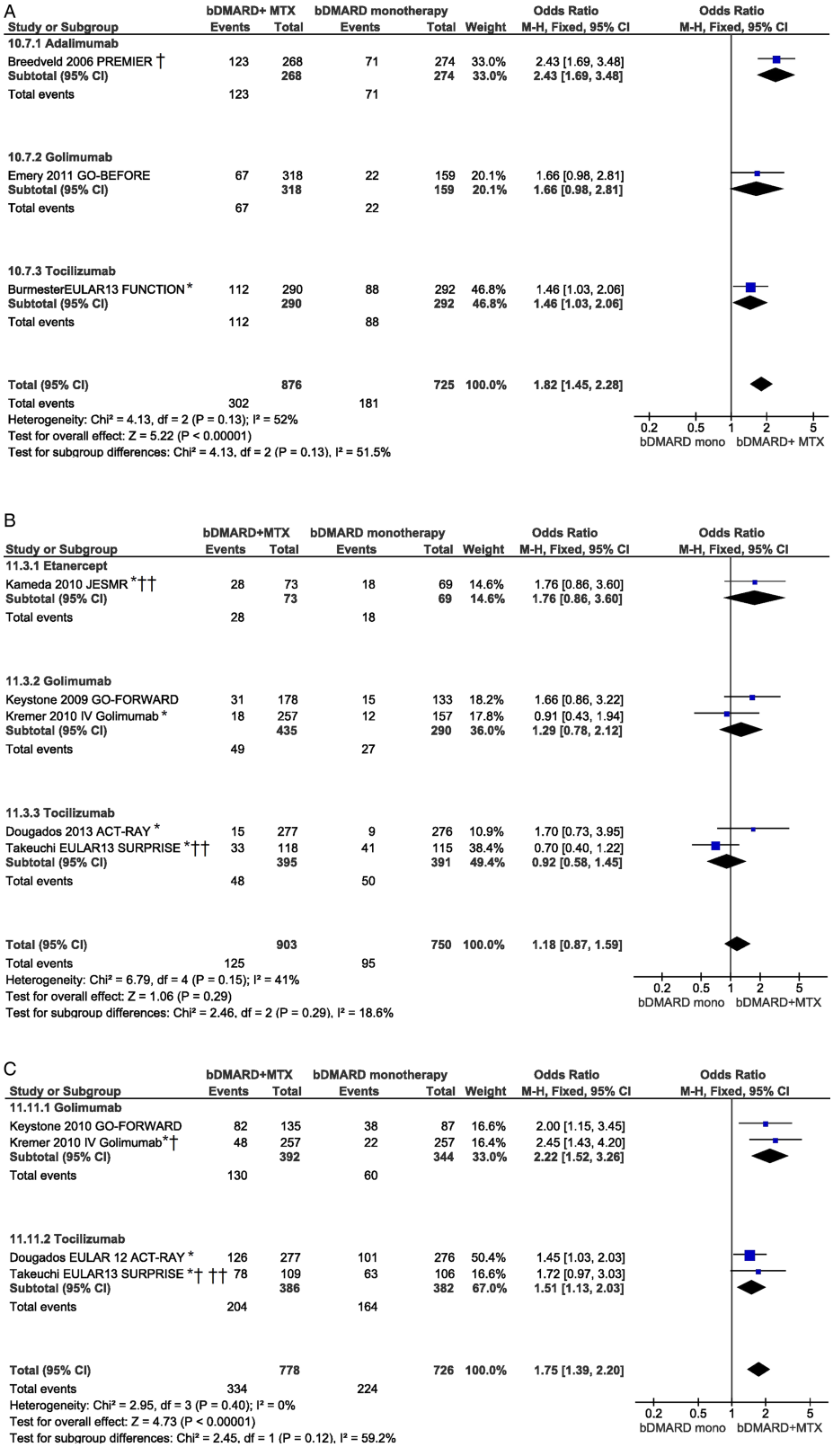

Figure 2 (A) Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-naive. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review[1]; † ACR 70 response at 12 months for Breedveld 2006 PREMIER; all other ACR 70 responses are at 6 months. (B) Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-incomplete responders. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review[1]; ACR 70 responses are at 6 months; †† open-label studies. (C) Risk ratios for the DAS28 remission comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-incomplete responders. *Additional study since the 2010 systematic literature review.[1]; † DAS28 remission at 6 months for Kremer 2010 IV Golimumab and Takeuchi EULAR 2013 SURPRISE and ACR 70 at 12 months for Keystone 2010 GO-FORWARD and DOUGADOS EULAR 2012 ACT-RAY; †† open-label study.

Biological DMARD stopping or dose reduction

Eleven studies evaluated bDMARD stopping or bDMARD dose reduction after achieving low disease activity or remission.[21 54 57 65–73] In DMARD-naive patients, the BeSt study reported that bDMARD discontinuation was possible but more likely in those receiving IFX+MTX as induction therapy compared to those receiving delayed IFX+MTX combination therapy (56% vs 29%, p=0.008 in the initial vs delayed groups, respectively.[63] In the HIT HARD study, however, stopping ADA in an open label manner after ADA+MTX induction therapy for 6 months resulted in similar clinical outcomes to those on MTX monotherapy from the outset at 1 year (DAS28 :3.2±1.4 vs 3.4±1.6, p=0.41).[21] In the OPTIMA study, a high proportion of patients who achieved low disease activity (LDAS28) at

Table 1 Randomised controlled trials (RCT) of head-to-head biological DMARDs (bDMARD) and bDMARD RCTs including biosimilar and targeted synthetic DMARDs—American College of Rheumatology (ACR) responses

Biological DMARD	Trial (reference)	Treatment group	Patients evaluated (n)	Time-point evaluated (months)	ACR20 (%)	p Value	ACR50 (%)	p Value	ACR70 (%)	p Value
A. Head-to-head bDMARD	Weinblatt 2013 (AMPLE)[15]	ABT 125 mg weekly +MTX	318	12	64.8	Referent	46.2	Referent	29.2	Referent
		ADA 40 mg every 2 weeks+MTX	328		63.4	NS	46.0	NS	26.2	NS
	Gabay 2013 (ADACTA)[51]	ADA 40 mg every 2 weeks	162	6	49.4	Referent	27.8	Referent	17.9	Referent
		TCZ 8 mg/kg every 4 weeks	163		65.0	0.0038	47.2	0.0002	32.5	0.0023
B. Biosimilar DMARD	Yoo ARD 2013 (PLANETRA)[74]	CT-P13 3 mg/kg+MTX	302*/248†	7	60.9*/ 73.3†	Referent	42.3†	Referent	20.2†	Referent
		IFX 3 mg/kg+MTX	304*/251†		58.6*/ 69.7†	NS	40.6†	NS	17.9†	NS
C. Targeted synthetic DMARD	van Vollenhoven 2012 (ORAL STANDARD)[76]	Placebo	106	6	28.3	Referent		Referent		Referent
		Tofacitinib 5 mg twice daily	196		51.5	<0.001		≤0.05		≤0.05
		Tofacitinib 10 mg twice daily	196		52.6	<0.001		≤0.05		≤0.05
		ADA 40 mg every 2 weeks	199		47.2	<0.001		≤0.05		≤0.05

All RCTs are in MTX incomplete responders.
*Intention-to-treat population.
†Per protocol populations.
ABT, abatacept; ADA, adalimumab; IFX, infliximab; MTX, methotrexate; NS, non-significant; RTX, rituximab; TCZ, tocilizumab.

6 months were able to maintain this outcome even after withdrawing the TNF-inhibitor. Maintenance, however, was somewhat higher in those continuing ADA compared to those who subsequently stopped bDMARD (18 month LDAS28: 91% vs 81% in the ADA-continue vs the ADA-stop groups, p=0.004, respectively).[67] Studies have also addressed the possibility of dose reduction. In MTX-naive RA, the PRIZE study reported approximately two-thirds of early RA patients who achieved DAS28-remission (DAS28<2.6) after 1 year with ETN 50 mg weekly+MTX were able to maintain this response at 2 years with ETN 25 mg weekly+MTX (sustained DAS 28 remission (DAS28<2.6 at weeks 76 and 91 with no steroid boost): 23.1% vs 40% vs 63.5% in the placebo vs MTX monotherapy vs ETN 25 mg weekly+MTX groups, respectively).[68] Thus, in this study, withdrawal of ETN was followed by a reduction in response in approximately 60% of the patients compared with ETN full dose continuation, while in OPTIMA, the reduction in targeted outcome was only about 10% following withdrawal of ADA. Maintenance of response in the majority of patients who reduced ETN dose was similarly shown in a MTX-IR group in the PRESERVE study[69] after achieving LDAS28 at 9 months (DAS28 remission at 21 months was 35% vs 66% vs 71% with MTX continuation after ETN withdrawal vs ETN25 mg weekly +MTX vs ETN50 mg+MTX) and in studies in established RA (STRASS and DOSERA).[72 73] (table 4)

Biosimilar DMARDs

The PLANETRA study, was a phase 3 RCT comparing the bsDMARD CTP-13 to IFX demonstrating similar efficacy between the two treatment groups (ACR20 response at week 30 61% vs 59% (95% CI −6% to 10%) for CT-P13+MTX vs IFX +MTX, respectively).[74] ACR50 and ACR70 responses were also similar with no significant between-group differences at 1 year[75] (table 1).

Targeted synthetic DMARDs in the context of existing bDMARDs

In the ORAL-STANDARD study, in MTX-IR RA, ACR responses for the oral JAK kinase inhibitor tofacitinib and ADA were both significantly higher than placebo[76] (table 1).

DISCUSSION

The increasing use of bDMARDs, particularly in different treatment strategies, as well as the introduction of newer therapies and emerging bsDMARDs, warranted a further review of the literature. The purpose of this SLR was to inform the update of the treatment recommendations being formulated by the EULAR Task Force.

This systematic literature review confirms the efficacy of bDMARDs particularly in combination with MTX. In the rather rare situation that patients treated with csDMARDs long-term may not tolerate MTX or another csDMARD, bDMARD monotherapy may be considered.[23 50 51] However, with superior long-term clinical and superior radiographic outcomes, combination therapy with a bDMARD+a csDMARD remains the optimal approach.

This review also evaluated head-to-head bDMARD studies. These data, among other evidence, have important implications for clinical practice. While filling a gap in comparative studies, however, new challenges arise, particularly as several meta-analyses have shown similar efficacy among bDMARDs (except anakinra), and that bDMARD combinations with csDMARDs convey superior efficacy to bDMARD monotherapy.

Table 2 Biological DMARD strategies studies without a treat-to-target approach—study outcomes

Patient group	Biological DMARD	Study (n=total number enrolled)	Outcome	Result
DMARD-naive	ABT	Emery 2010 (ADJUST)[56] (n=56)	Primary EP: Year 1: development of RA (ACR criteria)	Groups: ABT vs placebo 1/26 (46%) vs 16/24 (67%)
	ETN	Moreland 2012 (TEAR)*[18] (n=755)	Primary EP: DAS28-ESR from week 48 to week 102 Other: DAS28 ESR week 24 DAS28 ESR remission (%) week 102 ACR responses (%) at week 102 Radiographic non-progression (%) at week 102	(*completers only analysis*) No difference between groups (p=0.28) IE+IT vs SE+ST p<0.0001 IE/IT/SE/ST†: 56.5/ 59.1/ 52.9/ 56.5, p=0.93 ACR20 and ACR 50, p=NS between groups ACR70: IE+SE vs IT+ST 18.25 vs 11.3%, p=0.01 IE/IT/SE/ST 79.4/64.9/71.1/68.3, p=0.33 IE+SE vs IT+ST 76.8 vs 66.4, p=0.02
	IFX	van Vollenhoven 2009/ 2012 (SWEFOT)[16 60] (n=487)	Primary EP: EULAR good response at 12 months Other: EULAR good response at 24 months Mean radiographic progression (SD) at 2 years	Groups: MTX+SSZ+HCQ vs MTX+IFX‡ 25% vs 39%, (RR 1.59 [95% CI 1.1 to 2.3]), p=0.016 31% vs 38%, p=0.204 7.23 (12.72) vs 4 (10.05), p=0.009
MTX naive	ADA	Kavanaugh 2013[22] Fleischmann ACR 2012 (OPTIMA)[61] (n=1032)	Primary EP: Composite DAS28(CRP)<3.2 at week 78 and no radiographic progression from baseline to week 78 (mTSS ≤ 0.5) Other: Period 1: Stable LDA at weeks 22 and 26 Period 2: Week 78 DAS28CRP<3.2; ΔmTSS ≤0.5; DAS28CRP<3.2 and ΔmTSS≤0.5	Groups: ADA+MTX vs Placebo+MTX§ 44% vs 24% (p<0.001) 65% vs 65%; 86% vs 72% (p<0.001), 60% vs 48% (p<0.001)
	ETN	Emery 2009 (COMET)[50] (n=274)	2 year EP include: Remission (DAS28<2.6): Radiographic non-progression (mTSS≤0.5):	Groups: EM/EM, ME/E, M/EM, M/M¶ 62/108, 54/108, 51/88 and 33/94 (p<0.01 for EM/EM and M/EM vs M/M) 89/99, 74/99, 59/79 and 56/83 (p<0.01 EM/EM vs other groups)
MTX IR	ETN	O'Dell 2013 (RACAT)[19] (n=353)	Primary EP: Mean (SD) ΔDAS28 at week 48** Other: Week 24: Mean (SD) ΔDAS28 Mean (SD) ΔmTSS Week 48: Mean (SD) ΔmTSS	Groups: MTX+SSZ+HCQ vs ETN+MTX *(completers only analysis)* −2.12 (1.28) vs -2.29 (1.30) (p=0.26) −1.79 (1.20) vs −2.06 (1.35) (p=0.06) 0.42(1.91) vs 0.003 (3.62) (p=0.20) 0.54 (1.93) vs 0.29(3.32) (p=0.43)

*80% DMARD-naive.
†TEAR comparator groups: IE, immediate treatment with ETN+MTX; IT, immediate treatment with triple therapy; SE: step-up treatment from MTX monotherapy to ETN+MTX if DAS28 ESR ≥3.2 at week 24; ST: step-up treatment from MTX monotherapy to triple therapy (MTX+SSZ+HCQ) if DAS28 ESR ≥3.2 at week 24.
‡SWEFOT comparator groups: MTX monotherapy then randomisation to group (A) (MTX+SSZ+HCQ) or (B) (MTX+IFX) if not in LDA after 3–4 months.
§OPTIMA comparator groups: Period 1: ADA+MTX vs Placebo+MTX for 26 weeks: Period 2: Patients assessed for LDA (DAS28 (CRP)<3.2) at weeks 22 and 26 and categorised as responders or incomplete responders: In the ADA+MTX, responders may have been randomised to ADA withdrawal; in the Placebo+MTX arm, incomplete responders may have been randomised to starting ADA.
¶COMET: Randomisation at baseline for 2-year period to MTX monotherapy for 1 year then continue or add ETN or MTX+ETN for 1 year then continue or stop MTX. ('denotes treatment in the first year'/'denotes treatment in the second year'). E=etanercept; M=methotrexate.
**Original proposed primary endpoint=difference in proportion of participants with DAS28 ≤3.2 at week 48; changed due to unexpected low enrolment.
ABT, abatacept; ADA, adalimumab; DMARD, disease modifying antirheumatic drug; ETN, etanercept; HCQ, hydroxychloroquine; IFX, infliximab; LDA, low disease activity; MTX, methotrexate; NS, non-significant; Primary EP, primary endpoint; SD, standard deviation; SSZ, sulphasalazine; TT, triple therapy.

This SLR also highlights the different study populations and designs employed and providing important new information when considering first-line bDMARD therapy. Studies addressing different treatment strategies have shown earlier improvement in signs and symptoms with a more intensive initial treatment approach, with similar clinical outcomes achieved upon addition of bDMARDs in patients with insufficient response to MTX compared with initial bDMARD use. Nevertheless, effects on radiographic progression tend to be superior with initial bDMARD use. Additionally, use of treat-to-target strategies has demonstrated high clinical and radiographic responses. Several studies have shown similar outcomes with initial combination csDMARD and step-up to combination csDMARDs compared to initial bDMARD therapy. Under-recruitment and methods of data analysis have been noted to be of concern in some[16 18 19] and need to be taken into consideration when interpreting these findings as they may have potentially important impact on the study results.[77]

Although maintenance of low disease activity states is better with bDMARD continuation, there is some evidence for bDMARD dose reduction without loss of efficacy. With early bDMARD use, bDMARD and drug-free remission also seems more of a possibility. This highlights the need for more studies investigating the added benefit of initial induction therapy with a bDMARD compared to step-up to bDMARD following a csDMARD strategy. Related areas for research include the

Table 3 Biological DMARD strategy studies* with a treat-to-target approach—study outcomes

Biological DMARD	Study (n=total number enrolled)	Outcome	Result
ADA	Heimans 2013 (IMPROVED)[17] (n=610)	Primary EP:	Groups: MTX+high dose prednisolone (early DAS remission arm); MTX+HCQ +SSZ; MTX+ADA†
		1 year DAS44 remission (DAS<1.6):	68% ; 25% vs 41% (MTX+HCQ+SSZ vs MTX+ADA p<0.001)
		1 year DFR remission	32%; 1% vs 0%
		Other:	
		ΔmTSS<0.5	95%; 96%; 92%;
	Horslev–Petersen 2013 (OPERA)[53] (n=180)	Primary EP:	Groups: ADA+MTX vs Placebo+MTX
		1 year DAS28CRP<3.2	80% vs 76% (p=0.65)
		Other:	
		1 year DAS28CRP (median (95% CI)	2.0 (1.7 to 5.2) vs 2.6 (1.7 to 4.7) (p=0.009),
		1 year DAS 28 remission (DAS28<2.6)	74% vs 49% (p=0.0008), NNT 4.0 (2.6–9.1)
	van Eijk 2012 (STREAM)[58] (n=82)	Primary EP:	Groups: aggressive vs conventional care
		2 year median (IQR) ΔmTSS§	0 (0–1.1) vs 0.5 (0–2.5) NS
		Other:	
		2 year median remission (DAS<1.6)	66% vs 49% NS
ETN	Villeneuve ACR 2011 (EMPIRE)[57] (n=110)	Primary EP:	Groups: ETN+MTX vs Placebo+MTX
		1 year remission (NTSJ at week 52)	31% vs 29% (p=0.835)
IFX	Leirisalo–Repo 2012 (NEO-RACo)[52] (n=99)	Primary EP:	Groups: FIN-Raco+IFX vs FIN-Raco+Pla‡
		2 year modified ACR remission	66% vs 53% (p=0.19)
		Other:	
		2 year sustained modified ACR remission¶	26% vs 10% (p=0.042)
		DAS28 remission	Both groups: 82% (NS)
		2 year mean ΔmTSS§	−0.2 vs 1.4 (p=0.0058)
		2 year radiographic non-progression	80% vs 53% (p=−0.006)
	Nam 2013 (IDEA)[54] (n=112)	Primary EP:	Groups: IFX+MTX vs IV steroid (methylprednisolone)+MTX
		1 year ΔmTSS score (mean)	1.20 vs 2.81 (adjusted difference (95% CI) −1.45 (−3.35 to 0.45); p=0.132)
		Radiographic non-progression (mTSS<2.0)	81% vs 71% (OR 1.77 (0.56, 5.61); p=0.328)
		Other:	
		1 year DAS44 remission	49% vs 36% (OR 2.13 (0.91, 5.00); p=0.082)
		1.5 year (week 78) DAS44 remission	48% vs 50% (OR 1.12 (0.47, 2.68); p=0.792)

*All DMARD-naive.
†IMPROVED comparator arms: All patients treated with MTX+high-dose oral prednisolone. Those that achieved early remission (DAS<1.6 at 4 months): tapered prednisolone and persistent remission after 8 months tapered and stopped MTX. Those not in early remission were randomized to MTX+HCZ+SSZ (arm 1) or MTX+ADA (arm 2). For those in remission after 8 months, treatment was tapered to MTX monotherapy; for those not in remission: arm 1 changed to MTX+ADA and arm 2 increased ADA dose.
‡NEO-RACo: FIN-Raco+Pla=MTX+SSZ+HCQ+prednisolone+placebo for 26 weeks; FIN-Raco+IFX=MTX+SSZ+HCQ+prednisolone+IFX 3 mg/kg for 26 weeks.
§mTSS=van der Heijde-modified total Sharp score.
¶Sustained remission=remission at each visit from 6 to 24 months.
ADA, adalimumab; DAS, disease activity score (44 joint count); DFR, drug-free remission; ETN, etanercept; IFX, infliximab, LDA, low disease activity, MTX, methotrexate; NS, non-significant; NTJ, no tender or swollen joints (RAI+SJC=0); primary EP, primary endpoint.

search for predictors of response to targeted therapies (which patient is likely to respond to which targeted therapy); the search for prognostic risk factors (eg, the presence of baseline radiographic erosions[59]) identifying those patients who may benefit most from a more intensive, initial bDMARD treatment strategy; and the search for predictive factors that permit successful drug withdrawal.[21 68 78 79]

This SLR confirmed that there is still an absence of RCT evidence-base to guide optimal approach when switching from one bDMARD to another after TNFi failure.

Since the last review, newer therapies have emerged with studies demonstrating efficacy of the IFX bsDMARD CT-P13 and the tsDMARD tofacitinib. Drug development in the area of bsDMARDs continues with several other agents on the horizon.[80 81]

Our literature review has its limitations. In particular, the inherent challenges in ensuring accurate interpretation when analysing heterogeneous studies is acknowledged. Although key clinical outcomes were addressed, other outcomes including the impact of bDMARDs on work ability was beyond the scope of this review. Standard definitions of disease activity states (eg, DAS28 ≤3.2 for LDA) have been used although more recent insights suggest that such patients may still have ongoing disease activity, highlighting the deficiencies of such measures. The SLR also focused solely on RCTs. While these are regarded as the highest level of evidence, they reflect a more selected patient population, making data less applicable to a real-life population. In this regard, non-randomised studies and evidence from real-life clinical practice (eg, national registries) provides valuable information that complements RCTs. Synthesis of data from both sources is needed for optimal application of evidence base into daily practice.

Safety is another aspect of bDMARD therapy that needs consideration. Given the importance of this aspect, this topic has been reviewed in a separate SLR.[82] New evidence on the csDMARDs, glucocorticoid use as well as the tsDMARD has also been dealt with separately.[83]

In summary, review of the literature confirms the efficacy of bDMARDs, particularly in combination with a csDMARD, addresses their use in different treatment strategies with the potential for reduction in therapy particularly when early disease control is achieved and highlights new targeted and bsDMARDS in the treatment of RA. Finally, this review also identified some research agenda questions in the field of bDMARDs and RA which the updated EULAR recommendations[5] will address.

Table 4 Biological DMARD strategy studies addressing biological DMARD dose reduction or stopping—study outcomes

Patient group	Biologic	Study (n=total number enrolled)	Outcome	Result
DMARD-naive	ADA	Detert 2013 (HIT HARD)[21] (n=172)	Primary EP: Week 48 DAS28 (mean (SD)) Other: ACR responses (%) DAS28 remission (%)	Groups: ADA+MTX/ MTX vs Placebo MTX/MTX* 3.2 (1.4) vs 3.4 (1.6) (p=0.49) ACR 50: 52.6 vs 51.4 (p=0.88), ACR 70: 40.5 vs 34.0 (p=0.40) 42.4 vs 36.8 (p=0.47)
		Horslev–Petersen EULAR 2013 (OPERA)[53] (n=180)	Year 2: DAS28CRP (median (95% CI)) Remission (DAS28CRP<2.6)	Groups: ADA+MTX/ MTX vs placebo+MTX/MTX† 2.0 (1.7 to 4.4) vs 2.0 (1.7 to 4.5) (p=0.97) 66% vs 69% (p=0.79)
	IFX	van der Kooij 2009[66]/Klarenbeek 2011)[84]/Dirven 2011 (BeSt)[64] (n=508)	DFR (%) year 4; year 8 4 year joint damage progression>SDC (%)	Groups: 1 to 4‡ 14/12/8/18 (p=0.14); 18/19/17/15 (p=0.9) 51/54/38/31 (p<0.05 for group 4 vs groups 1 and 3 and for group 3 vs group 2)
		van der Kooij 2009 (BeSt)[63] (n=508)	Discontinuation of IFX due to sustained DAS44 ≤2.4 2 years after IFX initiation (%)	Groups: Initial vs delayed IFX: 56 vs 29 (OR(95% CI) 2.56 (1.27 to 5.16) p=0.008))
		van den Broek 2011 (BeSt)[85] (n=508)	Discontinuation of IFX due to sustained DAS ≤ 2.4 (for 6 months) (n) Sustained DAS remission after IFX cessation (n(%)) DFR (n(%)) Predictor of restarting IFX (for DAS>2.4)	Groups: Initial vs delayed IFX 77/120 vs 27/109 43/77 (56) vs11/27 (41) 15 (27) vs 0 after at least 1 year of follow-up HR (95% CI) 1.8 (0.9 to 3.7)
		Nam 2013 (IDEA)[54] (n=112)	Week 78: stopped IFX due to sustained remission (n(%))§	14/55 (25) of the IFX group
MTX naïve	ADA	Smolen EULAR 2012 (OPTIMA)[78] (n=1032)	Maintenance of DAS28<3.2 from week 52 to 78 in patient who achieved LDA at with ADA+MTX at weeks 22 and 26 (%)	Groups: ADA_continue vs ADA withdrawal 87 vs 65 (p=0.002)
		Emery EULAR 2011 (OPTIMA)[79] (n=1032)	Week 78 outcomes in patient who achieved LDA with ADA+MTX at weeks 22 and 26: ACR20/50/70 (%) DAS28 <3.2(%) DA28 <2.6(%) ΔmTSS≤0.5(%)	Groups: ADA_continue vs ADA_withdrawal 95/89/77 vs 94/80/65 (p=0.72/ 0.11/ 0.05) 81 vs 91 (p=0.04) 66 vs 86 (p=0.001) 89 vs 81 (0.06)
	ETN	Emery EULAR 2013 (PRIZE)††[68] (n=306)	Week 39 after achieving remission Sustained DAS remission ΔmTSS≤0.5(%)	Groups: ETN25+MTX vs MTX vs placebo 63.5 vs 38.5 vs 23.1 (ETN25+MTX vs MTX p=0.0051; ETN25+MTX vs placebo p<0.0001, MTX vs placebo 0.0595) 87.9 vs 96.4 vs 89.8 (ETN25+MTX vs MTX 0.1124; ETN25+MTX vs placebo 0.7609; MTX vs placebo 0.1929)
MTX IR	ETN	Smolen 2013 (PRESERVE)[71] (n=834)	Primary EP: Week 88 LDAS28 (%) in patients who achieved sustained LDA with ETN 50 mg weekly+MTX for 36 weeks	Groups: ETN50+MTX vsETN25+MTX vs placebo+MTX 82.6 vs 79.1 vs 42.6 ETN50+MTX vs PBO+MTX (mean difference (95% CI) 40.8 (32.5 to 49.1, p<0.0001) ETN25+MTX vs PBO+MTX (mean difference (95% CI) 35.9 (27.0 to 44.8), p<0.0001)
	TCZ	Huizinga EULAR 2013[70] (ACT-RAY) (n=556)	Week 104: TCZ discontinuation after achieving the protocol-defined sustained remission (%) Flare (%) Study DFR (%)	Groups: TCZ add-on vs switch 57 vs 47 (p=0.13) 85 vs 87 (p=0.075) 5.1 vs 1.8 (0.037)
Mixed DMARD IR	CZP	Smolen EULAR 2011/EULAR 2012 (CERTAIN)[71 86] (n=194)	Week 52 CDAI remission in patients who achieved CDAI remission at weeks 20 and 24	Remission retained in 3/17 prior CZP vs 2/6 placebo patients
Established RA	ADA & ETN	Fautrel ACR 2012/EULAR 2013 (STRASS)[72 87 88] (n=137)	18 months	Groups: S (spacing ADA & ETN injections) vs M (maintain full dose ADA & ETN)¶

Continued

Table 4 Continued

Patient group	Biologic	Study (n=total number enrolled)	Outcome	Result
			Taper an and stopping TNFi (n (%))	S-arm: 47 (73.4) tapered TNFi, of whom 24 (37.5) stopped
			Relapse occurred at least once (%)	81vs. 56, p=0.0009
			Structural damage progression (n (%))	In 4 (6.7) and 3 (4.5) patients (p=0.3)
	ETN	van Vollenhoven ACR 2012/ EULAR 2013 (DOSERA)[73 89] (n=91)	Week 48	Groups: ETN50 vs ETN25 vs placebo
			Non-failure** (%) in patients on ETN 50 mg weekly+MTX and LDA or DAS28 remission for ≥11 months	52 vs 44 vs 13
				ETN50 vs placebo :OR 7.2 (1.7–29.8 (p=0.007) ETN50
				ETN 25 vs placebo: OR 4.2 (1.0–17.0 (p=0.44) vs PBO, ETN25 vs ETN50 NS

*HIT HARD comparator groups: ADA+MTX vs placebo+MTX for 24 weeks. After 24 weeks, both groups treatment with MTX only.
†OPERA comparator groups: ADA+MTX vs placebo+MTX for 1 year. After 1 year, both groups treatment with MTX only.
‡BeSt comparator groups: Group 1 sequential monotherapy; Group 2 step-up combination therapy; Group 3 initial combination with prednisone; Group 4 initial combination with IFX.
§Sustained remission=DAS<1.6 for 6 months.
¶STRASS comparator groups: Patients in stable DAS28 remission (DAS28≤2.6 for ≥6 months) on ETN or ADA for ≥ 1 year with no structural damage progression on X-rays since last X-ray assessment, patients randomised to one of 2 arms: S (spacing ADA & ETN injections) vs M (maintain ADA & ETN as full regimen).
**Failure=DAS28 ≥3.2 and an increase of SDAS28 ≥0.6 or disease progression as determined by the investigator or patient.
††Sustained DAS remission=DAS28<2.6 at weeks 76 and 91, no corticosteroid boost between weeks 52–64.
ADA, adalimumab; csDMARD, conventional synthetic disease modifying antirheumatic drug; CZP, certolizumab pegol; DFR, drug free remission; ETN, etanercept; IFX, infliximab; LDA, low disease activity; mTSS, van der Heijde modified sharp scores; MTX, methotrexate; NS, non-significant; SDC, smallest detectable change; TCZ, tocilizumab.

Author affiliations
[1]Leeds Institute of Rheumatic and Musculoskeletal Medicine, University of Leeds, Chapel Allerton Hospital, and NIHR Leeds Musculoskeletal Biomedical Research Unit, Leeds Teaching Hospitals NHS Trust, Leeds, UK
[2]Academic Medical Center, University of Amsterdam, Amsterdam, and Hospital Garcia de Orta, Almada, Portugal
[3]Department of Rheumatology, Nîmes University Hospital, Montpellier I University, Nimes, France
[4]Department of Internal Medicine and Clinical Immunology, Graduate School of Medicine and Faculty of Medicine, Yokohama City University, Yokohama, Japan
[5]R4 de Reumatologia del Hospital de Valme, Seville, Spain
[6] Rheumatology Department, Paris 06 UPMC University, AP-HP, Pite-Salpetriere Hospital, Paris, France
[7]Academic Medical Center, University of Amsterdam, Amsterdam, and Atrium Medical Center, Heerlen, The Netherlands
[8]Division of Rheumatology, Department of Medicine 3, Medical University of Vienna, Vienna, Austria
[9]2nd Department of Medicine, Hietzing Hospital Vienna, Vienna, Austria

Acknowledgements The authors would like to thank Liz Neilly, University of Leeds, for help with the literature search; Liz Hensor, LIRMM University of Leeds and NIHR LMBRU Leeds Teaching Hospitals NHS Trust, for advice on the data and EULAR for funding support.

Contributors Each author has contributed to one or more of the following aspects of the manuscript—conception and design, acquisition, analysis and interpretation of data, drafting and revising the article.

Funding EULAR.

Competing interests These are summarised below as remuneration for consultation and/or speaking engagements ('R'), research funding ('F') or 'none'. JLN—R: UCB. SR—R: Fundação para a Ciência e Tecnologia. CGV—R: Abbvie, BMS, MSD, Pfizer, Roche-Chugai, UCB; F: Expanscience, Nordic Pharma, Pfizer. KT-none. ML-G- none; PE- R: MSD, Pfizer, Abbvie, Novartis, UCB, Roche, BMS, Lilly, Takeda, Janssen; F: MSD, Roche. LG—R: Abbvie, BMS, Chugai, Pfizer, Roche, UCB. RL—R: Abbott/AbbVie, Ablynx, Amgen, Astra-Zeneca, Bristol Myers Squibb, Centocor, Glaxo-Smith-Kline, Novartis, Merck, Pfizer, Roche, Schering-Plough, UCB, Wyeth; F: Abbott, Amgen, Centocor, Novartis, Pfizer, Roche, Schering-Plough, UCB, Wyeth. JSS—R: Abbott/Abbvie, Amgen, Astra-Zeneca, BMS, Celgene, Glaxo, Infinity, Janssen, Lilly, Medimmune, MSD, Novo-Nordisk, Pfizer, Roche, Samsung, Sandoz, Sanofi, UCB, Vertex; F: Abbott, BMS, MSD, Pfizer, Roche, UCB. MHB—R: Abbott/Abbvie, Bristol Myers-Squibb, Chugai, Pfizer, Roche; F: Pfizer.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Nam JL, Winthrop KL, van Vollenhoven RF, *et al*. Current evidence for the management of rheumatoid arthritis with biological disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of RA. *Ann Rheum Dis* 2010;69:976–86.
2 Knevel R, Schoels M, Huizinga TW, *et al*. Current evidence for a strategic approach to the management of rheumatoid arthritis with disease-modifying antirheumatic drugs: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010;69:987–94.
3 Smolen JS, Landewe R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs. *Ann Rheum Dis* 2010;69:964–75.
4 Dorner T, Strand V, Castaneda-Hernandez G, *et al*. The role of biosimilars in the treatment of rheumatic diseases. *Ann Rheum Dis* 2013;72:322–8.
5 Smolen JS, Landewé R, Breedveld FC, *et al*. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease modifying antirheumatic drugs—2013 update. *Ann Rheum Dis* 2013. Published Online First: 25 Oct 2013. doi:10.1136/annrheumdis-2013-204573
6 Smolen JS, van der Heijde D, Machold KP, *et al*. Proposal for a New Nomenclature of Disease Modifying Antirheumatic Drugs. *Ann Rheum Dis* 2013. Published Online First: 26 Sep 2013. doi:10.1136/annrheumdis-2013-204317
7 Arnett FC, Edworthy SM, Bloch DA, *et al*. The American Rheumatism Association 1987 revised criteria for the classification of rheumatoid arthritis. *Arthritis Rheum* 1988;31:315–24.
8 Aletaha D, Neogi T, Silman AJ, *et al*. 2010 rheumatoid arthritis classification criteria: an American College of Rheumatology/European League Against Rheumatism collaborative initiative. *Ann Rheum Dis* 2010;69:1580–8.
9 Cochrane Handbook for Systematic Reviews of Interventions Version 5.1.0 [updated March 2011]. The Cochrane Collaboration, 2011. In: Higgins JPT, Green S, eds. 2011. http://www.cochrane-handbook.org
10 Fries JF, Spitz P, Kraines RG, *et al*. Measurement of patient outcome in arthritis. *Arthritis Rheum* 1980;23:137–45.

11 Ware JE Jr., Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992;30:473–83.
12 Cella D, Lai JS, Chang CH, *et al*. Fatigue in cancer patients compared with fatigue in the general United States population. *Cancer* 2002;94:528–38.
13 Cella D, Yount S, Sorensen M, *et al*. Validation of the Functional Assessment of Chronic Illness Therapy Fatigue Scale relative to other instrumentation in patients with rheumatoid arthritis. *J Rheumatol* 2005;32:811–19.
14 Kameda H, Ueki Y, Saito K, *et al*. Etanercept (ETN) with methotrexate (MTX) is better than ETN monotherapy in patients with active rheumatoid arthritis despite MTX therapy: A randomized trial. *Mod Rheumatol* 2010;20:531–8.
15 Weinblatt ME, Schiff M, Valente R, *et al*. Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: findings of a phase IIIb, multinational, prospective, randomized study. *Arthritis Rheum* 2013;65:28–38.
16 van Vollenhoven RF, Ernestam S, Geborek P, *et al*. Addition of infliximab compared with addition of sulfasalazine and hydroxychloroquine to methotrexate in patients with early rheumatoid arthritis (Swefot trial): 1-year results of a randomised trial. *Lancet* 2009;374:459–66.
17 Heimans L, Wevers-de Boer KV, Visser K, *et al*. A two-step treatment strategy trial in patients with early arthritis aimed at achieving remission: the IMPROVED study. *Ann Rheum Dis* 2013.
18 Moreland LW, O'Dell JR, Paulus HE, *et al*. A randomized comparative effectiveness study of oral triple therapy versus etanercept plus methotrexate in early aggressive rheumatoid arthritis: The treatment of early aggressive rheumatoid arthritis trial. *Arthritis Rheum* 2012;64:2824–35.
19 O'Dell JR, Mikuls TR, Taylor TH, *et al*. Therapies for active rheumatoid arthritis after methotrexate failure. *N Engl J Med* 2013;369:307–18.
20 Aletaha D, Funovits J, Smolen JS. The importance of reporting disease activity states in rheumatoid arthritis clinical trials. *Arthritis Rheum* 2008;58:2622–31.
21 Detert J, Bastian H, Listing J, *et al*. Induction therapy with adalimumab plus methotrexate for 24 weeks followed by methotrexate monotherapy up to week 48 versus methotrexate therapy alone for DMARD-naive patients with early rheumatoid arthritis: HIT HARD, an investigator-initiated study. *Ann Rheum Dis* 2013;72:844–50.
22 Kavanaugh A, Fleischmann RM, Emery P, *et al*. Clinical, functional and radiographic consequences of achieving stable low disease activity and remission with adalimumab plus methotrexate or methotrexate alone in early rheumatoid arthritis: 26-week results from the randomised, controlled OPTIMA study. *Ann Rheum Dis* 2013;72:64–71.
23 Burmester GR, Rigby W, van Vollenhov R, *et al*. Tocilizumab (TCZ) in combination and monotherapy versus methotrexate (MTX) in MTX-naive patients (pts) with early rheumatoid arthiritis (RA): clinical and radiographic outcomes from a randomised, placebo-controlled trial. *Ann Rheum Dis* 2013;72:63.
24 Tak PP, Rigby WF, Rubbert-Roth A, *et al*. Inhibition of joint damage and improved clinical outcomes with rituximab plus methotrexate in early active rheumatoid arthritis: The IMAGE trial. *Ann Rheum Dis* 2011;70:39–46.
25 Bao J, Yue T, Liu W, *et al*. Secondary failure to treatment with recombinant human IL-1 receptor antagonist in Chinese patients with rheumatoid arthritis. *Clin Rheumatol* 2011;30:697–701.
26 Choy E, McKenna F, Vencovsky J, *et al*. Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatol UK* 2012;51:1226–34.
27 Kang YM, Park W, Park YE, *et al*. Efficacy and safety of certolizumab pegol (CZP) with concomitant methotrexate (MTX) in Korean rheumatoid arthritis (RA) patients (pts) with an inadequate response to MTX. *Ann Rheum Dis* 2012;71:666.
28 Kremer J, Ritchlin C, Mendelsohn A, *et al*. Golimumab, a new human anti-tumor necrosis factor alpha antibody, administered intravenously in patients with active rheumatoid arthritis: Forty-eight-week efficacy and safety results of a phase III randomized, double-blind, placebo-controlled study.[Erratum appears in Arthritis Rheum. 2010 Oct;62(10):3130]. *Arthritis Rheum* 2010;62:917–28.
29 Tanaka Y, Harigai M, Takeuchi T, *et al*. Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: Results of the GO-FORTH study. *Ann Rheum Dis* 2012;71:817–24.
30 Li Z, Zhang F, Kay J, *et al*. Safety and efficacy of subcutaneous golimumab in Chinese patients with active rheumatoid arthritis despite MTX therapy: results from a randomized, placebo-controlled, phase 3 trial. *Ann Rheum Dis* 2013;72:444.
31 Weinblatt M, Bingham CO III2, *et al*. Intravenous golimumab inhibits radiographic progression and maintains clinical efficacy and safety in patients with active rheumatoid arthritis despite methotrexate therapy: 1-year results of a phase 3 trial. *Ann Rheum Dis* 2013;72:238.
32 Genovese MC, Becker JC, Schiff M, *et al*. Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005;353:1114–23.
33 Smolen JS, Kay J, Doyle MK, *et al*. Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009;374:210–21.
34 Cohen SB, Emery P, Greenwald MW, *et al*. Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006;54:2793–806.
35 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.
36 Schoels M, Aletaha D, Smolen JS, *et al*. Comparative effectiveness and safety of biological treatment options after tumour necrosis factor alpha inhibitor failure in rheumatoid arthritis: systematic review and indirect pairwise meta-analysis. *Ann Rheum Dis* 2012;71:1303–8.
37 Weinblatt M, Fleischmann RM, Vollenhoven RF, *et al*. Efficacy and safety of certolizumab pegol in a broad population of patients with active rheumatoid arthritis: Week 28 results from a phase IIIB randomized controlled study. *Arthritis Rheum* 2011;1.
38 Emery P, Keystone E, Fleischmann R, *et al*. New provisional American College of Rheumatology and European League Against Rheumatism remission criteria: results from 2 randomized, controlled golimumab trials in patients with rheumatoid arthritis. *Ann Rheum Dis* 2012;71(Suppl 3):665.
39 Emery P, Fleischmann R, Van Der Heijde D, *et al*. The effects of golimumab on radiographic progression in rheumatoid arthritis: Results of randomized controlled studies of golimumab before methotrexate therapy and golimumab after methotrexate therapy. *Arthritis Rheum* 2011;63:1200–10.
40 Takeuchi T, Harigai M, Tanaka Y, *et al*. Goluimumab, a human anti-TNFα monoclonal antibody administered subcutaneously every four weeks as monotherapy in patients with acitve rheumatoid arthritis despite DMARD therapy:24-week results fo clinical and radiographic assessments. *Ann Rheum Dis* 2011;70:420.
41 Breedveld FC, Weisman MH, Kavanaugh AF, *et al*. The PREMIER study: A multicenter, randomized, double-blind clinical trial of combination therapy with adalimumab plus methotrexate versus methotrexate alone or adalimumab alone in patients with early, aggressive rheumatoid arthritis who had not had previous methotrexate treatment. *Arthritis Rheum* 2006;54:26–37.
42 Klareskog L, van der Heijde D, de Jager JP, *et al*. Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004;363:675–81.
43 Emery P, Fleischmann RM, Moreland LW, *et al*. Golimumab, a human anti-tumor necrosis factor alpha monoclonal antibody, injected subcutaneously every four weeks in methotrexate-naive patients with active rheumatoid arthritis: Twenty-four-week results of a phase III, multicenter, randomized, double-blind, placebo-controlled study of golimumab before methotrexate as first-line therapy for early-onset rheumatoid arthritis. *Arthritis Rheum* 2009;60:2272–83.
44 van Riel PL, Taggart AJ, Sany J, *et al*. Efficacy and safety of combination etanercept and methotrexate versus etanercept alone in patients with rheumatoid arthritis with an inadequate response to methotrexate: the ADORE study. *Ann Rheum Dis* 2006;65:1478–83.
45 van Riel PL, Freundlich B, MacPeek D, *et al*. Patient-reported health outcomes in a trial of etanercept monotherapy versus combination therapy with etanercept and methotrexate for rheumatoid arthritis: the ADORE trial. *Ann Rheum Dis* 2008;67:1104–10.
46 Kameda H, Kanbe K, Sato E, *et al*. Continuation of methotrexate resulted in better clinical and radiographic outcomes than discontinuation upon starting etanercept in patients with rheumatoid arthritis: 52-Week results from the JESMR study. *J Rheumatol* 2011;38:1585–92.
47 Takeuchi T, Kaneko Y, Atsumi T, *et al*. Adding tocilizumab or switching to tocilizumab monotherapy in RA patients with inadequate response to methotrexate: 24-week results from a randomized controlled study (SURPRISE study). *Ann Rheum Dis* 2013;72:62.
48 Dougados M, Kissel K, Sheeran T, *et al*. Adding tocilizumab or switching to tocilizumab monotherapy in methotrexate inadequate responders: 24-week symptomatic and structural results of a 2-year randomised controlled strategy trial in rheumatoid arthritis (ACT-RAY). *Ann Rheum Dis* 2013;72:43–50.
49 Dougados M, Kissel K, Conaghan PG, *et al*. Clinical, radiographic, and immunogenic effects after 1 year of tocilizumab (TCZ)-based treatment strategy with and without methotrexate (MTX) in RA: the ACT-RAY study. *Ann Rheum Dis* 2012;71:185.
50 Emery P, Breedveld F, Van Der Heijde D, *et al*. Two-year clinical and radiographic results with combination etanercept-methotrexate therapy versus monotherapy in early rheumatoid arthritis: A two-year, double-blind, randomized study. *Arthritis Rheum* 2010;62:674–82.
51 Gabay C, Emery P, van Vollenhoven R, *et al*. Tocilizumab monotherapy versus adalimumab monotherapy for treatment of rheumatoid arthritis (ADACTA): a randomised, double-blind, controlled phase 4 trial. *Lancet* 2013;381:1541–50.
52 Leirisalo-Repo M, Kautiainen H, Laasonen L, *et al*. Infliximab for 6 months added on combination therapy in early rheumatoid arthritis: 2-year results from an investigator-initiated, randomised, double-blind, placebo-controlled study (the NEO-RACo Study). *Ann Rheum Dis* 2013;72:851–7.
53 Horslev-Petersen K, Hetland ML, Junker P, *et al*. Adalimumab added to a treat-to-target strategy with methotrexate and intra-articular triamcinolone in early rheumatoid arthritis increased remission rates, function and quality of life. The OPERA Study: an investigator-initiated, randomised, double-blind, parallel-group, placebo-controlled trial. *Ann Rheum Dis* 2013.

54 Nam JL, Villeneuve E, Hensor EM, *et al*. Remission induction comparing infliximab and high-dose intravenous steroid, followed by treat-to-target: a double-blind, randomised, controlled trial in new-onset, treatment-naive, rheumatoid arthritis (the IDEA study). *Ann Rheum Dis* 2013. Published Online First: 29 Aug 2013. doi:10.1136/annrheumdis-2013-203440

55 Takeuchi T, Harigai M, Tanaka Y, *et al*. Golimumab, a human anti-TNF monoclonal antibody, administered subcutaneously every four weeks as monotherapy in patients with active rheumatoid arthritis despite DMARD therapy: 52-week results of clinical, radiographic and pharmacokinetic assessments. *Arthritis Rheum* 2011;1.

56 Emery P, Durez P, Dougados M, *et al*. Impact of T-cell costimulation modulation in patients with undifferentiated inflammatory arthritis or very early rheumatoid arthritis: a clinical and imaging study of abatacept (the ADJUST trial).[Erratum appears in Ann Rheum Dis. 2011 Aug;70(8):1519]. *Ann Rheum Dis* 2010;69:510–16.

57 Villeneuve E, Nam JL, Hensor E, *et al*. Preliminary results of a multicentre randomised controlled trial of etanercept and methotrexate to induce remission in patients with newly diagnosed inflammatory arthritis. *Arthritis Rheum* 2011;63:S177.

58 van Eijk IC, Nielen MM, van der Horst-Bruinsma I, *et al*. Aggressive therapy in patients with early arthritis results in similar outcome compared with conventional care: the STREAM randomized trial. *Rheumatology* 2012;51:686–94.

59 Kavanaugh A, Fleischmann R, Emery P, *et al*. Efficacy of addition, or continuation, of adalimumab in patients who did not achieve stable low disease activity with methotrexate or adalimumab plus methotrexate in the OPTIMA study. *Ann Rheum Dis* 2012;71:511.

60 Van Vollenhoven RF, Geborek P, Forslind K, *et al*. Conventional combination treatment versus biological treatment in methotrexate-refractory early rheumatoid arthritis: 2 Year follow-up of the randomised, non-blinded, parallel-group Swefot trial. *Lancet* 2012;379:1712–20.

61 Fleischmann R, van Vollenhoven RF, Smolen JS, *et al*. Long-Term Outcomes of Early Rheumatoid Arthritis Patients Initiated with Adalimumab Plus Methotrexate Compared with Methotrexate Alone Following a Targeted Treatment Approach. *Arthritis Rheum* 2012;64:S335.

62 Smolen JS, Fleischmann R, Emery P, *et al*. The OPTIMA study of methotrexate and adalimumab: 78-week outcomes in early rheumatoid arthritis patients based on achieving a low DAS28 target after 26 weeks. *Ann Rheum Dis* 2011;70:259.

63 van der Kooij SM, le Cessie S, Goekoop-Ruiterman YP, *et al*. Clinical and radiological efficacy of initial vs delayed treatment with infliximab plus methotrexate in patients with early rheumatoid arthritis. *Ann Rheum Dis* 2009;68:1153–8.

64 Dirven L, Van Den Bek M, Klarenbeek NB, *et al*. Eight year results of disease activity steered treatment in a large recent rheumatoid arthritis cohort: Clinical and radiological outcomes. *Arthritis Rheum* 2011;1.

65 Hørslev-Petersen K, Hetland ML, Junker P, *et al*. Improved remission rates acquired by adding adalimumab to methotrexate and intraarticular glucorticoid cannot be maintained after withdrawal of adalimumab. A 2-year investigator initiated randomised, controlled study on early rheumatoid arthritis. *Ann Rheum Dis* 2013;72(Suppl 3):236.

66 Van Der Kooij SM, Goekoop-Ruiterman YPM, De Vries-Bouwstra JK, *et al*. Drug-free remission, functioning and radiographic damage after 4 years of response-driven treatment in patients with recent-onset rheumatoid arthritis. *Ann Rheum Dis* 2009;68:914–21.

67 Kavanaugh A, Emery P, Fleischmann R, *et al*. Withdrawal of adalimumab in early rheumatoid arthritis patients who attained stable low disease activity with adalimumab plus methotrexate: Results of a phase 4, double-blind, placebo-controlled trial. *Arthritis Rheum* 2011;1.

68 Emery P, Hammoudeh M, FitzGerald O, *et al*. Assessing maintenance of reimssion with reduced dose etanercept plus methotrexate, methotrexate alone, or placebo in patients with early rheumatoid arthirtis who achieved remission with etanercept and methotrexate: the PRIZE study. *Ann Rheum Dis* 2013;72:399.

69 Smolen JS, Nash P, Durez P, *et al*. Maintenance, reduction, or withdrawal of etanercept after treatment with etanercept and methotrexate in patients with moderate rheumatoid arthritis (PRESERVE): a randomised controlled trial. *Lancet* 2013;381:918–29.

70 Huizinga TWJ, Donka T, Conaghan PG, *et al*. Clinical and radiographic outcomes at two years and the effect of tocilizumab (TCZ) discontinuation following sustained remission in the second year of the ACT-RAY study. *Ann Rheum Dis* 2013;72:63.

71 Smolen JS, Emery P, Ferraccioli G, *et al*. Maintenance of remission in rheumatoid arthritis patients with low-moderate disease activity following withdrawal of certolizumab pegol treatment: week 52 results from the CERTAIN study. *Ann Rheum Dis* 2013;71:361.

72 Fautrel B, Pham T, Tubach F, *et al*. Tapering TNF-Blockers in Established Rheumatoid Arthritis Patients in DAS28 Remission: Results of a DAS28-Driven Step-Down Strategy Randomized Controlled Trial. *Arthritis Rheum* 2012;64:4169.

73 van Vollenhoven RF, Østergaard M, Leirisalo-Repo M, *et al*. In Rheumatoid Arthritis Patients with Stable Low Disease Activity On Methotrexate Plus Etanercept, Continuation of Etanercept 50 Mg Weekly or 25 Mg Weekly Are Both Clinically Superior to Discontinuation: Results From a Randomized, 3-Armed, Double-Blind Clinical Trial. *Arthritis Rheum* 2012;64:4171.

74 Yoo DH, Hrycaj P, Miranda P, *et al*. A randomised, double-blind, parallel-group study to demonstrate equivalence in efficacy and safety of CT-P13 compared with innovator infliximab when coadministered with methotrexate in patients with active rheumatoid arthritis: the PLANETRA study. *Ann Rheum Dis* 2013.

75 Yoo DH, Racewicz A, Brzezicki J, *et al*. A phase 3 randomised controlled trial to compare CT-P13 with infliximab in patients with active rheumatoid arthritis: 54 week results from the PLANETRA study. *Ann Rheum Dis* 2013;72:73.

76 Van Vollenhoven RF, Fleischmann R, Cohen S, *et al*. Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012;367:508–19.

77 Fleischmann R, Kavanaugh A, Smolen J. Methodological aspects and the interpretation of clinical trial data: lessons from the TEAR trial. *Rheumatology* 2013;52:409–10.

78 Smolen JS, Emery P, Fleischmann R, *et al*. Biologic free disease control (BFDC) in early RA: predictors of successful withdrawal of adalimumab (ADA) after achieving stable low disease activitiy with ADA plus methotrexate (MTX) -data from the OPTIMA study. *Ann Rheum Dis* 2012;71:516.

79 Emery P, Smolen JS, Kavanaugh A, *et al*. Maintenance of biologic-free disease control in early rheumatoid arthritis patients after induction of low disease activity with adalimumab plus methotrexate. *Ann Rheum Dis* 2011;70:262.

80 Hurst SI, Ryan AM, Ng C-K, *et al*. Nonclinical assessments demonstrating the similarity of the proposed biosimilar PF-05280586 and rituximab. *Ann Rheum Dis* 2013;72:198.

81 Moctezuma JF, Martinez A, Enkerlin H, *et al*. Comparative, randomized, simple blind to evaluate efficacy and safety of Infinitam (etanercept), associated with methotrexate compared with Enbrel (etanercept) associated with methotrexate in patients with moderate and severe rheumatoid arthritis. *Ann Rheum Dis* 2013;72:234.

82 Ramiro S, Gaujoux-Viala C, Nam JL, *et al*. Safety of synthetic and biological DMARDs—a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2013. In press. doi:10.1136/annrheumdis-2013-204575

83 Gaujoux-Viala C, Nam J, Ramiro S, *et al*. Efficacy of conventional synthetic DMARDs, glucocorticoids and tofacitinib—a systematic literature review informing the 2013 update of the EULAR recommendations for management of rheumatoid arthritis. *Ann Rheum Dis* 2013; in press.

84 Klarenbeek NB, Guler-Yuksel M, Van Der Kooij SM, *et al*. The impact of four dynamic, goal-steered treatment strategies on the 5-year outcomes of rheumatoid arthritis patients in the BeSt study. *Ann Rheum Dis* 2011;70:1039–46.

85 Van Den Broek M, Klarenbeek NB, Dirven L, *et al*. Discontinuation of infliximab and potential predictors of persistent low disease activity in patients with early rheumatoid arthritis and disease activity score-steered therapy: Subanalysis of the BeSt study. *Ann Rheum Dis* 2011;70:1389–94.

86 Smolen JS, Emery P, Ferraccioli GF, *et al*. Efficacy and safety of certolizumab pegol after incomplete response to DMARDS in RA patients with low moderate disease activity: results from CERTAIN, a phase IIIB study. *Ann Rheum Dis* 2011;70:259.

87 Fautrel B, Pham T, Morel J, *et al*. Impact of progressive spacing of TNF-blocker injections on signs and symptoms of rheumatoid arthritis patients in DAS28 remission: the STRASS randomized controled trial. *Ann Rheum Dis* 2013;72:224.

88 Fautrel B, Gandjbakhch F, Foltz V, *et al*. Targeting the lowest efficacious dose for rheumatoid arthiritis patients in remission: clinical and structural impact of a step-down strategy trial based on progressive spacing of TNF-blocker injections (STRASS trial). *Ann Rheum Dis* 2013;72:72.

89 Vollenhoven RV, Franck-Larsson K, Leirisalo-Repo M, *et al*. In rheumatoid arthritis patients with stable low disease activity on methotrexate plus etanercept, continuation of etanercept at 50 mg or 25 mg weekly are both clinically superior to discontinuation: results frum a randomized, 3-arm, double-blind study. *Ann Rheum Dis* 2013;72:434.

Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis

Jackie L Nam, Sofia Ramiro, Cecile Gaujoux-Viala, Kaoru Takase, Mario Leon-Garcia, Paul Emery, Laure Gossec, Robert Landewe, Josef S Smolen and Maya H Buch

Ann Rheum Dis published online January 7, 2014

Notes

Nam JL, Ramiro S, Gaujoux-Viala C, *et al*. Efficacy of biological disease-modifying antirheumatic drugs: a systematic literature review informing the 2013 update of the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2014;73:516–28.

Figure 2 of this article represented the odds ratios but the legend described risk ratios. The corrected figure 2 is given below.

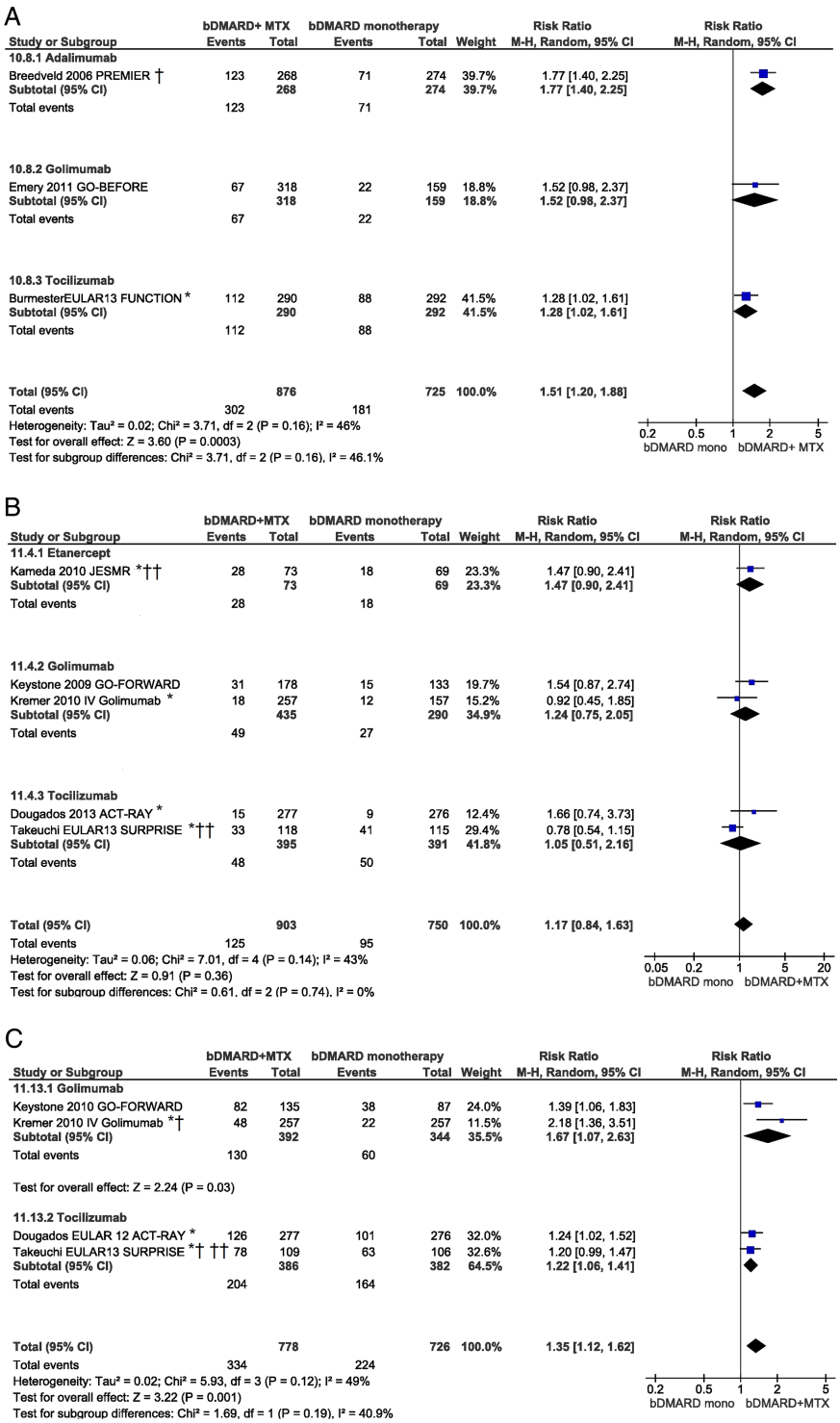

Figure 2 (A) Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-naive. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review$_1$; † ACR 70 response at 12 months for Breedveld 2006 PREMIER; all other ACR 70 responses are at 6 months. (B) Risk ratios for the ACR70 responses comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-incomplete responders. ACR, American College of Rheumatology; *additional study since the 2010 systematic literature review$_1$; ACR 70 responses are at 6 months; †† open-label studies. (C) Risk ratios for the DAS28 remission comparing the use of a biological disease-modifying antirheumatic drug (bDMARD) plus methotrexate (MTX) versus bDMARD monotherapy in patients with rheumatoid arthritis who are MTX-incomplete responders. *Additional study since the 2010 systematic literature review$_1$; † DAS28 remission at 6 months for Kremer 2010 IV Golimumab and Takeuchi EULAR 2013 SURPRISE and ACR 70 at 12 months for Keystone 2010 GO-FORWARD and DOUGADOS EULAR 2012 ACT-RAY; †† open-label study.

Ann Rheum Dis 2015;**74**:320. doi:10.1136/annrheumdis-2013-204577corr1