Effects of biologic disease-modifying anti-rheumatic drugs on the radiographic progression of rheumatoid arthritis: a systematic literature review

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ABSTRACT

Objective. *To evaluate the effect of biologic disease-modifying anti-rheumatic drugs (bDMARDs) on radiographic progression in patients with rheumatoid arthritis (RA).*

Methods. *A systematic review of electronic databases and conference proceedings was conducted through January 2015, to identify randomised controlled trials (RCTs) and observational studies that assessed the impact of bDMARDs [± conventional synthetic DMARDs (csDMARDs), mainly methotrexate (MTX)], versus csDMARDs alone, on radiographic progression in patients with RA.*

Results. *Following screening of >5000 records, 104 publications covering 63 studies were included. Of 34 RCTs in patients with early, active (n=13) or established RA (n=21) [abatacept (1, 2); adalimumab (4, 2); certolizumab pegol (1, 4); etanercept (3, 3); golimumab (1, 4); infliximab (1, 1); rituximab (1, 1); tocilizumab (1, 5)], combination therapy with a bDMARD and MTX had a significantly greater effect than placebo or MTX alone, in inhibiting radiographic progression. This included patients previously unresponsive, or who responded incompletely, to MTX treatment alone, and was supported by data from observational studies. Findings from a smaller subset of these and other RCTs supported superiority of combination therapy over bDMARD monotherapy, and bDMARD monotherapy over MTX, in slowing radiographic progression.*

Conclusion. *There is evidence from RCTs with a range of bDMARDs that improvement in radiographic outcomes for patients with early or established RA, when used in combination with MTX and to a lesser extent as monotherapy, are significantly greater than MTX alone. There was no evidence of a difference between bDMARDs on inhibition of radiographic progression.*

Introduction

The ultimate goal of treatment for rheumatoid arthritis (RA) is to reduce or prevent the functional impairment and structural damage that can occur over the course of the disease, and to achieve in the short term a state of sustained remission. Conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), most notably methotrexate (MTX) and corticosteroids, are the standard treatment of choice for RA due to consistent improvements achieved in clinical status (1, 2). csDMARDs have been shown to reduce or slow radiographic progression (3, 4). More recently, biologic DMARDs (bDMARDs) have provided an additional treatment option, achieving sustained disease control with inhibition of further joint damage (5-7).

Joint damage and treatment efficacy are typically assessed by radiography, although ultrasonography and magnetic resonance imaging have been suggested to offer possible alternatives (8). The modified total Sharp score (mTSS), and the Genant-modified Sharp score (GSS) are among the most commonly used scoring methods to quantify radiographic progression (9, 10). While they exhibit some level of agreement (9), results are not convertible from one scoring method to another. This therefore makes it difficult to compare radiographic data obtained from different studies (10). Here, we describe the findings from a systematic literature review (SLR) conducted with the aim of assessing the effect of bDMARDs (alone or in combination with csDMARDs) on radiographic progression and healing of erosion.

Materials and methods

Data sources

Data from randomised controlled trials (RCTs), non-RCTs and observational studies were retrieved from articles published in English, identified from searches of the following electronic databases: MEDLINE® (1946 to January 2015), Embase® (1988 to January 2015), The Cochrane Central Register of Controlled Trials (CENTRAL; up to January 2015), the Cochrane Database of Systematic Reviews (CDSR), the Health Technology Assessment (HTA) Database and the Database of Abstracts of Reviews of Effects (DARE). CENTRAL, CDSR, HTA and DARE were searched using the Cochrane Library interface. Manual searches were conducted of proceedings from the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR), review articles (including SLRs), commentaries and editorials (for the period from 2013 to January 2015). Congress abstracts were replaced with full articles where published since the search was conducted.

Search terms

These included bDMARDs and csDMARDs licensed for use in RA, combined with terms for radiographic progression (see Supplementary Tables I and II). bDMARDs and csDMARDs that had not been approved for the treatment of RA when the searches were conducted were excluded.

Eligibility criteria

Studies conducted with adult (aged ≥18 years) patients with RA according to ACR 1987 or EULAR/ACR 2010 classification criteria (or provided sufficient information to indicate patients met these criteria), with ≥12 weeks' follow-up, were included.

Study selection

One reviewer examined all publications for inclusion based on the title and abstract (Identification and Level 1 Screening). A second validating reviewer conducted a quality check of 10% of the screened studies, with ≥5% being the discrepancy level (based on the assigned exclusion codes) leading to re-evaluation. Full-text articles that qualified for inclusion were assessed for eligibility following a standard hierarchy of evidence (duplicates not picked up at Level 1, due to different titles, were excluded at this stage; Level 2 Screening). The first reviewer considered all full-text publications at Level 2 and the second reviewer considered all publications eligible for inclusion, as well as screening 20% of the excluded publications. Any uncertainties were resolved by consensus between the two reviewers.

Data extraction

Population demographic information, disease characteristics, treatment, outcomes [radiographic progression, erosion score (ES), joint space narrowing (JSN) score] and study information (*e.g.* design, duration, size, blinding) were extracted.

Assessment of risk of bias

RCTs were assessed for risk of bias using the National Institute for Health and Care Excellence single technology appraisal of manufacturers' submission of evidence (11) and Jadad (12) scoring tools (Supplementary Tables III and IV).

Ethics board approval was not required or sought, as this was a non-interventional study that did not involve patients.

Results

The findings of the literature search are summarised in Fig. 1. A total of 455 full-text publications and conference abstracts were analysed, and data extracted from 104 publications, relating to 63 separate studies. Non-RCTs and observational studies were captured as part of the search. However, the randomisation process, where used, and information on concealment, were generally not adequately described. Therefore, only the findings from 34 RCTs are described below. The Jadad scores for these trials ranged from 2 to 5 (Supplementary Table III). All the RCTs had a low risk of bias regarding randomization, baseline characteristics, patient withdrawals and statistical analysis (Supplementary Table IV). A total of 20/34 studies had an unclear risk of bias in terms of concealment of treatment allocation. In terms of blinding, 11/34 studies did not report the method used for blinding and were classified as having an unclear risk of bias. A total of 6/34 studies were single-blind or open-label and were assessed as having a high risk of bias. There was little difference in patient disease characteristics across studies, with the ranges reported generally reflecting patients with active, moderate to high disease activity (Table I).

Effect of bDMARDs on radiographic progression in MTX-naïve patients with RA

Definitions and baseline characteristics of early RA differ among studies, but generally include patients with <3 years' disease duration who have not previously been treated with MTX. The impact of bDMARDs on radiographic progression in MTX-naïve patients with RA based on RCTs is summarised in Table II.

The AGREE study was the only abatacept (ABA) publication identified describing a trial conducted in MTX-naïve patients. AGREE included only patients with baseline joint erosions, significantly less radiographic progression was seen in ABA + MTX-treated patients *versus* MTX alone at year 1 (13). The proportion of patients with no radiographic progression (ΔmTSS ≤0) was 61.2% (95% CI: 55.0–67.3) in the ABA + MTX group *versus* 52.9% (95% CI: 46.6–59.2) in the MTX group. Upon addition of open-label ABA to the MTX group, less progression was observed during year 2 than over year 1 (ΔmTSS, 0.25 *vs*. 1.49; $p<0.001$) (14). However, the cumulative structural damage observed to year 2 was higher in the latter group that initially received MTX alone than in those continuously treated with ABA + MTX (ΔmTSS from baseline to year 2, 1.75 *vs*. 0.84; $p<0.001$) (14).

Publications describing four adalimumab (ADA) studies conducted in MTX-naïve patients were identified. PREMIER was an active comparator-controlled trial of MTX-naïve RA patients with active disease (<3 years).

There was significantly less radiographic progression among patients in the ADA + MTX combination treatment arm at both years 1 and 2 than in patients in the MTX or ADA monotherapy arms (6). ADA monotherapy was also superior to MTX at years 1 and 2. OPTIMA also compared ADA + MTX with MTX. Significantly less radiographic progression was observed at week 26 in the combination *versus* the monotherapy arm (15). A similar outcome on radiographic progression was observed in HOPEFUL-1 (MTX-naïve Japanese patients). During the 26-week double-blind phase (Period 1), a greater proportion of patients did not experience ES worsening (≤0.5) in the ADA + MTX group (73.7%) *versus* the MTX alone group (42.2%; $p<0.001$) (16). During Period 2, where all patients received open-label ADA + MTX, radiographic progression slowed through week 52 in both groups, but patients who received ADA + MTX throughout exhibited less radiographic progression than those who had received MTX monotherapy during Period 1 (mean ΔmTSS 2.56 *vs*. 3.30; $p<0.001$) (17). In CONCERTO, where all patients (MTX-naïve) received open-label ADA in combination with different doses of MTX that were blinded to the investigator and participants, 77.6%, 76.8%, 72.0% and 64.3% of patients in the ADA + MTX (20 mg), MTX (10 mg), MTX (5 mg) and MTX (2.5 mg) groups, respectively, had no radiographic progression (ΔmTSS ≤0.5) at week 26 (18).

A single certolizumab pegol (CZP) study publication describing a trial in MTX-naïve patients was identified. In C-OPERA, patients with poor prognostic factors, defined by the presence of a high titre of anti-citrullinated protein antibody (ACPA) and either positive rheumatoid factor (RF), and/or erosion, were randomised in a double-blind manner to CZP + MTX or MTX alone. Patients receiving combination therapy showed significantly greater inhibition of radiographic progression relative to MTX at 24 and 52 weeks (19).

Four publications describing etanercept (ETN) studies conducted in MTX-naïve patients were identified. In the ERA study, patients with early, active RA received either ETN [10 mg or 25 mg twice-weekly (BIW)] or weekly oral MTX in a double-blind manner. Patients receiving ETN (25 mg BIW) monotherapy showed significantly lower radiographic progression compared with MTX up to 52 weeks (20).

In COMET, significantly ($p<0.0001$) more patients receiving ETN + MTX combination therapy [80% (95% CI: 75–85)] during the 52-week double-blind phase achieved radiographic non-progression (mTSS ≤0.5) than those receiving MTX alone [59% (53–65)] (21). This finding was also reflected in the difference in the change in mTSS from baseline, between treatment arms, which was considered to be driven more by ES rather than JSN (21). During year 2, significantly fewer patients who had received MTX during year 1 and who subsequently received ETN + MTX (22), attained radiographic non-progression [modified Sharp/van der Heijde score (SHS) ≤0.5] compared with those on combination therapy since baseline (75% *vs*. 90%; $p=0.009$) (22).

In the TEMPO study, radiographic progression and joint ESs were significantly lower in patients treated with ETN + MTX compared with MTX monotherapy at 52 weeks (23). In addition, patients on ETN monotherapy showed less radiographic progression than MTX alone (23). The TEAR study compared ETN + MTX with csDMARDs [sulfasalazine (SSZ), hydroxychloroquine (HCQ)] + MTX in patients with early, aggressive RA (24). In addition to those assigned to receive ETN + MTX or csDMARDs + MTX at baseline, those initiated on MTX monotherapy were stepped up to ETN + MTX or csDMARD + MTX at week 24 if the disease activity score in 28 joints using the erythrocyte sedimentation rate (DAS28-ESR) was ≥3.2. Despite a high risk of bias in this study, patients treated with ETN + MTX displayed less radiographic progression at year 2 compared with MTX + csDMARDs (24).

There was a single study describing golimumab (GLM) identified, the GO-BEFORE study, which was conducted in MTX-naïve patients. In this study, patients were randomly assigned to receive MTX + placebo (PBO) (Group 1), GLM (100 mg) + PBO (Group 2), GLM (50 mg) + MTX (Group 3) or GLM

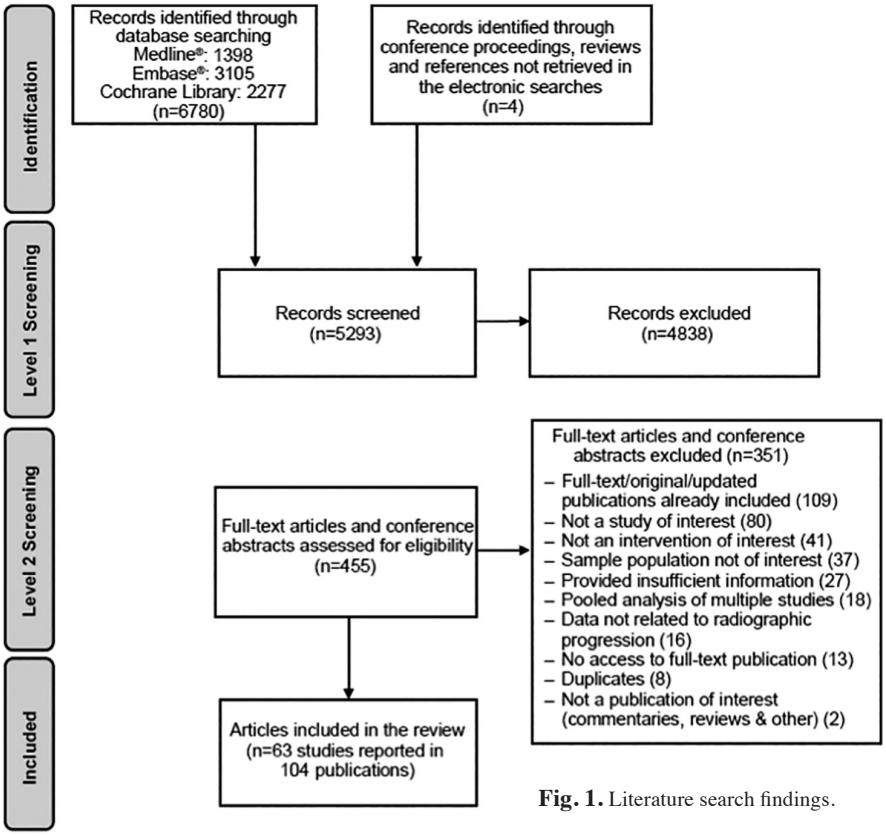

Fig. 1. Literature search findings.

Table I. Mean range of patient baseline characteristics in RCTs of bDMARDs (n=34).

Baseline data	ABA	ADA	CZP	ETN	GLM	INF	RTX	TCZ
Number of studies*	3	6	5	6	5	2	2	6
Age, yrs¥	49.7–54.0	50.4–57.3	49.2–56.0	48.4–58.1	48.2–54	50.0–54.0	47.9–52.8	49.5–53.4
Female, %	76.6–84.2	72.0–79.0	71.6–85.7	59.1–87.3	79.7–89.7	68–81	77–85	78.6–85.8
Disease duration, yrs¥	0.5–8.9	0.7–11.8	0.34–6.5	0.29–10.6	1.0–8.8	0.8–12.0	0.9–12.1	0.4–11.1
CRP, mg/dL¥	1.5–3.6	1.4–4.1	1.3–1.7	2.1–32.4	1.5–2.6	2.6–4.2	3.0–3.8	1.9–4.9
ESR, mm/h¥	59.8–61.8	≥28	39.1–51.0	32.4–59.7	43.7–47.9	43–52	48.0–62.0	45.9–71.0
RF-positive, %	75.5–96.1	77.4–87	75.5–89.4	75.0–91.7	76.1–86.5	71–84	79–87	64.1–91.0
ACPA positive, %	84–92.7	84.8	NR	67.3–72.6	66.7–80.9	NR	NR	81.9–87.0
DAS28 [ESR]¥	-	6.6	6.1–6.5	-	5.4–5.89	-	7.0–7.1	6.3–6.7
Erosion score¥	4.8–21.8	5.1–36.7	19.0–28.2	2.5–56.6	23.9–32.1	8.3–8.8	NR	3.3–31.7
JSN score¥	1.9–23.0	6.1–30.7	20.6–25.1	1.9–58.9	23.9–25.9	2.9–3.0	NR	2.3–28.7
Radiographic score¥•	13.6–44.9	11.2–72.1	36.5–52.7	4.4–114.5	13.3–58.0	11.2–82.0	7.4–48.3	28.3–60.4
Prior csDMARDs, %	2.7–43.3	10–100	0–100	22–100	100	NR	69–100	19.1–100
Prior bDMARDs, %	0–100	0	0–100	0–100	0	0–100	100	0–100

*AMPLE included both ABA and ADA. ¥Range of mean or median values.
•Total Sharp score (TSS), the modified total Sharp score (mTSS) or Genant-modified Sharp score (GSS). ABA: abatacept; ACPA: anti-citrullinated protein antibody; ADA: adalimumab; AMPLE: ABA *versus* ADA comparison in biologic-naïve RA subjects with background MTX; CRP: C-reactive protein; CZP: certolizumab pegol; DAS28: disease activity score in 28 joints; DAS28 [ESR]: DAS28 erythrocyte sedimentation rate; DMARDs: disease-modifying anti-rheumatic drugs; bDMARDs: biologic DMARDs; csDMARDs: conventional synthetic DMARDs; ETN: etanercept; GLM: golimumab; INF: infliximab; JSN: joint space narrowing; MTX: methotrexate; NR: not reported; RA: rheumatoid arthritis; RCT: randomised controlled trial; RF: rheumatoid factor; RTX: rituximab; TCZ: tocilizumab; yrs: years.

(100 mg) + MTX (Group 4). At week 28, patients with <20% improvement in both the tender joint count (TJC) and the swollen joint count (SJC) entered a double-blind early escape phase [Group 1 received GLM (50 mg) + MTX; Group 2 received GLM (100 mg) + MTX; Group 3 received GLM (100 mg) + MTX]. Overall GLM + MTX (Groups 3 and 4) inhibited radiographic progression significantly better than MTX alone up to week 52 (25).

Just one infliximab (INF) study that evaluated radiographic progression in MTX-naïve patients was identified. The ASPIRE study compared INF (3 mg/kg or 6 mg/kg) + MTX *versus* MTX + PBO, in MTX-naïve patients with RA of ≤3 years' duration. Radiographic progression was significantly lower in the INF+MTX treatment groups than in the MTX treatment group at 54 weeks (26).

A single rituximab (RTX) study publication describing a trial that evaluated radiographic progression in MTX-naïve patients was identified. In the IMAGE study, a significant reduction in radiographic progression was observed at 24 and 52 weeks with RTX (2 x 1000 mg) + MTX *versus* MTX alone (27). This treatment difference was maintained over 104 weeks (28).

The double-blind FUNCTION trial was the only tocilizumab (TCZ) study publication found that was conducted in MTX-naïve patients. FUNCTION was conducted in patients with early progressive RA. Patients who received TCZ (8 mg/kg) + MTX achieved significantly greater improvement in radiographic disease progression at week 52 than did patients treated with PBO + MTX (29).

Effect of bDMARDs on radiographic progression in patients with established RA with inadequate response to csDMARDs

The impact of bDMARDs on radiographic progression in patients with established RA based on RCTs is summarised in Table III. The RA patient populations included in these studies mainly comprised those not responding adequately to csDMARDs, including MTX. Only one study publication was identified (REFLEX) (30) that included patients who previously had an inadequate response (IR) to bDMARDs.

AIM was one of the two studies identified that evaluated ABA in patients with established RA and an IR to csDMARDs. AIM compared combination therapy with ABA + MTX *versus* MTX alone in patients with an IR to MTX. Combination therapy had a significantly greater impact on slowing progression of structural joint damage compared with MTX alone (31).

AMPLE is, to date, the largest head-to-head RA trial comparing two bDMARDs. This study was also the first to include radiographic outcomes and controlled data out to 2 years. Comparable radiographic outcomes were observed in the ADA + MTX and ABA + MTX groups in bDMARD-naïve patients with active RA and an IR to MTX. The investigators, but not the patients, were blinded to the treatments (32, 33).

The DE019 study was the only other study publication identified that utilised ADA in patients with established RA and an IR to csDMARDs (in this case, MTX). Significantly less radiographic progression, as measured by the change in mTSS to week 52, was observed in patients receiving ADA [40 mg every other week (eow)] + MTX or ADA [20 mg once weekly (QW)] + MTX, compared with those in the MTX group (34).

Four CZP study publications conducted in patients with established RA and an IR to csDMARDs were identified. In the HIKARI study, CZP monotherapy inhibited radiographic progression, to

Table II. Radiographic progression* following treatment of patients with early RA with bDMARDs in RCTs[¥].

bDMARD	Study and treatment			Duration (Weeks)				
	Monotherapy	Combination therapy	Treatment arm	24	26	52	54	104
ABA		AGREE (13)	PBO + MTX ABA + MTX			1.06 0.63 (p=0.04)		
ADA	PREMIER (6)		PBO + MTX ADA + PBO ADA + MTX			5.7 3.0 (p<0.001 vs. PBO + MTX) 1.3 (p=0.002 vs. ADA +PBO; p<0.001 vs. PBO +MTX)		10.4 5.5 (p<0.001 vs. PBO + MTX) 1.9 (p<0.001 vs. ADA + PBO and PBO + MTX)
		OPTIMA (15)	PBO + MTX ADA + MTX		0.96 0.15 (p<0.001)			
		HOPEFUL-1 (38)	PBO + MTX ADA + MTX		2.4 ± 3.2 1.5 ± 6.1 (p<0.001)			
		CONCERTO (18)	*ADA + MTX (2.5 mg)* *ADA + MTX (5 mg)* *ADA + MTX (10 mg)* *ADA + MTX (20 mg)*		*0.9* *0.3* *0.4* *0.2*			
CZP (p<0.001)		C-OPERA (19)	PBO + MTX CZP + MTX	0.86 0.26 (p=0.003)		1.58 0.36		
ETN	ERA (20)		PBO + MTX ETN (25 mg) + PBO	1.06 0.57 (p=0.001)		1.59 1.00 (p=0.11)		3.2 1.3 (p=0.001)
		COMET (21, 22)	PBO + MTX ETN + MTX			2.44 (1.45; 3.43) 0.27 (–0.13; 0.68)		
	TEMPO (23)		PBO + MTX ETN + PBO ETN + MTX			2.80 (1.08; 4.51) 0.52 (–0.10; 1.15: p=0.0469 vs. PBO + MTX) –0.54 (–1.00; –0.07; p=0.0006 vs. ETN; p<0.0001 vs. PBO + MTX)		
		TEAR (24)	ETN + MTX PBO + MTX/csDMARDs					0.64 1.69 (p=0.047)
GLM	GO-BEFORE (25)		PBO + MTX GLM + PBO			1.37 ± 4.56 0.41 ± 3.93 (p=0.006)		
INF		ASPIRE (26)	PBO + MTX INF (3 mg) + MTX INF (6 mg) + MTX				3.7 ± 9.6 0.4 ± 5.8 (p<0.001 vs. PBO + MTX) 0.5 ± 5.6 (p<0.001 vs. PBO + MTX)	
RTX		IMAGE (27, 28)	PBO + MTX RTX (2 x 500 mg) + MTX RTX (2 x 1000 mg) + MTX	0.701 0.580 0.328 (p<0.05 vs. PBO + MTX)		1.079 0.646 0.359 (p<0.001 vs. PBO + MTX)		1.95 0.76 0.41 (p<0.0001 vs. PBO + MTX)
TCZ	FUNCTION (29)		MTX + PBO TCZ (8 mg/kg) + PBO TCZ (4 mg/kg) + MTX TCZ (8 mg/kg) + MTX			1.14 0.26 0.42 0.08 (p=0.0001 vs. MTX + PBO)		

*Mean change from baseline in mTSS scores. (Standard deviations and 95% confidence intervals are included, where available).
[¥]All studies are double-blind unless otherwise indicated; open-label studies are indicated by italics. ABA: abatacept; ADA: adalimumab; CZP: certolizumab pegol; DMARDs: disease- modifying anti-rheumatic drugs; csDMARDs: conventional synthetic DMARDs; ETN: etanercept; GLM: golimumab; INF: infliximab; MTX: methotrexate; PBO: placebo; RA: rheumatoid arthritis; RCT: randomised controlled trial; RTX: rituximab; TCZ: tocilizumab.

Table III. Radiographic progression* following treatment of patients with established RA with bDMARDs in RCTs[¥].

bDMARD	Study and treatment			Duration (Weeks)		
	Monotherapy	Combination therapy	Treatment arm	24	52	54
ABA		AIMII (31)	PBO + MTX ABA + MTX		2.32 1.21	
		AMPLE • (32)	ABA + MTX		0.56 ± 2.62	
ADA		*AMPLE* • (32)	ADA + MTX		*0.74 ± 6.57*	
		DE019 • (34)	PBO + MTX		2.7 ± 6.8	
			ADA (20 mg QW) + MTX		0.8 ± 4.9 ($p \leq 0.001$ vs. PBO + MTX)	
			ADA (40 mg eow) + MTX		0.1 ± 4.8 ($p \leq 0.001$ vs. PBO + MTX)	
CZP	HIKARI • (35)		PBO ± csDMARDs (excluding MTX) CZP ± csDMARDs (excluding MTX)	2.45 0.48 ($p<0.0001$ vs. PBO ± csDMARDs)		
		RAPID-1 • (36)	PBO + MTX CZP (200 mg) + MTX CZP (400 mg) + MTX		2.8 0.4 ($p<0.001$ vs. PBO + MTX) 0.2 ($p<0.001$ vs. PBO + MTX)	
		RAPID-2 • (37)	PBO + MTX CZP (200 mg) + MTX CZP (400 mg) + MTX	1.2 0.2 ($p \leq 0.01$ vs. PBO + MTX) –0.4 ($p \leq 0.001$ vs. PBO + MTX)		
		J-RAPID • (38)	PBO + MTX CZP (100 mg) + MTX CZP (200 mg) + MTX CZP (400 mg) + MTX	2.8 1.0 0.2 ($p<0.01$ vs. PBO + MTX) 0.7 ($p<0.001$ vs. PBO + MTX)		
ETN	Takeuchi • (39)		PBO + MTX ETN (10 mg BIW) + PBO ETN (25 mg BIW) + PBO	5.11 2.42 ($p<0.0001$ vs. PBO + MTX) 1.74 ($p<0.0001$ vs. PBO + MTX)	9.82 5.19 ($p<0.0001$ vs. PBO + MTX) 3.33 ($p<0.0001$ vs. PBO + MTX)	
	JESMR • (40)		*ETN* *ETN + MTX*		*3.6* *0.8* *(p=0.06 vs. ETN)*	
GLM	GO-MONO • (41)		PBO GLM (50 mg) GLM (100 mg)	2.6 ± 4.7 1.9 ± 4.1 2.1 ± 10.4		
		GO-FORTH • (42)	PBO + MTX GLM (50 mg) + MTX GLM (100 mg) + MTX	2.51 ± 5.52 1.05 ± 3.71 (p=0.0203 vs. PBO + MTX) 0.33 ± 2.66 (p=0.0006 vs. PBO + MTX)		
		GO-FURTHER (5)	PBO + MTX GLM (2 mg/kg iv) + MTX	1.09 ± 3.19 0.03 ± 1.90 ($p<0.001$)	1.22 0.13 (p=0.001)	
	GO-FORWARD • (25)		PBO + MTX GLM (100 mg) + PBO GLM (50 mg) + MTX GLM (100 mg) + MTX	0.55 ± 2.35 0.27 ± 1.60 (p=NS vs. PBO + MTX) 0.60 ± 2.74 (p=NS vs. PBO + MTX) 0.23 ± 1.34. (p=NS vs PBO + MTX)	1.10 ± 4.68 0.89 ± 3.37 (p=NS vs. PBO + MTX) 0.93 ± 4.86 (p=NS vs. PBO + MTX) 0.15 ± 1.64 (p=NS vs. PBO + MTX)	

bDMARD	Study and treatment			Duration (Weeks)		
	Monotherapy	Combination therapy	Treatment arm	24	52	54
INF		ATTRACT • (43)	PBO + MTX INF (3 mg/kg/8wk) + MTX INF (3 mg/kg/4wk) + MTX INF (10 mg/kg/8wk) + MTX INF (10 mg/kg/4wk) + MTX			7.0 ± 10.3 1.3 ± 6.0 (p<0.001 vs. PBO + MTX) 1.6 ± 8.5 (p<0.001 vs. PBO + MTX) 0.2 ± 3.6 (p<0.001 vs. PBO + MTX) -0.7 ± 3.8 (p<0.001 vs. PBO + MTX)
RTX		REFLEX ‖ (30)	PBO + MTX RTX (2 x 1000 mg) + MTX	1.2 ± 3.3 0.6 ± 1.9 (p=NS)		
TCZ	*SURPRISE* • (44)		*TCZ (iv)* *TCZ (iv) + MTX*		*64%¶* *66%¶* *(p=0.92)*	
	BREVACTA• (45)		PBO (sc) + csDMARDs TCZ (sc) + csDMARDs	1.23 ± 2.816 0.62 ± 2.692 (p=0.0149)		
	SAMURAI • (46)		*csDMARDs* *TCZ (iv)*		*6.1 (4.2; 8.0)* *2.3 (1.5; 3.2: p<0.01)*	
	ACT-RAY ‖ (47)		*TCZ + PBO* *TCZ + MTX*	*0.35 ± 0.152* *0.18 ± 0.161 (p=0.20)*		
		LITHE ‖ (48)	PBO + MTX TCZ (4 mg iv) + MTX		1.13 0.34 (p<0.0001 vs. PBO + MTX)	
			TCZ (8 mg iv) + MTX		0.29 (p<0.0001 vs. PBO + MTX)	

*Change from baseline in mTSS• or GSS‖ scores. (Standard deviations and 95% confidence intervals are included, where available). ¥All studies are double-blind unless otherwise indicated; open-label studies are indicated in italics and single-blind studies are indicated in bold italics. ¶Proportion of patients with structural remission.
ABA: abatacept; ADA: adalimumab; BIW: twice-weekly; CZP: certolizumab pegol; DMARDs: disease-modifying anti-rheumatic drugs; csDMARDs: conventional synthetic DMARDs; ETN: etanercept; eow: every other week; GLM: golimumab; INF: infliximab; iv: intravenous; MTX: methotrexate; NS: not significant; PBO: placebo; RA: rheumatoid arthritis; RCT: randomised controlled trial; RTX: rituximab; sc: subcutaneous; TCZ: tocilizumab; QW: once weekly.

a significantly greater extent than PBO at 24 weeks in Japanese patients receiving a background of csDMARDs and in whom MTX cannot be administered (35). The RAPID-1 study (36) was conducted in patients with active RA with an IR to MTX. Significant differences between the CZP (200 mg or 400 mg) + MTX and PBO + MTX groups were observed at 52 weeks. However, no difference in inhibition of the progression of erosions and JSN was observed between the CZP + MTX groups. Post hoc analysis revealed that 69.0% and 71.6% of patients taking CZP (200 mg) + MTX and CZP (400 mg) + MTX, respectively, exhibited no radiographic progression (≤0-unit increase in mTSS), compared with 51.9% of patients taking PBO + MTX (p≤0.05). In the 24-week, RAPID-2 study using the same dosing regimen as RAPID-1, significant inhibition of radiographic progression with CZP (200 mg or 400 mg) + MTX, was observed, compared with those receiving PBO + MTX (37). A similar outcome on inhibition of radiographic progression was observed in the J-RAPID study (38), conducted in Japanese patients, for the CZP (200 mg or 400 mg) + MTX treatment arms. However, the difference in ΔmTSS for the CZP (100 mg) + MTX arm, with respect to PBO + MTX, was not significant.

Two ETN study publications in patients with established RA and an IR to csDMARDs were identified. In the study described by Takeuchi *et al*., which compared the efficacy of ETN *versus* MTX in Japanese subjects with active RA (39), the effects of ETN on radiographic progression were significantly greater than for MTX at 24 and 52 weeks. In JESMR (40), patients with active RA who had been taking MTX were randomised to either ETN + MTX or ETN alone. In this study, patients and physicians were not blinded to the treatments. Mean progression in mTSS at week 52 was not significantly different between treatment arms. However, a significant difference in favour of ETN + MTX was observed in radiographic progression between weeks 24 and 52 (0.3 *vs*. 2.5; p=0.03), supporting the superiority of combination therapy (40).

Four publications describing clinical trials of GLM conducted in patients with established RA and an IR to csDMARDs were identified. The first of these was GO-MONO, a 24-week trial in patients with active RA despite csDMARD therapy. This study compared GLM at doses of 50 mg and 100 mg with PBO. At week 16, all patients in the PBO arm crossed over to receive GLM (50 mg) in a double-blinded fashion (41). Less radiographic progression was observed in the GLM arms at both doses (50 mg and 100 mg) compared with PBO at 24 weeks. These differences were not significant, however. GO-FORTH followed a similar design but was conducted in patients with ac-

tive RA despite MTX treatment, with a double-blind early escape at week 16 for patients who had <20% improvement from baseline in TJC/SJC at week 14 (42). GLM (50 mg or 100 mg) + MTX was associated with significantly less radiographic progression than MTX monotherapy from baseline to week 24. GO-FURTHER assessed intravenous dosing of GLM (2 mg/kg) + MTX in patients with active RA despite MTX. This study demonstrated that patients receiving combination therapy with GLM (2 mg/kg) + MTX had significantly less radiographic progression based on mTSS and subscores *versus* MTX alone at week 24 (5). Patients initially randomised to MTX who commenced GLM rescue at weeks 16 and 24, reported a reduction in radiographic progression soon after GLM initiation. Radiographic progression scores in patients who commenced GLM rescue at weeks 16 and 24 were similar to those in patients who were initially randomised to GLM + MTX. In the GO-FORWARD study, in patients with active RA despite MTX therapy (using the same design as GO-BEFORE), unresponsive patients entered a double-blind early escape phase at week 16. Patients in the MTX + PBO arm who did not enter early escape crossed over to GLM (50 mg) at week 24. There were no significant differences in radiographic progression between the MTX and the GLM + MTX treatment arms (25).

A single publication describing a clinical trial of INF conducted in patients with established RA and an IR to csDMARDs was found. In the pivotal ATTRACT study, radiographic evidence of joint damage increased in the group given MTX, but not in the INF + MTX groups (ΔmTSS, 7.0 *vs*. 0.6; $p<0.001$) at week 54 (43).

Similarly, just one publication describing a clinical trial of MTX was identified. The REFLEX study examined the efficacy of RTX *versus* PBO, in patients with active RA with background MTX therapy and an IR to ≥1 anti-tumour necrosis factor (TNF) agents (INF, ADA, ETN) (30). For observed cases, the changes in radiographic end points at week 24 showed a trend toward less progression of joint damage in RTX + MTX-treated patients. The difference in the proportion of patients without new erosions was not significant between treatment groups.

Five publications detailing clinical trials of TCZ in patients with established RA with an IR to csDMARDs were identified. The first of these trials, SURPRISE, was a reader-blinded study comparing TCZ monotherapy (SWITCH) to TCZ + MTX (ADDON) in patients who were inadequate responders to MTX (44). Most patients (66% in ADDON and 64% in SWITCH; $p=0.92$) had structural remission (ΔmTSS ≤0.5) to week 52. However, there was no difference between treatment arms. BREVACTA (45) compared TCZ with PBO both by subcutaneous dosing, in a double-blind manner, in patients who had an IR to ≥1 DMARDs [that could include ≥1 anti-TNF agent in up to 20% of patients]. bDMARDs were discontinued prior to randomisation. Radiographic progression was significantly lower in the TCZ + csDMARDs group at week 24 compared with PBO + csDMARDs (45). SAMURAI compared TCZ and csDMARDs in patients with an IR to ≥1 csDMARD (46). Only the x-ray reader was blinded to treatment. At week 52, the TCZ monotherapy group showed significantly less radiographic change in mTSS than the csDMARD group (46). ACT-RAY was a double-blind trial comparing the addition of TCZ to ongoing MTX treatment with switching to TCZ + PBO in patients with RA who had an IR to MTX; this was augmented by a treat-to-target strategy from week 24 (47). There was no significant intergroup difference in mean change (GSS) from baseline at week 24. In the double-blind phase of LITHE, conducted in patients with moderate-to-severe RA with an IR to MTX, radiographic progression was significantly lower in patients treated with TCZ + MTX *versus* MTX at week 52 (48)

Discussion

This review aimed to evaluate the effects of bDMARDs (alone or in combination with csDMARDs) on radiographic progression and healing of erosion (reversal of JSN) compared with conventional treatment (csDMARDs) based on data derived from RCTs.

In patients with early, active RA or with established disease, there was evidence that combination therapy with a bDMARD and MTX had a significantly greater effect than MTX alone in inhibiting radiographic progression, with significant differences *versus* control arms seen as early as 24 weeks (19, 37, 38, 41, 42) and sustained up to 104 weeks (6) when administered in a double-blind manner. This benefit of combination therapy with a bDMARD and MTX *versus* MTX alone was observed in MTX-naïve patients and in patients with established RA who were previously unresponsive, or responded incompletely, to MTX alone. This observation is supported by two recent reviews that also highlight the increased efficacy of combination therapy compared with MTX alone (33, 49). The beneficial effects of combination therapy on radiographic progression have also been demonstrated in observational studies. For instance, there was no evidence of a difference between bDMARDs on inhibition of radiographic progression, illustrated by the similar effect of ABA and ADA, each in combination with MTX, on radiographic progression, in a head-to-head study (32). There is evidence that bDMARD alone is less effective than combination therapy (6, 23, 29), but superior to csDMARDs, mainly MTX (6, 20, 23).

The predictive value of baseline variables on progression of joint damage during bDMARD exposure was rarely examined. Results from an exploratory analysis (50) found that higher C-reactive protein (CRP) levels, increased ESR values and SJC were associated with greater joint damage progression in the MTX treatment arm, while little progression was seen in the bDMARD + MTX group, regardless of the abnormal levels of these parameters. The authors suggested early introduction of combination therapy may be appropriate for patients with an elevated acute-phase response and/or greater radiographic evidence of joint damage in the early phase of their disease. However, further assessment is needed on the predictive value of patient dis-

ease characteristics at baseline, in order to demonstrate the likely impact of b-DMARDs on radiographic progression. This review presents radiographic changes in RA patients treated with eight bDMARDs, although these cannot be compared directly. Therefore, the interpretation of the results requires careful consideration due to the variability of the available published data, including study type and design, patient populations and the methods for measuring radiographic progression, as well as the design of this SLR. Limited information was available for many of the bDMARDs, and data were absent for some of the radiographic outcomes. Heterogeneity of RA symptoms and outcomes, in patient baseline characteristics and in radiographic measures used to assess disease severity and progression, may have unduly influenced the reported outcomes. The combination of these factors meant that it was not possible to conduct a meta-analysis of the trials we identified. This analysis was limited to bDMARDs licensed for the treatment of RA. bDMARDs that have not been licensed for the treatment of RA include agents such as ocrelizumab, which has been evaluated in a variety of patient populations including those who showed an IR to MTX (51-53). However, it is worth noting that a recent review of four RCTs (54) reported that ocrelizumab in combination with MTX showed greater efficacy than MTX + PBO at 24 weeks, consistent with what is observed for the bDMARDs discussed here.

This review highlights that improvement in radiographic outcomes for patients with RA was greater with bDMARDs in combination with MTX, and to a lesser extent with bDMARD monotherapy, when compared with placebo or MTX treatment. The effects on radiographic progression appeared similar between the different bDMARDs; however, there was evidence that some bDMARDs, when used in combination with MTX, demonstrated the potential for radiographic repair.

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