Review

Achieving remission in clinical practice: lessons from clinical trial data

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ABSTRACT

This review examines the literature on the frequency of remission associated with different treatment approaches in early rheumatoid arthritis (ERA). Trials reporting remission outcomes were identified through searches of the CINAHL, EMBASE, and Medline (PubMed) databases from 2000 through August 2012. Additional literature was identified through hand searching. The proportion of patients achieving remission and/or radiographic non-progression was extracted from each study. Evidence was examined in the context of unified remission criteria and practical considerations for achieving and maintaining remission are discussed. The literature highlights the benefits of early treatment with disease-modifying anti-rheumatic drug (DMARD) combination therapy, combination therapy with a biologic, and tight control with a pre-specified treatment target in achieving remission in ERA. The added stringency of the 2011 remission criteria may increase the proportion of patients achieving true remission, while identifying predictors of sustained remission may also help patients achieve better radiographic and functional outcomes.

Introduction

Recent evidence suggests combination and early, target-driven therapy prevents progression to established disease and inhibits irreversible joint destruction (1-4). Systematic reviews have shown that combination DMARD therapy with or without a biologic may improve remission and other outcomes in ERA compared to monotherapy (5, 6). Targeted approaches with tight control may also improve remission outcomes compared to routine care (7, 8). Accordingly, treatment paradigms have evolved to initiate earlier, intensive therapy with DMARD or DMARD plus biological agents in ERA with the primary objective of achieving and maintaining remission.

Lack of a uniform, stringent and achievable remission definition has led to heterogeneity in reporting remission outcomes across studies. The American College of Rheumatology (ACR), European League Against Rheumatism (EULAR) and Outcome Measures in Rheumatology Initiative (OMERACT) developed two provisional consensus definitions of remission that could potentially be applied uniformly in clinical trials (9, 10). Although continued validation in observational data sets is required, the proposed criteria represent a significant advancement toward a uniform and stringent approach to assess remission in ERA.

This review examines the available literature on the frequency of remission associated with different treatment approaches in ERA and discusses how unified remission criteria may impact practice. Practical considerations for achieving and maintaining remission are discussed.

Methods

Search strategy

CINAHL, EMBASE, and Medline (PubMed) databases were searched to identify trials reporting remission outcomes in ERA (Fig. 1). Search terms were: 'rheumatoid arthritis' combined with 'remission', 'radiographic progression' or 'treatment'. The search period was from 2000 through September 2010. Impromptu searches were performed in PubMed and by hand to identify relevant updates published up to August 2012. Additional studies were identified by hand searching reference lists and electronic literature updates. Abstracts presented at ACR and EULAR annual meetings (2009–2010) were also searched (Fig.

1). Updates from EULAR 2011 were included if identified as relevant by authors. Searches were performed with the following limits: human, English language, clinical trials.

Inclusion/exclusion criteria

ERA was defined as disease duration ≤3 years, in accordance with recruitment criteria for many ERA trials. Phase III trials, observational studies and systematic reviews with meta-analysis reporting remission outcomes in ERA were included. Acceptable remission outcomes included those defined by ACR core set measures or cut-point thresholds for composite indices, including disease activity score (DAS), simplified disease activity index (SDAI) or clinical disease activity index (CDAI) (Table I). Animal studies, review articles, studies enrolling <20 patients and articles without abstracts were excluded. Publications were not otherwise excluded based on quality.

Analysis

Rates of remission and/or radiographic non-progression were extracted for each study. Monotherapy refers to MTX monotherapy, unless otherwise specified.

Results

Remission associated with conventional DMARD monotherapy vs. DMARD combination therapy

Remission outcomes have been reported in seven trials comparing conventional DMARD monotherapy to DMARD combination therapy in ERA (Table II). Although improved clinical response with DMARD combination therapy *versus* DMARD monotherapy was often reported, remission frequency was similar between groups in most trials, despite significant differences in clinical response.

In the COBRA trial (11), statistically significant differences in disease activity were observed between groups at 28 weeks. Clinical remission, using ACR preliminary criteria (occurrence and duration), was greater with combination *versus* SSZ monotherapy, but not statistically different (28% [n=21] *vs*. 16% [n=13], respectively; p=0.14). Most remissions were considered prob-

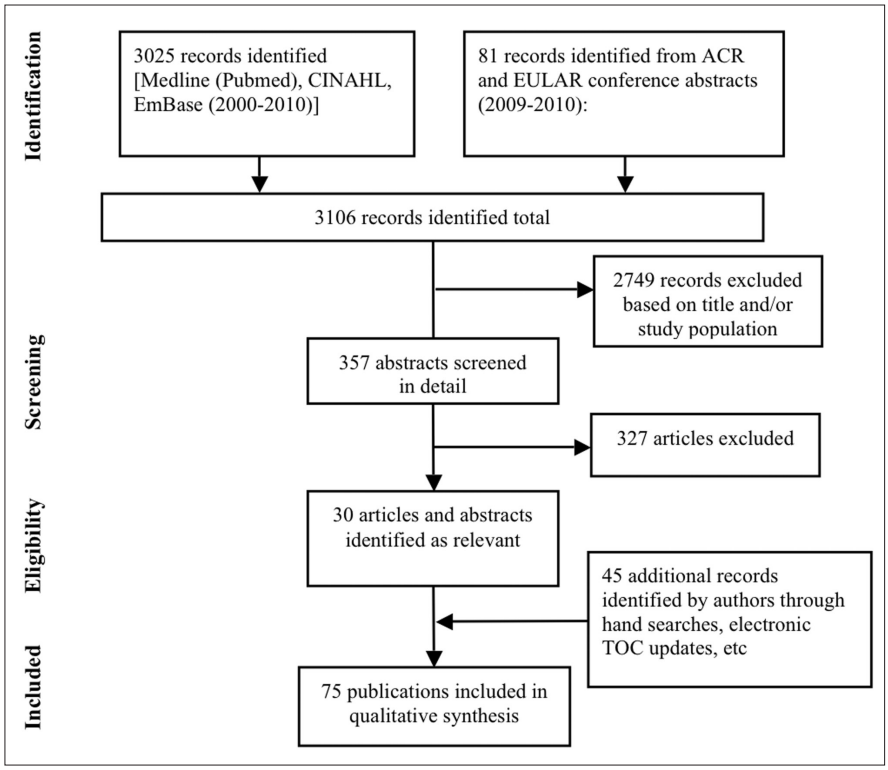

Fig. 1. Search strategy for identifying publications on the impact of early diagnosis and treatment on remission outcomes in ERA.

Table I. Summary of clinical remission outcomes commonly used in RA.

Remission criteria	Definition of remission
2011 ACR/EULAR remission criteria	*Boolean-based definition:* At any time point, patient must satisfy all of the following: - Tender joint count ≤1* - Swollen joint count ≤1* - C-reactive protein ≤1 mg/dl - Patient global assessment ≤1 (on a 0–10 scale)† *Index-based definition:* At any time point, patient must have a simplified disease activity index score of ≤3.3‡
ACR criteria	At least 5 of 6 of the following: • Absence or <15 minutes of morning stiffness • No fatigue • No joint pain • No joint tenderness or pain on motion • No soft tissue swelling in joints or tendon sheaths • No elevated ESR
EULAR criteria	
Disease activity score (DAS)	DAS <1.6
DAS28	DAS28≤2.6
Low disease activity score (LDAS)	DAS28≤3.2
Simplified disease activity index (SDAI)	SDAI ≤3.3
Clinical disease activity index (CDAI)	CDAI ≤2.8

*It is preferable to include feet and ankles also when evaluating remission.
†Suggested wording for patient global assessment is provided in refs. 9 & 10.
‡Defined as the simple sum of the tender joint count (using 28 joints), swollen joint count (using 28 joints), patient global assessment (0–10 scale), physician global assessment (0–10 scale), and C-reactive protein level (mg/dl).

able, defined as a patient who would be in remission when absence of fatigue was assumed, since fatigue data were not collected. After stopping prednisolone (week 28), clinical differences between groups were no longer significant and most remissions in the combination group ended. Over 56 weeks, 18 probable and 6 definite remission (total=32%) occurred in the combination group compared with 14 and 5, respectively, receiving SSZ alone (total=24%; p=0.38). Radiographic outcomes at weeks 28, 56 and 80 showed statistically significantly less progression among patients receiving combination *versus* SSZ monotherapy.

Fin-RACo compared combination (SSZ, MTX, HCQ and low-dose prednisolone) to single DMARD therapy (starting with SSZ; with or without low-dose prednisolone) (12). Using modified 1981 ACR remission criteria, 37% receiving combination therapy and 18% receiving DMARD monotherapy achieved remission at 2 years (p=0.003). Differences between groups could not be explained by inclusion of prednisolone in the combined regimen, since most patients receiving monotherapy also received low-dose prednisolone. Also, more patients receiving monotherapy were on prednisolone at the end of the study and had a higher median number of glucocorticoid injections during the trial. Both groups experienced increases in median Larsen score from baseline to year 2, but increases in Larsen score and number of eroded joints were greater with monotherapy (p=0.002 and p=0.006, respectively). Over 11 years follow-up, higher rates of minimal disease activity and remission, along with less long-term radiologic damage, were maintained with combination *versus* monotherapy (13, 14). However, choice of therapy beyond 2 years was not controlled and the impact of this beyond 2 years is unknown. Potential differences in the dose of individual agents between groups also make it difficult to attribute observed differences to an additive or synergistic effect of combination therapy.

Proudman *et al*. compared a combination regimen of MTX, CsA and corticosteroids to standard monotherapy with SSZ in untreated RA (15). Despite greater reductions in disease activity in the combination group, ACR20 responses were similar over 48 weeks: 10 probable and 7 definite remissions (total 43%) in the combination group compared to 11 probable and 4 definite (total 36%) in the monotherapy group (p=0.57). Approximately 10% in each group had persistent definite remission by study completion. Radiographic damage scores increased by a median of 1 (range 0–42.5) and 1.25 (range 0–72.5) in the combination and SSZ groups, respectively, at 48 weeks (p=0.28). Although this suggests aggressive combination therapy was not better than monotherapy, the study did not directly compare combination therapy to one of its components (*e.g*. MTX), and therefore does not provide fair comparison between groups or information on potential additive effects of the combination regimen.

Remission with initial monotherapy vs. combination therapy with a biologic

DAS remission was reported in all trials, but was the primary outcome only in more recent trials including COMET and AGREE (17-19). Remission frequencies among patients receiving combination therapies with a biologic were generally higher (Table II) and radiographic progression was decreased compared to DMARD monotherapy.

The ASPIRE trial compared MTX therapy with infliximab (3mg/kg or 6mg/kg) to MTX monotherapy (3). After 1 year, combination therapy improved ACR responses and DAS remission rates, and had significantly lower rates of radiographic progression (monotherapy: 1/9 *vs*. combination therapy: 1/30). There was no significant difference in efficacy between the two infliximab groups. Notably, a significant proportion of patients achieved disease control for 1 year with monotherapy (~15% achieved remission), although clinical and radiographic benefits with combination therapy exceeded those with monotherapy.

PREMIER and OPTIMA compared responses with MTX and adalimumab combination therapy *versus* MTX alone (1, 20). In the PREMIER trial, combination therapy yielded higher rates of DAS remission, ACR70 response (for ≥6 continuous months), and radiographic non-progression compared to monotherapy after 2 years. Significantly less radiographic progression was also reported in the adalimumab *vs*. MTX monotherapy groups at 6 months, 1 year and 2 years, although ACR responses and clinical remission outcomes were similar. In the 3-year follow-up with open-label adalimumab therapy, initial combination therapy had superior remission responses over the monotherapy groups, although differences between the three groups decreased by year five (21). At year five, better radiographic non-progression (mean ΔTSS from baseline) was achieved by patients who received initial combination therapy (2.9) than patients who received either initial adalimumab (8.7) or MTX monotherapy (9.7). Combination therapy in the OPTIMA study resulted in improved ACR and HAQ responses, and twice as many patients achieving DAS remission (combination therapy: 34% *vs*. monotherapy: 16%; p<0.001) at 26 weeks (20). In the subsequent 52 weeks, 86% *versus* 68% of the initial combination and monotherapy groups, who reached DAS28<3.2 and were randomised to continue their respective treatments, achieved remission (p=0.002) (22). Addition of adalimumab to MTX in patients not achieving DAS<3.2 halted radiographic progression and yielded remission outcomes comparable to those of the initial combination group.

COMET examined how continuation or alterations of the first-year treatment regimen affected 2-year clinical and radiographic outcomes (17, 18). Based on blinded randomisation, patients initially receiving MTX monotherapy (M) or combination therapy with etanercept + MTX (EM) either continued their initial regimen (M/M or EM/EM) or changed from MTX monotherapy to combination therapy (M/EM) or from combination therapy to monotherapy with etanercept (EM/E) in year two. After two years, a greater proportion achieved DAS28 remission in M/EM and EM/EM groups (58% and 57%,

Table II. Summary of clinical trials reporting clinical remission associated with combination DMARD and biologic use in ERA.

Study	Clinical remission definition	Duration of therapy	Treatment groups	n	Disease duration	% of patients in clinical remission	*p*-value
Combination therapy with DMARDs							
Boers *et al*. 1997 (COBRA) (11)	ACR remission	56 weeks	SSZ	79	4 mos	24%†	*p*=0.38
			SSZ + MTX (7.5 mg/wk) + Pred*	76	4 mos	32%†	
Möttönen *et al*. 1999 (FIN-RACo) (12)	ACR remission	2 years	Single DMARD ± Pred	98	7.3 mos	18%	*p*=0.003
			SSZ + MTX (7.5–15 mg/wk) + HCQ + Pred	97	8.6 mos	37%	
Rantalaiho *et al*. 2009 (FIN-RACo) (13)	ACR remission	2 years (11 years F/U)	Single DMARD ± Pred	70	7 mos	19%	*p*=0.017
			SSZ + MTX (7.5–15 mg/wk) + HCQ + Pred	68	6 mos	37%	
Proudman *et al*. 2000 (15)	ACR remission	48 weeks	SSZ	42	8.9 mos	10%	NR
			MTX (7.5–20 mg/wk) + CsA + IA MP	40	8.4 mos	13%	
Ferraccioli *et al*. 2002 (16)	ACR remission	3 years	MTX (10 mg/wk) then CsA‡	42	1.2 ± 0.8 yrs	9%	NR
			CsA then MTX‡	42	1.0 ± 0.8 yrs	9%	
			SSZ	42	2.0 ± 1.0 yrs	7%	
Hetland *et al*. 2008 (CIMESTRA) (67)	ACR remission	1 year	MTX (7.5–20 mg/wk)	71	< 6 months	28%	*p*=0.39
			MTX (7.5–20 mg/wk) + CsA	73	< 6 months	35%	
		2 years	MTX (7.5–20 mg/wk)	71	< 6 months	35%	*p*=0.52
			MTX + CsA (7.5–20 mg/wk)	73	< 6 months	41%	
Hetland *et al*. 2010 (CIMESTRA) (68)	ACR remission	5 years F/U	MTX (7.5–20 mg/wk)	69	< 6 months	52%	*p*=0.45
			MTX + CsA (7.5–20 mg/wk)	70	< 6 months	60%	
Combination therapy with a biologic							
St. Clair *et al*. 2004 (ASPIRE) (3)	DAS28 <2.6	54 weeks	MTX (7.5–15 mg/wk) + placebo	298	0.9 ± 0.7 yrs	15%	MTX *vs*. INF 3mg/kg: *p*=0.065
			MTX (7.5–15 mg/wk) + INF 3 mg/kg	373	0.8 ± 0.7 yrs	21%	MTX *vs*. INF 6mg/kg: *p*<0.001
			MTX (7.5–15 mg/wk) + INF 6 mg/kg	378	0.9 ± 0.8 yrs	31%	
Westhovens *et al*. 2009 (AGREE) (19)	DAS28 ≤2.6	1 year	MTX (7.5–20 mg/wk) + placebo	253	6.7 ± 7.1 mos	23%	*p*<0.001
			MTX (7.5–20 mg/wk) + ABT	256	6.2 ± 7.5 mos	41%	
Smolen *et al*. 2010 (OPTIMA)(20)	DAS28 <2.6	26 weeks	MTX (up to 20 mg/wk)	460	4.2 mos	16%	*p*<0.001
			MTX (up to 20 mg/wk) + ADA	466	4.2 mos	34%	
Breedveld *et al*. 2006 (PREMIER – Yr 1) (1)	DAS28 <2.6	1 year	MTX (20 mg/wk)	257	0.7 ± 0.8 yrs	21%	*p*<0.001 for MTX + ADA *vs*. MTX or ADA alone
			ADA	274	0.7 ± 0.8 yrs	23%	
			MTX (20 mg/wk)+ ADA	268	0.8 ± 0.9 yrs	43%	
		2 years	MTX(20 mg/wk)	257	0.7 ± 0.8 yrs	25%	
			ADA	274	0.7 ± 0.8 yrs	25%	
			MTX (20 mg/wk)+ ADA	268	0.8 ± 0.9 yrs	49%	
van der Heijde *et al*. 2010 (PREMIER – Years 3–5) (21)	DAS28 <2.6	5 years	MTX (20 mg/wk) → Open-label ADA	115	0.8 yrs	56%	–
			ADA → Open-label ADA	115	0.7 yrs	52%	–
			MTX (20 mg/wk)+ ADA → Open-label ADA	124	0.8 yrs	61%	–
Emery *et al*. 2008 (GO-BEFORE)(69)	DAS28 ≤2.6	24 weeks	Placebo + MTX (20 mg/wk)	160	1.2 yrs	28%	
			Placebo + 100 mg GLM	159	1.8 yrs	25%	*p*=0.572¶
			50 mg GLM + MTX (20 mg/wk)	159	1.0 yrs	38%	*p*=0.050¶
			100 mg GLM + MTX (20 mg/wk)	159	1.3 yrs	38%	*p*=0.069¶
			50 mg/100 mg GLM + MTX (20 mg/wk)	318	1.1 yrs	38%	*p*=0.031¶
Emery *et al*. 2008 (COMET – Yr 1) (17)	DAS28 ≤2.6	1 year	MTX (7.5–20 mg/wk)	268	9.3 ± 0.4 mos	28%	*p*<0.0001
			MTX (7.5–20 mg/wk) + ETA	274	8.8 ± 0.4 mos	50%	

Table II. (*continues*)

Study	Clinical remission definition	Duration of therapy	Treatment groups	n	Disease duration	% of patients in clinical remission	*p*-value
Emery *et al*. 2010 (COMET – Yr 2) (18)	DAS28 ≤2.6	2 years	EM/EM	111	8.4 ± 5.7 mos	57%	*p*=0.002 *vs*. M/M
			EM/E	111	9.1 ± 5.6 mos	50%	–
			M/EM	90	9.1 ± 6.0 mos	58%	*p*=0.003 *vs*. M/M
			M/M	99	8.7 ± 5.4 mos	35%	–
Emery *et al*. 2012 (COMET post-hoc analysis – Year 1) (23)	DAS28 <2.6	1 year	VERA: M	49	3.5 ± 0.5 mos	35%	–
			ERA: M	148	10.3 ± 5.2 mos	32%	–
			VERA: EM	63	3.6 ± 0.5 mos	70%	*p*=0.004 *vs*. ERA EM
			ERA: EM	157	10.7 ± 5.4 mos	48%	
Quinn *et al*. 2005 (70)	ACR remission	104 weeks	MTX (7.5–25 mg/wk) + placebo	10	6.0 ± 3.7 mos	20%	NR
			MTX (7.5–25 mg/wk) + infliximab	10	7.4 ± 4.6 mos	70%	
Durez *et al*. 2007 (71)	DAS28 ≤2.6	52 weeks	MTX (7.5–20 mg/wk)	14	0.45 ± 0.29 yrs	40%	*p*=0.039 for MTX *vs*. MTX+MP
			MTX (7.5–20 mg/wk) + MP	15	0.25 ± 0.33 yrs	70%	
			MTX (7.5–20 mg/wk) + infliximab	15	0.36 ± 0.31 yrs	70%	
Tak *et al*. 2011 (IMAGE) (27)	DAS28 <2.6	52 weeks	MTX (7.5–20 mg/wk) + placebo	213	0.91 ± 1.1	13%	–
			RTX (2X500 mg) + MTX (7.5–20 mg/wk)	227	0.99 ± 1.1	25%	*p*=0.001 *vs*. MTX
			RTX (2X1000 mg) + MTX (7.5–20 mg/wk)	230	0.92 ± 1.3	31%	*p*=0.0001 *vs*. MTX

*Sequential tapering and withdrawal of prednisolone and methotrexate in the second 28 weeks. †Includes probable and definite remission achieved at some point during follow-up. ‡SSZ was added after 12 months if improvement was less than ACR50 with the combination. ¶Comparision *versus* placebo + MTX groups.

ABT: abatacept; ADA: adalimumab; CsA: cyclosporine A; DAS: disease activity score; EM: etanercept + methotrexate; E or ETA: etanercept; HCQ: hydroxychloroquine; GLM: golimumab; IA: intraarticular; INF: infliximab; MP: *methylprednisolone; M or MTX: methotrexate; NR: not reported; Pred: prednisolone; SSZ: sulphasalazine.

respectively; *p*=non-significant) compared to M/M group (35%) (*p*=0.002 for EM/EM *vs*. M/M; *p*=0.003 for M/EM *vs*. M/M). However, delayed combination therapy resulted in fewer patients achieving radiographic non-progression (change in modified Sharp-van der Heijde score ≤0.5) compared with early, sustained combination therapy (M/EM=75% *vs*. EM/EM=90%; *p*=0.009) (18). Post-hoc analysis at year 1 supported the benefits of early diagnosis and treatment with EM over M (23). A significantly higher proportion of very early RA (VERA) (disease duration ≤4 months) patients achieved remission than ERA (>4 months and <2 years) with EM (70% *vs*. 48%, respectively; *p*=0.004), while insignificant responses were observed with monotherapy (35% *vs*. 32%, respectively). In contrast, similar proportions of VERA and ERA patients achieved radiographic non-progression with EM (81% *vs*. 80%, respectively), whereas there was a significant difference between VERA and ERA groups treated with monotherapy (74% *vs*. 50%; *p*=0.01).

AGREE evaluated the efficacy of abatacept in MTX-naive patients with characteristics associated with poor radiological outcomes – *i.e*. baseline erosions, rheumatoid factor (RF) and/or anti-cyclic citrullinated peptide-2 (ACPA2) seropositivity (19). At 1 year, patients receiving MTX + abatacept demonstrated improved ACR50/70/90 responses compared to MTX alone and a higher proportion achieved DAS28 remission (41% *vs*. 23%, respectively). Significantly less radiographic progression was observed with combination therapy *versus* monotherapy (mean ΔTSS=0.63 *vs*. 1.06, respectively; *p*=0.040), a significant finding given the presence of poor prognostic factors. Additionally, within the subgroup of patients who achieved radiographic non-progression, more non-progressors treated with combination therapy achieved greater remission, low disease activity score (LDAS) and ACR50/70/90 responses than those receiving monotherapy (24). In the 2-year extension study, addition of abatacept in the MTX-only group resulted in additional patients achieving DAS28-defined remission (44.5% *vs*. 26.9%), LDAS (60.4% *vs*. 43.2%) and improved ACR70 (49.8% *vs*. 31.7%) at year 2 compared to year 1 (25). Less radiographic damage from baseline was seen at year 2 with combination therapy compared to the original MTX-only group (change in TSS=0.84 *vs*. 1.75; *p*<0.001). A *post-hoc* analysis showed that disease duration at abatacept initiation may be an important factor affecting remission outcomes in MTX-intolerant patients, as ERA (≤2 years) patients had significantly higher rates of remission compared with those with established RA (≥10 years) at years 1–3 (ERA=35%, 32%, 46% *vs*. established RA=19%, 20%, 31%, re-

spectively; $p<0.01$ for year 1, $p<0.05$ for years 2 and 3) (26).

IMAGE examined rituximab (RTX) in combination with MTX as a non-licensed indication for ERA, with the primary endpoint being change in total Genant-modified Sharp score (mTSS) (27). Patients received MTX-alone, low-dose RTX+MTX or high-dose RTX+MTX. Compared to MTX-alone, high-dose RTX+MTX was associated with less joint damage progression (mean change in mTSS=1.079 *vs*. 0.359, respectively; $p=0.0004$) and significantly higher proportion of patients with no joint damage progression (53% *vs*. 64%, respectively; $p<0.05$), which corresponded with significant improvements in clinical outcomes. Within both RTX groups, remission (DAS28-ESR <2.6) was greater at week 52 compared to MTX-alone (31% and 25% *vs*. 13% for MTX alone; $p<0.001$ and $p<0.0001$, respectively). Notably, differences between low-dose RTX and MTX-alone were not significant for any radiographic outcomes, although significant differences were seen for clinical outcomes, including ACR20/50/70/90 responses. While such a disconnect has been reported previously, the observation that different doses of a therapy provides similar clinical responses but different radiographic outcomes is noteworthy. A definitive explanation for this observation is unknown. One hypothesis suggests higher doses may induce more complete B-cell depletion in non-peripheral compartments (*e.g*. synovial tissue) (27).

A meta-analysis demonstrated a pooled risk ratio in favour of combination therapy with a biologic *versus* monotherapy in DMARD-naïve patients for both remission outcomes (relative risk: 1.74; 95%CI 1.54–1.98) and radiographic non-pogression (relative risk: 1.30; 95%CI 1.01–1.68), although significant heterogeneity in reporting radiographic outcomes was seen across studies (5). The magnitude of improvement associated with combination therapy differed between remission (~74%) and radiographic outcomes (~30%), suggesting that combination therapy may have greater positive impact on clinical *versus* radiographic outcomes. Another meta-analysis including observational and randomised studies also showed combination DMARD therapy or DMARD therapy with an anti-tumour necrosis factor-alpha (TNF) agent increased clinical remission (ACR or DAS) compared to DMARD monotherapy (OR: 1.51; 95%CI 0.99–2.31 for combination DMARD; OR: 2.05; 95%CI 1.26–3.34 for anti-TNF agents) (6). Radiographic progression was reduced with combination therapy compared to monotherapy in remission patients.

Remission outcomes with tight control in ERA

Treat-to-target with tight control is an emerging strategy tailored to a patient's disease activity and aims to achieve a predefined level of low disease activity or remission within a specified timeframe (7, 8). Studies examining this strategy using non-biologic DMARDs have shown significant benefit in clinical and functional outcomes compared to routine care (Table III). Generally, these studies have either compared two different treatment protocols (*e.g*. BeSt study) or the same treatment using different treatment algorithms (*e.g*. CAMERA, TICORA).

CAMERA compared conventional and intensified MTX treatment with computer-guided modifications in a 2-year, open-label study (28). The intensive group was assessed monthly and treatment was intensified if predefined response criteria were not met. The conventional group was assessed every three months and treated according to common practice. The goal in both groups was remission, defined as zero swollen joints and 2 of the following: ≤3 tender joints, ESR ≤20mm/hr and patient global assessment ≤20mm. Over 2 years, 50% *vs*. 37% ($p=0.03$) achieved remission criteria, mean time to first remission was significantly shorter (10.4 [9.1–11.7] *vs*. 14.3 [12.6–16.1] months; $p=0.001$), and duration of remission was longer (11.6 [10.1–13.1] *vs*. 9.1 [7.6–10.6] months; $p=0.025$) with intensive *versus* conventional care, respectively. Patients achieving early good response also had less radiographic progression over time (29). Post-hoc analysis at 5 years showed these strategies provided long-term benefit, although remission levels decreased once the tight control strategy was no longer applied (29). This has important implications for implementation of intensified protocols in routine practice, as feasibility of monthly assessments remains challenging.

TICORA compared an intensive DMARD treatment strategy with routine care in a single-blind, randomised trial (30). Patients receiving intensive treatment were seen monthly and treatment was escalated at every assessment after three months if DAS>2.4. Routine care patients were assessed every 3 months and treatment adjustments were at the physician's discretion. At 18 months, the intensive group had higher rates of good response (DAS<2.4 and improvement >1.2 from baseline) and ACR70 response compared to routine care. Remission rates (DAS<1.6) were higher in the intensive group (65% *vs*. 16%, respectively; $p<0.0001$) and progression of erosion and total Sharp scores was reduced, although there was no difference in progression of joint space narrowing. Of note, intensive group patients received more parenteral triamcinolone than the routine group. While this supports intensified approaches, it is difficult to ascertain comparative benefits of tight control *versus* no tight control from this study alone, since different therapeutic algorithms were used.

BeSt compared clinical and radiographic outcomes among four treatment strategies, including sequential DMARD monotherapy (group 1), step-up combination therapy (group 2), initial combination therapy with tapered high-dose prednisone (group 3), and initial combination therapy with infliximab (group 4) (31). Adjustments were made every three months based on predefined DAS targets. After 1 year, a higher proportion in groups 3 and 4 reached the goal and sustained DAS44≤2.4 compared to group 1 (53%, 64%, 71% and 74% in groups 1–4 respectively; $p=0.004$ for group 1 *vs*. group 3; $p=0.001$ for group 1 *vs*. group 4; *p*-value not significant for other comparisons). A post-hoc analysis, nonetheless, showed

Table III. Studies using treat-to-target with tight control in patients with ERA.

Study	Disease duration	Treatment goal	Treatment groups	n	% achieving treatment goal	% achieving clinical remission[a]
Non-biologic Studies						
Gigor *et al*. 2004 (TICORA) (30)	<5 years	DAS low disease activity, defined as DAS <1.6	Intensive treatment	53	65%	65%
			Routine treatment	50	16%	16%
Verstappen *et al*. 2007 (CAMERA) (28)	<1 year	Sustained response for six months, defined as: • No swollen joints • 2 out of 3 criteria: - ≤3 painful joints - ESR ≤20 mm/h[1st] - VAS general well being ≤20 mm	Conventional treatment (MTX, 7.5 mg/week)	148	-	37%[b]
			Intensive treatment (MTX, 7.5 mg/wk + computer-aided treatment modifications)	151	-	50%
	<2 years	Remission, defined as fulfillment of 5 ACR criteria excluding fatigue and duration of remission	Combination DMARD	68	-	37%
			Single DMARD	70	-	19%
Bakker *et al*. 2012 (CAMERA-II) (62)	<1 year	Remission, defined as: • No swollen joints • 2 out of 3 criteria: - ≤3 TJC - ESR ≤20 mm/h - VAS general well being ≤20 mm	Intensive treatment (MTX,10 mg/wk + placebo + computer-aided treatment modifications)	119	-	61%
			Intensive treatment (MTX,10 mg/wk + 10mg/d prednisone + computer-aided treatment modifications)	117	-	72%
van Tuyl *et al*. 2008 (COBRA) (72)	3 mos	DAS ≤3.2 or CTX-II ≤150	COBRA treatment treated to DAS target	11	-	90%
			COBRA treatment treated to CTX-II target	10		
Biologic Studies[c]						
Van Eijk *et al*. 2011 (STREAM) (73)	≤2 yrs	Remission, defined as DAS44 <1.6	Aggressive treatment treated to DAS target[d]	42	-	66%
			Conventional treatment (MTX, SSZ or HCQ)	40	-	49%
Goekoop-Ruiterman *et al*. 2005 (BeSt - Year 1) (31)	≤2 yrs	Adequate clinical response, defined as DAS ≤2.4	Sequential monotherapy[e]	126	53%	-
			Step-up combination therapy[f]	121	64%	-
			Initial combination therapy with prednisone[g]	133	71%	-
			Intial combination therapy with infliximab[h]	128	74%	-
Klarenbeek *et al*. 2011 (BeSt – 5-year F/U) (33)	≤2 yrs	Adequate clinical response, defined as DAS ≤2.4	Sequential monotherapy[e]	111	-	46%[i]
			Step-up combination therapy[f]	94	-	51%[i]
			Initial combination therapy with prednisone[g]	113	-	65%[i]
			Intial combination therapy with infliximab[h]	116	-	81%[i]
Soubrier *et al*. 2009 (GUEPARD) (74)	<6 mos	Low disease activity, defined as DAS28 ≤3.2	Initial MTX monotherapy with step-up to ADA	32	65.6%	59.4%
			Initial combination therapy (MTX + ADA)	33	63.6%	39.4%

[a]As defined in individual clinical studies. [b]At two years; p=0.029. [c]No biologic studies have evaluated therapies against a routine care comparator. [d]Patients started with 15 mg/week MTX, then increased to 25 mg/week if response was insufficient. Subsequent steps for insufficient responders, MTX with adalimumab, MTX with SSZ, HCQ and prednisone, leflunomide monotherapy, and finally gold monotherapy. [e]Patients started with 15 mg/week MTX then increased to 25–30 mg/week if response was insufficient. Subsequent steps for insufficient responders were SSZ monotherapy, leflunomide monotherapy, MTX with infliximab, gold with methylprednisolone and MTX with CSA and prednisone. [f]Patients started with 15 mg/week MTX then increased to 25–30 mg/week if response was insufficient. For insufficient responders, SSZ was added, followed by the addition of HCQ and then by prednisone. Insufficient responders to this combination subsequently switched to MTX with infliximab, MTX with CSA and prednisone and finally to leflunomide. [g]Patients started with the combination of 7.5 mg/week MTX, 2,000 mg/day SSZ, and 60 mg/day prednisone (tapered in 7 weeks to 7.5 mg/day). For insufficient responders, MTX was augmented to 25–30 mg/week. If response was still insufficient, the combination was replaced by MTX with CSA and prednisone, followed by MTX with infliximab, leflunomide monotherapy, gold with methylprednisolone, and finally by azathioprine with prednisone. [h]Patients started with infliximab at 25–30 mg/week MTX with 3 mg/kg infliximab at weeks 0, 2, and 6 and every 8 weeks thereafter. After 3 months, the dose of infliximab was increased to 6 mg/kg/every 8 weeks if response was insufficient. [i]Of the 48% of all patients that were in clinical remission, defined as DAS44<1.6.

that even the systematic DAS-driven therapies of groups 1 and 2 provided significantly better remission outcomes than routine care (31% *vs*. 18%, respectively; p<0.005) (32). After five years, regardless of initial treatment, 48% of patients were in clinical remission (DAS44<1.6); and of those, 46%, 51%, 65% and 81% of patients in groups 1–4, respectively, attained remission on initial therapy (33). Although 23% of patients achieved drug-free remission, 46% had to re-start monotherapy due to relapse; consequently, only a small proportion sustained true drug-free remission (23%x46%=11%) (34). Yearly progression rates were similar between all groups at 7-year follow-up, suggesting DAS-steered therapy stabilises radiological damage regardless of treatment (35). Notably, a higher proportion

of group 2 eventually required addition of infliximab compared to group 1 (~50% *vs*. 20%, respectively), suggesting that tight control with conventional DMARD may reduce or delay need for addition of biologic therapy compared to initial conventional DMARD monotherapy. Post-hoc analysis also showed that two years after infliximab initiation, more patients receiving initial combination therapy discontinued infliximab because of good response compared to those adding infliximab after failing ≥3 traditional DMARDs (56% *vs*. 29%, respectively; p=0.008) (36). It remains unknown if higher discontinuation rates relate to lower baseline disease activity in patients capable of discontinuation.

Establishing uniform remission criteria

Remission outcome reporting has been heterogeneous, thus study comparisons are difficult. Studies comparing initial DMARD monotherapy to combination DMARD therapy generally used 1981 ACR remission criteria, which requires fulfillment of 5 of 6 criteria related to cessation of RA symptoms. These criteria and subsequent modifications have been criticised for being too strict, as few patients meet criteria for persistency, absence of fatigue and extra-articular features. This may partly explain similar remission rates observed between DMARD combination therapy and DMARD monotherapy, despite significant differences in other clinical responses. Studies comparing initial DMARD monotherapy to combination therapy with a biologic generally use a defined threshold of DAS. While more patients achieve remission, this definition allows for residual disease activity and up to 12 swollen joints if the level of acute-phase reactant and tender joint count (TJC) remain low (37). This may explain dissociation between clinical remission and continued structural deterioration observed with high-sensitivity imaging (38-40).

The ACR/EULAR 2011 remission criteria were developed to provide a stringent yet achievable definition, which could be used uniformly as a pre-specified outcome in clinical trials (9, 10). Two provisional definitions of remission were proposed based on analyses of predictive and face validity, using data from industry-sponsored trials with follow-up ≥2 years: i) Boolean definition whereby the TJC, swollen joint count, CRP (mg/dL), and patient global assessment (0–10 scale) all must be ≤1 at one point in time, or ii) SDAI≤3.3 at one point in time. In clinical settings without an acute-phase response measurement, the Boolean definition could be used without the CRP criterion or CDAI<2.8 could be used instead of the SDAI threshold. Several studies found that among the four Boolean criteria, PGA is often the limiting factor for reaching remission because patients fail to satisfy criteria related to their own assessment of disease activity, especially regarding factors other than inflammatory pain (41, 42). This highlights the importance of patient self-evaluation when applying these new remission definitions. Treatment, duration of remission, and measures of physical function and radiographic damage were excluded in the ACR/EULAR 2011 criteria, although the latter two were used to validate candidate definitions by assessing ability to predict future good radiographic and functional outcomes (9, 10).

SDAI and CDAI are more stringent composite indices, allowing for less residual activity than DAS-based thresholds and potentially up to 2 swollen or 2 tender joints or 1 swollen and 1 tender joint while in clinical remission (43). Accordingly, fewer patients fulfill remission criteria compared to DAS-based thresholds (9, 10, 43, 44), but are likely to experience less radiographic progression. While more stringent criteria may reduce residual disease activity, high-sensitivity imaging has shown clinically-relevant inflammation in joints with no clinical signs of inflammation, suggesting that clinical remission criteria alone may not reflect true remission (45). For instance, the BRASS study supported the inclusion of image-guided measures as a component of remission, since they found joint damage occurred even in patients achieving 2011 remission criteria (46). However, whether systemic inflammation seen with high-sensitivity imaging predicts future damage or disability remains unclear. During development of the 2011 remission criteria, existing data on validity of MRI and ultrasonography imaging in detecting disease activity were considered insufficient and thus require further investigation in the context of defining remission.

Predictors of remission

Examining potential predictors of remission may help achieve better radiographic and functional outcomes in ERA (Table IV). Age, sex, RF antibodies, baseline HAQ and DAS28 score, but not type of initial treatment, predicted DAS28 remission at 1 year in the Canadian ArThritis CoHort (CATCH) EIA cohort (50), while the IMPROVED study found that male sex, BMI, baseline DAS28 and HAQ scores, symptom duration and low joint counts were predictors for remission in patients treated with MTX and prednisone (51). Lack of response to initial therapy may also be an important predictor of rapid articular destruction, and ultimately not achieving remission (52). Furthermore, predictors of DMARD-free remission or sustained remission (defined as no current DMARD use, no swollen joints, and classification as DMARD-free remission by a rheumatologist for duration of ≥1 year) have been identified using two large ERA cohorts: Leiden Early Arthritis Clinic; British Early Rheumatoid Arthritis Study. Studies have identified and/or confirmed that low baseline DAS28, low CRP, less baseline TJC, absence of RF IgM and human leukocyte antigen (HLA) shared epitope alleles, non-smoking, short disease duration, and acute onset of symptoms are predictors of sustained remission (47-49). Despite low sustained remission rates (8–10%) in these cohort studies, these predictors may help guide initial treatment decisions.

Several studies evaluated the predictive value of ACPA in relation to radiographic outcomes and disease progression (53-56). Farragher *et al*. examined ACPA-positivity in relation to functional status and treatment response in a cohort with early inflammatory polyarthritis and found ACPA-positive patients had significantly worse outcomes

Table IV. Selected publications on predictors of remission or radiographic outcome.

Reference	Type of study	Predictors identified	
Predictors of remission			
Van der Woude *et al*. 2008 (49)	Cohort study	• Acute onset • Shorter symptom duration at inclusion • Non-smoking • Absence of RF IgM • HLA SE alleles	
Bombardier *et al*. 2010 (47)	Cohort study	• Low baseline DAS28 Score • Disease duration • CRP level	
Jayakumar *et al*. 2012 (75)	Cohort study	• Gender • Short duration of symptoms • Low tender joints at baseline	
Kuriya *et al*. 2010 (50)	Cohort study	• Age • Gender • RF antibody status • Baseline HAQ • Baseline DAS28	
Wevers-de Boer *et al*. 2012 (51)	Cohort study (IMPROVED trial data)	• Gender • Low joint counts • Baseline DAS • Baseline HAQ • Low BMI • ACPA	
De Vries Bouwstra *et al*. 2008 (54)	RCT (BeSt trial data)	• RF and ACPA were predictive of progressive disease only in patients treated with sequential monotherapy	
Katchamart *et al*. 2010 (58)	Systematic review	*Clinical variables:* • Male sex • Young age • Late-onset RA • Short disease duration • Non-smoker • Low baseline disease activity • Mild functional impairment • Early treatment with non-biologic DMARD combinations • Use of anti-TNF • Concurrent use of DMARD in anti-TNF-treated patients • Moderate or good response to treatments at the first 6 months	*Laboratory and radiographic variables:* • Absence of RF and ACPA • Low serum level of acute phase reactant, IL-2, and RANKL at baseline • MTHFR 677 T alleles and 1298 C alleles in the MTX-treated patients • MTR 2756A allele ± either SLC 19A180A allele or TYMS 3R-del6 haplotype in MTX +SSZ combination-treated patients • Low baseline radiographic damage
Predictors of radiographic outcome			
Forslind *et al*. 2004 (53)	Observational study	• Baseline Larsen score • ACPA • ESR	
Quinn *et al*. 2005 (70)	Cohort study	• ACPA antibodies measured at disease onset	
Mustila *et al*. 2011 (56)	Cohort study	• ACPA antibodies measured at baseline	

in HAQ scores, joint counts and DAS28 scores compared to ACPA-negative patients (57). Additionally, Mustila *et al*. found that ACPA-positivity correlated with radiographic progression even in patients initially treated with the FIN-RACo therapy (56). Absence of ACPA has been identified as a predictor of remission in several studies (58, 59), suggesting that clinical remission varies by ACPA status. Given these data and differences in disease characteristics among patients who are ACPA-positive and negative, stratifying remission outcomes by ACPA status is of interest. Two studies have shown ACPA-negativity is associated with achieving remission using multivariate analysis (59, 60); however, further studies quantifying remission outcomes are needed.

Studies have found that glucocorticoids have disease-modifying effects (61), and may be important predictors of remission. Although studies show that early use of low-dose prednisone as an adjunct to DMARD therapy retards radiographic progression and improves sustained remission outcomes (62, 63), there is no agreement on the optimal use of glucocorticoids in ERA (61).

Conclusion

This review highlights the benefits of early treatment with strategies including DMARD combination therapy, targeted treatment and combination therapy with a biologic compared to DMARD monotherapy in achieving remission in ERA. Patients with early disease benefit from earlier treatment with improved outcomes when using combination DMARD therapy or DMARD with a biologic. Tight control with pre-specified treatment targets improves clinical remission and other outcomes in ERA. Current consensus guidelines recommend regular follow-up every 1–3 months with treatment modifications within 3–6 months if the target is not reached (7, 8). Remission is often achievable in ERA, but varies considerably according to remission definition (42, 64). However, when definitions are assessed in accordance with functional ability and radiological progression, there is higher correlation amongst composite indices (DAS, SDAI, CDAI) (64). As such, clinical remission criteria alone may not reflect true remission, and inclusion of radiological and image-guided assessments may prove beneficial (42, 64). Early disease control with remission targets, appears to significantly impact disease states over time, HAQ, radiographic progression, and possibly joint replacement surgery (65). The impact of 2011 remission criteria on remission outcomes with these approaches is unknown, although increased stringency compared to DAS-based remission criteria may increase the proportion achieving true remission. Identifying predictors of sustained remission may also help customise optimal treatment and identify patients requiring monotherapy *versus* combination DMARDs and/or early initiation of biologics to halt radiographic damage in early disease. Early diagnosis facilitated by 2010 RA classification criteria may help with earlier treatment initiation, although this hypothesis requires further validation (66). Although safety aspects related to achieving remission were not discussed in this review, it is an important subject for future discussion.

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