Remission in Early Rheumatoid Arthritis

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ABSTRACT. ***Objective.*** We systematically reviewed remission as an outcome measure in observational studies and randomized controlled trials (RCT) in early rheumatoid arthritis (RA). Our objectives were to identify its frequency using different criteria, to determine the influence of different treatment strategies on remission, and to review the effects of remission on radiological outcomes.

Methods. Pubmed, Medline and Embase were searched using the following terms: Early Rheumatoid Arthritis or Early RA combined with Remission, Treatment, anti-Tumor Necrosis Factor (TNF) or Disease-modifying Antirheumatic Drugs (DMARD). Remissions were reported using American College of Rheumatology (ACR) criteria and Disease Activity Score (DAS) criteria.

Results. Seventeen observational studies (4762 patients) reported remission in 27% of patients, 17% by ACR criteria and 33% by DAS criteria. Twenty RCT (4 comparing DMARD monotherapies, 13 comparing monotherapy with combination therapies, 3 comparing combination therapies) enrolled 4290 patients. ACR remissions occurred in 16% receiving DMARD monotherapy and 24% combination therapies (random effects OR 1.69, 95% CI 1.12–2.36). DAS remissions occurred in 26% and 42%, respectively (OR 2.01, 95% CI 1.46–2.78). Observational studies showed continuing radiological progression despite remission. RCT showed less radiological progression in remission when treated with combination therapy compared to monotherapies.

Conclusion. Remission is a realistic treatment goal in early RA. Combination therapies using DMARD with or without TNF inhibitors increase remissions. Radiological progression occurred in remission but is reduced by combination therapies. ACR and DAS remission criteria are not directly comparable and standardization is needed. (J Rheumatol First Release June 1 2010; doi:10.3899/jrheum.091131)

Key Indexing Terms:
RHEUMATOID ARTHRITIS DISEASE-MODIFYING ANTIRHEUMATIC DRUGS
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Remission means absence of disease, with undetectable symptoms, signs and disease markers. It differs from "cure," which implies disease will not return. The advent of intensive treatment regimens has made remission a realistic treatment goal in early rheumatoid arthritis (RA). These intensive treatments include combinations of disease-modifying antirheumatic drugs (DMARD) and DMARD with biological therapies such as tumor necrosis factor (TNF) inhibitors[1-7] and they are associated with higher rates of remission.

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Several classification criteria have been developed for remission. Some criteria use categorical descriptions of remission. The American College of Rheumatology (ACR) remission criteria are the most important of these[8], and a number of variants have been described. Continuous composite measures are also used to define remission; the most commonly used are low scores using the Disease Activity Score (DAS)[9] or its modifications such as DAS28[10,11]. Radiological progression is not considered in these remission criteria in spite of its importance in longterm disability[12].

Despite remission being a key goal of RA treatment, its frequency associated with treatment has not been evaluated methodically. We have therefore systematically reviewed observational and randomized controlled trials (RCT) in early RA, with 3 aims. First, we identified the differences in the frequency of remission dependent on the criteria by which it is judged. Second, we determined how the frequency of remission is influenced by different treatment strategies. Finally, we reviewed the effects of remission on radiological outcomes.

MATERIALS AND METHODS

Search terms. Pubmed, Embase, and Medline were searched using the following search terms: Early Rheumatoid Arthritis or Early RA combined with Remission, Treatment, anti-Tumor Necrosis Factor, or Disease Modifying Antirheumatic Drugs. The search was limited to 1996-2008, English, and clinical trials.

Selection criteria. Studies were selected for inclusion using the following criteria: (1) RCT or observational studies; (2) patients fulfilled the ACR classification of RA; (3) disease duration < 3 years of diagnosis; (4) remission used as an outcome measure; and (5) the study enrolled > 40 patients.

Outcomes. We included DAS (and its modifications) or ACR (and its modifications) remissions as the clinical outcome measure. Radiological outcomes of patients in remission were also assessed.

Quality of trials. The quality of the trials was judged using the Jadad Scoring System[13].

Data extraction. Two researchers (MHYM, ICS) independently assessed studies for eligibility and extracted data on year of publication, population source, study design, study size, and followup period. When there were differences between observers, they reviewed the reports together and came to a joint conclusion.

Statistical analysis. Data from all studies were analyzed descriptively. RCT were analyzed using Review Manager 4.2.8 (Cochrane Collaboration, Oxford, UK). The random effects odds ratio (OR) model based on DerSimonian and Laird's method was used to estimate the pooled effect sizes[14]; this gives more equal weighting to studies of different precision in comparison to a simple inverse variance-weighted approach, so accommodating between study heterogeneity. It was reported with 95% confidence intervals (CI). For all metaanalyses, we performed Cochran's chi-square test to assess between study heterogeneity and quantified the I^2 statistic[15,16]. We considered a p value < 0.05 as significant. The number needed to treat (NNT) was calculated and reported with 95% CI.

In RCT with more than one "control" arm or "treatment" arm, the arm with the best outcome was selected for analysis.

RESULTS

Study selection. We identified 1660 citations for review; 52 were evaluated in detail and 37 studies were included in the final analysis. These comprised 17 observation studies and 20 RCT (Figure 1). The baseline characteristics of the observational studies and RCT are described in Tables 1 and 2A, respectively. From the available data, the patients enrolled into the RCT appeared to have higher disease activity.

The 17 observational studies (Table 1) followed patients for 2–10 years: 16 reported endpoint remissions and 1 reported remissions over 6 months at any point during followup. In total, 4762 patients entered these observational studies (3653 completing full followup); 972 (27%) achieved remissions.

The 20 RCT (Table 2) followed patients for 1–3 years. Their average Jadad score was 3.5 (range 1–5). Nineteen RCT reported endpoint remissions and 1 reported remission at any timepoint. Four trials evaluated DMARD monotherapies (2 monotherapy vs placebo/nonsteroidal antiinflammatory drugs (NSAID); 2 different monotherapies). Thirteen trials compared monotherapy with combination therapies. Three trials reported different combination strategies. Altogether, 4290 patients entered these trials; 1312 (31%) achieved remissions.

Remissions in observational studies. Eight studies reported remissions using ACR criteria; 5 excluded fatigue and 1 used low levels of pain (< 10 mm on visual analog scale). The overall remission rate was 261/1501 (17%). The maximum disease duration ranged from 5 to 24 months. The mean remission rate of patients with < 1 year disease duration was 18% and for < 2 years disease duration was 23%. The followup period ranged from 1 to 10 years. When these were subdivided into groups (< 3, < 6, and > 6 years), the mean remission rates were similar (20%, 21%, and 18%, respectively).

Four studies reported ACR remission rates in patients receiving only DMARD monotherapies; 165/1068 (15%) of

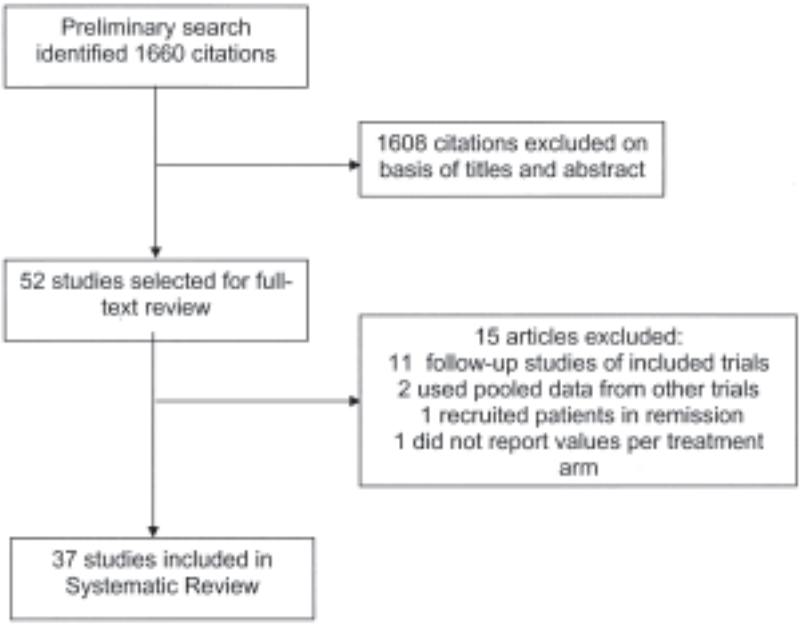

Figure 1. The process of the search strategy.

Table 1. Remissions in observational studies * remission over 6 months at any point. Results are mean values unless denoted "i" indicating median data; "ii", DAS.

Study	Year	Remission	Disease Duration, mo	Age, yrs	Female, %	RF+, %	ESR	DAS28	Followup, mo	DMARD	Number at Entry	Number at Followup	Remission, at Study End (%)
Prevoo[9]	1996	ACR	< 12	55[i]	63	78	—	—	72	Monotherapy	227	49	15 (31)
Eberhardt[38]	1998	ACR	< 24	—	63	75	29	—	60	Monotherapy	183	176	37 (20)**
Young[39]	2000	ACR	8	—	66	63	—	—	60	Monotherapy	941	732	94 (13)
Makinen[40]	2005	ACR	5	56	61	54	—	—	60	Monotherapy	127	111	19 (17)
Möttönen[41]	1996	ACR	< 24	46	75	63	30[i]	—	72	Combination included	142	142	45 (32)
Lindqvist[42]	2002	ACR	< 24	—	63	75	—	—	120	Combination included	183	163	30 (18)
Sanmarti[43]	2003	ACR	< 24	52	78	—	45	5.8	12	Combination included	65	60	12 (20)
Fransen[30]	2004	ACR	< 12	55	66	76	—	—	72	Combination included	424	77	9 (12)
Cantagrel[17]	1999	DAS	< 12	—	—	71	—	—	24	Not stated	108	108	15 (14)
Tengstrand[44]	2004	DAS	< 12	57	64	58	—	5.1	24	Monotherapy	844	844	279 (33)
Vázquez[45]	2007	DAS	< 24	55	81	74	40	5.7	24	Monotherapy	115	105	34 (32)
Khanna[46]	2007	DAS	< 14	51	—	100	43	5.5	24	Monotherapy	200	101	33 (33)
Gossec[47]	2004	DAS	< 12	51	73	81	40	4.1[ii]	60	Combination included	191	165	38 (23)
Forslind[48]	2007	DAS	≤ 12	58	64	60	—	5.3	60	Combination included	698	608	234 (39)
Proudman[23]	2007	DAS	< 24	56	76	61	42	5.3	36	Combination included	61	52	28 (54)
Sanmarti[49]	2007	DAS	< 24	55	81	74	40	5.7	24	Combination included	115	105	34 (32)
Machold[21]	2007	DAS	≤ 3	51	75	—	—	—	36	Combination included	138	55	16 (29)

these patients achieved remission. Four studies reported ACR remission in patients also receiving combination therapies; 96/442 (22%) patients achieved remission.

Nine studies used DAS-based remission criteria: 2 used DAS ≤ 1.6 and 7 used DAS28 ≤ 2.6. The overall rate of remission was 711/2143 (33%). The maximum disease duration ranged from 3 to 24 months. The mean remission rate of patients with < 1 year disease duration was 29% and for < 2 years' disease duration, 36%. The followup period ranged from 1 to 6 years. When these were subdivided into groups (< 3 and < 6 years), the mean remission rates were 32% and 31%, respectively. Three studies reported DAS remissions in patients receiving only DMARD monotherapies; 328/1057 (31%) achieved remission. Five studies reported remissions in patients receiving combination therapies; 350/985 (36%) achieved remission. One study did not describe the treatments used[17].

Remissions in clinical trials of DMARD monotherapies. Four RCT evaluated remissions with DMARD monotherapies: one compared DMARD (D-penicillamine) with placebo, one compared sulfasalazine with NSAID, and 2 compared different DMARD monotherapies. Three RCT used categorical remission criteria based on ACR remission (ACR derivative). Five out of 22 (12%) achieved remissions with placebo therapy. There were 89/469 (19%) patients in remission using DMARD monotherapy. One RCT used DAS-based remission criteria but did not identify remissions with DMARD monotherapy or NSAID[18].

Remissions in clinical trials of combination therapies. Thirteen RCT compared DMARD monotherapy with combination DMARD therapy (including biologics). Six used ACR-based remission criteria; 2 excluded fatigue and one excluded morning stiffness. They reported 75/472 (16%) patients achieved remissions with monotherapies and 112/467 (24%) with combination therapies. The maximum disease duration ranged from 12 to 36 months. The mean remission rate of patients with < 1 year disease duration was 19% with monotherapies and 24% with combination therapies, < 2 years disease duration was 15% with monotherapies and 24% with combination therapies, and < 3 years disease duration was 7% with monotherapy and 10% with combination therapy. The followup period ranged from 1 to 3 years. When these were subdivided into groups (< 1, < 2, and < 3 years), the mean remission rates were similar (17%, 14%, 7%, respectively, with monotherapies and 23%, 27%, and 9%, respectively, with combination therapies). Metaanalysis (Table 3 and Figure 2) showed that the random effects odds ratio for remissions with combination therapies compared with monotherapies was 1.69 (95% CI 1.21, 2.36). There was no evidence of significant heterogeneity. The number needed to treat was 12 (95% CI 8, 33).

Seven RCT used DAS remission criteria. In total, 318/1202 (26%) patients achieved remissions with monotherapies and 545/1287 (42%) with combination therapies. The maximum disease duration ranged from 6 to 36 months. The mean remission rate of patients with < 1 year disease duration was 26% with monotherapies and 41% with combination therapies, < 2 years disease duration 40% with monotherapies and 49% with combination therapies, and < 3 years disease duration 22% with monotherapy and 39% with combination therapy. The followup period ranged from 1 to 2 years. When these were subdivided into groups (< 1 and < 2 years), the mean remission rates were 26% and 31%, respectively, with monotherapies and 41% and 44%,

Table 2A. Summary of inclusion criteria of clinical trials. Results are mean values.

Study	Year	Control					Treatment				
		Age, yrs	Female, %	RF+, %	ESR	DAS28	Age, yrs	Female, %	RF+, %	ESR	DAS28
Monotherapy											
Eberhardt[50]	1996	53	63	80	36	—	50	52	67	32	—
Rau[51]	1997	54	60	68	41	—	57	72	54	41	—
Van Jaarsveld[52]	2000	56	69	67	42	—	57	64	65	41	—
Choy[18]	2002	58	74	54	—	5.3	57	76	58		5
Monotherapy vs combination therapy											
Boers[1]	1997	49	52	72	—	—	50	66	78	—	—
Möttönen[7]	1999	48	66	66	39	—	47	58	70	37	—
Proudman[53]	2000	50	55	79	31.4	5.1	51	65	80	39.1	5.4
Ferraccioli[54]	2002	59	86	55	43	—	59	86	73	52	—
Gerards[55]	2003	51	70	97	46	—	53	62	93	53	—
Wassenberg[56]	2005	50	65	47	40	—	53	75	43	44.5	—
St. Clair[57]	2004	50	75	71	43	6.7	50	68	73	44	6.7
Svensson[24]	2005	59	63	66	—	5.4	51	65	66	—	5.28
Allaart[3]	2006	54	68	67	DAS 44	4.5	54	66	64	DAS 44	4.3
Breedveld[6]	2006	52	74	—	—	6.3	52	72		—	6.3
Choy[2]	2008	54	67	66	—	5.8	55	67	72	—	5.6
Emery[4]	2008	52	73	—	49	6.5	51	74	—	47.8	6.5
Hetland[19]	2006	51	70	59	27	5.5	53	64	70	28	5.3
Combination vs combination therapy											
Verstappen[58]	2007	53	66	62	39	—	54	69	66	36	—
Saunders[59]	2008	55	79	72	45	6.9	55	76	69	36	6.8
Verschueren[20]**	2008	55	65	52	DAS28	CRP 4.76	45	63	79	DAS28	CRP 5.28

Table 2B. Remission in clinical trials (cases at end of followup).

Study	Year	Disease Duration, mo	Followup, mo	Remission	Control			Treatment		
					Cases	Treatment	Remission (%)	Cases	Treatment	Remission (%)
Monotherapy										
Eberhardt[50]	1996	24	24	ACR derivative	22	Placebo	5 (12)	21	D-Penicillamine	4 (12)
Rau[51]	1997	16	12	ACR derivative	87	MTX	10 (12)	87	GSTM	21 (24)
Van Jaarsveld[52]	2000	< 12	24	ACR derivative	107	HCQ	29 (27)	105	MTX (short lag)	25 (24)
Choy[18]	2002	< 12	12	DAS28	55	Diclofenac	0	62	SSZ	0
Monotherapy vs combination therapy										
Boers[1]	1997	< 24	12	ACR	76	SSZ	19 (24)*	79	SSZ/MTX/Pred	24 (32)*
Möttönen[7]	1999	< 24	24	ACR	98	SSZ or MTX	18 (18)	97	MTX/SSZ/HCQ/Pred	36 (37)
Proudman[53]	2000	< 12	12	ACR	42	SSZ	4 (10)	40	MTX/CSA/1A Methylpred	5 (13)
Ferraccioli[54]	2002	16	36	ACR	42	SSZ	3 (7)	42	MTX/CsA	4 (9)
Gerards[55]	2003	< 36	12	ACR	60	CsA	4 (7)	60	CsA/MTX	6 (10)
Wassenberg[56]	2005	< 24	24	ACR	86	DMARD	8 (9)	80	DMARD/Pred	13 (16)
St. Clair[57]	2004	< 36	12	DAS28	245	MTX	37 (15)	325	MTX/Infliximab	101 (31)
Svensson[24]	2005	< 12	24	DAS28	126	DMARD	42 (33)	116	DMARD/Pred	65 (56)
Allaart[3]	2006	< 12	24	DAS44	126	DMARD	58 (46)	128	MTX/Infliximab	54 (42)
Breedveld[6]	2006	< 36	24	DAS28	257	MTX	64 (25)	268	MTX/Adalimumab	131 (49)
Choy[2]	2008	< 24	24	DAS28	117	MTX	21 (18)	116	MTX/CsA/Pred	32 (28)
Emery[4]	2008	< 24	12	DAS28	263	MTX	73 (28)	265	MTX/Etanercept	132 (50)
Hetland[19]	2006	< 6	12	1. DAS28 2. ACR	68	MTX/IA Steroids	1. 23 (34) 2. 19 (28)	69	MTX/CsA/IA steroids	1.30 (43) 2.24 (35)
Combination vs combination therapy										
Verstappen[58]	2007	< 12	24	ACR derivative	148	Conventional MTX +/– CsA	55 (37)	151	Intensive MTX +/– CsA	76 (50)
Saunders[59]	2008	Mean 11.5†	12	DAS28	44	Step up	21 (45)	47	Parallel	16 (33)
Verschueren[20]**	2008	< 12	12	DAS28	17	Step up	No values	46	Step down	No values

* Achieving remission at some point during followup (probable and definite remissions included). ** Not randomized. Inclusion criteria of symptoms < 5 years but mean disease duration < 12 months (SD < 12 mo). GSTM: Gold sodium thiomalate; MTX: methotrexate; HCQ: hydroxychloroquine; SSZ: sulfasalazine; Methylpred: methylprednisolone; Pred: prednisolone; CsA: cyclosporin A.

Table 3. Metaanalysis of remission rates in randomized controlled trials of monotherapy versus combination therapy.

Subgroups	No. Studies	Monotherapy Cases	Monotherapy Remission	Combination Therapy Cases	Combination Therapy Remission	Random OR (95% CI)	Chi-square (p)
DAS remission	7	1202	318	1287	545	2.01 (1.46, 2.78)	19.1 (0.004)
ACR remission	7	472	75	467	112	1.69 (1.21, 2.36)	2.8 (0.84)
Steroids	3	328	91	315	132	1.95 (1.39, 2.73)	1.99 (> 0.05)
Anti-TNF	4	928	226	1383	390	2.05 (1.26, 3.34)	17.18 (0.0006)
Combination DMARD	10	841	200	953	294	1.51 (0.99, 2.31)	28.33 (0.0008)
Tight control regimes	2	246	95	248	142	2.23 (1.26, 3.97)	2.39 (> 0.05)

DAS: Disease Activity Score; ACR: American College of Rheumatology; TNF: tumor necrosis factor; DMARD: disease-modifying antirheumatic drug.

respectively, with combination therapies). Metaanalysis showed that the random effects OR for remissions with combination therapies compared with monotherapies was 2.01 (95% CI 1.46, 2.78) with DAS remissions criteria. There was significant heterogeneity within the studies. The number needed to treat was 6 (95% CI 5, 8). One trial reporting DAS and ACR remissions was included in both ACR and DAS remission analysis[19]. The effects of steroids, anti-TNF therapy, combination DMARD therapies, and tight-control regimes were also investigated using meta-analysis (Table 3). The random OR were similar in all subgroups (OR 1.51–2.23).

Three trials reported different combination strategies. One trial compared step-up and step-down combination regimens but was not randomized[20]; remission rates were similar with both treatments but no values were reported. Two RCT reported ACR or DAS-based remissions in 33%–50% of patients. Remission by any criteria occurred in 168/395 (43%) patients.

Remissions and radiological progression. Four observational studies reported radiological outcomes in patients in remission (Table 4). All showed some radiological progression (19%–54% of patients over 3–5 years) using varying radiological assessment methods. Three studies compared erosive progression in patients achieving remission to other cases: one study[21] reported lower erosive progression with lasting remission (19% vs 72%); 2 studies[22,23] found no differences.

Two RCT reported the effects of remission on radiological outcomes[3,24]. Both showed less radiological progression with combination treatments compared to monotherapies in patients in remission (Table 5).

DISCUSSION

Our systematic review showed that remission is becoming a realistic therapeutic target in early RA. Observational studies showed an overall remission rate of 17% with ACR remission criteria and 33% with DAS remission criteria. Many patients in clinical remission showed ongoing radiological progression. The RCT showed that more patients achieved remission when combination treatments were used (random OR 1.69–2.01 compared to DMARD monotherapies). There was less radiological progression in patients receiving combination therapies who were in remission.

This systematic review has several limitations. One issue is study heterogeneity. The studies varied in duration (12–120 months), design (observational and trials), treatment approaches (DMARD monotherapy and intensive combination regimens), and the classification of remission (ACR and DAS criteria). Most studies used single timepoints to define remission; this was usually at the end of followup. Those studies reporting remission rates over prolonged periods recorded fewer remissions. Another limitation is the focus on early RA, thereby excluding studies of patients with undifferentiated early inflammatory arthritis. The Norfolk Arthritis Register (NOAR) exemplifies such studies; it shows there are more remissions in milder forms of arthritis[25]. We excluded older "classic" studies, which go back several decades. Changes in the management of RA over the last 20 years mean these historical studies have limited current relevance. In addition, the difference between the effects of monotherapies versus combination DMARD therapies may be exaggerated due to the choice of DMARD in the monotherapy arm. Sulfasalazine is often used as DMARD monotherapy and is considered by some experts to be a "weaker" DMARD in comparison to methotrexate, although the relative efficacy of different DMARD is a contentious issue. There is also controversy over whether patients treated with steroids, particularly at high dosages, can be considered as being in remission. Some RCT[1,3] did use high-dose steroids at the beginning of treatment but these were rapidly reduced to 7.5 mg. We consider that low-dose prednisolone is acceptable and have included these reports in our analysis. Finally, it is important to bear in mind that differences between groups of patients are easier to demonstrate when there are high potentials for progression in contrast to low potentials for progression; the same is true in showing differences between highly effective and relatively ineffective treatments.

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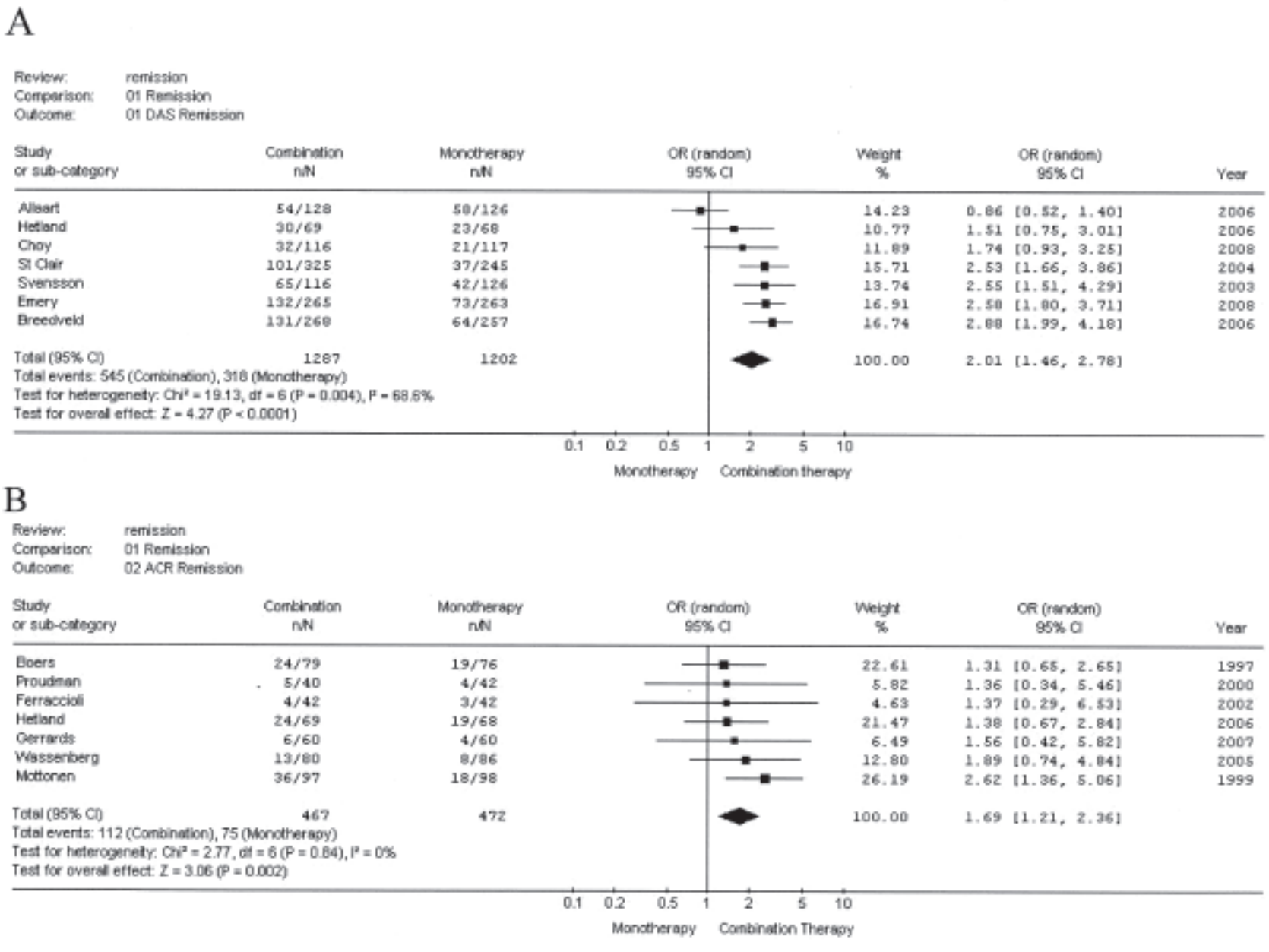

Figure 2. Metaanalyses of RCT using (A) DAS remission criteria; (B) ACR remission criteria.

Table 4. Summary of radiographic outcomes in observational trials of patients in remission.

Study	Year	Remission	Numbers at Followup	Radiographic Outcome
Makinen[40]	2005	ACR	111	Radiological remission (no new or increased erosions) at 5 years in 66 patients (55%)
Vázquez[45]	2007	DAS	105	Increase in Larsen score > 4 at 2 years: Remission 9/34 (27%); no remission 23/71 (34%)
Proudman[23]	2007	DAS	52	Increase in erosion score at 3 years: Remission 15/28 (54%); no remission 14/24 (58%)
Machold[21]	2007	DAS	55	New erosions over 3 years: Lasting remission* 3/16 (19%) no lasting remission 28/39 (72%)

* Lasting remission = DAS28 < 2.6 for > 1 year.

Table 5. Summary of radiographic outcomes in randomized controlled trials of patients in DAS remission.

Study	Year	Monotherapy	Combination Therapy
Svensson[24]	2005	Median change in Larsen Score at 2 years, Remission 2.5 (IQR 0.5–8.0)	Median change in Larsen Score at 2 years, Remission 1.0 (IQR 0–3.5)
Allaart[3]	2006	Continuous remission, 25% damage progression	Continuous remission, 3% damage progression

IQR: interquartile range.

The ACR remission criteria and DAS28 remission criteria were derived using different methods, leading to differences in their definitions. Clinicians need to either agree on one measure of remission or, if agreement proves impractical, report both. One crucial difference between these criteria is the reliance placed on fatigue by the ACR criteria. Wolfe and colleagues highlighted the disproportionate effect of fibromyalgic rheumatoid on fatigue, despite patients with this subtype having no more synovial inflammation[26]. Consequently, using fatigue to assess RA remission may disproportionally affect the assessment of fibromyalgic RA. Pain and fatigue are common in the general population, and Sokka and colleagues suggested most people aged over 50 years in the general population will not fulfil ACR remission criteria for RA due to these symptoms[27]. The majority of the trials in this systematic review that used ACR remission criteria excluded fatigue. Despite this, the ACR remission criteria remained more stringent than DAS28-based criteria as no swollen or tender joints are permitted in ACR remission criteria.

With DAS-based criteria, there is uncertainty about differentiating remission from low disease activity. The DAS-based remission criteria are derived from studies that showed that DAS ≤ 1.6 best indicates ACR remissions[9]. However, its conversion into DAS28 ≤ 2.6 is controversial[28]; other levels of DAS28 have been suggested to better reflect remission[29,30]. Conversely, patients in remission may have falsely higher scores due to fibromyalgia or comorbidities that can affect erythrocyte sedimentation rate, tender joint scores, and patient global scores. DAS is not the only continuous assessment of disease activity and remission; other examples include the Simple Disease Activity Index (SDAI) and the Clinical Disease Activity Index (CDAI). Current cutpoints for remission have been defined as 3.3 for the SDAI and 2.8 for CDAI[31,32]. A final issue is the value of repeated assessments for determining remission; it is uncertain how many times patients need to be assessed and over what period; for instance, is remission on a single occasion important or does it need to be sustained for 6 or 12 months?

The relationship between disease activity and radiographic progression in early RA remains a topic of debate. The followup study of Cohen, *et al* found that sustained clinical remission correlated with stability of radiological damage in most patients[33]. However, there was radiological progression in a proportion of patients (16.7%) in sustained remission, and 20% developed erosions in a previously unaffected joint between the third and fifth years. Other trials have also found radiological progression in patients in remission[34,35]. It is therefore uncertain whether radiographic progression is wholly dependent on joint inflammation[36]. Another explanation may be that current assessment tools for disease activity are insensitive at low levels of inflammation and fail to detect ongoing disease activity. As a key goal of treatment is to prevent joint damage, we suggest radiological remission should be considered as a criterion for remission. The effect of treatment on radiological outcomes in patients with remission is unclear. Our metaanalysis identified 2 RCT that reported radiographic outcomes in remission groups. They both found that combination therapy is associated with less radiographic progression in patients in remission when compared to monotherapy[3,24]. Prednisone or anti-TNF was used in the combination arms

of those trials in which there was reduced radiological progression. It is inappropriate to extrapolate results from these 2 trials to all combination DMARD regimens. Interestingly, a recent post-hoc analysis of the PREMIER study found that once patients are in sustained remission, there was no difference in radiographic progression across the treatment groups[37].

We conclude that remission is now a realistic treatment goal in early RA, particularly with the increased focus on patients receiving intensive combination treatment regimens. Currently, multiple remission criteria exist, but DAS28 remission criteria appear easier to achieve. The absence of a single standard for assessing clinical remission is a major hurdle in its use as a standardized outcome measure. In addition, radiological remission is currently not considered routinely in clinical trials, which is the key to preventing longterm disability. We consider that patients in true remission need to be in clinical as well as radiological remission. Currently, there is an urgent need for international consensus on assessing and reporting true remission states.

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