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Systematic review: Evidence for Predictive Validity of Remission on Long Term Outcome in Rheumatoid Arthritis

Lilian HD van Tuyl, MSc¹, Prof David T Felson, MD, MPH², Prof George Wells, MSc, PhD³, Prof Josef Smolen, MD⁴, Dr Bin Zhang, DSc², Prof Maarten Boers, MSc, MD, PhD¹, and the ACR & EULAR committee to define remission for clinical trials

¹ VU University Medical Center, Amsterdam, The Netherlands ² Boston University School of Medicine, Boston, USA ³ University of Ottawa, Ottawa, Canada ⁴ Medical University of Vienna, Vienna, Austria

Abstract

Objective—Remission is rapidly becoming a key endpoint in rheumatoid arthritis clinical trials, but its definition is not satisfactory. Although it is generally believed that achieving a state of remission will lead to better structural outcome, this has not been studied systematically. As a part of an undertaking to redefine remission, the current review describes the relationship between remission and long term structural outcome.

Methods—A systematic literature search of PubMed, Embase.com, and the Cochrane Library intersected three groups of terms: rheumatoid arthritis, remission and long term outcome. The search identified 1138 records, of which 14 were relevant to the research question.

Results—All the studies included in this review showed a relationship between remission and long term structural damage or disability. Patients that achieved a state remission, defined in various ways, showed less deterioration of function and radiographic progression compared to patients who did not reach a state of remission.

Conclusion—Patients who achieve a state of remission are less likely to show deterioration of function and radiographic progression compared to patients that do not reach a state of remission.

Keywords

Rheumatoid arthritis; remission; systematic review; predictive validity

INTRODUCTION

Treatment of rheumatoid arthritis (**RA**) has improved substantially in the past twenty years. Although RA is a chronic disease without a known cure, a state of remission or low disease activity is achieved by a substantial number of patients participating in clinical trials (1-3) and even patients in practice (4;5). In the Quantitative Patient Questionnaires in Standard Monitoring of Patients with Rheumatoid Arthritis (**QUEST-RA**) project, remission occurred frequently, but this depended strongly on the definition used: percentages of patients in remission varied from 9% for the American college of Rheumatology (**ACR**) definition of remission to 20% for the Disease Activity Score in 28 joints (**DAS28**) definition of

remission. Likewise, using the Care for RA database (**CARAbase**) (6), a recent study showed differences when different scores were employed, with the lowest proportions of remission observed with the simplified disease activity index (**SDAI**) followed by ACR remission criteria and DAS28 remission; in DAS28 remission, patients had up to 9 swollen joints, while in SDAI remission 1-2 swollen joints were seen in only 5% of the patients (7). In fact, DAS28 remission has often been seen to exceed ACR70 response rates (1;8), and sometimes even ACR50 response rates (9), indicating significant residual disease activity in many patients in DAS28 remission. The findings of these papers highlight the need for a uniform definition of remission in RA.

In a collaborative project, ACR and the European League Against Rheumatism (**EULAR**) have constituted a committee to redefine remission in RA. In its first publication, the committee concluded that a new remission definition should be strict, based on no or very low disease activity and should be validated against long-term outcomes, specifically physical function and radiographic progression (10). The committee agreed that the new definition of remission should be able to predict patients who achieve and remain in a state of remission, will have no or little progression of joint damage and less deterioration or more improvement in physical function. But is it possible to predict this favourable long term outcome based on a definition of remission? What is the current body of knowledge that proves that being in a state of remission for a certain period will lead to better outcomes compared to not being in remission?

This systematic review aims at collecting and reviewing all available evidence on the ability of remission (defined variously) to predict long term outcome (ie the stability of x-ray damage or stability of physical function). In other words, what is known about the predictive validity of the currently available remission definitions?

METHODS

For this review, we sought all articles that studied the relationship between remission (by any definition) and long term outcome in terms of function and radiological progression.

Literature search

A systematic literature search of PubMed (on 6 October 2008; primary search), Embase.com (on 20 October 2008), and the Cochrane Library (on 5 November 2008) identified studies addressing the longitudinal relationship between any kind of remission definition and long term RA outcome. The search did not include limitations for language. Search terms included medical subject headings (MeSH) or keywords when appropriate. The search intersected three groups of terms. The first group described the disease rheumatoid arthritis, the second group described the condition of remission according to any available definition, and the third group described the concept of long term outcome in terms of function and radiological progression. To be included in the review, the population studied must be patients with RA, remission as well as long term outcome must have been defined clearly and the measurement of remission had either to be concurrent with or precede the interval over which the long term outcome was assessed.

Two authors composed the search strategy (LvT and MB) in consultation with medical information specialists. For the exact strategy, see Table 1.

Data extraction

Titles and abstracts of citations resulting from the search were screened for relevance by LvT. This resulted in an initial set from which LvT and MB independently selected the full articles to be retrieved. The same reviewers independently assessed these for final eligibility

(Figure 1). Screening the references for articles identified other potentially relevant articles which were subsequently retrieved and assessed. Lastly, all members of the ACR/EULAR committee charged with defining remission were asked to review the final list of relevant articles and to identify other work (published or not) that could be relevant to the research question.

Analysis

Narrative summaries of the articles were compiled that highlighted the following characteristics: number of patients included in the study, disease duration at inclusion, the type of intervention/treatment that patients received during the study, the type of remission definition(s) used to classify patients as in or not in remission, percentage of patients achieving remission, the duration of remission, the follow-up time of the study and the assessment of outcome: lower radiological progression and/or lower Health Assessment Questionnaire (HAQ).

RESULTS

The PubMed, Embase.com and Cochrane library databases identified 1138 possible articles referring to remission in rheumatoid arthritis in relation to long term outcome. Figure 1 shows how the final selection of fourteen articles was made. Searches in Embase.com and The Cochrane Library did not provide additional articles. The expert committee provided one additional article and several relevant background articles. Checking the references of all relevant articles provided two additional articles.

Of the 14 studies, five used the DAS28<2.6 remission definition, the SDAI<3.3, DAS<1.6 and a modified version of the ACR criteria were used three times, the full ACR criteria were used two times, and the following definitions were all used one time: DAS28<2.4, rheumatologists judgement, patient reported remission, time averaged DAS<1.6, DAS28<2.6 for at least 1 year, DAS28<3.2, DAS28<2.84 and CDAI<2.8. Heterogeneity was also present in outcome measures. Table 2 presents specific details and sources of heterogeneity of all articles included in the review. Furthermore, all studies included in this review are summarized below, with articles discussing a similar research question grouped together into one of three themes: 1) studies reporting on the influence of remission on physical function in patients using DMARDs, 2) studies reporting on the influence of sustained remission on radiographic progression, and sometimes also physical function in patients using DMARDs and 3) studies reporting on the influence of sustained remission primarily on radiographic progression in patients using DMARDs & biologicals.

All studies showed that patients who achieve a state of remission, defined in various ways, show less deterioration of function and radiographic progression compared to patients who do not reach a state of remission.

The following two studies reported on the influence of remission on physical function in patients using DMARDs:

Laborie et al (2002) (11) performed a cross-sectional questionnaire study to assess very long-term clinical and functional outcomes in RA patients. Of 88 patients, 26 reported a current subjective remission, with a mean duration of 8.5 ± 5.9 months. Of these patients, 20% met the ACR remission criteria. Mean HAQ score for all patients was 1.11 ± 0.84 . The median HAQ score was somewhat lower in the subgroup reporting remission, although considerable overlap occurred with the other patients.

Lindqvist et al (2002) (12) studied the 10-year outcome in a prospective cohort of early RA patients. They showed that 133 patient (79%) had relapsing remitting disease (no active joints on examination at least at 1 follow-up visit during 10 years). These patients had a significantly lower HAQ ($p=0.013$) after 10 years than patients with continuous active disease (data not shown). At the 10 year follow-up visit 30(18%) patients were in remission for median 13 months.

The following studies reported on the influence of sustained remission on radiographic progression, and sometimes also physical function in patients using DMARDs:

Molenaar et al (2004) (13) studied the radiographic progression in RA patients in 'clinical remission' for at least the preceding 6 months. Clinical remission was defined as a normal erythrocyte sedimentation rate (**ESR**) and meeting 3 out of 4 remaining ACR remission criteria (fatigue not measured). In the study period the ACR remission definition (meeting 5 out of 5 ACR remission criteria) and the (original) DAS definition ($DAS < 1.6$) was applied. Radiographs of hands and feet were obtained at baseline, 1 and 2 years and were scored according to the Sharp/van der Heijde (**SvH**) (14;15) method. Of the 187 included patients, remission persisted in 52% in the total cohort, 59% of the patients in ACR remission and 42% in DAS remission. Compared to patients with an exacerbation during follow-up, patients in persistent clinical remission were less likely to have relevant radiographic progression ($\Delta SvH \geq 5$) with 23% vs 7% respectively ($P=0.001$). For the ACR criteria these percentages were 10 vs 7 ($p=0.053$) and for the DAS 17 vs 6 ($P=0.017$). Of the patients in persistent clinical remission (as defined by authors) for 2 years, 15% developed erosions in a previously unaffected joint. The authors concluded that radiological progression can occur during all three defined states of persistent clinical remission.

Aletaha et al (2005) (16) studied among other things the construct validity of the SDAI and DAS28 by evaluating the association between the time spent in SDAI and DAS28 remission and radiographic progression over 36 months in a cohort of 56 patients with RA. In this study, remission was defined as $SDAI \leq 3.3$ or $DAS28 < 2.4$. These cut-off values were calculated based on the expert opinion of 35 rheumatologists who judged the disease activity of paper patients (32 different patient profiles). Three groups were compared: patients never in remission, patients 3-18 months in remission, and patients 21-36 months in remission. They found that the longer the patient remained in SDAI remission or DAS28 remission, the less likely the patients were to progress radiologically ($P < 0.01$). A similar relationship was observed with patients in high disease activity: the longer patients remained in high disease activity, the more likely they were to progress radiologically.

Cohen et al (2007) (17) studied the radiographic progression over 5 years of early RA patients that reached sustained remission ($DAS < 1.6$ at the 3-year and 5-year evaluations). Radiographs and HAQs were obtained at baseline, 3 and 5 years. A total of 191 patients were included of whom 36% achieved remission at 3 years, 28% at 5 years, and 22% ($n=30$) patients were in sustained remission at both 3 and 5 years. This last group was compared with the 104 patients who did not achieve remission at either 3 or 5 years. The total Sharp/van der Heijde score (with interquartile range) at baseline in the remission and non-remission groups was 0.5 (0-7) and 2 (0-7) respectively. At 5 years they were 2.5 (0-14) and 13 (3-29). The progression of damage at 5 years was significantly higher in the group with persistent disease activity (Δ total SvH=7 (1-19)) compared to the sustained remission group (Δ total SvH=1.5 (0-5)) ($P=0.0014$). Still, 10 (33%) patients in sustained remission had a significant increase in radiographic damage between baseline and 5 years. This proportion was 57 (55%) for patients not in remission. Furthermore, 5 (17%) patients in sustained remission had significant radiographic progression between the 3rd and 5th year, and 6 patients developed erosions between the 3rd and 5th year in a previously unaffected joint.

Mean HAQ scores were already better at baseline in the remission group: 1.1 (0.7) for the remission group vs 1.4 (0.7) for the non-remission group. At 3 and 5 years the mean HAQ score was 0.2(0.4) and 0.1(0.3) for the remission group vs 0.7 (0.6) at both times for the non-remission group. A total of 28 (93%) patients in sustained remission had a HAQ score $\leq$ 0.5 at 5 years v 39 (38%) patients with persistent disease activity ($P<0.001$). The authors concluded that sustained clinical remission according to the DAS criteria <1.6 was associated with stability of radiological damage in most patients and a clear improvement of functional capacity over 5 years in a cohort of patients with early rheumatoid arthritis.

Brown and colleagues (2008) (18) evaluated the long-term significance of subclinical synovitis measured by imaging techniques in patients with clinical remission on conventional DMARD therapy, in relationship to structural outcome. A group of 90 RA patients in remission at baseline were followed for 12 months and radiographs, magnetic resonance imaging (MRI) and ultrasonography (US) were available at both time points. Remission was defined by physician's clinical judgment and had to be stable for at least 6 months; 54% fulfilled the ACR remission criteria and 56% fulfilled the DAS28 remission criteria ($\text{DAS28}<2.6$). A control group of 17 healthy subjects underwent the same imaging procedures. At 12 months, 17 of 90(19%) patients experienced a significant deterioration in their total radiographic joint damage scores that was larger than the smallest detectable change. Likewise, 11% of the patients in ACR remission and 12% in DAS28 remission also showed radiographic progression (data not shown). In a binary logistic regression analysis, the authors found that ACR remission protected for adverse structural outcome radiographically ($\text{OR}=0.33$, $P=0.054$). Furthermore, of 25 patients without painful, tender or swollen joints, 4 experienced radiographic progression. The authors concluded that structural progression occurs in RA patients treated with conventional DMARD therapy despite the presence of clinical remission.

Hafström et al (2008) (19) studied if remission ($\text{DAS28}<2.6$) induced by low-dose glucocorticoid treatment in the first two years of the BARFOT study had a sustained effect on radiological damage after 4 years. At 2 years, 55% ($n=35$) in the prednisolone group and 30% ($n=26$) in the no-prednisolone group were in remission. At 4 years, 40% of all 150 patients were in remission. Patients in remission at 2 years had significantly less radiographic damage and less change in radiological scores after 4 years compared to those not in remission. Longitudinal analysis showed that DAS28-remission at 2 years was significantly associated with lower Sharp scores during the entire course of observation. The HAQ score at both 2 and 4 years was significantly lower for the patient in remission at 2 years, irrespective of intervention group.

Mäkinen et al (2007) (20) reported the effect of sustained remission on radiographic outcome over 2 years in the FIN-RACo trial. Remission was defined by a modified ACR definition of remission excluding fatigue and by the $\text{DAS28}<2.6$. Sustained remission was defined as remission at 6, 12 and 24 months; radiographs were obtained at baseline, 6 and 24 months.

At 6 months, 31 patients were in mACR remission and 72 patients were in DAS28 remission. At 6, 12 and 24 months, 14 patients were in sustained mACR remission, compared to 54 patients who were in sustained DAS28 remission. The authors compared the radiographic progression of the patients in sustained remission, of the patients in remission at 6 but not at 12 or 24 months and of patients not in remission at 6 months. They found a median increase in Larsen score of 0 (95% CI 0-2) in patients in sustained ACR remission, 4 (95% CI 0-10) for patients in ACR remission at 6 months but losing it later and 4 (95% CI 2-8) for patients not in remission at 6 months. For the DAS28 definition of remission, these

numbers were 1 (95% CI 0-2), 4 (95% CI 2-16) and 6 (95% CI 2-10). The authors concluded that sustained remission protects against radiographic joint damage.

The following studies reported on the influence of sustained remission on radiographic progression in patients using DMARDs and biologicals:

Machold et al (2007) (21) performed a study to determine the frequency of erosive disease and the pace of radiological progression in an inception cohort of patients with very early RA, treated at the discretion of the treating physician. In a subgroup of 55 patients who completed 3 years follow up, 64% developed erosive disease. Longstanding DAS28 remission was seen in 16 patients and was associated significantly with the absence of erosive disease (5 (31%) of these had erosive disease, 2 already at baseline and 3 developed erosions during the 1st year and did not progress any further). Time in remission/low disease activity (DAS28<3.2) correlated negatively with progression in Larsen score. In a stepwise regression model, time in remission/low disease activity showed a significant contribution to overall outcome of damage progression, although the factors with the greatest influence were RF, anti-CCP, CRP and cumulative swollen joint count. Disease Modifying Anti Rheumatic Drugs (**DMARD's**) were used in all patients except two; four patients (all in the erosive group) received tumour necrosis factor (TNF)- α antagonists. The authors concluded that joint damage occurs despite very early treatment.

Landewé et al (2006) and **van der Heijde et al (2007)** (22;23) described the radiographic progression in patients included in the TEMPO trial receiving either MTX monotherapy, etanercept monotherapy or a combination of both. Landewé and colleagues studied the relationship between disease activity and 2-year radiographic progression in this dataset, and found that patients in remission (defined as a time averaged DAS below 1.4 during 1 year) showed less radiological progression than patients with a time averaged DAS above 3.7. They demonstrated that the relationship most often seen (remission or low disease activity leads to less radiographic progression) was not present in the subgroup of patients that was treated with a combination of MTX and etanercept. They suggest that inflammation is not the only cause of radiographic progression and thus that remission or low disease activity does not necessarily lead to less radiographic damage. Van der Heijde and colleagues studied the radiographic progression in patients reaching DAS (<1.6) and DAS28 (<2.6) remission. Although 682 patients started the study drug, 350 patients were withdrawn during the 3 years. DAS /DAS28 remission was reached by 145(28%)/152 (30%) in year 1, 154(37%)/157(38%) in year 2, and 117(38%)/124(41%) in year 3 (completers only). In patients who achieved DAS remission, radiographic remission (change in total sharp score ≤ 0.5) was also attained in 85%, 80%, and 56% of patients in the combination, etanercept, and methotrexate groups, respectively. Conversely, fewer patients in the group not achieving DAS remission showed stability of radiographic progression (change in total sharp score >0.5) (34%, 45%, and 58% of patients in the respective treatment groups).

In 2006, Smolen et al (24) also reported on data of the ASPIRE trial, with disease activity divided into tertiles with the lowest tertile a DAS<2.85. In the group that was treated with MTX monotherapy, patients with a higher DAS score at 14 weeks had more radiological progression between baseline and week 54 than those with lower DAS scores ($P<0.05$). There was little progression in the MTX+IFX group, even in patients in the highest DAS28 tertile. Analyses using SDAI tertiles to define disease activity produced similar results. The authors concluded that higher disease activity was associated with greater radiographic damage in the MTX group, while little progression occurred in the combination group.

Smolen et al (2008) (25) reported on data from the ASPIRE trial, studying the effectiveness of methotrexate (**MTX**) alone compared to MTX plus infliximab (**IFX**). Disease activity

was classified into 4 states with the SDAI $\leq$ 3.3 as remission. Of the 1049 patients who started the study, 155 (15%) patients reached SDAI remission at 54 weeks and the radiographic progression of these patients was lower than that of the patients in the other disease activity states. In general, patients treated with MTX plus IFX showed less radiographic progression across all disease activity states, while in patients using MTX monotherapy, joint damage increased with every disease activity category. 78 (7%) achieved SDAI remission at 14 weeks and these patients had very limited radiographic progression at week 54, even on MTX. This study showed that sustained remission even on MTX (if seen already at week 14) is associated with no radiographic progression on the group level.

In 2009, **Aletaha and colleagues** (26) studied the rate of radiological progression in patients in sustained remission in a post-hoc analysis of the PREMIER trial (comparing effectiveness of either methotrexate monotherapy, adalimumab monotherapy or a combination of both). They studied the radiographic damage in a subgroup of patients that was in sustained remission defined by SDAI $\leq$ 3.3 during months 12 and 24 of the PREMIER study, and compared the groups with an additional preceding remission period of either 3, 6 or 9 months. They found that the shorter the period of remission, the more likely some mild progression may be found, which was deemed a consequence of a carry-over effect of past periods of inflammation. The authors concluded that preceding disease activity is a relevant determinant for radiographic progression between two time points.

DISCUSSION

This systematic review identified only 14 studies reporting on the longitudinal relationship between a definition of remission and long term outcome of RA in terms of function and/or radiographic progression. Fortunately, all studies showed that patients who achieve a state of remission, defined in various ways, show less deterioration of function and radiographic progression compared to patients who do not reach a state of remission.

It is remarkable that there are only 14 studies that report on this subject, while these data are probably available in many follow-up studies of clinical trials.

Many studies had to be excluded because they reported on the relationship between remission and long term outcome at the same time point, studied the relationship between disease activity and long term outcome without defining remission, or collected all the relevant variables but did not look at the relationship between them. Although no limitations for year of publication were used, the oldest articles included in this review are from 2002, by Lindqvist et al and Laborie et al (11;12). We expected to find older articles, since the first official remission definition was proposed by Pinals et al in 1981 (27). On the other hand, remission did not occur often before the introduction of combination DMARD therapies and anti-TNF strategies in the last decade.

While all of the reviewed articles examined remission and stability of longer term outcomes, the temporal relation of remission to those longer term outcomes varied a bit from study to study. Most of the reviewed studies assessed remission *during the period* when longer term stability was also being assessed. Since change in longer term outcomes was occurring at the time remission was assessed, these studies might not be considered longitudinal. We are not sure if any of these studies evaluated remission preceding the period in which long term outcomes were assessed (e.g. remission at 6 months; long term outcomes from 6 months to 2 years).

Because the topic of this review is often not the primary goal of a study, our search strategy had to be sensitive enough to find the eligible articles, even when the topic was not mentioned in the abstract. Although we used a sensitive search strategy, it is possible that

relevant articles were missed, because these findings were reported in a sub analysis. Nevertheless, we believe we were comprehensive in our search, especially by including a round with the experts currently designing a new definition for remission in RA, who could not identify any additional relevant studies. The consistency of the results of the included articles makes it very likely that this is the true direction of the signal with those patients achieving a state of remission showing less deterioration of radiographic progression and function.

It is important to report on this specific research question because increasing numbers of trials use remission as an important outcome, assuming that this leads to favourable long term outcomes. The current review confirms that there is evidence for a longitudinal relationship between remission and long term RA outcome, but more research is needed to confirm this finding.

Another interesting development in the relationship between remission and radiographic progression is the so called ‘disconnect’ between disease activity and radiological damage as hypothesized by Kirwan et al (22;24;25;28;29). According to this hypothesis, disease activity (or inflammation) only partly explains long-term radiological damage. The articles by Landewé et al (22) and Smolen et al (25) included in this review strongly suggest that most patients treated with biologic therapies experience a virtual halt of radiographic progression, regardless of disease activity, whereas in patients treated with monotherapy there was increasing joint damage with increasing disease activity. In fact, all articles reporting some residual radiological progression with patients in remission lend support to the disconnect hypothesis. However, even on biologicals a slight progression of joint damage can be observed with increasing disease activity and especially high disease activity. Moreover, methods for identifying progression are insensitive in the setting of very low progression rates, as the smallest detectable difference is about 5 Sharp/van der Heijde points, while the progression is close to 0 (30). Furthermore, clinical methods are also unreliable in the setting of very low disease activity. The study by Brown et al (18) included in this review shows that radiographic progression in patients in clinical remission is mostly explained by subclinical joint inflammation detected by ultrasound and MRI. It thus remains possible that the reduction in association is in fact explained by subclinical synovitis occurring less frequently in patients in remission induced by biologic or combination therapies than in patients in remission induced by monotherapy. On the other hand, the study by Aletaha et al (26) and Smolen et al (25) suggests that it is primarily the sustained remission which will allow joint damage to halt, indicating that either a carry-over effect occurs or subclinical disease activity may still be present driving joint damage, before it is ultimately arrested. One way or the other, the validation of a remission definition based on clinical measurement must take account the reduced association between disease activity and structural damage demonstrated by these studies.

Although all remission definitions lead to reduced radiological progression, some definitions still allow significant residual disease activity while others are more strict, allowing no swollen or tender joints. This was presented at the first meeting of the ACR/EULAR remission workgroup (11), where it was summarized that remission definitions can roughly be categorised as either ‘strict’ (ACR, CDAI/SDAI, PAS/RAPID3) or ‘lax’ (the mACR criteria and the DAS28 definition), with the latter being very similar to the OMERACT definition for minimal disease activity (MDA) (8); It has been shown that the exclusion of the ankles and feet in reduced joint counts can give different results and should be used with caution in clinical practice (31;32). This might explain at least a proportion of the joint damage that occurs in such states of remission.

As can be learned from this review, the current concept of remission is complex and the development of a new definition a big challenge. This review, albeit of a very limited number of studies, offers consistent evidence that remission by all currently applied definitions is longitudinally related to radiological progression and physical function.

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PubMed: 643 Embase.com: 727 Cochrane library: 187	
	419 duplicate records removed
1138 records screened (title/abstract) LvT	
	1007 excluded (off topic)
131 records screened (title/abstract) by two independent reviewers (LvT and MB)	
	80 excluded (off topic, clearly wrong relation)
52 potentially relevant studies screened (full article)	
	41 excluded Reasons: - Similar research question, but not (all) correct variables are studied (n=15) - All variables are measured, but no relationship is studied (n=7) - Review (n=5) or editorial (n=1) - Cross-sectional relationship (n=5) - No long term outcomes (n=4) - Prediction of remission (n=4) - Not enough information (n=1)
11 studies included	
14 potentially relevant studies identified through reference checking 10 potentially relevant studies identified by the expert panel	
	21 excluded Reasons: - Similar research question, but not (all) correct variables are studied (n=12) - All variables are measured, but no relationship is studied (n=2) - Editorial (n=1) - No long term outcomes (n=4) - Prediction of remission (n=1)
3 studies included	
14 studies used in systematic review	

Figure 1.
Flow chart of literature selection

Table 1

Search strategies

Search	Topic	Result
PubMed 6 October 2008		
1	Disease: rheumatoid arthritis	
MeSH	((“Arthritis, Rheumatoid”[MeSH:NoExp] OR “Caplan's Syndrome”[MeSH]) OR “Felty's Syndrome”[MeSH]) OR “Rheumatoid Nodule”[Mesh]	
	OR	
Free Text	arthriti*[tiab] OR rheuma*[tiab] OR caplan[tiab] OR felty[tiab]	154812
2	Remission: by any definition	
MeSH	(“Remission Induction”[MeSH] OR “Remission, Spontaneous”[MeSH])	
	OR	
Free Text	remission[tiab] OR ((absence[tiab] OR minimal[tiab] OR low[tiab] OR no[tiab]) AND (disease activit*[tiab]))	87877
3	Long term RA outcome: function and radiographic progression	
MeSH	“Health Status Indicators”[MeSH]	
	OR	
Free Text	haq[tiab] OR aims2[tiab]	
	OR	
Free Text	((sharp[tiab] OR heijde[tiab] OR vanderheijde[tiab] OR larsen[tiab] OR genant[tiab]) AND (score[tiab] OR scoring[tiab] OR scores[tiab])) OR ((damage[tiab] AND radiograph*[tiab]) OR (radiologic*[tiab] AND progression[tiab])) OR disabilit*[tiab] OR “physical function”[tiab]	182241
4	Combination	
	#1 AND #2 AND #3	643
Embase.com 20 October 2008		
1	'rheumatoid arthritis'/de OR 'felty syndrome'/exp OR 'rheumatoid nodule'/exp OR 'pneumoconiosis'/exp	95,296
2	arthriti*:ti,ab OR rheuma*:ti,ab OR caplan:ti,ab OR felty:ti,ab	156,926
3	'remission'/exp	37,423
4	remission:ab,ti OR ((absence:ab,ti OR minimal:ab,ti OR low:ab,ti OR no:ab,ti) AND (disease:ab,ti AND activit*:ab,ti))	118,041
5	haq:ab,ti OR aims2:ab,ti OR ((sharp:ab,ti OR heijde:ab,ti OR vanderheijde:ab,ti OR larsen:ab,ti OR genant:ab,ti) AND (score:ab,ti OR scoring:ab,ti OR scores:ab,ti)) OR ((damage:ab,ti AND radiograph*:ab,ti) OR (radiologic*:ab,ti AND progression:ab,ti)) OR disabilit*:ab,ti OR 'physical function':ab,ti	86,823
6	'structural damage'	1,884
7	'health status'/exp	72,863

Search	Topic	Result
8	'international classification of functioning, disability and health'/exp	318
9	#5 OR #6 OR #7 OR #8	156,976
10	(#1 OR #2) AND (#3 OR #4) AND #9 AND [embase]/lim	727
Cochrane Library 5 November 2008		
1	(arthriti* OR rheuma* OR caplan OR felty):ti,ab,kw and (remission OR ((absence OR minimal OR low OR no) AND (disease AND activit*)):ti,ab,kw and (haq OR aims2 OR ((sharp OR heijde OR vanderheijde OR larson OR genant) AND (score OR scoring OR scores)) OR (damage AND radiograph*) OR (radiologic* AND progression) OR disabilit* OR (physical AND function*) OR (health AND survey*) OR (structural AND damag*) OR (health AND status) OR (international AND classification AND functioning)):ti,ab,kw	187

:ti,ab,kw = title and/or abstract and/or keywords; /de = descriptor, EMTTree-term not exploded; /exp = EMTTree term exploded; :ab,ti = abstract and/or title

Table 2

Description of the fourteen included studies, all finding a positive relationship between remission and outcome

Study (ref)	n	Disease duration (mean, y)	Study type	Intervention	Remission definition	% patients in remission	Remission duration	Follow up (y)	Remission beneficial for outcome measure: Radiological progression	HAQ scores	Contrast
Laborte 2002 (11)	88	20	Retro spective cohort	Rheumatologists' choice. DMARDs and glucocorticoids	-Patient reported -patient reported ACR criteria	29 7	Mean 8.5 mo	-	-	Median HAQ score	Patients in vs not in remission
Lindqvist 2002 (12)	168	0.9	Cohort	Rheumatologists' choice. DMARDs and glucocorticoids	mACR	79	Minimum 1 time point	10	-	Mean HAQ scores for patients after 10 y	Patients in relapsing remittive disease vs continuously active disease
Molenaar 2004 (13)	187	Median 7	Cohort	Rheumatologists' choice: DMARDs	-mACR + ESR -mACR -DAS<1.6	100 with 52 sustained 59 with 59 sustained 81 with 42 sustained	2.5 y	2	% of patients with Δ SvH ≥5	-	Patients in sustained remission vs with exacerbations
Aletaha 2005 (16)	56	?	Inception cohort	Unknown	SDAI<3.3 DAS28<2.4	?	Never vs 3-18 mo 21-36 mo	3	Change in Larson score between baseline and 3 y	-	three disease activity groups
Cohen 2007 (17)	134	0.7	Cohort	DMARDs	DAS<1.6	22 at 3 and 5 yrs	2 y	5	Change in SvH score at baseline, 3 and 5 y	Continuous and dichotomous HAQ scores	Patients in remission vs not in remission
Brown 2008 (18)	90	Median 7	Cohort	DMARDs	-Rheumatologists' judgement -ACR criteria -DAS28<2.6	100 54 56	Median 2 y before inclusion	1	Change in Genant modified Sharp score over 1 y	-	Patients in rheumatologist determined remission vs different assessment technique
Häfstrom 2008 (19)	150	0.5	RCT extension	1: DMARDs 2: DMARDs + pred	DAS28<2.6	55 at 2 yrs 40 at 4 yrs	Minimum 1 time point	4	Change in SvH and absolute scores at 0, 2 and 4 y	HAQ score at 2 and 4 y	Patients in remission vs not in remission at 2 y
Mäkinen 2007 (20)	169	<2	RCT	1: SSZ 2: SSZ + MTX + HCQ + pred	-mACR -DAS28<2.6	8 sustained vs 92 not sustained 32 sustained vs 68 not sustained	1.5 y	2	Change in Larson score between 0, 6, 12 and 24 mo	-	Patients not in remission, in remission and in sustained remission.

Study (ref)	n	Disease duration (mean, y)	Study type	Intervention	Remission definition	% patients in remission	Remission duration	Follow up (yr)	Remission beneficial for outcome measure:		
									Radiological progression	HAQ scores	Contrast
Machold 2007 (21)	55	<0.3	Cohort	Rheumatologists' choice, DMARDs + glucocorticoids + 4 patients anti-TNF	-DAS28<2.6 for at least 1 yr -DAS28<3.2	29 ?	1 y	3	Development of erosions yes/no, score, Larson-Scott	-	Patients in 4 different categories of disease activity
Landewé 2006 (22)	444	7	RCT	1: MTX 2: Etanercept 3: MTX+etanercept	Time averaged DAS (12 mo <1.6)	9	Mean 1 y	1	Annual change in SvH score, calculated from 0, 1 and 2 y data	-	Patients in 4 different disease activity categories.
Van der Heijde, 2008 (23)	332	7	RCT	1: MTX 2: Etanercept 3: MTX+etanercept	-DAS<1.6 -DAS28<2.6	28 at 1 yr 37at 2 yr 38at 3 yr 30 at 1 yr 38 at 2 yr 41 at 3 yr	Minimum 1 time point	3	Change in SvH score	-	Patients reaching DAS remission vs not reaching this state
Smolen 2006 (24)	1004	0.9	RCT	1: MTX 2: MTX + IFX 3mg/kg 3: MTX + IFX 6mg/kg	DAS28<2.84	30 at wk 14	Minimum 1 time point	1	Change in SvH between 0 and 54 wks	-	Patients in different disease activity states categorized by DAS28 tertiles
Smolen 2008 (25)	1049	0.9	RCT	1: MTX 2: MTX + IFX 3mg/kg 3: MTX + IFX 6mg/kg	-SDAIS3.3 -CDAI≤2.8 -DAS28<2.6	19at wk 14 15 at wk 54 20at wk 14 22 at wk 14	Minimum 1 time point	1	Change in SvH between 0 and 54 wks	-	Patients reaching remission at 14 wks, at 54 wks, or no remission
Aletaha 2009 (26)	510	0.7	RCT	1: MTX 2: Adalimumab 3: MTX + adalimumab	SDAI≤3.3	23	1 y vs preceding 3 mo 6 mo 9 mo	2	Change in total Sharp score during the second y of study while in remission	-	For patients with another 3, 6 or 9 months in remission

mACR: modified ACR criteria, often excluding fatigue