
What should be our treatment goal in rheumatoid arthritis today?

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ABSTRACT

Remission should be the treatment aim in management of rheumatoid arthritis (RA) today because joint damage may progress in RA patients with low disease activity but presumably does not progress in patients in clinical remission. However, stringent criteria are needed to define remission status, as some criteria in current use allow for considerable residual disease activity. Even using stringent criteria, remission is achievable in a sizable proportion of patients in clinical trials and practice. Defining remission requires an additional consideration: Should a patient who is receiving medication be regarded as in remission if disease is absent, or must the patient be off treatment to be considered to be in remission? A case is made for aiming for a definition of remission that includes patients who continue medication therapy.

Introduction

Only 20 years ago, rheumatoid arthritis (RA) was regarded as a relentlessly progressive disease. Treatments provided little hope of significantly modifying long-term disease outcome. The literature painted “a grim picture” suggesting “that both premature death and marked functional morbidity occur even in population-based analyses” and that “the long-term prognosis of rheumatoid arthritis is bad” (1-5). Rheumatologists lamented that “intervention with drugs appears to have short-term gains with little impact beyond 2 years” (6), that there was “little evidence that second-line agents yield benefits beyond 3 years” (7), and that “available evidence does not suggest that these drugs could alter the long-term outcome of rheumatoid arthritis” (8). Other authors stated that “the question ‘Does the use of second-line therapy confer long-term benefit on outcome measures in rheumatoid arthritis?’ remains unanswered” (9),

primarily because “there are too few technically adequate studies to permit even provisional conclusions” (10). In those days, drug continuation rates, which are considered to be a rough surrogate for drug effectiveness (11), generally did not exceed 18 months in more than 50% of the patients. Exemplifying the dilemma of those years, only methotrexate (MTX) was retained for an average of over 3 years (12-14). During the ensuing 20 years, we have witnessed significant advances. In clinical trial design and daily practice, widespread use is made of a variety of disease activity measures and response criteria that have been developed and validated (15-23). Reliable and valid quantitative methods are available for scoring radiographic damage (24-26) and functional assessment by patient self-report (27, 28). Together, they facilitate quantitative judgment of treatment response to disease-modifying antirheumatic drugs (DMARDs). In parallel, unique advances were made in the therapeutic arena: recognition of the importance of early treatment, emergence of MTX as a recognised DMARD with far greater effectiveness and safety than previously available DMARDs; and new biologic agents successfully expanded the results of treatment of RA (29-35).

Current state

Clinical trials of new agents now report overall American College of Rheumatology 20% improvement (ACR20) response rates in up to 80% of RA patients and important responses (ACR50 and more) in 40% to 60% of RA patients (36-38). Moreover, increasingly higher remission rates are reported in clinical trials (36-38), indicating that remission is achievable and thus a realistic therapeutic goal at this time. But how do we define remission? Do we need to attain remission? What are our treatment goals for RA?

RA research suffers from the absence of a single “gold standard” quantitative measure, such as blood pressure or blood glucose/HbA1c levels, to assess all patients in clinical trials or clinical care. Various signs and symptoms, such as joint swelling, tenderness, and pain reflect the underlying inflammatory process. Bone and cartilage destruction constitute an important manifestation of the disease process; they distinguish RA from many other arthritides and signify long-term damage and outcome. Finally, functional disability is a consequence of the disease process.

Joint damage is related to the inflammatory response, indicated by time-integrated and even singly measured acute phase reactant levels or disease activity indices (23, 39-44) (Fig. 1). Proinflammatory cytokines, which induce joint inflammation and the acute phase response (45), are also important contributors to osteoclastogenesis (46-50). Their level in RA joints is much higher than in other forms of arthritis (51) and appears to exceed the threshold for differentiation and/or activation of these cells (43, 48). It has been shown in clinical trial populations of RA patients that higher C-reactive protein (CRP) levels at baseline and/or higher joint counts at 3 months are associated with increased progression of radiographic damage despite treatment with high doses of MTX (43) (Fig. 2A, B). The association between degree of inflammation and joint destruction is relatively weak in early disease but increases over time (Fig. 1); it is stronger when composite indices, the acute phase response or swollen joint counts are used as indicators of inflammation compared to other individual variables (Fig. 1, 2), and do not only pertain to time averaged inflammatory responses but can also be discerned at a single point in time (23, 39, 42, 43, 52, 53).

Low disease activity or remission?

The ultimate goals of treating RA include: 1) relief of pain, stiffness, and swelling, with complete clearing of all signs and symptoms of inflammation; 2) prevention of newly evolving joint erosions and joint-space narrowing

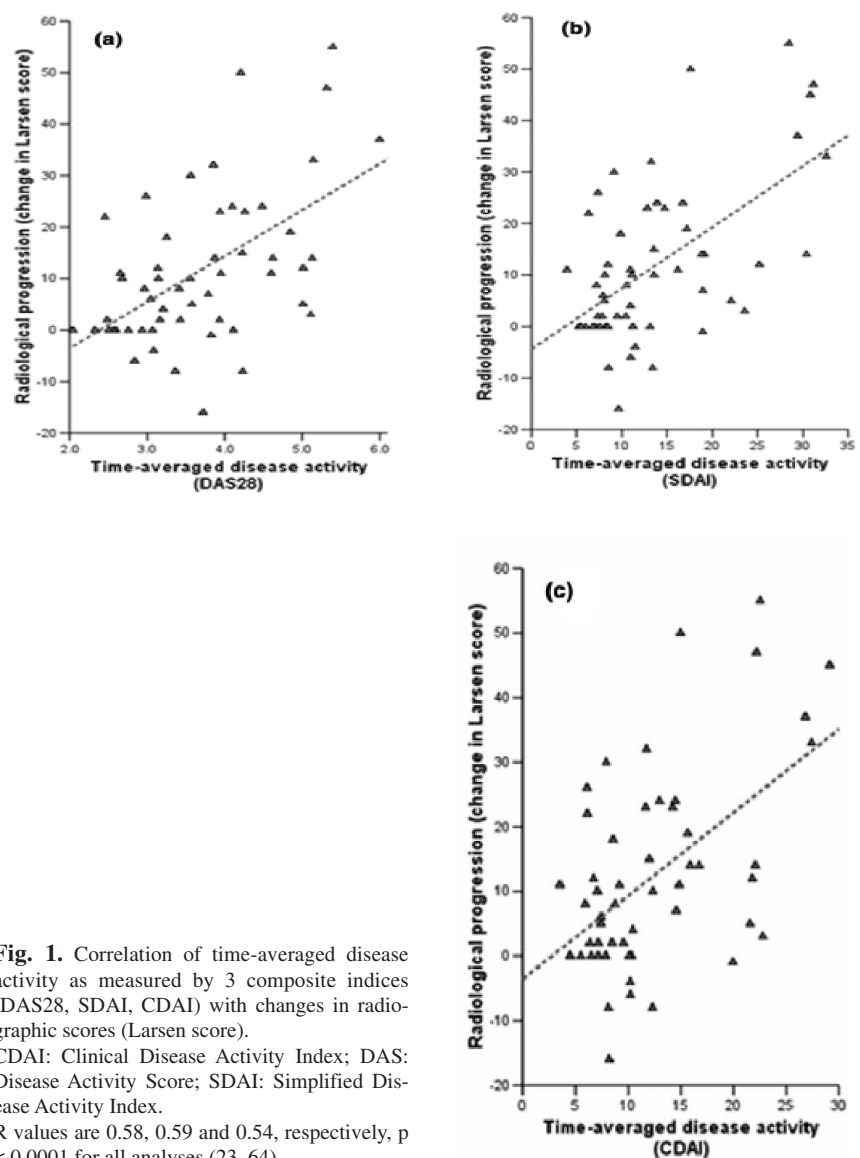


Fig. 1. Correlation of time-averaged disease activity as measured by 3 composite indices (DAS28, SDAI, CDAI) with changes in radiographic scores (Larsen score). CDAI: Clinical Disease Activity Index; DAS: Disease Activity Score; SDAI: Simplified Disease Activity Index. R values are 0.58, 0.59 and 0.54, respectively, $p < 0.0001$ for all analyses (23, 64).

(preferably even reversal of joint damage) and thus inhibition of the structural consequences of the disease process; and 3) restoration of functional abilities, including working capacity, that is, normalisation of the physical consequences of inflammation and damage.

In recent years, reaching a state of low disease activity has been hailed as a major success. The Food and Drug Administration (FDA) designates a sustained ACR70 response a “major clinical response” (54). An Outcome Measures in Rheumatoid Arthritis Clinical Trials (OMERACT) working group has defined a “minimal” disease activity state as an important treatment aim today, with low disease activity

defined as to be temporarily without symptoms but not necessarily free of disease or as a temporary disease activity score (DAS) ≤ 2.85 (55). However, progression of radiographic joint damage may be seen in patients taking MTX, even when disease activity is apparently low, such as with low (≤ 3) average swollen joint counts over 1 year of observation, or with average CRP levels < 0.8 mg/dL (Fig. 2) (43). Cumulative joint damage leads to long-term disability (42, 53, 56, 57). Thus, a state of low disease activity may be insufficient in some patients to prevent poor outcome of RA over time.

Therefore, only “no evidence of active disease” (58) should constitute the ideal situation to interfere with disease

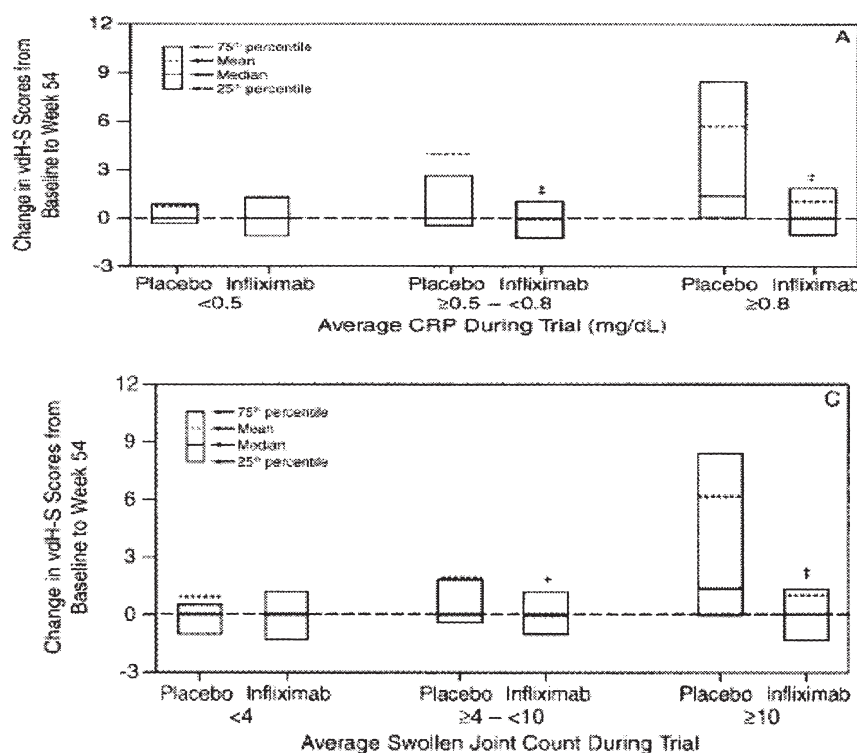


Fig. 2. Radiographic progression over 54 weeks by van der Heijde-S Sharp score in patients classified into tertiles according to average CRP levels or swollen joint counts during the ASPIRE trial.

ASPIRE: active-controlled study of patients receiving infliximab for the treatment of rheumatoid arthritis of early onset CRP; CRP: C-reactive protein.

(From: Smolen et al. Predictors of joint damage in patients with early rheumatoid arthritis treated with high-dose methotrexate without or with concomitant infliximab. Results from the ASPIRE trial. *Arthritis Rheum* 2006; 54: 702-10).

progression. This means, paradigmatically, 1) no swollen and tender joints (joint counts of “0”), 2) no increase in joint damage (change in radiographic assessment of “0” or even “-”), and 3) full functioning (Health Assessment Questionnaire [HAQ] = “0”). Since this ideal situation would reflect a “full” suppression of the inflammatory process, it would also be accompanied by a normal acute phase response (“normal” CRP and erythrocyte sedimentation rate [ESR]).

In the context of the various core set measures, this view of remission would likewise include pain and global assessments of close to “0” on a visual analogue scale. Importantly, many patients with RA have comorbidities that can confound measures of disease activity. Fibromyalgia may be accompanied by significant pain levels. Osteoarthritis as an independent process or as a result of RA joint damage may be associated with persistent tenderness or pain on motion, even if

inflammation is fully controlled. Even normal aging is associated with a decline of functional abilities as measured by the HAQ (59). Thus, care must be taken to distinguish signs and symptoms related to RA activity from those of other conditions.

Defining “remission” clinically

Having provided some evidence that remission rather than low disease activity should be our treatment goal today, the term “remission” must be clarified in greater detail. A variety of criteria and definitions of remission in RA are in use at this time (Table I). These criteria may be based on categorical means (54, 60) or composite indices (61-65). Sustained remission is required to fulfill ACR (≥ 2 months) and FDA (≥ 6 months) remission criteria. Moreover, the FDA requires maintenance of this state for ≥ 6 months while not taking any antirheumatic therapy. Is this truly a reasonable demand?

The FDA requirements differ consider-

ably from some definitions of remission in oncology, which may be defined as “a temporary abatement of the symptoms of a disease” (66, 67) or “complete...disappearance of the symptoms of cancer following treatment” (68). Moreover, the National Institutes of Health (NIH) have stated that “remission means to be temporarily without symptoms but not necessarily free of disease” and that frequently “the patient is asymptomatic but continues on chemotherapy” (66). Perhaps it is preferable to define separately the persistence of remission rather than to require specific time frames for a definition of remission. Remission in these definitions may not require the absence of therapy. Why should remission in RA require that state without therapy? Considerations of the underlying pathogenesis and patient outcomes rather than semantics might be better guidelines to definitions of remission.

While malignant diseases involve transformation of cells and growth and dissemination of such cells, RA involves a dysregulation of normal cellular and molecular events rather than resulting from abnormal cells or proteins. This abnormality may be persistent and, consequently, may require persistent treatment as has been indicated by an increased flare rate in patients who stopped treatment during clinical remission (69, 70). Thus, there is currently no reason to consider remission without therapy as a primary aim – this issue can be addressed in years to come. Rather, at present, we need to address the stringency of our definitions of remission.

Joint swelling and an increase in acute phase reactants are the most direct consequences of the inflammatory process. Therefore, these variables should be controlled as completely as possible to designate a state of remission – a threshold of 1 swollen and/or tender joint might be acceptable (or even too much). However, the ACR and, consequently also, the FDA remission criteria, by virtue of requiring meeting only 5 of 6 variables, do allow for the possibility of many swollen (or tender) joints to be present. Likewise, in contrast to the Simplified Disease Activity

Table I. Remission criteria.

Type	Name	Components/Formula	Requirements	Time	Extras
<i>Using categorical means</i>					
	ACR criteria (Pinals); Modified ACR criteria	No fatigue (only used for ACR, not modified ACR criteria)	5 of 6 for ACR criteria 4 of 5 for modified ACR criteria	2 months	
		No joint pain by history No joint tenderness or pain on motion No soft tissue swelling in joints or tendon sheaths No morning stiffness Westergren ESR < 30 mm/h in women, < 20 mm in men		2 months	
	FDA Guidelines for complete remission*	ACR criteria + radiographic arrest	Off therapy	6 months	
	FDA Guidelines for complete clinical response*	ACR criteria + radiographic arrest	On therapy	6 months	
<i>Using continuous numerical indices</i>					
	DAS	$0.54 \times \sqrt{\text{Ritchie}} + 0.065 \times \text{SJC44} + 0.33 \times \log_{\text{nat}}(\text{ESR}) + 0.0072 \times \text{GH}$	DAS < 1.6	Reported	
	DAS 28	$0.56 \times \sqrt{\text{TJC}} + 0.28 \times \sqrt{\text{SJC}} + 0.70 \times \log_{\text{nat}}(\text{ESR}) + 0.014 \times \text{GH}$	DAS28 < 2.6	Reported	DAS28 < 2.4 also proposed
	SDAI	SJC + TJC + PGA(cm) + TJC(cm) + CRP(mg/dL)	SDAI ≤ 3.3	Reported	
	CDAI	SJC + TJC + PGA(cm) + TJC(cm)	CDAI ≤ 2.8	Reported	

*Major clinical response: ACR70 response for ≥ 6 months (70% improvement in swollen and tender joints and in 3 of the following 5 variables: pain, patient global, evaluator global, ESR or CRP, HAQ).

ACR: American College of Rheumatology; CDAI: Clinical Disease Activity Index; CRP: C-reactive protein; DAS: Disease Activity Score; EGA: evaluator global assessment of disease activity; ESR: erythrocyte sedimentation rate; FDA: Food and Drug Administration; GH: global health by visual analogue scale (VAS); HAQ: Health Assessment Questionnaire; lognat: natural logarithm; PGA: patient global assessment of disease activity; Ritchie: Ritchie articular index; SDAI: Simplified Disease Activity Index; SJC: 28 swollen joint count; SJC44: 44 swollen joint count; TJC: 28 tender joint count.

Index (SDAI) and Clinical Disease Activity Index (CDAI) criteria, patients who meet DAS and DAS28 remission can have as many as 10 swollen joints (63, 71, 72). Thus, further clarification of criteria or definition of remission is required. The SDAI and CDAI criteria appear to be the most stringent, as they require the fewest abnormalities for most variables, at a level that is in accordance or even below that tolerated by a majority of surveyed rheumatologists (73, 74).

Structural damage, functional disability, and continuation of therapy in remission

A question remains as to whether both clinical and structural variables should be included in criteria for remission. Clearly, we wish to eradicate signs and symptoms *as well as* progression of joint damage. However, as noted above, abolition of signs and symptoms of inflammation will usually be accompanied or closely followed by a

halt in radiographic progression. Nevertheless, there may be agents that interfere with joint destruction while not reducing the inflammatory response (75-78). Such agents, by virtue of preventing joint damage, may reverse RA from a destructive to a non-destructive arthritis; pain and swelling could then be approached by different means. Importantly, however, just as a need exists for an optimal definition of clinical remission that has content, criterion, and face validity, no definition of “remission” of joint damage is currently available. Is it a change to zero, a change below the smallest detectable difference, which may be quite considerable, or other criterion (79)?

These considerations suggest that there may be advantages to separate clinical and structural remission criteria. Clinical remission may be defined in a way to specify that no or only minimal evidence of the inflammatory response is present. Clinical remission could be both a temporary phenomenon, indicating

the potential of a given agent to induce this state, and/or a longer-term phenomenon, the duration of which may be specified, for example, 2 months, 6 months, or more. Structural remission may require a halt of radiographic changes over at least a minimal time frame, for example, 6 or 12 months.

As noted above, remission may also be defined with regard to whether or not patients continue to take therapy. At present, achieving remission irrespective of treatment continuation is the optimal therapeutic goal. The ultimate aim, remission without therapy, might then be specially labeled, since this situation would portend a prospect for “cure”. The caveats in this respect, namely the risk of flares and the need for long-term observation, have been addressed before.

Finally, functional status is the facet of disease most important to individual patients and society and, therefore, must be addressed in regard to remission. Importantly, however, “functional”

remission may require special considerations given irreversible consequences of cumulative damage (57). This subject will be dealt with in a separate discussion (73). A state of clinical remission should not only prevent further progression of joint damage but also reduce functional disability to a minimal level (57).

Recent reports indicate that clinical remission according to rigorous criteria may be met over long periods. In one clinical trial, 45% of patients achieved remission according to the stringent SDAI criteria at least once over the period of 2 years, and in almost one third of those patients for prolonged periods of time (80). Moreover, sustained remission, by stringent criteria, was likewise seen in clinical practice in about 15% of patients (81). Thus, the potential for achieving remission is here today – it requires expansion, using more dynamic and intensive treatment strategies (82-84).

Final considerations

One major issue in consideration of remission is that we cannot predict response to therapy at present. As previously noted, surrogates of active disease, such as high levels of acute phase reactants, high joint counts, high values of composite scores, or functional measures, constitute predictive factors for development of severe, aggressive disease. In addition, high titer rheumatoid factor and anti-CCP autoantibodies are associated with erosive disease and poor outcomes (5, 43, 85-96). Thus, we have a reasonable capacity to identify RA patients who might have a poor prognosis. However, prediction of response to therapy (97, 98), especially predicting who might achieve remission, remain only marginal at this time. Remission may appear an overly ambitious goal with various impediments, such as insufficient responsiveness of the disease. However, remission is a realistic goal for many patients at this time. Better criteria and definitions will be of value to rheumatologists and their patients and hopefully will lead to increased levels of remission in the future.

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