
Partial control of Core Data Set measures and Disease Activity Score (DAS) measures of inflammation does not prevent long-term joint damage: Evidence from longitudinal observations over 5-20 years

T. Pincus¹, T. Sokka^{1,2}

¹Division of Rheumatology and Immunology, Department of Medicine, Vanderbilt University Medical Center, Nashville, Tennessee, USA; ²Department of Rheumatology, Jyväskylä Central Hospital, Jyväskylä, Finland.

Theodore Pincus, MD; Tuulikki Sokka, MD, PhD.

Please address correspondence and reprint requests to: Theodore Pincus, MD, Professor of Medicine, Division of Rheumatology and Immunology, Vanderbilt University School of Medicine, 203 Oxford House, Box 5, Nashville, TN 37232-4500, USA.

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ABSTRACT

Several reports concerning outcomes of rheumatoid arthritis (RA) document that measures of inflammatory activity [such as swollen joint count, tender joint count, and acute phase reactant, which are included in the Core Data Set or Disease Activity Score (DAS)] may be stable or improved over 5-10 years, while measures of damage (such as radiographic progression and joint deformity) may show contemporaneous progression. Therefore, studies which include only improvement in measures of disease activity cannot document overall improvement in patient status over 5-10 years. Studies designed to document favorable long-term effects of therapy in RA must include, at baseline and later follow-up evaluation, measures of damage, such as a radiograph, joint deformity, comorbidities, and extra-articular disease, in addition to measures of disease activity. The one prognostic measure which appears to detect both activity and damage in RA over short, intermediate, and long periods is a disability score on a patient questionnaire, which might be used by all rheumatologists at all patient encounters. The need for inclusion of accurate and relevant measures of damage appears of particular importance in the current era of biological drugs, in which the slowing or prevention of damage now appears a realistic goal in most patients with RA.

Introduction

A single measure is not available to serve as a “gold standard” to assess clinical status in patients with rheumatoid arthritis (RA). Therefore, the American College of Rheumatology (ACR) and European League Against Rheumatism (EULAR) have developed an index of 7

“Core Data Set” measures to assess outcomes in clinical trials of patients with RA (1-4). The ACR/EULAR Core Data Set includes a tender joint count, swollen joint count, physician global assessment, erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP), functional disability using a questionnaire such as the health assessment questionnaire (HAQ), pain, and patient global assessment, as well as a radiograph for studies of one year or longer. Another widely used index in studies of patients with RA is the disease activity index (DAI) (5-7). The DAI includes a tender joint count, swollen joint count, ESR or CRP, and patient assessment of general health. Responses to therapy are assessed as low, moderate and high disease activity at baseline and follow-up (5-7).

The measures included in the Core Data Set and DAI are sensitive to change over a period of weeks to months (Table I). They may be classified broadly as short-term measures primarily of disease activity - joint swelling, joint tenderness and ESR or CRP, or measures of activity and damage - functional disability, pain, and patient and physician and global assessment.

These activity measures may be contrasted to long-term measures primarily of joint damage and clinical outcomes, such as joint deformity, radiographic damage, work disability, joint replacement surgery, and premature mortality (8), which develop over years to decades. Only one measure of damage, radiographic score, is included in the Core Data Set, and only in clinical trials conducted over one year or longer (Table I). No other measures of damage or long-term outcomes are included in most clinical trials, although the physician's global assessment, and patient

Table I. Core Data Set Measures of Disease ACTIVITY and Joint DAMAGE in rheumatoid arthritis.

Type of measure	Disease ACTIVITY measures included in most clinical trials	Measures of disease ACTIVITY and/or joint DAMAGE included in most clinical trials	Joint DAMAGE markers and long-term OUTCOMES not included in most clinical trials
Joint count	Tenderness or pain on motion (C) Swelling (C)	Joint limited motion	Joint destruction Joint deformity Joint replacement surgery
Laboratory	Acute phase reactant - ESR or CRP (C)		
Radiographic			Radiographic damage (C*)
Patient questionnaire		Pain (C) Functional disability (C)	Joint replacement surgery Functional disability (C)
Global		ARA functional class Physician assessment of global status (C) Patient assessment of global status (C)	Work disability Comorbid diseases Extra-articular disease Premature mortality

(C) = Included in Core Data Set (2-4) recommended for use in clinical trials; * = Included in Core Data Set for studies longer than one year. ESR = erythrocyte sedimentation rate; CRP = C reactive protein.

assessment of functional disability, pain and global status are sensitive to both activity and damage.

Improvement of at least 20% in both tender and swollen joint counts, as well as three of the five additional measures (not including a radiograph), known as "ACR 20," is designated as ACR preliminary definition of improvement (9). Higher thresholds for improvement such as "ACR 50," and "ACR 70" have also been described (10). The ACR 20 response has been found to distinguish active DMARD therapy from placebo as effectively as ACR 50 and ACR 70 responses (9, 10).

It is not known to what extent suppression of inflammation at a level of 20% or 50%, i.e., ACR20 or ACR50, or to a low or moderate level in the DAS, will slow future damage. The question concerning how much suppression of inflammation is required to prevent long-term damage and poor outcomes was not an issue prior to the 1980s, as traditional DMARDs led to control at an ACR20 level in only a minority of patients, and even smaller minorities at ACR50 or ACR70. By contrast, powerful newer DMARDs such as methotrexate (11-13), cyclosporine A (14), leflunomide (15, 16), etanercept (17, 18), infliximab (19, 20), and anakinra (21,

22) appear to have the capacity to induce ACR 50 responses as well as to slow or prevent joint and bone damage and poor outcomes in many patients if used early in disease. However, aggressive therapy does increase the risk of adverse events and costs, albeit reducing the risk of "adverse effects" of RA itself (23). Therefore, it appears of considerable interest at this time to analyze the appropriate balance – to what extent inflammation must be controlled to slow or prevent long-term joint damage and poor outcomes.

Several reports have appeared over the

last two decades which document that Core Data Set or DAS measures of inflammatory activity may be stable or improved over periods of 5-10 years while measures of damage may progress (Table II). These reports indicate that damage, in the form of radiographic progression and/or increased functional disability, is common even when inflammatory indicators are improved, sometimes substantially. In this essay we summarize some of these reports. The essay is not regarded as a comprehensive summary, but does call attention to a problem which appears important in contemporary management of patients with RA.

Reports concerning improvement in inflammatory activity with contemporaneous progression of damage over 5-10 years

One of the earliest studies which called attention to the phenomenon of improved measures of activity and contemporaneous progression of damage was reported by Scott in 1984 (24). It was recognized that improvements in ESR over one year were seen in 75% of patients, while radiographic progression was also seen in almost all of the same patients (Fig. 1). Further reports by Dr. Scott indicated similar data over longer periods.

Another study reported in 1984 indicated that morning stiffness was improved in half of patients over nine years, while more than 90% of patients experienced progression of functional disa-

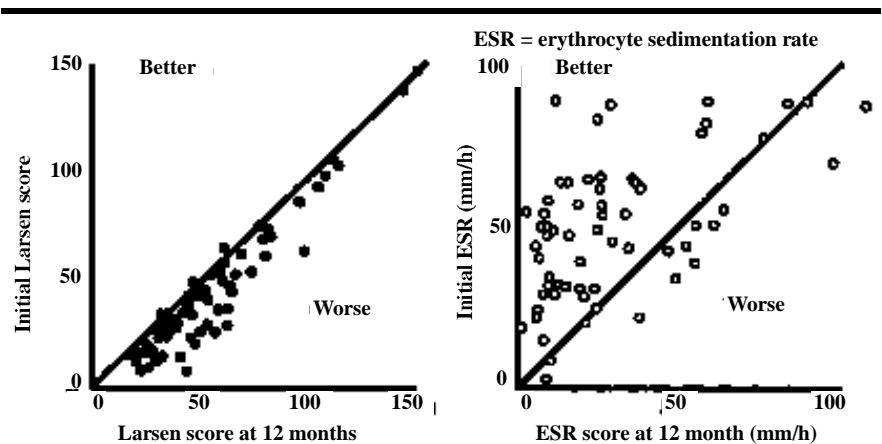


Fig. 1. Progression of radiological changes in RA. Reproduced from Scott D. et al. *Ann Rheum Dis* 1984; 43; 8-17, with permission from the BMJ publishing group.

Table II. Changes over 5-10 years in measures of Core Data Set measures of inflammatory activity and activity and damage, and measures of joint damage and outcomes in patients with rheumatoid arthritis.

Study, Year	Period of observation	Reference No.	Measures of inflammatory activity			Measures of inflammatory activity and joint damage		Measures of joint damage
			ESR	Joint Swelling	Joint tenderness	Functional capacity	Pain	Radiographic damage
Scott, 1984	10 years	(24)	Better	NA	NA	Better (Steinbrocker)	NA	Worse
Pincus, 1984	9 years	(25)	NA	NA	NA	Worse (Early questionnaire)	NA	NA
Hawley and Wolfe, 1992	10 years	(26)	Same	NA	Better	Worse (HAQ)	NA	NA
Egsmose, 1995	5 years: EARLY (E) DELAYED (D)	(28)	NA	E: Better D: Same	E: Better D: Better	E: Better D: Same	E: Better D: Same	E: Worse D: Worse
Fex, 1996	5 years	(29)	Same	NA	Better	Same (HAQ)	Same	Worse
Mulherin, 1996	6 years	(30)	Better	NA	Better	NA	Better	Worse
Callahan, 1997	5 years	(31)	Same	Better	Better	Same (MHAQ)	Better	Worse
Leirisalo-Repo, 1999	13 years	(32)	NA	Same	Better	Worse (HAQ)	Worse	Worse
Graudal, 2000	4-22 years	(33)	Better	Better	Better	NA	NA	Worse
Welsing, 2001	9 years	(34)	Same	Same	Same	Worse	NA	Worse

NA = not available; HAQ = Health assessment questionnaire; MHAQ = Modified health assessment questionnaire.

bility (25). Furthermore, grip strength and walking time also showed disease progression in these patients.

Hawley and Wolfe (26) found that joint tenderness, morning stiffness, ESR, hemoglobin, grip strength and global severity were improved, unchanged or slightly worse in 157 patients over two, five and ten years. However, HAQ disability scores showed substantial worsening, two and a half fold greater than

the effect size of any other clinical measure studied. In other reports, which included many of the same patients, there was also evidence of radiographic progression in most patients (27).

Egsmose *et al.* (28) reported improvement in measures of disease activity over 5 years, including the number of swollen joints, morning stiffness, Ritchie Articular Index for joint tender-

ness, and grip strength, with contemporaneous radiographic progression in a cohort of 75 patients who had RA of two years or less duration at baseline. Improvement in activity measures was lesser in patients in whom institution of anti-rheumatic therapy had been delayed compared to patients who received early treatment with Auranofin. Furthermore, radiographic progression was significantly less in patients who had received early treatment. HAQ disability scores were improved over five years in patients treated with early DMARDs, but were similar to baseline in those who had delayed DMARD therapy (28).

Fex *et al.* (29) examined changes over 5 years in 113 patients who had a mean duration of 11.4 months at baseline and were monitored prospectively for five years. Values for morning stiffness, pain, general health, Ritchie index, HAQ scores, ESR and hemoglobin were similar or improved from baseline after five years of observation. However, radiographic scores indicated significant progression in these patients.

Mulherin *et al.* (30) reported significant improvement in grip strength,

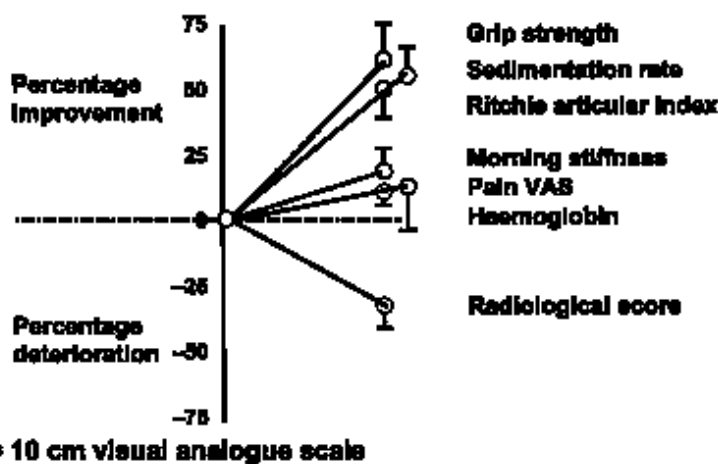


Fig. 2. Measures of activity and damage in patients with RA over 5 years.

Reproduced from Mulherin D. *et al. Br J Rheumatol* 1996; 35:1263-8 with the permission of the British Society of Rheumatology.

Changes in Measures in 100 Patients with Rheumatoid Arthritis Over 5 Years Determined by Effect Sizes

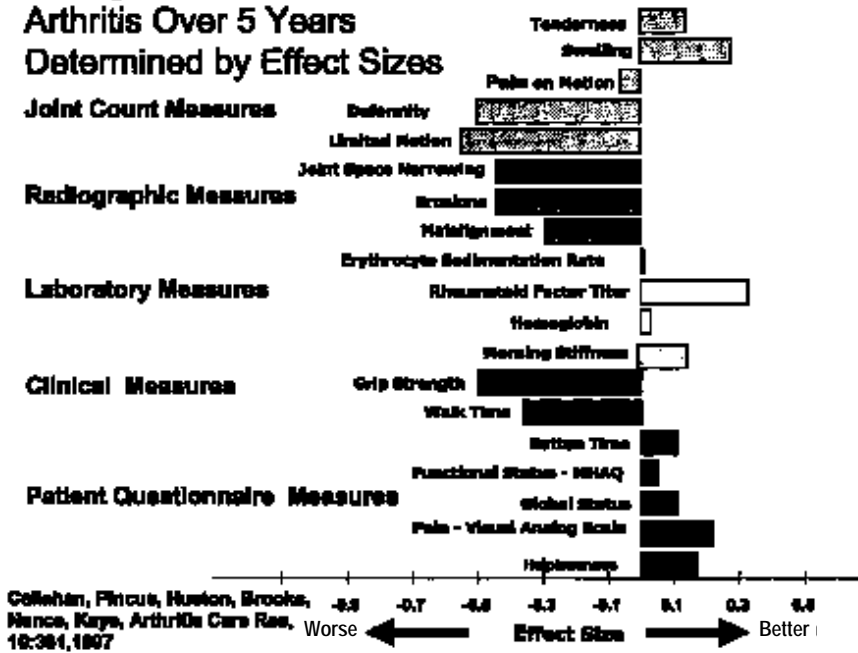


Fig. 3. Changes in measures in 100 patients with rheumatoid arthritis over 5 years determined by effect sizes (Reproduced with permission from John Wiley & Sons. ©1997 American College of Rheumatology).

Ritchie articular index, hemoglobin and ESR, and non-significant improvement in pain scores and morning stiffness, while there was significant progression of radiographic changes in 40 patients over six years (Fig. 2). They pointed out that “articular erosion continues in RA despite clinical improvement, and is accelerated in those with evidence of continuing synovial inflammation reflected in clinical and laboratory measures of disease activity.” Callahan *et al.* (31) reported that joint tenderness, swelling, ESR, hemoglobin, morning stiffness, pain, and modified health assessment questionnaire (MHAQ) results were unchanged or improved over five years in 100 patients, while scores for radiographic damage as well as joint deformity, grip strength and walking time indicated disease progression (Fig. 3). The effect size of scores for joint swelling indicated improvement at 20% level, suggesting that this level of improvement may not necessarily be associated with prevention of radiographic progression. Leirisalo-Repo and colleagues (32) reported stable or improved swollen joint counts and tender joint counts, with

progression of Larsen radiographic scores, 2-13 years after baseline in 145 patients with RA who had disease for only a mean of 7.9 months at baseline. Furthermore, HAQ scores were improved at years 2 and 3, possibly reflecting improvement in the component of the HAQ sensitive to disease activity, but showed evidence of progressive disability after 8 years. Graudal *et al.* (33) found improvement in joint swelling, ESR, and hemoglobin, while radiographic progression in most of 112 patients with RA over 4-22 years. There was some relation between the severity of joint swelling, high ESR and low hemoglobin with subsequent radiographic progression, while the association of joint tenderness with radiographic progression was weak. Radiographic damage was greater in patients with greater inflammatory activity over time. Welsing *et al.* (34) found that disease activity according to the DAS remained more or less the same over 9 years in patients with early RA. However, functional capacity worsened after an initial improvement, and radiographic scores worsened over the 9 year observation period.

Discussion

Although the extent of improvement in measures of disease activity in the above studies cannot be computed accurately without the primary data, some of the data suggest changes at a level of 20% or even 50%, while further damage is apparent. Perhaps there is slowing, rather than prevention, of damage, relative to the “natural history” of RA, which cannot be studied in the absence of treatment over the last 20 years because of obvious ethical considerations (35). DMARD therapy does slow radiographic progression (36). However, evidence of long-term radiographic progression and worsening HAQ scores while measures of inflammation were improved remains disappointing. In theory, the goal of treatment of any disease is a “cure” or “remission.” Indeed, criteria for remission in RA have been established (37). However, these criteria are rarely met in clinical trials or clinical care. A “cure” is not yet possible in diseases characterized by dysregulation of normal host control mechanisms, such as RA, hypertension, diabetes, and most other chronic non-infectious disease, as the mechanisms of dysregulation remain poorly understood (38). However, it is well-established that “tight control” of the consequences of dysregulation through long-term (lifetime) therapy results in lesser vascular damage in diabetes (39) increased survival in hypertension (40), and improved survival in RA (12, 13). While the goal of controlling inflammation to prevent long-term damage seems appropriate for patients with RA, a 20%, 50%, or even 70% level may not be adequate. We have suggested that favorable values of quantitative measures known to predict mortality, such as good functional status on a health assessment questionnaire (HAQ) or a modified version, might serve as possible “target values” for therapeutic interventions, as in management of diabetes and hypertension (41), analogous to low DAS scores. Such target values could serve as alternatives to remission criteria or levels of changes in the ACR Core Data Set index to identify a favorable response to therapy (41). In addition to evidence that partial con-

trol of Core Data Set and DAS measures may be associated with progression of damage in RA, there exist some intrinsic problems with these measures which may compromise their capacity to assess patients with RA. Joint count measures of swelling and tenderness may be normal in patients with histologic synovitis (42-44), and/or abnormal ultrasound and MRI scan results. Furthermore, in a study of leflunomide compared to methotrexate and placebo, measures of swollen and tender joints were improved in patients who received placebo, while patient self-report measures of pain, functional disability on the HAQ or modified HAQ (MHAQ) and CRP did not improve significantly (16). Indeed, the relative efficiencies of patient measures were greater than those for joint tenderness and swelling (45), perhaps suggesting that the investigator's desire to influence disease activity may actually influence measurement.

Problems with other core Data Set measures are also seen. A normal ESR is seen in up to 40% of patients at their first visit (46), and the ESR tends to be stable over the long-term course of RA (47). Global scores are often unchanged despite significant disease progression (48, 49).

The HAQ and radiographic scores appear to be the only effective core data set markers to document long-term progression of RA. It is not known to what extent suppression of inflammation at a level of 20% or 50%, or reduction of the DAS to moderate or low levels will suppress slow future damage.

Conclusions and suggestions for possible improvement in assessment of RA

The data presented here raise a concern that partial control of inflammation according to measures of inflammatory activity in a short-term clinical trial may not be translated into optimal or even clinically adequate long-term clinical effectiveness to prevent joint damage. Therefore, ACR 20, 50 or 70 responses, may be reassessed as more powerful DMARDs are used earlier in disease and in combination (50). The ultimate goal of treatment at this time

might be complete control of inflammatory activity toward remission to prevent long-term structural damage over long-term.

Measures of damage, such as joint deformity, radiographic damage, and comorbidities, or markers which identify either activity and/or damage such as grip strength, walk time, button test, extra-articular disease (51), and functional status self-report questionnaire (8), are required to document severe long-term outcomes in RA. Measures of damage, other than patient questionnaire responses, are insensitive for clinical trials and other short-term studies. Furthermore, they often are normal and therefore not recorded in inception cohort studies. If long-term studies of RA include only measures of activity, outcomes will appear more favorable than if measures of damage are also included.

Some implications of these observations might include:

1. Studies designed to analyze the long-term course in RA should include baseline measures of both activity and damage, such as a radiograph, joint deformity, comorbidities, and extra-articular disease. These measures should be recorded even if all damage markers are normal at baseline. A pragmatic method involving four pages to record all relevant baseline data has been termed a Standard Protocol to Assess Rheumatoid Arthritis (SPERA) (52).
2. Documentation of improvement in measures of activity only may not necessarily indicate overall improvement in patient status over 5-10 years. A conclusion that the patient is better over periods after a baseline assessment requires evidence that progression of damage has been slowed or prevented.
3. The one prognostic measure which appears to detect both activity and damage in RA over short, intermediate, and long periods is the HAQ disability score, or similar patient questionnaire score, which might be used by all rheumatologists at all patient encounters (53, 54).

Rheumatologists and health professionals can better serve people with RA

through improved understanding of the uses and limitations of different measures of activity and damage. Such understanding will continue to promote improving outcomes for most people with RA.

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