Links Between Radiological Change, Disability, and Pathology in Rheumatoid Arthritis

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ABSTRACT. The relationship between the development of radiographic joint destruction in rheumatoid arthritis and its longterm consequences for the patient is not well understood. Two objectives for further research have been identified: elucidating this relationship and relating pathological processes to the features visible on radiographs. Extrapolation from a proposed model suggests that if radiographic progression is suppressed early in the disease, it might take many years before the benefit can be clearly appreciated against a background of variation within individual patients. Two approaches have recently been brought to bear on this issue, including a detailed modeling of medium term observations from a single dataset and a review of a large number of published studies. There are a number of reservations about the notion of a minimum clinically important change, but one possibility for defining such a change for radiographs is in relation to longterm functional outcome. (J Rheumatol 2001;28:881–6)

Key Indexing Terms:
RADIOGRAPHY RHEUMATOID ARTHRITIS OUTCOME AND PROCESS ASSESSMENT

In rheumatoid arthritis (RA), damage on radiographs is considered an important outcome measure. There are a variety of methods of scoring radiographs, none of which is ideal. At OMERACT IV there was an imaging module that addressed the strength and weaknesses of different scoring methods[1]. It was recognized that the relationship between the development of radiographic joint destruction in RA and its longterm consequences for the patient is not well understood. Two objectives for further research were identified: elucidating this relationship and relating pathological processes to the features visible on radiographs. This paper focuses on progress made in these two areas from analysis of clinical study findings.

RELATION BETWEEN RADIOGRAPHIC DAMAGE AND LONGTERM FUNCTIONAL OUTCOME

It may be that, in the long term, joint destruction visible on radiographs will result in functional loss and noninflammatory, endstage joint pain. There has been a notion that, in clinical practice, patients may have less inflammation (and less variation in inflammatory signs and symptoms) as their disease duration extends. Radiographic destruction correlates only moderately with late stage functional loss in cross sectional studies[2]. It is possible that other structural factors (such as loosening of the joint capsule and subsequent subluxation) may also contribute to longer-term functional change. Nevertheless, it seems intrinsically sensible to link radiographic progression to functional decline. One view of this relationship is encapsulated in Figure 1, where the effect of joint destruction comes to dominate disability late in disease, while inflammatory joint symptoms are the main determinant of disability early in disease.

Based on presentations and discussions at OMERACT IV, and at a subsequent (but unreported) imaging group workshop held at the American College of Rheumatology Meeting in 1998, a number of predictions were identified that flowed from this model. These included the suggestion that the correlation between disability and inflammation will initially be high but will decrease with increasing disease duration. Second, fluctuations in disability will be less in long-standing disease. Third, the correlation between radiographic damage and disability will increase with increasing disease duration.

Extrapolation from the proposed model suggests that if radiographic progression is suppressed early in the disease, it might take many years before the benefit can be clearly appreciated against the background of variation within individual patients[3]. Two approaches have recently been brought to bear on this issue and are reviewed here. They are a detailed modeling of medium term observations from a single dataset[4] and a review of a large number of published studies[5].

EXTRAPOLATION FROM MEDIUM TERM OBSERVATIONS

The need for a very long term view makes it difficult to investigate the detailed consequences for disability of a reduction in radiographic change by using randomized controlled trials (RCT) of interventions that slow or even

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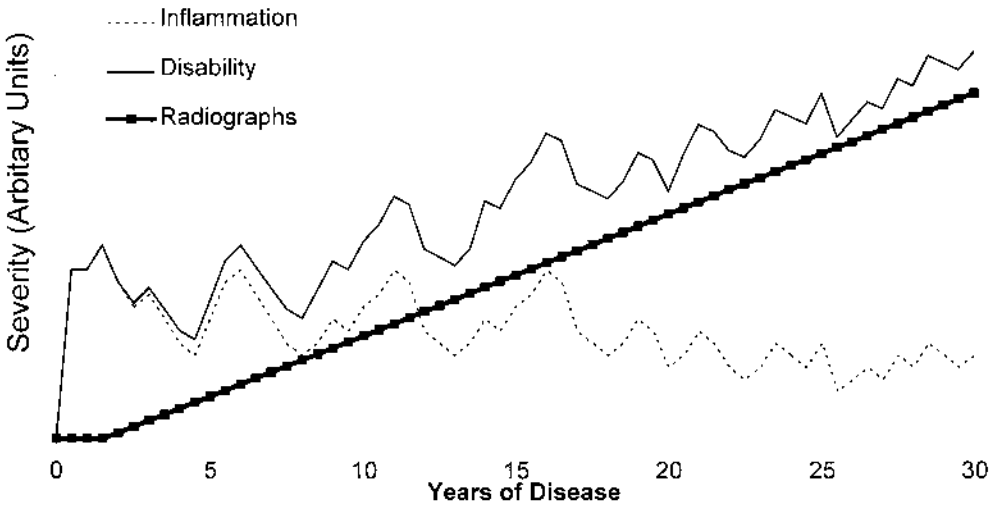

Figure 1. A previously published[3] schematic of "progression" in RA. Initially inflammation and subsequently radiographic progression are the dominant contributors to disability in an individual patient.

stop radiographic progression. Further, recruitment of patients for RCT is often determined by the severity of their disease, which would add a systematic bias to patient selection and might affect the subsequent interpretation of any longer term followup results.

Data from an observational study[4] that measured both joint damage and functional outcome at times that were unrelated to clinical status have been analyzed as one attempt to provide a means of testing the hypothetical model previously published[3] and establishing the possible variables of the relationship. Patients were taking part in a study of different methods of outpatient hospital followup for rheumatoid arthritis[4] and entry to the study was not determined by current disease status. Hand radiographs were taken at 0 and 24 months and clinical status was measured every 3 months by postal questionnaire, including pain, patient assessment of disease activity, and physical function (using the Health Assessment Questionnaire[6,7]).

Individual patient variations in the clinical variables were compared to each patient's disease duration, and examples from 10 illustrative patients of different disease duration are shown in Figures 2–4. Most patients show substantial variation in both pain and disease activity irrespective of the patient's disease duration. Figure 5 shows the extent of variation in reported disease activity for all 105 patients with adequate data. When the standard deviations for disease activity for each patient were calculated, they were not correlated with disease duration ($r^2 = 0.0008$). Pain scores

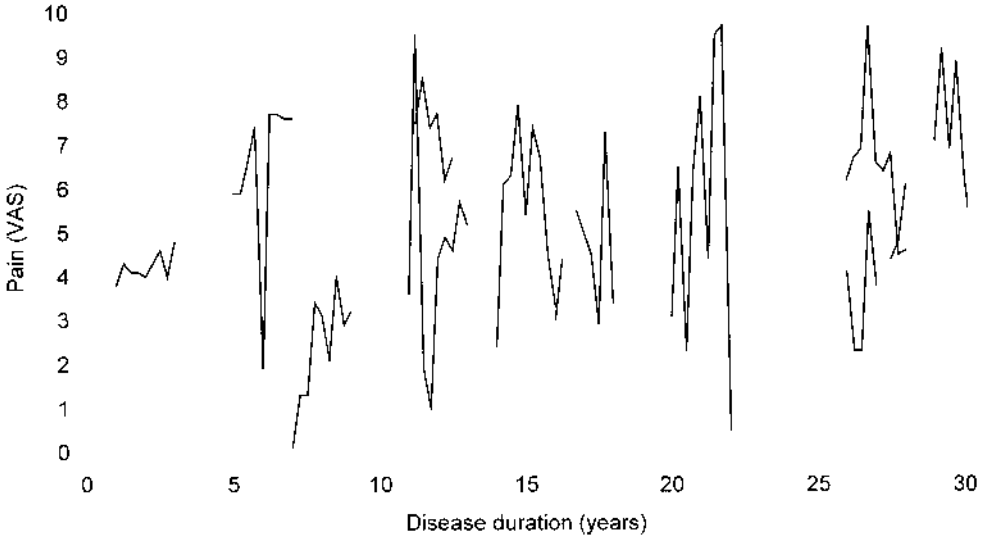

Figure 2. Pain measured every 3 months in 14 illustrative patients with RA. Each line represents the values from a single patient, plotted against disease duration for that patient at the time the assessments were performed.

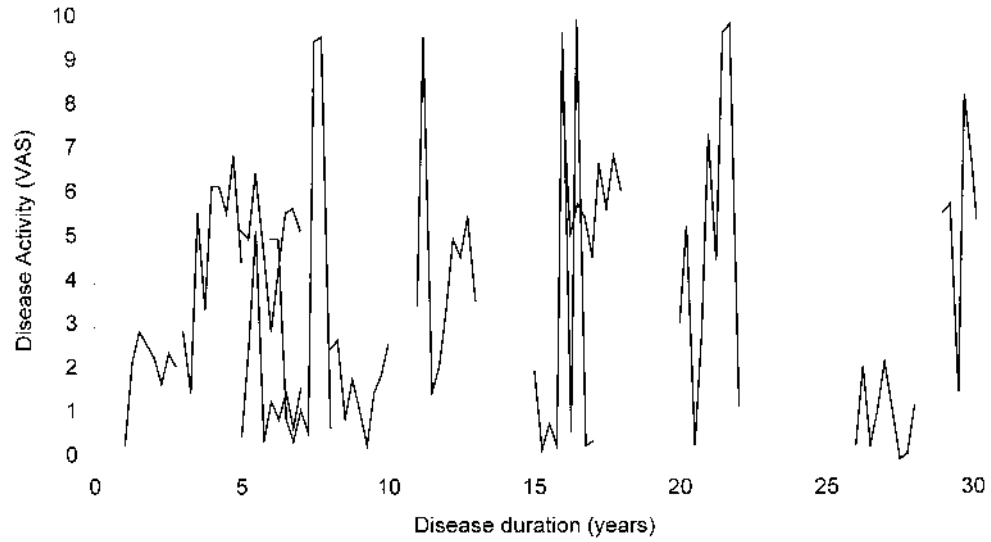

Figure 3. Disease activity measured every 3 months in 14 illustrative patients with RA. Each line represents the values from a single patient, plotted against disease duration for that patient at the time the assessments were performed.

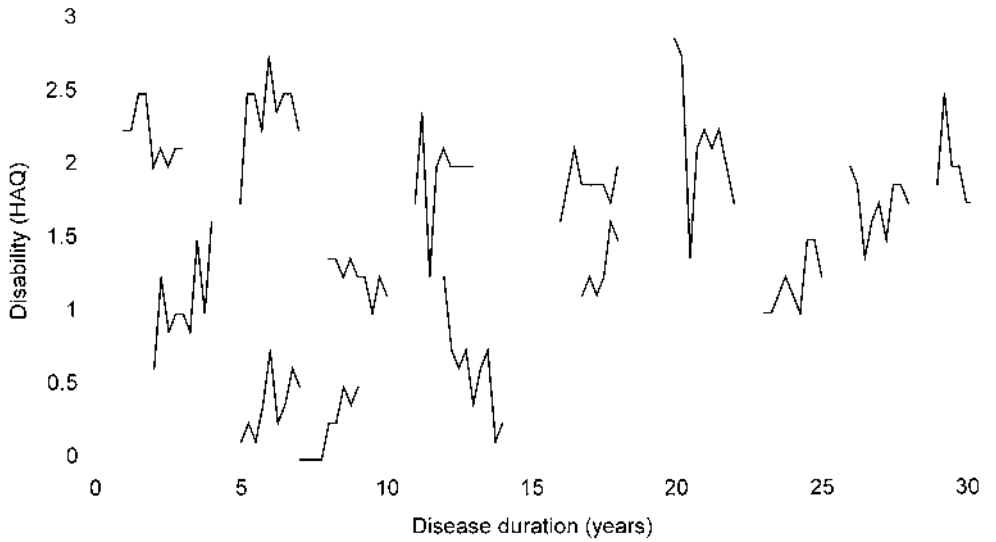

Figure 4. Disability (HAQ) measured every 3 months in 14 illustrative patients with RA. Each line represents the values from a single patient, plotted against disease duration for that patient at the time the assessments were performed.

were also highly variable and were not related to disease duration. The model was therefore modified and constrained to provide the within-patient variance revealed by this analysis.

The progression of radiographic damage was modeled by linear regression applied to the Larsen scores. The extent of radiological damage was related to disease duration ($r = 0.518$). Over a disease duration of 0 to 30 years, the mean Larsen score increased by 133%. Mean disability increased by only 25% over the same time period. However, disability was more closely correlated with disease activity ($r = 0.588$) than with radiographic damage ($r = 0.312$) ($p = 0.014$).

The observed variations in pain, disability, and radiographic progression have been incorporated into a revised model, which captures the variations actually measured in practice. This revised model is shown in Figure 6. As initially anticipated[3], radiographic damage tends to develop a gradually closer relationship with disability as the severity of damage increases. However, the persistent variation in disease activity remains the major determinant of disability, both late in the disease and in patients with substantial radiographic change.

The proposed relationship between the measures of inflammatory disease, radiographic progression, and

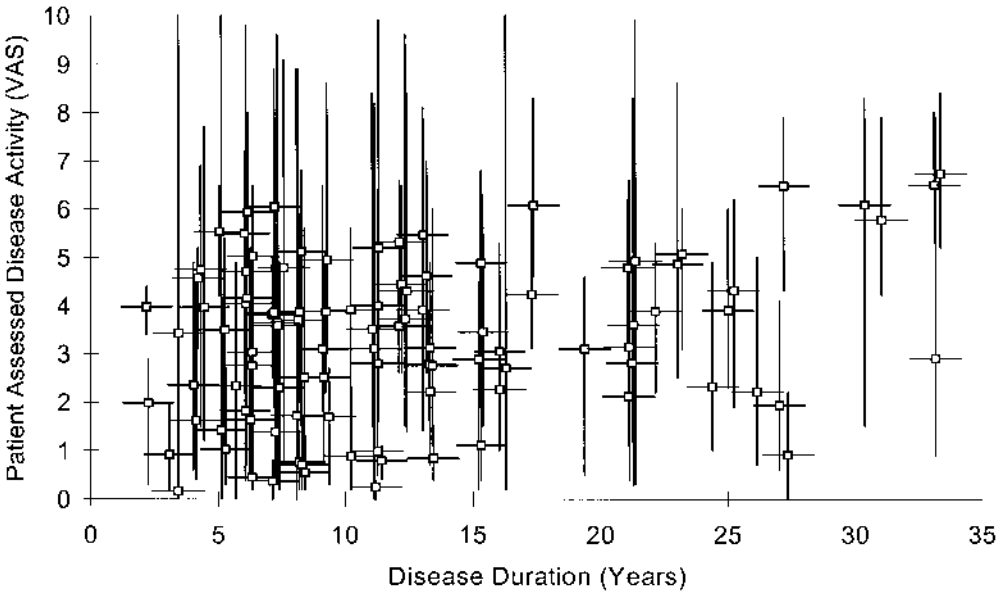

Figure 5. Reported disease activity and disease duration in 105 patients. Each point represents the mean disease activity and mean disease duration for one patient. Vertical lines show the range of disease activity reported. Horizontal lines show the range of disease duration covered by the reports (some patients have been slightly displaced to allow easier viewing).

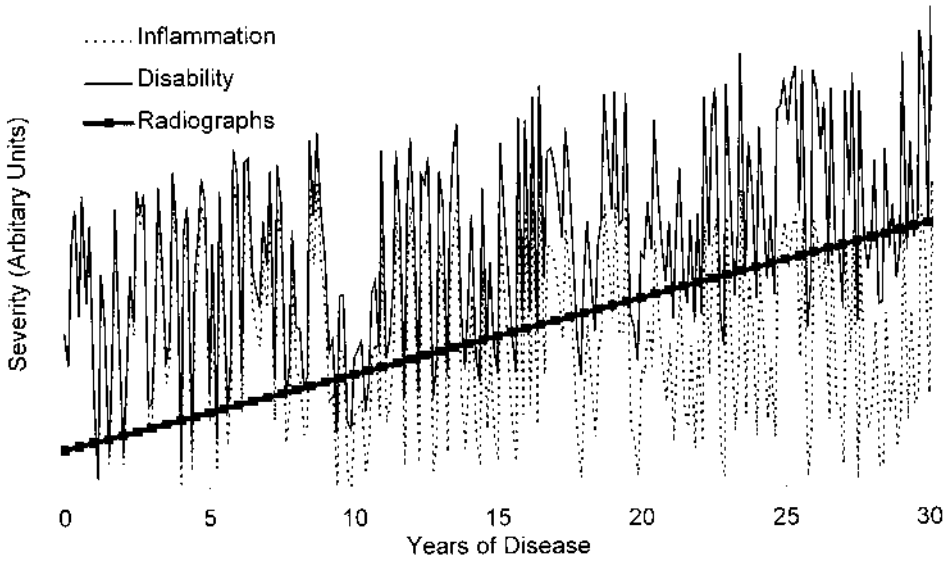

Figure 6. A revised schematic of "progression" in RA[4] incorporating the data from the present analysis. Inflammation and radiographic progression contribute to the development of disability in an individual patient. Variability in inflammation and disability are much greater than previously postulated.

longterm disability is based on the assumption that radiographic progression is about linear over about 30 years. A linear progression rate for radiographic damage is not essential to the concept embodied in the model, and if different relationships emerge as more data accumulate about patterns of development of joint destruction, these can be incorporated. The essential concept is that the accumulation of radiographic damage and its contribution to disability is slow relative to the short term changes in disability caused by variations in inflammation.

LONGTERM OBSERVATIONAL STUDIES

Recently Scott and colleagues published a valuable analysis of longterm radiographic and functional outcome[5]. This review included 25 published reports (identified from a search of Medline and Current Contents databases) that

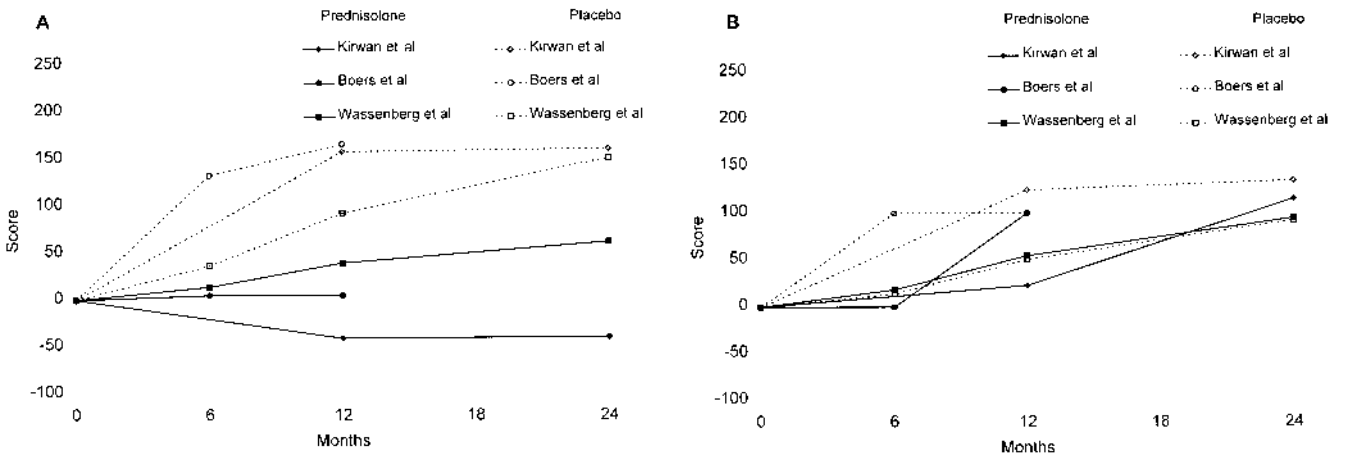

Figure 7. Progression of (A) erosions and (B) joint space narrowing in patients treated with prednisolone.

enabled the link between the two to be explored. From their analysis, the authors concluded that joint damage progressed constantly over the first 20 years of disease and accounted for about 25% of disability in established RA. In early RA (< 5 yrs) there was no correlation. Between 5 and 8 years of disease duration the correlation was r = 0.3 to 0.5, and after 8 years of disease duration the correlation was r = 0.3 to 0.7. However, while the link between joint damage and disability was strongest in later years, there remained very large short term variations in the disability of individual patients throughout the course of the disease.

These findings, based on an overview of published studies undertaken in a variety of settings, are almost identical to the results from the detailed modeling of a single dataset presented above. They support the model of disease progression shown in Figure 6. The predictions that emerged from the first version of the model (Figure 1) are proven to be only partially correct. The correlation between inflammation and disability remains high, and fluctuations in disability remain large, throughout the course of the disease. However, radiographic damage does develop an increasing correlation with disability as the disease progresses.

USING THESE DATA TO CONSIDER A MINIMUM CLINICALLY IMPORTANT CHANGE IN RADIOGRAPHIC SCORE

There are a number of reservations about the notion of a minimum clinically important change, but one possibility for defining such a change for radiographs is in relation to longterm functional outcome[8]. These data, derived from two different approaches to exploring that relationship, lead to broadly similar conclusions. They are that joint damage as revealed by radiographic change (as currently measured) probably contributes to the development of increasing disability, but its contribution will never be as great as that related to inflammatory change or other forms of functional loss. Further analysis of the slope of the regression equations and the extent of variation between patients will provide an indication of how much change is measurable within groups of patients of a given size and over a given time period.

Relating this to the variation in disability within patients will provide an indication of what longterm reduction in disability might result from a specified reduction in the rate of radiographic progression. This information can then be related back to published trials with substantial[9-12] or modest[13-15] reductions in radiographic progression to discover whether these reductions will have measurable effects on functional outcome in the long term. In this way, a "data driven" description can be derived of how much benefit will be achieved by treatments that slow radiological progression. In the face of the large between-patient variations in rates of disease progression, and the relatively loose relationship between radiographic damage and disability, it seems unlikely that the contribution of progressive joint damage to increasing disability will ever be easily detectable within individual patients. Even using the less variable model shown in Figure 1, it has been estimated that up to 10 years' observation might be required to do so[3]. In order to detect it and to assess whether intervention may cause changes, studies of groups of patients large enough to provide sufficient power will be required.

RELATION BETWEEN RADIOGRAPHIC DAMAGE AND PATHOLOGICAL PROCESSES

Based on consideration of the pathology of RA, it has been suggested that two aspects of joint damage may behave differently in relation to treatment with glucocorticoids[3]. These are erosions, which represent destruction of juxtaarticular bone, and joint space narrowing, which represents generalized cartilage loss. There have been a number of recent therapeutic studies of the effects of glucocorticoids on radiographic progression of RA in which these two

aspects of joint damage have been measured separately. One has been published in full[9], a second is in abstract form[11], and the third is based on a reanalysis of radiographs from the ARC Low Dose Glucocorticoid study[16]. In all three, the progression of erosive destruction was halted by the use of prednisolone, while that of joint space narrowing was unaffected (Figure 7a and 7b). These findings reinforce the need to keep in mind the possibility that assumptions about clinical and investigative observations may change as a greater understanding of disease mechanisms is achieved[3].

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Papers presented at the Omeract 5 Conference, Toulouse, France, May 4–8, 2000:

Part 1: Minimal Clinically Important Differences

Part 2: Cost Effectiveness

Part 3: Imaging I. Radiography

Part 4: Imaging II. Magnetic Resonance Imaging; and Drug Safety

Part 4 will appear in the May issue of *The Journal*.