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CLINICAL IMPROVEMENT AND RADIOLOGICAL DETERIORATION IN RHEUMATOID ARTHRITIS: EVIDENCE THAT THE PATHOGENESIS OF SYNOVIAL INFLAMMATION AND ARTICULAR EROSION MAY DIFFER

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SUMMARY

The contrast between clinical improvement and radiological deterioration in rheumatoid arthritis (RA) is striking. We characterized this relationship using serial disease activity measures and radiographs of hands and feet in 40 RA patients observed over 6 yr. All disease activity measures improved, including grip strength, Ritchie index (RI), haemoglobin and erythrocyte sedimentation rate (ESR) (all $P < 0.0001$). In contrast, articular erosion increased ($P < 0.0001$). Radiological change during the study correlated with RI ($r = 0.49$), haemoglobin ($r = -0.56$) and ESR ($r = 0.53$). Radiological status at review also correlated with these variables ($r = 0.36$, -0.44 and 0.36, respectively). 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. Since many therapies in RA suppress inflammation, but not erosion, these findings suggest that the pathogenesis of articular erosion may differ from that of synovial inflammation.

KEY WORDS: Rheumatoid arthritis, Hand radiography, Foot radiography, Laboratory measures.

RHEUMATOID arthritis (RA) is characterized by articular and systemic inflammation associated with progressive polyarticular destruction [1]. The striking contrast between improvement in measures of disease activity and radiological deterioration has been observed in many longitudinal studies [2–4]. Given this divergence between the clinical and radiological course, there is clearly no ideal single measure of outcome for these patients [5, 6]. There is now international acceptance of a panel of clinical, laboratory and radiological measures which may better reflect the overall disease course [7].

We have also observed improvement in disease activity accompanied by radiological deterioration in a cohort of patients with RA observed for a mean period of 6 yr. To characterize this paradox further, we completed a detailed examination of the relationship between clinical and laboratory measures of disease activity and the radiological course in these patients.

PATIENTS AND METHODS

Patients

Patients who presented with active RA to St Vincent's Hospital entered a prospective study in 1984–1987 as previously described [8, 9]. All patients had classic or definite RA at enrolment, as defined by the 1958 American Rheumatism Association diagnostic criteria [10]. Patients were excluded if they had previously received any disease-modifying drugs or any oral or intra-articular corticosteroids. All patients gave informed consent and the study was approved by St Vincent's Hospital Ethics Committee.

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Clinical and laboratory assessment

Patients were assessed at enrolment to the study and were later reviewed over a 12 month period. For the purpose of review, patients were invited to attend at a special clinic: for all patients who did not attend for review, it was established whether they were living, or the cause of death if they had died. Demographic details and disease duration (the period between onset of symptoms and time of examination) were recorded at enrolment and at review. Patients completed an Arthritis Impact Measurement Scale (AIMS) questionnaire at the time of review [11]. Six clinical and laboratory variables were used to assess disease activity at entry and at review, as previously described [12]: (i) duration of morning stiffness, using a 1–4 scale (1 = < 10 min; 4 = > 120 min); (ii) pain, with a 10 cm visual analogue scale; (iii) grip strength (mean of three readings per hand measured with an anaeroid dynamometer inflated to 30 mmHg); (iv) Ritchie articular index; (v) full blood count; (vi) sedimentation rate (Westergren method). The term clinical course refers to change observed in these variables between enrolment and review; and clinical outcome to their value at review. Current non-steroidal anti-inflammatory, corticosteroid or disease-modifying therapy and previous disease-modifying therapy since enrolment were documented at review.

Radiological assessment

Radiographs of hands and feet were obtained at enrolment and at review. Articular damage was quantified at the metacarpophalangeal, proximal interphalangeal (including the thumb), carpal and metatarsophalangeal joints using the Larsen method by a blinded observer (DM) (coefficient of variance = 3.4%) [13]. The term radiological outcome refers to the radiological score at review and

radiological course to radiological change during the study, measured by two methods. Firstly, by actual change in radiological score, representing the difference between radiological score at enrolment and at review. However, patients with more extensive articular destruction at enrolment had less scope for further deterioration. Thus, the actual change in radiological score may not represent an ideal measure of change. The percentage change (change in score as a percentage of radiological score at enrolment) could not be calculated where the score at enrolment was zero. Thus, standardized percentage change was used, as previously described [14], where actual change was expressed as a percentage of total change possible in each patient:

$$\frac{(\text{radiological score at review} - \text{radiological score at enrolment}) \times 100\%}{(\text{maximum possible radiological score} - \text{radiological score at enrolment})}$$

Statistical analysis

Patients were included in any analysis only where relevant data were complete, using StatviewSE+ Graphics™ (Abacus Concepts, Inc., Berkeley, CA, USA) statistical software on a Macintosh computer. Data were compared by two-sample or paired *t*-tests. Correlations were sought using simple regression. A P value of <0.05 was considered significant.

RESULTS

Demographic results

Fifty-seven patients were enrolled, 48 patients were alive at the time of review and 40 attended for review. Their demographic details at enrolment and at review are described (Table I). Eight further patients were alive, but not reviewed: three were well—one had emigrated; five required on-going medical care—one with end-stage renal failure required chronic haemodialysis. Nine patients had died: four from complications of cardiovascular disease, three from disseminated neoplasia and two from respiratory disease.

At review, 29 (73%) patients were taking daily non-steroidal anti-inflammatory drugs and 17 (43%) were taking daily oral corticosteroids (only one patient was taking >7.5 mg prednisolone daily). At the time of review, 28 (70%) patients were taking a disease-modifying drug including methotrexate (12 patients), gold salts (seven), sulphasalazine (four) and other disease-modifying drugs (five). Since enrolment, all patients had received at least one disease-modifying drug, 13 had received two, and nine had received three or more disease-modifying drugs. Since enrolment, gold salts had been prescribed for 33 patients, methotrexate for 16, anti-malarial drugs for 13, sulphasalazine for eight and D-penicillamine for six.

Clinical and laboratory results

All patients completed an AIMS questionnaire at review. The AIMS scores in the RA patients were significantly higher than those reported previously in a healthy Irish population [15]. The median (interquartile range) AIMS physical score was 1.7 (0.8–3.5), social activity score was 3.5 (2.0–6.0), pain score was 4.3 (2.3–7.0), psychological score was 1.8 (1.2–3.4) and global score was 2.2 (1.5–3.9).

Clinical and laboratory variables measured at enrolment and at review are described (Table I). Among patients in the present study, significant improvement was observed in all clinical and laboratory measures of disease activity, particularly Ritchie articular index, haemoglobin and sedimentation rate (Table I, Fig. 1). More detailed analysis demonstrated that >90% had an improvement in

TABLE I
Demographic, disease activity and radiological details at enrolment and at review

Variable	At enrolment*	At review*	P†
Age (yr)	46.4 (13.3) (20–72)	52.4 (13.6) (26–80)	
Sex (male:female)	12:28		
Disease duration (yr)	2.4 (2.9) (0.2–12.0)	8.5 (3.3) (4.6–18.4)	
Duration of follow-up (yr)		6.1 (1.1) (4.0–8.0)	
Rheumatoid factor (%+)		93	
RAPA‡ reciprocal titre (if RF+)		790 (1234) (40–5120)§	
Measures of disease activity			
Morning stiffness¶	2.9 (1.1) (1–4)[38]	2.1 (1.2) (1–4)[40]	< 0.0006
Pain VAS‖	4.7 (2.6) (0.7–9.7)[37]	3.2 (2.5) (0.0–8.3)[40]	< 0.005
Grip strength (mmHg)	128 (62) (40–284)[35]	177 (76) (69–300)[39]	< 0.0001
Ritchie articular index	16 (12) (0–45)[37]	7 (6) (0–19)[39]	< 0.0001
Haemoglobin (g/dl)	12.0 (1.0) (9.6–13.4)[39]	13.1 (1.3) (10.9–15.6)[39]	< 0.0001
Sedimentation rate (mm/h)	59 (30) (11–124)[39]	19 (12) (4–47)[40]	< 0.0001
Larsen radiological score			
Hands and feet	38 (36) (0–140)[36]	88 (40) (12–158)[39]	< 0.0001

*Results are expressed as the mean (S.D.) (range) unless otherwise stated. The number in superscript is the number of patients, where data are available.
†P value for comparison between enrolment and review data.
‡RAPA, rheumatoid arthritis particle agglutination.
§Data expressed as the mean (median) (range).
¶1–4 scale.
‖VAS, 0–10 cm visual analogue scale.

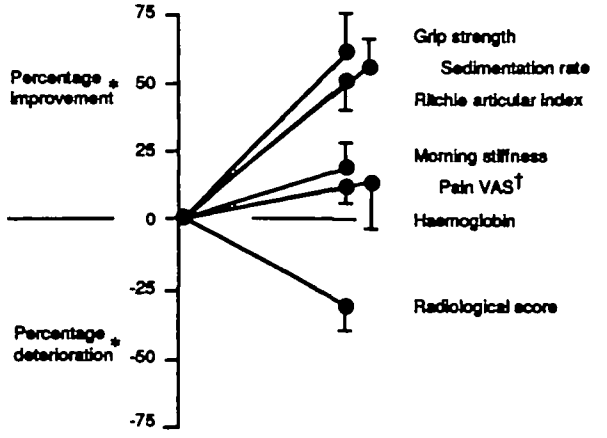

FIG. 1.—Contrast between improvement in measures of disease activity and deterioration in Larsen radiological score. S.E.M. bars are indicated. *Improvement is the mean actual change between enrolment and review expressed as a percentage of the value at enrolment; deterioration is the mean actual change expressed as a percentage of the total change possible. †VAS, 10 cm visual analogue scale.

sedimentation rate (36 of 39 patients), ⩾80% had an improvement in Ritchie articular index (31 of 37), morning stiffness (31 of 38) and grip strength (28 of 35), and 75% had a rise in haemoglobin (28 of 38) (Fig. 2).

Radiological results

Radiographs at review were available in 39 patients and serial (enrolment and review) radiographs were available in 30 patients. Despite improvement in measures of disease activity, there was evidence of increased articular destruction (Fig. 1). The mean radiological score deteriorated significantly between

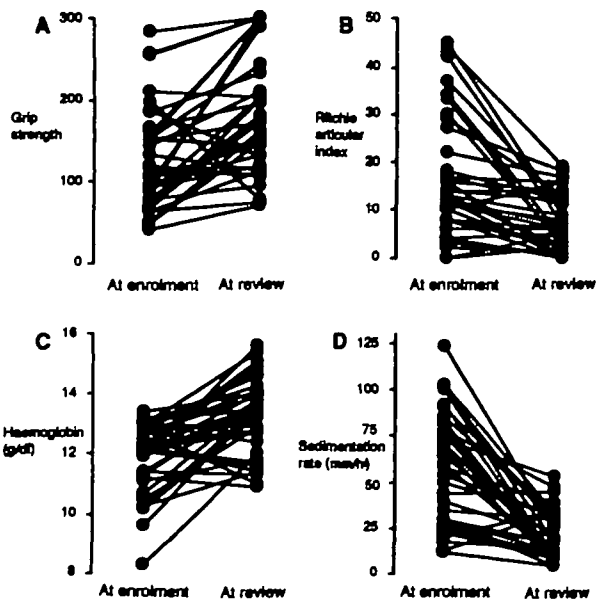

FIG. 2.—Improvement in paired measures of grip strength (mmHg) (A), Ritchie articular index (B), haemoglobin (g/dl) (C) and sedimentation rate (mm/h) (D) measured at enrolment and at review.

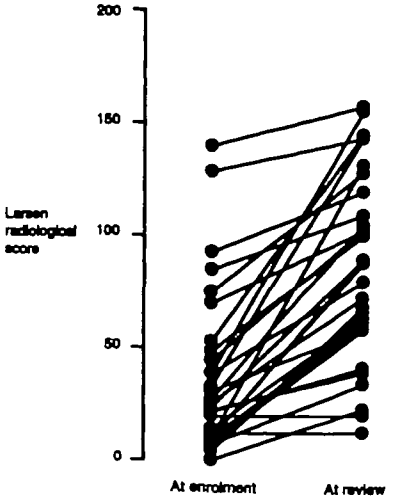

FIG. 3.—Deterioration in paired Larsen radiological scores measured at enrolment and at review.

enrolment and review ($P < 0.0001$) (Table I). Only two patients had no change in their radiological score during the study (Fig. 3).

Relationship of clinical, laboratory and radiological data

Given the contrast between improvement in measures of disease activity and increased articular destruction, the relationship between the clinical course and articular erosion was examined in detail. Firstly, there was no correlation between any of the measures of disease activity present at the time of enrolment and either the degree of articular damage at enrolment or the change in articular damage during the period of observation. Thus, measures of disease activity at enrolment did not predict the radiological course.

Several correlations were observed between a number of measures of disease activity at the time of review and the radiological course. Ritchie articular index, haemoglobin and sedimentation rate correlated with both actual and standardized change in

TABLE II
Correlation matrix between radiological change and change in disease activity at review

	Change in radiological score*	
Variable	Actual change†	Standardized change‡
Morning stiffness	0.00	0.03
Pain VAS§	0.29	0.32
Grip strength¶	0.35	0.41 (<0.03)
Ritchie articular index	0.47 (<0.01)	0.49 (<0.01)
Haemoglobin¶	0.56 (<0.002)	0.56 (<0.002)
Sedimentation rate	0.57 (<0.001)	0.53 (<0.003)

*Values represent the correlation coefficient (r value) with the P value in parentheses where this was significant ($P < 0.005$).

†Actual difference between radiological score at enrolment and at review.

‡Actual change in radiological score expressed as a percentage of total change possible.

§VAS, 10 cm visual analogue score.

¶All negative correlations.

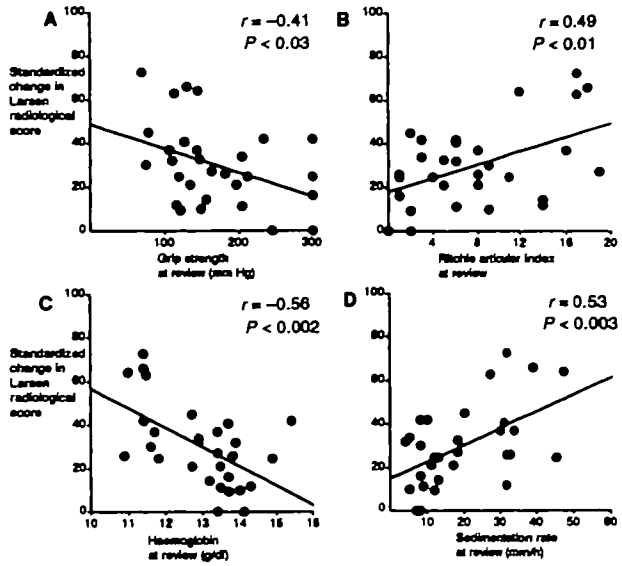

FIG. 4.—Correlations between standardized percentage change in Larsen radiological score* and grip strength (mmHg) (A), Ritchie articular index (B), haemoglobin (g/dl) (C) and sedimentation rate (mm/h) (D), all measured at review. *Standardized percentage change is the actual change in radiological score expressed as a percentage of the total change possible.

radiological scores (Table II, Fig. 4). These measures of disease activity also correlated with the degree of articular erosion observed at the time of review. Thus, Ritchie articular index ($r = 0.36$, $P < 0.05$), haemoglobin ($r = -0.44$, $P < 0.001$) and sedimentation rate ($r = 0.36$, $P < 0.05$) measured at the time of review also reflected radiological outcome.

DISCUSSION

This study has examined in detail the paradox of clinical improvement and radiological deterioration in a cohort of patients with RA observed over 6 yr. The observation that the clinical and radiological course in RA may follow diverging paths is not, of itself, new [2–4]. Scott *et al.* [2] described significant improvement in clinical and laboratory measures in 64 patients observed over 1 yr who had evidence of continuing joint destruction. They also described improvement in the sedimentation rate in 88 patients observed over 10 yr who demonstrated radiological deterioration. Sany *et al.* [3] observed improvement in the duration of morning stiffness, Ritchie articular index and sedimentation rate in 37 patients observed over 31 months, combined with radiological deterioration in 83% of their subjects. Capell *et al.* [4] also observed improvement in most measures of disease activity, combined with increased articular destruction in hand radiographs, in 92 patients observed for 10 yr.

However, few studies have completed a detailed examination of the paradoxical relationship between the clinical and radiological course in RA [16–19]. In examining this area, groups have sought clinical or laboratory variables which have predicted future radiological change or reflected past radiological deterioration. Van Zeben *et al.* [19] observed that most measures of disease activity were not useful predictors of the radiological course in a prospective study of 132 female patients with RA observed over 6 yr. Although the presence of fewer inflamed joints at entry was associated with less articular destruction after 6 yr, other measures of disease activity, such as morning stiffness, sedimentation rate and haemoglobin level, did not predict the radiological course. Factors other than measures of disease activity, such as older age, female sex, insidious onset, presence of RF, HLA-DR4 and nodules have been shown to predict more severe radiological destruction [18, 19]. However, some measures of disease activity can reflect the radiological course in later disease [2, 20]. Scott *et al.* [2] found that patients with a persistently low sedimentation rate had significantly less articular erosion over 10 yr. Fuchs *et al.* [20], in a cross-sectional study of 148 patients, described a correlation, albeit weak, between articular destruction in the hand and joint tenderness. Although neither study included other measures of disease activity, their results are clearly consistent with the findings in the present study.

The natural history of RA is of progressive articular damage of varying severity, particularly during the early years of the disease [21]. The findings of the present study have highlighted that measures of joint swelling, tenderness and function, as well as laboratory measures which reflect synovial inflammation, can demonstrably improve in most patients whilst articular damage continues [22]. The observed correlations between these measures of disease activity and radiological parameters suggest that they are markers for accelerated articular erosion. Synovial inflammation and its clinical expression represent a composite of multiple microscopic events, including vascular proliferation, accumulation of several mononuclear cell populations and secretion of inflammatory mediators such as cytokines, prostaglandins, free radicals, metalloproteinases and autoantibodies [1]. Many therapeutic modalities in RA have been shown to influence the clinical expression of synovial inflammation and several of its cellular, molecular and histological components [23–28]. However, despite demonstrable and prolonged modification of several inflammatory pathways, progressive articular erosion has been demonstrated [29]. These observations suggest that those mechanisms which underlie articular damage may differ from those which are primarily responsible for the clinical and biological manifestations of synovial inflammation. We have previously demonstrated that synovial macrophages, but not lymphocytes, correlated with the radiological course and outcome in RA, whereas both lymphocytic and non-lymphocytic cell populations correlated with measures of disease activity [30]. In addition, there are animal models of progressive articular erosion occurring in the absence of lymphocytic involvement [31]. It is possible that synovial macrophages, and other non-lymphocytic cell populations, such as fibroblasts, together with their secreted products, may play a

critical role in mediating articular destruction, a role which continues even when there is little evidence of synovial inflammation and which may be little affected by conventional therapeutic interventions. On the other hand, manifestations of synovial inflammation may reflect both lymphocytic and non-lymphocytic populations in the synovium, and are responsive to conventional therapeutic interventions. Undoubtedly, there is interplay between macrophages, fibroblasts and lymphocytes in the synovium in RA which may vary according to the stage of the disease. The clinical, laboratory and radiological data in the present study derive from observations made at two points during the course of the disease. Thus, it cannot be determined precisely when the observed change in these measures occurred. However, the potential for macrophages and fibroblasts to act independently of other mononuclear cell populations has been described [31, 32].

These observations have a number of practical implications. It is clearly inadequate to rely on either clinical, laboratory or radiological data alone to monitor progress in patients with RA. Whilst clinical or laboratory evidence of synovial inflammation should arouse concern, since they appear to be markers for increased articular erosion, articular erosion appears to continue in patients with little evidence of active disease. This need to distinguish between disease activity and articular destruction is being increasingly recognized [6, 22]. New therapeutic modalities are needed which regulate not only features of synovial inflammation, but also slow or arrest articular destruction. In this regard, newer therapies which target macrophages and their products have yielded promising results [28, 33, 34].

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