

Is It Possible to Predict Radiological Damage in Early Rheumatoid Arthritis (RA)? A Report on the Occurrence, Progression, and Prognostic Factors of Radiological Erosions over the First 3 Years in 866 Patients from the Early RA Study (ERAS)

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ABSTRACT. Our aim was to assess the occurrence, progression, and prognostic features for radiological damage in early rheumatoid arthritis (RA). We recruited an inception cohort of patients from rheumatology departments in 9 hospitals beginning in 1986. Standard clinical and laboratory assessments and radiographs of hands and feet were made at baseline and yearly, and scored using Larsen's method. The study included 866 patients with radiographic scores at baseline and at 3 years, of whom 279 (32%) had erosive damage at baseline, and 609 (70%) by 3 years. Baseline and first-year values for Larsen erosion score, rheumatoid factor (RF), erythrocyte sedimentation rate (ESR), hemoglobin, nodules, swollen joint count, grip strength, duration of symptoms, and presence of RA-associated shared epitope were all risk factors for 3 year radiological outcome. In the non-erosive group at baseline (68%), high RF and ESR correctly predicted erosions or not by 3 years in 67%. Severity of erosions was correctly predicted by Larsen and swollen joint scores at baseline (82% correct), and Larsen score and ESR at one year (90% correct). In conclusion, most patients had evidence of radiological erosions by 3 years, despite early treatment with conventional drug therapy. Prognosis for radiological outcome was possible using routinely obtained clinical and laboratory measures. Ninety percent correct classification, even at one year, is likely to be useful to clinicians managing treatment options in early RA. (J Rheumatol 2004;31 Suppl 69:48–54)

Key Indexing Terms:

RHEUMATOID ARTHRITIS
HLA

RADIOLOGICAL OUTCOME

LARSEN SCORES
PROGNOSTIC FACTORS

Radiological appearances in rheumatoid arthritis (RA) vary from none to marked destructive changes, even within the first 3 years¹. Reports on the occurrence and time to severe radiological changes in RA have varied considerably, because selection criteria and disease duration vary so much between randomized drug trials and longterm observational studies². Small sample sizes and short or variable followup have limited the findings from some of the small number of reported inception cohorts. There is little agreement concerning radiological progression rates in RA, for which linear, fast-slow, slow-fast, and sigmoid curves have all been described³. Many of the published studies on radiological outcome have also investigated potential predictive factors, and again the wide variation in results has depended on study design, duration of RA, and radiological scoring methods².

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The Early Rheumatoid Arthritis Study Group (ERAS) started an inception cohort in 1986, designed to overcome the problems of limited numbers and followup, and of possible patient selection bias from one center^{4,5}. Compiling standardized data on a large sample of patients over a long followup period from different regions gives the opportunity of characterizing with greater precision differences in radiological progression and possible differences between centers. Such outcomes could be used to compare conventional clinical management of RA with more recent developments in RA therapies, and to develop prognostic factors. As an observational study, ERAS was designed to provide data not generally available from short-term randomized studies. We present here radiological progression early in disease in conventional clinical settings rather than a randomized controlled trial environment.

This article summarizes previous reports on radiological progression and prognostic factors in inception cohorts over 3 years. These results are compared to our own study of 866 patients, conducted in normal clinical settings and using conventional drug therapies for early RA in the 1990s.

PREVIOUS STUDIES

The earliest studies, started in the 1960s from Bath⁶ and London, UK⁷, reported that erosions (Kellgren/Lawrence method⁸) were already present in 29% of around 100 patients at presentation (within 1 year of onset), increasing to 43%, 89%, and 99% by 1, 2, and 3 years' followup. Important findings were first involvement of feet in 36% compared to hands (16%), and both feet and hands (48%); and 48% of erosive patients did not progress after 3 years. This latter figure was higher than the 26% erosive RA patients who did not progress over 5 years reported from a Swedish cohort⁹. Many of these findings were largely confirmed in the Nijmegen/Groningen study of 147 patients started in the 1980s¹⁰. After 3 years, 70% had radiographic damage (Sharp's method¹¹), all of whom could be identified by 1 year. Biannual radiographs showed that the rate of progression was highest in the first year, with flattening of

the curve in the next 2 years, whereas the study from Leiden¹² (Kellgren/Lawrence method) in 135 women showed a linear increase over 6 years. In contrast to these, a community based study of inflammatory joint disease reported that, of 185 patients who developed erosions using Larsen's method¹³, only 66% did so by 2 years, and patients continued to develop erosions after 3 years¹⁴. Of the patients who had serial radiographs in a study from Wichita¹⁵, a constant rate of damage over time was seen for all components of Sharp's method. Thus, although the rate of progression of radiographic changes over the first few years of early RA varies in the reported studies, the frequency of radiographic erosions or not at 3 years was very similar at around 70%.

Using baseline clinical and laboratory measures to predict radiological outcome with univariate analysis, the majority of studies are consistent in reporting initial radi-

Table 1. Clinical features at baseline versus 3 year erosion scores. Values are No. (%).

	Total	Larsen Erosion Score at 3 Years			
		0	1	2-5	> 5
Sex	866 (100)	257 (30)	147 (17)	250 (29)	212 (24)
Male	297 (34)	90 (30)	52 (18)	82 (28)	73 (25)
Female	569 (66)	167 (29)	95 (17)	168 (30)	139 (24)
Age onset					
< 45	206 (24)	63 (31)	33 (16)	60 (29)	50 (24)
45-60	350 (40)	103 (29)	64 (18)	95 (27)	88 (25)
> 60	310 (36)	91 (29)	50 (16)	95 (31)	74 (24)
RA symptoms					
6	442 (51)	145 (33)	84 (19)	128 (29)	85 (19)
12	264 (30)	76 (29)	44 (17)	75 (28)	69 (26)
18	90 (10)	20 (22)	10 (11)	26 (29)	34 (38)
24	70 (8)	16 (23)	9 (13)	21 (30)	24 (34)
RF 0 yrs					
Neg	230 (27)	97 (42)	45 (20)	47 (20)	41 (18)
+/-	75 (9)	26 (35)	13 (17)	19 (25)	17 (23)
+	232 (27)	49 (21)	42 (18)	78 (34)	63 (27)
+++	319 (37)	83 (26)	43 (13)	102 (32)	91 (29)
Nodules					
None	793 (92)	244 (31)	136 (17)	228 (29)	185 (23)
Present	73 (8)	13 (18)	11 (15)	22 (30)	27 (37)
Erosion score 0 yr					
0	587 (68)	249 (42)	111 (19)	156 (27)	71 (12)
1	95 (11)	6 (6)	31 (33)	35 (37)	23 (24)
> 1	184 (21)	2 (1)	5 (3)	59 (32)	118 (64)
ACR 0 yrs					
< 4	242 (28)	98 (40)	43 (18)	61 (25)	40 (17)
≥ 4	624 (72)	159 (25)	104 (17)	189 (30)	172 (28)
HLA shared epitope					
nil	199 (29)	86 (43)	24 (12)	43 (22)	46 (23)
x1	317 (45)	79 (25)	60 (19)	100 (32)	78 (25)
x2	143 (21)	33 (23)	26 (18)	41 (29)	43 (30)
?	38 (5)	10 (26)	3 (8)	14 (37)	11 (29)
FGGrade 0 yrs					
I	273 (32)	85 (31)	46 (17)	75 (27)	67 (25)
II	516 (60)	151 (29)	92 (18)	156 (30)	117 (23)
III	74 (9)	20 (27)	8 (11)	18 (24)	28 (38)
IV	3 (0)	1 (33)	1 (33)	1 (33)	0 (0)

Larsen erosion scores based on quartiles.

ographic scores, RF, and acute phase reactants as predictors of radiological damage by around 3 years. However, the reliability and strength of these prognostic markers varies considerably². Other baseline features have had variable success, including articular indices, disease activity scores, various established and novel laboratory measures, and genetic markers. RF alone has been reported to predict erosions or not in 70%¹⁶, and using regression methods, a combination of various independent clinical, laboratory, and genetic factors have achieved better classification (up to 85%) in a number of reports^{2,12,15-18}. The only consistent baseline prognostic factors from these reports were initial radiographic scores and RF. Disease activity as a laboratory measure [erythrocyte sedimentation rate (ESR) or C-reactive protein] or a composite score featured in many. The role of HLA-DRb1 genes remains controversial. Despite many investigators reporting positive, but varying degrees of association of HLA-DRb1*04 RA-associated alleles with radiological damage^{12,17-19}, others have questioned their predictive value²⁰⁻²².

MATERIALS AND METHODS

Consecutive patients with RA were recruited from ordinary outpatient clinics of 9 rheumatology departments if symptoms of RA had lasted less than 2 years and second-line medication had not been used, as described^{4,5}. Patients who did not fulfil the 1987 revised American College of Rheumatology (ACR) criteria for RA²³ continued to be followed and subjected to subgroup analysis when appropriate. Only patients who completed 3-year followup and had radiography of adequate quality for scoring²⁴ have been included in the analysis. Trained metrologists made baseline and yearly clinical assessments, which were standard measures at the time the study started in 1986 as described^{4,5}. These were similar to those recommended later by national²⁵ and international bodies²⁶. They included articular indices for both swollen¹⁶ and tender joints²⁷, Stanford Health Assessment Questionnaire²⁸, visual analog pain scale, grip strength, ESR, and RF. Disease activity (Disease Activity Score) was based on articular indices and ESR²⁹. Baseline and yearly radiographs of hands and feet were digitized onto CD-ROM and scored randomly by one observer using Larsen's method¹³. Intraobserver reliability was checked regularly, as described²⁴.

For this report we have used Larsen's erosion score as outcome. DNA was extracted from stored blood samples and HLA-DRb1 type assigned using sequence oligonucleotide typing, and the number of copies of the RA-related shared epitope was determined³⁰.

Treatment profiles. All centers followed the framework of the published UK guidelines for management of RA²⁵, which includes the provision of therapy services, appropriate orthopedic interventions, and sequential use of second-line drugs (disease modifying antirheumatic, DMARD) together with symptom relieving measures, and judicious use of steroids. Combination therapy was used in severe and nonresponsive RA. The DMARD used were chosen according to physician preference, although dosage schedules employing graduated regimens were previously agreed according to standard practice for each drug. Reasons for discontinuation were based on clinical judgments and coded according to loss or lack of effect, to adverse events, both reasons, remission, or miscellaneous (e.g., pregnancy).

Statistical analysis. Summary statistics have been used to demonstrate the differences in clinical, laboratory, and genetic features with radiological outcome. All continuous variables have been categorized into quartiles. Univariate analysis included odds ratio (OR) with 95% confi-

Table 2. Odds ratios: clinical/laboratory/HLA data at baseline and 1 year for 3 year Larsen erosions. A. Cutoffs for 3 year radiography: erosive or non-erosive, clinical/laboratory, median values.

Variable	Odds Ratio	95% Confidence Bounds	
Baseline			
Nodules	2.09	1.08	4.05
HLA-DR shared epitope (≥ 1)	2.57	1.72	3.85
Rheumatoid Factor	2.43	1.72	3.44

Table 2B. Cutoffs: median values of both radiographs at 3 years, and clinical/laboratory data at 0/1 year.

Variable	Odds Ratio	95% Confidence Bounds	
Baseline			
Duration symptoms	1.86	1.30	2.66
Nodules	1.87	1.13	3.12
HLA shared epitope (≥ 1)	1.63	1.17	2.28
ESR	1.86	1.41	2.43
Hemoglobin	1.49	1.14	1.95
Rheumatoid Factor	2.24	1.68	2.98
Erosions	8.47	5.89	12.16
Year 1			
Joint score	1.47	1.08	2.00
HAQ	1.53	1.16	2.02
Grip	1.61	1.22	2.12
ESR	2.16	1.63	2.87
Hemoglobin	1.54	1.17	2.04
DAS	1.39	1.05	1.84
Rheumatoid Factor	2.64	1.92	3.63
Erosions	12.43	7.69	20.08

Table 2C. Cutoffs: worst quartiles for both clinical/laboratory data at 0/1 year and radiographs at 3 years.

Variable	Odds Ratio	95% Confidence Bounds	
Baseline			
Duration symptoms	1.80	1.09	2.96
Nodules	1.77	1.08	2.89
HLA shared epitope (≥ 1)	1.49	1.03	2.18
ESR	1.72	1.24	2.38
Hemoglobin	1.54	1.12	2.13
Rheumatoid Factor	1.82	1.32	2.50
Erosion score	7.33	5.30	10.12
Year 1			
HAQ	1.44	1.00	2.06
Grip	1.46	1.06	2.03
ESR	2.56	1.84	3.57
Hemoglobin	2.29	1.65	3.17
Rheumatoid Factor	2.67	1.81	3.94
Erosion score	11.20	6.81	18.43

dence intervals (CI) to demonstrate associations between individual variables at baseline and at 1 year with 3-year Larsen erosive scores. Logistic regression was used to identify combinations of the same clinical and laboratory measurements at baseline and at 1 year to predict radiographic damage at 3 years. To validate each model, the analysis of possible risk factors was confined to a randomly selected subgroup of the cohort (60%), which was then tested in the remaining 40%.

Table 3. Logistic regression. All clinical and laboratory variables, either at baseline or at one year, were entered in stepwise logistic regression to predict radiological outcome at 3 years. Odds ratios [Exp (B)] and 95% confidence intervals (CI) are shown for variables selected in each model. Classification tables are shown for the random 60% of sample used to generate prognostic variables, and percentages shown are the sensitivity, specificity, positive and negative predictive values. To validate each model, the same variables were tested in remaining 40% not used in the analysis. A. Prognostic variables for erosive disease. Dependent (outcome) variable: erosions or not by 3 years. Independent variables: baseline features. Only patients non-erosive at baseline are included (n = 587).

Variable	Variables in the Equation		
	Exp (B)	Lower	Upper
RF (1)	2.0834	0.8540	5.0827
RF (2)	4.4387	2.4257	8.1222
RF (3)	2.4039	1.4055	4.1117
ESR (1)	1.9203	1.0607	3.4766
ESR (2)	1.3197	0.7347	2.3708
ESR (3)	2.6174	1.3809	4.9611

		Predicted		Percent Correct
		None N	Erosive E	
Observed				
None	N	80	75	51.61%
Erosive	E	47	163	77.62%
		62.9%	68.4%	

Overall 66.58% (67.30% in test sample).

Table 3B. Severity of erosions. Dependent variable: none, mild, moderate versus severe erosions at 3 years. Independent variables: baseline features (n = 850, 16 patients excluded from model because of missing baseline data).

Variable	Variables in the Equation		
	Exp (B)	Lower	Upper
Joint score (1)	1.6701	0.8662	3.2199
Joint score (2)	1.4400	0.7055	2.9393
Joint score (3)	0.6294	0.2894	1.3689
Nodules (1)	2.5575	1.1851	5.5195
Larsen score (1)	1.6758	0.7250	3.8734
Larsen score (2)	4.6712	2.1284	10.2517
Larsen score (3)	7.8447	2.7590	22.3045
Larsen score (4)	10.2049	3.0094	34.6057
Larsen score (5)	52.2020	20.4579	133.2027

		Predicted		Percent Correct
		None → mod N	Severe S	
Observed				
None → mod	N	382	15	96.22%
Severe	S	70	51	42.15%
		84.5%	77.2%	

Overall 83.59% (79.20% in test sample).

Table 3C. Severity of erosions predicted by 1st year variables (n = 649 because of missing 1 year variables or radiographs).

Variable	Variables in the Equation		
	Exp (B)	Lower	Upper
ESR (1)	0.4782	0.1600	1.4294
ESR (2)	1.4869	0.5583	3.9597
ESR (3)	2.1879	0.8112	5.9012
Larsen score (1)	8.5530	3.4290	21.3338
Larsen score (2)	5.6047	1.5823	19.8533
Larsen score (3)	36.9551	7.4721	182.7698
Larsen score (4)	18.2750	4.8648	68.6521
Larsen score (5)	150.6869	38.7564	169.8762

		Predicted		Percent Correct
		None → mod N	Severe S	
Observed				
None → mod	N	302	6	98.05%
Severe	S	30	32	51.61%
		90.9%	84.2%	

Overall 90.27% (87.20% in test sample).

Patient sample. Eight hundred sixty-six patients were followed for 3 years and had Larsen scores of hands and feet at baseline and at 3 years: 279 (32%) had erosive damage at baseline, and 609 (70%) by 3 years. A summary of the clinical characteristics of the cohort at study entry is shown in Table 1 (column 1). The characteristics of the patient sample at presentation were fairly typical of early RA cohorts, with differences between centers being generally on a minor scale. Median duration of symptoms of RA prior to presentation to a rheumatologist and entry to study was 6 (4–11) months, thus indicating early RA. Eighty percent of patients received at least one DMARD at a median of 7 weeks from first presentation to rheumatology clinics (68% within 3 months and 87% by 12 months). Preference for first DMARD was sulfasalazine in 73%, intramuscular gold in 10%, D-penicillamine in 7%, oral gold (3%), antimalarials (3%), methotrexate (3%), and various others (azathioprine, cyclosporine, cyclophosphamide). Steroids in doses of 7.5 mg daily or more for 12 months or more were used in 16%.

RESULTS

Univariate analysis. Table 1 compares demographic and baseline variables with radiographic changes at 3 years. Table 2A–2C shows the values of individual clinical, laboratory, and genetic variables, both at baseline and at 1 year, that had predictive ability for radiological outcomes. Odds ratios > 2 for predicting erosions or not were baseline RF, nodules, and shared epitope (Table 2A). In Tables 2B, 2C, 3-year outcome (dependent variable) was severity of Larsen erosion score. The cutoff for risk factors was median in Table 2B and worst quartile in Table 2C. Odds ratios > 2 were RF and erosion score at baseline, and ESR and hemoglobin at 1 year.

Multivariate analysis. Independent clinical and laboratory factors that were, in combination, predictive for 3-year Larsen erosion scores are shown in Table 3A–3C. In order to

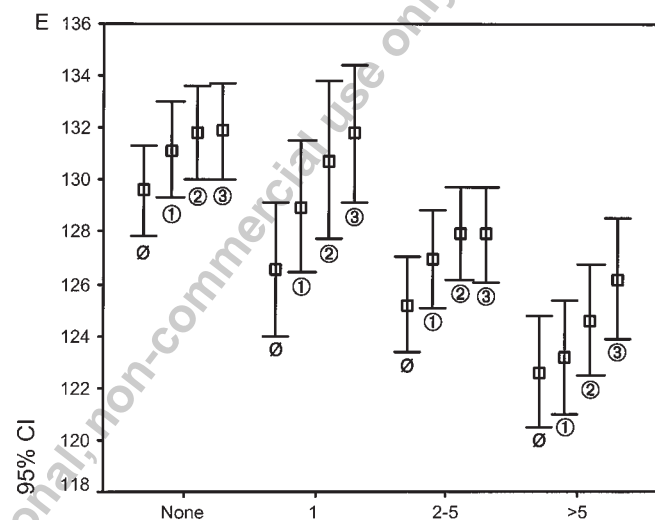
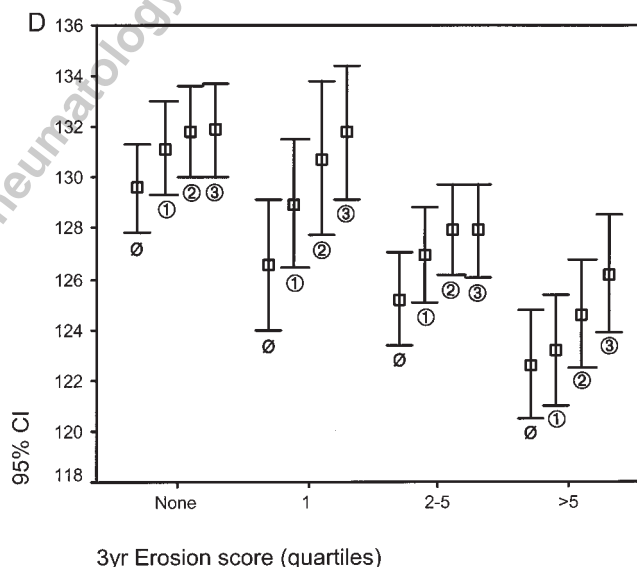
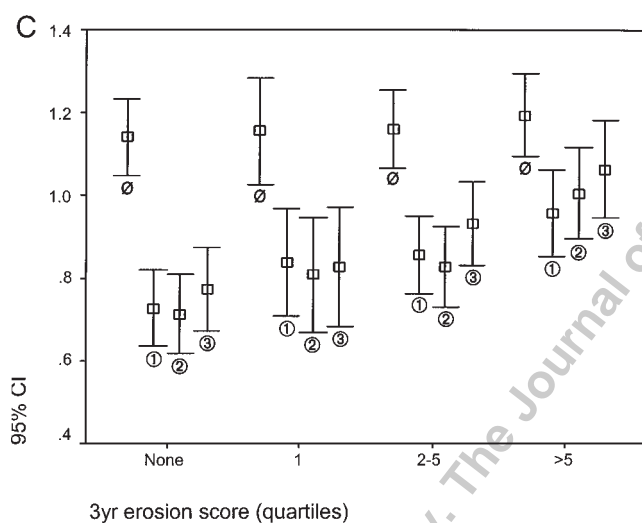
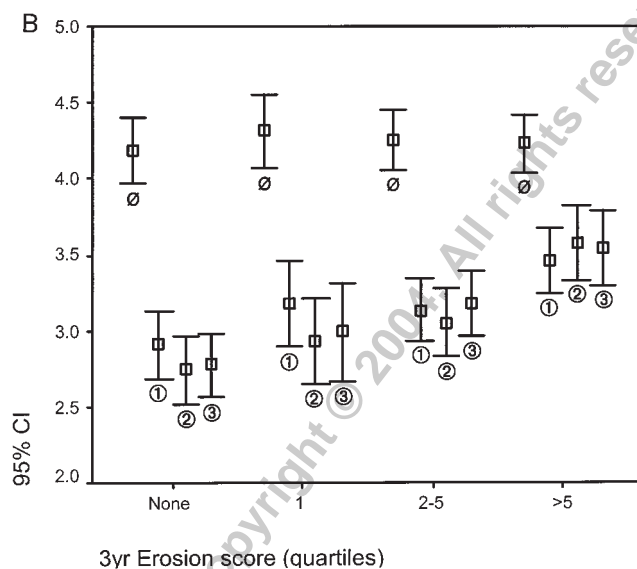
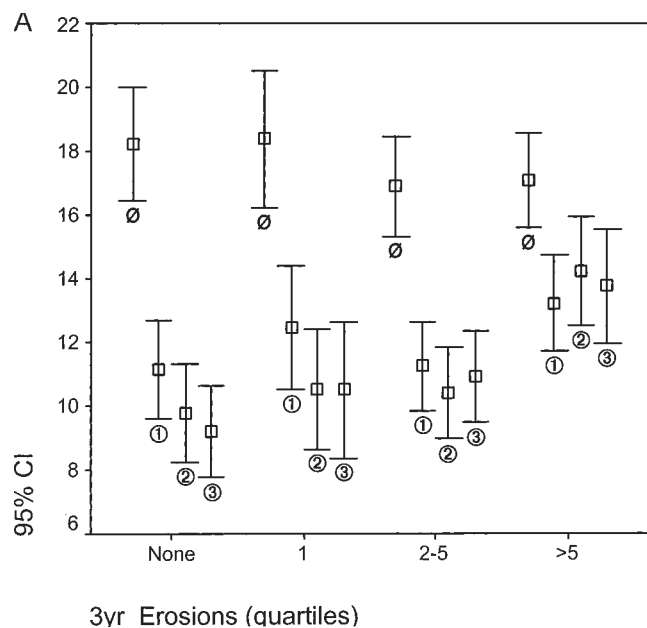


Figure 1. Larsen scores over time according to clinical and laboratory features. These show changes in swollen joint count (A), Health Assessment Questionnaire (B), Disease Activity Score (C), ESR (D), and hemoglobin (E) over 3 years, for each quartile of Larsen erosion scores by 3 years. Values are mean with 95% confidence intervals.

predict erosive disease or not by 3 years from baseline variables, only non-erosive patients at baseline (68%) were included in the first model (Table 3A). RF and ESR classified non-erosive and erosive RA overall in 67% (sensitivity 52%, specificity 78%, positive predictive value 68%). Severity of erosions or not was correctly classified in 82% overall by baseline erosion score, swollen joint count, and nodules (Table 3B; sensitivity 96%, specificity 42%, positive predictive value 77%). This improved to 90% using first year variables, i.e., first year erosion score and ESR (sensitivity 98%, specificity 52%, positive predictive value 84%; Table 3C). The validity of each model was tested in the random 40% subset of the cohort not used in the analysis, and confirmed the prognostic value of these variables.

Larsen scores over time according to clinical and laboratory features (Figure 1). These show changes in swollen joint count, Health Assessment Questionnaire, Disease Activity Score, hemoglobin, and ESR over 3 years for each quartile of Larsen erosion scores by 3 years, and the importance of 1 year values over baseline.

DISCUSSION

This study provides a view of the progress of radiological change in conventionally treated RA prior to the biologic era in a closely monitored group of patients from different regions of England. Radiological outcome by 3 years has been clearly defined, with evidence of radiological erosions at baseline in 32%, and in 70% by 3 years. When the other non-erosive criteria for radiological change described by Larsen were included¹³, only 14% had normal radiographs at 3 years. Similarly to some other studies^{7,12}, we found a linear increase in damage.

The identification of factors indicative of poor outcome early in the course of RA is crucial for tailoring treatment and supporting coping mechanisms. The strength and reliability of prognostic factors vary, largely according to the outcome measure of interest, and radiological damage has been more consistently predicted than function². Despite a large cohort, we have not been able to improve on the 70–85% successful classification reported from other studies using baseline variables for radiological outcome. However, 90% correct classification was achieved with routinely obtained clinical and laboratory measures at 1 year. Even at this stage, this is likely to be useful to clinicians managing treatment options in early RA. Genetic data, although associated with worse radiographic damage, did not improve the predictive power of the more easily obtained laboratory measures of RF and ESR. A relationship between function and radiological change has been described in other studies, but generally in late disease², so our finding of an association between first year HAQ and severity of erosions will be explored in greater detail using the 5-year data set.

Our figures illustrate objectively the magnitude of RA

damage, and are important in planning for the kind and extent of services required for managing RA even in early stages. The main strengths of this study include the chance to study RA from its earliest stages prior to the use of second-line drugs; the relatively few exclusion criteria, which are so restrictive in clinical trials, thus reflecting actual clinical practice; little variation in disease duration because all patients have the same followup (3 years from entry); regular and at least once yearly followup, using standard assessments, as part of normal good clinical practice; this has ensured data have been collected prospectively and missing data are kept to a minimum; default at followup has been accounted for in the majority. Possible sources of bias in this study arise as a result of left censoring (milder RA not being referred to hospital outpatients), right censoring (more severe RA not surviving 3 years), and treatment effects. Most patients received at least one DMARD, 87% within the first year, at a median of 7 weeks, and in 72% the same first drug was used, as was common practice in England in the late 1980s and early 1990s³¹. Thus although the subtle effects of different DMARD tried first and subsequent changes cannot be accounted for, patients were being treated early in a conventional manner. The assessment of drug treatment effects is limited in observational studies because of nonrandom assignment of therapy. None the less, newer agents can only be described as “disease modifying” if they can be shown to alter radiological damage in the long term. This cohort will permit a comparison of these new drugs with a well described historical standard reflecting management and costs of RA during the 1990s. The ERAS database now holds 10-year followup data, and more detailed analyses of radiographic progression and functional changes are under way.

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