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# Individual Relationship Between Progression of Radiological Damage and the Acute Phase Response in Early Rheumatoid Arthritis. Towards Development of a Decision Support System

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**ABSTRACT.** *Objective.* Evaluation of the individual relationship between C-reactive protein (CRP) production or erythrocyte sedimentation rate (ESR) and progression of radiologic damage in early rheumatoid arthritis (RA), to improve the predictive value of monitoring the acute phase response.

*Methods.* The relationship was modeled mathematically using adjustments for discontinuity in the radiographic scoring system and for clustering in the occurrence of score points in the initial phase. The model was evaluated in a prospective study of 149 patients with early RA, monthly CRP assays, and 6-monthly Sharp scores of radiographs of the hands and feet.

*Results.* Time integrated CRP values correlated closely with radiologic progression in each patient, but there was considerable variation between individuals with similar radiographic scores. The theoretical model accommodated these results, and based on CRP measurements and radiographic scores over 6 months, it provided a k value for each patient that reflected the individual relationship between CRP and radiologic damage. Using this k value combined with actual CRP levels over 3 and 6 years, the model accurately predicted the extent of radiologic progression that was actually observed at these times. Best results were obtained using estimation of the k value from 6 or 12 month observational data. The model has been incorporated into a software program for routine clinical use that indicates the levels to which CRP should fall to prevent further joint damage. Similar results were obtained for ESR.

*Conclusion.* A model has been established defining the individual relationship between time integrated CRP and ESR values, reflecting rheumatoid disease activity, and progression of radiologic damage. It accurately predicts outcome from 6 months after presentation and can be used as a practical decision support system. (*J Rheumatol* 1997;24:20-27)

*Key Indexing Terms:*

RHEUMATOID ARTHRITIS  
RADIOLOGICAL PROGRESSION

ACUTE PHASE RESPONSE  
C-REACTIVE PROTEIN

The recent trend to start aggressive therapy early in rheumatoid arthritis (RA) is based on increasing evidence that irreversible joint destruction may start during the first months

of the disease, and that early changes in the small joints are predictive of future disability, including damage in large joints<sup>1-4</sup>. Radiological assessment of progressive arthropathy in RA is a direct and objective measure of outcome. It reflects the results of chronic arthritis, including enzymatic degradation of cartilage and erosion of bone, that are essentially irreversible<sup>5,6</sup>. Radiological damage thus represents the cumulative effects of the disease during the preceding period, but is independent of current disease activity.

There are several objective markers that identify patients with RA at risk of a progressive course and poor outcome<sup>7</sup>. Since treatment that modifies the rheumatoid process may alter the outcome, it is important to determine which of the variables associated with activity reflect most closely those aspects of the disease responsible for a particular measure of outcome. Transformation of serially measured process variables into time integrated values, by calculating the area under the curve (AUC), is very useful for this purpose and permits comparison with outcome measures, such as radiological damage, that are cumulative.

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The acute phase response, measured directly by determination of the serum C-reactive protein (CRP) concentration or indirectly by the erythrocyte sedimentation rate (ESR), is a sensitive objective indicator of both the activity and the extent of synovial inflammation<sup>8,9</sup>, and several studies have shown that persistent reduction of ESR and CRP values is accompanied by reduced progression of radiological damage<sup>10,11</sup>. We have reported a highly significant correlation between time integrated values of ESR and CRP and radiological progression in a large cohort of patients with RA during the first 3 years of the disease<sup>12</sup>. However, there was wide variation between individuals in the absolute values of CRP or ESR corresponding to particular levels of disease activity and joint damage. This limits the use of acute phase reactants as indicators of radiological progression in clinical practice since time integrated values cannot be translated directly into radiologic scores in the individual patient. We evaluated these interindividual differences and developed a model to describe the individual relationship between CRP and radiological progression during the first years of the disease.

## MATERIALS AND METHODS

All patients attending our clinics with classical or definite RA according to the 1958 American Rheumatology Association (ARA) criteria, with joint symptoms compatible with arthritis for less than one year, and who had not previously received disease modifying antirheumatic drugs (DMARD), were invited to participate in a prospective study. All patients met these inclusion criteria at study entry. Retrospectively 146 of the 149 patients also fulfilled the 1987 ARA criteria. We analyzed data from 149 patients who had completed 3 years of followup, and from a subgroup of the first 54 of the 149 patients who completed 6 years of followup. At monthly visits during the first 3 years, and at 3-monthly visits thereafter, clinical and laboratory measurements were performed, including CRP levels by ELISA<sup>13</sup>. IgM rheumatoid factor (RF) was measured by ELISA<sup>14</sup> at study entry. The sera of all 149 patients were typed for HLA-DR locus. Radiographs of hands and feet were obtained every 6 months during the first 3 years (N = 149). In the subgroup of 54 patients who completed 6 years of followup, radiographs were obtained after 6 years as well. Joint damage in the hands and feet was assessed by Sharp's method<sup>15</sup> with some modifications, in particular inclusion of the foot joints, as described by van der Heijde, *et al*<sup>16</sup>. Radiographs were assessed in chronological order per patient by 2 observers. The interobserver variation was assessed in 120 pairs of radiographs and yielded a correlation of > 0.90 for the total scores. Erosions were counted in 56 joints/joint areas, with a maximum erosion score of 5/joint/joint area: 10 metacarpophalangeal (MCP) joints, 8 proximal interphalangeal (PIP) joints, 2 interphalangeal (IP) joints of the thumbs, left (L) and right (R) first metacarpal bone, L and R radius and ulnar bone, L and R trapezium+trapezoid (as one unit), L and R navicular bone, L and R lunate bone, 2 IP joints of the big toes, and 10 metatarsophalangeal (MTP) joints. The maximum erosion score in these 12 foot joints was 10/joint: 5 points for the proximal side and 5 points for the distal side of the joints. Therefore, 24 foot joint areas were assessed for erosions with a maximum of 5 points/area. Joint space narrowing was assessed in 42 joints, graded from 0 to 4/joint: 10 MCP joints, 8 PIP joints, L and R 3rd, 4th and 5th carpometacarpal joints, L and R multangular-navicular joints, L and R capitate-navicular-lunate joints, L and R radiocarpal joints, 10 MTP joints, and 2 IP joints of the big toes. The maximum numbers of erosions in the hands and feet are 160 and 120, and the maximum scores for joint space narrowing are 120 and 48, respectively, giving a maximum total score (X score) of 448. The progression of radiological damage over

a time period ( $\delta$ -X score) was determined by subtracting the initial score from the final score. During the first 3 years, the monthly CRP levels were transformed into time integrated values by plotting CRP levels against time (weeks) and calculating the AUC for each monthly interval by means of the trapezoidal rule. Cumulative AUC values were calculated for each 6 month period ( $\delta$ -CRP AUC) between consecutive radiographic studies by summation of the monthly AUC values. For the period from 3 to 6 years of followup, time integrated CRP values were calculated similarly using 3-monthly CRP levels.

Patients were treated with nonsteroidal antiinflammatory drugs (NSAID) and DMARD as clinically indicated, with hydroxychloroquine or sulfasalazine as the first choice among DMARD, followed in order by intramuscular gold, D-penicillamine, azathioprine, and methotrexate. Low dose corticosteroids were allowed as adjuvant therapy.

*Theoretical model.* A theoretical mathematical model was developed to describe the relationship between quantitative assessment of progression of radiological damage, represented by the X score, and cumulative disease activity, represented by time integrated CRP values. This model comprises the following variables: (1) the number of joints (n) included in the scoring system, (2) the maximum possible radiologic score per joint (m) (resulting in a total maximum score of N), (3) the observed score per joint (p), (4) the cumulative disease activity over time CRP AUC, and (5) the individual relationship between disease activity and joint damage in each patient is represented by a constant (k).

Assuming a proportional relationship between the rate of progression of radiological damage on the one hand, and disease activity (CRP level) and the residual joint area still available for damage (m-p) on the other hand, then the rate of progression/joint can be expressed as  $k \cdot \text{CRP} \cdot (m-p)$ . Assuming further that joint scores develop randomly, then the relationship between radiological damage (sum of observed p values) and cumulative disease activity can be expressed in the equation:

$$\text{radiological damage} = N \cdot (1 - e^{-k \cdot \text{CRP AUC}}) \quad (1)$$

The value of k is assumed to be constant in each individual patient, but may show considerable variation between patients. The product  $k \cdot \text{CRP AUC}$  thus corresponds to the cumulative effect of disease, or "disease dose," in each individual. The relationship between  $k \cdot \text{CRP AUC}$  and radiological damage is shown in Figure 1 (curve a), using  $N = 448$  according to the scoring system.

Fitting the model to the actual assessment of radiologic scores will improve when the following points are taken into consideration:

*Discrete character of the score.* Unlike radiological damage, which is basically a continuous process, a radiologic scoring system like Sharp's method produces a discrete variable (score), expressed by integers. As the disease advances, the scores per joint at any given time will be randomly distributed between "just received a score point" and "about to receive a score point," and therefore the radiologic scores estimated by the model will lag behind the radiological damage with a mean of 0.5 for each joint. This is accommodated in equation 2:

$$\text{radiologic score} = N \cdot (1 - e^{-k \cdot \text{CRP AUC}}) - 0.5n \quad (2)$$

in which  $n = 98$  (56 for erosions + 42 for narrowing; domain restricted to results  $\geq 0$ ). The curve expressed by this formula is shown in Figure 1, curve b.

*Synchronous occurrence of scoring points.* In the initial phase of disease, score points tend to be more or less synchronized. Theoretically, at the starting point of the disease (a time point we do not know exactly), no joint is damaged yet, and all joints are perfectly synchronized at exactly 1.0 score point away from their first score. Therefore, in the very early stages of the disease, it may be expected that several joints will reach their first score at about the same moment, in contrast to a more random distribution later on. To account for this phenomenon, we treated as binomial variable the chance of developing a score point, assuming a simultaneous start, a variable rate of progression between different sites, and equal spacing of the scores per site relative to the disease dose. The chance of  $p_i$  of devel-

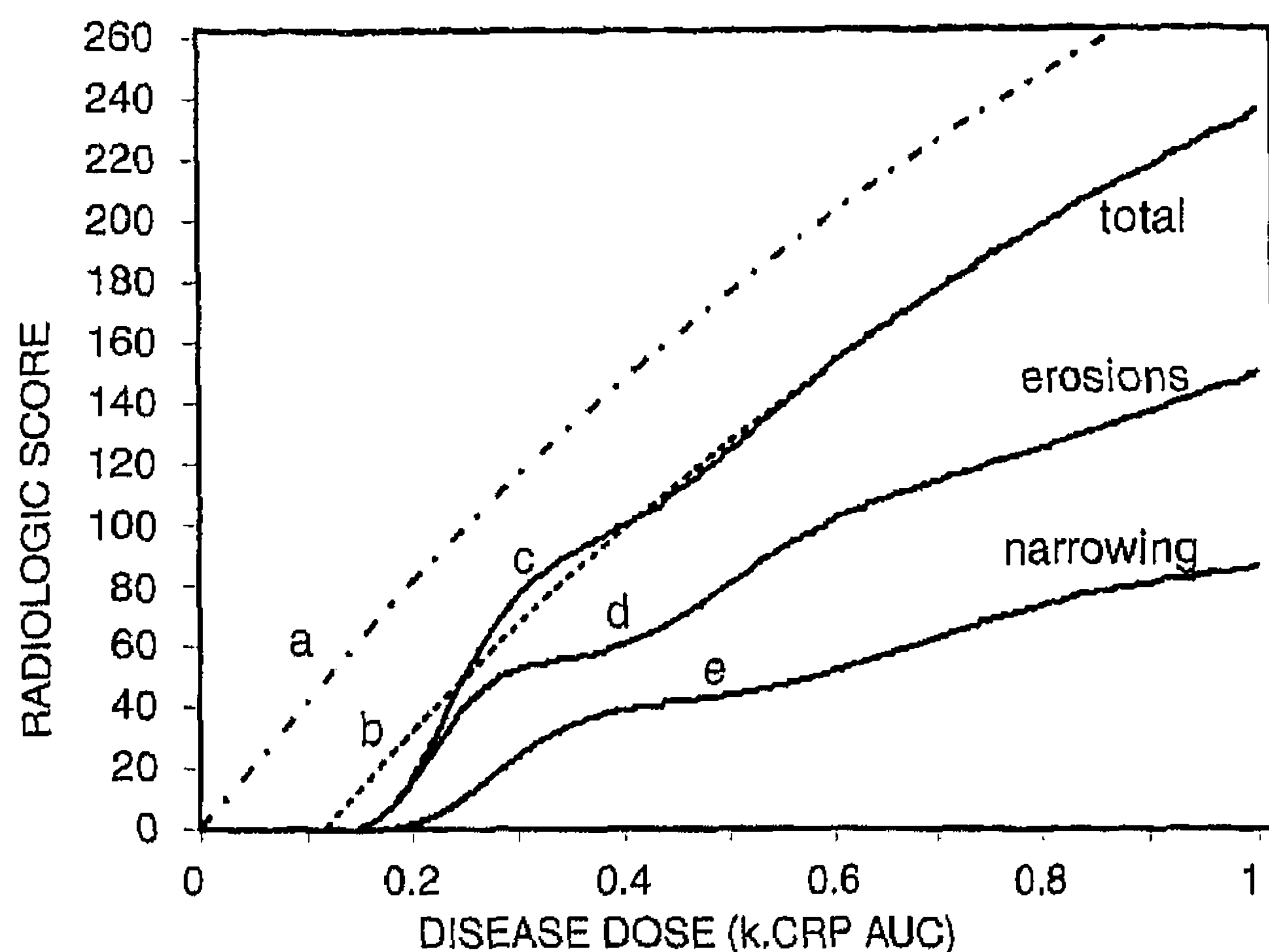


Figure 1. Model for the uniform relationship between individual time integrated CRP values (CRP AUC) and radiological progression ("disease dose" =  $k \cdot \text{CRP AUC}$ ). Curve a: relationship according to equation 1:  $X \text{ damage} = N \cdot (1 - e^{-k \cdot \text{CRP AUC}})$ . Curve b: adjustment of curve a for discontinuous scoring (equation 2). Curve c: adjustment of curve b for synchronous scoring in the lower range of radiologic scores (equation 7). Curve c results from combining curve d and curve e. Curve d: adjusted relationship for erosions only. Curve e: adjusted relationship for narrowing only.

opening a score point  $i$  is proportional to the damage  $(1 - e^{-k \cdot \text{CRP AUC}})$  and inversely related to the proportion of existing score points ( $i/m$ ):

$$p_i = (1 - e^{-k \cdot \text{CRP AUC}}) \cdot m / i \cdot y \quad (3)$$

As the real starting point is unknown, we have to rely on relative values, using as a reference point the situation where  $(1 - e^{-k \cdot \text{CRP AUC}}) = i/m$  and where 50% of sites will have reached score point  $i$  ( $p_i = 0.5$ ). Thus,  $p_i = i/m \cdot m / i \cdot y = 0.5$ , which means that  $y = 1/2$ .

All other values of  $(1 - e^{-k \cdot \text{CRP AUC}})$  can thus be expressed relative to  $i/m$  as

$$i/m - (1 - e^{-k \cdot \text{CRP AUC}}) \quad (4)$$

This formula can be transformed using the chance  $p_i$  as expressed in equation 3 and substitution of  $y$  with  $1/2$

$$i/m - (1 - e^{-k \cdot \text{CRP AUC}}) = i/m - (1 - e^{-k \cdot \text{CRP AUC}}) \cdot (m/2i) \cdot (2i/m)$$

When  $(1 - e^{-k \cdot \text{CRP AUC}}) \cdot (m/2i)$  is replaced with  $p_i$  according to equation 3, the resultant equation is

$$(1/2 - p_i) \cdot (2i/m) \text{ or } \Delta p_i \cdot (2i/m) \quad (5)$$

where  $\Delta p_i$  is the distance on the disease dose scale to the point  $i/m$ .

Assuming a binomial distribution of  $p_i$  the SD of  $p_i$  will be

$$\sqrt{(p_i \cdot (1 - p_i)) / N} \text{ and the SD of } (1/2 - p_i) \cdot (2i/m) \text{ will be } \sqrt{(2i \cdot p_i \cdot (1 - p_i)) / mN} \quad (6)$$

In this way for each disease dose the distance to the point where 50% of sites will have reached score point  $i$  can be expressed in the number of SD as:

$$((1/2 - p_i) \cdot (2i/m)) / (\sqrt{(2i \cdot p_i \cdot (1 - p_i)) / mN}) \quad (7)$$

From the distance in SD ( $z$ ) the percentage of  $n$  with score  $i$  can be estimated using the table of probabilities for the standard Gaussian or normal distribution. Multiplying this percentage with  $n$  will yield the number of sites with score  $i$ . This procedure can be repeated for each value of  $i$  and the results summed to produce the overall curves for erosions and narrowing separately (because of the different  $m$  values for erosions and narrowing) and will result in curves d and e, respectively.

Summing these 2 curves yields curve c in Figure 1, representing the final theoretical model.

**Calculations and statistics.** Multivariate regression analysis was performed after log transformation of X scores, CRP levels, and k values. Patients were categorized according to sex, RF status, and HLA type. Spearman rank analysis was used for single correlations.

"True" k values were calculated with the use of curve c of Figure 1, in those patients who showed a rise in X scores during the total time period of 3 years. Their first positive X score was read from the curve to yield the "disease dose" at that moment, and the disease dose after 3 years was assessed using curve c and the X score after 3 years. The change in disease dose was divided by the concomitant change in CRP AUC to result in the individual true k values.

In those patients showing radiological progression during the first 3 years, the k values were also calculated for the time intervals 0-6, 0-12, 0-18, 0-24, and 0-30 months, provided that at least 2 positive scores were found within the respective period. For intervals during which the X score did not increase, the change was set at 0.5. For the comparison of predicted and observed scores absolute differences were used for scores  $\leq 20$  points, whereas relative differences were used for scores  $> 20$  points. Ratios between the estimated k values for the respective time intervals 0-t ( $k_t$ ) and true (3 years) k values were log transformed before further treatment. In addition, log transformation was performed of the ratios of predicted and observed scores for observed scores  $> 20$  points. Agreement is given as the mean, its 95% confidence interval (CI), and the 95% limits of agreement (mean difference  $\pm 1.96$  SD of differences) for absolute differences (observed scores  $\leq 20$ ) and as their antilogs for the ratios<sup>17</sup>. The standard error (SE) of the estimation of k values and the prediction of scores is given as a percentage of the mean  $(e^{\text{SD}} - 1) \cdot 100\%$ .

Estimation of the k value from entry data was performed using the formula describing the relative weight of independently contributing prognostic factors. A p value  $< 0.05$  was considered statistically significant.

## RESULTS

**Patients and treatments.** From the 149 patients with at least 3 years followup (Table 1), a subgroup of 54 patients had completed 6 years followup at the time of analysis. The only significant difference between these 54 patients and the rest was their age, median 50 and 55 years, respectively ( $p < 0.05$ ). During the first 3 years, 133 patients were treated with DMARD, mainly hydroxychloroquine, intramuscular gold, and sulfasalazine, either as the only DMARD, or in succession. Ten patients were treated with methotrexate or azathioprine. Thirteen patients were taking additional low dose corticosteroids during some of the followup period.

**Radiologic results and prognostic factors.** Total radiologic scores (X scores) after 0.5, 1, 2, and 3 years and the X scores after 6 years are shown in Table 2. Progression of radiological damage was observed in 82, 117, 121, 123, 123, 123 patients during time intervals of 0-6, 0-12, 0-18, 0-24, 0-30, and 0-36 months, respectively. Multivariate regression analysis was performed using a selection of variables based on previous studies on prognostic factors in this patient group<sup>14,18</sup>. No data for HLA-DR subtypes were

Table 1. Patient characteristics at study entry (n = 149).

Age (yrs), median (range)	53 (16-77)
Sex f:m, no. of patients (%)	94:55 (63:37)
IgM RF positive ( $\geq 10$ IU/ml), no. of patients (%)	121 (81)
Initial CRP level (mg/l), median (range)	20 (0.1-260)
HLA-DR4, no. of patients (%)	90 (60)
HLA-DR2, no. of patients (%)	29 (16)
Duration of complaints at study entry (weeks), median (range)	26 (6-52)



Table 2. Development of radiologic scores over 3 yrs (n = 149) and 6 years of followup (n = 54).

Followup (yrs)	3 Year Followup (n = 149)		6 Year Followup (n = 54)	
	Median	Interquartile Range	Median	Interquartile Range
0	1	0-6	1	0-4
0.5	6	1-15	4.5	1-18
1	12	1-19	7.5	2-28
2	20	4-44	16.5	4-51
3	23	6-53	21	5-71
6			51	18-108

available. The result showed that progression of radiological damage over 3 years was significantly related (multiple R = 0.683) to the initial X score ( $p < 0.001$ ), RF positivity ( $p < 0.001$ ), initial CRP level ( $p < 0.001$ ), absence of HLA-DR2 ( $p < 0.002$ ), and younger age ( $p < 0.03$ ). There was no relationship to HLA-DR4 ( $p = 0.52$ ) or sex ( $p = 0.77$ ). However, when RF was omitted as an independent variable, HLA-DR4 appeared to contribute significantly.

*Time integrated CRP values and radiologic progression.* Spearman rank correlation coefficients between CRP AUC values and radiologic progression over the first 3 years were, respectively, 0.656 ( $p < 0.001$ ) for the whole group of 149 patients and 0.651 ( $p < 0.001$ ) for the subgroup of 54. For this subgroup, the correlation coefficient over 6 years was 0.666 ( $p < 0.001$ ). In each individual, the relationship between  $\delta$ -X score and  $\delta$ -CRP AUC approximated a straight line, indicating that the individual relationship was rather constant over time (Figure 2).

*Calculated individual true k values.* Individual k values were calculated as described in Materials and Methods. The individual k value represents the individual ratio between CRP production, as a variable of inflammatory activity, and the rate of progression of radiologic damage. The k value could be calculated in the 123 patients showing radiological progression during the 3 year followup (k values cannot be calculated in patients without radiological damage). The geometric mean of the k values was  $18.9 \times 10^{-6}$  l/mg CRP/week, with a range from  $0.9 \times 10^{-6}$  to  $401.6 \times 10^{-6}$  l/mg CRP/week, showing the wide interindividual variance in this variable, yielding a coefficient of variance of 192%.

*The k value and radiologic progression.* After inclusion of the individually calculated k values, multivariate regression analysis identified highly significant correlation coefficients between progression in X score over 3 years and positive RF, initial CRP level, and k value (all  $p < 0.001$ , multiple R = 0.919). In contrast to the analysis for characteristics at entry without k values, initial X score ( $p = 0.20$ ), absence of HLA-DR2 ( $p = 0.84$ ), and age ( $p = 0.63$ ) no longer correlated with the 3 year radiologic progression; HLA-DR4 ( $p = 0.60$ ) and sex ( $p = 0.25$ ) were still not related. The k value itself correlated (multiple R = 0.62) with RF positivity, absence of HLA-DR2, initial X score (all  $p < 0.001$ ), and

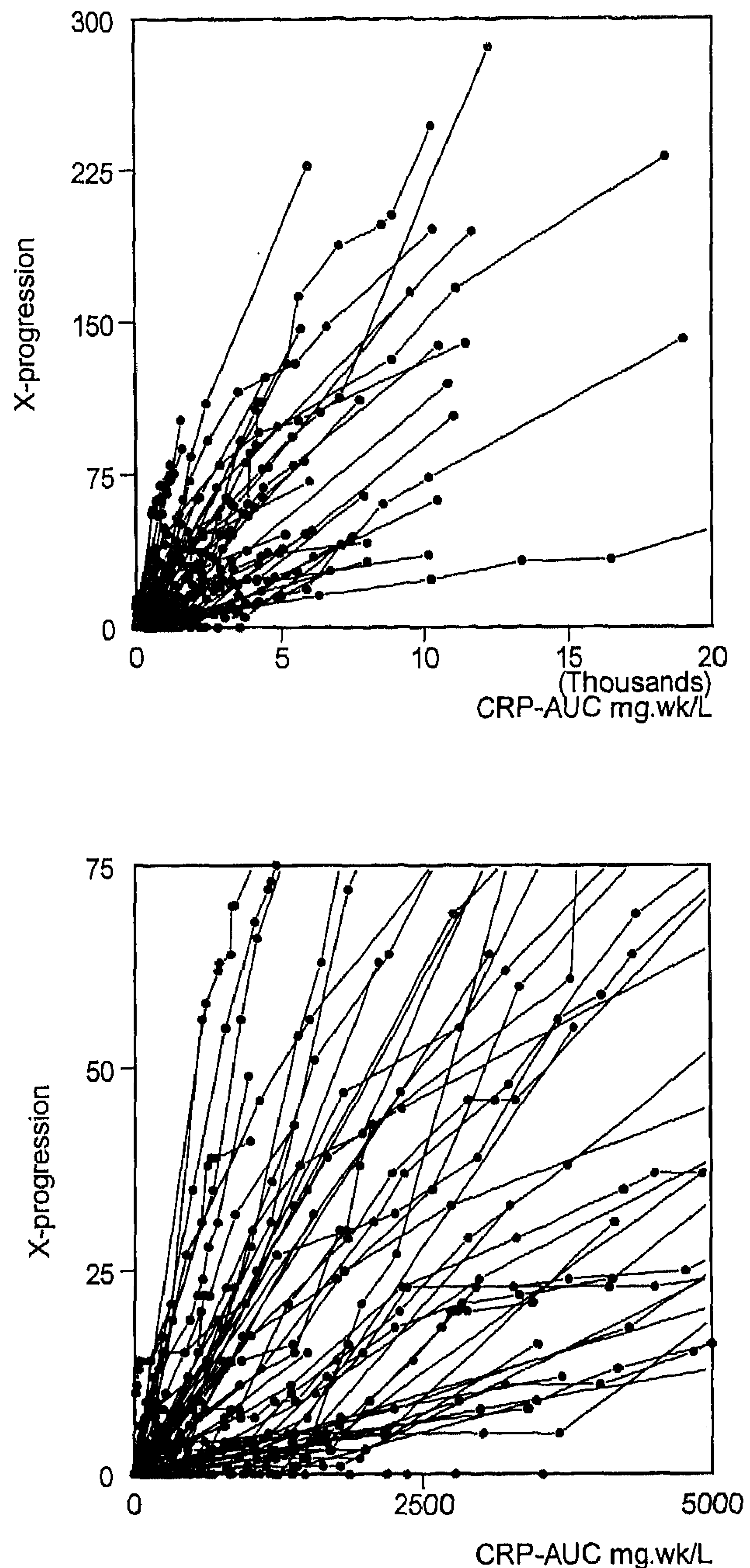


Figure 2. (a) Intraindividual relations between time integrated CRP values (CRP AUC) and radiologic progression during 6 years of followup (N = 54). (b) Enlargement of the lower left corner of (a).

younger age ( $p = 0.004$ ). The equation describing the relative weight of independently contributing prognostic factors was equation A:

$$\ln(k \cdot 10^3) = -4.185 - 0.022 \cdot \text{age} + 1.089 \cdot \text{RF} - 0.952 \cdot \text{HLA-DR2} + 0.299 \cdot \ln(X_0 + 1) \quad (\text{A})$$

where RF and HLA-DR2 were treated as categorical variables.

*Estimation of k value in very early disease and validation of the model.* The k value used in the regression analysis was

derived from the results of the full 3 year followup. In clinical practice, however, an accurate estimate of  $k$  after a shorter time interval would be useful to predict disease outcome reflected by radiologic score. To be regarded as clinically useful a model should enable a reliable estimate of the  $k$  value as early as 6–12 months after diagnosis.

To assess its predictive accuracy,  $k$  values were estimated at different time intervals (0–6, 0–12, 0–18, 0–24, 0–30 months) and expressed as a percentage of the true  $k$  value derived from the full 36 month period. The results are given in Table 3. The  $k$  values are stable in time, being slightly overestimated in the first 24 months compared to the true  $k$  value. The agreement between estimated  $k$  value and true  $k$  value increases with the length of the interval.

*Accuracy of the  $k$  value and its predictive use.* As described above,  $k$  values over 3 year data could be calculated in those patients showing X progression during this period ( $N = 123$ ). In 82/123 patients with an initial X score  $> 0$ ,  $k$  values could be calculated after 6 months, and in 117/123 patients with a 6 month X score  $> 0$ ,  $k$  values after 1 year could be

calculated. In patients with X score  $> 20$  points relative values were compared, whereas absolute values were used for the comparison in patients with an X score of  $\leq 20$  points.

At first, X scores at 3 years were predicted using  $k$  values obtained from data at entry using equation A and the actual CRP levels during the 3 year followup. The predicted results were compared with the X scores actually observed after 3 years (Figure 3a and Table 4). Of the 82 patients with an initial X score  $> 0$ , 19 patients had an observed score below 21 after 3 year followup. In these patients, the predicted scores were not statistically different from the observed scores, though the 95% limits of agreement ranged from  $-39$  to  $+25$ . In the 63 patients with an observed X score of  $> 20$  points after 3 year followup, the predicted scores were statistically different from the observed scores (85%, Table 4) with a SE for predicted scores of 56%.

Second, X scores at 3 years were predicted using  $k$  values obtained with data from the first half year using curve b and the actual CRP levels during the 3 year followup in the same 82 patients. For observed scores of  $\leq 20$  points, the

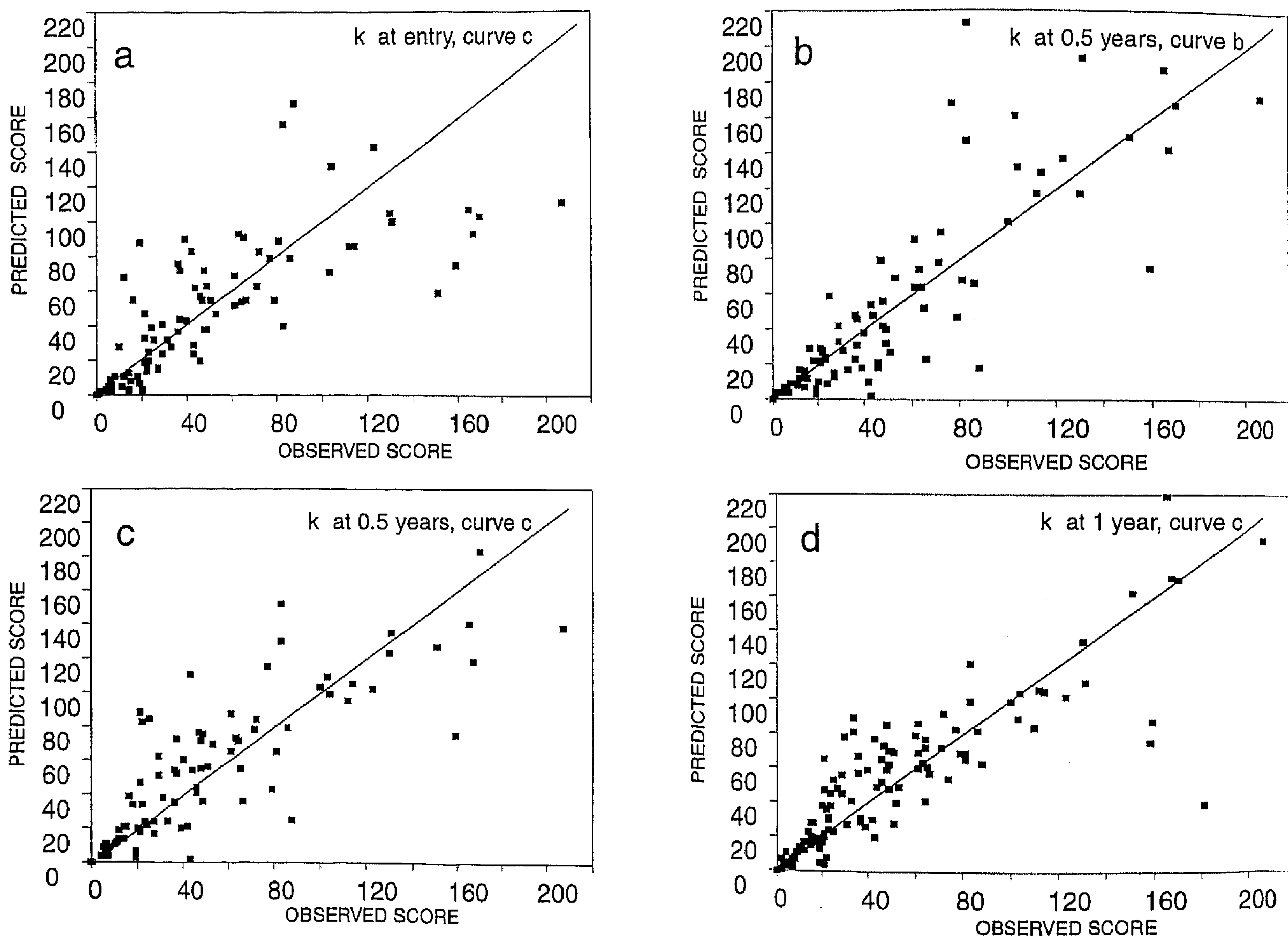


Figure 3. Relation between predicted X score and observed X score after 3 years in patients with X progression during 3 year followup and an initial X score  $> 0$  ( $N = 82$ ), or X score  $> 0$  after 6 months ( $N = 117$ ). (a) Using  $k$  value estimated from initial characteristics and curve c as a reference ( $N = 82$ ). (b) Using  $k$  value derived from 6 months observational data and curve b as a reference ( $N = 82$ ). (c) Using  $k$  value derived from 6 months observational data and curve c as a reference ( $N = 82$ ). (d) Using  $k$  value derived from 12 months observational data and curve c as a reference ( $N = 117$ ).



Table 3. Agreement of k values estimated over different time periods and expressed as a percentage of the true k values, derived from full 36 month data.

Interval (mo)	N	k Value, % of 3 Yrs Value	95% CI	SE, % of Mean
At entry	123	74.5	62.1–89.3	179
0–6	82	115.5	99.3–134.3	101
0–12	117	113.6	103.8–124.2	64
0–18	121	113.1	105.1–121.8	51
0–24	123	107.1	99.9–115.0	49
0–30	123	101.7	99.4–103.9	13
0–36	123	100.0		

N: number of patients with radiological progression over a period of 3 years who had at least 2 X scores > 0 within the respective time intervals.

predicted scores were not statistically different from the observed scores, though the 95% limits of agreement ranged from –15 to +12. For observed scores of > 20 points after 3 years, the predicted scores were only 87% of the observed ones, with a SE of 88% (Figure 3b and Table 4).

Third, X scores at 3 years were predicted using k values obtained with data from the first half year using curve c and the actual CRP levels during the 3 year followup in the same 82 patients. For observed scores of ≤ 20 points the predicted scores were not statistically different from the observed ones, with 95% limits of agreement from –14 to +19. For observed scores of > 20 points the predicted scores were not statistically different (104%) from the observed ones, with a SE of 72% (Table 4 and Figure 3c).

Fourth, X scores after 3 years were predicted using the k value calculated from the 1 year data using curve c and the actual CRP values over 3 years. The k value could be estimated in the 117 patients with an X score > 0 at 6 months. In 34 of them the observed score at 3 years was ≤ 20 points. The predicted scores were statistically slightly above the observed ones, with 95% limits of agreement ranging from –10 to +13. In the other 83 patients with an observed score > 20, the predicted scores were not statistically different from the observed ones (109%), with a SE of 57% (Table 4 and Figure 3d).

Finally, the 1 year k values derived from curve c and

actual CRP values over 6 years were used to predict the X score at 6 years in the subgroup of 54 patients. As only 4 patients had X scores of ≤ 20 points, separate calculation of the lower range using absolute values was omitted. In the 43 patients with X score > 0 at 6 months, the predicted scores were 97% of the observed ones (95% CI from 85 to 112%, 95% limits of agreement from 44 to 215%) with a SE of 51%.

The influence of specific drug treatments on the k value could not reliably be evaluated, because insufficient numbers of patients were treated with one specific DMARD throughout the study period (according to the followup protocol DMARD could be changed as clinically indicated, independent of the radiographic intervals). We evaluated the data of those patients who were treated with a specific DMARD during at least 9 months of the first year of the study. If this main drug was added to the independent variables in the analysis, no significant differences in k values of the first year were found for hydroxychloroquine, sulfasalazine, or gold.

*Use of ESR instead of CRP.* Use of ESR instead of CRP as the indicator of acute phase response yielded essentially the same results in this model.

## DISCUSSION

Our study evaluates the monitoring of disease activity aimed at prediction of radiologic outcome in early RA for individual patients. The results of radiologic damage of our patients are in agreement with the work of others, indicating that a majority of patients with RA will develop radiologic joint damage of hands and feet within the first year of the disease<sup>1,2</sup>. Inclusion of the foot joints in the assessment of early joint damage is important because early abnormalities may occur in the absence of radiological damage in hands or wrists<sup>19,20</sup>. This early, largely irreversible joint damage is a major argument for starting potentially effective drug treatment soon after presentation<sup>21</sup>. The factors that predicted radiologic progression in our patients were those commonly reported in the literature<sup>7,22–24</sup>, including RF, HLA-DR4, absence of HLA-DR2, and high disease activity (measured

Table 4. Agreement of predicted and observed X scores over 3 years: comparison of different k values.

	k Value at Entry, Curve c	k Value at 0.5 yrs, Curve b	k Value at 0.5 yrs, Curve c	k Value at 1 yr, Curve c
Values > 20	N = 63	N = 63	N = 63	N = 83
Mean at 3 yrs (%)	85	87	104	109
95% CI of mean	76–95	75–102	89–122	99–121
95% LOA	35–203	25–300	31–358	46–263
SE (% mean)	56	88	72	57
Values ≤ 20	N = 19	N = 19	N = 19	N = 34
Mean at 3 yrs (abs)	6	–2	2	2
95% CI of mean	–4–17	–5–2	–2–6	0–4
95% LOA	–39–52	–15–12	–14–19	–10–13

LOA: limits of agreement.

by CRP levels), and they contributed independently to outcome with an explained variance of 46%. When analyzed together in a multivariate regression analysis, RF and absence of HLA-DR2 appeared to have a predictive value higher than HLA-DR4, indicating RF may act as a surrogate marker for HLA-DR4. Reports concerning the contribution of age are contradictory<sup>25,26</sup>. Although prognostic factors assist early identification of patients at risk of progressive disease, and radiologic damage can be predicted better if data concerning the course of the disease during the first 6 months are included<sup>18</sup>, the predictive value for individual patients remains limited.

The acute phase response is a suitable marker for longterm objective monitoring of disease activity, and it has been shown to be related to the progression of radiologic damage. The low basal levels, rapid increase, and short half-life of CRP compared with fibrinogen, which is mainly responsible for the ESR, are arguments in favor of CRP measurement. Furthermore, the only determinant of circulating CRP levels is the synthesis rate of CRP, so that the time integrated CRP (CRP AUC) is a proper measure of cumulative CRP production<sup>27</sup>.

The significant overall correlation between time integrated CRP values and radiologic progression, previously reported in these patients over 3 year followup<sup>12</sup>, was confirmed here for followup of 6 years in a subgroup of 54 patients and is in agreement with the study of Hassell, *et al*<sup>28</sup>. However, the wide interindividual variation of the relationship between CRP levels and radiologic progression limits the use of single CRP measurements for the prediction of outcome in individual patients. Knowledge at an early stage of the disease of the specific relationship between CRP levels and radiologic progression in each patient would enable the clinician to identify those at risk, and to determine the range of CRP levels within which joint damage would be limited.

We have therefore developed and validated a model to describe the individual relationship between CRP levels and radiologic progression, which accounts for the discontinuity of the radiologic damage scoring system and the problem of synchronous scoring as radiologic damage begins.

The *k* value, representing the individual relationship between CRP levels and radiologic progression, indeed showed wide interindividual variation, with a coefficient of variance of 192%. Therefore, it is important to estimate the *k* value as soon as possible to adjust the estimation of the prognosis of an individual patient.

Estimates of individual *k* values from entry data can be made in early disease, though slight overestimation tends to occur during the phase of declining CRP levels, because radiologic score and CRP levels are slightly out of phase, as we have shown<sup>12</sup>. In our data there appears to be substantial overestimation up to 2 years when using the *k* value from entry characteristics. The SE of the estimated *k* value

improves from 179% when using entry data, to 101 and 64% using 6 month data and 1 year data, respectively (Table 3). It is essential to use a model that takes into account synchronous scoring in early disease (curve c), as the predicted score will be underestimated using a model that includes only the discontinuity of scoring (curve b). From a clinical point of view, underestimation is more difficult to correct with regard to treatment than overestimation. The SE of the predicted score at 3 years using 1 year data amounts to 57%. Yet the error in the predicted score is much lower than the observed interindividual variation of 192% of the relationship between CRP production and radiologic progression, which one would have to deal with if the *k* value is not used for prediction of radiologic progression. The SE of the predicted scores at 3 and 6 years, using 1 year data for the estimation of the *k* value, are similar (57 and 51%, respectively). This indicates that longterm prediction with acceptable accuracy is possible.

Calculations of *k* values and prediction of radiological progression were performed irrespective of the specific drug treatments. Analysis of the influence of DMARD on *k* values yielded no drug specific differences for hydroxychloroquine, sulfasalazine, or gold. These findings support the assumption that any treatment that affects radiological progression also affects CRP and ESR proportionally.

The present model can thus be used as the basis of a decision support system in which monitoring of CRP and regular radiologic scoring during followup enable the *k* value of individual patients to be determined with progressively greater precision. This in turn can be used to predict radiologic progression with increasing accuracy, and, importantly, to determine levels of CRP below which further radiologic damage should not occur. The model is unsuitable for patients with no radiologic damage after 6 or 12 months. However, such cases usually have a good prognosis, and in the present series only 4 of 21 individuals with no damage at 6–12 months developed lesions after 3 years.

For routine clinical use the model has been incorporated into a software program in which it is combined with the prognostic factors of each patient, and consecutive CRP levels during followup are translated into a radiologic prognosis, assuming that CRP production will remain unchanged. This prognosis is then updated with each new CRP measurement and with the revised *k* value obtained after each set of radiographs has provided the current X score. It should be emphasized that this interpretation of CRP values with regard to radiological progression in the individual patient can support, but not replace, clinical decision making. A decision support system is not a "brain prosthesis," but rather an instrument bringing together the knowledge and the expertise needed to solve complex clinical problems. Although the model has been designed for use with CRP measurements, its performance using the ESR as an indicator of the acute phase response was very similar. This



is not surprising, as the ESR is essentially a time integrated variable reflecting disease activity during the preceding several weeks. Further detailed analysis, with particular reference to lower range values, will be required to establish whether CRP, ESR, or possibly the other sensitive acute phase reactant, serum amyloid A protein, is the best indicator of the acute phase response in this system. Regarding the good correlation between radiologic progression and swollen joint counts<sup>29</sup>, analysis of the performance of clinical variables may be warranted. Further detailed analysis will be needed to establish the mechanism by which certain factors influence the k values. Meanwhile, the performance of the present CRP model in monitoring the effects of drug treatment is being assessed in a prospective study in patients with early RA.

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