The Level of Inflammation in Rheumatoid Arthritis Is Determined Early and Remains Stable Over the Longterm Course of the Illness

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ABSTRACT. ***Objective.*** To determine whether the level of inflammatory activity, determined by the erythrocyte sedimentation rate (ESR), changes over the longitudinal course of rheumatoid arthritis (RA); whether the level of inflammatory activity identified early in RA predicts longterm inflammatory status; and whether RA "burns out" after many years of inflammatory activity.

Methods. A total of 21,866 consecutive ESR determinations from 1897 patients with RA were analyzed to determine the association of inflammatory activity, as estimated by ESR, with duration of disease. Data were modeled by generalized estimating equations and random selection fractional polynomial regression models, controlling for age, sex, and calendar date.

Results. In a nonlinear fashion, ESR decreased by 4 mm/h over the first 10 years of disease, remained stable over the next 25 years, and increased slightly thereafter. Patients treated more recently had lower ESR values. Patients with recent onset of RA, when stratified in quartiles of ESR, maintained their position over time.

Conclusion. Although ESR decreases by 4 mm/h over the first 10 years of disease, it remains stable or rises thereafter. The course of RA, as modeled by the ESR, appears to be "set" early in the disease and good and bad prognosis groups can be identified within the first 2 years. There is no evidence of general "burned out" RA or a lessening of disease activity with long duration of disease. Our findings tend to suggest that the ("usually treated") natural history of RA prior to introduction of anti-tumor necrosis factor agents is toward some degree of improvement in the early years. If the newer and combination therapies are indeed substantially better than what has been available, they must show a shifting of the curve downward, not just in the early years where it has occurred historically, but over the entire course of the illness. (J Rheumatol 2001;28:1817–24)

Key Indexing Terms:
INFLAMMATION ERYTHROCYTE SEDIMENTATION RATE
RHEUMATOID ARTHRITIS LONGITUDINAL OUTCOME

Rheumatoid arthritis is characterized by inflammation of joints, seen as joint swelling and tenderness, and by elevation of the erythrocyte sedimentation rate (ESR) and C-reactive protein[1-17]. If inflammatory activity is not controlled, or only partially controlled, joint damage results, seen as joint deformity and radiographic progression[18-20]. The goal of treatment has been to control inflammatory activity in order to prevent joint damage[7,15,21-24].

Control of inflammatory activity has been achieved using a variety of drugs, including nonsteroidal antiinflammatory drugs (NSAID) and disease modifying antirheumatic drugs (DMARD), in short term clinical trials[25-27]. However, over long periods, most of these drugs have been discontinued[28–31] and inflammation has been only partially controlled. Historically, most patients treated according to the traditional pyramid[32] or sequential[33] strategy experienced poor longterm outcomes[34], including severe functional declines[34], radiographic progression[35-37], considerable economic losses, work disability[38,39], need for joint replacement[40] and premature mortality[34,41,42].

The course of inflammation over many years has not been studied in great detail. There is a pervasive thought that RA may "burn out" with time, which may have emerged from observations in a few patients with long duration or endstage RA who appear to have no disease activity. However, there is evidence that while measures of inflammation tend to be unchanged or improved over 5–10 years, joint deformity and radiographic damage continue to progress[18,20,43,44], suggesting that some level of persistent inflammatory activity is seen over long periods.

In addition to these concerns, the longitudinal course of inflammatory activity in RA has not been documented, and

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most attempts have utilized cross sectional data, data that are usually substantially left-censored (or not including all patients developing RA). Of particular interest is how RA behaves at the beginning of the illness, since conclusions about the effect of early aggressive therapy may, in fact, be determined by the natural course of RA as much as by treatment, an issue that remains unresolved.

We modeled inflammation by the use of the ESR, one of the 6 American College of Rheumatology and European League Against Rheumatism disease activity criteria[45,46]. There are a number of difficulties in modeling inflammation. Except for swollen joints, which were not available in this data set, all the other criteria except ESR might be expected to measure both inflammation and destruction. For example, joint pain, visual analog scale (VAS) pain, VAS global, and HAQ disability all would be altered by longterm destructive disease. The ESR, however, is not influenced by previous damage, and is a pure measure of RA inflammation so long as other factors that influence the ESR, such as age and sex, are controlled for[1,17]. In this study we use ESR as a surrogate for inflammation, and model the effect of disease duration on ESR in 2 separate but allied analyses.

MATERIALS AND METHODS

Patient population. The Wichita data bank, which contains serial data on 1897 patients with RA, was utilized. This data bank contains prospectively collected data on all (N = 1897) RA patients seen for clinical care at the Wichita Arthritis Center between 1974 and 2000. The details of the data bank have been published[36,38,40]. During this period of time, the 1897 patients had 26,442 clinic visits, and 21,866 of these visits (82.8%) included collection of an ESR. The reason for not obtaining an ESR included clinic visits occurring after a brief duration of followup when laboratory testing was inappropriate, or when laboratory testing was not permitted by patient or insurer. Considering all observations, patients who had a clinic visit with a missing ESR were slightly younger (56.8 vs 59.2 yrs), had higher Health Assessment Questionnaire (HAQ) scores (1.35 vs 1.30) and pain scores (1.51 vs 1.39), and more frequently were men (25.3 vs 28.3%). However, all patients contributed ESR determinations to the study, and all observations were included in the analyses.

The Westergren ESR was performed in the same laboratory over the course of the study, as described[17,47].

Statistical methods. Data were analyzed using Stata 6.0[48]. Fractional polynomial regression was performed on a randomly selected per-patient sample using the Royston method[49]. In these analyses 44 fractional polynomial models were fit. The best fitting model is shown in Table 2 and Figure 1. Each polynomial term resulted in information gain and was significantly better, alone and in combination, than the linear model. The p value for improvement by the logarithmic term over the linear model was 0.006, and for the additional improvement by the power term was 0.004.

After examination of the results of this model, a second fractional polynomial analysis was performed, this time using all observations, and the fractional polynomial terms that were derived were used as variables in general estimating equations (GEE). GEE is a form of Generalized Linear Models (GLM) that properly handles longitudinal data. In the analyses of this report we used the Huber/White/sandwich (robust) estimator of variance and an exchangeable correlation structure. This method produces consistent standard errors even if the within-group correlations are not as hypothesized by the specified correlation structure. The use of GEE allows the intrapatient correlation to be accounted for and random intercepts to be modeled explicitly, but at a cost of a wider standard error. GEE analyses also allow for missing data, unbalanced designs, and unequal lengths of followup.

All p values are 2 tailed, and the level of statistical significance was set at 0.05.

RESULTS

Demographic and clinical characteristics. The characteristics of the study patients are shown in Table 1. Most (90.5%) were rheumatoid factor positive, and 72% of patients were women. The average age and disease duration was 50.2 and 11.4 years. The maximum length of followup was 23.3 years, and the mean ESR was 34.1 mm/h.

The longitudinal course of ESR in RA — all patient data. To evaluate associations between ESR and disease duration, a single randomly selected observation from each patient was analyzed by regression using fractional polynomials. The results of this analysis indicated that a nonlinear model best fit the data by providing significant statistical improvement over a linear model alone. The data are shown in Table 2 and Figure 1.

The use of per-patient randomly selected observations may be considered a way to summarize each patient's contribution, but makes use of only 1897 of the 21,866 observations and does not consider the intrapatient correlation and the full longitudinal nature of the data. Therefore additional analyses were undertaken using GEE. To obtain the appropriate fractional polynomials for the GEE analyses, fractional polynomial regression was again run, this time using all 21,866 observations. The identified fractional polynomials were then used as the explanatory variables in the GEE analysis. The robust GEE analysis, which more appropriately accounts for the correlation structure of the data, indicated that only the natural log disease duration component, age, and calendar date were statistically significant in this model. This analysis was confirmed by graphic inspection, and a final reduced model is shown in Table 3 and Figure 2.

The ESR is known to increase with age and is greater in women than men. In addition, change in therapy or patient population may possibly alter ESR rates as a function of calendar time. Therefore age, sex, and date were added as

Table 1. Demographic and clinical variables for 1897 patients with RA.

Variable	Mean, %	Overall SD	Minimum	Maximum
Age	50.2	13.3	14.6	96.4
Sex (% male)	28.3			
Disease duration (yrs)	11.4	9.0	0.03	63.3
Clinic followup (yrs)	5.5	5.0	0	23.3
Rheumatoid factor +	90.5%			
ESR (mm/h)	34.1	25.1	0	147
HAQ disability	1.3	0.8	0	3

SD is the overall SD (within plus between). The mean is the unweighted mean of all observations (N = 21,866). The average number of observations per patient was ~11.5.

Table 2. Fractional polynomial regression analyses in 1897 randomly selected observations from 1897 patients with RA.

Variable	Coefficient	SE	T	p	Lower 95% CI	Upper 95% CI
Duration 1*	–1.817	0.497	–3.656	0.000	–3.099	–0.536
Duration 2*	0.143	0.039	3.628	0.000	0.041	0.244
Age	0.267	0.040	6.733	0.000	0.165	0.369
Sex	–0.311	1.257	–0.247	0.805	–3.551	2.930
Observation date	–0.002	0.000	–7.036	0.000	–0.002	–0.001
Constant	33.491	0.763	43.917	0.000	31.525	35.458

*Duration 1 = logn(X) + .0403. Duration 2 = X^3–.8862, where X = duration/10.
F(5, 1883) = 23.36, Prob > F < 0.000, R-squared = 0.058, Root MSE = 24.496
Deviance 17438.650.

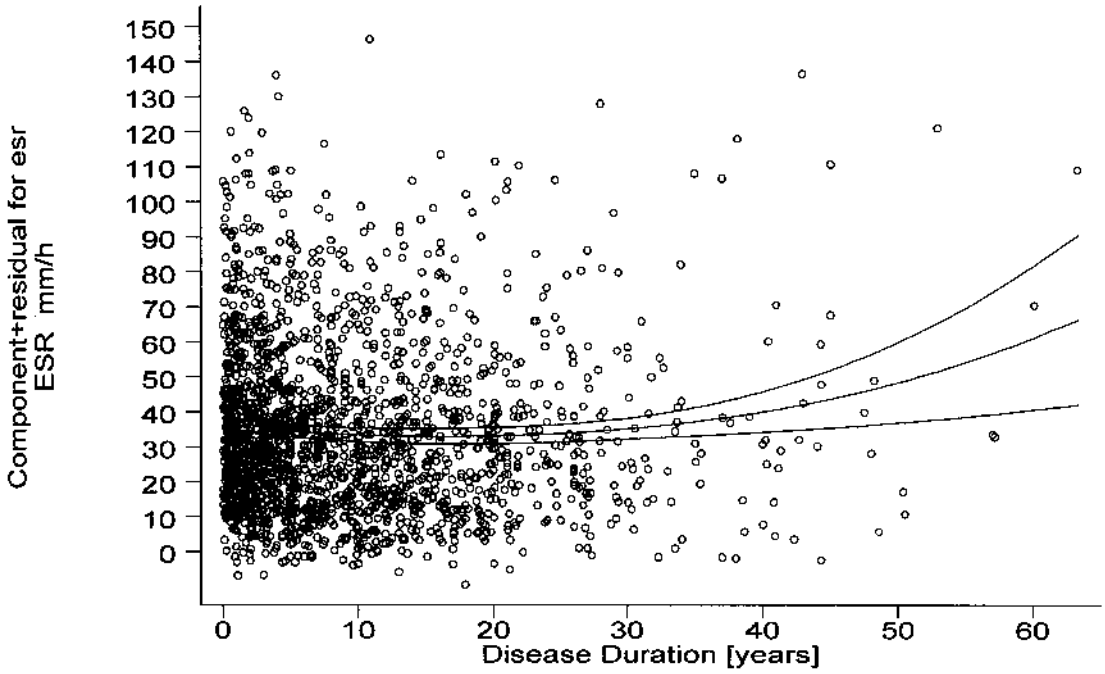

Figure 1. Graph of ESR versus disease duration as modeled in a fractional polynomial regression. One randomly selected observation was selected per patient. Lines are predicted value of ESR and 95% CI. Data points give an idea of the relative distribution of ESR values over the duration of disease. Only 1897 of the 21,866 ESR values are represented here. Following additional analyses, the full ESR data are illustrated in Figure 2. Predicted values are adjusted for age and calendar date at mean values, and for sex at the female level. As shown, data points and predicted ESR values represented a component-plus-residual plot (also known as a partial residual plot).

covariates to all models. As can be seen in Tables 2 and 3, age and date were significantly associated with ESR and all models, and sex was significant in the polynomial regression model. To help the reader by providing a comparison, we determined the increase in ESR as a function of age in patients with noninflammatory disorders (osteoarthritis and fibromyalgia) over the same time period of this study. For 4054 patients having 7183 observations, GEE analysis indicated that the ESR increased by 0.160 mm/h (standard error, SE, 0.163) per year or 1.6 mm/h per 10 years of followup or age.

Remembering that the values of ESR are adjusted to female sex (about a 1.5 mm/h difference), the data of Figure 2 show that the ESR at the beginning of disease averages 37 mm/h. By 10 years of disease the ESR falls to 33 mm/h, a difference in 4 mm/h. Thereafter the ESR remains constant over the next 20 years of disease, and rises slightly after that.

Predicting ESR outcomes in those with recent onset RA. Although the data above describe the average course of ESR, an important clinical question is the stability of ESR over time and the extent to which initial ESR status predicts final status. To answer these questions patients with less

Table 3. Generalized estimating equation (GEE) analysis in 21,866 observations from 1897 patients with RA.

Variable	Coefficient	SE	T	p	Lower 95% CI	Upper 95% CI
Duration*	–1.960	0.399	–4.909	< 0.001	–2.988	–0.931
Age	0.352	0.032	11.025	< 0.001	0.270	0.434
Observation date	–0.001	0.0001	–7.22	< 0.001	–0.002	–0.001
Constant	33.038	0.537	61.448	< 0.001	31.653	34.423

*Duration = logn(X) – 1.283, where X = duration/10.
Wald chi2(3) = 204.66, Prob > chi2 = < 0.001. Analyses used an exchangeable correlation structure and robust standard errors.

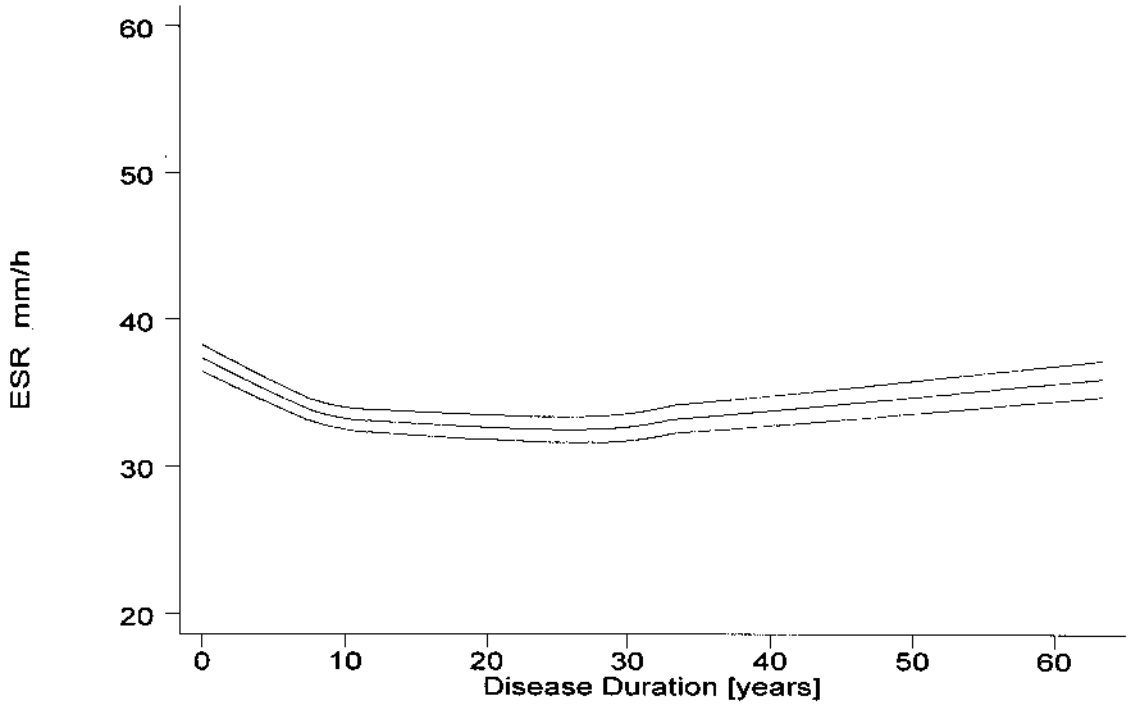

Figure 2. Graph of ESR versus disease duration. Lines are predicted ESR and associated standard errors. Estimates were obtained using a generalized estimating equation with robust standard errors. Predicted values are adjusted for age and calendar date at mean values. Predicted values and error lines were smoothed using lowess regression.

than 2 years' disease duration at the time they were first seen in clinic were stratified into 4 quartiles based on (1) the first ESR and (2) the average ESR during the first 2 years of clinic followup (Table 4). A series of analyses were performed, following on the methods above. Briefly, for each quartile of the 2 groups, fractional polynomial regression was performed followed by separate GEE analyses. Data were combined into 2 graphs, Figures 3 and 4.

Figure 3 shows that, during followup, patients in the 4 quartiles maintain their relative positions. Figure 4, based on average ESR over the first 2 years of followup, shows both the changes that occur over the first 2 years as well as the continuing separation of the ESR classes. In the figures, confidence intervals are omitted to improve graph readability. However, the issue whether the groups are indeed

Table 4. Quartiles of ESR at the first clinic visit and as the mean of clinic visits over the first 2 years of followup.

Quartile	N	Mean	SD	Minimum	Maximum
1st visit data					
1	183	11.54	5.45	0.00	20.00
2	185	28.03	4.19	21.00	35.00
3	181	44.10	5.36	36.00	54.00
4	174	79.59	19.97	55.00	135.00
2 year mean data					
1	181	12.22	4.74	0.40	18.02
2	181	24.94	3.38	18.10	30.34
3	183	37.19	4.51	30.43	45.67
4	178	63.54	15.49	46.00	128.30

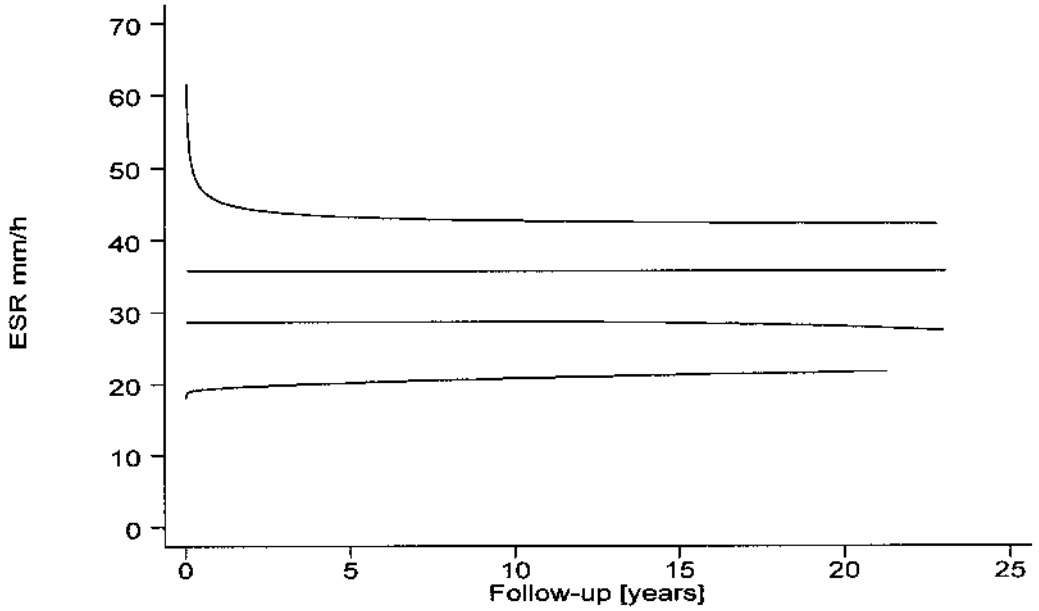

Figure 3. Graph of ESR versus disease duration for 4 quartiles of ESR as determined at the first clinic visits. Patients (n = 835) had disease duration of less than 2 years at first clinic visit.

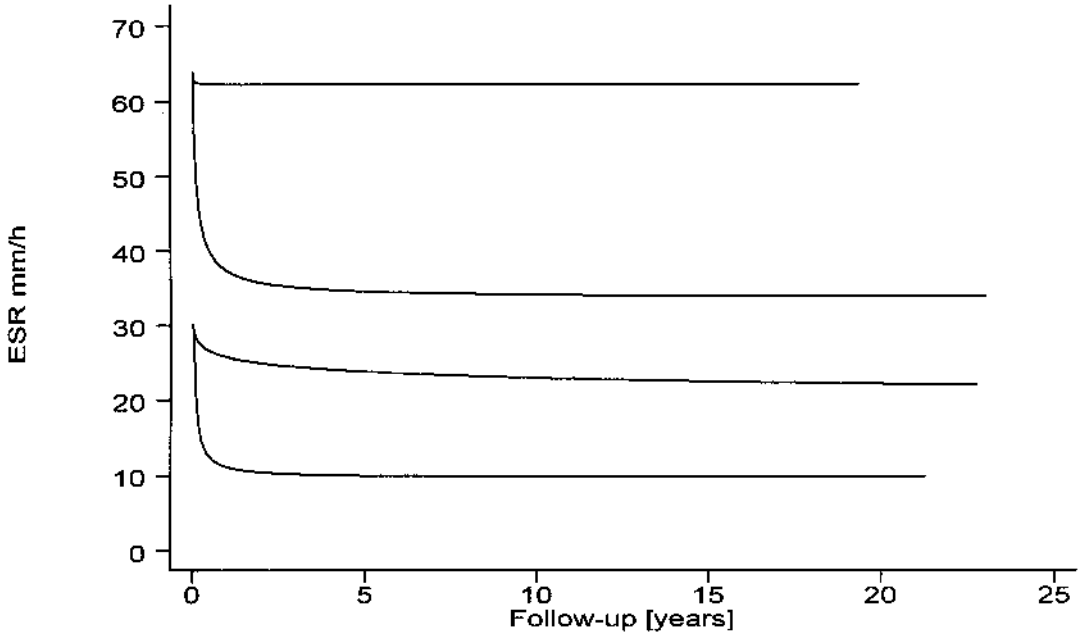

Figure 4. Graph of ESR versus disease duration for 4 quartiles of ESR as determined by average 0–2 year values. Patients (n = 835) had disease duration of less than 2 years at first clinic visit.

separate is important. To describe group differences, GEE regressions were performed on observations after the first 2 years of followup so that the regression would not be biased by the initial classification data. Linear rather than nonlinear models were used because the curves of Figures 3 and 4 are flat after 2 years. In addition, no covariates were added to the model because the main interest was patient differences.

For the quartiles obtained at the first clinic observation, post-2 year ESR data for the 2nd, 3rd, and 4th quartiles were increased compared to the 1st quartile by [coefficient (SE)] 8.3 (2.1), 16.6 (2.3), and 22.1 (2.4). For the quartiles obtained as an average of the first 2 year data the increases are 12.8 (7.3), 24.1 (0.9), and 50.2 (1.7). All quartiles differed at $p < 0.001$.

The quartile analysis shows that groups identified as to the extent of inflammation (ESR) early in the course of RA maintain their group differences over time. However, the mean values of the regression analyses presented here may give the wrong impression that patients are homogeneous within groups. As shown in Figure 5, patients in the 4th quartile, classified by average 0–2 years values, vary substantially in the subsequent, post-2 year followup observations. When observations from patients classified by first visit ESR were examined (Figure 6), similar variability was seen. But in this group there were many more low values. The differences between these 2 figures indicate that predictability of outcome is improved when 0–2 year data are used rather than 1st visit data.

DISCUSSION

The results of this study represent an outcome of RA during the years 1974 through early 2000, generally before leflunomide and anti-tumor necrosis factor (TNF) agents came into use. Almost all patients were treated with DMARD, and in the last decade of the study methotrexate was prescribed to new RA patients and those not doing well taking their current DMARD. As shown in Tables 2 and 3, patients seen more recently had lower ESR values. The magnitude of this change is important. From Table 3, over a 10 year period the ESR reduction would be about 5.1 mm/h. It is possible that this represents the use of better therapy (methotrexate) in later years, but it also may represent premature deaths of patients with the most severe RA, or a change in practice pattern. Even so, the possibility that methotrexate might alter the course of RA in this way is compatible with the data.

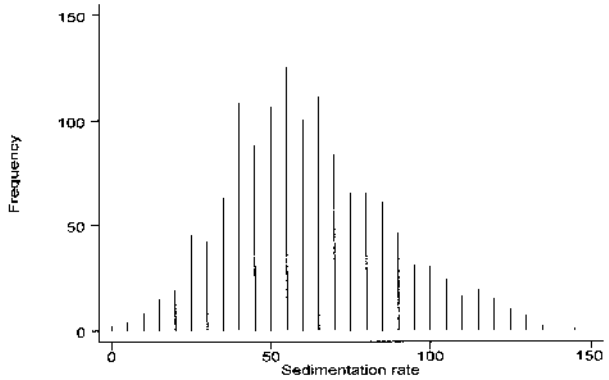

Figure 5. Distribution of 4th quartile ESR values for patients identified on the basis of 0–2 year classification. Data are for the years following the 0-2 year followup period.

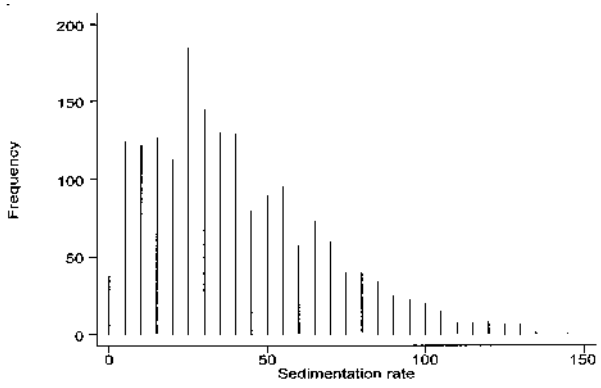

Figure 6. Distribution of 4th quartile ESR values for patients identified on the basis of first visit classification. Data are for the years following the 0–2 year followup period. Note improvement compared to Figure 5.

ESR, hence disease activity, is greatest early in RA, but the maximum difference between RA at onset and RA in the period 10–35 years is only 4 mm/h; and the average difference of the first 10 years compared with years 10–35 is only 2 mm/h. These data show that RA activity is greatest early in disease, but that RA remains active over the entire course of illness in many patients, including most in whom it was abnormal at first observation. One limitation of these observations in regard to short duration RA is that we are dealing with treated patients seen in rheumatology practices. It seems possible that untreated patients with short duration of disease would have even greater ESR values.

Another important result of this study is that, even before the common use of anti-TNF drugs and combination therapy, RA improved during the first few years of treatment. Although it is now common to attribute improvement in early RA to the use of new and more aggressive therapies, our findings tend to suggest that the ("usually treated") natural history of RA is toward some degree of improvement in the early years. If the newer and combination therapies are indeed substantially better than what has been available, they must show a shifting of the curve downward, not just in the early years where it occurs in any event, but over the entire course of the illness.

However, a signal observation from this study is that the inflammatory course of RA, as measured by the ESR, is set very early in the course of the illness. When patients with RA of less than 2 years' duration were classified according to the quartile of their ESR, these quartile positions were maintained over time. The challenge of new therapy is to change this positioning.

Except for patients in quartile 1, none of the RA patients "did well" as far as inflammation estimated by the ESR was concerned. Data such as we have presented suggest that, as a minimum, patients in quartiles 2–4 should all receive "best" treatment. Waiting for patients to improve does not appear to be a good strategy, for while some will improve, most will not, and will suffer progressive disease damage.

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