SCIENTIFIC PAPERS

Clinical significance of rheumatoid factors in early rheumatoid arthritis: results of a follow up study

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Abstract

Serum rheumatoid factors (RF) were measured yearly in 135 women with rheumatoid arthritis by the Waaler-Rose and latex fixation tests and IgM, IgA, and IgG RF were measured by enzyme linked immunosorbent assays (ELISAs). The patients were followed up from an early phase of the disease for a mean duration of six years. Patients with a persistently positive RF test, irrespective of the type of test used, had more radiological abnormalities, more disease activity, worse functional ability, more extra-articular manifestations, and needed more treatment with second line drugs than patients with persistently negative or variably positive and negative test results during the follow up. Increased RF levels, especially a high level of IgA RF within three years of the onset of symptoms, was prognostic for a more severe disease outcome six years after the onset of symptoms.

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The presence of autoantibodies that react with antigenic determinants on the Fc part of IgG (rheumatoid factors (RFs)) is a common feature of rheumatoid arthritis (RA). High levels of serum RFs, as detected by agglutination tests, are generally thought to imply a poor prognosis in patients with RA.^{1–5}

The agglutination tests most often used for the determination of RFs are the Waaler-Rose and latex fixation tests, which mainly detect antibodies of the IgM class. Developments in enzyme linked immunosorbent assay (ELISA) techniques have facilitated quantitative measurements of RF isotypes. The superiority, if any, of the information obtained for clinical practice is not yet well established, however.

The results of cross sectional and longitudinal studies of the association between RF isotypes and clinical parameters of RA including disease activity, the severity of joint erosions, functional ability or the need for treatment with second line drugs are controversial.^{6–19} Similarly the results of six studies on the prognostic value of RF isotypes are inconsistent.^{20–25}

As our prospective study of female patients with RA has now been in progress for six years we took the opportunity to investigate the associations between the results of ELISAs for serum RF isotypes and various parameters of the course of the disease.

Patients and methods

This investigation was started as a case-control study to determine the preventive effect of oral contraceptive use on the incidence of RA.²⁶ The study was started in 1984 at the department of rheumatology of the Leiden University Hospital in the Netherlands, which is the only referral clinic for rheumatic disorders in a district of about 300 000 inhabitants. All consecutive women who attended the outpatient clinic for the first time between 1982 and 1986 who had recent symptoms of RA (less than five years) and who were aged 20–50 years at the first visit were initially considered. Patients with RA were defined as those who fulfilled the American Rheumatism Association (ARA) criteria for definite RA.²⁷ Later in the study it was also noted whether the patients with RA met the new ARA criteria for RA²⁸ at some time during the course of the disease. In total 138 patients with definite RA entered the study.

FOLLOW UP OF PATIENTS

The patients with RA were seen once a year with each examination consisting of a detailed interview, physical examination, assessment of functional ability, scoring of wrist, hand, and foot radiographs, and collection of serum samples. Throughout the study clinical assessments were made by two of us (JMWH and DvZ).

Prescribed second line drugs (hydroxychloroquine, gold salts, sulphasalazine, D-penicillamine, azathioprine, methotrexate, and cyclosporine) were noted.

The joints were examined for tenderness, pain on motion (by the articular index²⁹) and for soft tissue swelling. Groups of joints—for example, metacarpophalangeal or proximal joints—were considered as one joint. The presence of nodules and other extra-articular manifestations of RA such as pleuritis, pericarditis, episcleritis, vasculitic skin lesions, neuropathy, Felty's syndrome, and Sjögren's syndrome was recorded.

Functional ability was measured by the Steinbrocker classification criteria³⁰ and by a Dutch Health Assessment Questionnaire (HAQ)³¹ which was derived from, and used a structure identical to, that developed by Fries *et al.*^{31a} To relate the HAQ score to the physical state of RA a scale of 0–3 was used, where 0·0–0·5 = completely self sufficient with hardly any difficulties in performing activities of daily

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living, 0.5–1.25=reasonably self sufficient but minor and even some major difficulties in performing activities of daily living, 1.25–2.0=still self sufficient, but has many major problems with activities of daily living, and 2.0–3.0=severely handicapped.

Radiographs of the hands, wrists, and feet were assessed blindly by two of us according to the criteria of Kellgren.³² Erosions and joint space narrowing were scored on a five point scale, where 0=no abnormalities, 1=doubtful abnormalities, 2=mild but definite abnormalities, 3=moderate erosions, and 4=severe destructive lesions or ankylosis, or both. The total number of affected joints was defined as the number of joints having erosions or joint space narrowing, or both, with a score of 2, 3, 4. The maximum possible number of affected joints was 50; thus the maximum possible radiological score was 200.

RHEUMATOID FACTOR TESTS

At each yearly visit tests for serum RF were performed by the latex fixation test³³ and Waaler-Rose assay.³⁴ The intertest variability during the period of the study was tested by comparing the results with reference serum samples and was generally less than 10%. The results were expressed as international units (IU) as defined by the World Health Organisation (WHO). The latex fixation test was considered positive at a level >12.50 IU (titre 1/4) and the Waaler-Rose test at a level >25.0 IU (titre 1/16). At each visit a blood sample was collected and from 1984 onwards serum samples were stored at -20°C. In November 1990 IgM, IgA, and IgG RF were measured in the collected samples by an ELISA using mouse monoclonal antibodies recognising a defined epitope on the Fc part of immunoglobulins, together with the biotin/streptavidin enhancement system as described previously.³⁵ A serum sample from a patient with classical RA which reacted excep-

tionally strongly in the ELISA for IgM, IgA, and IgG RF was used as a standard in all RF ELISA assays. This serum was calibrated against the reference serum from the WHO and was found to contain 500 IU/ml IgM RF. The IgA and IgG RF levels from this serum sample were arbitrarily set at 500 U/ml. The normal range of RF isotypes was determined by testing serum samples from 100 bloodbank donors aged 20–50 years and fixed at the mean (2 SD). Using this method IgM RF was considered to be positive at a level >3 IU, IgA RF at >4 IU, and IgG RF >60 IU.

ANALYSIS

The patients with RA were divided into three groups based on the pattern of the serum RF tests during the follow up period. We distinguished patients with persistently positive tests, persistently negative tests, and variably positive and negative tests. Progression of the clinical parameters obtained by yearly examination of patients with persistently positive, variably positive and negative, and persistently negative results of the Waaler-Rose, latex, IgM, IgA, and IgG RF tests during follow up was assessed by repeated measures analysis of variance (ANOVA).³⁶ Overall tests for time, group, and group by time interaction effects were used.

To determine the prognostic value of the presence of serum RF we evaluated patients with available results of serum RF tests within three years of the onset of symptoms. The first available serum RF test from these patients was taken. Three patient groups were arbitrarily defined according to the serum RF level where 0=within the normal range, 1=moderately increased (>25 Waaler-Rose ≤200, >12.50 latex ≤100, >3 IgM RF ≤100, >4 IgA RF ≤30, and >60 IgG RF ≤220), and 2=strongly increased (Waaler-Rose >200, latex >100, IgM RF >100, IgA RF >30, and IgG RF >220). We compared the clinical parameters obtained six years after the onset of symptoms in these patient groups. Furthermore the correlations of the absolute RF levels as measured within three years of the onset of symptoms with the various clinical parameters in individual patients six years after the onset of symptoms were calculated. If there were missing values for clinical parameters of year 6 from symptom onset, data of year 5 were used. The mean period between the first available RF test and the clinical parameters obtained was 4.3 years for the Waaler-Rose and latex tests and 3.8 years for the ELISAs.

Differences between the two groups were tested by the Mann-Whitney U test. Correlations were estimated with Spearman's rank correlation coefficient.

Results

Serum samples were available in 135 patients with RA out of the original cohort of 138 patients with RA. Baseline characteristics of these patients are given in table 1. The period between the first visit to the outpatient clinic and the first available serum RF test result was smaller and the number of available test results higher for the Waaler-Rose and latex tests than for the ELISAs. This is due to the fact that the

Table 1 Baseline characteristics of 135 female patients with definite rheumatoid arthritis according to the 1958 American Rheumatism Association (ARA) criteria. Data given as mean (SD)

Age (years) at onset of symptoms	36.3 (8.64)
Period between onset of symptoms and first visit to the outpatient clinic (years)	1.59 (1.50)
Follow up time from onset of symptoms (years)	6.26 (2.23)
Period between first visit to the outpatient clinic and first available RF* test (years)	
Waaler-Rose and latex tests	0.18 (0.60)
IgM, IgA, IgG RF ELISA†	1.41 (1.38)
Number of RF tests per patient	
Waaler-Rose and latex tests	4.85 (1.44)
IgM, IgA, IgG RF ELISA	3.64 (1.22)
Percentage of patients fulfilling 1987 ARA criteria	93

*RF=rheumatoid factor.

†ELISA=enzyme linked immunosorbent assay.

Table 2 Percentage of 135 female patients with rheumatoid arthritis with either persistently negative, variably positive and negative, or persistently positive test results during follow up as determined by the Waaler-Rose and latex agglutination tests and enzyme linked immunosorbent assay (ELISA) for IgM, IgA, and IgG rheumatoid factor (RF)

	Agglutination test		ELISA		
	Waaler-Rose	Latex	IgM RF	IgA RF	IgG RF
Persistently negative	38	40	27	24	8
Variably positive and negative	39	39	11	27	18
Persistently positive	23	21	62	49	74

Waller-Rose and latex tests were performed from the beginning of the study whereas RF isotypes were measured later from stored serum samples which were collected only after 1984.

Table 2 gives the percentage of patients with persistently positive, persistently negative, and variably positive and negative results of the different serum RF tests during follow up. The IgM RF test was superior to the other RF tests in the discrimination of patient groups with persistently negative and persistently positive results of serum RF because, compared with the other RF tests, fewer patients had variably positive and negative results during follow up. The IgG RF test was persistently negative in only 8% of the patients.

RADIOLOGICAL ABNORMALITIES

At the latest visit erosions were present in 76% of the patients with RA. The figure shows the mean erosion scores during follow up of patient groups with persistently positive, variably positive and negative, and persistently negative results of the serum RF tests. Repeated measures ANOVA showed that there was an increase over time of the mean erosion score in all groups. The progression rate and the mean erosion score during follow up was higher in the patient groups with persistently positive results of the serum RF tests than in the patient groups with persistently negative tests, however, whereas the results of the patient groups with variably positive and negative tests were between these values. The differences in progression rate between the patient groups defined by the persistently positive and negative results of RF tests were statistically significant for all RF tests ($p < 0.0001$ in all instances) as were the differences in the mean erosion score between

these groups during follow up ($p < 0.05$ in all instances). No single RF test was clearly superior in the discrimination of patients with different grades of joint erosions.

Similar results were found when patient groups with different results of RF tests were compared for the total number of radiologically affected joints (erosions or joint space narrowing, or both; data not shown).

DISEASE ACTIVITY

Patients with persistently negative RF tests had on average more swollen joints at the onset of symptoms than during the following years, whereas patients with persistently positive tests had a lower number of swollen joints at the onset of symptoms than during the following years. A similar trend was not found for the Ritchie score. When averaged over the entire follow up period the mean number of swollen joints score was higher in the patient groups with persistently positive results of the serum RF tests than in the patient groups with persistently negative tests (for all serum RF tests, $p < 0.05$). The average number of swollen joints in the patient groups with variably positive and negative results of serum RF tests were between these values. The Ritchie score tended to be higher in the patient groups with persistently positive results of the serum RF tests than in the patient groups with persistently negative tests but the differences were not statistically significant.

FUNCTIONAL ABILITY

The mean Steinbrocker classification and mean HAQ score increased over time in all patient groups but the rate of progression was similar in

Mean erosion scores during follow up of 135 female patients with rheumatoid arthritis with either persistently negative (—○—), variably positive and negative (—●—), or persistently positive (—□—) test results for serum rheumatoid factor (RF) as determined by the Waller-Rose and latex fixation tests and ELISA for IgM RF, IgA RF, and IgG RF. Radiographs of wrists, hands, and feet, as well as serum samples for RF determinations were obtained once a year during follow up.

Table 3 Comparison of serum rheumatoid factor (RF) levels at disease onset with clinical parameters of the disease six years after the onset of symptoms. Patients with available results of serum Waaler-Rose and latex agglutination tests and enzyme linked immunosorbent assay (ELISA) for IgM, IgA, and IgG RF within three years of the onset of symptoms are divided into three groups according to the RF level (0=within the normal range; 1=moderately increased; 2=strongly increased). The means and standard deviation (SD) of clinical parameters after six years of follow up from the onset of symptoms are given. The correlation coefficients (r) of the RF levels with these clinical parameters are also listed

Patient group		Agglutination test					
		Waaler-Rose (WR)			Latex		
0		≤25		(n=41)	≤12.50		(n=35)
1		>25 WR≤200		(n=28)	>12.50 latex≤100		(n=31)
2		>200		(n=15)	>100		(n=18)
Clinical parameter	Patient groups with different levels of RF	Mean	SD	r	Mean	SD	r
Erosion score	0	31.6	36.5		28.2	37.0	
	1	38.3	27.1	0.22	34.7	28.7	0.38*
	2	36.3	29.0		48.0†	24.4	
No of swollen joints	0	3.0	2.5		2.8	2.4	
	1	4.1	3.2	0.22	3.9	3.6	0.38*
	2	3.9	3.4		4.3	2.3	
Ritchie score	0	8.2	7.2		8.4	7.3	
	1	10.9	6.6	0.08	10.8	8.2	0.15
	2	11.7	11.3		10.5	8.7	
Health Assessment Questionnaire score	0	0.72	0.61		0.80	0.62	
	1	0.84	0.60	0.19	0.85	0.64	0.17
	2	1.0	0.81		0.75	0.73	
Steinbrocker classification	0	1.44	0.50		1.46	0.51	
	1	1.57	0.50	0.02	1.52	0.51	0.06
	2	1.33	0.48		1.39	0.50	
No of prescribed second line drugs	0	1.0	0.8		1.0	0.8	
	1	1.2	0.9	0.21	1.1	0.9	0.18
	2	1.3	1.2		1.2	1.1	

*p<0.01; **p<0.001.

†Difference between groups 0 and 2 statistically significant.

‡Difference between groups 0 and 1 statistically significant.

§Difference between groups 1 and 2 statistically significant.

all groups. When averaged over the entire follow up period the mean HAQ score and Steinbrocker classification were higher in the patient groups with persistently positive results of the serum RF tests than in the patient groups with persistently negative tests, whereas the results of the patient groups with variably positive and negative tests were between these values. The differences were not statistically significant except for the difference in Steinbrocker classification between a persistently positive and a persistently negative IgM RF test (p<0.02).

NUMBER OF PRESCRIBED SECOND LINE DRUGS

The mean number of prescribed second line drugs increased over time in all patient groups. The rate of progression and the mean number of prescribed second line drugs during follow up was higher in the patient groups with persistently positive results of the serum RF tests, however, than in the patient groups with persistently negative tests, whereas the results of the patient groups with variably positive and negative tests were between these values. The differences in progression rate between the patient groups formed because of the persistently positive and negative results of RF tests were statistically significant for all RF tests (p<0.05 in all instances) except for IgG RF. The differences in the mean number of prescribed second line drugs between these patient groups were statistically significant for the Waaler-Rose, latex, and IgM RF tests (p<0.05 in all instances).

NODULES AND OTHER EXTRA-ARTICULAR MANIFESTATIONS

At the latest visit rheumatoid nodules were present in 7% and other extra-articular mani-

festations in 6% of the patients. The occurrence of these manifestations was more common in patients with persistently positive results of the RF tests than in patients with persistently negative tests in whom the occurrence of these manifestations was less than 1%. Only the differences in the occurrence of nodules between the patient groups with persistently negative and the groups with persistently positive latex and IgM RF tests were statistically significant (p<0.01 and p<0.04 respectively).

PROGNOSTIC VALUE OF THE VARIOUS SERUM RF TESTS

To determine the prognostic value of the presence and level of serum RF we evaluated patients with available results of serum RF tests within three years of the onset of symptoms. The prognostic value was evaluated in two ways. First we compared the means of the various clinical parameters measured six years after the onset of symptoms in three patient groups formed according to the initial level of serum RF (0=within the normal range, 1=moderately increased, and 2=strongly increased). Second the correlation of the absolute RF levels with the clinical parameters in individual patients was calculated. Table 3 gives the results of this analysis.

CORRELATION OF RF LEVELS

Table 4 gives the correlation coefficients of serum RF levels as measured in 736 individual serum samples by the Waaler-Rose, latex, IgM, IgA and IgG RF tests. There was a strong correlation between serum RF levels measured by the various ELISAs and a moderate correlation between RF levels measured by the conventional agglutination tests. Weak correlations were

ELISA								
IgM RF			IgA RF			IgG RF		
≤3		(n=15)	≤4		(n=15)	≤60		(n=3)
>3 IgM RF≤100		(n=23)	>4 IgA RF≤30		(n=23)	>60 IgG RF≤220		(n=28)
>100		(n=14)	>30		(n=14)	>220		(n=21)
Mean	SD	r	Mean	SD	r	Mean	SD	r
14.9†	21.0		14.2†	16.2		0†	0	
41.9	34.4	0.22	32.0§	28.2	0.57*	26.6§	31.8	0.34
51.4†	41.2		67.7†	41.1		56.1†	34.2	
1.9†	2.0		2.1	2.0		1.7	2.1	
4.6	3.7	0.28	3.6	2.7	0.57*	2.9	2.6	0.37
3.3	2.2		4.8†	4.0		4.5	3.5	
5.3‡	5.5		6.5	6.1		5.3	4.2	
13.3	8.4	0.14	10.5	8.6	0.47*	9.4	8.5	0.18
7.2	6.6		10.4	8.3		9.9	7.6	
0.69	0.65		0.61	0.62		0.69	0.14	
0.86	0.63	0.29	0.84	0.53	0.58**	0.79	0.69	0.35
0.86	0.86		0.98	0.70		0.82	0.55	
1.40	0.51		1.27	0.46		1.67	0.58	
1.61	0.50	0.19	1.57	0.51	0.30	1.46	0.51	0.11
1.36	0.50		1.57	0.51		1.48	0.51	
0.8	0.8		0.9	0.8		0.3	0.6	
1.3	0.9	0.05	1.1	0.8	0.32	1.1	0.9	0.17
1.4	1.2		1.6	1.2		1.3	1.0	

Table 4 Correlation coefficients between rheumatoid (RF) levels as determined in all serum samples by the Waaler-Rose and latex agglutination tests and enzyme linked immunosorbent assay (ELISA) for IgM, IgA, and IgG RF. The serum samples were obtained once a year during follow up in 135 female patients with definite rheumatoid arthritis

	Agglutination test		ELISA		
	Waaler-Rose	Latex	IgM RF	IgA RF	IgG RF
Agglutination test					
Waaler-Rose	1	0.37**	0.18**	0.11*	0.16**
Latex		1	0.10*	0.04	0.27**
ELISA					
IgM RF			1	0.99**	0.91**
IgA RF				1	0.91**
IgG RF					1

*p<0.05; **p<0.001.

found between serum RF levels as measured by the ELISA and serum RF levels as measured by the conventional agglutination tests.

Discussion

In this prospective study we investigated the clinical significance of serum RF isotypes as measured by ELISA, and serum RF as measured by agglutination tests in a well defined cohort of patients with RA followed from an early phase of their disease for a mean duration of six years. It was shown that there were significantly more and more progressive radiological abnormalities of the joints in patients with persistently positive serum RF tests compared with patients with persistently negative tests, irrespective of the type of test used. The same results were found for the number of prescribed second line drugs with nearly all RF tests investigated. The number of swollen joints, Ritchie score, HAQ score, and Steinbrocker classification were also higher in patients with persistently positive RF tests compared with patients with persistently negative RF tests, but only the differences in the number of swollen joints for all RF tests and the difference in Steinbrocker classification for

the IgM RF test were statistically significant. Patients with persistently negative RF tests had on average more swollen joints at the onset of symptoms than during the following years, whereas patients with persistently positive tests tended to have a gradually increasing number of swollen joints. The frequency of nodules and other extra-articular manifestations was low but also more common in patients with persistently positive RF tests. The values of the various clinical parameters in patients with variably positive and negative results of the RF tests were generally between those of patients with persistently negative and persistently positive RF tests.

Analysis focused on the prognostic value of the different RF tests showed that there were more erosions after six years of follow up from the onset of symptoms in patient groups with moderately or strongly increased results of the RF tests measured within the first three years from the onset of symptoms than in patients with RF levels within the range of healthy controls. Furthermore for the latex, IgM, IgA and IgG RF tests there were more erosions in patients with strongly increased RF levels than in patients with moderately increased levels. Comparison of absolute RF levels with the number of erosions showed the strongest correlation for IgA RF. Analysis of the prognostic value of the different RF tests with regard to parameters of disease activity, functional ability, and the need for second line drug treatment showed that patients with moderately or strongly increased RF levels tended to have higher values of these parameters than patients with RF levels within the range of healthy controls. Comparison of absolute RF levels with the different clinical parameters showed the strongest correlation between the IgA RF test and the number of swollen joints, Ritchie index, and HAQ score.

Summarising these results it can be concluded that patients with a persistently positive serum RF test, independent of the type of test used, generally have more radiological abnormalities, more disease activity, worse functional ability, more rheumatoid nodules and other extra-articular manifestations, and are in need of more treatment with second line drugs than patients with a persistently negative RF test. A positive RF test within three years of the onset of symptoms is of prognostic value for the development of more erosions, more persistent disease activity, and the need for more treatment with second line drugs. The determination of the level of serum RF within three years of the onset of symptoms is informative especially for the IgA RF because of the strong correlation with radiological abnormalities, disease activity parameters, and the HAQ score after six years from the onset of symptoms.

In three cross sectional studies on the association between serum RF isotype levels and radiological abnormalities of the joints^{6 17 19} an association between the presence of IgA RF and radiological abnormalities was found but, in contrast to the present study, this association was not found for IgM and IgG RF. In another cross sectional study⁷ none of the serum RF isotypes was associated with radiological abnormalities. The relation between serum RF isotypes and disease activity confirms the results of several cross sectional and longitudinal studies^{6-12 14-16 18} though the isotype shown to correlate with the parameters for disease activity varied between the studies. Our finding of a relation between serum RF isotypes and worse functional ability confirms the results of two studies,^{15 19} one giving an association between worse functional ability and IgG and IgM RF, and the other giving an association only with IgM RF. The finding of an association between RF isotypes and the need for more treatment with second line drugs is in line with the results of one transversal study,¹⁹ though the association was only found for IgM RF.

Five studies have evaluated the prognostic value of serum RF isotypes early in the disease. The study by Teitsson *et al*²⁰ with a follow up duration of two to four years showed that a positive test for serum IgA RF within one year of the start of active synovitis was, in contrast to positive tests for IgM and IgG RF, predictive for the development of erosions, poorer grip strength, and the need for more treatment with second line drugs. These results are partly consistent with our finding of a stronger correlation between initial IgA RF levels and the various clinical parameters after six years of follow up compared with levels of other RF isotypes, but are in contrast to the finding that all positive RF tests were predictive for the development of more severe disease. Teitsson *et al* based their conclusion on seven patients with an isolated increase in serum IgA RF.²⁰ In this study serum levels of different RF isotypes were strongly correlated and none of the patients had an isolated positive test for IgA RF early in the disease (data not shown). A second study²² reported a correlation of positive serum IgA and IgM RF tests within one year of the onset of

symptoms with more radiological abnormalities and worse functional ability after a mean follow up of 10 years. Furthermore the levels of IgM and IgA RF were correlated with the time of onset of erosions. In a third study²³ with a follow up duration of two years both an initially positive IgM and IgA RF test were predictive for the development of more erosions. The differences were small, however, and not statistically significant. In a fourth study with a follow up duration of one year no correlation was found between the levels of serum RF isotypes and the Ritchie articular index either at the time of testing, within 18 months of the onset of symptoms, or one year later. In a fifth study²⁴ neither a positive Waaler-Rose test nor positive IgM, IgA, and IgG RF test within two years of the diagnosis RA were associated with the presence of radiological abnormalities after two years of follow up. An expansion of this study has now been published²⁵ and except for a correlation between IgG RF levels and the change in progression rate between radiological scores in the first and second year no associations were found between rheumatoid factor isotypes and radiological abnormalities.

Discrepancies between the results of various studies of the association between clinical parameters of RA and serum RF isotypes may be due to several factors. There were considerable differences in patient selection and study design as well as differences in the techniques used to measure RF isotypes. The results of this study suggest an additional factor, namely the absence of any one particular RF isotype which is particularly related to the manifestations of RA. The serum levels of the different RF isotypes appeared to be highly correlated and no RF isotype measured during the course of the disease was clearly superior with respect to the association with disease parameters.

Many laboratories will replace the agglutination tests by the ELISA for the detection of RF. ELISAs are more sensitive, easier to perform, and more reproducible than the conventional agglutination tests.^{6 7 35} As the introduction of this test offers the possibility of obtaining information on RF isotypes the question arises as to which information is most useful for evaluating the severity of the disease. (The value of RF isotypes in the diagnostic process was not addressed in this study.) All patient groups with persistently positive results of RF isotype tests had more severe disease compared with those with persistently negative results. In the discrimination between patients who are likely to have either a mild or a severe disease course, however, repeated measurements of the IgM RF test were superior to the IgA and IgG RF tests because fewer patients had variably positive and negative results. The IgG RF test has the disadvantage of being negative for few patients. With respect to the prognostic value of the RF isotypes both the IgM and IgA RF tests were superior to the IgG RF test in the identification of patient groups with different disease severity. An advantage of the IgA RF test over the IgM RF test was the strong association of high levels of IgA RF within three years of the onset of symptoms

with a more severe disease after six years of follow up from the onset of symptoms. Therefore we conclude that the measurement of IgM and IgA RF early in the disease will give valuable information on the severity of RA and the prognosis. This information may prove to be useful for the optimum clinical management of the disease.

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