The functional affinity of IgM rheumatoid factor is related to the disease duration in patients with rheumatoid arthritis

A Saraux, B Bendaoud, M Dueymes, P Le Goff, P Youinou

Abstract

Objective—To determine the relevance of the functional affinity of IgM rheumatoid factor (RF) to the clinical and serological characteristics of patients with rheumatoid arthritis.

Methods—The functional affinity of IgM RF of 57 seropositive rheumatoid arthritis patients was evaluated by an enzyme linked immunosorbent assay based on the use of a chaotropic agent. The inhibition index was taken as an estimate of functional affinity. The patient group was divided into high functional affinity subgroup 1 (functional affinity < 0.5, n = 37) and low functional affinity subgroup 2 (functional affinity > 0.5, n = 20). The medical records of all patients were reviewed with a particular note of the disease activity and the articular damage score.

Results—The disease duration was shorter (P < 0.01) in subgroup 1 patients [7.9 (SD 6.4) years] than in subgroup 2 patients [13.4 (11.29) years], so that Ritchie’s, Lee’s, and Steinbrocker’s indices were lower in the former than in the latter (P < 0.01, 0.001, and 0.01, respectively). In contrast, erythrocyte sedimentation rates, C reactive protein concentrations, antinuclear antibody, and HLA DR4 prevalences were similar in the two subgroups.

Conclusions—Different forms of RF are present during progression of the disease.
Serum samples were examined for the functional affinity of IgM RF. This procedure has been described previously. Briefly, functional affinity of IgM RF was determined using the chaotropic agent diethylamine in enzyme linked immunosorbent assay (ELISA). Samples were serially diluted on plates (Nunc) coated with Fc fragments of human IgG (Jackson), in the presence or absence of 10 mM diethylamine (Sigma). The plates were incubated at 37°C for 90 minutes, and washed three times with phosphate buffered saline containing 0.05% Tween 20 (PBS-T). HRP conjugated F(ab')2 anti-human IgM (Jackson) was then added at 37°C for 60 minutes. After three washings, colour was developed with H2O2 and O-phenyl-enediamine and absorption was measured at 492 nm on a Titertek Multiskan (Flow). Doseresponse curves were plotted and the fall in log titre was taken as an estimate of functional affinity. Thus high functional affinity interactions between RF and IgG were reflected by a low inhibition index, whereas low functional affinity interactions gave high inhibition index values. The arithmetic mean of inhibition indices was 0.53 (SD 0.31). The inhibition indices of RF in the samples studied are given in fig 1.

**STATISTICAL ANALYSIS**

All the results are expressed as an arithmetic mean and range. Data were analysed using $\chi^2$ test (or Fisher exact test where appropriate), and by the non-parametric Kruskall-Wallis H test. Linear regression analysis were used where indicated. All tests were performed using the Epi-Info and SPSS statistical analysis packages.

**Results**

We found no correlation between the age of the patients and the inhibition indices of IgM RF ($r = 0.18$, $P > 0.05$, data not shown), whereas the disease duration was correlated with the inhibition indices of IgM RF ($r = 0.41$, $P = 0.002$) (fig 2). As expected, we found a significant correlation between the inhibition indices and Ritchie’s index ($r = 0.28$, $P = 0.05$) (fig 3), Lee’s index ($r = 0.35$, $P = 0.01$) (fig 4), and radiological indices (interphalangeal, metacarpophalangeal, and carpal scores, $r = 0.51$, 0.27, and 0.37 respectively, $P = 0.01$, 0.05, and 0.01 respectively) (fig 5). However, in our population, two subgroups of patients tended to be separated on the basis of these figures. The patients were thus arbitrary divided into two subgroups: subgroup 1 consisted of 37 patients with high functional affinity of IgM RF (0.5), and subgroup 2 consisted of 20 patients with low functional affinity of IgM RF (>0.5). The two groups were statistically treated in similar fashion.

Disease duration was longer in subgroup 2 patients than in the subgroup 1 patients ($P = 0.01$). Subgroup 2 patients had a lower Ritchie’s index ($P = 0.01$) and Lee’s index ($P = 0.001$) than subgroup 1 patients, but disease duration was significantly longer in subgroup 2 than in subgroup 1. Furthermore, the radiological scores appeared to be significantly worse ($P < 0.01$) and disease duration significantly longer ($P = 0.01$) in subgroup 2 than in subgroup 1 (table 2). In contrast, extra-articular manifestations, ESR, C reactive protein, AAN and HLA DR4 prevalences were similar in the two subgroups (tables 1 and 2).

The most striking observation was thus the association between disease duration and the functional affinity of RF. These data provide evidence for the existence of distinct functional affinity forms of IgM RF in rheumatoid arthritis patients early and late in disease.
The B cell compartment producing the Fc binding to the Fc fragment of IgG is expanded in rheumatoid arthritis patients and the repertoire of these B cells is shifted toward autoantibodies with monoreactivity and high affinity for the Fc autoantigen. In contrast to rheumatoid arthritis patients, RF production in normal subjects is a transient phenomenon which is the consequence of antigenic stimulation and it subsequently decreases in level.

These findings suggest that B cells producing RF might be under strict regulatory control both in normal subjects and in patients with rheumatoid arthritis. It is an intriguing question as to how RF are regulated.

The fact that there is no increase in affinity with the accumulation of mutations in a group of clonally related RF from an immunised normal donor supports the view that there is a controlling mechanism to limit the affinity of RF autoantibodies. Relevant to this interpretation is the recent finding of the rescue of plasma cells from apoptosis by bone marrow and rheumatoid arthritis synovium fibroblasts. As a result, RF might be overproduced within the synovium, leading to mutations and higher affinity of the antibodies. In rheumatoid arthritis patients, IgM RF can undergo affinity maturation without controlling mechanism. The higher affinity of the rheumatoid arthritis derived RF may contribute to the pathogenesis of the disease.

However, locally produced RF may be more important than circulating RF in disease pathogenesis. Interestingly, the functional affinity of IgM RF has been reported to be reduced after a two month treatment with slow acting drugs. The concomitant effect on IgG glycation suggest that there is some connection between RF activity and the carbohydrate load of the targeted molecules.

The goal of this study was to compare the features of rheumatoid arthritis patients with IgM RF of high and low functional affinity. The only difference between the two subgroups was the disease duration. In contrast, extra-articular manifestations and biological findings did not differ between the two groups.

Interestingly, Newkirk et al did not find significant differences in age, swollen joint

Discussion

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Table 1 Extra-articular manifestations, antinuclear antibodies, and HLA DR4 in patients with rheumatoid arthritis

<table>
<thead>
<tr>
<th></th>
<th>Group I (high avidity)</th>
<th>Group II (low avidity)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex ratio F/M</td>
<td>30/7</td>
<td>13/7</td>
<td>0.19</td>
</tr>
<tr>
<td>Raynaud’s phenomenon</td>
<td>3/37 (8%)</td>
<td>1/20 (5%)</td>
<td>0.56</td>
</tr>
<tr>
<td>Vasculitis</td>
<td>2/37 (5%)</td>
<td>0/20 (0%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Nodules</td>
<td>9/37 (24%)</td>
<td>7/20 (35%)</td>
<td>0.39</td>
</tr>
<tr>
<td>Antinuclear antibodies</td>
<td>14/37 (38%)</td>
<td>6/20 (30%)</td>
<td>0.64</td>
</tr>
<tr>
<td>HLA DR4</td>
<td>26/30 (87%)</td>
<td>9/11 (82%)</td>
<td>0.60</td>
</tr>
</tbody>
</table>

Table 2 Disease activity in patients with rheumatoid arthritis. Values are means (SD)

<table>
<thead>
<tr>
<th></th>
<th>Group I (high avidity)</th>
<th>Group II (low avidity)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58.1 (14.75)</td>
<td>63.6 (13.72)</td>
<td>0.3</td>
</tr>
<tr>
<td>Disease duration (years)</td>
<td>7.9 (6.37)</td>
<td>13.4 (11.29)</td>
<td>0.01</td>
</tr>
<tr>
<td>Lee’s index</td>
<td>11.89 (7.05)</td>
<td>17.35 (4.88)</td>
<td>0.001</td>
</tr>
<tr>
<td>Ritchie’s index</td>
<td>11.29 (9.6)</td>
<td>17.05 (8.8)</td>
<td>0.009</td>
</tr>
<tr>
<td>Steinbrocker’s index</td>
<td>2.12 (0.75)</td>
<td>2.73 (0.46)</td>
<td>0.007</td>
</tr>
<tr>
<td>C reactive protein (mg l⁻¹)</td>
<td>45.81 (36.29)</td>
<td>42.3 (43.19)</td>
<td>0.48</td>
</tr>
<tr>
<td>ESR (mm/h)</td>
<td>57.43 (35.59)</td>
<td>54.35 (33)</td>
<td>0.78</td>
</tr>
<tr>
<td>Fibrin (g l⁻¹)</td>
<td>48.6 (17.5)</td>
<td>49.58 (18)</td>
<td>0.89</td>
</tr>
<tr>
<td>Haemoglobin (g l⁻¹)</td>
<td>11.19 (16.31)</td>
<td>10.84 (15.55)</td>
<td>0.31</td>
</tr>
</tbody>
</table>

Table 3 Linear correlation of inhibition indices of IgMRF and Ritchie’s indices.

<table>
<thead>
<tr>
<th>Inhibition indices</th>
<th>Distances</th>
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<tbody>
<tr>
<td>0</td>
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<tr>
<td>10</td>
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<td>160</td>
<td>320</td>
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<td>180</td>
<td>360</td>
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</table>

Figure 3 Linear correlation of inhibition indices of IgMRF and Ritchie’s indices.

Figure 4 Linear correlation of inhibition indices of IgMRF and Lee’s indices.

Figure 5 Linear correlation of inhibition indices of IgMRF and interphalangeal articular damage (Steinbrocker’s indices).

Figure 6 Linear correlation of inhibition indices of IgMRF and C reactive protein.

Figure 7 Linear correlation of inhibition indices of IgMRF and ESR.

Figure 8 Linear correlation of inhibition indices of IgMRF and Fibrin.

Figure 9 Linear correlation of inhibition indices of IgMRF and Haemoglobin.

Figure 10 Linear correlation of inhibition indices of IgMRF and Xrays: Interphalangeal.

Figure 11 Linear correlation of inhibition indices of IgMRF and Xrays: Metacarpophalangeal.

Figure 12 Linear correlation of inhibition indices of IgMRF and Xrays: Carpals.
index, extra-articular manifestations (excluded number of nodules), and ESR between rheumatoid arthritis patients with high and low avidity of RF. In contrast, they did not find significant differences in disease duration between the two groups, but disease duration was longer (and with a lower range) in their study than in our own work. The absence of clinical or radiological differences between high and low functional affinity IgM RF groups suggests that functional affinity has no diagnostic values in rheumatoid arthritis.

In conclusion, our findings support the contention that different forms of RF are present throughout the development of the disease. These data suggest that rheumatoid patients downregulate the functional affinity of IgM RF without effect on clinical features.

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Ann Rheum Dis 1997 56: 126-129
doi: 10.1136/ard.56.2.126

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