Is measurement of rheumatoid factor isotypes clinically useful?

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Rheumatoid factor (RF) antibodies are directed against the Fc part of IgG. Raised levels are found in most patients with rheumatoid arthritis (RA), but sometimes also in other connective tissue diseases, chronic infections, malignancy, and even in a small proportion of apparently healthy subjects.1

Rheumatoid factor has mostly been measured by agglutination techniques, such as the Rose-Waaler and latex tests, which do not discriminate between RF isotypes. It is possible, however, to measure individual RF isotypes with radio-immunoassay or enzyme linked immunosorbent assay (ELISA). Raised levels of IgM, IgG, IgA, and IgE RF have been reported in patients with RA.2-4

Despite intensive research for decades it is not known why patients with RA produce increased amounts of RF, but RF complexes are thought to have a role in the propagation of the arthritis by intra-articular activation of various inflammatory effector mechanisms. This may especially apply to IgG RF, which can form large aggregates because of its dual role as an antigen and antibody. Clearly, however, large amounts of RF are not necessary for the development of RA as some patients have undetectable levels of RF and patients with hypoglobulinaemia or agammaglobulinaemia can develop chronic polyarthritis that has features in common with RA.5 6

Several studies have focused on the clinical significance of RF isotypes in RA, but methods for measuring RF and selecting patients for study have varied.

Technical considerations

It may be difficult to compare individual studies because different methods for measuring RF have been used. Most investigators now use the ELISA system but despite this numerous technical details may influence the results. Table 1 lists some of these variables and the options that have been used. Other variables, such as type of coating surfaces, may also influence the sensitivity and reproducibility of the results. Rabbit IgG seems to be most commonly used as antigen. Furthermore, some investigators treat the serum samples with enzymes (pepsin, papain) or reducing agents (dithiothreitol, 2-mercaptoethanol) before testing IgG and IgA RF to minimise interference due to IgM RF or dissociate IgG RF bound in immune complexes (hidden RF). These treatments may reduce the binding avidity of the RF isotypes, however, and thus give rise to false negative results.

Predictive and diagnostic considerations

It has been shown that an increase of RF can precede the onset of clinical RA7-9 and this may particularly apply to the IgA and IgG RF isotypes.10 11 Symptom free subjects with increased IgA RF with or without concomitant increase of other RF isotypes carry a greater risk of developing RA than those with other RF isotype patterns.11 Furthermore, in a population study the prevalence of RA was found to be highest among subjects with persistently raised IgA RF combined with either IgG or IgM RF.11

Although there are only a few reports on the prevalence of individual RF isotype profiles in RA, a combined increase of IgM and IgA RF seems to be the most common RF combination in patients with seropositive RA,11-13 and an increase of IgA or IgG RF, or both, has been claimed to be almost exclusively associated with RA.14 Furthermore, a fivefold increase in the prevalence of IgM and IgG RF has been reported in symptom free members of families with multiple cases of RA, but a similar increase in the prevalence of IgA RF was not noted,15 suggesting that IgA RF may be more disease specific than other RF isotypes. Thus several observations indicate that an increase of the IgA RF isotype is more specific for RA than other RF isotypes.

Prognostic significance

In a cross sectional study on seropositive arthritis most patients with RA had a combined increase of IgM and IgA RF, whereas in most patients with a milder form of polyarthritis only one RF...
isotype was raised, predominantly IgM RF.16 Furthermore, RA patients with raised IgA RF only were younger and had a shorter disease course than patients with increased IgM RF or IgM and IgA RF. This suggests that in patients with RA increase of the IgA RF isotype may precede increase of IgM RF. It is important to note in this context that only about 30% of patients with increased IgA RF only are ‘sero-positive’ when tested by conventional agglutination techniques.17 A substantial proportion of patients with early RA and with poor prognosis (see below) may therefore be judged ‘sero-negative’ when tested only by agglutination. This is because agglutination tests preferentially detect the polymeric IgM RF. Conversely, patients with increased IgM RF only and good prognosis may be strongly positive in the conventional agglutination tests.

In a prospective study of patients with early polyarthritis Teitsson and coworkers noted a positive correlation between raised IgA RF and the development of bone erosions.3 A similar association has been reported in other prospective and retrospective studies,2 18-23 though such correlation has not always been found4 24 (table 2). Recruitment of patients to the study by Teitsson and coworkers3 was restricted to early polyarthritis regardless of whether American Rheumatism Association criteria were fulfilled, whereas most other studies have been confined to patients with established RA. These differences in selection criteria are likely to be important in view of the early appearance of IgA RF in relation to IgM RF. It should also be pointed out that human IgG or immune complexes were used as antigens in those studies where no correlation was found between IgA RF and bone erosions, whereas rabbit IgG was used in most of the other studies. It is therefore possible that the difference in antigen (human v rabbit IgG) may also partly explain the discrepancies noted in the relation between bone erosions and RF isotypes.

It has been found that IgM RF increases with age and disease duration in patients with RA, whereas IgA RF did not show such association.16 25 It has also been reported that RF levels can be influenced by drug treatment, including non-steroidal anti-inflammatory drugs.26-28 Thus the prognostic value of measuring RF isotypes may be maximum during the early stages of RA before drug treatment has influenced the RF production and irreversible joint damage has occurred.

**Table 2** Published studies on the association between rheumatoid factor (RF) isotypes and bone erosions in rheumatoid arthritis

<table>
<thead>
<tr>
<th>Report (reference)</th>
<th>Design of study*</th>
<th>Association observed between bone erosions and RF isotypes</th>
</tr>
</thead>
</table>
| Tarkowski and Nilsson (2) | C | IgA RF
| Teitsson et al (3) | P | IgM, IgG RF
| Armanou et al (18) | P | IgA RF
| Fouquet et al (19) | P | IgM, IgG RF
| Gioud-Paquet et al (4) | P | IgM, IgG, IgD, IgE RF
| Montonen et al (20) | P | IgA RF†
| Winska Willoch et al (21) | P | IgM, IgG, IgA, IgE RF
| Twoma et al (22) | P | IgM, IgG, IgA RF‡
| Eggemeyer et al (23) | P | IgM, IgG, IgA RF
| Eberhardt et al (24) | C | IgM, IgG, IgA RF
| Jönsson et al (11) | C | IgM, IgG, IgA RF

*C=cross sectional or retrospective analysis; P=prospective study.
†Not significant owing to low numbers of patients with non-erosive disease course.
‡Over 90% of patients with an increase of these RF isotypes developed bone erosions.

**Table 3** Published studies on the association between rheumatoid factor (RF) isotypes and disease activity

<table>
<thead>
<tr>
<th>Report (reference)</th>
<th>Parameters assessed*</th>
<th>Association observed between disease activity and RF isotypes</th>
</tr>
</thead>
</table>
| Pope and McDuffie (29) | ESR | IgG RF
| McDougal et al (30) | IDA | IgG RF
| Tarkowski and Nilsson (2) | IDA | IgM> IgA RF
| Lessard et al (31) | AI, ESR | IgG RF
| Withington et al (32) | IDA, GS, ESR | IgG> IgA RF
| Silverstein et al (33) | IDA | IgG> IgA RF
| Highton et al (13) | AI, ESR | IgG> IgM RF
| Wessendorf et al (14) | AI | IgG> IgM RF
| Truedson et al (34) | AI | IgG> IgM RF
| March et al (35) | AI | IgG> IgM RF
| Gioud-Paquet et al (4) | IDA | IgM> IgA RF

*ESR=erythrocyte sedimentation rate; IDA=index of disease activity; AI=articular index; GS=grip strength.
†Not significant owing to low numbers.
theless, that the IgA and IgG RF isotypes show a better correlation with extra-articular manifestations than IgM RF. Interestingly, IgG RF seems to be associated with rheumatoid nodules and vasculitis.\textsuperscript{30, 36, 38, 39} whereas the IgA RF isotype has a stronger association with symptoms originating from mucosal membranes and secretory organs\textsuperscript{17, 37} (table 4). IgA RF in patients with Sjögren's syndrome has been found to be mostly polymeric,\textsuperscript{40} but the relation between IgA RF polymerism and the disease course or bone erosions in RA has not yet been analysed.

**HLA associations**

It is generally agreed that seropositive RA has a more severe course than seronegative RA.\textsuperscript{41, 42} Increased prevalence of HLA-DR4 has been found in seropositive (Rose-Waaler positive, IgM RF positive) RA patients than in the normal population.\textsuperscript{43, 44, 45} As discussed above, patients with raised IgA RF may develop more severe disease than patients with increased IgM RF.\textsuperscript{46} It has also been reported that RA patients with mild non-progressive disease have increased prevalence of HLA-DR1, whereas most patients with severe RA have HLA-DR4 associated with DQw7.\textsuperscript{47, 48}

It is therefore possible that increased IgA RF is associated with HLA-DR4 combined with DQw7, and isolated increase of IgM RF with HLA-DR1 in patients with polyarthritis.

**Conclusions**

Measurement of RF isotypes is clinically useful. Symptom free subjects with increased IgA RF have a greater risk of developing RA. An increase of IgA RF, especially if combined with IgM RF, is diagnostically more specific for RA than other RF isotypes or a positive agglutination test. Furthermore, an increase of IgA RF should alert the doctor to consider a more radical treatment because of the relatively strong association between IgA RF and the development of bone erosions. It is important to realise that most patients with increase of IgA RF only, who may have a bad prognosis, are negative when tested by conventional agglutination techniques. In contrast, patients with raised IgM RF only and a good prognosis may be strongly positive when tested by agglutination.

However, measurement of RF isotypes is not useful for monitoring disease activity in patients with RA. Other laboratory parameters, such as erythrocyte sedimentation rate and C reactive protein, are probably better in this respect. Interesting observations have been made on the association between IgA or IgG RF and extra-articular manifestations, but further studies are required to elucidate this relationship.

Table 4 Published studies on the association between rheumatoid factor (RF) isotypes and extra-articular manifestations

<table>
<thead>
<tr>
<th>Report (reference)</th>
<th>Extra-articular manifestations*</th>
<th>Association observed between extra-articular manifestations and RF isotypes</th>
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<tbody>
<tr>
<td>Hay et al (36)</td>
<td>N</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Elkon et al (37)</td>
<td>S</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>McDougall et al (30)</td>
<td>V</td>
<td>IgG RF, IgA$\rightarrow$IgM RF</td>
</tr>
<tr>
<td>Tarkowski and Nilsson (2)</td>
<td>N, V, S, O</td>
<td>IgE$\rightarrow$IgG RF, IgM RF</td>
</tr>
<tr>
<td>Mizushima et al (38)</td>
<td>V</td>
<td>IgG$\rightarrow$IgA RF, IgM RF</td>
</tr>
<tr>
<td>Elkon et al (39)</td>
<td>N, V</td>
<td>IgG$\rightarrow$IgA RF, IgM RF</td>
</tr>
<tr>
<td>Westedt et al (14)</td>
<td>V</td>
<td>IgG$\rightarrow$IgA RF, IgM RF</td>
</tr>
<tr>
<td>Gouël-Paquet et al (4)</td>
<td>S, O</td>
<td>IgG, IgM RF</td>
</tr>
<tr>
<td>Loijkstra et al (17)</td>
<td>S, O</td>
<td>IgM RF</td>
</tr>
</tbody>
</table>

* N=nodes; S=symptoms from secretory organs and mucosal membranes, including Sjögren’s syndrome; V=vasculitis, O=other/undefined extra-articular manifestations.


