VIEWPOINT

Is measurement of rheumatoid factor isotypes clinically useful?

Thorbjörn Jónsson, Helgi Valdimarsson

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 radioimmunoassay 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 RA,⁷⁻⁹ 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 ¹² 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 pointed in references in where most 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 or 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.1625 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.

Disease activity and extra-articular manifestations

Data on the association between parameters of disease activity in RA (Ritchie index, joint count, grip strength, erythrocyte sedimentation rate, C reactive protein, etc) and RF isotypes have been conflicting (table 3). A stronger association between disease activity and IgA RF (or IgG RF) than IgM RF has been reported by some.131429-34 but others have found the opposite24 or no significant relation at all.35 Correlation, when found, has been weak and therefore not clinically useful.

Several studies have also dealt with the relation between RF isotypes and extra-articular manifestations in RA, but again the findings have not been uniform. Table 4 shows, never-

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### 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>
<tbody>
<tr>
<td>Tarkowski and Nilsson (2)</td>
<td>C</td>
<td>IgA RF</td>
</tr>
<tr>
<td>Teitsson et al (3)</td>
<td>P</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Arman et al (18)</td>
<td>C</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Fouquet et al (19)</td>
<td>C</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Goujon-Paquet et al (4)</td>
<td>C</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Mönttinen et al (20)</td>
<td>P</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Wünska Willoch et al (21)</td>
<td>P</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Tsuji et al (22)</td>
<td>P</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Eggenspeier et al (23)</td>
<td>C</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Eberhardt et al (24)</td>
<td>P</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
<tr>
<td>Jönsson et al (11)</td>
<td>C</td>
<td>IgA RF, IgM, IgG RF</td>
</tr>
</tbody>
</table>

*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>
<tbody>
<tr>
<td>Pope and McDuffy (29)</td>
<td>ESR</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>McDougall et al (30)</td>
<td>IDA, IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Tarkowski and Nilsson (2)</td>
<td>IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Lessard et al (31)</td>
<td>IDA, IDA, ESR</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Withington et al (32)</td>
<td>IDA, IDA, IDA, IDA, IDA, IDA, IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Silvestris et al (33)</td>
<td>IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Higham et al (34)</td>
<td>IDA, IDA, IDA, IDA, IDA, IDA, IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Wendell et al (35)</td>
<td>IDA, IDA, IDA, IDA, IDA, IDA, IDA</td>
<td>IgA RF, IgM RF</td>
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<tr>
<td>Truedson et al (36)</td>
<td>IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>March et al (37)</td>
<td>IDA, IDA, IDA, IDA, IDA, IDA, IDA, IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
<tr>
<td>Goujon-Paquet et al (4)</td>
<td>IDA</td>
<td>IgA RF, IgM RF</td>
</tr>
</tbody>
</table>

*ESR=erythrocyte sedimentation rate; IDA=index of disease activity; AI=articular index; GS=grip strength.
†Not significant owing to low numbers.
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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>
</tr>
</thead>
<tbody>
<tr>
<td>Hay et al (36)</td>
<td>N</td>
<td>IgG RF</td>
</tr>
<tr>
<td>Elkon et al (37)</td>
<td>S</td>
<td>IgA RF</td>
</tr>
<tr>
<td>McDougall et al (30)</td>
<td>V</td>
<td>IgG RF</td>
</tr>
<tr>
<td>Tarkowski and Nilsson (2)</td>
<td>N, V, S, O</td>
<td>IgG&gt;IgA&gt;IgM RF</td>
</tr>
<tr>
<td>Mizushima et al (38)</td>
<td>V</td>
<td>IgG&gt;IgA&gt;IgM RF</td>
</tr>
<tr>
<td>Elkon et al (39)</td>
<td>V</td>
<td>IgG&gt;IgA&gt;IgM RF</td>
</tr>
<tr>
<td>Wedsted et al (14)</td>
<td>V</td>
<td>IgG&gt;IgA&gt;IgM RF</td>
</tr>
<tr>
<td>Gioud-Paquet et al (4)</td>
<td>S, O</td>
<td>IgG&gt;IgA RF</td>
</tr>
<tr>
<td>Løvkvist and others (17)</td>
<td>S, O</td>
<td>IgG&gt;IgA RF</td>
</tr>
</tbody>
</table>

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

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 about the association between IgA or IgG RF and extra-articular manifestations, but further studies are required to elucidate this relationship.


It is generally agreed that seropositive RA has a more severe course than seronegative RA. 41 42 Increased prevalence of HLADR4 has been found in seropositive (Rose-Waaler positive, IgM RF positive) RA patients than in the normal population. 8 43 44 As discussed above, patients with raised IgA RA may develop more severe disease than patients with increased IgM RF. 16 It has also been reported that RA patients with mild non-progressive disease have increased prevalence of HLADR1, whereas most patients with severe RA have HLADR4 associated with DQw7. 45 It is therefore possible that increased IgA RF is associated with HLADR4 combined with DQw7, and isolated increase of IgM RF with HLADR1 in patients with polyarthritis.

Conclusions

Measurement of RF isotypes is clinically useful. Symptomatic 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 increased 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.


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