Prognostic factors in early rheumatoid arthritis

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Abstract

The current paradigm for rheumatoid arthritis suggests that persistent synovitis leads to erosive joint damage, progression of which results in functional disability. Studies of X-ray progression followed for 1–9 yr have shown that 40–83% of subsequent progression can be predicted by a combination of prognostic factors such as joint involvement, high levels of C-reactive protein and rheumatoid factor (RF) positivity. There are similar findings for predictors of functional disability in studies followed for 2–15 yr. The most consistent prognostic feature is RF positivity, which is equally important in predicting joint damage and functional disability. Immunoglobulin A RF and the co-presence of RF with anti-keratin or anti-filaggrin antibodies may increase levels of prediction. Added value of genetic predictors over that of RF remains inconclusive. Therefore, therapeutic management should be individualized. Cases with active disease and seropositive RF tests merit aggressive therapy; conversely, cases with little synovitis and seronegative tests require conservative management.

KEY WORDS: Prognostic factors, Early rheumatoid arthritis, X-ray progression, Functional disability.

The current disease paradigm suggests that persistent synovitis leads to erosive damage and that progression of erosive damage itself results in functional disability. As there is evidence to suggest that treatment with slow-acting or disease-modifying drugs suppresses rheumatoid synovitis [1] and reduces long-term disability [2], it is logical to assume that such therapy should be focused on those patients most likely to have poor outcomes. This explains the focus on identifying sensitive and specific prognostic factors in early disease.

In all chronic diseases, a number of factors predict poor outcome. These include the severity of the disease itself, late presentation, multiple health problems, poverty and old age. The same is seen in rheumatoid arthritis (RA), in which severe arthritis with multiple joint involvement [3–6], rheumatoid factor (RF) positivity [3–11], high C-reactive protein (CRP) and erythrocyte sedimentation rate (ESR) [4, 8, 11, 12], and nodules all predict poor outcome. Other accepted predictors of poor outcome include slow onset, co-morbidities, onset in old age and female gender.

The key outcomes in RA are joint damage and functional disability, both of which slowly increase during the 10–25 yr course of the disease. This paper will evaluate data from selected peer-reviewed publications on both early and established RA to assess how joint damage, functional disability, their interrelationship and prognostic factors (number of joints involved, acute-phase response, RF positivity and genetic disposition) affect disease outcome. The key assessment measures for predicting outcome were disease activity parameters (laboratory, clinical and genetic) for joint inflammation, the Larsen or Sharp scores for joint damage and the Health Assessment Questionnaire (HAQ) for functional disability.

Results

Rate and predictors of X-ray progression

An analysis of six longitudinal studies [10, 13–17] in which patients were followed for up to 20 yr demonstrated that average damage before 5 yr of disease duration approximated 16% of maximum damage and increased to ~40% of maximal damage after 20 yr (Fig. 1). In the 19-yr study, which had the largest cohort of patients studied (n = 256), radiographic damage occurred at a constant rate throughout the course of the disease, i.e. progression was not greater in early RA and reduced in late RA [14]. However, when progression was analysed in two other studies as a mathematical function of disease duration in individual patients as opposed to the group, varying patterns of progression were observed [10, 15]. These range from models that show non-progressive (<1%), slow onset, then exponential (9%), slow onset, then linear (30%), fast onset, then stable (11%), fast onset, then decreasing progression (30%) and a sigmoid pattern (20%) in one study [15]. The second study also detected great variability in patterns of progression [10], in keeping perhaps with the clinical picture of RA with episodes of flares and remissions.
Studies of X-ray progression in 50–200 patients followed for 1–9 yr have shown that 43–83% of subsequent progression can be predicted by a combination of initial factors, such as joint involvement [3–6, 11], RF positivity [3–8, 11, 12], acute-phase response [4, 8, 12] and genetic predisposition [8, 12] (Table 1). In all but one study, RF positivity showed a clear correlation to X-ray progression.

**Rate and predictors of functional disability**

A similar picture emerges when the rate of progression of functional disability is analysed in RA. HAQ scores increase with disease duration; for example, in a sample of 400 out-patients, those with a mean baseline disease duration of 7.5 yr had HAQ scores of ≤1.0 and those with a duration of 14.2 yr had HAQ scores that were ≥2.0 [18]. In four studies based on HAQ scores spanning a disease duration of 18 yr [19–21] (D. L. Scott, unpublished observations), maximal disability increased from 30% at 7 yr of disease duration to ~50% at 18 yr, i.e. an annual rate of increase of ~1.5% (Fig. 2).

Predictors of functional disability followed for 2–15 yr in studies of 65–720 patients [5, 22–28] are shown in Table 2. Several of these studies demonstrate that poor functional status at presentation is one of the best predictors of subsequent outcome. RF positivity and levels of ESR and CRP were also associated with progression of functional disability. Genes, however, were not predictive of functional disability [5, 27].

**Early RA studies: evaluating prognostic factors**

**Factors predictive of X-ray progression**

A total of 175 patients with early inflammatory polyarthritis referred to the Norfolk Arthritis Register were reviewed after 12 months, at which time erosions, X-rays and predictive factors were evaluated [6]. The most reliable factors for predicting erosions were positive RF titres, swelling of two or more large joints and disease duration of at least 3 months. A combination of these factors could predict erosion status in 79% of the patients.

The extent to which early radiographic joint damage can be predicted by joint inflammation was investigated in a 1 yr study of patients with newly diagnosed RA (>12 months disease duration) [11]. Predictive factors identified by regression analysis included RF positivity, radiographic damage at baseline and cumulative joint inflammation. Odds ratios for progression of radiographic damage were 12 for RF positivity, 5 for baseline radiographic damage and 2 for cumulative joint inflammation.

Several early studies have demonstrated a relationship between acute-phase response, especially CRP levels, and radiological evidence of joint damage [29, 30]. In a prospective study of 110 patients with early RA (<1 yr of disease onset) followed for a period of 3 yr, radiographic progression was analysed in relation to serial CRP levels over time [9]. The authors concluded that although there was a highly significant correlation between radiographic progression and CRP levels, the wide variation observed because of interindividual differences complicates the prognostic use of CRP levels.

The predictive capacity of ESR levels in relation to X-ray progression was evaluated in 46 patients with established RA (disease duration ≥4 yr) [31]. While average ESR levels increased with gradient in Larsen score, the correlation was not high enough to warrant use in clinical practice. However, ESR levels showed significant correlation ($r = 0.27, P < 0.0001$) to long-term X-ray progression in 256 patients seen at <2 yr from disease onset and followed for 19 yr [14]. Other

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**Table 1. Predictors of X-ray progression: summary of nine key studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study duration</th>
<th>RF</th>
<th>Joint count</th>
<th>Acute phase</th>
<th>HLA</th>
<th>Variation explained (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Feigenbaum et al.</td>
<td>50</td>
<td>5</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>80</td>
</tr>
<tr>
<td>Kaarela</td>
<td>200</td>
<td>9</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>–</td>
<td>43</td>
</tr>
<tr>
<td>Young et al.</td>
<td>149</td>
<td>3</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>70</td>
</tr>
<tr>
<td>Van der Heijde et al</td>
<td>147</td>
<td>2</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>83</td>
</tr>
<tr>
<td>Van Zebeden et al.</td>
<td>132</td>
<td>6</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>76</td>
</tr>
<tr>
<td>Van Leeuwen et al.</td>
<td>149</td>
<td>3</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>46</td>
</tr>
<tr>
<td>Van der Heide et al</td>
<td>128</td>
<td>1</td>
<td>+</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>75</td>
</tr>
<tr>
<td>Brennan et al.</td>
<td>175</td>
<td>1</td>
<td>+</td>
<td>+</td>
<td>–</td>
<td>+</td>
<td>80</td>
</tr>
<tr>
<td>Plant et al.</td>
<td>74</td>
<td>8</td>
<td>–</td>
<td>–</td>
<td>+</td>
<td>+</td>
<td>53</td>
</tr>
</tbody>
</table>
prognostic factors showing significant correlation to X-ray progression identified in this study were grip strength \( r = -0.76, P < 0.001 \) and RF \( r = 0.36, P < 0.04 \).

**Factors predictive of functional disability**

When median HAQ scores were evaluated at 5 yr in 732 patients in the Early Rheumatoid Arthritis Study group, those with higher initial HAQ scores showed greater increases in HAQ scores, as did women (A. Young, personal communication).

Factors correlating with functional disability were evaluated in a cross-sectional study of 706 early RA patients with disease duration <4 yr [32]. Patients from four European countries were enrolled (Norway, France, The Netherlands and Northern Ireland). Articular index, female gender, ESR level and disease duration correlated significantly with increased HAQ scores. It is noteworthy that regression analyses affecting HAQ scores yielded similar results when analysed separately in patients from the four countries. Contrary to reports from other studies [5, 19, 21], there was a lack of correlation between IgM RF levels and disability. The authors allude to this lack of correlation to the short disease duration of the sample population (range 0–4 yr, mean 2 yr) and aggressive use of DMARDs in seropositive patients.

**Rheumatoid factor positivity**

Correlation of RF positivity to functional disability was reported as early as 1962 [33]. In 301 patients studied, the 10 yr review indicated that patients who were seronegative showed a good prognosis, while 95% of seropositive individuals had a poor prognosis. As noted previously, in a prospective study of 681 patients followed for a period of 11.9 yr, RF positivity at presentation was one of the best predictors of disability [21]. In a cohort of 100 early RA patients followed for 5 yr, RF positivity at onset was again predictive of more severe disease outcome [19]. In a more recent report, in a group of 142 patients with early RA (disease duration 7 months at onset) followed for 6.2 yr, high disease activity and RF positivity were the best predictors of poor prognosis [34]. In 132 young women with early RA (mean age 36.4 ± 8.6 yr) followed for a period of 6 yr, van Zeben and colleagues [5] reported that X-ray progression again related to RF positivity, with low rates of X-ray progression being associated with seronegativity, and high rates with seropositivity.

**Rheumatoid factor subtypes**

The above studies consistently demonstrate that RF seropositivity at onset of RA is associated with increased progression of joint damage and disability. With the availability of isotype-specific assays for RF, several studies have investigated the association of various RF isotypes in relation to disease progression. Several studies have reported an association between IgA RF positivity and more active disease and increased joint damage [35–37]; however, others have failed to find an association [26].

It has been suggested that the differences observed in the association of RF isotypes to disease outcome could be related to the source of antigen used in these assays [38]. Different antigens (rabbit IgG vs horse IgG) were used to measure RF levels in 140 patients with RA. The results indicated that, when tested against the rabbit antigen, the serum of patients positive for IgA and IgM RF showed significantly increased disease activity and joint damage; these differences were either smaller or absent when tested against the horse antigen. Similar results with the use of rabbit IgG antigen were seen in data reviewed from 25 other studies involving 1894 patients [38]. Thirteen of these studies that used the

**TABLE 2. Predictors of functional disability: summary of eight key studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of patients</th>
<th>Study duration</th>
<th>Assessment</th>
<th>Clinical</th>
<th>Laboratory</th>
<th>Gene</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacoby et al [22]</td>
<td>100</td>
<td>11</td>
<td>FC</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Fleming et al [23]</td>
<td>100</td>
<td>5</td>
<td>FC</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Isomaki et al [24]</td>
<td>275</td>
<td>3</td>
<td>FC</td>
<td>+</td>
<td>–</td>
<td>ESR</td>
</tr>
<tr>
<td>Rasker and Cosh [25]</td>
<td>65</td>
<td>15</td>
<td>FC</td>
<td>+</td>
<td>+</td>
<td>–</td>
</tr>
<tr>
<td>Eberhardt et al [26]</td>
<td>89</td>
<td>2</td>
<td>HAQ</td>
<td>+</td>
<td>+</td>
<td>+</td>
</tr>
<tr>
<td>Van Zeben et al [5]</td>
<td>132</td>
<td>8</td>
<td>HAQ</td>
<td>+</td>
<td>–</td>
<td>+</td>
</tr>
<tr>
<td>Eberhardt et al [27]</td>
<td>99</td>
<td>5</td>
<td>HAQ</td>
<td>–</td>
<td>–</td>
<td>–</td>
</tr>
<tr>
<td>Talamo et al [28]</td>
<td>720</td>
<td>3</td>
<td>FC</td>
<td>–</td>
<td>–</td>
<td>+</td>
</tr>
</tbody>
</table>

FC = functional capacity.
rabbit antigen showed association with poor disease outcome. In the remaining 12 studies in which human IgG antigen was used, six showed associations with poor outcome, while five showed no link.

As shown in Fig. 3, in a study of 132 patients with established RA [38] (D. L. Scott, unpublished observations), seropositive patients showed more X-ray damage than seronegative patients; this was apparent with all three RF subtypes, but more so with IgA. Patients testing positive for IgM RF only had milder disease than patients who were positive for IgA RF, with or without IgM RF [38]. In another study, total IgA RF titres were estimated in 144 patients with established RA [36]. Measures of disease activity, acute-phase response and joint damage were all significantly higher in patients with elevated IgA RF as compared with RF-negative cases. Subclasses of IgA RF (IgA1 and IgA2 RF) were also measured in this study and did not provide additional information to clinical status compared with total IgA RF levels.

Other marker antibodies of RA in addition to RF include the anti-keratin, anti-filaggrin and anti-perinuclear factor antibodies. In a study of 156 patients with established RA, those who were negative for both IgA and anti-keratin antibodies had a lower rate of X-ray progression than those who were positive for both antibodies [39]. More recently, a Finnish study of 306 patients with recent onset arthritis reported significant agreement among tests for anti-filaggrin, anti-keratin and anti-perinuclear factor antibodies [40]. Further, the anti-filaggrin antibody test detected 10 of the 22 RF-negative erosive cases, especially those with a large number of erosive joints involved. Therefore, the data would suggest that anti-filaggrin antibody testing may be a useful supplementation to RF in predicting erosions.

Genetics and outcome in RA

The association between RA and specific class II major histocompatibility complex alleles is well established. Subtypes of HLA-DR4 associated with RA show conservation of the ‘shared epitope’, an amino acid sequence in the third hypervariable region (HVR3) of the β chain. In a longitudinal study conducted in the UK, the effect of RF positivity and HVR3 expression on the risk of developing erosions was evaluated in 120 early RA patients, 57 with other arthropathies and 347 healthy controls [41]. The presence of either RF positivity or HVR3 conferred a relative risk of 13.5 in development of erosions. When both factors were present, the relative risk was 8.1. A study with similar objectives conducted in Japan in 198 patients with early RA and 150 controls showed that the homoyzogous states for DRB1 and the shared epitope were associated with polyarthritis development but not with radiographic progression at presentation or at 12 months [42]. Association of HLA susceptibility and clinical expression of RA was studied by genomic tissue typing in 78 patients with recent onset RA in The Netherlands [43]. While patients expressing DR1 and DR4 had higher disease activities, the association was not obvious after correction for RF positivity. HLA-DR tissue typing yielded no additional information to RF status, thereby undermining its use as a prognostic factor for individuals. In another study in The Netherlands, the relationship of genetic markers (studied using serological and cellular methods) to function and radiographic progression was investigated in 142 patients with early RA treated with the ‘sawtooth’ strategy. The DR1 and DR4 alleles again showed no prognostic significance for the functional or radiographic outcome of patients.

Conclusions

Prognostic factors identifying patients who are at risk of poor outcome would allow timely intervention at an early disease stage aimed at preventing worsening of disease and limiting joint damage. This is clearly an area that deserves more investigation, especially since to date features identified with poor prognosis, such as involved joint numbers and acute-phase response, evolve with the disease and may not be evident at initial presentation. As seen above, the most consistent prognostic factor appears to be RF positivity, which is equally important in predicting joint damage and functional disability. There is some evidence that IgA RF is the most predictive. The presence of RF with anti-keratin or anti-filaggrin antibodies may provide higher levels of prediction. There is debate about the added value of genetic predictors over and above that for RF; the balance of opinion is against them having a major role.

We are not yet at the juncture of curing RA, but have at our disposal several new therapies (used singly or in combinations) that can reduce patients’ pain and joint inflammation and, most importantly, alter the course of the disease by decreasing the progression of joint damage. The goal of therapy should be to control symptoms of joint pain and inflammation, minimize loss of function and reduce the progression of joint damage. The studies reviewed clearly demonstrate the importance of outcome measures such as radiological deterioration and functional status; poor functional status at presenta-
tion is probably one of the best predictors of subsequent outcome.

It is difficult to move from predicting the outcomes of groups of RA patients to predicting the future of individual cases. At the present time, the evidence favours a cautious approach. Cases with active disease and sero-positive tests for RF merit aggressive therapy; conversely, cases with little synovitis and seronegative tests require a cautious approach. Cases with active disease and seropositive tests for RF merit aggressive therapy; conversely, cases with little synovitis and seronegative tests require conservative management (Table 3). With the current practice of treating RA aggressively and at an increasingly early phase, the clinical judgement of rheumatologists remains paramount in disease management.

Therefore, in addition to further research on identifying prognostic factors to detect early RA, the efforts of the early arthritis clinics [44–46] and early referral to specialist care [1, 47, 48] are likely to improve long-term disease outcome and should be encouraged.

### References

26. Eberhardt KB, Rydgren LC, Pettersson H, Wollheim FA.


