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Progressive and Nonprogressive Rheumatoid Arthritis Over a 10-Year Period in Japan

KEN WATANABE, SHIROU URATA, KAZUHIRO SUZUKI, Mitsunari Ohba, and YOSHIYUKI INAGAKI

ABSTRACT. We followed 207 patients with rheumatoid arthritis who were registered at our hospital over a 10-year period from between 1989 and 1990. The number of patients who were still treated at our hospital in 2001 was 87. Sixty patients had died, 39 had changed hospitals, 11 had interrupted treatment, and 10 had not had further followup. The patients at our hospital in 2001 were divided into 2 groups: progressive and nonprogressive disease. We compared clinical and laboratory data obtained for the 2 groups from the initial examination against data obtained from the final examination. The progressive group had a greater number of operations, used a greater variety of disease modifying antirheumatic drugs, and received higher dosages of steroids than the nonprogressive group. In the progressive group the levels of C-reactive protein, erythrocyte sedimentation rate, and IgG were significantly higher, while the levels of hemoglobin were lower at final laboratory examination. However, the initial laboratory examination revealed no significant differences between these groups that could be used to predict the likely progression of disease. (J Rheumatol 2004;31 Suppl 69:27–29)

Key Indexing Terms:
LONGTERM FOLLOWUP RHEUMATOID ARTHRITIS PROGNOSTIC FEATURES

The natural history of treated rheumatoid arthritis (RA) can be assessed by measuring synovitis, disability, quality, and joint damage. The increased comorbidity and the mortality of RA also reflect it. A number of prognostic factors suggest severe RA is likely: RA is worse in the elderly, in women, and in patients with low socioeconomic status. It is also worse in patients who are HLA-DR4 positive with persisting disease activity as well as cases positive for rheumatoid factor (RF). Recent research has shown that patients with positive results in anti-CCP ELISA assays are more likely to show progressive disease. A particular focus of research interest has been the prediction of erosive damage. RF positivity, persisting disease activity, and an elevated acute phase response are all important predictors, although there is a lag between synovial inflammation and joint damage.

Longterm observational studies, including those by Jacoby, Rasker and Cosh, and Sokka, have helped define the natural history of treated RA. We now report experience from a single center in which RA patients were examined during the course of their treatment over a 10-year period. The patients were divided into 2 groups: progressive and nonprogressive disease. Those patients with “progressive” RA had a deterioration of their condition. We compared clinical and laboratory data obtained for the 2 groups from the initial examination against data obtained from the final examination.

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PATIENTS AND RESULTS
The Department of Rheumatology was opened in 1989. RA patients who conformed to the diagnosis of RA as set forth by the American Rheumatism Association (ARA, now the American College of Rheumatology) were registered. One hundred sixty-nine patients were registered in 1989 and 38 patients in 1990. We followed up 207 RA patients over a 10-year period. We treated RA patients primarily with non-steroidal antiinflammatory drugs (NSAID) and disease modifying antirheumatic drugs (DMARD). Where necessary, we administered steroids and performed operations.

Initial status. A total of 207 patients were studied: 166 were female and 41 male. Their average age at the time of the initial examination was 56.5 years and their average disease duration was 10.1 years. Using Steinbrocker’s classification patients were rated initially as follows: anatomical stage 1: 42 patients, Stage 2: 3, Stage 3: 85, and Stage 4: 47 patients. Patients were rated as: functional class 1: 39 patients, Class 2: 121, Class 3: 40, and Class 4: 7 patients.

Patient status in 2001 (after 10-year followup). A total of 87 patients were still receiving treatment. Sixty patients had died, 39 had changed hospital, 11 had interrupted treatment, and in 10 cases there was no followup.

Mortality. The mean age at death was 70.1 years. Deceased patients comprised 45 women and 15 men with an average disease duration of 18.0 years. The number of deceased patients at initial examination: Class 1: 3 patients, Class 2: 29, Class 3: 23, and Class 4: 5 patients.

Causes of death are summarized in Table 1. Sixteen patients (2%) died of infection. The next greatest cause of death was malignant neoplasm in 11 cases (18%), followed by cerebrovascular disease in 8 (13%), cardiac disease in 6 (10%), and dementia in 5 cases (8%).

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Table 1. Causes of death in patients with RA.

<table>
<thead>
<tr>
<th>Cause of Death</th>
<th>Number of Cases (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Infection</td>
<td>16 (27)</td>
</tr>
<tr>
<td>Malignant neoplasm</td>
<td>11 (18)</td>
</tr>
<tr>
<td>Cerebrovascular disease</td>
<td>8 (13)</td>
</tr>
<tr>
<td>Cardiac disease</td>
<td>6 (10)</td>
</tr>
<tr>
<td>Senile dementia</td>
<td>5 (8)</td>
</tr>
<tr>
<td>General weakening</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Renal disease</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Gastrointestinal disease</td>
<td>2 (3)</td>
</tr>
<tr>
<td>Other</td>
<td>3 (5)</td>
</tr>
<tr>
<td>Unknown</td>
<td>3 (5)</td>
</tr>
</tbody>
</table>

**Functional class.** Table 2 shows the change in number of patients for each functional class. After the initial examination, Class 1 represented 19%, Class 2 59%, Class 3 19%, and Class 4 3%. After the final examination Class 1 represented 6%, Class 2 58%, Class 3 28%, and Class 4 9%.

**Features in the nonprogressive group.** The nonprogressive group comprised 44 patients; 5 remained in Class 1 after initial and final examinations, and 39 remained in Class 2 after the initial and final examinations. The average condition of this group over a 10-year period was Class 1.9 in both initial and final examinations.

**Features in the progressive group.** The progressive group comprised 24 patients; 4 patients moved from Class 1 at initial examination to Class 3 after final examination, 1 patient moved from Class 1 at initial to Class 4 after final, 17 patients from Class 2 at initial to Class 3 after final, and 2 from Class 2 at initial to Class 4 after final examination. The average condition of the progressive group over a 10-year period was categorized as Class 1.8 at initial and Class 3.1 after final examination.

**Nonprogressive versus progressive group.** We compared differences in clinical factors in the 2 groups; results were analyzed by Student t and Mann-Whitney U tests. At initial examination, we compared age, disease duration, number of ARA diagnostic criteria, number of major operations, variety of DMARD, and steroid dosage. The progressive group needed a significantly greater number of operations, used a greater variety of DMARD, and received higher dosages of steroids than the nonprogressive group. The progressive group also had higher levels of CRP, ESR and IgG, and RF, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), IgG, IgA, IgM, C1q, and anti-agalactosyl IgG antibodies. In the progressive group, the levels of CRP, ESR, and IgG were significantly higher, and the levels of Hb were lower during the 2001 laboratory examinations.

Finally we compared the 2 groups with respect to differences in laboratory data from the initial examination (Table 5). We analyzed RF, CRP, ESR, and Hb. The initial examination revealed no significant differences between these groups. We were unable to identify criteria that would aid in the prediction of RA.

**DISCUSSION**

We analyzed 207 RA patients over a 10-year period at our hospital; 60 patients died and 87 were still receiving treatment at our hospital in 2001. The mortality was comparable to previous studies from Japan.

The condition of 40 of the 87 patients was worse after the 10-year period. The progressive group needed a greater number of operations, used a greater variety of DMARD, and received higher dosages of steroids than the nonprogressive group. The progressive group also had higher levels of CRP, ESR and IgG, and RF, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), hemoglobin (Hb), IgG, IgA, IgM, C1q, and anti-agalactosyl IgG antibodies. In the progressive group, the levels of CRP, ESR, and IgG were significantly higher, and the levels of Hb were lower during the 2001 laboratory examinations.

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**Table 3.** Comparison of clinical features.

<table>
<thead>
<tr>
<th></th>
<th>Nonprogressive Group</th>
<th>Progressive Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>51.0</td>
<td>55.0</td>
<td>NS</td>
</tr>
<tr>
<td>Disease duration, yrs</td>
<td>11.0</td>
<td>10.4</td>
<td>NS</td>
</tr>
<tr>
<td>Number of diagnostic criteria of RA</td>
<td>5.1</td>
<td>5.2</td>
<td>NS</td>
</tr>
<tr>
<td>Average number of operations</td>
<td>0.0</td>
<td>0.3</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Average number of DMARD</td>
<td>2.0</td>
<td>2.8</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>Doses of steroids, mg</td>
<td>0.8</td>
<td>3.4</td>
<td>&lt; 0.05</td>
</tr>
</tbody>
</table>

**Table 4.** Comparison of final laboratory features.

<table>
<thead>
<tr>
<th></th>
<th>Nonprogressive Group</th>
<th>Progressive Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF, IU/ml</td>
<td>110</td>
<td>131</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>1.8</td>
<td>3.0</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>52</td>
<td>75</td>
<td>&lt; 0.01</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>12</td>
<td>11</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>IgG, mg/dl</td>
<td>1434</td>
<td>1712</td>
<td>&lt; 0.05</td>
</tr>
<tr>
<td>IgA, mg/dl</td>
<td>379</td>
<td>446</td>
<td>NS</td>
</tr>
<tr>
<td>IgM, mg/dl</td>
<td>115</td>
<td>125</td>
<td>NS</td>
</tr>
<tr>
<td>C1q, µg/ml</td>
<td>1.8</td>
<td>2.9</td>
<td>NS</td>
</tr>
</tbody>
</table>

**Table 5.** Comparison of initial laboratory features.

<table>
<thead>
<tr>
<th></th>
<th>Nonprogressive Group</th>
<th>Progressive Group</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>RF, IU/ml</td>
<td>284</td>
<td>204</td>
<td>NS</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>1.8</td>
<td>1.9</td>
<td>NS</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>60</td>
<td>65</td>
<td>NS</td>
</tr>
<tr>
<td>Hb, g/dl</td>
<td>11.6</td>
<td>11.9</td>
<td>NS</td>
</tr>
</tbody>
</table>
lower levels of Hb at final examination. However, the initial laboratory examination revealed no significant differences between these 2 groups.

Disability in RA is associated with high pain scores\(^{16}\) and other features of active RA. A cross-sectional study of 259 North American RA patients\(^{17}\) showed disability correlated with joint counts, ESR, global self-assessment, and radiographic scores. Another cross-sectional study of 706 European RA patients showed the Ritchie Articular Index and ESR correlated with Health Assessment Questionnaire (HAQ) scores\(^{18}\). Other variable factors that influence HAQ include RF positivity\(^{19,20}\), especially IgA RF\(^{21}\), fatigue, which is related to pain\(^{22}\), and depression, with higher HAQ scores in depressed patients\(^{23,24}\).

Previous studies from Japan have shown that risk factors in progression of RA include a high Lansbury index, type of RA (more erosive subset and mutilating disease), and high levels of C1q\(^{25-30}\). We believe that the prognosis of RA patients who have severe disease is poor; moreover patients with RA whose levels of CRP, ESR, and IgG are elevated substantially and whose Hb levels are low need aggressive treatment. However, in this study we were unable to identify any criteria that aided the prediction of progressive RA.

ACKNOWLEDGMENT
We thank Drs. Susumu Nagai and Fumio Kasuya of Asahikasei for their help with the statistical analyses of the results. We also thank the orthopedic staff at our hospital for their assistance gathering data for RA patients.

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