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Chapter 4

How to define baseline erosiveness to predict radiologic progression in Rheumatoid Arthritis?

LETTER TO THE EDITOR

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To the Editor,

Baseline erosiveness is one of the most potent predictive factors for a severe destructive disease course of Rheumatoid Arthritis (RA), that is also used in daily practice. There is however no uniform definition of erosive disease at disease onset. The definitions used in studies were highly variable; definitions used are amongst others any radiological evidence of erosions, a cortical break of ≥2 mm or presence of ≥2 or ≥3 erosions. The lack of a generally accepted definition makes studies on this subject incomparable. Moreover it prevents the use of radiological information at disease presentation in a consistent manner in clinical practice.

Recently, the radiologic criterion to classify RA according to the 2010-criteria was presented and defined as the presence of at least three erosive joints. Here an erosive joint was defined as a metacarpophalangeal (MCP), proximal interphalangeal (PIP), metatarsophalangeal (MTP) or wrist joint with a broken cortex on an X-ray. As such this measure is easy applicable in clinical practice. This prompted us to (I) evaluate the accuracy of baseline erosiveness expressed by the number of erosive joints to predict radiographic progression on the short term and long term and (II) to evaluate whether an optimal cut-off for the level of baseline erosiveness to predict severe joint damage progression can be determined.

Early arthritis patients included between 1993 and 2006 in the Leiden Early Arthritis Clinic that at first presentation were diagnosed with RA (according to the 1987 or the

Figure 1. Progression in Sharp van der Heijde score over 7 years of follow-up for RA-patients with different numbers of erosive joints at first presentation (A) and with different numbers of erosive joints used as cut-off (B) Depicted are the mean Sharp van der Heijde scores over 7 years of disease as predicted by multivariate normal regression analyses taking advantage of within patient correlations between serial radiologic measurements and adjusting for age, gender and inclusion period (as a proxy for different treatment strategies). In (A) SHS-data are presented for the absolute number of erosive joints, in (B) the cut-off for erosiveness is defined using different numbers of erosive joints.
Serial hand and foot radiographs were made at first presentation and on a yearly basis during follow-up. The number of joints with a cortex break was determined from the baseline radiographs, assessing bilateral MTP, PIP, MCP and wrist joints. Two outcomes were assessed: rapid radiological progression (RRP) on the short term and long term progression of joint destruction during 7-years of disease. RRP was defined as an increase of ≥5 Sharp-van der Heijde-points in 1 year, a change larger

### Table 1. Characteristics of RA-patients with different numbers of erosive joints at first presentation (A) and the test characteristics and predictive values for developing rapid radiological progression during the first year of the disease (B)

#### (A) Exact number of erosive joints

<table>
<thead>
<tr>
<th>No patients N(%)</th>
<th>Women N(%)</th>
<th>Age mean±SD</th>
<th>Smoker N(%)</th>
<th>ACPA+ N(%)</th>
<th>Sympt dur (wks) mean±SD</th>
<th>CRP mg/l mean±SD</th>
<th>RRP* N(%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none 137 (19.5)</td>
<td>108 (78.8)</td>
<td>45.4 (13.6)</td>
<td>32 (25.8)</td>
<td>61 (48.0)</td>
<td>24.1 (23.1)</td>
<td>20 (30)</td>
<td>27 (26.2)</td>
</tr>
<tr>
<td>1</td>
<td>99 (14.1)</td>
<td>72 (72.7)</td>
<td>50.6 (15.7)</td>
<td>33 (34.7)</td>
<td>45 (47.4)</td>
<td>25.6 (19.5)</td>
<td>22 (22.9)</td>
</tr>
<tr>
<td>2</td>
<td>78 (11.1)</td>
<td>52 (66.7)</td>
<td>53.1 (14.4)</td>
<td>25 (33.8)</td>
<td>44 (57.1)</td>
<td>27.3 (21.3)</td>
<td>31 (30)</td>
</tr>
<tr>
<td>3</td>
<td>77 (11.0)</td>
<td>51 (66.2)</td>
<td>56.1 (15.2)</td>
<td>19 (26.0)</td>
<td>48 (64.0)</td>
<td>28.3 (25.3)</td>
<td>22 (26)</td>
</tr>
<tr>
<td>4</td>
<td>69 (9.8)</td>
<td>45 (65.2)</td>
<td>57.7 (14.7)</td>
<td>17 (27.0)</td>
<td>39 (59.1)</td>
<td>25.6 (21.2)</td>
<td>33 (33)</td>
</tr>
<tr>
<td>5</td>
<td>38 (5.4)</td>
<td>23 (60.5)</td>
<td>62.9 (12.9)</td>
<td>10 (28.6)</td>
<td>19 (51.4)</td>
<td>18.6 (11.8)</td>
<td>35 (40)</td>
</tr>
<tr>
<td>≥6</td>
<td>189 (27.0)</td>
<td>116 (61.4)</td>
<td>67.4 (11.4)</td>
<td>42 (24.0)</td>
<td>92 (49.2)</td>
<td>27.8 (22.6)</td>
<td>37 (40)</td>
</tr>
<tr>
<td>Total</td>
<td>687</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

#### (B) Number of erosive joints used as cutoff

<table>
<thead>
<tr>
<th>No patients N(%)</th>
<th>RRP N(%)</th>
<th>Sensitivity (95%CI)</th>
<th>Specificity (95%CI)</th>
<th>PPV (95%CI)</th>
<th>NPV (95%CI)</th>
<th>LR+ (95%CI)</th>
<th>LR – (95%CI)</th>
<th>AUC (SEM)</th>
</tr>
</thead>
<tbody>
<tr>
<td>none 103 (18.7)</td>
<td>27 (26.2)</td>
<td>0.87 (0.82-0.91)</td>
<td>0.22 (0.18-0.27)</td>
<td>0.41 (0.37-0.46)</td>
<td>0.74 (0.64-0.82)</td>
<td>1.12 (1.04-1.21)</td>
<td>0.57 (0.39-0.83)</td>
<td>0.55 (0.025)</td>
</tr>
<tr>
<td>≥1 447 (81.3)</td>
<td>184 (61.1)</td>
<td>0.87 (0.72-0.83)</td>
<td>0.41 (0.36-0.47)</td>
<td>0.45 (0.4-0.51)</td>
<td>0.75 (0.68-0.81)</td>
<td>1.33 (1.19-0.49)</td>
<td>0.69 (0.024)</td>
<td>0.60 (0.025)</td>
</tr>
<tr>
<td>≥2 364 (66.2)</td>
<td>165 (50.2)</td>
<td>0.87 (0.72-0.83)</td>
<td>0.41 (0.36-0.47)</td>
<td>0.45 (0.4-0.51)</td>
<td>0.75 (0.68-0.81)</td>
<td>1.33 (1.19-0.49)</td>
<td>0.69 (0.024)</td>
<td>0.60 (0.025)</td>
</tr>
<tr>
<td>≥3 296 (53.8)</td>
<td>142 (42)</td>
<td>0.87 (0.6-0.73)</td>
<td>0.55 (0.49-0.6)</td>
<td>0.48 (0.42-0.54)</td>
<td>0.73 (0.67-0.78)</td>
<td>1.48 (1.28-0.72)</td>
<td>0.73 (0.49-0.73)</td>
<td>0.61 (0.025)</td>
</tr>
<tr>
<td>≥4 231 (42)</td>
<td>116 (55)</td>
<td>0.87 (0.6-0.73)</td>
<td>0.55 (0.49-0.6)</td>
<td>0.50 (0.44-0.57)</td>
<td>0.70 (0.65-0.75)</td>
<td>1.62 (1.34-1.96)</td>
<td>0.79 (0.59-0.79)</td>
<td>0.61 (0.025)</td>
</tr>
<tr>
<td>≥5 177 (32.2)</td>
<td>92 (44)</td>
<td>0.87 (0.37-0.5)</td>
<td>0.75 (0.7-0.79)</td>
<td>0.52 (0.44-0.59)</td>
<td>0.68 (0.63-0.72)</td>
<td>1.73 (1.37-2.21)</td>
<td>0.75 (0.66-0.850)</td>
<td>0.59 (0.025)</td>
</tr>
<tr>
<td>≥6 146 (26.5)</td>
<td>78 (37)</td>
<td>0.87 (0.75-0.83)</td>
<td>0.53 (0.45-0.62)</td>
<td>0.67 (0.62-0.72)</td>
<td>1.84 (1.4-2.43)</td>
<td>0.79 (0.71-0.88)</td>
<td>0.59 (0.025)</td>
<td>0.59 (0.025)</td>
</tr>
<tr>
<td>Total 550</td>
<td>211 (38.4)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
than the smallest detectable difference that is also associated with functional decline.9
The serial X-rays were SHS-scored by two readers; the within reader-ICC was 0.87 and
0.91, the between-reader ICC was 0.89. Relations between the number of erosive joints
and the progression of joint destruction over a maximum follow-up period of seven years
were tested by multivariate normal regression analyses taking advantage of within patient
correlations between serial radiologic measurements.10 Analyses were adjusted for age,
gender and inclusion period, as a proxy for different treatment strategies. The treatment
strategy applied was different in different periods; patients included in 1993-1995 were
initially treated with NSAIDs, patients included in 1996-1998 were initially treated with
chloroquine or sulphasalazine and patients included after 1999 were promptly treated
with methotrexate. Only 4.7% of the patients was treated with anti-TNF at any moment
during the follow-up period.10

687 patients had baseline radiographs. The baseline characteristics are shown in Table
1A. In 550 patients an X-ray was made at both baseline and year-1. In total, 211(38.4%)
patients had RRP, this frequency increased per category of erosive joints (Table 1A). Subse-
quently, patients were categorized using different numbers of erosive disease as cut-off for
baseline erosiveness (Table 1B). With every increase in number of erosive joints as cut-off,
the specificity and LR+ increased but the sensitivity and LR- decreased. The AUC was the
highest for the cut-offs ≥3 or ≥4 joints, but the differences were small. Subsequently, the
progression in Sharp van der Heijde score over 7 years of follow-up for RA-patients with
different numbers of erosive joints at first presentation was studied. Additionally, the Sharp
van der Heijde scores over 7 years were studied when different numbers of erosive joints
were used as cut-off and patients were grouped accordingly (Figure 1). Every increase in
cut-off was associated with more severe SHS-progression and no clustering of lines was
observed.

As one may expect, every increase in the number of erosive joints at RA onset is associ-
ated with an increased chance on short term and long term progression of joint damage.
Although further studies in other cohorts are required, we could not identify an obvious
single cut-off point to define baseline erosiveness in relation to prediction of joint damage
progression.
Chapter 4

REFERENCE LIST


