Which Measure of Inflammation to Use? A Comparison of Erythrocyte Sedimentation Rate and C-Reactive Protein Measurements from Randomized Clinical Trials of Golimumab in Rheumatoid Arthritis

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ABSTRACT. Objective. To assess clinical utility of measurements of C-reactive protein (CRP) versus Westergren erythrocyte sedimentation rate (ESR) in evaluating patients with rheumatoid arthritis (RA).

Methods. Data from 3 randomized clinical trials of golimumab involving 1247 patients with RA in which ESR and CRP were obtained at baseline and Week 24, along with standard measures of clinical disease activity [swollen and tender joint counts, global disease activity assessment, composite Disease Activity Scores (DAS) and Clinical Disease Activity Index (CDAI)], were utilized.

Result. Both ESR and CRP were significant predictors of swollen joint count (p < 0.001 for each). Only 4.5% of patients with no swollen joints had elevated CRP and normal ESR, but 15.2% had elevated ESR and normal CRP. ESR and CRP correlated significantly (Pearson r = 0.59, p < 0.001) with each other. DAS-ESR and DAS-CRP were highly correlated (r = 0.96, p < 0.001) with each other, although DAS-ESR values were slightly lower than the DAS-CRP values at the upper end of the range (DAS > 8). Both ESR and CRP were significantly associated with CDAI (p < 0.001 for each).

Conclusion. It is not necessary to obtain both ESR and CRP measures for clinical disease activity assessment in clinical trials of RA. Neither test adds significantly to clinical measures of disease activity including joint counts and global assessments. Where available, the CRP alone may be preferred for disease activity assessment as a simple, validated, reproducible, non-age-dependent test.

Key Indexing Terms: ACUTE-PHASE REACTANTS RHEUMATOID ARTHRITIS OUTCOME AND PROCESS ASSESSMENT
To determine the clinical utility of CRP versus ESR in assessing inflammation in patients with RA, we have, for the first time, used paired samples from randomized clinical trials enrolling more than 1200 patients.

**RESULTS**

A total of 1247 patients contributed 2417 patient visits. The average patient age at enrollment was 50.7 years; 81.5% of patients were female (Table 1).

ESR and CRP values correlated significantly with each other (Pearson r = 0.59, p < 0.001; Figure 1). A total of 185 patient visits had 0 swollen joints, 422 visits had SJC of 1–4, and 1803 visits had > 4 swollen joints. Age and sex were both significantly associated with the SJC. Female patients were 1.35 times more likely to have more swollen joints than men (OR 1.35, 95% CI 1.08, 1.70). Older patients were also more likely to have higher SJC (OR 1.11 per 10-yr increase, 95% CI 1.03, 1.18). Both ESR and CRP were also significant predictors of SJC (p < 0.001 for each). Higher ESR correlated with greater patient age; the CRP had no such correlation.

Sensitivity and specificity were assessed for ESR and CRP using the dichotomous response of SJC ≤ 4 versus > 4. The ROC curve shows CRP has slightly higher sensitivity and specificity than ESR (Figure 2). This analysis revealed c-indices (area under the ROC curve) of 66.0% (95% CI 63.5%, 68.5%) for ESR and 67.3% (95% CI 65.0%, 69.6%) for CRP. The difference in c-index values was not statistically significant (p = 0.29). Results were similar for TJC (c-index 69.7% for ESR and 70.1% for CRP).

Examination of ESR and CRP elevation for patients in each category of SJC revealed that the majority (73.6%) of patients with no swollen joints had normal ESR and CRP values (Table 2). Only 4.5% of patients with no swollen joints had elevated CRP and normal ESR, but 15.2% had a normal CRP and elevated ESR. Among patients with 1–4 swollen joints, 50.7% had normal values for both ESR and CRP. In patients with more than 4 swollen joints, both the ESR and CRP were normal in 29.4% of patients, and both were elevated in 39.7% of patients. The correlation between ESR and CRP was highest among the patients with no swollen joints (r = 0.598) and lowest among patients with 1–4 swollen joints (r = 0.425).

Linear regression models of the association between either ESR or CRP and CDAI revealed both ESR and CRP were significantly associated with CDAI (p < 0.001 for each). The adjusted R-square values were 8.5% for ESR alone, 9.8% for CRP alone, and 11.1% for ESR and CRP together. The association of ESR and CRP with SDAI was slightly better, with an adjusted R-square of 14.8% for ESR and CRP together. The CDAI and SDAI correlated highly with each other (r = 0.996).
The DAS-ESR and DAS-CRP were highly correlated ($r = 0.96, p < 0.001$) with each other. The DAS-ESR values were slightly lower than the DAS-CRP values at the upper end of the range (DAS > 8; Figure 3). Both the DAS-ESR and DAS-CRP were highly correlated with CDAI ($r = 0.94$ for DAS-ESR, $r = 0.99$ for DAS-CRP; $p < 0.001$ for both).

**Table 1.** Distribution of demographics and disease activity measures in 2417 RA patient visits.

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>No. of Observations</th>
<th>Mean ± SD or no. (%)</th>
<th>Correlation Coefficient with ESR*</th>
<th>Correlation Coefficient with CRP*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yrs</td>
<td>2417</td>
<td>50.7 ± 12.3</td>
<td>0.06</td>
<td>0.01 (NS)</td>
</tr>
<tr>
<td>Female</td>
<td>2417</td>
<td>1971 (81.5%)</td>
<td>−0.13</td>
<td>−0.02 (NS)</td>
</tr>
<tr>
<td>ESR, mm/h</td>
<td>2390</td>
<td>35.0 ± 26.3</td>
<td>1.0</td>
<td>0.59</td>
</tr>
<tr>
<td>CRP, mg/dl</td>
<td>2397</td>
<td>1.75 ± 2.68</td>
<td>0.59</td>
<td>1.0</td>
</tr>
<tr>
<td>Swollen joint count</td>
<td>2410</td>
<td>11.7 ± 10.2</td>
<td>0.25</td>
<td>0.28</td>
</tr>
<tr>
<td>Tender joint count</td>
<td>2410</td>
<td>21.8 ± 17.1</td>
<td>0.21</td>
<td>0.18</td>
</tr>
<tr>
<td>Patient VAS</td>
<td>2403</td>
<td>49.7 ± 27.3</td>
<td>0.30</td>
<td>0.35</td>
</tr>
<tr>
<td>Physician VAS</td>
<td>2403</td>
<td>45.2 ± 25.5</td>
<td>0.33</td>
<td>0.41</td>
</tr>
<tr>
<td>DAS-ESR</td>
<td>2369</td>
<td>6.18 ± 1.98</td>
<td>0.53</td>
<td>0.44</td>
</tr>
<tr>
<td>DAS-CRP</td>
<td>2383</td>
<td>5.71 ± 1.84</td>
<td>0.39</td>
<td>0.48</td>
</tr>
<tr>
<td>CDAI</td>
<td>2394</td>
<td>43.0 ± 27.8</td>
<td>0.28</td>
<td>0.29</td>
</tr>
<tr>
<td>SDAI</td>
<td>2377</td>
<td>44.8 ± 28.6</td>
<td>0.33</td>
<td>0.36</td>
</tr>
</tbody>
</table>

*Pearson correlation coefficients for correlations with ESR and log (CRP). All p values < 0.001 unless specified. ESR: erythrocyte sedimentation rate; CRP: C-reactive protein; VAS: visual analog scale; DAS (DAS28): Disease Activity Scale (components: 28 joints assessed for swelling and tenderness, ESR or CRP, patient global health assessment on a VAS; arithmetic transformation required); CDAI: Clinical Disease Activity Index (components: 28 joints assessed for swelling and tenderness, patient global disease activity assessment on a VAS, evaluator global disease activity assessment on a VAS); SDAI: Simplified Disease Activity Index (components: 28 joints assessed for swelling and tenderness, patient global disease activity assessment on a VAS, evaluator global disease activity assessment on a VAS, CRP in mg/dl (0.1–10.0). NS: nonsignificant.
DISCUSSION

Both ESR and CRP are widely used in assessing disease activity in RA. These measures are often used interchangeably, or even redundantly, although it is not clear that performing both adds any additional information. Indeed, it has been suggested that neither may be necessary in the assessment of disease activity in the clinic, as results may add little or nothing to clinical measures of SJC/TJC and patient and physician global assessments.

Our model containing both ESR and CRP provided a c-index of 68.8%. These results indicate CRP alone is as good as or better a predictor of SJC than ESR alone. There is little incremental value in assessing both ESR and CRP.

While linear regression models of the association between either ESR or CRP and CDAI revealed both ESR and CRP to be significantly associated with CDAI (p < 0.001 for each), and the adjusted R-square values to be quite low (8.5% for ESR alone, 9.8% for CRP alone, and 11.1% for ESR and CRP together), indicating little variability in CDAI was explained by either ESR or CRP. In other words, while a high ESR or CRP corresponds to a high CDAI, it is not possible to predict the CDAI knowing only the ESR or CRP. Results were similar for the SDAI, or even slightly better (adjusted R-square 14.8% for ESR and CRP together), most likely due to use of CRP in the SDAI calculation.

We also found that DAS-ESR and DAS-CRP were highly correlated (r = 0.96, p < 0.001). Both DAS-ESR and DAS-CRP were also highly correlated with CDAI; the correlation was slightly but not significantly higher for DAS-CRP. This strong linear relationship indicates that DAS-ESR and DAS-CRP can be used interchangeably. While other investigators have suggested that DAS-CRP may underestimate disease activity, we did not find this to be the case; indeed it appears that DAS-ESR values are slightly lower than DAS-CRP values at the upper end of the range (DAS > 8).

Neither ESR nor CRP showed perfect correlation with SJC. The correlation between ESR and CRP was highest among the patients with no swollen joints (r = 0.598) and lowest among patients with 1–4 swollen joints (r = 0.425). In patients with no swollen joints, both were normal in 73.6% of visits, while ESR was elevated with a normal CRP in 15.2% of these patient visits, compared to only 4.5% who had an elevated CRP and normal ESR. This relationship of more patients with an elevated ESR and normal CRP than with elevated CRP and normal ESR was also noted in patients with swollen joints. However, 6.7% of patient visits with no swollen joints had both an elevated ESR and CRP. Even in patients with more than 4 swollen joints, both measures were elevated in only 39.7% of patient visits, and both were normal in 29.4% of patient visits.

From a clinical standpoint, the good correlation with no swollen joints suggests that the ESR and CRP add nothing to the information gained by joint examination reflecting no evidence of inflammation. In patients with many (> 4) swollen joints, the ESR and CRP appear to add no further information to the clinical assessment, which detected true inflammation. When perhaps the ESR or CRP might be expected to be most helpful in assessing the degree of inflammation in a patient with 1–4 swollen joints, the correlation was particularly poor. In this case, it is a matter of

Table 2. Comparison of ESR and CRP values by swollen joint count.

<table>
<thead>
<tr>
<th>Swollen Joint Count</th>
<th>Total No. with Both Measures</th>
<th>Both Normal, n (%)</th>
<th>CRP Elevated and ESR Normal, n (%)</th>
<th>ESR Elevated and CRP Normal, n (%)</th>
<th>Both Elevated, n (%)</th>
<th>Correlation Coefficient Between ESR and CRP</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>178</td>
<td>131 (73.6)</td>
<td>8 (4.5)</td>
<td>27 (15.2)</td>
<td>12 (6.7)</td>
<td>0.598</td>
</tr>
<tr>
<td>1–4</td>
<td>416</td>
<td>211 (50.7)</td>
<td>39 (9.4)</td>
<td>76 (18.3)</td>
<td>90 (21.6)</td>
<td>0.425</td>
</tr>
<tr>
<td>&gt; 4</td>
<td>1775</td>
<td>522 (29.4)</td>
<td>199 (11.2)</td>
<td>350 (19.7)</td>
<td>704 (39.7)</td>
<td>0.482</td>
</tr>
<tr>
<td>Overall</td>
<td>2373</td>
<td>864 (36.4)</td>
<td>247 (10.4)</td>
<td>454 (19.1)</td>
<td>808 (34.1)</td>
<td>0.591</td>
</tr>
</tbody>
</table>

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.
speculation whether the patient with joint pain in fact has true inflammation when the ESR or CRP are elevated and the joint examination reveals no evidence thereof. Assessment of factors other than joint swelling, such as presence of infections, malignancy, or anemia, that might have contributed to elevation of one or both of these measures was beyond the scope of this study.

Measurement of acute-phase reactants has incremental value in disease assessment in clinical trials, although our results demonstrate how poorly they correlate with presence of swollen joints, as both are frequently normal in patients with active swelling. Just as is the case in the calculation of ACR20 and DAS scores in clinical trials, acute-phase reactants add modest incremental value to standard patient- and physician-derived measures of disease activity\textsuperscript{3,5,9}. An elevated CRP has apparent usefulness as a marker of progressive radiologic damage in the absence of joint swelling, but assessment of this was beyond the scope of our study\textsuperscript{15}. Certainly, however, our results demonstrate that it is not necessary to obtain both measures for clinical disease activity assessment, and that where available, the CRP alone may be preferred for disease activity assessment as a simple, validated, reproducible, non age-dependent test that, in comparison to the ESR, is a labor, time, and cost-saving assay.

ACKNOWLEDGMENT
Ms Crowson and Dr. Matteson thank Centocor for providing the data from the clinical trials upon which this study is based.

REFERENCES
Crowson CS, Rahman MU, Matteson EL. Which measure of inflammation to use? A comparison of erythrocyte sedimentation rate and C-reactive protein measurements from randomized clinical trials of golimumab in rheumatoid arthritis. J Rheumatol 2009;36:1606-10. A sentence in the Results section, page 1608, left column, line 2, should read as follows: “The DAS-ESR values were slightly higher than the DAS-CRP values at the upper end of the range (DAS > 8; Figure 3).” A sentence in the Discussion section, page 1609, right column, line 14, should read as follows: “While other investigators have suggested that DAS-CRP may underestimate disease activity, we did not find this to be the case; indeed it appears that DAS-ESR values are slightly higher than DAS-CRP values at the upper end of the range (DAS > 8).” We regret the error.

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