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.
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Key Indexing Terms:
ACUTE-PHASE REACTANTS RHEUMATOID ARTHRITIS
OUTCOME AND PROCESS ASSESSMENT

The erythrocyte sedimentation rate (ESR, Westergren) and C-reactive protein (CRP) have been used for over 80 years as measures of inflammation for diseases such as rheumatoid arthritis (RA). CRP is a direct and quantitative measure of the acute-phase reaction. The ESR, conversely, indirectly measures the acute-phase reaction; its value lies in its simplicity and it is relatively inexpensive. However, most recent studies tend to favor CRP over ESR in assessing inflammation, mainly because ESR is affected by a multitude of factors, including a wide normal range of results, moderate specificity and sensitivity, low to moderate reproducibility, and poor quality control compared to the CRP. Although determining ESR is inexpensive, the fact that the test is done manually and is time-consuming, with results requiring more than 1 hour in many clinical laboratories including the Mayo Clinical Laboratory, the actual total cost of performing the CRP is only slightly lower than that of the ESR (A. Sanger, Mayo Medical Laboratory, personal communication).

In the assessment of disease activity in RA, ESR and CRP have performed similarly in observational studies, whereby it has been suggested that the CRP has greater sensitivity to change, while the composite Disease Activity Score (DAS) using the CRP may underestimate disease activity[1-4]. The acute-phase reactants ESR and CRP have been incorporated into composite disease activity measures such as the American College of Rheumatology (ACR) ACR20/50/70, DAS and Simplified Disease Activity Index (SDAI)[3,5-7]. These composite measures have been used in

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longitudinal cohort studies and clinical trials, the results of which have suggested that in routine clinical practice a Clinical Disease Activity Index (CDAI) that does not incorporate either of the acute-phase reactants may be as useful as composite measures that do[8,9].

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 that 1200 patients.

MATERIALS AND METHODS

Participants. Data pertaining to disease activity in adult patients with RA were obtained from 3 clinical trials sponsored by Centocor, Inc. (Malvern, PA) that examined golimumab with or without methotrexate (MTX) versus placebo + MTX in MTX-naive patients (GO-BEFORE Trial), golimumab ± MTX versus placebo + MTX in patients with inadequate response to MTX (GO-FORWARD Trial), or golimumab ± MTX, and/or sulfasalazine and/or hydroxychloroquine versus placebo ± MTX, and/or sulfasalazine and/or hydroxychloroquine in patients previously treated with tumor necrosis factor-α (TNF-α) inhibitors (GO-AFTER trial)[10-13]. Full study entry criteria are enumerated in the references. For the GO-BEFORE and GO-FORWARD trials, all were required to have active RA, defined as ≥ 4 swollen joints (out of 66 total) and ≥ 4 tender joints (out of 68 total) and at least 2 of the following: C-reactive protein (CRP) ≥ 1.5 mg/dl (normal range 0 to 0.6 mg/dl) or erythrocyte sedimentation rate (ESR) by the Westergren method ≥ 28 mm/h; at least 30 min of morning stiffness; bone erosion determined by radiograph and/or magnetic resonance imaging (MRI); or anticyclic citrullinated peptide (anti-CCP) antibody-positive or rheumatoid factor (RF)-positive. For the GO-AFTER study, only 4 swollen and 4 tender joints were required at enrollment.

Disease activity assessment. The following measures were assessed at baseline and Week 24 for each patient: ESR, CRP, swollen and tender joint counts (SJC, TJC), and patient and physician visual analog scale (VAS) score for global disease activity. Age, sex and treatment assignment were also provided. Using these data, DAS-ESR, DAS-CRP, CDAI, and SDAI were calculated[6,8].

Elevated ESR was defined as > 22 mm/1 hour for males and > 29 mm/1 hour for females. ESR was performed using a standard kit (Sediplast ESR, LP Italiana SpA, Milan, Italy) immediately after venipuncture at each site. CRP was done at a single central laboratory; > 0.8 mg/dl was considered to be elevated.

Statistical analysis. Data distributions and correlations were examined for 12 distinct groups of measurements defined by unique combinations of the 3 trials (GO-BEFORE, GO-FORWARD, GO-AFTER), 2 treatment arms (placebo ± MTX, golimumab ± MTX) and 2 study visits (baseline, Week 24). These groups are GO-BEFORE/placebo/baseline, GO-BEFORE/placebo/Week 24, GO-BEFORE/golimumab/baseline, GO-BEFORE/golimumab/Week 24, GO-FORWARD/placebo/baseline, GO-FORWARD/ placebo/Week 24, GO-FORWARD/golimumab/baseline, GO-FORWARD/golimumab/Week 24, GO-AFTER/placebo/baseline, GO-AFTER/ placebo/Week 24, GO-AFTER/golimumab/baseline, and GO-AFTER/golimumab/Week 24. The distributions of CRP values were right-skewed. Log-transformation resulted in approximately normally distributed CRP values; the resultant values were used for all analyses. Since correlations between ESR and CRP were consistent across the 12 groups (using either Pearson correlations with log CRP or Spearman correlations with CRP), the data were combined for all analyses. The primary unit of analysis was a patient visit; each patient contributed 2 sets of measurements (i.e., 2 study visits). For the purposes of this analysis, these are considered to be independent observations, and the analyses ignore the potential correlation within patients.

Proportional odds models (an extension of logistic regression for more than 2 levels of response based on cumulative logits) were used to examine the association between SJC (categorized as 0, 1–4, > 4 swollen joints) and ESR or CRP. Models were adjusted for age and sex. Sensitivity and specificity were obtained for dichotomized SJC (0–4 vs > 4). The c-index, equivalent to the area under the receiver-operator characteristic (ROC) curve, was used to compare the logistic regression models. Linear regression was employed to examine the association between CDAI or SDAI (as continuous measures) and ESR or CRP. Locally weighted regression methods were used to obtain the smooth line of association shown in Figure 1[14].

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 patientss 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 ($r = 0.996$).

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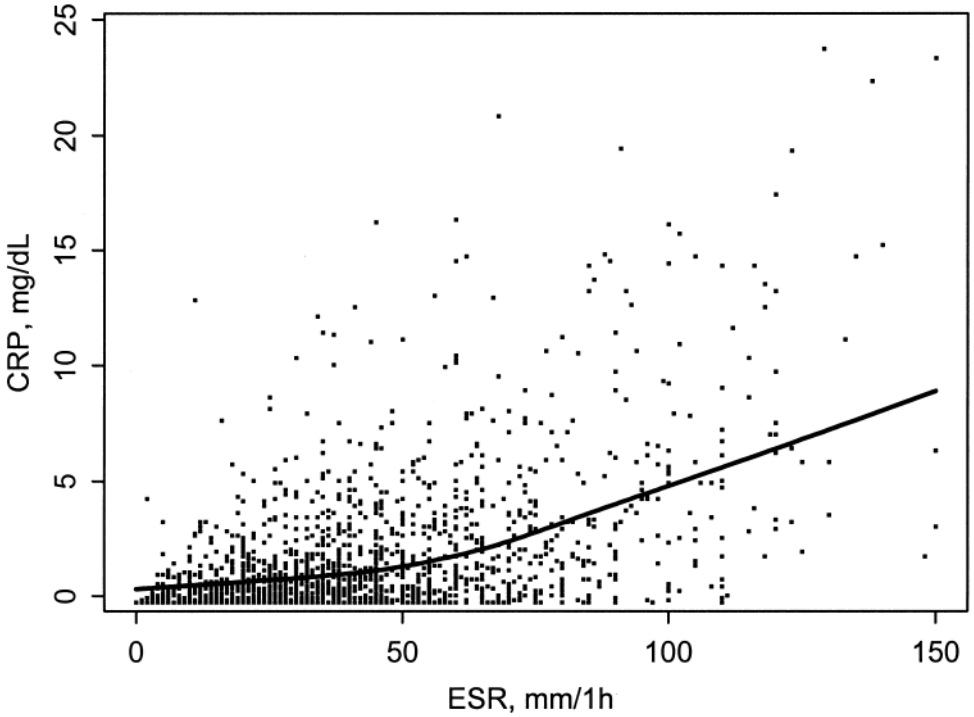

Figure 1. Plot of erythrocyte sedimentation rate (ESR) versus C-reactive protein (CRP) for 2417 RA patient visits with a smooth line of association.

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

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

* 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.

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).

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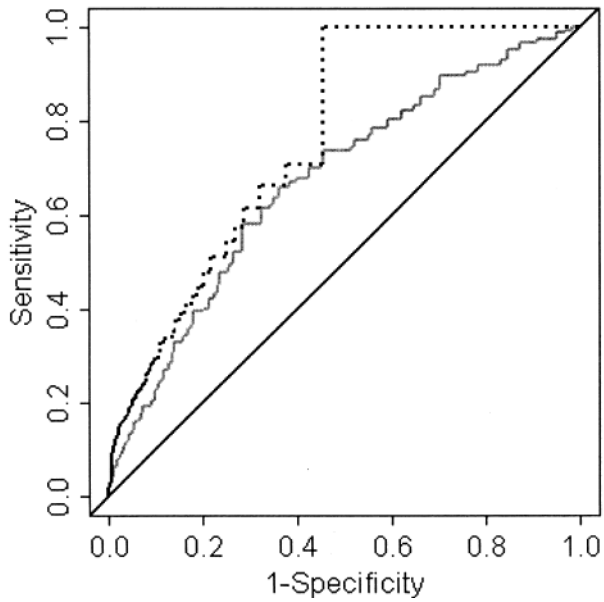

Figure 2. Receiver operator characteristic plot for erythrocyte sedimentation rate (dotted line) and C-reactive protein (grey solid line) predicting swollen joint count (≤ 4 swollen joints vs > 4 swollen joints).

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[9].

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.

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

CRP: C-reactive protein; ESR: erythrocyte sedimentation rate.

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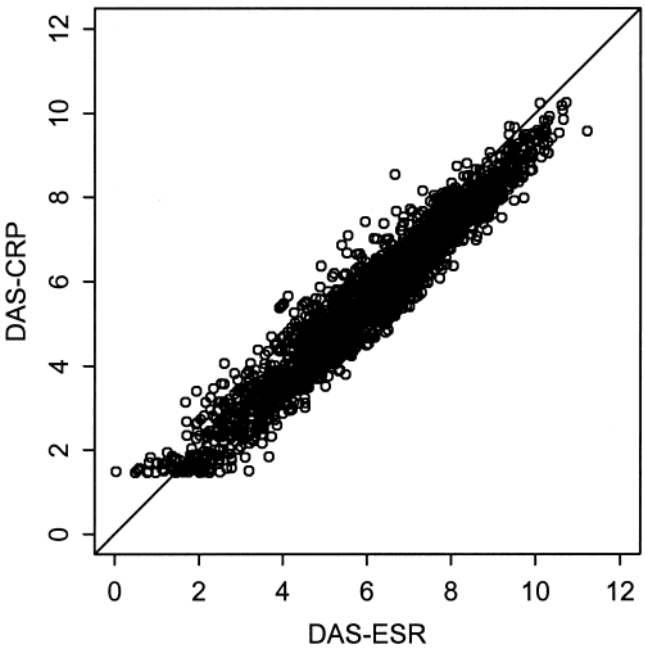

Figure 3. Plot of disease activity score (DAS) using the erythrocyte sedimentation rate (DAS-ESR) versus the DAS C-reactive protein (DAS-CRP).

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[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[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.

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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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