

## Is Erythrocyte Sedimentation Rate the Preferable Measure of the Acute Phase Response in Rheumatoid Arthritis?



In this issue, Michael Ward<sup>1</sup> compares the acute phase reactants erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP) for their ability to detect change during studies of disease modifying antirheumatic drugs (DMARD) in patients with rheumatoid arthritis (RA). In a metaanalysis of 63 clinical trials or observational studies of RA treatment, 89 treatment arms with DMARD therapy included sufficient paired data of both ESR and CRP at baseline and at 4 to 24 weeks to determine the treatment effect sizes for both measures of acute phase reactant changes. Recent studies with minocycline, leflunomide, etanercept, infliximab, and anakinra (but not adalimumab) were included, along with studies of traditional DMARD and DMARD combinations. Only 6 of the studies were published before 1988, and most were published within the past 10 years.

Placebo treatment arms were not included in this analysis, and one study of prednisolone was excluded as an outlier because it reported very large effect sizes after only 4 weeks of treatment. Effect sizes for the 89 treatment arms ranged widely from -0.22 to 3.89 for ESR, and 0.02 to 1.46 for CRP. Pooled effect sizes for values at 4, 8, 12, 16, and 24 weeks after baseline were determined by weighting the number of subjects in each arm by its effect size at that time point, and ranged from 0.29 to 0.65 for ESR, and 0.39 to 0.59 for CRP. Differences between pooled weighted effect sizes for ESR and CRP were calculated for each of these time points, although the amount of available data varied at the different time points. At 12, 16, and 24 weeks the pooled effect sizes for ESR were 0.09 to 0.11 units greater than those for CRP. Effect size for CRP was 0.05 greater than that for ESR at week 4 and 0.06 greater at week 8, but these differences were not statistically significant because of fewer subjects at these time points. The authors concluded that ESR is more sensitive to change than CRP and may be the preferred measure of the acute phase response in RA.

These interesting findings are derived from a large number of clinical trials and appear to reflect real differences in the sensitivity to change of the 2 measures. The clinical significance of an effect size difference of 0.09 or 0.11, however, is not clear. Standing alone, these values would be considered to be "small" effect sizes, but they may be sufficient to influence the statistical significance of a composite outcome measure in a large clinical trial, and may influence trial design.

Effect size is a statistical representation of change over time in a measure that is standardized by dividing the change value by the standard deviation of its baseline values for the cohort being considered. If there is great variability among the baseline values of the cohort, the standard deviation will be large and the effect size relatively smaller, whereas if there is little variability among baseline values, the standard deviation will be small and the effect size relatively larger if the average change value is the same. Effect size is a unitless expression of change and is widely used in metaanalyses to compare or pool the results of multiple studies, increasing the statistical power of studies that have been too small to individually demonstrate statistical significance. Effect size can also be used to compare the sensitivity to change of various outcome measures, as was done in the report by Ward.

The ESR has been part of the tool kit of physicians since before there were rheumatologists. Measuring the distance that erythrocytes in anticoagulated whole blood fall during 1 hour in a standardized tube is simple and easily done in a doctor's office or local laboratory, and does not require any chemical reagents or complex calculations by a computer. When promptly done with freshly drawn blood, the ESR is reliable and reproducible, and has been useful in the differential diagnosis of inflammatory disorders and to monitor responses to therapy. However, ESR is sensitive to various conditions; it decreases with increases in the time and

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storage temperatures between drawing the specimen and performing the assay. It increases if the tube is not vertical or if it is subject to vibration, e.g., by a centrifuge on the same laboratory bench. Values are also affected by red blood cell size, shape, and hematocrit<sup>2,3</sup>, as well as the age and sex of the patients.

Two methods have been commonly used to assay the ESR. The Westergren method is preferred because it is relatively linear, although it requires a special citrate tube. The Wintrobe method can be performed on blood from an EDTA tube commonly used to measure complete blood cell count, is slightly more sensitive than the Westergren method at modest ESR levels, but has a major drawback in that it tends to plateau at about 50–55 mm/h. In the metaanalysis by Ward<sup>1</sup>, only 51% of the studies specified that the Westergren method was employed; the remaining studies did not report the method. ESR increases with moderate increases in fibrinogen (an acute phase protein) and with major increases in immunoglobulin concentrations<sup>2,3</sup> that increase rouleaux formation and the subsequent surface-to-volume ratio that favors erythrocyte sedimentation. It is estimated that about 60–70% of an increase in ESR is attributable to fibrinogen because of its neutralizing effects on red blood cell (RBC) sialic acid residues that typically inhibit RBC aggregation and rouleaux. Fibrinogen is among the acute phase proteins produced by the liver in response to inflammation and is upregulated primarily by interleukin 6 (IL-6), tumor necrosis factor (TNF), and IL-1. Consequently, biologic response modifiers, such as anti-TNF interventions, may directly interfere with cytokines controlling the level of putative markers of disease activity. Plasma concentrations of fibrinogen slowly increase by 2- to 3-fold, and peak levels are seen 7 to 10 days after an appropriate stimulus<sup>3,4</sup>. ESR is a component of the remission criteria for RA<sup>5</sup>, and was an essential element in the original Disease Activity Score (DAS)<sup>6</sup>.

CRP was discovered and named in 1930 because it bound to the C-polysaccharide of the pneumococcal cell wall, resulting in calcium-dependent precipitation. It is a cyclic pentameric molecule of 5 protomers, each consisting of 206 amino acids. CRP binds to the phosphocholine binding sites of foreign pathogens and damaged host cells, and also contains Clq and Fc-gamma receptor-binding sites, thus providing a mechanism to eliminate foreign pathogens and damaged host tissue<sup>4</sup>. It is stable in frozen plasma or serum and can be accurately assayed from these stored frozen specimens. CRP concentrations increase within 4 hours after an appropriate stimulus, peak within 24 to 72 hours, and may increase as much as 1000-fold<sup>4</sup>. They promptly return to normal when the underlying inflammation resolves. Thus CRP values can accurately reflect current clinical activity of inflammation/tissue injury found in RA. Many methods have been utilized to assay circulating levels of CRP, and even the reporting units can vary (internationally as mg/l,

but in the United States as mg/dl, a log difference). In the Ward report<sup>1</sup> the measurement methods for CRP were reported in only 23% of the studies. Consequently, it is unclear how much widening of the standard deviation and subsequent impact on effect size is influenced by these differences in laboratory techniques for not only CRP, but also ESR.

Wolfe<sup>7</sup> has suggested that CRP measures the acute phase response, but that ESR measures elements of chronicity and severity of RA in addition to the acute phase response. He found that ESR correlates better than CRP with measures that are not acute phase proteins, such as immunoglobulins, rheumatoid factor, and anemia. He concluded that CRP appears to be a better test for acute phase responses, but ESR may measure aspects of general severity of RA better than CRP, even though it is a poorer measure of inflammation<sup>7</sup>. These observations are supported by the findings of the metaanalysis by Ward<sup>1</sup>, in that the effect sizes for changes in CRP were slightly greater than those for ESR when assayed 4 or 8 weeks after the initiation of treatment, whereas effect sizes for changes in ESR were greater than those for CRP 12, 16, and 24 weeks after starting treatment, when the slower changes in fibrinogen levels have stabilized and non-acute phase changes in immunoglobulins, rheumatoid factors, and hematocrit are occurring.

Are composite outcome measures affected differently by the use of ESR or CRP? When we used either CRP or ESR to calculate the American College of Rheumatology response measure (ACR20) responders in an observational cohort of patients with early RA, the differences in ACR20 responder rates were 0.4% at 6 months, 0.2% at 12 months, and 2.0% at 24 months. The mean Disease Activity Score value calculated using actual ESR values was  $4.043 \pm 1.52$  (SD), compared to  $4.045 \pm 1.51$  when ESR was imputed from actual CRP values using a nomogram<sup>8</sup>, suggesting similarity of the 2 measures when used in these composite outcome measures.

Is it helpful to measure both CRP and ESR? Wolfe<sup>7</sup> found discordance between CRP and ESR in 28% of 774 patients with RA. High ESR ( $\geq 20$  mm/h) and low CRP ( $< 0.75$  mg/dl) were noted in 20%, and high CRP ( $\geq 0.75$  mg/dl) with low ESR ( $< 20$  mm/h) was present in 8%. High CRP/high ESR was associated with worse clinical status, followed by high CRP/low ESR, high ESR/low CRP, and low ESR/low CRP in that order, when assessed by clinical variables such as joint counts, grip strength, Health Assessment Questionnaire disability index, pain, and global severity<sup>7</sup>.

Despite the slight advantage of ESR for later time points, as noted in the metaanalysis<sup>1</sup>, CRP is probably a better measure for use in large multi-investigator clinical trials because it is stable and can be performed on frozen specimens by a central laboratory. The report by Ward<sup>1</sup>, across a varied spectrum of individual therapeutic studies, measures

reductions in acute phase proteins as a function of time. It assumes that responses to traditional DMARD and the newer biologic response modifiers are reasonable to group together for analysis based on their rate and level of impact on disease. It should be noted that this study does not claim to address the more critical question of which surrogate marker correlates best with actual improvement in clinical, functional, or structural outcome with a given therapy. It only measures the change over time after initiation of therapy compared to baseline. In the 9 treatment arms that used a TNF inhibitor, the effect size of CRP was modestly better than that of ESR at 4 weeks (2 of 2 studies), 16 weeks (one of one study), and 24 weeks (7 of 9 studies). ESR may be preferable for single-investigator studies if specimen collection and handling can be closely controlled. In view of substantial evidence that treatments that control CRP and ESR reduce radiographic joint damage<sup>9,10</sup>, it is worthwhile for clinicians to follow the ESR or CRP when treating individual RA patients. If they can do ESR in their office or a reliable local laboratory that can report the results within one or 2 hours, ESR may have advantages for monitoring individual responses to DMARD therapy.

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