To the Editor:

We read with interest the article of Ward and colleagues who measured serially circulating interleukin-2 receptor (sIL2R) levels in rheumatoid arthritis (RA) (1). The authors found no significant partial correlations between changes in sIL2R concentrations (assessed every 2 weeks for up to 60 weeks in 24 patients with RA) and changes in seven other measures of disease activity. Those consisted of tender and affected joint count, physician and patient global assessment, patient pain score, Health Assessment Questionnaire Disability Index, and the erythrocyte sedimentation rate and were, with one exception, considered the most accurate measures of disease activity in a previous study (2). In view of the lack of correlations the authors suggest that RA exacerbations are either not accompanied by T cell activation or that the latter is not reflected by changes in sIL2R levels.

The role of the T cells in the pathogenesis of RA is still unclear but they are likely involved in early phases of the disease. Chronic synovitis and its exacerbations, however, may be sustained by other cells such as macrophages and synovial cells (3).

Herein we would like to comment on some aspects of the study by Ward et al. (1). Previous reports have uniformly shown that sIL2R concentrations are elevated in patients with active RA and other autoimmune diseases and this is considered to reflect activation of the immune system, especially the T cells (4–6). Decreases in sIL2R levels have been observed during treatment with corticosteroids (7–9), methotrexate (10–12), cyclosporin (13–14), and amiprilose HCl (Therafectin) (6) but not with intramuscular gold (8, 15), oral gold, sulfasalazine (15), azathioprine (10, 16), or NSAIDs (17). Despite the different design and follow-up times of these studies, their results suggest that antirheumatic drugs differ in their effects on immune activation as represented by sIL2R levels. In their study, Ward et al. (1) did not prescribe a standard treatment. Though the regression models used by the authors may have adjusted for initial therapy, treatment was changed in 15 patients (65%) during the study. This may have introduced bias due to switching from one second-line drug to another (n = 7), increasing the dosage (n = 5), and prescription of additional antirheumatic drugs (n = 3) (2).

In patients with active RA, decreases in circulating sIL2R levels whether significant (6, 10, 18) or not (11, 17) have been reported to coincide or precede (7, 19) clinical improvement. Ward et al. (1) used a broad definition of active RA based exclusively on the presence of at least six swollen or tender joints and not in other usually required additional measures of disease activity, such as an elevated erythrocyte sedimentation rate (ESR) or morning stiffness. The study included patients with “mildly or moderately” active arthritis (2) but there was no clear definition of disease exacerbation or improvement. The authors showed that changes in sIL2R levels did not occur simultaneously (or within 2 to 4 weeks) with other, mostly clinical, parameters of disease activity but did not examine the correlations with an outcome (either clinical or radiological) after a longer follow-up.

In light of previous studies showing only moderate (7, 18–21) or absent (3, 10, 11, 15, 22) correlations between sIL2R and clinical parameters of disease activity, the results reported by Ward et al. are not surprising. However several laboratory measurements including C reactive protein, ESR (6, 7, 10, 11, 15, 16, 19, 21) anemia (23), platelet counts (7), interleukin-6, soluble tumor necrosis factor receptors (10), and granulocyte–macrophage colony stimulating factor (24) have been reported to correlate with sIL2R levels and most of these were not examined by Ward et al. (1).

We propose that the role of measuring sIL2R levels in the short and long-term management of RA should be clarified in further longitudinal studies which include a clear definition of disease activity, avoid changes in antirheumatic therapy, and, whenever possible, standardize for other factors which may influence sIL2R measurements such as disease duration, stress, mood disturbances (20), and the circadian rhythm (25).

REFERENCES


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REPLY

To the Editor:

Dr. Barrera raises several interesting questions regarding our longitudinal study of the relationship between serum interleukin-2 receptor (sIL-2R) levels and arthritis activity in patients with rheumatoid arthritis (1). One concern is whether changes in drug treatment over time might have been responsible for the limited associations we found between changes in sIL-2R levels and arthritis activity. While different medications may affect sIL-2R levels to different degrees, a uniform treatment protocol, either within or among patients, is not necessary to examine the concordance of changes in different measures of arthritis activity. The phenomenon under study is the degree to which temporal changes in sIL-2R levels correlate with changes in other measures of arthritis activity. The direction of the change (either clinical improvement or worsening) and the cause of the change in clinical status (either natural fluctuation in arthritis activity or start of a new medication) are not important modifying factors in
this analysis. If a change in the state of T cell activation is a prominent factor mediating clinical arthritis activity, and if all sIL-2R levels accurately reflect this underlying state of T cell activation, then changes in sIL-2R levels should reflect changes in arthritis activity. Treatment with a very effective medication may improve clinical arthritis activity greatly, but should similarly decrease sIL-2R levels. The clinical improvements resulting from treatment with a less effective medication should be associated with less substantial decreases in sIL-2R levels. It is the association between changes in clinical arthritis activity and sIL-2R levels that we assessed.

Because the opportunity to examine relationships between different measures of arthritis activity is greatest among patients with active arthritis, we restricted study entry to such patients. Over the course of observation, we did not categorize patients as either improved or worsened, because such definitions would have necessarily been arbitrary. In addition, any categorization of continuous variables, such as joint count measures, global assessments, and sedimentation rates, would decrease the statistical power of any associations that might be drawn between sIL-2R levels and clinical measures. Appreciation of the relationship between short-term changes in clinical arthritis activity and sIL-2R levels may be gained from our Fig. 1 (1).

For the physician and patient global assessments represented in this figure, readers may determine their own definition of “flare.” Marked worsening of arthritis, as judged by either the examining physician or the patient, was often not associated with increases in sIL-2R levels. In some cases, large decreases in sIL-2R levels were measured during these time periods.

The arthritis activity measure we used were primarily clinical measures. However, the correlation of sIL-2R level and the sedimentation rate (partial correlation = −0.12) was no better than those of the clinical measures. Correlations between changes in sIL-2R level and the hemoglobin level (partial correlation = −0.11; \( P = 0.85 \)) and the platelet count (partial correlation = 0.04; \( P = 0.31 \)) were also not significant. We did not examine other laboratory measures.

The absence of a temporal association between changes in sIL-2R levels and a number of clinical and laboratory measures of arthritis activity, and the poor sensitivity to change of sIL-2R levels over short periods of time, suggests that sIL-2R is not a useful evaluative measure in rheumatoid arthritis. Longitudinal study of several different measures of T cell activation will help clarify whether the discordance between arthritis activity and sIL-2R levels noted in this study is due to the limited role of T cells in mediating clinical exacerbations or to the limitations of serum measurements of this particular marker of T cell activation.

REFERENCES


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