Response

To the Editor:

We appreciate the support of Teramoto and colleagues for the concepts outlined in our recent commentary in CHEST (August 2010), which include the importance of a multidisciplinary approach to evaluating interstitial pneumonia (IP) and emphasize the usefulness of specific autoantibodies, such as cyclic citrullinated peptide (CCP), as part of the assessment for connective tissue disease-associated interstitial lung disease (CTD-ILD). Teramoto and colleagues also briefly describe a patient without synovitis who presented with organizing pneumonia and anti-CCP antibody positivity, who later developed the articular manifestations of rheumatoid arthritis (RA). In our and others’ experience, this is not an uncommon scenario, and it supports the notion that lung disease may be the first manifestation of a CTD and that surveillance for evolving extrathoracic features is needed when caring for patients with “idiopathic” IP. Interestingly, we have recently identified a sizable cohort of patients with anti-CCP positivity and IP without prior history of CTD or the articular features of RA. Although a few of these patients have developed the synovitis of RA within a short interval of follow-up, the vast majority have not. Because these patients with ILD have a highly specific autoantibody in the absence of defining extrathoracic CTD features, and because without inflammatory arthropathies they cannot be defined as having RA, we have proposed that it is important to distinguish them from the category of idiopathic IP and consider them to have lung-dominant CTD. With prospective assessments of these types of more precisely characterized and classified phenotypes, we hope that important questions regarding their pathobiology, natural history, and therapeutic responsiveness will be answerable. Finally, we emphasize that a classification of lung-dominant CTD conveys that this entity is distinct from both idiopathic IP and from definite CTD-ILD and that these patients require surveillance for evolution to more defined forms of CTD.

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Interpreting the P Value

To the Editor:

We read with interest the recently published article in CHEST (September 2010) by Harvey and Lang on hypothesis testing, study power, and sample size. The authors remind us that although the α level is typically arbitrarily set at 0.05, other values may be important to consider, depending on whether a type 1 error would carry better or worse consequences than a type 2 error in a given study. In addition, as rightly pointed out, statistically significant results do not invariably translate into clinically meaningful results. There is another point, often overlooked, that we would like to emphasize with regard to the P value. We illustrate this through analogy with diagnostic test performance characteristics.

The sensitivity of a clinical test is the probability that the test is positive in a patient who has the disease. Specificity is the probability that the test is negative in a patient without the disease. These diagnostic test characteristics require that disease status already be known. However, patients (and physicians) would usually rather know the probability that a patient has the disease, given a specific test result. This probability can be derived by application of Bayes theorem and an estimate of the pretest probability of disease.

As Harvey and Lang note, the P value is the “... probability of observing a result as extreme or more extreme as the one observed,...” if in truth there is no difference between the groups. As for a diagnostic test, this must be contrasted with what we would usually rather know: the probability that the hypothesis tested is in fact true, given the study results. To evaluate this probability, a similar Bayesian approach, incorporating an estimate of the “pre-study” probability that the hypothesis is true, is required. The interpretation of the P value should therefore take into account not only rates of type 1 and type 2 error and the consequences that would occur by making them but also the pretest probability that a tested hypothesis is true in the first place. For example, a statistically significant P value (often P < .05) in a study evaluating an improbable hypothesis should be approached with a healthy dose of skepticism. Similarly, a statistically nonsignificant P value, even with adequate power, may not represent strong evidence in support of the null hypothesis if the pretest probability that the alternative hypothesis is true is high.

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Response

To the Editor:

We appreciate Drs Maldonado and West’s interest in our article in CHEST (September 2010).1 They are correct to point out that our article did not address Bayesian analysis of research studies, but we did not intend it to. Although Bayesian approaches are often used in analyzing diagnostic test characteristics, as the authors note, Bayesian applications in analyzing research studies are not as straightforward. To begin with, the a priori (ie, pretest) probabilities required for Bayesian statistics are usually more easily available for diagnostic tests than they are for research studies. In the simplest instance, the a priori probability for a diagnostic test can be estimated by the rate of occurrence of the disease of interest in the population. In addition, the results of any previous tests (eg, a chest radiograph) will further refine the a priori probability for subsequent tests (eg, a chest CT scan). Such a priori probabilities are usually not available for research studies,2,3 although 50% can be chosen to reflect the uncertainty of the ultimate outcome. Of note, Rosenthal4 illustrates how both Bayesian and frequentist analyses can produce similar results when an a priori probability of 50% is chosen for the Bayesian analysis.

Drs Maldonado and West’s advice to consider “probable” and “improbable” hypotheses has merit, but if the a priori probability for a given outcome is overall “probable” or “improbable,” is it ethical to conduct the study? Is there truly equipoise?5,6 Thus, their advice should be tempered when applying it to clinical research. We do, however, completely agree with them that P values are only one of many factors that should be considered when interpreting the results of a research study. The hypothesis tested and the reasons for testing it; the estimated effect size; the precision of the estimate; the research design; the probable sources of error, confounding, and bias; and the biologic plausibility of the results should also inform the overall interpretation of the research.

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Activity of Clarithromycin in Mucosa-Associated Lymphoid Tissue-Type Lymphomas

Antiproliferative Drug or Simple Antibiotic?

To the Editor:

The report in CHEST (September 2010) by Ishimatsu et al1 of two cases of pulmonary mucosa-associated lymphoid tissue (MALT)-type lymphoma successfully treated with clarithromycin is in line with our recently reported phase 2 trial.2 Our trial showed that a 6-month regimen of oral clarithromycin (500 mg bid) is feasible and active in heavily pretreated patients with MALT-type lymphoma arising in different organs, with an objective response rate of 38%, mostly in lymphomas occurring in the ocular adnexae. In our series, there were no cases of pulmonary MALT lymphoma, and cases reported by Ishimatsu and colleagues1 expand the spectrum of MALT lymphomas sensitive to this macrolide.

It is important to understand the mechanism of action of clarithromycin in these lymphomas. Even if the list of MALT lymphomas associated with infectious agents is growing, both of our studies seem to suggest that clarithromycin activity resulted from a direct antiproliferative effect instead of an antimicrobial-mediated consequence. In fact, sinusomonal syndrome persisted after clarithromycin in the first patient treated by Ishimatsu and colleagues,1 and Helicobacter pylori eradication was ineffective in the second one. In our series, all infections from H pylori or Chlamydia pneumoniae were successfully eradicated years before trial enrollment.2 The role of macrolides as potential antineoplastic and immunomodulatory agents is supported by three levels of evidence. First, in vitro studies have shown the capability of these antibiotics to induce antitumor activity of macrophages, natural killer cells, and CD8 cytotoxic T cells2; to reduce neutrophil production of IL-8; to inhibit tumor necrosis factor (TNF)-α production from the statistics book, Statistics for Medical Writers and Editors. Mr Lang receives royalties from the statistics book, How to Report Statistics in Medicine. How to Report Statistics in Medicine.