REFERENCES


Response

To the Editor:

We appreciate Drs Maldonado and West's interest in our article in CHEST (September 2010). 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, although 50% can be chosen to reflect the uncertainty of the ultimate outcome. Of note, Rosenthal 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 overly "probable" or "improbable," is it ethical to conduct the study? Is there truly equipoise? 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.

Bart J. Harvey, MD, PhD
Toronto, ON, Canada
Thomas A. Lang, MA
Davis, CA

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 al 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. 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 colleagues 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, sinobronchial syndrome persisted after clarithromycin in the first patient treated by Ishimatsu and colleagues, and Helicobacter pylori eradication was ineffective in the second one. In our series, all infections from H pylori or Chlamydia psittaci were successfully eradicated years before trial enrollment. The role of macrolides as potential antineoplastic and immunomodulatory agents is supported by three plastic and immunomodulatory agents is supported by three studies, although 50% can be chosen to reflect the uncertainty of the ultimate outcome. Of note, Rosenthal 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 overly "probable" or "improbable," is it ethical to conduct the study? Is there truly equipoise? 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.

Bart J. Harvey, MD, PhD
Toronto, ON, Canada
Thomas A. Lang, MA
Davis, CA

Affiliations: From the Department of Family and Community Medicine, and the Department of Surgery (Dr Harvey), Dalla Lana School of Public Health, University of Toronto; and Tom Lang Communications and Training (Mr Lang).

Financial/nonfinancial disclosures: The authors have reported to CHEST the following conflicts of interest: Dr Harvey receives royalties from the statistics book, Statistics for Medical Writers and Editors. Mr Lang receives royalties from the statistics book, How to Report Statistics in Medicine.
and vascular endothelial growth factor activity; to enhance intracellular cytostatic concentrations; to suppress the production of TNF-α and IL-6 in adenocarcinoma cells; to induce apoptosis in lymphoid tumor cells; and to be substrates of P-glycoprotein, a molecule strongly linked to anticancer drug resistance. Second, in vivo studies have shown that oral clarithromycin is associated with encouraging results in murine models of lung cancer and potentiate cytostatics in mice inoculated with melanoma cells. Third, the use of clarithromycin, alone or in combination with other immunomodulatory agents (lenalidomide, dexamethasone), was associated with encouraging results in trials on multiple myeloma and Waldenström macroglobulinemia and in anecdotal cases of relapsed Hodgkin’s lymphoma and gastrointestinal MALT lymphoma.

Despite this amount of evidence in favor of a direct antitumor activity of clarithromycin and other macrolides, the involvement of undetected microorganisms sensitive to these antibiotics cannot be excluded in our studies, and it is important to underline that several bacteria cause chronic infections by persistent, inactive (quiescent) forms that are unresponsive to antibiotics but that can respond in the case of prolonged treatment like that performed in our studies. Thus, additional experience with clarithromycin treatment, with adequate biologic investigations, is needed to explore its antineoplastic mechanisms.

Andrés J. M. Ferreri, MD
Milan, Italy

Affiliations: From the Unit of Lymphoid Malignancies, Medical Oncology Unit, Department of Oncology, San Raffaele Scientific Institute.

Financial/nonfinancial disclosures: The author has reported to CHEST that no potential conflicts of interest exist with any companies/organizations whose products or services may be discussed in this article.

Correspondence to: Andrés J. M. Ferreri, MD, Unit of Lymphoid Malignancies, Medical Oncology Unit, Department of Oncology, San Raffaele Scientific Institute, Milan, Italy; e-mail: andres.ferreri@hsr.it

© 2011 American College of Chest Physicians. Reproduction of this article is prohibited without written permission from the American College of Chest Physicians (http://www.chestpubs.org/site/misc/reprints.xhtml).

DOI: 10.1378/chest.10-2454

REFERENCES


Response

To the Editor:

Dr Ferreri’s letter notes the efficacy of clarithromycin as an antiproliferative drug in the treatment of mucosa-associated lymphoid tissue (MALT)-type lymphoma based on their phase 2 trial of patients who received clarithromycin for 6 months following various pretreatments, including doxycycline and our report of two patients with pulmonary MALT lymphoma successfully treated with clarithromycin without control of the underlying chronic infectious diseases. We are also interested in the direct antineoplastic effect of clarithromycin on MALT lymphoma in addition to the antimicrobial effect described by Ferreri.

We should not overlook the fact that reports of MALT lymphoma successfully treated with clarithromycin only cover a few organs, such as the ocular adnexae and lungs, as Govi et al3 and we have reported. Therefore, we agree with Ferreri that the involvement of undetected microorganisms sensitive to clarithromycin cannot be excluded in cases in which MALT lymphoma is improved by clarithromycin.

However, we anticipate a direct antineoplastic effect of clarithromycin on two grounds. First, the pathogenesis of MALT lymphoma may be associated with the inhibition of apoptosis via nuclear factor (NF) activation and B-cell lymphoma-extra large (Bcl-xL) expression: MALT lymphoma typically originates from chronic inflammation (eg, from Helicobacter pylori gastritis in the stomach or Sjögren syndrome in the salivary glands), which has been reported to cause antiapoptosis via NF-κB activation.3 On the other hand, several genetic aberrations have been identified in MALT lymphomas, one of which is apoptotic inhibitor 2-MALT1 chimeric gene, which encodes the protein that plays a role in NF-κB activation and correlates well with resistance to H pylori-eradication treatment of gastric MALT lymphoma. Furthermore, in vivo overexpression of Bcl-xL protein, which is reported to be induced by NF-κB and is associated with inhibition of apoptosis, was observed in gastric MALT lymphoma-like lesions in H pylori-infected mice. Second, clarithromycin may affect apoptosis and NF-κB activation: clarithromycin was reported to suppress Bcl-xL expression, resulting in apoptosis directly in human-activated lymphocytes, and to inhibit NF-κB activation in human peripheral blood mononuclear cells.

In summary, we speculate that clarithromycin might directly regulate the suppressed apoptosis in MALT lymphoma caused by chronic inflammation even if that inflammation is uncontrolled and that it might have a direct antineoplastic effect on MALT...