Effect of Azithromycin on Endothelial Function of Patients With Coronary Artery Disease and Evidence of Chlamydia pneumoniae Infection

To the Editor:

Parchure et al recently published the results of a study that suggest that treatment with azithromycin had a favorable effect on endothelial function in patients with documented coronary artery disease and serological evidence of Chlamydia pneumoniae infection. The authors assume that the presence of C pneumoniae antibody is an accurate indicator of infection, but in reality, we have no way of accurately determining who is infected based on serological studies. Recent evidence indicates substantial problems with interlaboratory reproducibility using the microimmunofluorescence (MIF) assay, even though this is the only serological assay recommended by the Centers for Disease Control (CDC). The CDC also stated that there are no validated serological criteria for chronic or past infection. The MIF assay is not standardized, and cross-reactions occur with other Chlamydia species and possibly with other bacteria, including Bartonella and Legionella species. However, the serological method used by Parchure et al was not even specified, and thus the significance of an anti-C pneumoniae IgG titer $\geq$16 is unclear. Classifying a titer $\geq$32 as “high” is probably inappropriate, as it is only 1 dilution higher than the inclusion cutoff titer of 16, and one 2-fold dilution is within the standard error of the MIF assay.

Studies that have examined atherosclerotic plaque from coronary arteries for C pneumoniae by culture, polymerase chain reaction, or immunocytochemical staining have not found a correlation between identification of the organism in tissue and anti-C pneumoniae antibodies.

Another assumption is that the dosage and duration of therapy with azithromycin used is effective in eradicating C pneumoniae from a possible intravascular focus. This is not supported by available data on treatment of C pneumoniae infections. Azithromycin at a dose of 500 mg on day 1 followed by 250 mg/d for 4 days had only 80% efficacy in eradicating C pneumoniae from the nasopharynx of adults with culture-documented C pneumoniae pneumonia. However, Katlin et al recently reported that a 30-day treatment with azithromycin at concentrations achievable in the pulmonary epithelial lining fluid (4 $\mu$g/mL), which is 16$\times$MIC, reduced but did not eliminate the organism in an in vitro model of continuous infection. The effect seen with azithromycin may have been secondary to the drug’s immunomodulatory effect rather than treatment of a putative C pneumoniae infection. The inclusion of patients with no detectable anti-C pneumoniae antibody could have helped to differentiate a nonspecific anti-inflammatory effect from a specific anti-chlamydial effect.

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Response

Dr Hammerschlag raises 2 important points: 1) the meaning of positive Chlamydia pneumoniae (CPn) serology and difficulties associated with the interpretation of serological assays, and 2) the mechanism responsible for the beneficial effects of azithromycin as seen in our study. Regarding the first point, manuscript editing resulted in omission of details regarding serological methods. Expert personnel in our laboratory investigated the presence of IgG CPn antibodies using the microimmunofluorescence (MIF) assay. As most researchers in the field, we are aware of the difficulties in the interpretation of MIF results and the limitations of IgG antibody titer measurement as an indicator of CPn infection. Incidentally, we have addressed these very issues in a recent editorial article. Unfortunately, patients with negative titers were not included in the study. However, we compared the effects of azithromycin in patients with “lower” ($\leq$1:32) and “higher” (>1:32) IgG titers and also in patients with the “lowest” versus the “highest” (>1:256) IgG titers and found that the beneficial effects of azithromycin treatment were unrelated to serological status. This is in agreement with results of our recent placebo-controlled study that showed improved clinical outcome with azithromycin treatment in patients with acute coronary syndromes. The study, which included a large proportion of patients with negative CPn serology, showed that the effect of the antibiotic was independent of CPn serological findings.

Regarding the second point, we indicated in the manuscript that it is debatable whether the beneficial effects of azithromycin on endothelial function were due to its antimicrobial effects or to other mechanisms. We agree with Dr Hammerschlag that it is unlikely that the antibiotic regimen used in the study could have resulted in the eradication of the bacterium from intravascular locations. Hence, in our discussion of results, we suggested that azithromycin’s effects could have been secondary to its anti-inflammatory actions. Dissecting the mechanisms responsible for the beneficial effects of antibiotics in angina patients is not an easy task. Our study was not designed to assess mechanisms of action but to investigate whether antibiotics actually had an effect on endothelial dysfunction. Given the positive results of our study, it would be important to ascertain whether these were due to azithromycin’s antibacterial effects, its anti-inflammatory actions, a direct effect on the endothelium, or a combination of these and perhaps other factors. As suggested by Dr Hammerschlag, and also noted in our paper, further long-term follow up studies in seropositive and seronegative patients and healthy
subjects may contribute, at least in part, to the resolution of this crucial issue.

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