Early Carotid Atherosclerosis and Chlamydia pneumoniae Seropositivity: Are There Arguments to Treat With Antibiotics?

To the Editor:

Sander et al 1 recently published the results of a prospective, double-blind, randomized trial in which they reported the follow-up data of a 30-day roxithromycin therapy on intima-to-media thickness progression of the common carotid artery in 272 consecutive Chlamydia pneumoniae (Cp)–positive and Cp-negative patients with ischemic stroke. No significant differences in cardiovascular events were found between both groups after 2 and 4 years of follow-up. In that study, the identification of patients infected with Cp, and consequently the whole study setup, was based on positive serology (IgG and IgA) measured with the microimmunofluorescence (MIF) test.

Although still considered as the gold standard in Chlamydia serology, the MIF test has been criticized extensively because of cross-reactions between the major outer membrane proteins of the different Chlamydia species, improper interpretation of results, and the use of in-house tests that lack standardization. In the study of Peeling et al, 2 reproducibility for the MIF test among different research laboratories was found to be 60% to 80%. Moreover, in our study by Hoymans et al, 3 we demonstrated that the choice of serological assay considerably affects Cp antibody detection. However, by using the MIF test, we found an IgG titer of ≥1:16 in 88 (83%) of 106 patients referred for diagnostic coronary angiography, but also in 89 (79%) of 112 healthy control individuals, the difference obviously being not statistically significant. Furthermore, at present there is still no reliable and validated serologic marker for determining chronic or persistent Cp infection.

Among the evidence cited by Sander et al 1 for considering Cp as a potential causative agent in atherosclerosis, histopathological examination was mentioned. In a second study by Hoymans et al, 4 we identified the anti-Cp antibody immunoreactive vascular sites as ceroid deposits, and this in the absence of contamination problems with nested PCR for Cp from histopathological examinations, mainly as a result of recent advances in PCR techniques using real-time PCR may allow an accurate, high-throughput detection of Cp in peripheral blood mononuclear cells—as a marker for endovascular Cp infection—is a powerful approach to determining chronic infection. 1,5

Ieven et al pointed out that uncertainties of results with polymerase chain reaction (PCR) analysis for Cp from histopathological examinations occur, mainly as a result of operator dependency and the fact that the detection rate may vary markedly with the primer used. 5 However, Cp has been demonstrated not only by PCR analysis but also by culturing of viable Cp from carotid plaque material, detection of chlamydial HSP 60 in all carotid plaque specimens positive for Cp specific antigen, 6 and retrieval of Cp-reactive T lymphocytes from human atherosclerotic plaques. 1 These results imply that Cp is a key microbial organ that causes atheroma developments in the carotid artery. Additionally, recent advances in PCR techniques using real-time PCR may allow an accurate, high-throughput detection of Cp. 7

We agree with Ieven et al that macrolides have anti-inflammatory, antioxidant, or antimicrobial actions. 5 However, using trial protocols that include Cp-negative control groups, it will be possible to differentiate the antibacterial efficacy from other macrolide effects. Additionally, treating Cp infection in carotid artery plaque with roxithromycin, this regime resulted in Cp eradication of 69% versus only 25% for nontreated patients and thus demonstrates the role of Cp for atherosclerosis. 5

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Response

We appreciate the interest of Ieven and colleagues in our work. They discussed the possible shortcomings of the microimmunofluorescence (MIF) test technique that we used in our study, but as they stated correctly, the MIF test is still considered the gold standard in Chlamydia pneumoniae (Cp) serology. 1 We used the most widely taken MIF assay to determine Cp seropositivity, 2 which has already been used in several other studies. In the study of Peeling et al, 3 the overall agreement with the reference standard titers was 80% and the range 60% to 90%. Based on these findings Peeling et al 3 stated that the MIF test, if performed properly, is sensitive and specific for the serodiagnosis of Cp infections.

In contrast to the cited study by Hoymans et al, 4 we used clearly higher cutoff titers for Cp positivity (IgG ≥1:64 or IgA ≥1:16) to reduce the possibility of including “false” positive patients. Using this definition, we identified only 46% Cp-positive subjects in our group of patients over age 55 with cerebrovascular diseases. There is growing evidence that the combined use of IgA titers and the detection of Cp DNA in peripheral blood mononuclear cells—as a marker for endovascular Cp infection—is a powerful approach to determining chronic infection. 1,5

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