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Secondary Prevention Antibiotic Treatment Trials for Coronary Artery Disease

J. Thomas Grayston, MD

Considerable interest was generated in the possible causative role of Chlamydia pneumoniae in coronary artery disease (CAD) by the publication of a small pilot study in London of antibiotic treatment of CAD that reduced coronary events. Persons familiar with antibiotic treatment of chlamydia were skeptical that the brief treatment schedule in the London trial (azithromycin either one or two courses once daily for 3 days) could have a significant effect on chlamydia. Because of the great importance of CAD and a possible new treatment, further human experimentation was justified. Anderson and coworkers and Muhlestein and colleagues at the LDS hospital and the University of Utah made a useful contribution by quickly undertaking a pilot study, Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection With Chlamydia (ACADEMIC), to see if the surprising findings of the English study could be repeated. It was important to perform this study because some cardiologists had begun inappropriate antibiotic treatment of patients after publication of the English study.

In the article by Muhlestein et al in this issue, we learn that no miraculous reduction in cardiovascular events was seen in 2 years after a more reasonable 3 months of antibiotic treatment. Whether the modest decrease (statistically not significant) in events in the treated group during the second year of observation indicates a treatment effect can be determined only in a larger study. It is important to emphasize, as did Muhlestein et al, that the ACADEMIC study was not adequately powered (not enough subjects) to prove that antibiotic treatment of CAD does not reduce events. There were 300 subjects in the Utah study, whereas 3500 to 4000 are needed to show whether a reduction in events of a clinically significant 20% to 25% follows antibiotic treatment.

In a preliminary publication of the ACADEMIC study results at 6 months, Anderson et al showed that the antibiotic treatment group had some lower values for inflammation markers than did the subjects given placebo. They also found that their more prolonged treatment did not reduce C pneumoniae antibody titers as had been reported by the London group. If these serum markers were also studied after 2 years, the results would be of interest.

There are now at least two adequately powered CAD treatment trials under way (3500 to 4000 subjects) that should give a definitive answer to whether antibiotic treatment can reduce cardiac events. One, the Weekly Intervention With Zithromax for Atherosclerosis and Related Disorders (WIZARD) study that is sponsored by the Pfizer Co, has a 3-month treatment schedule similar to the ACADEMIC trial. The other, the Azithromycin Coronary Events Study (ACES), is sponsored primarily by the NHLBI. Treatment in this trial is for 1 year with a 4-year observation period. Results are not expected until late 2003.

All of the above trials used azithromycin as the antibiotic for treatment because of its proven effectiveness against chlamydia and its excellent intracellular penetration. The only place chlamydia are susceptible to antibiotics is inside the infected cell. The long intracellular half-life of this antibiotic allows once-per-week dosing. Other treatment trials of CAD with other antibiotics are being planned or initiated.

The subjects in the ACADEMIC trial and the other trials mentioned above had stable CAD. One other small pilot trial began treatment with roxithromycin when the subjects were hospitalized with a coronary episode. Again, this trial was too small (200 subjects) to give a definitive answer, but there was evidence of protection early in the observation period. It is conceivable that antibiotic therapy could have a favorable effect in persons with unstable disease.

What will be the significance of the results of the treatment trials, and how will the results contribute to understanding the role of C pneumoniae infection in the pathogenesis of atherosclerosis and the diseases caused by atherosclerosis?

That there might be an association of C pneumoniae with atherosclerosis was first suggested by seroepidemiological findings that persons with CAD more frequently had antibody against C pneumoniae. That an association does exist was proved by finding the organism in atherosclerotic tissue. There are now 50 studies of atherosclerosis tissue for the presence of C pneumoniae. The organism was found in all but 4 of the studies. The organism was demonstrated by 4 different methods: immunocytochemistry with C pneumoniae–specific monoclonal antibody (the most sensitive), polymerase chain reaction, electron microscopy (original method), and isolation. In studies from laboratories using immunocytochemistry with or without polymerase chain reaction, the organism was found in 40% to 100% of the atherosclerotic lesions examined. Although the finding of a pathogenic organism in the diseased tissue (and not in normal tissue) is suggestive, it does not prove a causal association.
Observational studies (seroepidemiology and tissue studies) cannot prove causation. To prove causation, experimental studies are needed. It is not expected that a single innovative study can answer the question of whether \textit{C pneumoniae} does or does not cause atherosclerosis. Rather, an accumulation of evidence from a variety of different studies will be required. These will include basic mechanisms, animal models, and antibiotic treatment trials.

Studies of basic mechanisms by which \textit{C pneumoniae} might cause atherosclerosis have shown some possibilities.\textsuperscript{11,12} Animal model studies in rabbits and mice have clearly shown that when the organism is inoculated into the respiratory tract, it can soon be found in the aorta, presumably transmitted by mononuclear cells.\textsuperscript{13} Inflammatory lesions, possibly early atherosclerotic lesions, have been demonstrated in animals on normal diets.\textsuperscript{14} In mice or rabbits that were fed cholesterol or had genetic defects causing hypercholesterolemia, \textit{C pneumoniae} respiratory infection accelerates development of atherosclerosis.\textsuperscript{15,16} Early antibiotic treatment of the \textit{C pneumoniae} infection blocked the accelerating effect of \textit{C pneumoniae}.

So far, there are no definitive findings from secondary prevention antibiotic treatment trials. Although considerable expectation has been built up about the results of the adequately powered trials now underway, it is important to consider what they can and cannot tell us about an infectious cause of atherosclerosis. The hypothesis on which the trials are being conducted is that \textit{C pneumoniae} plays a causative role in atherosclerosis and that antibiotic treatment directed against \textit{C pneumoniae} will decrease complications of atherosclerosis.

\textit{C pneumoniae} could play a causative role in one or more of the many different stages in the development of atherosclerosis, which is a nearly life-long disease process. It could be in initiation of the disease or in the development or acceleration of the process. The animal model studies most strongly support \textit{C pneumoniae} involvement, along with lipids, in the development and acceleration of the disease but do not rule out a role in the initiation of the disease. The organism could also play a role in the final stages of the disease when complications of atherosclerosis lead to such events as myocardial infarction. The treatment trials will give information only on this final stage of the process. There are no animal models of these late complications of atherosclerosis, so human trials are justified.

If there is a significant decrease in cardiac events in the treatment arm of the clinical trials, it will provide evidence that \textit{C pneumoniae} plays a causative role in the pathogenesis of complications of atherosclerosis, in this case CAD. This evidence will be indirect in that there is the unlikely possibility that the antibiotic effect is on an unknown organism rather than \textit{C pneumoniae}. There is also an unlikely possibility that a positive result could be due to the anti-inflammatory effect of macrolide antibiotics. This effect should not continue after the antibiotic administration has stopped. A decrease in events will not provide any knowledge concerning the role of \textit{C pneumoniae} in the initiation or development of atherosclerosis.

If there is not a significant decrease in cardiac events in the treatment arm of the clinical trials, it will suggest that antibiotic treatment should not be used in CAD and that \textit{C pneumoniae} does not play a causative role in complications of atherosclerosis. What it will not do is provide evidence that \textit{C pneumoniae} does or does not play a role in the initiation or progression of atherosclerosis.

A negative result from the clinical trials will clearly dampen interest in the association of \textit{C pneumoniae} and atherosclerosis, probably more than it should. The organism will still be present in most atherosclerotic lesions, and the animal studies will be watched for more pro or con data.

A positive result will raise interesting and difficult issues about who should receive antibiotic treatment.

References

Key Words: Editorials • coronary disease • antibiotics • \textit{Chlamydia pneumoniae}