Antibiotic Treatment Trials for Secondary Prevention of Coronary Artery Disease Events

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The TWAR organism was described as a cause of respiratory infection in 1986.1 In 1989, it was declared a new species of Chlamydia and named Chlamydia pneumoniae.2 In 1988, Saikku et al3 reported a small seroepidemiological study suggesting a possible association between TWAR infection and atherosclerosis. Information on the association of C pneumoniae and atherosclerosis has accumulated rapidly since that time. More than 20 seroepidemiological studies have confirmed an association, and several have failed to find it.4 The seroepidemiological studies have been most useful in calling attention to the possibility of an association rather than suggesting possible mechanisms.

That an association between C pneumoniae and atherosclerosis exists has been shown definitively in a series of studies demonstrating C pneumoniae organisms in atherosclerotic tissues. The organism has been demonstrated in atherosclerotic plaques by electron microscopy, by immunocytochemistry using monoclonal antibodies, by polymerase chain reaction (PCR), and by isolation of the organism.5–7 More than 20 reports have appeared that demonstrate the presence of the organism in atherosclerotic plaques by 1 or more of these techniques. Except for a few studies using PCR only, the organism has been found in from 50% to 100% of the tissues studied. In most of the studies, the organism could not be found in normal-artery tissue.

Although the association of C pneumoniae and atherosclerosis has been established beyond a reasonable doubt, the significance of the association for the etiology of atherosclerosis and its progression and complications is unknown. Studies of this association should now be directed at determining whether or not the organism plays a causal role in atherosclerosis and its complications. Two methods for determining an etiologic role are now being examined. One is secondary prevention studies in humans, called ACADEMIC. As we would expect from these investigators, the study is not powered to determine an effect on events in both placebo-treated and untreated controls, and the unexpected fall in antibody titers in those treated who did not have events.

The fact that there was no miraculous effect on CAD events in the interim report of the ACADEMIC study should not be accepted as a negative finding. As the authors point out, their study is not powered to determine an effect on events, not at 6 months nor at the projected end of the study at 2 years. It is probable that ≥10 times as many subjects would be required to have adequate power to detect a true protective effect.

Interestingly, by studying several well-established markers of inflammation, Anderson et al have found a favorable reduction in those receiving antibiotic at 6 months but not at 3 months. Determination of the inflammatory markers later in this study may give an indication of whether the 3-month...
course of antibiotic therapy was adequate or too short, as in the Gurfinkel study.

There are now at least 2 large secondary prevention antibiotic trials under way, which appear to be adequately powered to determine an effect on CAD events. Both of the trials of which I am aware use azithromycin in once-a-week treatment. The WIZARD (Weekly Intervention with Zithromax against Atherosclerotic-Related Disorders) trial, sponsored by the Pfizer Company, is treating 3500 subjects with prior myocardial infarction and Chlamydia pneumoniae antibody for 3 months and planning a 2.5-year observation. The ACES (Azithromycin Coronary Events Study) trial, sponsored by the NHLBI, will treat 4000 subjects with evidence of CAD, irrespective of antibody status, for 1 year, with a planned 4-year observation period.

If Chlamydia pneumoniae plays a role in the etiology of atherosclerosis and its complications, the role could be at the initiation of the disease, in the progress of the disease, or in the complicating events. Secondary prevention studies with antibiotics, if they have a favorable effect in reducing events, will suggest but not prove that control of Chlamydia pneumoniae infection reduces events. It is possible but unlikely that the anti-inflammatory effect of macrolide antibiotics could account for a favorable effect on complications of atherosclerosis or that the antibiotic could be acting on another microorganism instead of Chlamydia pneumoniae. Conversely, if antibiotic therapy fails to reduce events, it would suggest that the pathogenesis of coronary artery events is not modified by treatment for Chlamydia pneumoniae, but it will not rule out the possibility that Chlamydia pneumoniae plays a role in the initiation or progression of atherosclerosis, as has been suggested by animal model studies.

Despite the uncertainties that will remain, if antibiotic treatment does significantly reduce the incidence of CAD events, it will be an important advance in treatment of a major disease.

References

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