Editorial

Antibiotic Treatment of Atherosclerotic Cardiovascular Disease

J. Thomas Grayston, MD

It is just 17 years since Chlamydia pneumoniae was first described and 14 years since the first observational evidence of a possible association of the organism with coronary heart disease (CHD). For 5 years there was little interest in this association, but it has subsequently attracted an increasing number of investigators. The question of an association was settled by the frequent demonstration of C. pneumoniae in atherosclerotic lesions. However, understanding the pathogenic significance of the organism in the lesions has remained elusive.

See p 1253

Efforts to determine the pathogenic role of C. pneumoniae have included animal model studies, mechanistic studies, and clinical trials of antibiotic treatment. In rabbits and mice, C. pneumoniae pulmonary inoculation causes acceleration of atherosclerosis in the presence of elevated lipids. This effect of C. pneumoniae can be prevented by antibiotic treatment shortly after inoculation but not after the organism becomes established in the arteries. There are now a variety of studies of basic mechanisms that have shown ways that C. pneumoniae could play a role in the pathogenesis of atherosclerosis.

With the publication in this issue of Circulation of a clinical trial of antibiotic treatment of patients after acute myocardial infarctions, there are now 12 published clinical trials of antibiotic treatment for secondary prevention of atherosclerotic cardiovascular disease. Two additional trials, not yet published, were presented at the 2002 Annual Scientific Sessions of the American College of Cardiology. They are Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders (WIZARD) and AZithromycin in Acute Coronary Syndromes (AZACS). Nine of the 14 trials studied prevention of events of CHD. Five studied changes in arteries.

Treatment Trials of Secondary Prevention of Coronary Heart Disease

Table 1 lists information on 8 small trials involving CHD. Small trials include those with an inadequate number of subjects and length of observation to provide a convincing result. For example, in the study reported in this issue, power calculations called for a sample size of 3922. Because of slow recruitment, the study was restricted to 872 subjects. The power calculations for the Azithromycin Coronary Events Study (ACES) also called for 4000 subjects. Although the estimated event rate and the length of observation can change the number of subjects needed, none of the trials in Table 1 have anywhere near enough subjects to be adequately powered.

In addition to the limitations of small numbers of subjects and short observation periods, most of these trials had very limited courses of antibiotic treatment. All used a macrolide antibiotic known to be effective against C. pneumoniae. Treatment for 3, 6, or 7 days is a course for acute infection with Chlamydia and entirely inadequate for chronic infection. The first trial from London in which subjects were given either one or two 3-day courses of azithromycin was reported as positive. I have previously described the errors in study design and the inadequate treatment course of this trial.

The short antibiotic courses used in the London and ROXIS studies influenced the treatment course in a number of subsequent studies. This was despite efforts in cardiology journals in 1998 and 1999 to educate cardiologists about the microbiology of Chlamydia and treatment requirements for chronic Chlamydia infection.

There is a large body of experience with antibiotic treatment of chronic Chlamydia trachomatis and Chlamydia psittaci infections, the other Chlamydia species that infect humans. Successful treatment has been uncommon and has required vigorous, long-term, carefully controlled antibiotic administration. The life cycle of Chlamydia explains why treatment is difficult. The infectious, extra cellular, nonreplicating form of the organism (elementary body) is not susceptible to antibiotics. It may remain viable in the body for weeks to months before reinfecting a susceptible cell. This is why eradication of the organism after acute infection is difficult. Furthermore, the intracellular replicating form (reticulate body) is susceptible to antibiotics is capable of entering a ”persistent” phase for an indeterminate time that is not susceptible to antibiotics.

Based on experience treating chronic Chlamydia infections and knowledge of the life cycle of the organism, I recommended that the treatment course in clinical trials with CHD be for one year. It is understandable that concern over antibiotic resistance would affect study design. The majority of the trials in Table 1 used subjects with acute coronary syndromes. Having subjects with higher expected event rates allows for shorter trials. Most of the trials did not have major government or industry support. They are more in the nature of pilot studies. The longest treatment course in Table 1 was 3 months.
Before undertaking these trials, it was not known whether 3 months of treatment would influence chronic *C. pneumoniae* infection. Results are mixed for the two trials in Table 1 with 3-month treatment courses. Additional information on the effect of a 3-month treatment course is available from the WIZARD trial. Table 2 shows that the WIZARD trial is the only one of three large, adequately powered, trials that has been completed. Overall, the trial was considered negative because the 7% reduction in events was not statistically significant. There was in the treated group a significant 33% reduction in death and MI during the first six months of the trial (P=0.02). Although the results at all time periods favored the azithromycin group, there was a consistent loss of treatment effect by time, with a trend that was significant. This fall-off of treatment effect after the three months of antibiotic raises the question of whether a longer course of antibiotic might be much more effective. The ACES trial, which has many protocol similarities with WIZARD, may answer this question. The PROvastatin Or atorVastatin Evaluation and Infection Therapy (PROVE IT) trial, which uses subjects with unstable disease, also has long-term treatment. Gatifloxacin, a new fluoroquinolone, is given for the first 10 days of each month for the duration of the trial. This trial is event-driven and is expected to end in the second half of 2003. The ACES trial ends in December 2003 and should be reported in the spring of 2004.

### Treatment Trials Against Atherosclerotic Vascular Diseases

Table 3 shows antibiotic treatment trials utilizing noninvasive measurements of aortic aneurysm growth and carotid artery thickness, peripheral vascular disease symptoms, and restenosis after stent placement in coronary arteries. Although these trials were small, the end points were available in all subjects, not just those with events. This allowed statistically significant results (although the power was low). All of these trials showed a positive effect of the antibiotic (usually roxithromycin, a macroline). In the study of restenosis, an effect was seen only in subjects with high titer (≥512) *C. pneumoniae* antibody. Although atherosclerosis plays a role in each of the arterial diseases in Table 3, the pathogenesis of aortic aneurysm and of restenosis have differences from the occlusive diseases.

There are also differences between the pathogenesis of coronary events and atherosclerosis. Plaque instability and rupture are thought to play a larger role in coronary events than occlusive disease. Because of all these differences in pathogenesis it is difficult to hypothesize where, if anywhere, *C. pneumoniae* has an effect. These various clinical trials may help to identify a role for *C. pneumoniae* in atherosclerotic disease.

### Conclusions

The reported trials of antibiotic treatment of CHD events suffer from two major shortcomings: the courses of treatment were too short to be effective against a chronic Chlamydia infection and the size of the trials, with one exception, were too small to offer convincing evidence for either negative or positive results. Because of these shortcomings, it is not yet known whether antibiotics have a place in treatment of CHD.

If the positive results of the trials of arterial disease can be repeated with larger numbers, they will offer evidence suggesting that *C. pneumoniae* is involved in the pathogenesis of atherosclerosis.

When the PROVE IT and ACES trials have been reported, there should be a better and perhaps definitive conclusion about the usefulness of antibiotic treatment for the secondary prevention of CHD. If the trials are positive there will be a new therapy for CHD and an additional type of evidence for a pathogenic association of *C. pneumoniae* and atherosclerosis. If the trials are negative there will be less interest in the association, but they will say little about the possible role of

### TABLE 1. Small Clinical Trials: Antibiotics and CHD

<table>
<thead>
<tr>
<th>Location</th>
<th>Name</th>
<th>Population</th>
<th>No.</th>
<th>Antibiotic</th>
<th>Course</th>
<th>Observe</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>London²</td>
<td>na</td>
<td>Post-MI</td>
<td>60</td>
<td>Azithromycin</td>
<td>3 or 6 days</td>
<td>11/2 yrs.</td>
<td>Positive</td>
</tr>
<tr>
<td>Buenos Aires³</td>
<td>ROXIS</td>
<td>Acute CS</td>
<td>202</td>
<td>Roxithromycin</td>
<td>30 days</td>
<td>6 mos.</td>
<td>+/-</td>
</tr>
<tr>
<td>Utah⁴</td>
<td>ACADEMIC</td>
<td>Stable CAD</td>
<td>302</td>
<td>Azithromycin</td>
<td>3 mos</td>
<td>2 years</td>
<td>Negative</td>
</tr>
<tr>
<td>Finland⁵</td>
<td>CLARIFY</td>
<td>Acute CS</td>
<td>148</td>
<td>Clarithromycin</td>
<td>85 days</td>
<td>11/2 yrs.</td>
<td>Positive</td>
</tr>
<tr>
<td>Bangkok⁶</td>
<td>na</td>
<td>Acute CS</td>
<td>84</td>
<td>Roxithromycin</td>
<td>30 days</td>
<td>3 mos.</td>
<td>Negative</td>
</tr>
<tr>
<td>London⁷</td>
<td>STAMINA</td>
<td>Acute CS</td>
<td>325</td>
<td>Azithromycin</td>
<td>7 days</td>
<td>1 year</td>
<td>Positive</td>
</tr>
<tr>
<td>Germany⁸</td>
<td>ANTIBIO</td>
<td>Acute MI</td>
<td>872</td>
<td>Roxithromycin</td>
<td>6 wks</td>
<td>1 year</td>
<td>Negative</td>
</tr>
<tr>
<td>Los Angeles*</td>
<td>AZACS</td>
<td>Acute CS</td>
<td>1400</td>
<td>Azithromycin</td>
<td>3 days</td>
<td>6 mos.</td>
<td>Negative</td>
</tr>
</tbody>
</table>

Acute CS indicates acute coronary syndrome.  
+/− Positive result at 1 month decreasing until no significant difference at 6 months.  
*Presented at 2002 Annual Scientific Session of the American College of Cardiology

### TABLE 2. Large Clinical Trials: Antibiotics and CHD

<table>
<thead>
<tr>
<th>Name</th>
<th>Population</th>
<th>No.</th>
<th>Antibiotic</th>
<th>Course</th>
<th>Observe</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>WIZARD</td>
<td>Stable post MI</td>
<td>7000</td>
<td>Azithromycin</td>
<td>3 mo</td>
<td>1–4 years</td>
<td>7% event reduction</td>
</tr>
<tr>
<td>PROVE IT</td>
<td>Acute CS</td>
<td>4000</td>
<td>Gatifloxacin</td>
<td>2+ years, intermittent</td>
<td>2+ years</td>
<td>Expected March 2004 or earlier</td>
</tr>
<tr>
<td>ACES</td>
<td>Stable CHD</td>
<td>4000</td>
<td>Azithromycin</td>
<td>1 year</td>
<td>4 years</td>
<td>Expected spring 2004</td>
</tr>
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</table>
C. pneumoniae in the initiation and acceleration of atherosclerosis. 15

References

Key Words: Editorials ■ clinical trials ■ Chlamydia pneumoniae ■ antibiotics ■ atherosclerosis

TABLE 3. Clinical Trials: Antibiotics and Vascular Disease

<table>
<thead>
<tr>
<th>Location</th>
<th>Population</th>
<th>No.</th>
<th>Antibiotic</th>
<th>Course</th>
<th>Observe</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Finland9</td>
<td>AAA growth</td>
<td>32</td>
<td>Doxycycline</td>
<td>3 months</td>
<td>11/2 years</td>
<td>Positive, $P&lt;0.05$</td>
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<tr>
<td>Denmark6</td>
<td>AAA growth</td>
<td>92</td>
<td>Roxithromycin</td>
<td>28 days</td>
<td>11/2 years</td>
<td>Positive, $P=0.02$</td>
</tr>
<tr>
<td>Zurich10</td>
<td>Peripheral VD*</td>
<td>40</td>
<td>Roxithromycin</td>
<td>28 days</td>
<td>21/2 years</td>
<td>Positive, $P&lt;0.05$</td>
</tr>
<tr>
<td>Munich11</td>
<td>Carotid thickness*</td>
<td>272</td>
<td>Roxithromycin</td>
<td>30 days</td>
<td>2 years</td>
<td>Positive, $P&lt;0.01$</td>
</tr>
<tr>
<td>Munich12</td>
<td>Restenosis</td>
<td>1010</td>
<td>Roxithromycin</td>
<td>28 days</td>
<td>1 year</td>
<td>+/-</td>
</tr>
</tbody>
</table>

*All patients had C. pneumoniae antibody titer $\geq 128$.

/-+ indicates negative overall but positive in subjects with C. pneumoniae antibody titer $\geq 512.$
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