

IS HEART DISEASE INFECTIOUS?

Inflammation, potentially due to infection, plays a central role in the genesis of atherosclerotic lesions. Inflammatory cells, including macrophages and T-lymphocytes and inflammatory cytokines, are present at all stages in both native and experimental atherosclerosis. In vitro, viruses and bacteria, including herpes groups, viruses and pneumonia, can infect endothelial cells, macrophages and smooth muscle cells. They all cause inflammation and produce atherosclerotic changes. In animal models, Marek's disease and chlamydia pneumonia in mice and rabbits cause experimental atherosclerosis. However, the role of human atherosclerosis and its complications remains unproven. The most evidence is supported with chlamydia pneumonia, which has been isolated throughout the vascular tree. Chlamydia pneumonia has been isolated in aortic aneurysms, major arteries and heart valves. There have been reports of successful cultures of chlamydia from atherosclerotic tissue.

What do the studies show?

Two small, randomised, controlled trials with erythromycin compounds, which can eradicate chlamydia, have been performed.

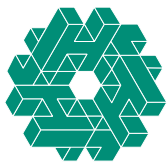
The first study screened male patients post-myocardial infarction (MI) for chlamydia pneumonia antibodies. Patients with the highest titer were randomised to azithromycin or placebo for three to six days. There was a trend towards benefit, with five of 20 (25%) control versus three of 40 (8%) patients having had a clinical cardiovascular event during the followup. Patients were followed for 180 days. Severe recurrent ischemia, MI or cardiac deaths occurred in 8.7% of patients assigned to azithromycin and in 14.6% of patients assigned to placebo. Anti-chlamydia pneumonia IgG titers were unchanged in both groups, while C-reactive protein (CRP) levels decreased in both groups, with a more significant decrease in the antibiotic arm. Elevated CRP levels predicted the need for revascularization.¹

The second study looked at 202 patients with unstable angina or non-Q wave MI. In the randomised study, 102 patients were assigned to a 30-day course of roxithromycin, 150 mg, twice daily (a second-generation macrolide not yet approved in Canada). At day 30, the primary triple and double endpoint rates were 9% and 4% in the placebo group compared to 2% and

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0% in the roxithromycin group. In this trial, roxithromycin seems to extend the benefit of preventing death and re-infarction for at least six months after the initial treatment.²

Some large clinical studies

WIZARD (weekly intervention with azithromycin for an atherosclerosis and its related disorders) included 7,724 patients. These patients, who were at least six weeks post-stable MI with a low positive level of chlamydia antibody titer of ($> 1/16$), were randomised to azithromycin. Azithromycin, 600 mg, was administered daily for three days and was followed by weekly therapy for 12 weeks. Initially, there was an early potential benefit. By the end of the trial, however, a non-significant reduction of 7% was noted. It appeared there may be potential benefit in diabetics, males and smokers, but the main results of this trial were non-significant. Whether prolonged antibiotic therapy in these subgroups would have shown a different outcome awaits results of ongoing clinical trials.³

The AZACS (azithromycin on recurrent acute coronary syndromes) trial evaluated a four-day course of azithromycin in 1,439 patients with acute ischemic syndromes and followed them for six months. Fifty per cent of patients had an acute MI while 42% were admitted with unstable angina pectoris. Eighty per cent of patients had a positive chlamydia antibody titer. Ninety-seven per cent of patients were treated within three weeks of their admission, with the vast majority treated three to four days after their event. Mortality occurred in 3.3% of patients taking placebo versus 2.8% taking azithromycin. The composite endpoint of MI, death, or revascularization occurred in 14.3% of patients taking azithromycin versus 14.9% taking placebo. Patients with a positive

or negative chlamydia antibody titer both showed no benefit.⁴

The ANTIBIO (antibiotic therapy after an acute MI) trial included a total of 872 patients admitted to hospital with acute MI. They were randomised within 49 hours to usual treatment plus six weeks' treatment with either roxithromycin or placebo. At 12 months, mortality rates were similar (6%) in the two groups ($P = 0.739$). There was no other difference in any other cardiovascular event. This trial was hampered by a slow recruitment (3,922 patients originally planned) and an 18% dropout rate within the roxithromycin arm due to gastrointestinal side effects. ANTIBIO is the latest in a series of negative trials of macrolide antibiotics in these patients.⁵

Physician's Perspective

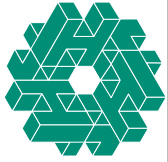
The first observation is to rely on the totality of the information provided. Both patients and physicians have been fooled by small under-powered clinical trials and by observational data.

Atherosclerosis is the vessel's response to injury. We are well aware of the conventional risk factors, such as high cholesterol, diabetes, cigarette smoking and hypertension, leading to atherosclerosis.

Infectious agents, including helicobacter pylori, cytomegalovirus and chlamydia, are associated with human atherosclerosis, but the association is causal at this stage. Future ongoing clinical trials looking at longer duration of therapy may show different results.

Certainly, there is still interest in whether erythromycin compounds will decrease the progression of atherosclerosis by treating chlamydia pneumonia. The large randomised controlled trials so far have been negative.

The trials presented at the American College of Cardiology and at the European Heart




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Meeting were much larger and encompassed a broad range of patients at risk for future vascular insults. Erythromycin compounds were evaluated in patients right after an acute ischemic insult for short course therapy of antibiotics, and in stable patients post-MI who had been treated for 12 weeks. Ongoing clinical trials will look at a longer duration of antibiotic therapy. In addition, it may be extremely important to treat against chlamydia around an acute exposure to this infection and not after a cardiovascular event.

We have much to learn. Again, the large trials completed are disappointingly negative. The question of whether or not heart disease is infectious is still unknown. Chlamydia and other organisms have been found in atherosclerotic plaque and may be an innocent bystander or causally related. More research is needed as well as a better understanding of basic science

dealing with infection and heart disease. What can be said today is that simply giving a short course of antibiotics in patients with established vascular disease does not prevent future vascular insults.

Currently, physicians should not consider antibiotic treatment as part of a preventive strategy in the treatment of atherosclerosis. 

References

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5. The trial was presented at the European Heart meeting September 2002 in Berlin, Germany.

Remember This..



Remembering is difficult... but even more difficult if you have Alzheimer Disease. A disease, which affects the brain, erases memory, and eventually takes life itself.

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