

Oral azithromycin in extended dosage schedule for chronic, subclinical *Chlamydia pneumoniae* infection causing coronary artery disease: a probable cure in sight? Results of a controlled preliminary trial

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Purpose: Two mega trials have raised the question as to whether the hypothesis that infection plays a role in atherosclerosis is still relevant. This controlled preliminary trial investigated an extended dose of azithromycin in the treatment of *Chlamydia pneumoniae* infection causing coronary artery disease (CAD).

Patients and methods: Forty patients with documentary evidence of CAD were screened for immunoglobulin G titers against *C. pneumoniae* and grouped into either the study group (patients with positive titer, $n = 32$) or control group (patients with negative titer, $n = 8$). Cases who met inclusion criteria could not have had coronary artery bypass graft surgery or percutaneous coronary intervention in the preceding 6 months. Informed consent was obtained from every patient. Baseline blood samples were analyzed for red blood cell indices, serum creatinine, and liver function tests, and repeated every 2 months. A primary event was defined as the first occurrence of death by any cause, recurrent myocardial infarction, coronary revascularization procedure, or hospitalization for angina. Patients in the study group received 500 mg of oral azithromycin once daily for 5 days, which was then repeated after a gap of 10 days (total of 24 courses in the 1-year trial period). The control group did not have azithromycin added to their standard CAD treatment.

Results: In the study group, 30 patients completed the trial. Two patients had to undergo percutaneous coronary intervention in the initial first quarter of the 1-year trial period. In the control group, one patient died during the trial, one had to undergo coronary artery bypass graft surgery, and one had percutaneous coronary intervention.

Conclusion: The patients tolerated the therapy well and there was a positive correlation between azithromycin and secondary prevention of CAD.

Keywords: azithromycin, *Chlamydia pneumoniae*, coronary artery disease

Introduction

Of the approximately 600 million bacteria inside and outside of the human body, the majority are commensal. Despite the widespread use of potent antiplatelet agents and statins, the rate of recurrent ischemic events within 2–6 months after an initial episode of acute myocardial infarction and unstable angina remains high (12%–20%).^{1–3} The first association between microorganisms and coronary artery disease (CAD) came from a study in Finland, which showed that high titers of immunoglobulin A and G (IgG)

antibodies to *Chlamydia pneumoniae* occurred significantly more often in men with myocardial infarction and chronic coronary artery disease (CAD) than in age-matched randomly selected controls.⁴ While the serological data elicited some general interest in the topic, it was the unexpected finding by Shor et al that created much interest.⁵ Using electron microscopy, they noticed chlamydia-like structures in the walls of coronary arteries obtained at necropsy. These findings were confirmed by polymerase chain reaction in an international collaborative study,⁵ and this was followed by further confirmation.⁶

The possibility of the role of *C. pneumoniae* in the pathogenesis of CAD was further strengthened by an animal study in which intranasal infection of rabbits with *C. pneumoniae* was shown to induce or accelerate atherosclerosis,⁷ and then further still by a study in which azithromycin prevented the acceleration of atherosclerosis induced by *C. pneumoniae* in rabbits.⁸

Since then, evidence has been accumulating on the role of *C. pneumoniae* – a species of Gram-negative, obligate, intracellular pathogen which commonly causes a spectrum of lower and upper respiratory tract disease in humans and has been implicated in the etiology/pathogenesis of atherosclerosis. Although there is evidence that *C. pneumoniae* is associated with atheromatous lesions, it is difficult to resolve whether it is a primary cause of disease or a secondary invader. Is this the germ theory of disease revisited? Is *C. pneumoniae* an innocent bystander in CAD? The possibility that chronic inflammatory/degenerative diseases previously thought to be noninfectious may indeed be infectious and thus treatable with antibiotics is dramatically exemplified by the response of peptic ulcer disease to antibiotic therapy directed against *Helicobacter pylori*⁹ and chronic plaque psoriasis to antibiotic therapy directed against *Streptococcus pyogenes*.¹⁰ The detection of *C. pneumoniae* in young subjects suggests the possibility that it has a primary role in the etiology of atherogenesis, but does not prove it.¹¹ Still, the presence of *C. pneumoniae* in atherosclerotic lesions raises the strong possibility that antichlamydial antibiotic treatment might have a favorable effect on the course of CAD.

The WIZARD (Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorders) study failed to find a long-term benefit, even though a favorable trend was noted during and shortly after 3 months of azithromycin treatment.¹² More recent trials, ACES (Azithromycin and Coronary Events Study)¹³ and PROVE IT-TIMI 22 (Pravastatin Or Atorvastatin Evaluation and Infection Therapy),¹⁴ also reported a negative outcome. However, these studies do

not disprove the hypothesis that chronic infection with *C. pneumoniae* is atherogenic, and their negative outcome may be either due to inadequate dosage of azithromycin or an advanced stage of CAD.¹⁵ Had the negative outcome been due to an advanced stage of the disease, no significant antibiotic protection – even during the initial 6 months of the trial – would have been observed, so what probably went “off target” in the WIZARD trial was the inadequate regimen of azithromycin.

As chronicity is a hallmark of *C. pneumoniae* infection which is susceptible to macrolides, its trial with an optimum dose is still justified, especially when taking the public health importance of CAD into consideration.¹³ Thus, oral azithromycin was chosen, due to its antichlamydial efficacy, in an extended dosage schedule.^{16–18}

Patients and methods

Forty patients with documentary evidence of CAD (including stable angina, unstable angina, and >3 months post-myocardial infarction) were enrolled in the present trial (Table 1). IgG titers of *C. pneumoniae* were measured in all patients by enzyme Immuno-Assay. Those who met the inclusion criteria could not have had a coronary artery bypass graft or percutaneous coronary intervention in the preceding 6 months nor received antibiotics in the preceding 3 months.

After a screening visit at which *C. pneumoniae* antibody titers were measured, patients with an IgG titer of

Table 1 Baseline characteristics of patients

Characteristics	On azithromycin (n = 32)	Control (n = 8)
Mean age	56 years	60 years
Sex (male:female)	26:6	6:2
Cardiac risk factors		
Current smokers	4	–
Dyslipidemia	32	6
Family history	7	2
Diabetes mellitus	6	1
Hypertension	20	5
Medical history		
Angina	16	3
Congenital heart failure	3	1
Ejection fraction < 35%	8	3
Last myocardial infarction	14 months	12 months
Concomitant medicine		
Aspirin/clopidogrel	27	6
ACE inhibitor	20	7
Statin	22	7
β-blocker	20	6
Calcium channel block	10	3

Abbreviation: ACE, angiotensin-converting enzyme.

C. pneumoniae of 1:16 or greater were assigned to receive oral azithromycin (ie, the study group). Those subjects with a negative titer (or titer less than 1:16) were assigned to the control group and did not have azithromycin added to the already prescribed standard CAD treatment.

Baseline blood samples were analyzed for red blood cell indices, serum creatinine, and liver function tests, and repeated every 2 months. C-reactive protein estimation was done initially and at the end of the 1-year trial period. Informed consent was obtained from all patients.

A primary event was defined as the first occurrence of death by any cause, recurrent myocardial infarction, coronary revascularization procedure (coronary artery bypass graft surgery or percutaneous coronary intervention), or hospitalization for angina.

Patients in the study group received 500 mg of oral azithromycin once daily for 5 days, which was repeated after a gap of 10 days (total of 24 courses in the 1-year trial period). This is a comparable dose to one that was recently used to effectively treat chronic plaque psoriasis.¹⁹ Long-term azithromycin therapy has been well tolerated in previous trials with minor gastrointestinal side effects (eg, nausea and diarrhea).^{19,20} A statistical χ^2 test was applied.

Results

Of the 32 patients in the study group receiving azithromycin in addition to their normal CAD treatment, 30 patients completed the 1-year trial period without any untoward event. The remaining two patients had to undergo percutaneous coronary intervention in the initial first quarter of the 1-year trial period.

In the control group, one died during the trial, one had to undergo coronary artery bypass graft surgery, and one had a percutaneous coronary intervention.

No significant association between *C. pneumoniae* titers and outcome of treatment results was observed. In addition, no association between *C. pneumoniae* titers and the likelihood of developing a primary event was seen within the group of patients in the study and control groups.

C-reactive protein was positive in 15 patients in the study group, which became negative in twelve patients after the 1-year trial period. No difference was noted in the three C-reactive protein-positive cases in the control group.

Mild gastric intolerance and mild diarrhea were reported in six patients who did not require discontinuation of therapy. Remaining patients tolerated the therapy well.

The data were analyzed using a χ^2 test. There was a significant positive correlation between the administration of

azithromycin and secondary prevention of CAD ($\chi^2 = 7.006$; degrees of freedom = 1; $P < 0.01$).

Discussion

Two large, high-quality, and convincingly negative clinical trials for the secondary prevention of CAD, WIZARD¹² and ACES,¹³ raised the question as to whether the hypothesis that infection plays a role in atherosclerosis is still relevant.¹⁵

Evidence that vascular inflammation is an important mechanism involved in all stages of atherogenesis continues to accumulate. Such evidence has legitimately raised the question of whether infection is one of the inflammatory stimuli that operate in the pathophysiology of atherothrombosis – either locally, within vascular tissue, or systemically – through inflammatory mediators. The web of causation in a multifactorial disease does not imply that CAD cannot be controlled unless the entirety of multiple causes or chains of causation, or at least a number of them, are appropriately controlled or removed. This is not the case. Rather, sometimes removal or elimination of only one link or chain may be sufficient to control a disease provided that the link is sufficiently important in the pathogenesis. Thus, in a multifactorial event like CAD, individual factors are by no means of equal priority. The relative importance of these factors may be expressed in terms of relative risk. A meta-analysis of serological studies has upheld the association between *C. pneumoniae* antibody (IgG) and CAD,²¹ and overall the relative risk of disease occurring in patients with *C. pneumoniae* antibody is 2–2.6 times greater than in those without antibody.^{11,22}

Ten clinical trials testing antibiotics for the secondary prevention of CAD have been published,¹³ as well as a few others on its role in carotid,²³ aorta,²⁴ and peripheral artery²⁵ occlusions. Of these, only the WIZARD trial was adequately powered to give definitive results.¹² In the WIZARD trial, azithromycin treatment was given as 600 mg once weekly for 2–12 weeks after an initial dose of 600 mg/day for 3 days in the first week.¹² Its results were similar to the findings of ACES (in which participants were randomly assigned to receive either a 600 mg azithromycin tablet or a matching placebo tablet once weekly for 1 year)¹³ in that they also failed to support the use of antibiotic therapy for CAD. The WIZARD trial, however, did report some antibiotic protection from events during the first 6 months of the trial – a result not repeated by ACES.¹³

In regards to the clinical trials of antibiotic therapy directed at atherosclerotic changes in the carotid arteries,²³ peripheral arteries,²⁵ and the aorta,²⁴ each trial reported that

antibiotic therapy had a significant favorable effect on the progression of disease. These positive results may be considered preliminary; however, if repeated in larger mega trials, they will offer convincing evidence suggesting *C. pneumoniae* is involved in the pathogenesis of atherosclerotic occlusive disease.¹³

The relationship between psoriasis and myocardial infarction has appeared in a recent publication where it was concluded that psoriasis may confer an independent risk of myocardial infarction, and the relative risk was greatest in young patients with severe psoriasis (3.1%).²⁶ Recently, it was hypothesized that chronic, subclinical infection of the throat with group A streptococci is the sole etiology involved in the development of psoriatic lesions.¹⁰

Several mechanisms have been suggested by which infection could contribute to atherogenesis. These include cytopathologic effects of infection on endothelial and smooth muscle cells causing endothelial dysfunction,^{27,28} formation of circulatory toxins or immune complexes that could deposit on vessel walls and elicit an inflammatory response,²⁹ and induction or alterations in serum lipid metabolism.³⁰ Results of laboratory studies have been cited to support all three mechanisms.²²

As the rate of a recurrent ischemic event is as high as 12%–20% after an initial episode of acute myocardial infarction/unstable angina, only two patients in the study group (6.3%) needing to undergo percutaneous coronary intervention in the initial 3 months of the 1-year study period certainly suggests a significant beneficial role of azithromycin in extended dosage in the treatment of CAD. These two patients who developed a primary event probably had an advanced CAD or the serum levels of the antibiotic were not sufficient to control their disease progression. The length of treatment to choose for this study was difficult to determine. Knowledge of the biology of chronic *C. pneumoniae* infection suggests that short-term treatment is inadequate for a lasting benefit. The elementary body form of the organism is the infectious nonreplicating form, and it is not susceptible to the action of antibiotics. Elementary bodies may exist in the body for weeks, or longer, and cause new cellular infection. Although short-term treatment might kill replicating organisms in atheroma and temporarily reduce inflammation, it would be unlikely to eliminate the organism from the lesion. Thus, in planning the appropriate length of treatment for a trial, safety both for subjects and the community should be considered. In 1998, Grayston recommended 1 year as the treatment period for *C. pneumoniae* trials.³¹

Azithromycin and *C. pneumoniae* may be the bridge in the therapeutic and etiological lacuna of CAD if results of this preliminary controlled trial are replicated in future mega trials.

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Disclosure

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