

Macrolide Antibiotic Treatment and Atherosclerotic Cardiovascular Disease-Present Status

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Introduction

Various factors may initiate the atherosclerotic process, but recently several line of evidences have implied an association between chlamydia infection and atherogenesis. Seroepidemiological, histopathological and animal studies seem to support an active role of this agent in the pathogenesis of atherosclerosis (1-4). Recently, association of antibodies to chlamydial lipopolysaccharide with the endovascular presence of chlamydia pneumoniae in carotid artery disease and detection of chlamydia pneumoniae in dendritic cells in atherosclerotic lesions is well suggested (1,2). If this association exists then exposure to certain antibiotics like macrolide antibiotic which are effective against this pathogen may positively effect the natural course in patients with coronary heart disease. However, pilot clinical trials of preventive antibiotic treatment in patients with coronary disease have shown conflicting results, with some studies supporting (5-9) and others not supporting the benefit of intervention in such patients (10-14). Hence various recent trials in this regard are reviewed in the present article.

Positive Trials

Roxithromycin treatment for 28-30 days has been shown to prevent the progression of early carotid atherosclerosis in chlamydia pneumoniae seropositive patients (5). The clarithromycin in acute coronary syndrome patients in Finland (CLARIFY) study showed a beneficial effect of a 3-33month therapy with clarithromycin in patients with acute non-q-wave coronary syndromes after 1.5 year (6). The recently presented results of South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA)

indicated superiority of a combination antibiotic therapy after one year in patients with acute coronary syndrome (7). Another study suggested that exposure to anti-chlamydial antibiotic during three months after acute myocardial infarction is associated with small survival benefit (8). Most recently in one of the trial azithromycin has been shown to produce positive effect on fibrinolysis, as increased level of tPA were observed in treatment group (9).

Negative Trials

In Azithromycin Coronary Artery Disease Elimination of Myocardial Infection with Chlamydia (ACADEMIC) study, 302 patients seropositive for chlamydia pneumoniae with stable coronary artery disease did not show any benefit after 3-month treatment with azithromycin (10). Similarly, another study conducted in Bangkok failed to show any benefits in patients of acute coronary syndrome with the use of roxithromycin (11). Antibiotic Therapy After an Acute Myocardial Infarction (ANTIBIO) study also suggested no beneficial effects of a six week treatment with roxithromycin 300mg daily in 872 patients with acute myocardial infarction during a follow-up of 12 month. There was no difference in the total mortality (6.5% in the roxithromycin group compared with 6% in the placebo) and no differences at 12 months for the combined end point of death, myocardial infarction, stroke or angina pectoris leading to hospitalization (12). Most recently, Weekly Intervention with Zithromax for Atherosclerosis and its Related Disorder (WIZARD) trial is the only one of the large, adequately powered trials that has been completed (13). Overall the trial was considered negative because of the

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7% reduction in the atherosclerosis related events were not statistically significant. Similarly in another recent trial, treatment with azithromycin did not result in reduction of either individual end points or any of the primary end points in acute coronary patients (14).

Present Status

There are conflicting reports presently to ascertain the role of macrolide antibiotic treatment in atherosclerotic cardiovascular disease. In general, the larger trials, which included more patients, showed negative results compared with smaller trials. This indicate that if there is a beneficial effect of macrolide treatment on top of standard therapy in patient with coronary artery disease, it might be very small (5-9). Some obvious concern may be antibiotic resistance and non susceptibility of organism to antibiotic, that would effect study design. Even it appears from the negative trials that type of macrolide, type of patients with coronary artery disease duration of therapy and selection of patients by being seropositive for chlamydia pneumoniae did not seem to have major impact on the effect of treatment with macrolide (10-14). Therefore, at present it is very difficult to say conclusively that macrolide therapy has a role in coronary artery disease patient and no recommendation for its use in secondary prevention of atherosclerosis can yet be made. However, larger adequately powered studies are needed to make definitive conclusions about the effectiveness of antibiotic intervention, which are effective against this pathogen, in such patients in future.

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