

## Effect of Roxithromycin Treatment on the Endothelial Function of *Chlamydia pneumoniae* Seropositive Men Suffering From Peripheral Arterial Occlusive Disease

To the Editor:

Parchure et al<sup>1</sup> have recently reported that azithromycin therapy for 5 weeks significantly improved flow-mediated dilation (FMD) of the brachial artery in *Chlamydia pneumoniae* seropositive men suffering from coronary heart disease. Our group has recently reported that roxithromycin treatment for 1 month significantly improved the walking distance and reduced the number of revascularization procedures in *C pneumoniae* seropositive men suffering from peripheral arterial occlusive disease.<sup>2</sup> In this prospective, randomized, double-blind, placebo-controlled study, we also investigated the effect of roxithromycin on the endothelial function.

Determination of radial artery hemodynamics was performed at study entry, at the end of 1-month treatment with either roxithromycin or placebo, and at the 6-month follow-up. Radial artery diameter was measured using a high-precision A-mode echo-tracking device (NIUS 02, Asulab) to determine FMD and glyceryl trinitrate-induced dilation, which was  $10.9 \pm 4.2\%$  (mean  $\pm$  1 SD). At baseline, no FMD of the radial artery could be detected in 6 of 20 patients in the placebo group and in 9 of 20 patients in the roxithromycin group. FMD remained absent in these patients throughout the study period. The results for patients with FMD detectable at baseline were as follows. In 11 roxithromycin-treated patients, FMD increased from  $2.06 \pm 2.20\%$  to  $3.06 \pm 2.47\%$  during 1-month treatment ( $P=0.07$ , Wilcoxon matched pairs test), and decreased again to  $2.41 \pm 2.23\%$  after 6 months. In 14 placebo-treated patients, FMD remained unchanged throughout the study period, ie,  $3.03 \pm 1.34\%$  at baseline,  $3.07 \pm 1.41\%$  after 1 month, and  $3.04 \pm 1.03\%$  at 6 months follow-up.

Parchure et al<sup>1</sup> demonstrated a marked and significant improvement of FMD by macrolide treatment, whereas we found only some (not significant) improvement of FMD if this parameter was detectable at baseline, and no improvement of FMD if this parameter was not detectable at baseline. This may be explained by differences in the study populations. Patients in our study suffered from advanced atherosclerosis, ie, 50% of the patients had undergone revascularization procedure(s) in the year before the study. Our patients as compared with those of Parchure et al study were older (71 versus 55 years) and had a higher prevalence of smoking (88% versus 13%) and hypertension (68% versus 30%). Despite higher serum lipids, our patients were less often treated with lipid lowering drugs (48% versus 75%).

The effect of macrolide treatment on endothelial function probably depends on the stage of atherosclerosis from which *C pneumoniae* seropositive patients suffer. In the case of advanced atherosclerosis, little or no improvement of endothelial function may result from macrolide therapy. This was the case in our study.

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1. Parchure N, Zouridakis EG, Kaski JC. Effect of azithromycin treatment on endothelial function in patients with coronary artery disease and evidence of *Chlamydia pneumoniae* infection. *Circulation*. 2002;105:1298–1303.

2. Wiesli P, Czerwenka W, Meniconi A, et al. Roxithromycin treatment prevents progression of peripheral arterial occlusive disease in *Chlamydia pneumoniae* seropositive men. *Circulation*. 2002;105:2646–2652.

### Response

Wiesli and Schulthess speculate on the reasons for the apparent discrepancies between their results<sup>1</sup> using roxithromycin and our findings with azithromycin<sup>2</sup> with regard to the effects of antibiotic therapy on endothelial dysfunction. Wiesli et al<sup>1</sup> assessed the effects of 1-month roxithromycin treatment on exercise capacity, atheromatous plaque area, radial artery flow mediated dilatation (FMD), and clinical endpoints in patients with peripheral vascular disease and *Chlamydia pneumoniae* (CPn) seropositivity. Patients were assessed at study entry and at 1 and 6 months after antibiotic treatment. Over 30% of the patients in the placebo group and almost 50% in the roxithromycin group had markedly blunted baseline endothelial-dependent FMD responses. In these patients, FMD did not improve after antibiotic treatment. However, patients in whom at least some degree of FMD was present at baseline showed an improved response after roxithromycin treatment compared with placebo. In the study by Wiesli et al,<sup>1</sup> antibiotic treatment resulted in carotid plaque regression (soft plaques) and beneficial long-term effects on clinical endpoints, despite the fact that C-reactive protein levels were not reduced and FMD remained practically unaffected by the antibiotic treatment. An antibacterial effect of roxithromycin was postulated, although a direct antiinflammatory effect could not be ruled out.

Our study showed a significant improvement of FMD and other markers of endothelial activation, such as e-selectin and von Willebrand Factor, after 5-week treatment with azithromycin compared with placebo. The beneficial effects of azithromycin on FMD were independent of CPn antibody titers and C-reactive protein levels, which makes interpretation of the mechanism of action of azithromycin difficult in this particular setting.

In attempting to explain the differences between the 2 studies, Wiesli and Schulthess rightly point out that their patients were older and had more extensive atherosclerotic disease and there were also a larger proportion of smokers compared with our patients. It is conceivable that older age, a larger number of risk factors, and more advanced and extensive atheromatous disease may account for the differences. However, patient selection may not be the only reason for the different responses to antibiotic therapy. Varied and complex mechanisms are involved in the atherogenic process, and these are likely to differ in different individuals. Genetic and environmental factors, as well as the stage of atherosclerotic vascular disease, are likely to play a vital role in modulating the response of the individual to a given intervention. Head to head comparisons are also needed between roxithromycin and azithromycin in patients with vascular disease to ascertain whether these antibiotics differ in their antiinflammatory actions and effects on endothelial function.

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2. Parchure N, Zouridakis E, Kaski JC. Effect of azithromycin treatment on endothelial function in patients with coronary artery disease and evidence of *Chlamydia pneumoniae* infection. *Circulation*. 2002;105:1298–1303.