Effect of a short antibiotic treatment with roxithromycin on circulating adhesion molecules after coronary stenting: a single-center pilot trial

Pietro Vandoni, Benedetto Morelli*, Liliana Lazzati*, Roberto Citterio**, Arnaldo Poli, Raffaela Fetiveau, Maurizio D'Urbano, Francesco Cafiero, Enrico Viganò**, Stefano De Servi

*Division of Cardiology, *Department of Transfusion Medicine, **Division of Microbiology, Civic Hospital, Legnano (MI), Italy*

Key words:
Antibiotic treatment; Cell adhesion molecules; Coronary stenting.

Background. **The aim of this study was to assess the effect of periprocedural antibiotic treatment with roxithromycin on circulating cell adhesion molecules and restenosis after coronary stent implantation.**

Methods. **Case-control study enrolling 25 consecutive patients submitted to coronary stenting for stable, single-vessel coronary artery disease, treated with 300 mg roxithromycin once daily for 5 days, starting 2 days before the procedure (group R). Twenty-five patients, matched for lesion site, length and diameter, as control group (group C). The serological status for *Chlamydia pneumoniae* (CP) infection (IgG, ELISA) was assessed in all patients. The plasma concentrations of soluble intercellular adhesion molecule-1 (sICAM-1), E-selectin and C-reactive protein at 1 month after coronary stenting were compared with baseline values. Binary restenosis (≥ 50%) was also evaluated at 6 months.**

Results. **sICAM-1 significantly decreased at 1 month in group R vs group C (371 ± 181 vs 573 ± 273 ng/ml, p = 0.005). This decrease was more evident in patients with a positive serology for CP (CP+) (group R 373 ± 131 vs group C 597 ± 255 ng/ml, p = 0.014). Antibiotic treatment had no effects on circulating E-selectin levels at 1 month (56.7 ± 97 vs 49.8 ± 62 ng/ml, p = 0.54). The restenosis rate (9/50, 18%) was similar in the two groups (group R 5/25 [20%], group C 4/25 [16%]). The restenosis rate was similar in the CP+ vs CP- group (6/35 [17%] vs 3/15 [20%]).**

Conclusions. **A short course of treatment with roxithromycin at the time of coronary stenting induces a significant reduction in the sICAM-1 levels at 1 month but apparently does not influence the restenosis rate.**

(Ital Heart J 2004; 5 (9): 667-672)

Received June 24, 2004; revision received July 26, 2004; accepted July 27, 2004.

Address:

Dr. Pietro Vandoni

*U.O. di Cardiologia
Ospedale Civile
Via Candiani, 2
20025 Legnano (MI)
E-mail: pietrovandoni@hotmail.com*

In the pathogenesis of the inflammatory process leading to atherosclerosis, the role of infectious agents remains poorly understood. Several recent data confirm that chronic infections increase the risk of coronary or peripheral artery disease by potentiating the action of traditional risk factors[1,2]. In this still hypothetical process, the endothelium acts as an active playground of inflammatory and immune responses to different injuries such as those due to hypercholesterolemia and pathogens. Inflammatory cells release cytokines which modify the endothelial antiadhesive and anticoagulant properties, inducing increased expression of cellular adhesion molecules (CAMs)[3]. These CAMs facilitate transendothelial migration of leukocytes into the arterial wall, a phenomenon that, albeit beneficial in physiological conditions, is thought to be the first step in the pathogenesis of the atherosclerotic process[4]. Soluble forms of CAMs are detectable in the serum and reflect an increased production by the endothelium which is believed to be the principal site of expression[5]. Increased circulating levels of adhesion molecules, such as soluble intercellular adhesion molecule-1 (sICAM-1) and endothelial/leukocyte adhesion molecule-1 (ELAM-1 or E-selectin), occur in a number of pathological settings such as sepsis, cancer, vasculitis, dyslipidemia[6] and even after percutaneous coronary intervention (PCI)[7-9]. This reflects endothelial activation following vessel wall injury.

Among other pathogens, *Chlamydia pneumoniae* (CP), an obligate intracellular bacterium identified less than two decades ago, is one of the most actively studied, and it has been associated with the development of coronary artery disease (CAD)[2] as well

as with restenosis following PCI[10]. Although there are conflicting data regarding the effect of antibiotic therapy on the secondary prevention of CAD and restenosis, some data suggest that antichlamydial therapy could, to some extent, prevent cardiac events in patients with previous acute coronary syndromes[11] and restenosis in patients undergoing PCI[12]. Our study was conceived as a small pilot study aimed at investigating the effects of a short periprocedural treatment with roxithromycin on the circulating levels of sICAM-1 and E-selectin 1 month after stent implantation, in patients with stable CAD. The influence of the serological status for infection with CP on the adhesion molecule response to antibiotic treatment was also evaluated. We hypothesized that the inflammatory outburst related to the balloon trauma and stent implantation could be attenuated by the periprocedural antibiotic therapy and could result in lower circulating adhesion molecule levels and possibly lower restenosis rates.

Methods

Study population. Over a 6-month period in which 430 patients underwent PCI in our clinic, 50 patients undergoing elective PCI for stable CAD (effort angina or silent ischemia) were included in the study. The first 25 patients were consecutively enrolled if they met the following inclusion criteria: age between 40 and 75 years and the presence of one ≥ 75% stenosis, at least 3.0 mm in length, in one of the coronary artery branches. Patients with more than one critical coronary stenosis amenable to PCI were excluded. The presence of acute or chronic inflammatory disease, renal insufficiency or neoplastic disease was a clinical criterion for exclusion. This first subset of patients was treated with roxithromycin (group R). With the same enrollment criteria, 25 subsequent patients with stable CAD and single-vessel disease, matched for lesion site, length and diameter were enrolled as the control group (group C).

Study treatment and follow-up. All patients received aspirin (75 mg daily) plus ticlopidine (500 mg daily), starting 2 days before the procedure and continued with double antiplatelet therapy up to 1 month.

Group R patients received a short course of antibiotic therapy with the macrolide roxithromycin, 300 mg once daily for 5 days, starting 2 days before PCI.

All patients underwent clinical follow-up inclusive of effort testing at 3-4 months and were submitted to coronary angiography at 6 months or earlier if clinically indicated. Restenosis was defined as > 50% diameter stenosis of the treated lesion at quantitative coronary angiography.

The ethics committee of our Institution approved the study protocol and all patients gave written informed consent before enrollment.

Laboratory methods. Fasting blood samples were collected after 20 min of rest before starting the antibiotic and double antiplatelet treatment. The serum obtained by centrifugation was frozen at -80°C until it was analyzed. The serum levels of sICAM-1 and E-selectin were measured by the immunoenzymatic method (ELISA) using "Euroclone sICAM-1" and "Euroclone sELAM-1" kits (Celbio). In our assay, the laboratory coefficient of variation was < 10% for both sICAM-1 and E-selectin.

Anti-CP antibody titers (IgG) were measured in all patients using a commercially available ELISA kit (CP IgG Eurospital). Values > 1 in the optical density/cut-off ratio were considered positive for previous CP infection (CP+). C-reactive protein was dosed using a commercially available immunonephelometric assay.

Statistical analysis. The concentrations of soluble CAMs were measured in ng/ml and expressed as means ± SD. Differences between the means were analyzed using the Student's t-test. All analyses were two-sided, and a p value ≤ 0.05 was considered as statistically significant.

Results

All patients completed the follow-up and were submitted to control angiography at 6 months. The demographic and clinical characteristics are presented in table I. The mean age, sex distribution and risk factors, a history of myocardial infarction and the use of drugs that could modify the coronary response to stent placement such as statins, were not significantly different between the two groups (Table I).

The prevalence of anti-CP IgG antibodies was similar in the two groups (group R = 17 patients [66%], group C = 18 patients [72%]). The mean basal levels of C-reactive protein were low, reflecting the stability of CAD in the enrolled patients (group R 0.48 ± 0.74 vs 0.53 ± 0.68 mg/dl in group C), and remained unchanged at 1 month (group R 0.44 ± 0.81 vs 0.57 ± 0.64 mg/dl in group C). No difference was observed in the baseline C-reactive protein levels relative to the CP

Table I. Baseline demographic and clinical profiles.

	Group R (n=25)	Group C (n=25)
Age (years)	62 (44-72)	65 (41-69)
Sex (M/F)	20/5	22/3
Hypertension	11 (44%)	10 (40%)
Smokers	12 (48%)	9 (36%)
Diabetes	6 (24%)	5 (20%)
Statin therapy	14 (56%)	17 (68%)
ACE-inhibitors	4 (16%)	3 (12%)

serology (CP+ 0.44 ± 0.68 vs 0.57 ± 0.9 mg/dl, p = 0.53).

Basal sICAM-1 levels were similar in the two groups (group R 453 ± 262 vs 502 ± 335 ng/ml in group C, p = 0.5) but were significantly lower at 1 month in group R vs group C (371 ± 181 vs 573 ± 273 ng/ml, p = 0.005) (Fig. 1).

Basal sICAM-1 levels were not affected by the serology for CP infection (551 ± 233 ng/ml in CP+ vs 477 ± 392 ng/ml in CP-, p = 0.42). The decrease in sICAM-1 levels 1 month following antibiotic therapy was more evident in patients with a positive serology for CP (baseline: group R/CP+ 371 ± 182 vs 453 ± 262 ng/ml in group C/CP+, p = 0.19; at 1 month: group R/CP+ 373 ± 131 vs 597 ± 255 ng/ml in group C/CP+, p = 0.014) (Fig. 2).

Antibiotic treatment did not significantly modify circulating E-selectin levels (baseline: group R 45.7 ± 58 vs 44.5 ± 78 ng/ml in group C, p = 0.45; at 1 month: group R 56.7 ± 97 vs 49.8 ± 62 ng/ml in group C, p = 0.54) (Fig. 3).

Angiographic results. All patients completed the angiographic follow-up at 6 months. In 4 patients of group R and 3 of group C coronary angiography was performed earlier due to symptom onset or because of a positive stress test. The overall incidence of binary restenosis was low (9/50, 18%) and was similar in the two groups (5 patients in group R [20%] vs 4 patients in group C [16%]). Target lesion revascularization was performed in 7 out of 9 patients with restenosis > 50% (4 in group R and 3 in group C).

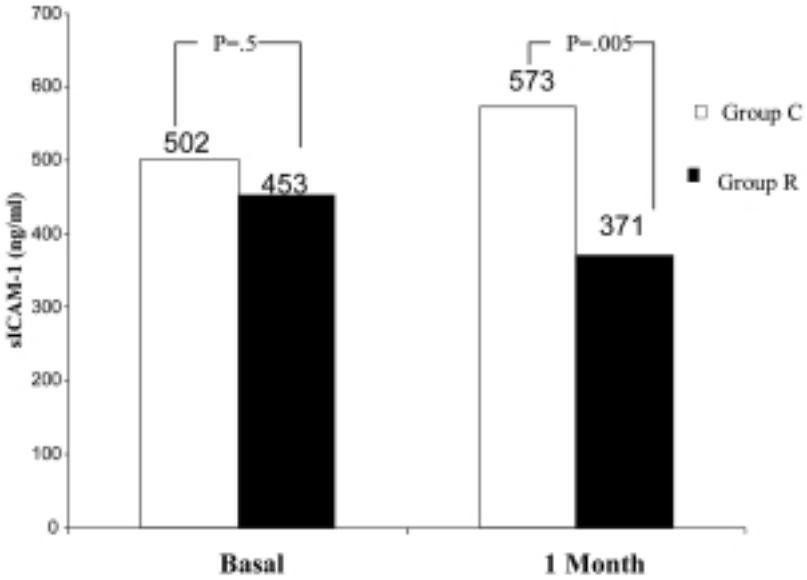

Figure 1. *Soluble intercellular adhesion molecule-1 (sICAM-1) levels 1 month following percutaneous coronary intervention in antibiotic-treated patients (group R, n = 25) vs controls (group C, n = 25).*

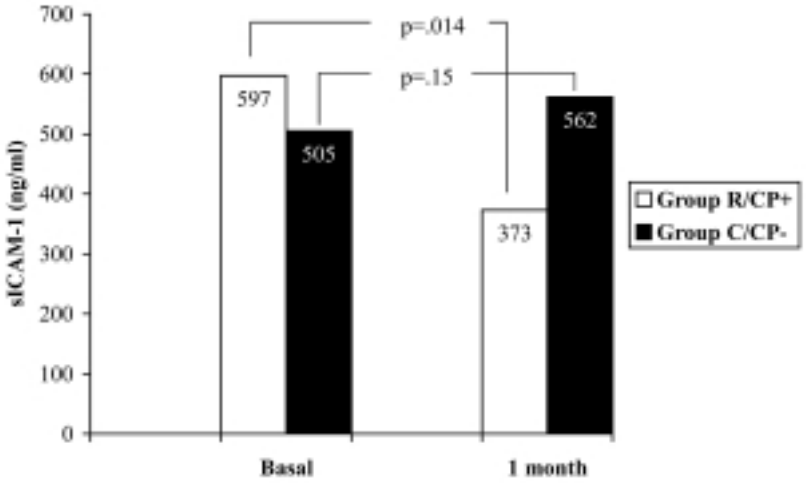

Figure 2. *Concentration of soluble intercellular adhesion molecule-1 (sICAM-1) in group R (n = 17) and group C (n = 18) at baseline and at 1 month in patients with serological evidence of Chlamydia pneumoniae (CP) infection.*

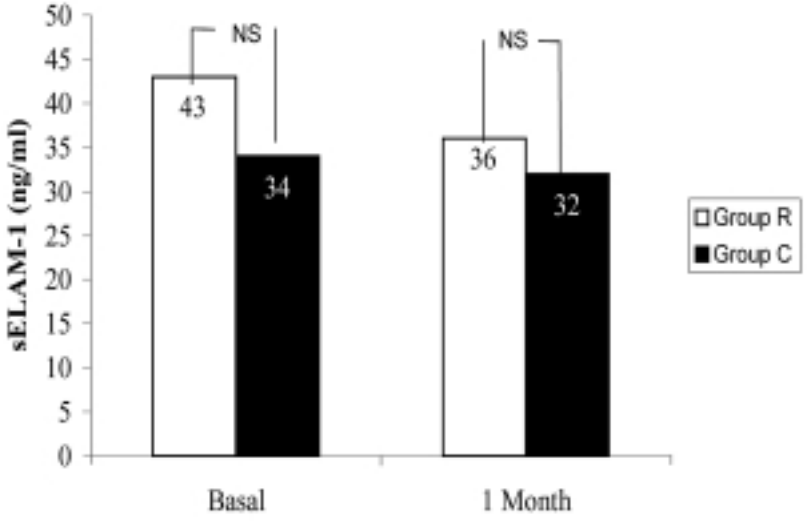

Figure 3. *Concentration of E-selectin (soluble endothelial leukocyte adhesion molecule-1 [sELAM-1]) in group R and group C at baseline and at 1 month.*

The binary restenosis rate was not modified by the serological status for CP infection (6/35 [17%] in CP+ group vs 3/15 [20%] in CP- group).

The baseline and 1-month values of sICAM-1 and E-selectin did not differ between patients with or without in-stent restenosis (Table II).

Discussion

The main finding of this small pilot study is that in case of elective PCI for stable CAD, a very short periprocedural antibiotic treatment with the macrolide roxithromycin is able to induce a higher 1-month decrease in the plasma concentrations of sICAM-1 compared to that observed in a conventionally treated control group. This effect appears to be more evident in patients with a previous CP infection. Periprocedural antibiotic treatment did not modify E-selectin concentrations. On the other hand, treatment with roxithromycin did not modify the restenosis rate, and CAM plasma levels in the first month after PCI were not predictive of the occurrence of restenosis.

Significance of cell adhesion molecule concentrations in atherosclerosis and post-percutaneous coronary intervention restenosis. Adhesion and subsequent migration of circulating leukocytes are critical early events in the pathogenesis of atherosclerosis[13]. However, the exact pathophysiological role of ICAM-1 in this condition has not yet been clearly defined, even though overall it is considered a marker of endothelial activation[5].

Indeed, a number of studies have confirmed that sICAM-1 concentrations are good predictors of cardiovascular events among both healthy men[14] and patients with stable CAD[15,16] as well as unstable coronary syndromes[17].

Whether increased plasma levels of ICAM-1 and/or E-selectin are associated with an increased risk of restenosis is less certain but previous studies describe a positive correlation between sICAM-1 or E-selectin levels and restenosis in patients treated with primary coronary angioplasty for myocardial infarction[18], or with lower limb percutaneous transluminal angioplasty for intermittent claudication[19]. The inflammatory process resulting from balloon barotrauma and stent

Table II. Soluble intercellular adhesion molecule-1 (sICAM-1) and E-selectin levels in patients with and without restenosis according to treatment group.

	Restenosis (n=9)				No restenosis (n=41)			
	Group R (n=5)	Group C (n=4)	Total	p	Group R (n=20)	Group C (n=21)	Total	p
sICAM-1								
Baseline	495	462	478	NS	504	484	495	NS
1 month	369	562	464	NS	348	502	425	NS
E-selectin								
Baseline	49.8	56.9	53.4	NS	48.1	43.9	45.9	NS
1 month	50.3	54.4	52.4	NS	57.2	49.6	57.2	NS

Values are expressed as means.

implantation plays an important role in the pathophysiology of restenosis after an initially successful procedure[20,21]. It has been hypothesized that CAMs act as mediators in the process of intimal hyperplasia within the implanted stent. Recently, Inoue et al.[8] were able to detect an increase in sICAM-1 levels only in coronary sinus blood samples but not in peripheral blood samples and in a subsequent study[22] the same authors correlated the coronary sinus blood levels of sICAM-1 with the restenosis rate after cutting balloon angioplasty. In our study, the CAM levels were evaluated 1 month after PCI. This was in accordance with the purpose of the study, designed to identify possible changes in the levels of biochemical markers as indicators of the restenosis phenomenon during its evolution. Moreover, patients with stable angina were selected on purpose, in order to avoid that changes in inflammatory indexes would reflect clinical instability and/or be correlated with minor areas of myocardial necrosis.

Effects of antichlamydial therapy on coronary events and restenosis. Previous studies on antibiotic therapy in the secondary prevention of CAD have produced conflicting results. Although several small trials have suggested that macrolides may reduce event rates in patients with acute coronary syndromes[23] or prior myocardial infarction[24], recent large-scale trials such as ACADEMIC[25,26], failed to show an increased benefit of antibiotic treatment over placebo. Nevertheless, positive results have recently been published. In the CLARIFY[27] and in the STAMINA trials[11], antibiotic treatment significantly reduced adverse cardiac events in patients with acute coronary syndromes. Sander et al.[28] found that a 1-month course of roxithromycin was able to reduce the progression of early carotid atherosclerosis during the subsequent 2 years in patients with high CP antibody titers. Previous infection with *Cytomegalovirus*, CP and *Helicobacter pylori* did not modify neointimal proliferation after coronary angioplasty with stent implantation as assessed in the angiographic and intravascular ultrasound study of Schiele et al.[29]. Neumann et al.[30] reported no effect on the major cardiac event rate at 1 year in 1010 patients undergoing coronary stenting (50% presenting with an acute coronary syndrome) randomly assigned to treatment with roxithromycin or placebo. Nevertheless, patients with high CP antibody titers and submitted to coronary stenting showed a relevant reduction, attributable to roxithromycin, in the restenosis rate[12]. As for other "markers" of inflammation such as C-reactive protein, the true problem is to clearly define the active role of these molecules in the pathogenesis of atherosclerotic disease and to assess whether a therapeutic intervention that is effective in reducing the concentration of CAMs, is also effective in decreasing clinical events.

Significance and limitations of the present study. In this context, the results of our study are controversial because, on the one hand they show that a short treatment course with roxithromycin at the time of coronary angioplasty, which is associated with an inflammatory outburst, is able to reduce sICAM-1 levels 1 month after the procedure, particularly in patients with a positive serology for CP. On the other hand, this reduction in sICAM-1 concentrations did not apparently modify intimal hyperplasia after stent implantation. The stability of CAD, as confirmed by the low C-reactive protein levels, is a possible explanation for the lack of correlation between the soluble CAM levels and restenosis in the patients enrolled in our study. In addition, the very low incidence of restenosis in this study may have prevented us from detecting any difference in the levels of adhesion molecules in the 9 patients who developed a restenosis as compared with the 41 who did not. Furthermore, a more prolonged antibiotic treatment could have further reduced the sICAM-1 plasma levels, possibly resulting in a positive effect on the restenotic process. Finally, the lack of a beneficial action on restenosis could be simply related to the limited number of patients included in this study. We finally recognize that the binary restenosis rate is an insensitive method to evaluate post-stent intimal hyperplasia and that the use of intravascular ultrasound could be more appropriate to detect the potential antirestenotic effect of roxithromycin.

It is not clear why antibiotic treatment reduced the sICAM-1 but not the E-selectin plasma levels. The short duration of the antibiotic treatment and the different kinetics of production of different CAMs from the endothelium may explain these discrepancies.

Other limitations of the present study should also be considered. Since we did not randomize patients to treatment with roxithromycin vs placebo, we cannot exclude bias in the selection of patients for antibiotic treatment. However, all 50 patients were enrolled in the study consecutively. Moreover, the endpoint variables (sICAM-1, E-selectin and C-reactive protein) were blindly determined by our laboratory.

Our results could have been enhanced had we selected only CP+ patients for enrolment. Moreover, the serological status was determined using ELISA and expressed as a densitometric ratio (negative < 1, positive > 1) and not by means of microimmunofluorescence which permits one to define the CP serum antibody titers. In fact, Neumann et al.[12] found that roxithromycin was able to reduce restenosis only in patients with high CP antibody titers.

In conclusion, although the results of this small pilot study are controversial, they may represent a useful contribution in stimulating further research in the field of atherosclerosis as well as of restenosis prevention. Roxithromycin should be considered as a potentially effective drug for this purpose in selected patients and envisaged as an adjunctive therapy in the developing technology of drug-eluting stents.

References

1. Roivainen M, Viik-Kajander M, Plosuo T, et al. Infections, inflammation, and the risk of coronary heart disease. Circulation 2000; 101: 252-7.
2. Muhlestein JB. Bacterial infections and atherosclerosis. J Investig Med 1998; 46: 396-408.
3. Cybulsky MI, Gimbrone MA Jr. Endothelial expression of a mononuclear leukocyte adhesion molecule during atherogenesis. Science 1991; 251: 788-91.
4. Jang Y, Lincoff A, Plow E, Topol EJ. Cell adhesion molecules in coronary artery disease. J Am Coll Cardiol 1994; 24: 1591-601.
5. Rothlein R, Mainolfi EA, Czajkowski M, Marlin SD. A form of circulating ICAM-1 in human serum. J Immunol 1991; 147: 3788-93.
6. Hackman A, Abe Y, Insull W, et al. Levels of soluble cell adhesion molecules in patients with dyslipidemia. Circulation 1996; 93: 1334-8.
7. Kurz RW, Graf B, Gremmel F, Wurnig C, Stockenhuber F. Increased serum concentrations of adhesion molecules after coronary angioplasty. Clin Sci (Lond) 1994; 87: 627-33.
8. Inoue T, Sakai Y, Morooka S, Hayashi T, Takayanagi K, Takabatake Y. Expression of polymorphonuclear leukocyte adhesion molecules and its clinical significance in patients treated with percutaneous transluminal coronary angioplasty. J Am Coll Cardiol 1996; 28: 1127-33.
9. Inoue T, Hoshi K, Yaguchi I, Iwasaki Y, Takayanagi K, Morooka S. Serum levels of circulating adhesion molecules after coronary angioplasty. Cardiology 1999; 91: 236-42.
10. Libby P, Egan D, Skarlatos S. Roles of infectious agents in atherosclerosis and restenosis: an assessment of the evidence and need for future research. Circulation 1997; 96: 4095-103.
11. Stone AF, Mendall MA, Kaski JC, et al. Effect of Treatment for Chlamydia pneumoniae and Helicobacter pylori on markers of inflammation and cardiac events in patients with acute coronary syndromes. South Thames Trial of Antibiotics in Myocardial Infarction and Unstable Angina (STAMINA). Circulation 2002; 106: 1219-31.
12. Neumann FJ, Kastrati A, Miethke T, et al. Effect of antibiotic treatment against Chlamydia pneumoniae with roxithromycin on neointima proliferation after coronary stent placement. (abstr) J Am Coll Cardiol 2001; 37 (Suppl A): 48A.
13. Ross R. The pathogenesis of atherosclerosis: a perspective for the 1990s. Nature 1993; 362: 801-9.
14. Morisaki N, Saito I, Tamura K, et al. New indices of ischemic heart disease and aging: studies on the serum levels of soluble intercellular adhesion molecule-1 (ICAM-1) and soluble vascular cell adhesion molecules-1 (VCAM-1) in patients with hypercholesterolemia and ischemic heart disease. Atherosclerosis 1997; 131: 43-8.
15. Ridker PM, Hennekens CH, Roitmn-Johnson B, Stampfer MJ, Allen J. Plasma concentration of soluble intercellular adhesion molecule-1 and risk of future myocardial infarction in apparently healthy men. Lancet 1998; 351: 88-92.
16. Wallen NH, Held C, Rehnqvist N, Hjemdahl P. Elevated serum intercellular adhesion molecule-1 and vascular cell adhesion molecule-1 among patients with stable angina pectoris who suffer cardiovascular death or non-fatal myocardial infarction. Eur Heart J 1999; 20: 1039-43.
17. Mulvihill NT, Foley JB, Ghaisas N, Murphy R, Crean P, Walsh M. Early temporal expression of adhesion molecules in patients with unstable angina and subendocardial myocardial infarction. Am J Cardiol 1999; 83: 1265-7.
18. Kamijikkoku S, Murohara T, Tayama S, et al. Acute myocardial infarction and increased soluble intercellular adhesion molecule-1: a marker of vascular inflammation and a risk of early restenosis? Am Heart J 1998; 136: 231-6.
19. Belch JJ, Shaw JW, Kirk G, et al. The white blood cell adhesion molecule E-selectin predicts restenosis in patients with intermittent claudication undergoing percutaneous transluminal angioplasty. Circulation 1997; 95: 2027-31.
20. De Servi S, Mazzone A, Ricevuti G, et al. Granulocyte activation after coronary angioplasty in humans. Circulation 1990; 82: 140-6.
21. Versaci F, Gasapardone A, Tomai F, et al. Immunosuppressive therapy for the prevention of restenosis after coronary artery stent implantation (IMPRESS Study). J Am Coll Cardiol 2002; 40: 1935-42.
22. Inoue T, Sakai Y, Hoshi K, Yaguchi I, Fujito T, Morooka S. Lower expression of neutrophil adhesion molecule indicates less vessel wall injury and might explain lower restenosis rate after cutting balloon angioplasty. Circulation 1998; 97: 2511-8.
23. Gurfinkel E, Bozovich G, Beck E, Testa E, Livellara B, Mautner B. Treatment with the antibiotic roxithromycin in patients with acute non-Q wave coronary syndromes. The final report of the ROXIS Study. Eur Heart J 1999; 20: 121-7.
24. Gupta S, Leatham EV, Carrington D, Mendall MA, Kaski JC, Camm AJ. Elevated Chlamydia pneumoniae antibodies, cardiovascular events, and azithromycin in male survivors of myocardial infarction. Circulation 1997; 96: 404-7.
25. Anderson JL, Muhlestein JB, Carlquist JF, et al. Randomized secondary prevention trial of azythromycin in patients with coronary artery disease and serological evidence for Chlamydia pneumoniae infection. The Azithromycin in Coronary Artery Disease: Elimination of Myocardial Infection with Chlamydia (ACADEMIC) Study. Circulation 1999; 99: 1540-7.
26. Muhlestein JB, Anderson JL, Carlquist JF, et al. Randomized secondary prevention trial of azythromycin in patients with coronary artery disease. Primary clinical results of the ACADEMIC Study. Circulation 2000; 102: 1755-60.
27. Sinisalo J, Mattila K, Valtonen V, et al, for the Clarithromycin in Acute Coronary Syndrome Patients in Finland (CLARIFY) Study Group. Effect of 3 months of antimicrobial tratment with clarithromycin in acute non-Q-wave coronary syndromes. Circulation 2002; 105: 1555-60.
28. Sander D, Winbeck K, Klingelhofer J, Etgen T, Conrad B. Reduced progression of early carotid atherosclerosis after antibiotic treatment and Chlamydia pneumoniae seropositivity. Circulation 2002; 106: 2428-33.
39. Schiele F, Batur MK, Seronde MF, et al. Cytomegalovirus, Chlamydia pneumoniae, and Helicobacter pylori IgG antibodies and restenosis after stent implantation: an angiographic and intravascular ultrasound study. Heart 2001; 85: 304-11.
30. Neumann F, Kastrati A, Miethke F, et al. Treatment of Chlamydia pneumoniae infection with roxithromycin and effect on neointima proliferation after coronary stent placement (ISAR-3): a randomised, double-blind, placebo-controlled trial. Lancet 2001; 357: 2085-9.