[Frontiers in Bioscience E4, 2618-2621, June 1, 2012]

Rosuvastatin effect on intima media thickness in adult vs elderly patients

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1. ABSTRACT

The benefits of cardiovascular therapies such as statins for the treatment of atherosclerosis have been well documented. Many studies have demonstrated important benefits in patients with asymptomatic carotid atherosclerosis. We have evaluated the effect of low dose of rosuvastatin on asymptomatic carotid atherosclerosis in elderly versus adult subjects. Among 640 participants in the Asymptomatic Carotid Atherosclerotic Disease In Manfredonia Study (ACADIM Study) forty-five patients (21 adults, 24 elderly) with hypercholesterolemia and asymptomatic carotid atherosclerosis on baseline carotid ultrasound investigation (CUI) were examined with repeat CUI after one treatment year with rosuvastatin (ROS) (10 mg/day). Total and low density lipoprotein cholesterol decreased significantly ($p<0.001$) while high density lipoprotein cholesterol increased significantly ($p<0.001$) during the intervention. Mean decrease in carotid intima media thickness (CIMT) of the right and left common carotid arteries were higher in adult versus elderly subjects ($p<0.04$ for each), even if in both group there was a significant regression in carotid atherosclerosis respect to baseline values ($P<0.001$). These results confirm the reduction in IMT of the CCAs in response to ROS at a low dose in a one-year treatment period, even if in elderly subjects this effect is lower respect to adult. The treatment of asymptomatic carotid atherosclerosis defined by CIMT started in the adult age is more effective.

2. INTRODUCTION

Carotid atherosclerosis begins in youth, a crucial period when modification of atherosclerotic process may have the greatest impact. Failure to diagnose atherosclerosis at this stage misses a major opportunity to prevent the long-term consequences of cardiovascular disease (CVD), which is the world's leading cause of death and is projected to remain the number one cause of global mortality (1). Most cases of CVD are preventable, that it begins in childhood, and that the extent and progression of the disease to adulthood are positively associated with both lipid and non-lipid risk factors.

Exposures to risk factors at a young age leave a lasting imprint. This is validated by studies that report a better correlation between adult carotid intima media thickness (CIMT) to risk factors measured in childhood rather than contemporaneous risk factors (2,3). CIMT is a well-recognized marker of early, generalized atherosclerosis, widely used in epidemiologic studies and randomized intervention trials (4,5), and correlated with coronary atherosclerosis (6).

Delaying diagnosis and treatment of atherosclerotic process increases the lifetime risk of developing coronary heart disease (CHD) (7). Collectively, these observations irrefutably attest to the importance of early diagnosis in the natural history of CVD and

appropriately matching the intensity and type of intervention with the extent of disease and time of disease progression. The aim of this study was to evaluated the effect of one-year treatment with low dose of rosuvastatin (ROS) on asymptomatic carotid atherosclerosis in elderly versus adult subjects.

3. SUBJECT AND METHODS

3.1. Study design

The Asymptomatic Carotid Atherosclerosis DIsease in Manfredonia Study (ACADIM Study) is a prospective, cross-sectional study conducted between August 2006 and May 2007 in a randomly selected population of 640 participants who were asymptomatic with respect to carotid artery disease and seen at the Cardiology Unit of San Camillo de Lellis Hospital (Manfredonia, Foggia, Italy). The ACADIM study was conducted in collaboration with the Department of Biomedical Sciences (Section of Human Nutrition and Clinical Biochemistry) of "G. Annunzio" University (Chieti, Italy), and Laboratory Analyses of San Camillo De Lellis Hospital (Manfredonia, Foggia, Italy).

3.2. Subjects

During the study period, 800 potential participants underwent a carotid ultrasound investigation (CUI) of the extracranial carotid arteries (common, internal and external). Of the 800 participants screened at baseline, 232 had carotid atherosclerosis (CIMT $\geq$ 0.8 mm) of whom 45 also had hypercholesterolemia and were statin-naive. This group formed the study population of the one-year treatment trial on the effect of ROS on increased CIMT that was conducted between December 2006 and November 2008. Of this study group, 9 patients were concurrently receiving another pharmacological treatment (4 received treatment for arterial hypertension, 2 for non-insulin dependent diabetes mellitus, 1 for hypothyroidism, 1 for gout and 1 for bronchial asthma).

3.3. Inclusion/exclusion criteria

Participants were considered to be asymptomatic for carotid artery disease if they had never experienced a transient ischemic attack (TIA), amaurosis fugax or stroke. Hypercholesterolemia was defined as an elevation of low density lipoprotein cholesterol (LDL-C) values above 130 mg/dL (8). After receiving information about the purpose of the study, participants signed an informed consent before blood sampling and carotid ultrasound investigation (CUI). Potential participants were excluded if they had symptomatic carotid artery disease, current infectious or inflammatory disease, recent operations or endovascular interventions, bilateral carotid occlusion, monoloteral/bilateral stent implantation or monolateral/bilateral endoarterectomy. The study was performed in accordance with the Helsinki Declaration of 1975 as revised in 1983 and approved by the ethical review committee and by the Medical Director of the San Camillo de Lellis Hospital, Manfredonia (Foggia, Italy).

3.4. End points

The primary end point evaluated in this study was the change in CIMT in the right and left common carotid arteries (CCAs) after the therapy period (one year) with ROS (10 mg/day). CUI was performed by means of a colour-coded ACUSON Sequoia^{C512} carotid duplex instrument with a 7.5-MHz linear transducer (Siemens Medical Solutions USA, Inc). The investigation included longitudinal and transverse examinations of both of the carotid arteries. Both diameter reductions were measured and calculated at the site of maximal stenosis in the extracranial CCAs according to the European Carotid Surgery Trial (ECST) method (9).

The measurements of CIMT were performed approximately 10 mm proximal to the carotid bulb or 20 mm proximal to the flow divider. CIMT was measured between the leading edge of the first echogenic line (lumen-intima interface) and the second echogenic line (upper layer of the adventitia) in the far (deeper) artery wall. All measurements were performed on frozen, enlarged images (2x) at the end of a heart cycle (end diastole), and the transducer was oriented in the mediolateral direction. Measurements were performed on both CCAs, and the larger of the two values was used in data analysis (10).

Increased CIMT indicative of carotid atherosclerosis was defined as a thickness between 0.9-1.2 mm; substantial carotid atherosclerosis with focal echo-structures encroaching into the vessel lumen where the CIMT was > 1.2 mm was defined as a carotid plaque. These cut-offs were chosen because they have been used in previous randomised clinical trials where CIMT was the endpoint of interest (11).

3.5. Clinical and laboratory data

After CUI, medical history and data from physical examination were collected. Fasting venous blood samples were obtained at the baseline visit. Measurements included total cholesterol (TC), high density lipoprotein cholesterol (HDL-C), low density lipoprotein cholesterol (LDL-C) and triglycerides (TG). All investigators and laboratory personnel were blinded to the participants' status. Antecubital venous blood samples from all participants were handled identically and blindly through all stages of blood collection, storage, retrieval and analytic processing.

Safety was assessed by adverse event reports (myalgia, myopathy) and clinical laboratory data (creatine kinase > 10 times the upper limit of normal; hepatic transaminases > 3 times the upper limit of normal) performed at every clinic visit during the study period. Adverse events were reported at the baseline visit and at the end of the study. Significant abnormal laboratory values or other physical findings were recorded as adverse events.

3.6. Statistical analysis

Data were analysed by using SPSS statistical software (version 15.0 for Windows; SPSS Inc., Chicago). For each baseline characteristic, the mean value or the corresponding percent of study participants was calculated. The significance of changes in CIMT was examined using the paired Student *t*-test. Associations between

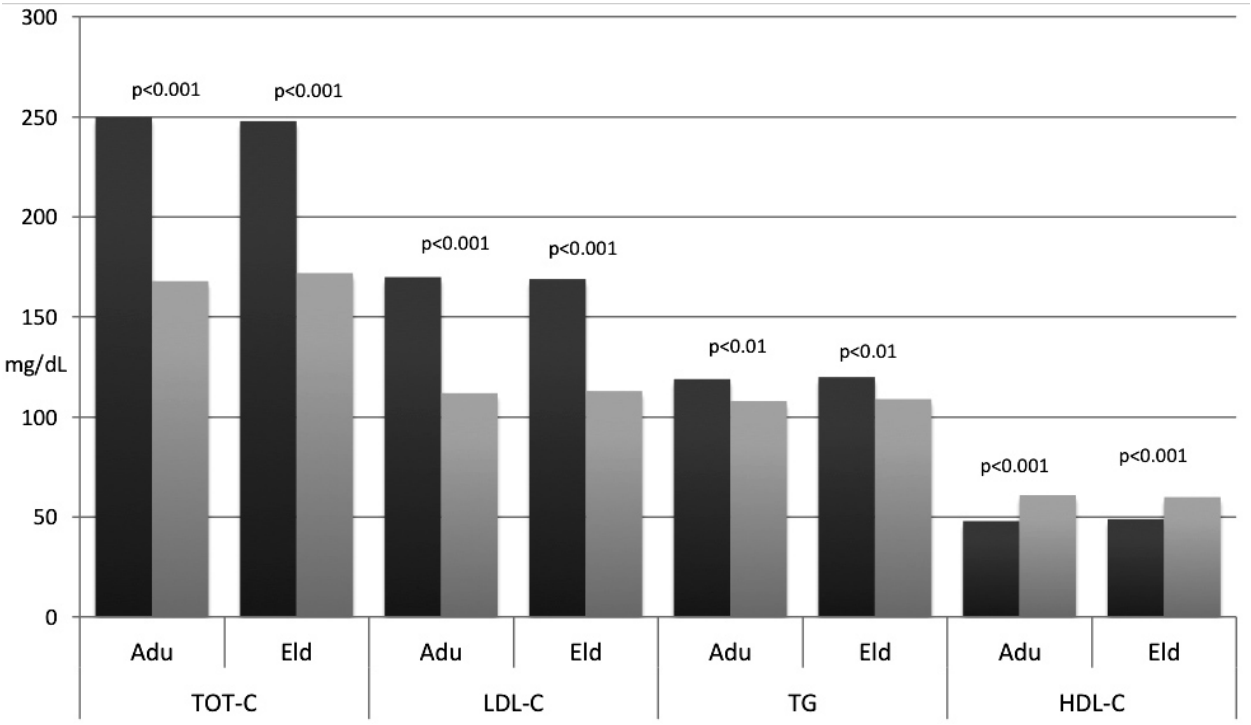

Figure 1. Effect of treatment with one year of rosuvastatin 10 mg/day on lipid parameters in adult and elderly subjects.

demographics, lifestyle and changes in CIMT were examined using linear regression models. A two-tailed *p* value < 0.05 was considered significant. Difference between two groups was assessed by analysis of variance (ANOVA).

4. RESULTS

The mean (± SD) age and body mass index [BMI] of study population was 55.7 ± 6.4 years and 26.8 ± 2.9 [kg/m^2]. Of the 45 participants, 21 (46.66%) were adults and 24 (53.33%) were elderly**.** Means (± SD) for lipid profile parameters and left and right CIMT values before and after treatment during the one-year study period are summarised in Table 1**.**

TC, LDL-C and TG decreased significantly, while HDL-C increased significantly. ROS treatment determined a 31.72% total mean reduction in LDL-C level (adult, 170 mg/dL vs 112 mg/dL -34.11% [-58 mg/dL] p<0.001; elderly, 169 mg/dL vs 113 mg/dL -33.13% [-56 mg/dl] p<0.001, and a 31.72% mean reduction in TC level (adult, 250 mg/dL vs 168 mg/dL -32.80% [-82 mg/dL]; elderly, 248 mg/dL vs 172 mg/dL -30.64% [-76 mg/dl] p<0.001.

HDL-C increased significantly after the treatment with ROS respect to baseline values (adult, 48 mg/dL vs 61 mg/dL +21.31% [+13 mg/dL] p<0.001; elderly, 49 mg/dL vs 60 mg/dL +18.33 [+11 mg/dl] p<0.001). Even TG decrease significantly respect to baseline values (adult, 119 mg/dL vs 108 mg/dL -9.24% [-11 mg/dL] p<0.01; elderly, 120 mg/dL vs 109 mg/dL -9.16% [-11 mg/dl] p<0.01 (Figure 1). Both the left and right CIMT decreased significantly with ROS treatment over the course of the study. In adult subjects the CIMT of the left CCA decreased by 0.26 mm (1.21 mm vs 0.95 mm p<0.001 - 21.48%), and the CIMT of the right CCA decreased by 0.29 mm (1.19 mm vs 0.90 mm p<0.001 - 24.34%).

In elderly subjects the CIMT of the left CCA decreased by 0.23 mm (1.28 mm vs 1.05 mm p<0.001 - 17.9%) and the CIMT of the right CCA decreased by 0.22 mm (1.29 mm vs 1.07 mm p<0.001 -17.05%).

Throughout this one-year study period, the treatment with ROS was well tolerated both in adult than elderly subjects. No treatment-related adverse events leading to death, serious injury or clinical events were reported during the study. No patients had clinically significant elevations in hepatic transaminases (GOT, GPT).

5. DISCUSSION

During the last 20 years accumulated evidences have demonstrated that the treatment with statins is associated with the reduction of CV risk and CV events. This is the basis of scientific and public health treatment with cholesterol lowering drugs. ROS, a synthetic advanced statin, possesses a greater number of binding interactions with HMG-CoA reductase and has a high affinity for the active site of the enzyme (12). Atherosclerosis is often diagnosed at an advanced stage when symptoms appear, even if vascular abnormalities such subclinical atherosclerosis (CIMT and plaques) are detectable before clinical manifestations of atherosclerotic disease.

Our results demonstrate that regression of subclinical atherosclerosis (as defined by CIMT) both in adult than in elderly patients can be detected after a one-year treatment with low treatment dose of ROS (10 mg/day). In the case of ROS, controlled clinical trials using same vascular end-points (progression and/or regression of CIMT) have been performed. In particular a randomized, double-blind, placebo-controlled study (Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin [METEOR]) of 984 subjects (mean age 57 years) with CHD risk factor or a 10-year Framingham Risk Score (FRS) < 10%, modest CIMT thickening (1.2–3.5 mm), and elevated LDL-C (mean, 154 mg/dL), was conducted in 61 primary care centers in the United States and Europe.

Participants received either a 40-mg dose of ROS or placebo. In the ROS group, the mean baseline LDL-C level of 155 mg/dL declined to 78 mg/dL (mean reduction 49%). Subjects with an FRS < 10% and evidence of subclinical atherosclerosis, taking ROS, experienced significant reductions in the rate of progression of maximum CIMT over 2 years vs placebo (13).

For to evaluate the impact of ROS treatment on carotid atherosclerosis, magnetic resonance imaging (MRI) was used to non-invasively assess changes in atherosclerotic plaque morphology and composition. The Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic resonance Imaging ObservatioN (ORION) trial is a randomized, double-blind study used 1.5-T MRI to image carotid atherosclerotic plaques at baseline and after 24 months of ROS treatment. 43 hypercholesterolemic patients with fasting LDL-C between 100 and 250 mg/dL and 16% to 79% carotid stenosis by CUI were randomized to receive either a low (5 mg) or high (40/80 mg) dose of ROS.

In these patients with moderate hypercholesterolemia, ROS treatment was associated with a reduction in percent of lipid-rich necrotic core, whereas the overall plaque burden remained unchanged over the course of 2 years of treatment (14). The results of this study and of the previous one support the idea that long term treatment with ROS stabilizes carotid plaques. In our study we have found a significant reduction in LDL-C (approximately 35%) and an increase in HDL-C (approximately 20%).

The degree of LDL-C reduction is important to achieve the treatment goals suggested by international guidelines. The NCEP III recommends a goal of less than 100 mg/dL for patients at high risk for CHD. On the basis of available clinical trials, there is no evidence that achieving and maintaining such low levels of LDL-C result in excess adverse effects. Among the most potent statins, rosuvastatin is capable of getting the majority of patients to their LDL-C goals (15,16).

In our study ROS produced a favorable effect on HDL-C, which is an independent marker of cardiovascular risk. Early epidemiological studies have identified low levels of HDL-C (40 mg/dL) to be an independent determinant of increased CV risk (17). The beneficial effects of HDL-C on the CV system have been attributed to its ability to remove cellular cholesterol, as well as its anti-inflammatory, antioxidant and antithrombotic properties, which act in concert to improve endothelial function and inhibit atherosclerosis, thereby reducing CV risk (18).

As such, raising HDL-C in patients with aggressively lowered LDL-C provides an additional strategy for addressing the residual CV risk present in these patients groups. Studies suggest that for every 1.0 mg/dL increase in HDL-C, absolute CV risk is reduced by 2% to 3%, in a 4-year follow-up. Raising HDL-C can be achieved by both lifestyle changes and pharmacological means, the former comprising mainly smoking cessation, aerobic exercise, weight loss and dietary manipulation. Therapeutic strategies to increase HDL-C include niacin, fibrates, thiazolidinediones and bile acid sequestrants (19).

ROS, which produces an increase in HDL-C in the range of 4 to 6 mg/dL, is expected, through this mechanism, to be responsible for an additional CV risk reduction in the range of 8% to 6%. Support for these new data come from the JUPITER study, which was stopped before the programmed end of the study because of excess benefit for high-risk individuals receiving ROS treatment (20). It is suggested that pronounced LDL-C reduction, in association with significant HDL-C increase, are the bases of a marked preventive action of ROS.

Our study demonstrate a significant reduction of CIMT both in adults than in elderly patients, even if this reduction is significantly higher in adult respect to elderly patients. Many published studies demonstrate that carotid and femoral IMTs increase significantly with age and the CIMT is greater in men compared with women (21). In the National for Longevity Sciences–Longitudinal Study of Aging (NILS–LSA) [22)], the CIMT increased significantly with age in both genders.

Results of published randomized controlled trials have shown that interventions able to lower LDL-C concentrations can significantly reduce the incidence of CHD, CIMT, and other major vascular events in a wide range of individuals (adult and elderly) (23). Many studies with relevant clinical outcomes measures support the importance of ROS therapy to reduce risk for CVD. However, many patients with cardiovascular events do not have elevated LDL-C levels as currently defined by national guidelines. Thus, it is important to develop more strategies to identify patients at risk for future events and to develop new interventions to reduce risk in these patients, such the individuation and treatment of subclinical atherosclerosis (CIMT) (24). These observations suggest that current statin-based CVD prevention strategies require further refinement to better identify patients at risk for CVD, guide the level of aggressiveness of the intervention.

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Key Words: rosuvastatin**,** intima media thickness, carotid atherosclerosis, carotid arteries, atherosclerosis, ultrasound, ACADIM Study.

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