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Original Article

Improved endothelial function after short-term therapy with evolocumab

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KEYWORDS:
Evolocumab;
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Brachial artery vasoreactivity test

BACKGROUND: The reduction of cholesterol levels with cholesterol-lowering therapy may improve endothelial function. Lipid-lowering therapy has been greatly enhanced by the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies. Less is known of the effect of PCSK9 inhibitors on endothelial function of subjects with hypercholesterolemia.

OBJECTIVE: To assess whether treatment with PCSK9 inhibitors may improve endothelial function evaluated by brachial artery vasoreactivity test.

METHODS: Brachial artery vasoreactivity test was performed in 14 consecutive patients with previous myocardial infarction before and after 2 months of therapy with evolocumab 140 mg twice in a month. Mean brachial artery diameter, velocity time integral, flow-mediated dilation (FMD) and low-density lipoprotein (LDL) cholesterol levels were also evaluated.

RESULTS: After 2 months of treatment with evolocumab, mean total cholesterol levels decreased from 245 ± 41 to 128 ± 30 mg/dL ($P < .001$, –48%), and LDL levels from 176 ± 43 to 71 ± 26 mg/dL ($P = .001$, –59%); FMD conversely increased from 6.3 ± 4.1% to 8.8 ± 6.3% ($P = .004$, +40%). Improvement in FMD was proportional to reduction of LDL levels ($r = 0.69$, $P = .006$). Therapy with evolocumab increased brachial artery diameter during vasoreactivity test (peak values 0.39 ± 0.09 vs 0.36 ± 0.11 cm, $P = .010$; final values 0.36 ± 0.10 vs 0.34 ± 0.10 cm, $P = .001$), and velocity time integral (peak levels 96 ± 1 vs 85 ± 9 cm, $P = .045$).

CONCLUSIONS: Two months of treatment with evolocumab 140 mg may improve endothelial function in subjects with increased cardiovascular risk. The improvement in endothelial function is proportional to LDL reduction.

Introduction

Endothelial dysfunction may represent the first clinical manifestation of atherosclerosis.[1,2] Increased circulating levels of cholesterol may be associated with an impaired endothelial function,[3] as well as hypertension and diabetes.[4,5]

By contrast, the reduction of cholesterol levels with cholesterol-lowering therapy may lead to an improved

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endothelial function[6,7] expressed by a better flow-mediated dilation (FMD).[8]

Lipid-lowering therapy has been greatly enhanced by the introduction of proprotein convertase subtilisin/kexin type 9 (PCSK9) antibodies.[9] Therapy with PCSK9 antibodies, alone or in addition to statins or ezetimibe, may reduce low-density lipoprotein (LDL) cholesterol levels by 50% to 70%, with circulating LDL levels after therapy of 30 mg/dL.[10]

Less is known of effect of PCSK9 inhibitors on endothelial function of subjects with previous myocardial infarction. We therefore sought to assess whether treatment with PCSK9 inhibitors may improve endothelial function evaluated by brachial artery vasoreactivity test.

Methods

One hundred fifty consecutive patients with hypercholesterolemia and previous myocardial infarction were screened for possible therapy with evolocumab. According to Italian reimbursement rules, evolocumab can be reimbursed exclusively in case of statin intolerance or inefficacy in reaching goal levels according to European Society of Cardiology guidelines despite treatment with high-intensity statins plus ezetimibe.[11]

Exclusion criteria were renal failure (serum creatinine >1.3 mg/dL), liver failure (transaminase levels above upper level of normal), abnormally increased circulating levels of creatine kinase and lactate dehydrogenase, and myocardial infarction in the previous 6 months.

After preliminary screening, 14 patients (12 male, 2 female) were eligible for evolocumab and were enrolled in the study; all patients had a prior myocardial infarction and did not reach LDL goals despite treatment with high-dose statin and ezetimibe. Therapy with evolocumab 140 s.c. twice in a month was therefore started. Brachial artery vasoreactivity test was performed before treatment with evolocumab and after 2 months of therapy as follows. Mean brachial artery diameter and velocity time integral, further expressing, beyond responsiveness of the brachial artery at the elbow, the responsiveness of arterioles in the distal arm and hand, which determine blood flow, were contextually measured. Cholesterol total and LDL levels were also assayed before and after treatment.

FMD test

FMD tests have been performed in a quiet and temperature-controlled room. A linear 7.5 to 10 MHz probe with a Philips iE33 ultrasound machine have been used to frame an ultrasound window right above the elbow; then, the probe has been locked in a stereotaxic instrument. A starting frame has been frozen and then acquired to calculate the artery diameters; then a sample of the brachial blood flow is taken through the velocity–time integral of a pulsed wave Doppler scan, using a correction angle of 60°. We, then, inflated the cuff at a pressure at least 50 mm Hg over the patient systolic blood pressure, to close the brachial artery for a standard time of 5 minutes. Each still frame has been acquired via a longitudinal section view of the brachial artery before its closure and, after the cuff deflation, every 30 seconds for 3 minutes. The FMD was then calculated as the percentage of variation between the top postischemic diameter and the basal mean diameter.[12]

Statistical analysis

Continuous variables were expressed as mean ± standard deviation and compared with Student's t-test or Mann-Whitney U-test as required, categorical variables as percentages and compared with χ^2 or Fisher test as required. The Kolmogorov-Smirnov test was used to identify variables with normal distribution.

Repeated measures were compared with Student's t-test for paired groups or Wilcoxon test as required.

Linear regression was used to test correlation between continuous variables. Multivariable analysis was used to correct the effect of potential confounders.

A $P < .05$ was considered as statistically significant.

Results

After 2 months of treatment with evolocumab, mean total cholesterol levels decreased from 245 ± 41 mg/dL to 128 ± 30 mg/dL ($P < .001$, –48%), and LDL levels from 176 ± 43 mg/dL to 71 ± 26 mg/dL ($P = .001$, –59%); FMD values, conversely increased from 6.3 ± 4.1% to 8.8 ± 6.3% ($P = .004$, +40%) (Fig. 1). Improvement in

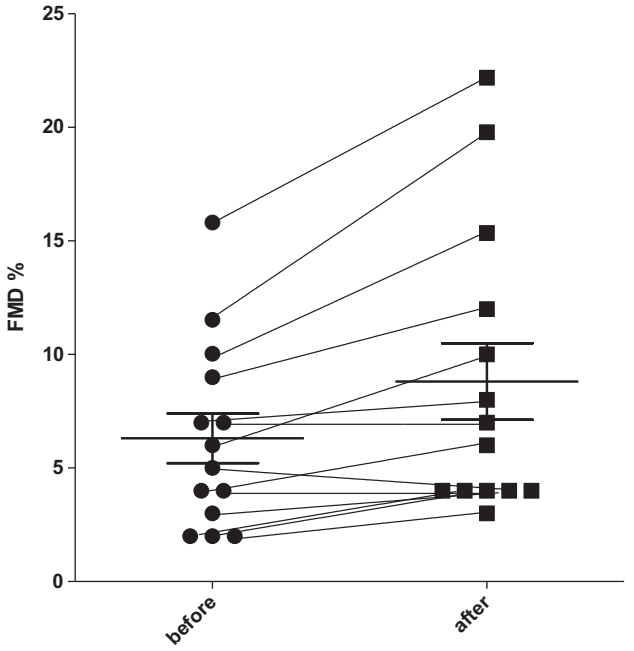

Figure 1 Flow-mediated dilation before and after 2 months of treatment with evolocumab 140 mg ($P < .05$).