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Original research article

The possibility of reducing the Lp-PLA2 mass level using simvastatin monotherapy and combination therapy with ezetimibe

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ARTICLE INFO

Article history:
Received 2 February 2015
Received in revised form
23 March 2015
Accepted 25 March 2015
Available online 25 April 2015

Keywords:
Lipoprotein-associated phospholipase A2
Simvastatin
Ezetimibe
Coronary heart disease

ABSTRACT

Aim: To assess the impact of combined treatment with simvastatin and ezetimibe or treatment with simvastatin only on lipoprotein-associated phospholipase A2 mass level in patients with coronary heart disease.

Methods: One hundred patients with angiographically documented coronary atherosclerosis took part in the investigation. Lp-PLA2 mass level and cholesterol fractions were determined at baseline and after 6 months of treatment. Lp-PLA2 mass was determined by PLAC Test; DiaDexus, Inc.

Results: Combined treatment with ezetimibe and simvastatin led to significantly greater declines in Lp-PLA2 and lipid profile compared with treatment only with simvastatin ($P < 0.05$). Combination therapy with ezetimibe and simvastatin 20 mg/day proved to be as effective as monotherapy with simvastatin 80 mg/day on the effect on Lp-PLA2 mass level and lipids ($P < 0.05$). Lp-PLA2 mass level was initially higher in patients with three-vessel coronary artery disease, compared with patients with one-vessel coronary artery disease while baseline levels of lipids and hs-CRP did not differ significantly.

Conclusions: Combined treatment, using half the dose of simvastatin, led to greater reduction of Lp-PLA2 mass level total cholesterol and LDL-C, compared to monotherapy with simvastatin. Due to the steady decline of target levels of LDL-C, which leads to prescribing high doses of statins (and it is not always possible because of the presence of co-morbidities), combination therapy with statin and ezetimibe is a reliable alternative, which allows not only to largely reduce LDL-C but also to significantly reduce such important participants of atherosclerosis process and markers of inflammation, as Lp-PLA2 and CRP.

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http://dx.doi.org/10.1016/j.crvasa.2015.03.012

Introduction

One of the key factors in the development of atherosclerosis is a chronic systemic inflammation with local specific manifestations in the intima of the vessels. Inflammation plays a major role in the genesis and progression of atherosclerotic plaques, its evolution in the vulnerable plaque rupture and loosening tire [1]. In recent years, lipoprotein-associated phospholipase A2 (Lp-PLA2), which is a marker of intravascular inflammation, has attracted the attention of scientists. Numerous studies have demonstrated the role of Lp-PLA2 as a risk factor for cardiovascular disease and a direct participant in the development and progression of atherosclerosis.

Lp-PLA2 is associated mainly with low-density lipoproteins (LDL), whereas a small proportion of circulating enzyme is also associated with high-density lipoproteins (HDL) and lipoprotein-a. Mechanistically, Lp-PLA2 hydrolyzes oxidatively altered phospholipids that have shortened sn2 fatty acids to produce oxidized fatty acids and lysophosphatidylcholine, a function that deems Lp-PLA2, a pro-atherogenic agent [2–5]. Increased Lp-PLA2 testifies not only to coronary artery disease [6], but also can further define prognosis and the risk of vascular complications [6–16]. Lp-PLA2 reflects the presence and intensity of intravascular inflammation, the marker of which it is.

Using the classic risk factors cannot account for all cases of coronary events in patients with normal lipid profile [17]. That is why, the FDA approved a definition Lp-PLA2 as a screening test that predicts a patient's risk for future CHD events. ACC/AHA and ESC have recommended Lp-PLA2 definition for asymptomatic or moderate and high risk patients to clarify the risks and to decide beginning or increasing the lipid-lowering therapy [18–21].

The ability to influence on intravascular inflammation (Lp-PLA2) as well as on non-specific inflammation (hs-CRP) relates to the pleiotropic effects of statins, and it is realized, sometimes, regardless of the lipid-lowering effect of statins.

Information that hypolipidemic drugs, particularly statins, reduce the level of Lp-PLA2 suggests that Lp-PLA2 can be considered as a target for the therapy action to suppress inflammatory processes and achieve stabilization of atherosclerotic plaque formation [22]. It has been shown that statins – pravastatin, atorvastatin, rosuvastatin and simvastatin – significantly lowered Lp-PLA2 levels [22–35], but is it possible for combination therapy: ezetimibe with lower doses of statins? As a powerful lipid-lowering effect of the combination of ezetimibe and a statin is known, our aim was to evaluate the possibility of reducing the intravascular inflammation using combination therapy with a lower dose of the statin.

Materials and methods

One hundred patients with angiographically documented coronary atherosclerosis took part in the investigation. All patients included in the study, even with previously established CHD, had not taken lipid-lowering drugs for at least 6 months before inclusion in the study. Patients were randomly assigned into two treatment groups: a group of active treatment (combination therapy group) took ezetimibe 10 mg/day in combination with simvastatin, and the control group (group monotherapy) took simvastatin only. The distribution of patients in the two treatment groups was performed by using envelopes. No other randomization criteria were used. The distribution of patients did not influence the results of the previous coronary angiography or the lipid profile. The results of coronary angiography were used to confirm the presence of CHD and in more detail were evaluated after enrollment.

The initial dose of simvastatin in all patients included in the study was 20 mg/day, regardless of the chosen strategy of therapy (monotherapy group or combination treatment group). The dose of simvastatin was titrated up to 40 or 80 mg/day every 6 weeks, if it was necessary, according to the achievement of the target level of LDL-C <2.5 mmol/L. After achieving the target level of LDL-C and confirming measurements, the dose of simvastatin was unchanged for 6 months (until the end of the study). Simvastatin dose titration results are shown in Fig. 1.

The study excluded patients with acute coronary syndrome, myocardial infarction, which are less than 6 months, family hyperlipidemia, severe liver disease and kidney

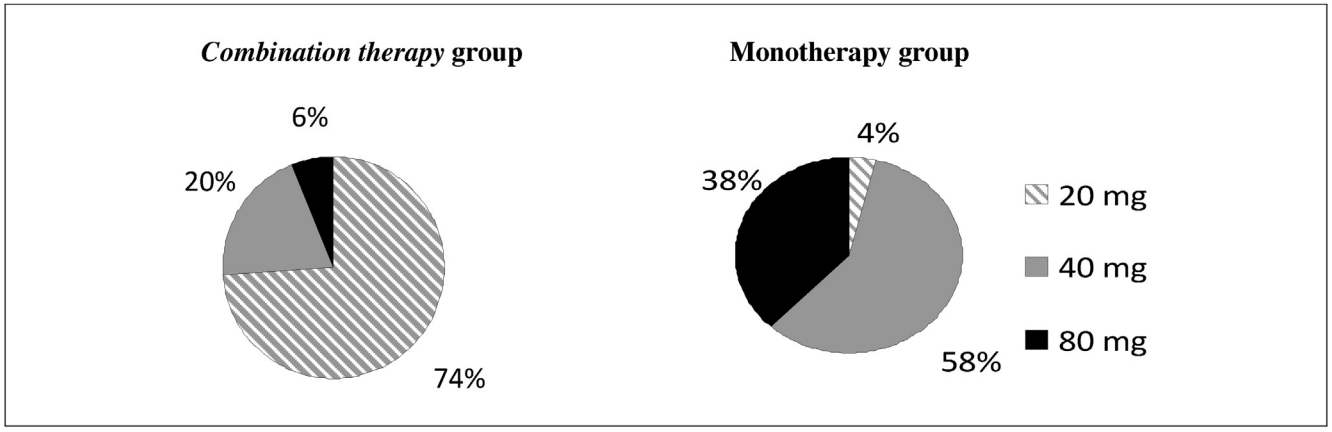

Fig. 1 – Distribution simvastatin doses in combination therapy and monotherapy.