Additive Effects of Statin Combined With Ani-togênios
Converting Enzyme Inhibitor on Vasomotion in
Hypercholesterolemic Patients
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Background: HMG-CoA reductase inhibitor, statins and ramipril prevented or retarded the progression of coronary heart disease in large-scale, clinical studies. Ezetimibe also plays an important role in the pathogenesis of atherosclerosis. By understanding the mechanisms of the biological effects of statins and anitogênios converting enzyme inhibitor therapies differ, we studied the vascular responses to these therapies in hypercholesterolemic patients.

Methods: We administered simvastatin 80 mg and placebo or ramipril 10 mg daily during 2 months with washout 2 months to 32 hypercholesterolemic patients. This study was randomized, double-blind, placebo-controlled, crossover in design.

Results: Results: Simvastatin alone or combined with ramipril significantly changed lipoproteins, and improved the percent flow-mediated dilator response (FMD) to hyperemia from 4.9±2.1% to 5.8±1.9% by 48±48% and from 4.6±3.3% to 4.7±4.1% by 9½±9½%, respectively (both P<0.001) and reduced plasma levels of nitrite from 8.8±44.7±32 μM by 0.5±2% and from 8.3±38 to 6.5±29 μM by 13±30%, respectively (P=0.183 and P=0.012, respectively), and plasma levels of malondialdehyde (MDA), a marker of free radical from 1.3±3.5 to 1.1±0.5±5 μM by 9±9% and from 1.3±3.5 to 1.2±0.5 μM by 9±9%, respectively (P=0.440 and P=0.564, respectively). Compared with baseline measurements. However, simvastatin combined with ramipril changed to greater extent FMD and plasma levels of nitrite and MDA than simvastatin alone. Conclusions: Compared with simvastatin alone, added ramipril to simvastatin showed additive effects on flow-mediated dilatation and the plasma levels of nitrite and MDA in hypercholesterolemic patients.

Atorvastatin Suppresses the Expression of CD40 Ligand and P-Selectin on Platelets in Patients With Hypercholesterolemia
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Background: Hypercholesterolemia (HC), a risk factor for cardiovascular disease, is associated with inflammation and the prothrombotic state. Recently a CD40-CD40 ligand (CD40L) interaction and the activation of platelet was claimed to play a major role in the pathogenesis in atherosclerosis. The aim of the study was to characterize the in vitro expression of CD40L and p-selectin in patients with HC and to investigate whether atorvastatin (ATOR), a potent lipid-lowering agent, can influence the levels of these molecules and TNF-α.

Methods: Twelve patients with polygenic HC (total cholesterol >220 mg/dL, or LDL >130 mg/dL) without other associated inflammatory disease and 14 normal controls were enrolled in this study. All patients were on 2×10 mg ATOR for 1 week before and after 8 weeks of ATOR therapy in patient group. After isolation, half of the platelets were stimulated by the addition of ADP (5 μmol/L). Flow cytometry was used to analyze the expression of CD40L and p-selectin. TNF-α was measured by ELISA.

Results: Expression of TNF-α is correlated with VLDL and LDL/HDL ratio (p=0.02, r=0.50) and LDL/HDL ratio (p=0.02, r=0.39). In normal controls, the expression of CD40L and p-selectin increased significantly after the stimulation of ADP. In patients, the expression of CD40L did not differ with or without ADP stimulation before treatment (CD40L: 0.57±0.55 vs 0.51±0.19 mean fluorescence intensity [MFI]; P=NS), but after 8 weeks of ATOR therapy, the addition of ADP can significantly increase the expression of CD40L (0.5%±0.17 vs 0.5±0.45 MFI; P=0.026). In the same time, after 8 weeks of ATOR therapy, the expression of CD40L and p-selectin decreased significantly (CD40L: 0.57±0.55 vs 0.25±0.17; P=0.034; p-selectin: 2.3±1.4 vs 1.06±0.67; P=0.006).

Conclusion: In this short term study, ATOR can down-regulate the expression of CD40L and p-selectin on platelets in patients with HC. We also found that the level of TNF-α was correlated with LDL/HDL ratio. We supposed that in addition to its effect on decreasing the cholesterol level, ATOR can influence the interaction of CD40L and the expression of p-selectin which may aesse the promonocytosis powerful of platelets in patients with HC.

Ezetimibe Coadministered With Atorvastatin Compared to Atorvastatin Alone in the Attainment of Low-Density Lipoprotein Goals Among High-Risk Patients With Hypercholesterolemia
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Background: This study evaluated ezetimibe (EZE) coadministered with atorvastatin (ATOR) in patients with heterozygous familial hypercholesterolemia, coronary heart disease, or multiple cardiovascular risk factors. Methods: After dietary stabilization, a 6- to 10-week washout, and ATOR run-in period (open-label ATOR 10 mg/day), 621 patients were enrolled in a randomized, double-blind, placebo-controlled, parallel study with baseline LDL-C and TG ≤500 mg/dL on ATOR 10 mg every other day treatment to two treatment arms: EZE; ATOR 10 mg or double-blind ATOR (10 mg) administered daily for 4 weeks. The ATOR dose was doubled if LDL-C was >100 mg/dL after 4 and/or 9 weeks of treatment (maximum 80 mg/dL with ATOR alone; 40 mg/day with coadministration). Patients were randomized to EZE + ATOR 10 mg (n=312) vs. placebo every other day for treatment to two arms: ATOR 10 mg or double-blind ATOR (10 mg) administered daily for 4 weeks. The ATOR dose was doubled if LDL-C was >100 mg/dL after 4 and/or 9 weeks of treatment (maximum 80 mg/dL with ATOR alone; 40 mg/day with coadministration).

Results: Of 312 patients randomized to EZE + ATOR 10 mg/day followed by response-based titration of ATOR significantly increased the proportion of patients reaching target LDL-C ≤100 mg/dL at week 14. Results: Addition of EZE to ATOR 10 mg/day followed by response-based titration of ATOR significantly increased the proportion of patients reaching target LDL-C to 22% (673/305) versus titration of ATOR alone at 7% (233/316; P<0.001 vs. Placebo). The final (week 14) LDL-C reduction from randomization was 31.2% versus 16.9% (P<0.001). EZE + ATOR was well tolerated with a safety profile similar to ATOR alone. Conclusion: Addition of EZE to ongoing ATOR provides significantly greater LDL-C reduction than continued doubling of ATOR dose alone, and results in 3 times as many patients reaching target LDL-C. This offers a highly efficacious and well tolerated new treatment approach in hypercholesterolemia.

Ezetimibe Coadministered With Low Dose Statins in Primary Hypercholesterolemia: Lipid Profiles Comparable to High-Dose Statin Monotherapy
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Background: Ezetimibe (EZE), a novel cholesterol absorption inhibitor, significantly lowers LDL-C and TG and raises HDL-C. The addition of EZE to low-dose statins may result in similar LDL-C reductions as achieved with high-dose statin monotherapy. Methods: Data were analyzed from 4 Phase III, randomized, double-blind, placebo-controlled studies in pts with primary hypercholesterolemia in which EZE 10 mg + statin 10 mg was compared with Pbo + higher doses of statin alone (simvastatin (S) 80 mg, atorvastatin (A) 80 mg, pravastatin (P) 40 mg, or lovastatin (L) 40 mg). After dietary stabilization (-5% or Step 1), a 2-week screening period and a 4-wk, Pbo lead-in period, pts with baseline LDL-C ≤145 to ≤250 mg/dL and TG ≤350 mg/dL were randomized to EZE + statin or Pbo + statin daily for 12 weeks.

Results: EZE + statin 10 mg resulted in similar LDL-C reductions as those achieved with higher doses of statins alone (table) and comparable or greater effects on HDL-C and TG compared to statin monotherapy. The effects of EZE on LDL-C were independent of the statin tested. EZE had an excellent safety profile and was well tolerated. Conclusion: The addition of EZE 10 mg to low doses of statins (10mg) provides similar effects on LDL-C, HDL-C, and TG compared to high-dose statin monotherapy (80mg, 40mg, 10mg, 40mg). The addition of EZE to statins provides an alternative to higher dose statins for therapy of hypercholesterolemia. Percent Change from Drug Free Baseline to Endpoint