ARTICLE ORIGINAL / ORIGINAL ARTICLE

BENEFIT AND TOLERABILITY OF THE COADMINISTRATION OF EZETIMIBE AND ATORVASTATIN IN ACUTE CORONARY SYNDROME PATIENTS

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Hamdan R, Hajj F, Kadry Z, Kassab R, Salame E, Aboujaoude S, Azar R, Badaoui G. Benefit and tolerability of the coadministration of ezetimibe and atorvastatin in acute coronary syndrome patients. J Med Liban 2011 ; 59 (2) : 65-69.

ABSTRACT • BACKGROUND AND AIM : The effect of ezetimibe-statin combination on inflammatory markers in acute coronary syndrome is unknown. The aim of our study is to evaluate the effect of this combination on the lipid profile, the CRP hs and the sCD40 ligand levels in acute coronary syndrome (ACS) patients.

METHODS : This is a randomized, double-blind study including 93 patients admitted for ACS randomized in 2 groups, ezetimibe 10 mg + atorvastatin 10 mg *vs* atorvastatin 20 mg + placebo, for 12 weeks follow-up; blood samples were collected for lipid profile, ALT, AST, CRP and sCD40L at baseline, 12 hours, 4 weeks, and 12 weeks.

RESULTS : There was no significant difference in total cholesterol levels, HDL, LDL, CRP, but there was a significant decrease in sCD40L levels in the ezetimibe combination group, with less side effects in the combination group, mainly myalgia ($p = 0.012$).

CONCLUSION : Ezetimibe combination with low dose statin in patients in acute coronary syndrome could be a safe, potent therapy to reduce LDL level with anti-inflammatory effect.

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RÉSUMÉ • OBJECTIF : L'effet de l'association ezetimibe-atorvastatine au cours d'un syndrome coronarien aigu sur les marqueurs inflammatoires est inconnu ; le but de notre étude est d'évaluer l'effet de cette association sur le profile lipidique, la CRP ultrasensible, et sur les taux du CD40 ligand dans les syndromes coronariens aigus.

MÉTHODES : C'est une étude randomisée en double aveugle incluant 93 patients hospitalisés pour syndrome coronarien aigu, randomisés en deux groupes, ezetimibe 10 mg + atorvastatine 10 mg *vs* atorvastatine 20 mg + placebo pour un suivi de 12 semaines, des prises de sang pour profil lipidique, SGOT, SGPT, CRP et CD40Ls ont été effectuées au début, à 12 heures, à 4 et à 12 semaines.

RÉSULTATS : Il n'y avait pas de différence significative dans les taux de cholestérol total, HDL, LDL et CRP, mais nous avons eu une diminution significative du taux de CD40L dans le groupe ayant pris l'association ezetimibe, avec moins d'effets secondaires dans ce groupe, notamment moins de myalgie ($p = 0,012$).

CONCLUSION : L'association ezitimibe avec faible dose de statine en cas de syndrome coronarien aigu semble être une thérapie efficace, bien tolérée avec des effets anti-inflammatoires.

BACKGROUND

Intensive therapy should be considered in all patients admitted to the hospital for acute coronary syndrome (ACS). Achieving very low levels of LDL-cholesterol often requires high doses of a statin or a combination therapy.

Benefit from statin therapy involves mechanisms (pleiotropic effects) that are important early after an ACS, including plaque stabilization, reversal of endothelial dysfunction, decreased thrombogenicity, and reduced inflammation [1].

Although ACS appears to be caused by rupture of an unstable coronary plaque that appears as a single lesion on angiography, systemic effects, such as inflammation, are more widespread within the coronary circulation and lead to instability of multiple plaques [2-4]. Thus, interventions aimed only at the culprit lesion may not be optimal.

C-reactive protein (CRP) is an acute phase protein that is present in increased concentrations in the setting of inflammation, the serum concentration of CRP is a risk factor for cardiovascular disease and increased serum CRP concentration at admission is a marker of a worse short- and long-term prognosis in patients with an ACS. Clinical trials have provided supportive evidence for the suggestion that the benefit of statin therapy after an ACS can be attributed, at least in part, to a reduction in serum CRP.

CD40 ligand is a transmembrane protein expressed on T cells, B cells, mast cells, basophils, eosinophils, natural killer cells, macrophages, endothelial cells, vascular smooth muscle cells, and activated platelets. It is also found in plasma as a soluble protein, sCD40L. As a consequence of CD40L binding to its receptor (CD40), several inflammatory processes are initiated, like the expression

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by macrophages and smooth muscle cells of proteolytic enzymes that can weaken the extra cellular matrix. In ACS patients, levels of CD40L in the peripheral blood are elevated and those levels have been associated with increased risk of cardiovascular events. Furthermore, elevated levels of CD40L predict the risk of MI or stroke in healthy individuals [5]. Statins, glitazones, glycoprotein IIb/IIIa inhibitors, and clopidogrel have been demonstrated to effectively reduce CD40L levels both in vitro and in vivo; to our best knowledge the effect of ezetimibe on the serum soluble CD40 ligand level has not been studied.

Ezetimibe coadministered with statin, a dual inhibition treatment strategy that targets both cholesterol absorption and synthesis, is an effective therapeutic option for patients with hypercholesterolemia, providing significant incremental reductions in LDL-C levels.

The effect of ezetimibe on serum CRP levels was studied in many publications with the combination simvastatin-ezetimibe [6-8] and in another for atorvastatin-ezetimibe [9]. These studies addressed a cohort of hypercholesterolemic patients, none of these studies was conducted in patients presenting for ACS.

Our aim is to compare the efficacy and safety of ezetimibe (10 mg) plus atorvastatin (10 mg) versus atorvastatin (20 mg) in subjects admitted to our hospital for acute coronary syndrome.

The effect of this combination will be studied on the lipid profile, the CRP hs level, the sCDL40 levels and the correlation between the achieved levels of CRP and sCDL40 and the achieved levels of LDL-C as well as the tolerability.

METHODS

This was a randomized, single center, double-blind, placebo-controlled trial. Patients were randomized equally to 1 of 2 daily treatments for 12 weeks: ezetimibe 10 mg (Acotral) + atorvastatin 10 mg (Liponorm 10 mg) *vs* placebo + atorvastatin 20 mg (Liponorm 20 mg).

Treatment was initiated within 24 h after randomization.

The primary efficacy analysis was the effect of this combination on the lipid profile, the CRP hs level, the sCDL40 level, the correlation between the achieved levels of CRP and sCDL40 and the achieved levels of LDL-C as well as the tolerability.

Patients

Ninety-three consecutive patients admitted to our hospital for acute coronary syndrome (ACS) were included, 70 men and 23 women.

Requirement for the diagnosis of ACS were typical signs and symptoms of cardiac ischemia and electrocardiogram abnormalities like T-wave tenting or inversion, ST-segment elevation or depression (including J-point elevation in multiple leads), and pathologic Q waves.

All patients provided written informed consent.

Exclusion criteria included:

- Known sensitivity to either atorvastatin or ezetimibe.
- Known impairment of renal function, active or chronic hepatic or hepatobiliary disease.
- Unexplained elevation of transaminases.
- Unstable endocrine or metabolic diseases known to influence serum lipids.
- Infectious or inflammatory disease capable of altering inflammatory markers.
- Patients treated with statin or ezetimibe within six weeks before admission.

Design

This randomized, double-blind trial was conducted in conformance with good clinical practices and consisted of three phases. The protocol was reviewed and approved by our hospital ethic committee. First blood sample was collected at baseline, in the 12 hours after admission for the dosage of: Total cholesterol, LDL and HDL, TG, alanine transaminase (ALT), aspartate transaminase (AST), CRP and sCD40L. All the patient physical information needed for the study was collected by the same doctor: weight, BMI, blood pressure. Second blood sample was collected at 4 weeks for the same dosage and a questionnaire for side effects chart was filled, and again at 12 weeks. LDL-C was measured directly by ultracentrifugation (ß-quantification; direct LDL-C) and also calculated by the Friedewald equation. Total cholesterol and triglyceride levels were quantified enzymatically with the Hitachi 747 analyzer (Roche Diagnostics Corporation). Total HDL-C was determined enzymatically after selective removal of LDL-C and VLDL-C by heparin and manganese chloride precipitation. A C-reactive protein (CRP) was quantified by means of high-sensitivity immunonephelometry (hs-CRP; Dade Behring, Inc). sCD40L was quantified by an enzyme-linked immunosorbent assay (Quantakine®, Human soluble CD40 Ligand Immunoassay, R&D systems, Minneapolis, MN, USA).

All clinical laboratory analyses were conducted at the central laboratory at Hôtel-Dieu de France Hospital.

All qualifying lipid determinations, as well as lipid profiles after visit 1, were blinded to the investigators and study sponsor.

Safety was evaluated through regular monthly phone calls to the patient, the patient's doctor observations, vital signs, physical examinations, and laboratory tests at one and three months.

Statistical analysis

Data were checked for normality with D'Agostino-Pearson statictics. In case of deviation of normality, the Box-Cox transform was used to bring data towards normality. When appropriate, the non parametric Mann Whitney test was used to compare continuous data between groups. The overall comparison of the main data between the two groups was based on repeated measures two-way ANOVA. All statistical tests are bilateral. A *p*-value less then 0.05 was considered significant.

All computations were done using SPSS v13.0 software (Chicago, Illinois).

RESULTS

Of 110 individuals screened, 93 met the eligibility criteria and were randomly assigned: 47 in group A (atorvastatin 10 mg + ezetimibe 10 mg) and 46 in group B (atorvastatin 20 mg + placebo).

Patients' characteristics are shown in table I. Two patients were lost to follow-up, one in each group. There was no significant difference in total cholesterol levels evolution (Table II), HDL (Table III), LDL (Table IV), CRP (p = 0.18), between the two groups but there was a significant decrease in sCD40L levels (Fig. 1) in the ezetimibe combination group. Surprisingly and interestingly we noticed a similar reduction in total cholesterol and LDL levels in the two groups at 4 weeks and a slight reincrease below baseline levels at 12 weeks which is a known phenomenon in acute coronary syndromes.

Tolerability and side effects

Study treatment was discontinued early in two patients (4.3%) in group A for side effects, mainly myalgia, versus 10 patients (22.2%) in group B with a statistically significant difference (p = 0.012). Other side effects including increasing CPK (p = 0.7), ALAT (p = 0.8) and ASAT (p = 0.5) were not significant between the two groups.

DISCUSSION

Coadministration of ezetimibe with the 10 mg dose of atorvastatin provided a similar reduction in LDL-C, comparable to the reduction obtained with the 20 mg dose of

TABLE I PATIENTS' CHARACTERISTICS

	Group A N (mean)	Group B N (mean)	*p*
Age	46 (60.9)	45 (58.9)	*0.4*
BMI	46 (26.1)	45 (28.5)	*0.2*
Waist circumference	46 (96.7)	44 (101.3)	*0.9*
Total cholesterol	45 (5.0)	45 (5.4)	*0.7*
HDL	46 (0.9)	46 (0.9)	*0.2*
LDL	43 (3.2)	44 (3.4)	*0.07*
Triglycerides	46 (1.9)	45 (2.0)	*0.9*
ASAT	46 (69.3)	45 (55.4)	*0.2*
ALAT	44 (51.2)	44 (38.3)	*0.2*
CPK	46 (625.7)	46 (494.5)	*0.5*
CRP	46 (22.7)	46 (14.1)	*0.09*
CD40L	46 (1209.4)	42 (863.3)	*0.07*

BMI: body mass index
HDL: high density lipoproteins
LDL: low density lipoproteins
ASAT: aspartate transaminase
ALAT: alanine amino transferase
CPK: creatine phospho kinase
CRP: C-reactive protein
CD40L: cluster differentiation 40 ligand

TABLE II TOTAL CHOLESTEROL LEVEL EVOLUTION BETWEEN THE TWO GROUPS

		Group	Mean	N	*p*
Total cholesterol	1	A	5,0	43	
		B	5,4	35	
Total cholesterol	2	A	3,1	43	
		B	3,8	35	
Total cholesterol	3	A	4,3	43	
		B	3,9	35	
					0.5

TABLE III HDL CHOLESTEROL LEVEL EVOLUTION BETWEEN THE TWO GROUPS

		Group	Mean	N	*p*
HDL	1	A	0.9	44	
		B	0.9	35	
HDL	2	A	0.8	44	
		B	0.9	35	
HDL	3	A	0.9	44	
		B	1.0	35	
					0.2

TABLE IV LDL CHOLESTEROL LEVEL EVOLUTION BETWEEN THE TWO GROUPS

		Group	Mean	N	*p*
LDL	1	A	3.2	41	
		B	3.4	34	
LDL	2	A	1.6	41	
		B	2.1	34	
LDL	3	A	1.8	41	
		B	2.1	34	
					0.6

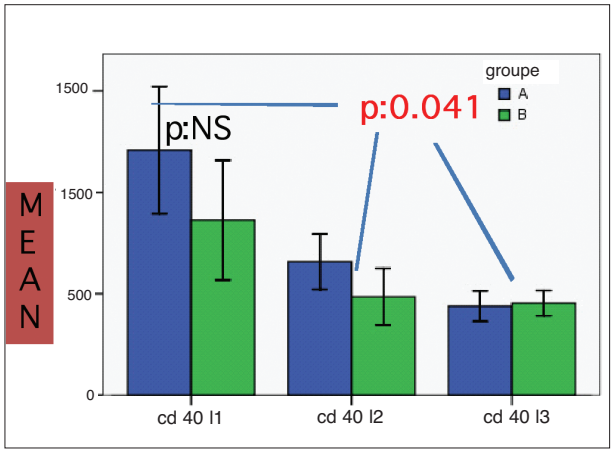

FIGURE 1. sCD40L evolution between the two groups.

atorvastatin from baseline to final assessment, less side effects and less withdrawal from therapy. The need for high statin doses in clinical practice, may limit their routine optimum use, thus limiting the achievement of the recommended LDL goals, and most patients do not receive sufficient LDL-C reductions to reach target [10]. The Atorvastatin Comparative Cholesterol Efficacy and Safety Study (ACCESS) was a randomized study comparing the efficacy and safety of five statins and their ability to reduce LDL cholesterol to the National Cholesterol Education Program (NCEP) target level; overall, at initial doses, LDL-C goals were met in 15% of patients receiving pravastatin or fluvastatin, 28% of patients receiving lovastatin, 38% of patients receiving simvastatin and 53% of patients receiving atorvastatin and in the highest-risk category of CHD even fewer patients can achieve the ATP (Adult Treatment Panel) goal of LDL-C < 100 mg/dL: 6% to 43% [11]. In patients with documented atherosclerosis receiving the starting doses of a statin, reaching goal at the starting dose was 1% for fluvastatin, 10% for lovastatin, 22% for simvastatin and 32% for atorvastatin [12]. This difficult LDL-C goal has been expanded in ATP III to include individuals with noncoronary atherosclerosis, diabetes mellitus, and multiple risk factors conferring 10-year CHD risk > 20%, doubling the number of individuals with this highest-risk category.

In our study the combination of ezetimibe plus atorvastatin was overall well tolerated. No hepatitis, jaundice, or other clinical signs of liver dysfunction were reported. For all patients who continued the treatment there were no statistically difference in the plasma levels of ALT, AST or CPK. In stable patients coadministration of ezetimibe provided greater median reduction in hs-CRP than atorvastatin alone (-41% versus -31%, $p < 0.01$); median reductions across combination therapy groups (varying doses of atorvastatin) ranged from 25% to 62% and were generally larger than those observed with statin monotherapy [9]. Similar reductions in hs-CRP were observed when ezetimibe was added to another statin [13]. Patients in our population were in ACS, the effect on the CRP level was the same in the two groups. This effect although controversial with literature can be partially supported by the ENHANCE study results [14] and on the other hand it is the first time the effect of ezetimibe on CRP is studied on acute coronary syndrome patients. However, the level of sCD40L was significantly lower at final assessment in group A suggesting a pleiotropic and an anti-inflammatory effect of the combination, possibly resulting from combining the different mechanisms of action of these agents (inhibition of cholesterol synthesis by the statin and inhibition of cholesterol absorption across the intestinal wall by ezetimibe).

The effect of ezetimibe on atherosclerosis is controversial. First, the ENHANCE study [14] comparing ezetimibe plus simvastatine versus simvastatine monotherapy on atherosclerosis progression in familial hypercholesterolemia, using as indicator the carotid artery intima media thickness (CA-IMT), failed in its primary endpoint, CA-IMT regression. These unexpected results were explained mainly by the fact that population with familial hypercholesterolemia had virtually normal baseline IMT due to their previous extensive treatment with statin, which may have rendered their arteries relatively unresponsive to further LDL-C reduction, whereas the SANDS study, another study evaluating the effect of ezetimibe on carotid atherosclerosis but this time in type 2 diabetes, showed that reducing LDL to aggressive targets resulted in similar regression of CA-IMT in patients who attained equivalent LDL reductions from a statin alone or statin plus ezetimibe [15].

According to our results the combination of ezetimibe with low-dose atorvastatin was a well-tolerated option to a higher dose atorvastatin monotherapy with less side effects, more compliance to treatment and to the best of our knowledge this is the first study showing this pleiotropic effect of such a combination on the sCD40L at the ACS phase. This has an important therapeutic implication that is limited by the raising concerns of cancer risk after the SEAS trial results, studying the intensive lipid lowering with simvastatin and ezetimibe in aortic stenosis [16]. This study, beside showing no difference in aortic valve events and ischemic events in patients with aortic stenosis in the simvastatin-ezetimibe group, showed also an increased risk of cancer in this group, not associated with the degree of LDL-C lowering, whereas in SHARP and IMPROVE-IT combined, there was no overall excess of cancer [17]. The available results from these three trials do not provide enough evidence and follow-up of longer duration should allow a more reliable assessment of the balance of risks and benefits.

Study limitations include short duration (12 weeks), which precludes analysis of long-term efficacy and safety, and exclusion criteria that prevent extrapolation of the results to other populations. The sample size was too small.

Larger studies are needed to confirm this effect.

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