DUAL INHIBITION OF THE TWO SOURCES OF CHOLESTEROL. THE MODERN METHODOLOGY OF REDUCING CARDIOVASCULAR RISC

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Abstract

This study evaluated the efficacy and safety of Ezetimibe co-administered with Simvastatine therapy in 104 hypercholesterolemic patients with coronary heart disease (CHD) or diabetes who had not achieved their low-density lipoprotein cholesterol (LDL-C) goal <100mg/dl while on a stable dose of Simvastatine 20mg/day. Significantly more patients achieved an LDL-C goal <100mg/dl with Ezetimibe than Placebo (51% vs. 35%). Compared to Placebo, co-administration of Ezetimibe with Simvastatine led to significantly greater reductions in LDL-C, total cholesterol, triglycerides, non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein B; HDL-C was as well increased. Co-administration of Ezetimibe and Simvastatine was well tolerated, with an overall safety profile similar to Simvastatine alone.

key words*: Simvastatine; Ezetimibe; low-density lipoprotein cholesterol; cardiovascular risk; hypercholesterolemia.*

Background

Although LDL-C is the primary target of drug therapy, guidelines for the treatment of hypercholesterolemia vary by country. Studies show that, in clinical practice, many high-risk patients treated for hypercholesterolemia fail to reach guideline-specific treatment goals with statin monotherapy [1, 2, 3]. Statins demonstrate a relatively flat dose–response curve with only an additional 6% reduction in LDL-C obtained for every doubling of the dose, while side-effects are linearly related to dose. Thus, starting patients on a more efficacious lipid-lowering strategy that reduces the need for statin-based titration should increase the likelihood of LDL-C goal attainment while avoiding the safety risks associated with high-dose statin therapy. Co-administration of Ezetimibe with statins, a treatment strategy targeting both the synthesis and intestinal absorption of cholesterol, has been shown to produce significant incremental reductions in LDL-C beyond that achieved by

either agent alone. This treatment regimen may be especially advantageous for CHD patients or diabetes patients [5, 6] who frequently fail to attain optimal LDL-C levels with the highest doses of the most effective statins.

Study model

The study included a total of 104 patients and has stretched over a period of one year Feb. 2009 to February 2010. The patients were randomly divided into two groups, one receiving a lipid lowering treatment with Simvastatin 20mg and a placebo, the other group Simvastatin 10mg and Ezetimibe 10mg. All patients included in the study were withdrawed from any other lipid lowering treatment except for the one with Simvastatin 20mg for at least 6 weeks before the randomization. Both study groups were homogeneous in regards to number of patients per group and sex repartition. During the study period the patients were evaluated at least 2 times in order to asses the alterations in the lipid fraction profile for each arm of the study (first mandatory visit at 3 months from the enrolment). The final evaluation and the analysis of all data took place in the 12th month of the study.

Results

The co-administration of Ezetimibe 10mg with a dose of Simvastatin 20mg has proven to be more effective in reducing LDL-C values in compare with the monotherapy with Simvastatine 20mg. Ezetimibe co-administered together with Simvastatine reduced LDL-C levels by up to 51%, while Simvastatine therapy resulted in a reduction in LDL-C levels of 35% (Figure 1).

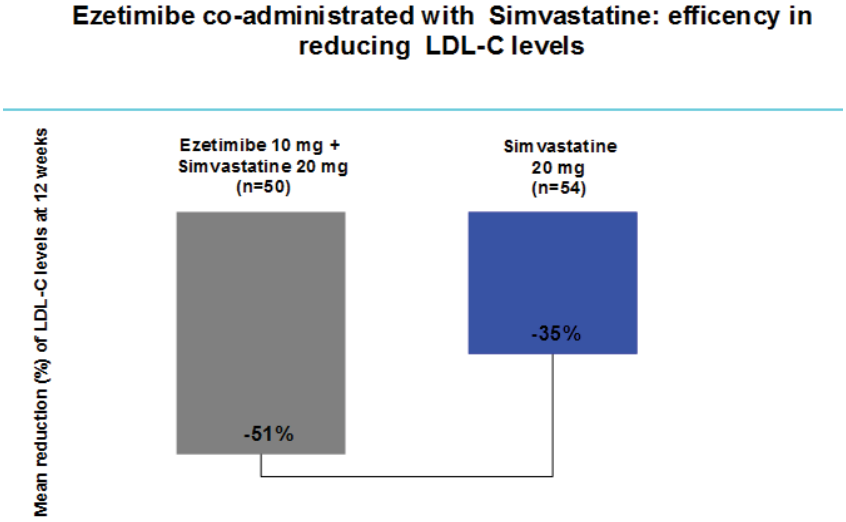

Fig. 1. The efficency in reducing LDL-c levels between the co-administration therapy and the Simvastatine monotherapy

Time wise both treatment strategies tend to behave in a similar way, meaning, after 3 months of treatment, maximal LDL-C reduction values are obtained and these values remain constant throughout the 12 months of treatment (Figure 2).

The coadministration therapy of Ezetimibe and Simvastatine greatly improves the global lipid profile in comparison with the monotherapy with Simvastatine. Concentrations of triglycerides, non-HLD-C and of Apo protein B were reduced by 12.8%,

23.5% and 19.4% with the coadministration regimen. Moreover, the levels of HLD-C increased with 1.3% from baseline (Figure 3).

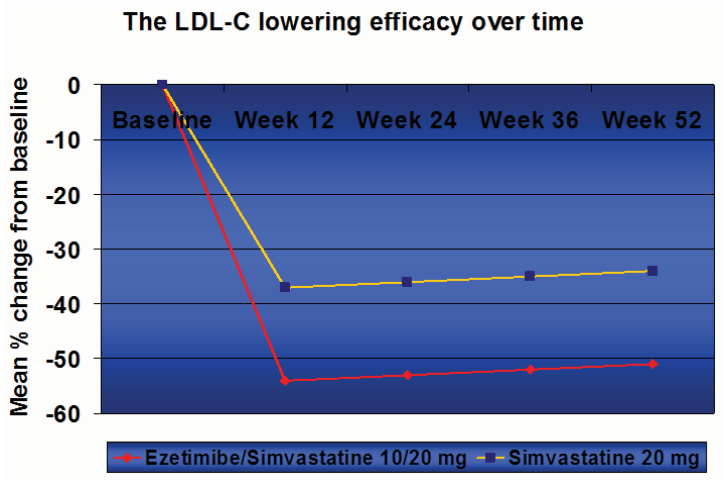

Fig. 2. The efficacy in reducing LDL-c levels between the co-administration therapy versus the Simvastatine monotherapy in raport to time of treatment

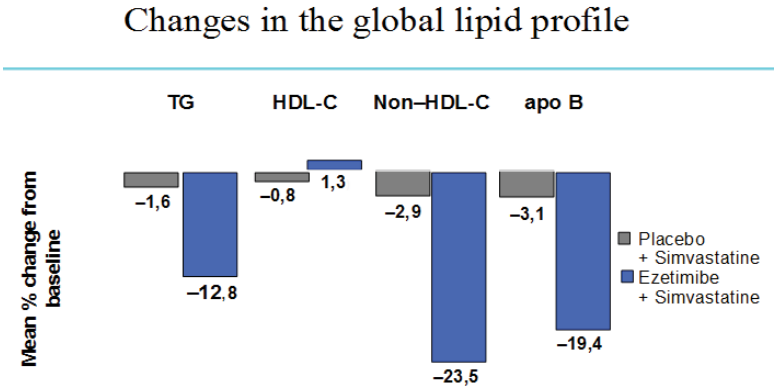

Fig. 3. The changes in the lipid profile between the co-administration therapy versus the monotherapy

The coadministration therapy of Ezetimibe and Simvastatine greatly improves the global lipid profile in comparison with the monotherapy with Simvastatine. Concentrations of triglycerides, non-HLD-C and of Apo protein B were reduced by 12.8%, 23.5% and 19.4% with the coadministration regimen. Moreover, the levels of HLD-C increased with 1.3% from baseline (Figure 3).

In regards to the safety profile of the treatment regimens, there were no meaningful differences between Ezetimibe/simvastatine and Simvastatine alone, especially with respect to the important muscle and liver adverse events. Elevations in hepatic transaminases with Ezetimibe/Simvastatine [7] were reversible and not associated with clinical evidence of hepatotoxicity. Increases of transaminases are a well-known effect of statin therapy and occur with almost all lipid-lowering agents (Figure 4).

There were several inconveniences noted regarding both treatments, with Ezetimibe and with Simvastatine. Ezetimib is a relatively pricey drug, it is not of first intent for patients with metabolic syndrome (diabetes mellitus, atherogenic dyslipidemia or family dyslipidemia) and it is efficient only in

association with a statin. The statin therapy presents adverse effects the most important of witch is liver toxicity, also it has a limited efficacy when administrated as monotherapy.

Liver and muscular safety profile

	Placebo + Simvastatine (nr=50) (% of patients)	Ezetimibe + Simvastatine (nr=54) (% of patients)	P value
ALT ≥3×ULN*	0,2	0,5	NS
AST ≥3×ULN*	0,1	0,2	NS
CK ≥10×ULN*+/- muscular sympoms	0,0	0,0	NS

ULN- upper limit of normal

*Results based on eighter two consecutive determinations or on one last determination ≥3 × ULN, or a single value ≥3 × ULN followed by a value of <3 × ULN for more than 2 days since the last drug administration of the study.

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Fig. 4. The incidence of liver enzyme elevations and muscular symptoms with the two treatments

Discussion

Epidemiologic studies reveal that elevated serum cholesterol is associated with an increased risk of CV morbidity and mortality. Moreover, as cholesterol levels decrease, the risk of cardiac endpoints decreases. However, based on the evidence that lower is better, it is apparent that growing numbers of patients require more intensive lipid-lowering therapy. Because standard doses of statins provide a 30% to 40% reduction in LDL-C levels, a statin alone may not be sufficient to achieve optimal LDL-C goals (<70mg/dL [<1.8mmol/L]) in patients with CHD and/or diabetes. Inhibition of cholesterol absorption with Ezetimibe and of the production with Simvastatin provides greater LDL-C lowering versus Simvastatin alone [6, 7, 8] and provides an effective approach that is consistent with the new "lower is better" treatment paradigm. This study of hypercholesterolemic patients with CHD or CHD-risk equivalent disease, with elevated LDL-C despite prior treatment with Simvastatine 20 mg/day, clearly demonstrated that the strategy of adding Ezetimibe to Simvastatine therapy enables more CHD patients to reach LDL-C treatment goals than Placebo plus Simvastatine. Co-administration of Ezetimibe with Simvastatine for 12 months allowed 51% of patients to achieve an LDL-C goal <100mg/dl compared with 35% patients in the Placebo plus Simvastatine group. In general, the enhanced ability of the co-administration regimen to facilitate goal attainment was consistent across the patient subgroups examined [age, sex, body mass index and patient history of disease (diabetes and hypertension)] and baseline LDL-C. The incremental mean per cent LDL-C reduction from baseline, observed in this study for Ezetimibe plus Simvastatine vs. Placebo plus Simvastatine alone was consistent with those seen in similarly designed studies conducted in low- and high-risk patients with hypercholesterolemia.

The combination of Ezetimibe and Simvastatine also produced significantly

greater reductions in TC (total cholesterol), TG (triglycerides), non-HDL-C and apo B and increases in HDL-C relative to Placebo plus Simvastatine. Co-administration therapy with Ezetimibe plus Simvastatine was well tolerated in this high-risk population and had a favourable safety profile. Major safety concerns with statin therapy include the rare occurrence of serious muscle-related adverse events (myopathy and rhabdomyolysis) and the potential for elevating serum transaminases. There were no clinically meaningful differences between Ezetimibe plus Simvastatine and Placebo plus Simvastatine groups with regard to the incidence of clinical or laboratory adverse events, including those related to muscle and liver toxicity. Although the low incidence of adverse events, especially abnormalities in liver transaminases, is note worthy.

Conclusions

This study confirms the greater efficacy of Ezetimibe plus Simvastatine and demonstrates that co-administering Ezetimibe can facilitate LDL-C goal attainment in hypercholesterolemic patients with CHD. Thus, through dual inhibition of cholesterol absorption and synthesis, Ezetimibe co-administered with Simvastatine provides high-risk patients with a greater ability to achieve optimal LDL-C levels.

REFERENCES

1. **Gerd Assmann , Frank Kannenberg , Dena R. Ramey , Thomas A. Musliner , Stephen W. Gutkin and Enrico P. Veltri.** Effects of ezetimibe, simvastatin, atorvastatin, and ezetimibe–statin therapies on non cholesterol sterols in patients with primary hypercholesterolemia *Current Medical Research and Opinion*® Vol. 24, No. 1, 249–259. 2008.

2. **J . M. Cruz-Ferna´ Ndez, G. V. Bedarida, J . Adgey, C. Allen, A. O. Johnson-Levonas, R. Massaad.** Efficacy and safety of ezetimibe co-administered with ongoing atorvastatin therapy in achieving low-density lipoprotein goal in patients with hypercholesterolemia and coronary heart disease. 2005 Blackwell Publishing Ltd *Int J Clin Pract* June 59, 6, 619–627, 2005.

3. **C. Brohet, S. Banai, A.M.W Alings, R. Massaad, M.J. Davies, C. Allen.** LDL-C goal attainment with the addition of ezetimibe with ongoing simvastatine treatment in coronary heart disease patients with hypercholesterolemia. *Current Medical Research and Oppinion* vol.21 no.4, 571-578, 2005.

4. **Christie M. Ballantyne, MD,a Nicola Abate, MD,b Zhong Yuan, MD, PhD,c Thomas R. King, MPH,c and Joanne Palmisano,** MDc Houston and Dallas, Tex, and West Point, Pa. Dose-comparison study of the combination of ezetimibe and simvastatin (Vytorin) versus atorvastatin in patients with hypercholesterolemia:The Vytorin Versus Atorvastatin (VYVA) Study. *Am Heart J* 149:464-73, 2005.

5. **C. Constance, S. Westphal, N. Chung, M. Lund, C. McCrary Sisk, A. O. Johnson- Levonas, R. Massaad and C. Allen.** Efficacy of ezetimibe/simvastatin 10/20 and 10/40 mg compared with atorvastatin 20 mg in patients with type 2 diabetes mellitus. The Authors Journal Compilation, Diabetes, **Obesity and Metabolism Blackwell Publishing Ltd**. 2007.

6. **A.L Catapano, M.H. Davidson, C.M. Ballantyne, W.E Brady, R.A. Gazzara, J.E. Tomassini** Lipid altering eficacy of the ezetimibe/simvastatine single tablet versus rusovastatine in hypercholesterolemic patients. *Current Medical Research and Opinion*® vol.22, no.10, pages 2041-2053, 2006.

7. **L. Laforest, T. Souchet, C. Ritleng, G. Desamericq, A. Kieffer, P. Le Jeunne, E. Van Ganse.** LDL-cholesterol goal attainment according to cardiovascular risk level in patients receiving lipid-lowering therapy in primary care. *Journal of*

Atherosclerosis Research vol.199, issue 2, pages 368-377.

8. Adrian Brady, Glenn Davies, Hege Urdahl, Don Yin, Evo Alemao, John Cook. Ezetimibe Plus statin versus doubling of statin dose in patients not at target on statin monotherapy. *European Society of Cardiology Vienna* Austria September 5, 2007.

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