Effects of Combined Ezetimibe and Simvastatin Therapy as Compared With Simvastatin Alone in Patients With Type 2 Diabetes

A prospective randomized double-blind clinical trial

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FOR THE EZETIMIBE AND SIMVASTATIN IN DYSLIPIDEMIA OF DIABETES (ESD) STUDY GROUP*

OBJECTIVE — To assess the effects of inhibited gastrointestinal cholesterol absorption in statin-treated dyslipidemic patients.

RESEARCH DESIGN AND METHODS — In a multicenter prospective randomized double-blind placebo-controlled trial, we primarily compared by ANCOVA the effect of 2-month ezetimibe (10 mg/day) or placebo therapy on LDL cholesterol serum levels in 108 type 2 diabetic patients with albuminuria <200 μg/min and total cholesterol concentrations >135 mg/dl despite simvastatin treatment (40 mg/day).

RESULTS — Unlike placebo, ezetimibe decreased LDL cholesterol from 99 ± 31 to 66 ± 22 mg/dl, total cholesterol from 162 ± 36 to 124 ± 30 mg/dl, and apolipoprotein B from 83 ± 22 to 64 ± 18 mg/dl ($P < 0.0001$ for all changes versus placebo). A total of 72 and 17% of patients on ezetimibe or placebo achieved LDL levels <70 mg/dl, respectively ($P < 0.0001$). Treatment was well tolerated.

CONCLUSIONS — Adding ezetimibe to simvastatin therapy helps to improve the proatherogenic lipoprotein profile in type 2 diabetic patients who fail to reach recommended lipid targets with statin therapy alone.

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Inhibited gastrointestinal cholesterol absorption by add-on ezetimibe therapy (1) reduced cholesterol levels in patients with persistent dyslipidemia despite statin therapy (1–6). Advantages of dual- versus single-drug lipid-lowering therapy, however, could not be definitely established, since the effects of ezetimibe combined with a given dosage of a statin were compared with those of monotherapy with another competitor statin (4,5) or even with the same statin but given at higher dosages (2). To address this issue, the Ezetimibe and Simvastatin in Dyslipidemia of Diabetes (ESD) study (ClinicalTrials.gov identifier: NCT00157482) compared the lipid-lowering effects of ezetimibe or placebo added on the same background statin therapy in type 2 diabetic patients with persistent hypercholesterolemia despite HMG-CoA reductase inhibition.

RESEARCH DESIGN AND METHODS

— ESD was an academic multicenter prospective randomized double-blind placebo-controlled trial independently designed, conducted and monitored by the investigators of the Clinical Research Center for Rare Diseases "Aldo & Cele Daccò" and three diabetology units in Italy. The protocol was approved by the ethical committees of all institutions. Patients provided written informed consent according to the Declaration of Helsinki. Data were handled and reported without sponsor involvement. Authors had full access to data and critically revised and finally approved the manuscript.

The 18- to 70-year-old type 2 diabetic subjects with total cholesterol concentrations >135 mg/dl despite lipid-lowering therapy, serum creatinine <1.5 mg/dl, and urinary albumin excretion <200 μg/min were eligible for study participation. Individuals with recent cardiovascular events, primary hyperlipidemia, or hepatic or muscle disease; who were pregnant or lactating; who were treated with steroids, immunosuppressive agents, fibrates, niacin, or cholestyramine; or who were unable to provide informed consent were excluded (ClinicalTrials.gov identifier: NCT00157482).

After a 4-week wash-out from previous lipid-lowering therapy (if any), and a 2-month run-in with 40 mg/day simvastatin, eligible patients were randomly al-

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Table 1—*Patients characteristics at randomization (Pre) and at the end of the treatment period (Post) according to study treatment*

Variable (unit)	Ezetimibe		Placebo	
	Pre (n = 54)	Post (n = 53)	Pre (n = 54)	Post (n = 54)
Clinical parameters				
BMI (kg/m^2)	29.0 ± 4.2	28.8 ± 4.3	28.8 ± 4.1	28.9 ± 4.1
Systolic blood pressure (mmHg)	136 ± 13	133 ± 13	131 ± 15	131 ± 15
Diastolic blood pressure (mmHg)	79 ± 7	78 ± 7	78 ± 8	77 ± 7
Metabolic parameters				
Serum glucose (mg/dl)	160 ± 44	168 ± 43	162 ± 50	159 ± 44
HbA_{1C} (%)	5.8 ± 1.5	5.5 ± 1.2	5.5 ± 1.1	5.5 ± 1.2
Renal function				
Serum creatinine (mg/dl)	0.90 ± 0.18	0.91 ± 0.17	0.87 ± 0.20	0.88 ± 0.21
Serum urea (mg/dl)	42 ± 12	43 ± 12	39 ± 12	39 ± 11
Urinary albumin excretion (μg/min)	5.2 (2.8–10.3)	4.7 (3.3–11.8)	4.6 (3.4–7.2)	4.7 (3.3–9.6)
Lipids				
Total cholesterol (mg/dl)	162 ± 36	124 ± 30*	154 ± 30	158 ± 32‡
HDL cholesterol (mg/dl)	48 ± 11	45 ± 12*	50 ± 12	50 ± 11§
LDL cholesterol (mg/dl)	99 ± 31	66 ± 22*	91 ± 28	94 ± 32‡
LDL <70 mg/dl	7 (13.0)	38 (71.7)†	14 (25.9)	9 (16.7)†‡
Triglycerides (mg/dl)	123 ± 95	108 ± 77	106 ± 65	104 ± 62§
Apolipoprotein A (mg/dl)	134 ± 23	138 ± 27	139 ± 20	143 ± 23
Apolipoprotein B (mg/dl)	83 ± 22	64 ± 18*	81 ± 23	81 ± 22‡
Safety parameters				
Aspartate transaminase (IU/l)	23 ± 7	24 ± 9	21 ± 5	21 ± 6
Alanine transaminase (IU/l)	25 ± 10	27 ± 10	23 ± 9	23 ± 8
γ-Glutamyl transferase (IU/l)	33 ± 39	35 ± 37	30 ± 30	29 ± 27
Creatinine phosphokinase (IU/l)	147 ± 140	143 ± 120	113 ± 60	115 ± 70

Data are means ± SD, medians (interquartile range), or n (%). *$P < 0.01$ and †$P < 0.0001$ vs. Pre (Bonferroni adjusted paired t test or McNemar χ^2 test). ‡$P < 0.0001$ and §0.05 vs. ezetimibe (ANCOVA or χ^2 test).

located to 2-month add-on treatment with 10 mg/day ezetimibe or placebo. Demography and clinical and laboratory data were recorded at inclusion, randomization, and study end.

Laboratory parameters were centrally measured by an automatic analyzer (Beckman Synchron CX9). Glycosylated hemoglobin was measured by high-performance liquid chromatography (normal laboratory range 3.53–5.21%; Beckman System Gold Chromatograph). Urinary albumin excretion was measured in three consecutive overnight urine collections by nephelometry (Array 360 System; Beckman, Milan, Italy) in sterile urine.

LDL cholesterol was the primary outcome. Based on average levels observed in statin-treated type 2 diabetic patients with normo- or microalbuminuria referred to our research center, we predicted LDL serum levels of 90 ± 12 mg/dl at randomization. Assuming a 20% reduction on ezetimibe and no change on placebo, 51 patients per group were required in order to have 80% power to detect a statistically significant difference ($P < 0.05$) between the two study arms in LDL change from baseline to study end. To account for a 5% dropout rate, 54 patients per group had to be randomized.

Patients were centrally randomized to ezetimibe or placebo on a 1:1 ratio within blocks of four according to a computer-generated randomization list. Patients and investigators were blinded to treatment. Analyses were by intention to treat. Characteristics of patients were compared by χ^2 test, Fisher exact test, unpaired t test, or Wilcoxon rank-sum test as appropriate. Within-group treatment effects were assessed by repeated-measures ANOVA followed by paired t tests or by McNemar χ^2 test (between-group effects by ANCOVA, adjusting for the measurement at randomization or by χ^2 test). The multiple pairwise comparison issue was addressed using Bonferroni adjustment. Analyses were performed using SAS version 9.1 (SAS Institute, Cary, NC). Data were expressed as mean ± SD or median (interquartile range) or number (%) unless otherwise specified. All P values were two-sided. Statistical significance was set at the 0.05 level.

RESULTS — Of 114 screened subjects, 108 fulfilled the selection criteria and were randomized. One patient randomized to ezetimibe eventually withdrew his consent; thus, 53 patients on ezetimibe and 54 on placebo completed the study. Main characteristics at randomization (Table 1) including age (65.7 vs. 65.2 years), proportion of males (63.0 vs. 55.6%), and proportion of current smokers (44.6 vs. 55.6%) were similar in the ezetimibe and placebo group, respectively, whereas the proportion of subjects with a family history of coronary heart disease was higher (51.9 vs. 29.6%) in the ezetimibe group.

LDL and total cholesterol and apolipoprotein B significantly decreased by 30.9, 21.6, and 19.6%, respectively, compared with randomization in patients given ezetimibe, but did not change appreciably in individuals on placebo (Table 1). These trends were significantly different between groups ($P < 0.0001$ for all comparisons). At study end, 4.2-fold more subjects on ezetimibe than on placebo achieved an LDL level of ≤70 mg/dl (Table 1). Serum HDL cholesterol and triglycerides decreased on ezetimibe but

not on placebo. Both changes were significantly different between groups (Table 1). After randomization, urinary albumin excretion did not appreciably change in both groups (Table 1).

Treatment was well tolerated. No significant increases in serum creatinphosphokinase and transaminase levels were observed in both arms (Table 1). Four patients on ezetimibe and one on placebo had transient sinus bradycardia that recovered spontaneously without treatment withdrawal.

CONCLUSIONS — In type 2 diabetic patients with normo- or microalbuminuria and persistent dyslipidemia despite background therapy with a fixed dose of simvastatin, 2-month add-on treatment with ezetimibe significantly ameliorated the lipid profile and, compared with placebo, increased by fourfold the proportion of patients achieving the LDL target currently recommended for people with diabetes (7,8). This effect exceeded the lipid-lowering effect of combined therapy reported in previous series, most likely because here we compared ezetimibe with placebo in subjects given the same dosage of simvastatin, whereas previous studies compared combined therapy with simvastatin given at higher dosages (2) or with another more powerful statin (4,5). However, our study was underpowered to assess whether cholesterol reduction may affect albuminuria per se (9–11), independent of 3-hydroxy-3methyl-glutaril-coenzyme A (HMG-CoA) inhibition (12). As previously reported (13), combined treatment was remarkably well tolerated. However, because there were four cases of transient sinus bradycardia in the ezetimibe arm, this therapeutic option should be considered with caution in subjects with bradyarrhythmias. In conclusion, adding ezetimibe to simvastatin therapy helps improve the pro-atherogenic lipoprotein profile in type 2 diabetic patients while avoiding the drawbacks of maximizing statin doses.

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No other potential conflicts of interest relevant to this article were reported.

P.R. and G.R. had the original idea. P.R. and D.C. contributed to the data analyses. S.R., I.I., A.P., A.C.B., R.T., and A.B. were in charge of patient selection, monitoring, and care. O.D. monitored the study. B.E.-I. implemented the database. S.F. performed the laboratory analyses. D.C. wrote the initial draft, and P.R. wrote the final version of the manuscript. All the authors revised and approved the final version.

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