ORIGINAL ARTICLE doi: 10.1111/j.1463–1326.2004.00420.x

Efficacy and safety of ezetimibe co-administered with simvastatin in thiazolidinedione-treated type 2 diabetic patients

L. M. Gaudiani,[1] A. Lewin,[2] L. Meneghini,[3] I. Perevozskaya,[4] D. Plotkin,[4] Y. Mitchel[4] and S. Shah[4]

[1]Marin Endocrine Associates, Greenbrae, CA, USA
[2]National Research Institute, Los Angeles, CA, USA
[3]University of Miami School of Medicine, Diabetes Research Institute, Miami, FL, USA
[4]Merck Research Laboratories, Rahway, NJ, USA

Aim: In patients with type 2 diabetes mellitus (T2DM), combination therapy is usually required to optimize glucose metabolism as well as to help patients achieve aggressive targets for low-density lipoprotein cholesterol (LDL-C) and other lipid parameters associated with cardiovascular risk. The thiazolidinediones (TZDs) are increasingly being used for both their blood glucose-lowering properties and their modest beneficial effects on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C). Ezetimibe, an intestinal cholesterol absorption inhibitor, has a mechanism of action that differs from that of statins, which inhibit hepatic cholesterol synthesis. We compared the lipid-modifying efficacy and safety of adding ezetimibe to simvastatin, vs. doubling the dose of simvastatin, in TZD-treated T2DM patients.

Methods: This was a randomized, double-blind, parallel group, multicentre study in T2DM patients, 30–75 years of age, who had been on a stable dose of a TZD for at least 3 months and had LDL-C > 2.6 mmol/l (100 mg/dl) prior to study entry. Other antidiabetic medications were also allowed. Following 6 weeks of open-label simvastatin 20 mg/day, patients were randomized to the addition of either blinded ezetimibe 10 mg/day ($n = 104$) or an additional blinded simvastatin 20 mg/day (total simvastatin 40 mg/day; $n = 110$) for 24 weeks. Patients were stratified according to TZD type and dose (pioglitazone 15–30 vs. 45 mg/day; rosiglitazone 2–4 vs. 8 mg/day).

Results: LDL-C was reduced more ($p < 0.001$) by adding ezetimibe 10 mg to simvastatin 20 mg (−20.8%) than by doubling the dose of simvastatin to 40 mg (−0.3%). Ezetimibe plus simvastatin 20 mg also produced significant incremental reductions in non-HDL-C ($p < 0.001$), very low-density lipoprotein cholesterol ($p < 0.05$) and apolipoprotein B ($p < 0.001$) relative to simvastatin 40 mg. There were no differences between the groups with respect to changes in TG and HDL-C levels, and both treatments were well tolerated.

Conclusions: Co-administration of ezetimibe with simvastatin, a dual inhibition treatment strategy targeting both cholesterol synthesis and absorption, is well tolerated and provides greater LDL-C-lowering efficacy than increasing the dose of simvastatin in T2DM patients taking TZDs.

Received 29 November 2003; returned for revision 22 April 2004; revised version accepted 16 June 2004

Introduction

Patients with type 2 diabetes mellitus (T2DM) are two to three times more likely to die from coronary heart disease (CHD) than non-diabetic patients [1,2]. Both the National Cholesterol Education Program (NCEP) Adult Treatment Panel (ATP) III and the American Diabetes

Correspondence:
Linda M. Gaudiani, MD, Marin Endocrine Associates, 900 South Eliseo Drive, Suite 201, Greenbrae, CA 94904, USA.
E-mail:
lmgmd@earthlink.net

Association (ADA) guidelines recommend that T2DM be classified and managed as a CHD risk equivalent with a target low-density lipoprotein cholesterol (LDL-C) goal of less than 2.6 mmol/l (100 mg/dl) [3,4].

The thiazolidinediones (TZDs), rosiglitazone and pioglitazone are insulin-sensitizing agents that improve glycaemic control and may prevent β-cell exhaustion [5,6]. Thiazolidinediones may have modest beneficial effects on triglycerides (TG) and high-density lipoprotein cholesterol (HDL-C); however, they have also been shown to raise total cholesterol and LDL-C, potentially increasing the need for more aggressive pharmacological intervention in order to achieve NCEP and ADA lipid goals. Statins are the most effective LDL-C-lowering agents available. Retrospective subgroup analyses of the Scandinavian Simvastatin Survival Study [7] and Cholesterol and Recurrent Events trial [8] provided strong evidence that statin therapy significantly reduces the incidence of coronary events in patients with diabetes mellitus. A recently published prospective analysis from the Heart Protection Study confirmed and expanded upon the earlier findings [9]. Treatment with simvastatin 40 mg reduced the incidence of major vascular events by approximately 25% in the total diabetic population ($n = 5963$), and in a subset of diabetic patients with relatively low-baseline LDL-C levels [< 3.0 mmol/l (< 116 mg/dl)], suggesting that T2DM patients may benefit from further LDL-C-lowering therapy regardless of their pre-treatment LDL-C level. A recent study in 253 T2DM patients on a stable dose of TZD illustrated that treatment with simvastatin 40 mg for 24 weeks was well tolerated and led to significant improvements in the plasma levels of LDL-C and other lipid parameters without affecting glycaemic control [10].

In some patients, higher dose statin therapy may be associated with an increased incidence of adverse effects. Thus, combining low-dose statin treatment with a second lipid-lowering agent may be more desirable than increasing the statin dose. Furthermore, despite the impressive LDL-C-lowering efficacy of statins, some T2DM patients need additional reductions beyond that which can be achieved with a statin alone to achieve ADA and NCEP ATP III lipid goals.

Ezetimibe is a cholesterol absorption inhibitor that effectively blocks biliary and dietary cholesterol absorption at the brush border of the intestine without affecting the absorption of fat-soluble vitamins or TG [11–13]. The co-administration of ezetimibe with statins, including simvastatin, compared with treatment with statins alone, has previously been shown to produce significant incremental reductions in plasma levels of LDL-C [14–17]. The clinical benefit of LDL-C lowering with ezetimibe alone or co-administered with statins has not yet been assessed in outcomes trials.

As ezetimibe and simvastatin affect blood cholesterol levels via different mechanisms of action (inhibition of intestinal cholesterol absorption vs. decreased hepatic synthesis of cholesterol), using them as dual therapy may be an advantageous LDL-C-lowering treatment strategy for patients with T2DM. The present study was conducted to evaluate the LDL-C-lowering efficacy and safety of ezetimibe 10 mg/day added to ongoing simvastatin 20 mg, compared with doubling the dose of simvastatin in TZD-treated T2DM patients.

Patients and Methods

Patients

Patients included in this study were on a stable dose ofTZD for at least 3 months and received open-label simvastatin 20 mg for 6 weeks prior to randomization. Patients were enrolled from two different sources. The first group of patients had been on a stable dose of rosiglitazone or pioglitazone while completing a 24-week study of simvastatin 40 mg compared with placebo (rollover patients) [10]. The second group of patients were newly recruited patients with T2DM on a stable dose of TZD for 3 months with LDL-C > 2.6 mmol/l (100 mg/dl) at study entry or prior to initiation of pre-study statin therapy. To ensure consistency between the rollover and newly recruited patients, the eligibility requirements for the previous study from which rollover patients were recruited were identical to those of the current study. Rollover patients were not re-screened; these patients were eligible if they had been on a stable dose of TZD for at least 3 months, had not had a myocardial infarction or cardiovascular surgery within 3 months of study entry, and if they met those criteria listed below pertaining to the use of concomitant or contraindicated medications. New patients were eligible to participate if they were men, post-menopausal women or pre-menopausal women highly unlikely to conceive, 30–75 years of age with a diagnosis of T2DM (HbA1c $\leq 9\%$), who had been treated with a stable dose of pioglitazone (15–45 mg/day) or rosiglitazone (2–8 mg/day) for at least 3 months. Stable therapy with other antidiabetic medications was also allowed. In addition, for patients entering the study already treated with a statin, they had to have had a plasma LDL-C > 2.6 mmol/l (100 mg/dl) and TG < 6.8 mmol/l (600 mg/dl) prior to initiation of pre-study statin therapy. Exclusion criteria included a diagnosis of type 1 diabetes mellitus, type I or

V hyperlipidaemia, or homozygous familial hypercholesterolaemia; a history of hyperlipidaemic pancreatitis; uncontrolled hypertension; active liver disease, renal insufficiency [creatinine $>159\,\mu mol/l$ (1.8 mg/dl)], or hypercholesterolaemia secondary to hypothyroidism; myocardial infarction, percutaneous coronary angioplasty, stent insertion, coronary bypass surgery or stroke within 3 months; and liver transaminase levels $>30\%$ above the upper limit of normal (ULN), creatine kinase (CK) $>50\%$ above ULN, or fasting plasma C-peptide ≤ 0.5 ng/ml. Patients could not be taking warfarin or warfarin-like compounds, or any potent inhibitors of cytochrome P450 3A4, and must have discontinued any lipid-lowering agent other than statins at least 6 weeks before enrolment. Women could not be taking cyclical sex hormones; constant dose hormone replacement therapy was acceptable. Patients were excluded if they had previously participated in a study evaluating ezetimibe, or if they had any condition or therapy which, in the opinion of the investigator, might pose a risk to the patient or confound the results of the study. Institutional review board approval was obtained at each study centre, and all patients provided written informed consent prior to screening.

Study Design

This randomized, double-blind, two-arm, parallel group study was conducted at 26 centres in the United States. Eligible patients received open-label simvastatin 20 mg during a 6-week lipid stabilization period [week -6 through week 1 (day 1)], and then were randomized to receive ezetimibe 10 mg or simvastatin 20 mg in addition to the open-label simvastatin 20 mg, for 24 weeks [week 1 (day 1) through week 24]. Clinic visits occurred at weeks -6 (screening), 1 (day 1, randomization), 6, 12 and 24 (active treatment). In order to achieve balance between the treatment groups for TZD used and dose, patients were stratified according to drug and dose (pioglitazone 15–30 vs. 45 mg/day; rosiglitazone 2–4 vs. 8 mg/day).

The primary objective of this study was to assess the LDL-C-lowering efficacy of ezetimibe 10 mg plus simvastatin 20 mg compared with simvastatin 40 mg in TZD-treated T2DM patients. Secondary objectives were to assess the proportion of patients in both treatment arms who achieved NCEP ATP III LDL-C target levels [<2.6 mmol/l (100 mg/dl)]; to evaluate the safety and tolerability of ezetimibe plus simvastatin co-administration; and to assess treatment effects on other parameters including: HDL-C; TG; total cholesterol (TC); non-HDL-C; very low-density lipoprotein cholesterol (VLDL-C); apolipoproteins (apo) B, A-I, C-III and E; free fatty acids (FFA); the ratios of TC : HDL-C, LDL-C : HDL-C and apoB : apoA-I; high-sensitivity C-reactive protein (hs-CRP); and fibrinogen.

Safety parameters of interest included the incidence of myopathy (muscle symptoms accompanied by CK increases >10 times ULN); clinically important changes in CK, ALT, AST, HbA1c, fasting serum glucose (FSG), fasting serum insulin (FSI), haematocrit and body weight. Pre-specified reasons for discontinuation included the following: myopathy; persistent (two consecutive) CK increases >10 times ULN with or without symptoms or greater than five times ULN with symptoms; persistent greater than three times ULN increases in ALT; and two consecutive TG values >11.3 mmol/l (1000 mg/dl).

Laboratory Analyses

All laboratory analyses were performed at Medical Research Laboratories (Highland Heights, KY, USA), which is certified by the National Heart, Lung, and Blood Institute, Centers for Disease Control Part III Program [18]. Concentrations of TC, TG and HDL-C were measured enzymatically [19]. High-density lipoprotein cholesterol was measured after precipitation of LDL and VLDL by heparin–manganese chloride [20], and LDL-C was determined by beta quantification. The apolipoproteins (A-I, B, C-III and E) were measured by radioimmunoassay [21] and hs-CRP was quantified by high-sensitivity immunonephelometry (Dade Behring, Deerfield, IL, USA).

Statistical Analysis

All analyses were based on a modified intention-to-treat population, which included all patients with a baseline and at least one post-treatment measurement. For all efficacy and safety variables, the week 1 pre-drug measurement (while on open-label simvastatin 20 mg) was used as the baseline value. For all efficacy endpoints, except hs-CRP and fibrinogen, endpoint was defined as the average of weeks 6, 12 and 24 values. Percent change from baseline to week 24 was assessed for hs-CRP, fibrinogen and select safety parameters.

Between-group comparisons of percent change from baseline for primary and secondary efficacy parameters were tested using an analysis of variance model (ANOVA) with factors for treatment, study centre, TZD type stratum (pioglitazone or rosiglitazone) and TZD dose stratum (pioglitazone 15–30 vs. 45 mg/day; rosiglitazone 2–4 vs. 8 mg/day). Where indicated, a non-parametric equivalent was used to test between-group comparisons.

The proportion of patients reaching LDL-C goal was assessed using a logistic regression model containing terms for treatment, centre, TZD type stratum and baseline percent difference from LDL-C goal.

Results

Patients

Of 291 patients screened, 214 were randomized, 110 to simvastatin 40 mg and 104 to ezetimibe plus simvastatin 20 mg. Twenty-one (19.1%) patients in the simvastatin group and 11 (10.6%) in the ezetimibe plus simvastatin group, respectively, discontinued the study for the following reasons: adverse events (AE) [five (4.5%) and two (1.9%)]; lost to follow-up [three (2.7%) and two (1.9%)]; withdrawn consent [six (5.5%) and one (1.0%)]; protocol deviation [one (0.9%) and four (3.8%)]; and other [six (5.5%) and two (1.9%)]. The treatment groups were generally balanced with regard to age, gender, race, body mass index, baseline lipid levels and diabetes-related parameters (HbA1c, FSG and FSI) (table 1). There was a slight difference in TZD usage; more patients in the simvastatin monotherapy group (54.5%) than in the combination group (47.1%) were taking pioglitazone. Use of metformin and sulphonylureas was similar in the treatment groups, but more patients in the simvastatin monotherapy group were taking insulin (18.2 vs. 10.6%). Forty-one percent of the patients enrolled in this trial had previously completed a 24-week study, evaluating the efficacy and safety of simvastatin 40 mg in TZD-treated patients [10]. The demographics and baseline lipid values were similar in the patients enrolled from the two sources.

Table 1 Characteristics of TZD-treated type 2 diabetes mellitus patients after 6 weeks on simvastatin 20 mg

	Simvastatin 40 mg (n = 110)	Ezetimibe + simvastatin 20 mg (n = 104)
Age (years)		
Mean	58.3	57.8
Range	37–78	35–80
Gender, n (%)		
Male	61 (55.5)	62 (59.6)
Female	49 (44.5)	42 (40.4)
Race, n (%)		
Caucasian	61 (55.5)	55 (52.9)
Black	13 (11.8)	16 (15.4)
Hispanic	30 (27.3)	25 (24.0)
Other	6 (5.5)	8 (7.7)
TZD dosage stratum, n (%)		
Pioglitazone ($\leq$ 30 mg/day)	36 (32.7)	28 (26.9)
Pioglitazone (45 mg/day)	24 (21.8)	21 (20.2)
Rosiglitazone ($<$ 8 mg/day)	14 (12.7)	23 (22.1)
Rosiglitazone (8 mg/day)	36 (32.7)	32 (30.8)
Other antidiabetes medications, n (%)		
Insulin	20 (18.2)	11 (10.6)
Metformin	64 (58.2)	58 (55.8)
Sulphonylureas	58 (52.7)	63 (60.6)
Diabetes-related parameters, mean (SD)		
BMI (kg/m^2)	33.7 (6.8)	32.5 (5.9)
HbA1c (%)	7.3 (1.1)	7.3 (1.3)
Fasting serum glucose (mmol/l)	8.2 (2.6)	7.9 (2.2)
Fasting serum insulin (pmol/l)	97.9 (96.5)	102.8 (166.7)
Baseline lipids* [mean (SD); mmol/l]		
TC	4.34 (0.76)	4.45 (1.04)
LDL-C	2.37 (0.63)	2.43 (0.74)
TG (median)	1.71 (1.25)	1.69 (1.30)
HDL-C	1.27 (0.28)	1.23 (0.28)
Hs-CRP [median (SD); mg/l]	1.8 (3.1)	1.8 (3.6)
Fibrinogen [median (SD); μmol/l]	11.6 (3.7)	12.5 (3.3)

BMI, body mass index; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; TG, triglycerides; TZD, thiazolidinediones.
*After 6 weeks of treatment with simvastatin 20 mg.

Changes in Efficacy Parameters

Baseline levels of LDL-C after 6 weeks on simvastatin 20 mg were 2.37 and 2.43 mmol/l (91.4 and 93.7 mg/dl) in the simvastatin monotherapy and ezetimibe plus simvastatin arms, respectively. The addition of 10 mg ezetimibe to simvastatin 20 mg produced an additional 20.8% reduction in LDL-C, compared with −0.3% change in LDL-C when the simvastatin dose was doubled to 40 mg (between-group $p < 0.001$) (table 2; figure 1). The corresponding absolute reductions in LDL-C were −0.52 and −0.04 mmol/l (−20.2 and −1.5 mg/dl). In view of the less than expected response to doubling the dose of simvastatin and because the LDL-C percent change values had a slightly more skewed distribution than what is normally observed (possibly due to the low baseline levels), a pre-specified non-parametric model was examined as a sensitivity analysis. The non-parametric model yielded similar between-treatment differences and conclusions; however, it gave somewhat different point estimates for treatment effects (−24.7% for the addition of ezetimibe to simvastatin 20 mg vs. −4.9% for doubling the dose of simvastatin from 20 mg to 40 mg; between-group $p < 0.001$); the −4.9% point estimate is more in line with the 6% decrement in LDL-C that would be expected when doubling the dose of simvastatin. The consistency of treatment effect on LDL-C was tested in subgroups of patients defined by sex, age (< 65 vs. ≥ 65 years), race (white, black, hispanic and others), TZD type and dosage stratum, and baseline levels of TG [< 2.3 vs. ≥ 2.3 mmol/l (200 mg/dl)], and LDL-C [< 3.4 vs. ≥ 3.4 mmol/l (130 mg/dl)] (figure 2). All treatment-by-subgroup interaction tests were non-significant indicating that the effect of treatment on LDL-C was consistent across the subgroups. Thirty-three percent of the patients were above goal for LDL-C at randomization; of these, 75.7% (28/37) in the ezetimibe plus simvastatin 20 mg group vs. 39.4% (13/33) in the simvastatin 40 mg only group had LDL-C < 2.6 mmol/l (100 mg/dl) at the end of the study (based on the average LDL-C of weeks 6, 12 and 24). Significantly, larger reductions with ezetimibe plus simvastatin compared with simvastatin monotherapy were also observed for TC, apoB and other apoB-containing lipoproteins (table 2; figure 1), as well as for VLDL-C ($p < 0.05$; table 2) and the ratios of TC or LDL-C to HDL-C and apoB to apoA-I ($p < 0.001$ for all; table 2).

There was no difference between the treatment groups in the change in HDL-C, apoA-I, TG, apoE, FFA and fibrinogen compared with the baseline value on simvastatin 20 mg (table 2). Median plasma levels of hs-CRP were lower in patients on ezetimibe plus simvastatin relative to simvastatin monotherapy, but the difference was not statistically significant (table 2).

Table 2 Effects of treatment on lipid parameters and hs-CRP

	Simvastatin 40 mg			Ezetimibe + Simvastatin 20 mg			
	n*	Baseline† [mean (SD); mmol/l]	Least square mean (SD) % change	n*	Baseline† [mean (SD); mmol/l]	Least square mean (SD) % change	Between-group p-value
LDL-C	107	2.37 (0.63)	−0.3 (22.8)	103	2.43 (0.74)	−20.8 (22.3)	<0.001
TC	107	4.34 (0.76)	−1.5 (15.5)	103	4.45 (1.04)	−14.5 (15.2)	<0.001
Non-HDL-C	107	3.08 (0.80)	−1.7 (20.7)	103	3.23 (1.02)	−20.0 (21.3)	<0.001
ApoB (mg/dl)	102	96.2 (21.5)	−1.8 (23.2)	96	100.5 (28.8)	−14.1 (23.5)	<0.001
Triglyceride‡	107	1.71 (1.25)	0.9 (31.8)	103	1.69 (1.30)	−3.6 (29.7)	0.291
VLDL-C‡	106	0.65 (0.46)	1.7 (55.1)	102	0.67 (0.55)	−16.3 (34.1)	<0.050
HDL-C	107	1.27 (0.28)	0.3 (12.4)	103	1.23 (0.28)	0.2 (12.1)	0.948
ApoA-I (mg/dl)	102	151.5 (23.1)	−2.5 (12.1)	96	148.1 (25.9)	−1.5 (12.7)	0.506
TC : HDL-C	107	3.6 (1.0)	0.1 (17.6)	103	3.8 (1.2)	−13.4 (17.3)	<0.001
LDL-C : HDL-C	107	2.0 (0.7)	1.6 (21.7)	103	2.1 (0.7)	−20.0 (22.3)	<0.001
ApoB : ApoA-I	102	6.6 (0.2)	1.5 (25.2)	96	0.7 (0.2)	−12.1 (25.5)	<0.001
ApoC-III (mg/dl)	102	35.3 (12.8)	0.2 (29.3)	96	37.0 (17.0)	−5.9 (29.4)	0.095
ApoE (mg/dl)	102	3.4 (1.0)	3.2 (29.3)	96	3.7 (1.5)	1.3 (29.4)	0.605
FFA‡	89	0.46 (0.3)	10.7 (62.0)	96	0.42 (0.3)	14.9 (59.5)	0.796
Hs-CRP (mg/l)‡	90	1.8 (3.1)	1.6 (77.5)	96	1.8 (3.6)	−12.5 (69.6)	0.139
Fibrinogen‡	88	396.0 (126.5)	2.2 (20.5)	95	424.0 (110.7)	2.8 (19.6)	0.969

Apo, apolipoprotein; FFA, free fatty acids; HDL-C, high-density lipoprotein cholesterol; hs-CRP, high-sensitivity C-reactive protein; LDL-C, low-density lipoprotein cholesterol; TC, total cholesterol; VLDL-C, very low density lipoprotein cholesterol.

*Modified intention-to-treat population, which includes patients with baseline and at least one post-baseline measurement.

†After 6 weeks of open-label SIMVA 20 mg.

‡Values are medians (SD of the median).

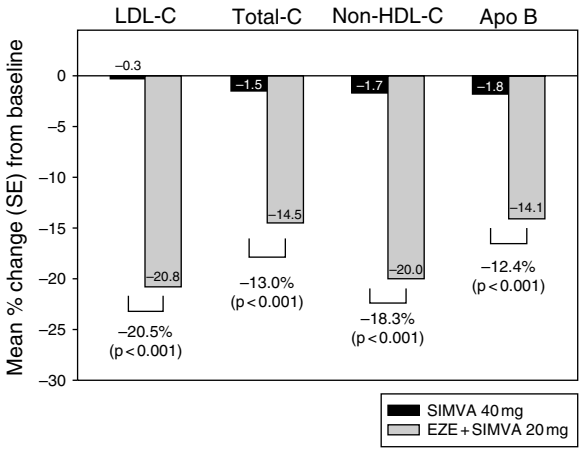

Fig. 1 Mean percent change (SE) in plasma levels of low-density lipoprotein cholesterol (LDL-C), total cholesterol (TC), non-high-density lipoprotein cholesterol (non-HDL-C) and apolipoprotein (apo) B from baseline to study endpoint (average of weeks 6, 12 and 24). EZE, ezetimibe; SIMVA, simvastatin.

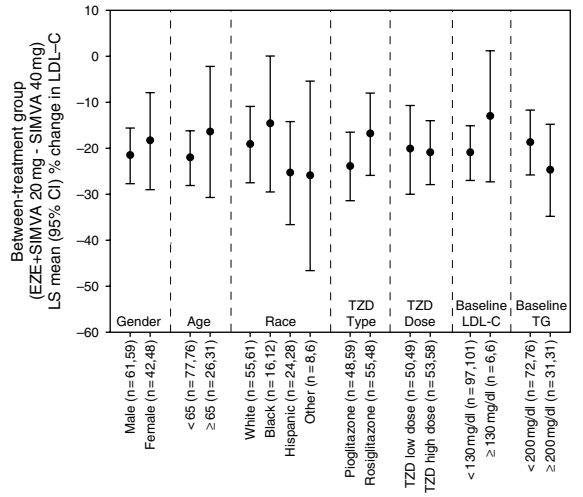

Fig. 2 Incremental between-treatment group (EZE plus SIMVA 20 mg – SIMVA 40 mg) differences for mean percentage reduction in low-density lipoprotein cholesterol (LDL-C) across patient subgroups. Data are expressed as least square (LS) mean percentage change from baseline [95% confidence interval (CI)]. EZE, ezetimibe; SIMVA, simvastatin; TG, triglycerides; TZD, thiazolidinediones.

Safety

The incidence of AE was similar between the treatment groups (table 3), and there were no significant differences in the incidence of any individual AE. While 11 (10.0%) simvastatin monotherapy patients and 19 (18.3%) ezetimibe plus simvastatin patients experienced AE determined by the investigator to be possibly, probably or definitely treatment related, only three (2.7%) and one (1.0%) patients from the two groups, respectively, discontinued due to treatment-related AE. There were no deaths or discontinuations due to serious AE, and none of the serious AE reported was attributed to the study drug. There were no cases of myopathy. One patient in the ezetimibe plus simvastatin group had an increase in CK to $\geq$10 times ULN on the last scheduled visit, which was reported as being possibly related to treatment, but was also coincident with excessive physical activity. The patient's CK returned to baseline level within 1 week. Only one patient in each treatment group had $\geq$ three times ULN increases in ALT on two consecutive occasions. Both elevations were asymptomatic and resolved upon discontinuation of treatment. No patient experienced consecutive elevations in AST to $\geq$ three times ULN. There were no significant differences between the simvastatin 40 mg and ezetimibe plus simvastatin 20 mg treatment groups, respectively, with regard to changes in body mass index (−1.1 vs. −0.5 kg/m^2), haematocrit (−0.1 vs. 0.0%); HbA1c (−0.0 vs. 0.1%), FSG [0.60 vs. 0.01 mmol/l (10.8 vs. 0.2 mg/dl)] or FSI [3.5 vs.−11.8 pmol/l (0.5 vs. −2.2 μIU/ml)]. None of the laboratory AE reports of increased HbA1c or FSG was considered to be treatment related by the investigator. Of the five reports of anaemia, only one (in the simvastatin 40-mg group) was labelled as treatment related. Five patients in each treatment group experienced peripheral oedema (a known side effect of TZD therapy); two cases in each group were due to worsening of a pre-existing condition and only two cases (one in each treatment group) were classified as possibly, probably or definitely related to treatment.

Discussion

Coronary heart disease is the leading cause of death in T2DM patients [22]. The United Kingdom Prospective Diabetes Study [23] demonstrated that regulating glucose alone does not significantly reduce the risk of macrovascular disease among T2DM patients. Thus, most T2DM patients require therapy to address lipid as well as glucose abnormalities. As more drugs become available for treating T2DM, it is important to evaluate their efficacy and safety when given in combination. Ezetimibe is the first in a new class of cholesterol-lowering drugs that block the absorption of dietary and biliary cholesterol at the intestinal epithelium. This novel mechanism of action is complementary to that of statins, which inhibit hepatic synthesis of cholesterol.

Table 3 Adverse events

	Simvastatin 40 mg (n = 110)	Ezetimibe + simvastatin 20 mg (n = 104)
Adverse events (AE)		
Treatment-related clinical AE*	11 (10.0)	19 (18.3)
Serious clinical AE	1 (0.9)	5 (4.8)
Discontinuations due to AE†	5 (4.5)	2 (1.9)
Discontinuations due to treatment-related AE†	3 (2.7)	1 (1.0)
Individual AE of interest		
Clinical		
Anaemia	4 (3.6)	1 (1.0)
Oedema	5 (4.5)	5 (4.8)
Weight gain	0	1 (1.0)
Myopathy	0	0
Laboratory		
Increased HbA1c	3/105 (2.9)	1/102 (1.0)
Increased fasting serum glucose	2/108 (1.9)	1/104 (1.0)
Proteinuria‡	0	0
ALT $\geq$3$\times$ ULN (consecutive)	1/107 (0.9)	1/103 (1.0)
AST $\geq$3$\times$ ULN (consecutive)	0	0
CK $\geq$10$\times$ ULN	0	1/103 (1.0)§

ALT, alanine aminotransferase; AST, aspartate aminotransferase; CK, creatine kinase; ULN, upper limit of normal.
*Considered by the investigator to be possibly, probably or definitely due to treatment.
†Clinical and laboratory AE.
‡Based on investigator assessment of dipstick results.
§Asymptomatic and considered to be possibly treatment-related by the investigator, but also coincident with excessive exercise.

Therefore, the present study examined the lipid-altering efficacy and safety of adding ezetimibe to ongoing simvastatin 20 mg vs. doubling the dose of simvastatin from 20 to 40 mg in T2DM patients on stable TZD therapy with or without other antidiabetic agents.

The addition of ezetimibe 10 mg to simvastatin 20 mg was significantly more effective at reducing LDL-C than doubling the dose of simvastatin from 20 to 40 mg (between-group difference: -20.5%; $p < 0.001$). Significant incremental reductions in LDL-C were observed in all patient subgroups regardless of age, sex, race, TZD agent and dose, and baseline levels of LDL-C and TG. Although the average LDL-C of the patients in this trial was below the NCEP goal of 2.6 mmol/l (100 mg/dl) after the simvastatin 20 mg lipid stabilization period and prior to randomization, among those patients who were above the LDL-C goal of 2.6 mmol/l (100 mg/dl) at randomization, a greater proportion of patients in the ezetimibe plus simvastatin group (28/37; 76%) attained goal by the end of the study compared with the simvastatin 40 mg group (13/33; 39%). Findings from the Heart Protection Study showed that the clinical benefit of simvastatin therapy (i.e. significant reduction in major vascular events) was observed even among a cohort of patients ($n = 3421$) whose pre-treatment LDL-C was < 2.6 mmol/l (100 mg/dl) [24]. Furthermore, diabetic patients with LDL-C < 3.0 mmol/l (116 mg/dl) at baseline ($n = 2426$) also realized a significant 27% reduction in major vascular events [9]. Thus, to date, an LDL-C threshold has not been identified, below which further reduction yields no additional clinical advantage. The LDL-C response observed in the ezetimibe group (-20.8%) was similar to what was reported in another study where ezetimibe was added to ongoing statin therapy [25]. However, the LDL-C response for doubling the dose of simvastatin (-0.3%) was less than the 6% incremental reduction that is normally observed when the statin dose is doubled. Possible explanations are that the expected difference was not observed due to chance or was related to the low LDL-C baseline values. The distribution of percent change in LDL-C was somewhat skewed; therefore, in a non-parametric sensitivity analysis, the percent reduction in LDL-C (-4.9%) was closer to the expected 6% reduction. The lower than expected response may also be related to the unique qualities of the TZD-treated T2DM patient population studied. In two previous studies, one using simvastatin 40 mg [10] and the other using atorvastatin 10 and 20 mg [26], the percent LDL-C reductions in TZD-treated T2DM patients were lower than what is typically seen in hypercholesterolaemic patients at those statin doses. However, other studies have not shown a differential LDL-C response to simvastatin therapy of diabetic vs. non-diabetic patients [7,27]. It is unclear what was responsible for the blunted

response to a doubled dose of simvastatin; however, in both analyses, the incremental difference in LDL-C reduction between ezetimibe plus simvastatin and simvastatin monotherapy was similar. These findings suggest that aggressive LDL-C lowering can be achieved more effectively by combining ezetimibe and simvastatin to exploit their complementary mechanisms of action, than by increasing the dose of simvastatin alone.

Consistent with the effects on LDL-C, greater reductions in TC, apoB and non-HDL-C were also seen with the addition of ezetimibe to 20 mg simvastatin compared with doubling the simvastatin dose to 40 mg. Both non-HDL-C and apoB have been shown to be predictive of future cardiovascular disease [28,29]. Non-HDL-C represents a measure of the cholesterol in apoB-containing lipoproteins including LDL, VLDL and remnant intermediate density lipoproteins, and is considered by some to be a better estimate of CHD risk than LDL-C, particularly in patients with elevated TG [28]. The NCEP has identified non-HDL-C as a secondary target of therapy for patients with TG levels $\geq$ 2.3 mmol/l (200 mg/dl) [3]. Although there was a numerical advantage for the ezetimibe group in lowering TG compared with simvastatin alone, the difference did not reach statistical significance. Plasma levels of HDL-C were not changed significantly by either treatment beyond the levels achieved on open-label simvastatin 20 mg. The baseline HDL-C levels of the patients in this study were relatively high for T2DM patients [1.2 mmol/l (48 mg/dl)], possibly due to the fact that both simvastatin and the TZDs are known to increase HDL-C [30–32].

The inflammatory marker, hs-CRP, has been shown to predict CHD risk in various populations [33]. Statins lower blood concentrations of hs-CRP, and recently, ezetimibe was shown to produce incremental hs-CRP lowering when co-administered with simvastatin [34]. In the present study, hs-CRP was reduced more by ezetimibe plus simvastatin 20 mg than by simvastatin 40 mg; however, the difference was not statistically significant. The lack of statistical significance may be due to the high variability of hs-CRP and the relatively small sample sizes.

The 24-week duration of this study was considered adequate to evaluate safety concerns of chronic concomitant therapy in this patient population, particularly with regard to glycaemic control. Ezetimibe was well tolerated and had an excellent safety profile in TZD-treated T2DM patients. Although more AE in the ezetimibe plus simvastatin group were classified by the investigators as drug related, only one patient in this group was discontinued due to treatment-related AE, compared with three in the simvastatin 40 mg group. There was no evidence of muscle or liver toxicity in either treatment group, and there were no differences between the treatments for any of the side effects associated with TZD use including oedema, weight gain and anaemia. Ezetimibe also had no effect on insulin sensitivity or diabetes status as evidenced by a lack of effect on levels of HbA1c, glucose, insulin and FFA. The FFA responses were highly variable; the slight increases from baseline in both treatment groups were similar to those observed in the previous study [10] in patients receiving placebo or simvastatin 40 mg, and thus, likely reflect regression to the mean effects.

This is the first study to evaluate the efficacy and safety of ezetimibe plus a statin in TZD-treated T2DM patients. Two recent studies demonstrated that simvastatin 40 mg and atorvastatin 10 and 20 mg were well tolerated and led to significant improvements in the plasma levels of LDL-C and other major lipid parameters without compromising the beneficial effects of the TZDs on glycaemic control [10,26]. The potential for pharmacokinetic (PK) interaction among simvastatin, ezetimibe and either of the TZDs is minimal. Rosiglitazone is unlikely to interact with simvastatin as it does not inhibit or induce CYP 3A4 [35]. Although pioglitazone is metabolized, in part, by CYP 3A4, and has the potential to induce CYP 3A4 *in vitro* [36], a PK interaction study showed that pioglitazone had no significant effect on the HMG-CoA reductase inhibitory activity derived from simvastatin [37]. Ezetimibe undergoes glucuronidation in the intestine and liver. Pharmacokinetic studies with rosiglitazone or pioglitazone have not been conducted; however, no significant PK interactions between ezetimibe and simvastatin were detected [38].

In conclusion, the addition of ezetimibe 10 mg to simvastatin 20 mg was significantly more efficacious than doubling the dose of simvastatin from 20 to 40 mg in lowering LDL-C and other lipid parameters in T2DM patients taking pioglitazone or rosiglitazone. Furthermore, ezetimibe was well tolerated, had few side effects, and did not compromise the beneficial effects of the TZDs on glycaemic control. Thus, the co-administration of ezetimibe and simvastatin, a dual inhibition treatment strategy affecting both the synthesis and absorption of cholesterol, appears to be a more effective LDL-C-lowering therapy than statin titration alone for TZD-treated T2DM patients.

Acknowledgements

The authors would like to thank Dr Darbie Maccubbin, Merck Research Laboratories, for her assistance with the preparation of this manuscript. This study was sponsored by Merck/Schering-Plough Pharmaceuticals, North Wales, PA, USA.

References

1 Garcia MJ, McNamara PM, Gordon T, Kannell WB. Morbidity and mortality in diabetics in the Framingham population. Sixteen year follow-up. Diabetes 1974; **23:** 105–111.

2 Stamler J, Vaccaro O, Neaton JD, Wentworth D. Diabetes, other risk factors, and 12-yr cardiovascular mortality for men screened in the Multiple Risk Factor Intervention Trial. Diabetes Care 1993; **2:** 434–444.

3 National Cholesterol Education Program (NCEP). Executive Summary of the Third Report of the National Cholesterol Education Program (NCEP) Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults (Adult Treatment Panel III). JAMA 2001; **285:** 2486–2497.

4 American Diabetes Association. Dyslipidemia management in adults with diabetes. Diabetes Care 2004; **27** (Suppl. 1)**:** S68–S71.

5 Evans AJ, Krentz AJ. Recent developments and emerging therapies for type 2 diabetes mellitus. Drugs 1999; **2:** 75–94.

6 Goldstein BJ. Differentiating members of the thiazolidinedione class: a focus on efficacy. Diabetes Metab Res Rev 2002; **18:** S16–S22.

7 Haffner SM, Alexander CM, Cook TJ *et al.* (for the Scandinavian Simvastatin Survival Study Group). Reduced coronary events in simvastatin-treated patients with coronary heart disease and diabetes or impaired fasting glucose levels. Arch Intern Med 1999; **159:** 2661–2667.

8 Goldberg RB, Mellies MJ, Sacks FM *et al.* (for the CARE Investigators). Cardiovascular events and their reduction with pravastatin in diabetic and glucose-intolerant myocardial infarction survivors with average cholesterol levels: subgroup analyses in the Cholesterol and Recurrent Events (CARE) trial. Circulation 1998; **98:** 2513–2519.

9 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 5963 people with diabetes: a randomised placebo-controlled trial. Lancet 2003; **361:** 2005–2016.

10 Lewin A, Kipnes M, Meneghini L *et al.* Efficacy and safety of treatment with simvastatin in thiazolidinedione-treated type 2 diabetic patients. Clin Ther 2004; **26:** 379–389.

11 Van Heek M, France C, Compton DS *et al.* In vivo metabolism-based discovery of a potent cholesterol absorption inhibitor, SCH58235, in the rat and rhesus monkey through the identification of the active metabolites of SCH48461. J Pharm Exp Ther 1997; **283:** 157–163.

12 van Heek M, Farley C, Compton DS, Hoos L, Davis HR. Ezetimibe selectively inhibits intestinal cholesterol absorption in rodents in the presence and absence of exocrine pancreatic function. Br J Pharmacol 2001; **134:** 409–417.

13 Knopp RH, Gitter H, Truitt T *et al.* Effects of ezetimibe, a new cholesterol absorption inhibitor, on plasma lipids in patients with primary hypercholesterolemia. Eur Heart J 2003; **24:** 729–741.

14 Davidson MH, McGarry T, Bettis R *et al.* Ezetimibe coadministered with simvastatin in patients with primary hypercholesterolemia. J Am Coll Cardiol 2002; **40:** 2125–2134.

15 Ballantyne CM, Houri J, Notarbartolo A *et al.* Effects of ezetimibe coadministered with atorvastatin in 628 patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Circulation 2003; **107:** 2409–2415.

16 Kerzner B, Corbelli J, Sharp S *et al.* Efficacy and safety of ezetimibe coadministered with lovastatin in primary hypercholesterolemia. Am J Cardiol 2003; **91:** 418–424.

17 Melani L, Mills R, Hassman D *et al.* Efficacy and safety of ezetimibe co-administered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003; **24:** 717–728.

18 Myers GL, Cooper GR, Winn CL, Smith SJ. The Centers for Disease Control-National Heart, Lung, and Blood Institute Lipid Standardization Program: an approach to accurate and precise lipid measurements. Clin Laboratory Med 1989; **9:** 105–135.

19 Steiner P, Freidel J, Bremmer W, Stein E. Standardization of micromethods for plasma cholesterol, triglyceride and HDL-cholesterol with the clinics' methodology. J Clin Chem 1981; **19:** 850–851.

20 Warnick G, Albers J. A comprehensive evaluation of the heparin manganese precipitation procedure for estimating high-density lipoprotein cholesterol. J Lipid Res 1978; **19:** 65–76.

21 Stein E, Kreisberg R, Miller V, Mantell G, Washington L, Shapiro DR. Effects of simvastatin and cholestyramine in familial and nonfamilial hypercholesterolemia. Arch Intern Med 1990; **150:** 341–345.

22 Gu K, Cowie CC, Harris MI. Mortality in adults with and without diabetes in a national cohort of the US population, 1971–93. Diabetes Care 1998; **21:** 1138–1145.

23 UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). Lancet 1998; **352:** 837–853.

24 Heart Protection Study Collaborative Group. MRC/BHF Heart Protection Study of cholesterol lowering with simvastatin in 20,536 high-risk individuals: a randomised placebo-controlled trial. Lancet 2002; **360:** 7–22.

25 Gagne C, Bays H, Weiss S *et al.* Efficacy and safety of ezetimibe added to ongoing statin therapy for treatment of patients with primary hypercholesterolemia. Am J Cardiol 2002; **90:** 1084–1091.

26 Freed MI, Ratner R, Marcovina SM *et al.* Effects of rosiglitazone alone and in combination with atorvastatin on the metabolic abnormalities in type 2 diabetes mellitus. Am J Cardiol 2002; **90:** 947–952.

27 Miller M, Dobs AS, Yuan Z, Battisti W, Borisute H, Palmisano J. Effectiveness of simvastatin therapy in raising HDL-C in patients with type 2 diabetes and low HDL-C. Curr Medical Res Opin 2004; **20:** 1087–1094.
28 Frost PH, Havel RJ. Rationale for use of non-high-density lipoprotein cholesterol rather than low-density lipoprotein cholesterol as a tool for lipoprotein cholesterol screening and assessment of risk and therapy. Am J Cardiol 1998; **81:** 26B–31B.
29 Lamarche B, Moorjani S, Lupien PJ *et al.* Apolipoprotein A-I and B levels and the risk of ischemic heart disease during a five-year follow-up of men in the Quebec cardiovascular study. Circulation 1996; **94:** 273–278.
30 Illingworth DR, Crouse JR, Hunninghake DB *et al.* A comparison of simvastatin and atorvastatin up to maximal recommended doses in a large multicenter randomized clinical trial. Curr Med Res Opin 2001; **17:** 43–50.
31 Sood V, Colleran K, Burge MR. Thiazolidinediones: a comparative review of approved uses. Diabetes Technol Ther 2000; **2:** 429–440.
32 Inzucchi SE. Oral antihyperglycemic therapy for type 2 diabetes. JAMA 2002; **287:** 360–372.
33 Pearson TA, Mensah GA, Alexander RW *et al.* Markers of inflammation and cardiovascular disease: application to clinical and public health practice: a statement for healthcare professionals from the Centers for Disease Control and Prevention and the American Heart Association. Circulation 2003; **107:** 499–511.
34 Sager P, Melani L, Lipka L *et al.* Effect of coadministration of ezetimibe and simvastatin on high-sensitivity C-reactive protein. Am J Cardiol 2003; **92:** 1414–1418.
35 Lebovitz HE. Differentiating members of the thiazolidinedione class: a focus on safety. Diabetes Metab Res Rev 2002; **18:** S23–S29.
36 Sahi J, Black CB, Hamilton GA *et al.* Comparative effects of thiazolidinediones on in vitro P450 enzyme induction and inhibition. Drug Metab Dispos 2003; **31:** 439–446.
37 Prueksaritanont T, Vega JM, Zhao J *et al.* Interactions between simvastatin and troglitazone or pioglitazone in healthy subjects. J Clin Pharmacol 2001; **41:** 573–581.
38 Kosoglou T, Meyer I, Veltri EP *et al.* Pharmacodynamic interaction between the new selective cholesterol absorption inhibitor ezetimibe and simvastatin. Br J Clin Pharmacol 2002; **54:** 309–319.

Appendix

The Ezetimibe Simvastatin/Thiazolidinedione Study Group consisted of the following investigators: Stephen Aronoff, MD, Dallas, TX; Harold Bays, MD, Louisville, KY; Marshall Block, MD, Phoenix, AZ; Vito Campese, MD, Los Angeles, CA; Kent Carpenter, MD, Charlotte, NC; Leon Davis, MD, Montgomery, AL; Samuel Engel, MD, Norwalk, CT; Norman Fishman, MD, Chesterfield, MO; David Fitz-Patrick, MD, Honolulu, HI; Ruth Ann Fitzpatrick, MD, Upland, PA; Linda M. Gaudiani, MD, Greenbrae, CA; Charles B. Herring, MD, Wilmington, NC; Kenneth S. Hershon, MD, New Hyde Park, NY; William A. Kaye, MD, West Palm Beach, FL; Rashid A. Khairi, MD, Indianapolis, IN; Mark S. Kipnes, MD, San Antonio, TX; M. James Lenhard, MD, FACE, Newark, DE; Sam Lerman, MD, FACE, Hollywood, FL; Andrew J. Lewin, MD, Los Angeles, CA; Thomas W. Littlejohn III, MD, Winston-Salem, NC; Luigi F. Meneghini, MD, Miami, FL; Kenneth Schaefer, MD, Peoria, AZ; Allen Sussman, MD, Renton, WA; Ruenrudee Suwannasri, MD, St Louis, MO; Barbara Troupin, MD, San Diego, CA; Richard L. Weinstein, MD, Walnut Creek, CA, USA.