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Safety and Efficacy of Long-Term Co-Administration of Fenofibrate and Ezetimibe in Patients With Mixed Hyperlipidemia

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OBJECTIVES This study sought to determine the long-term safety and efficacy of co-administered fenofibrate (FENO) and ezetimibe (EZE) in patients with mixed hyperlipidemia.

BACKGROUND Both EZE and FENO offer complementary benefits to the lipid profile of patients with mixed hyperlipidemia.

METHODS After completing the 12-week randomized, double-blind base study that compared EZE 10 mg, FENO 160 mg, FENO 160 mg plus EZE 10 mg, and placebo in patients with mixed hyperlipidemia, patients continued into a double-blind, 48-week extension phase. Those patients in the FENO plus EZE and FENO groups continued on their respective base study treatment, and patients in the EZE and placebo groups were switched to FENO plus EZE and FENO, respectively.

RESULTS Of the 587 patients who completed the base study, 576 continued into the extension study ($n = 340$ in FENO plus EZE and $n = 236$ in FENO). The FENO plus EZE produced significantly greater reductions in low-density lipoprotein-cholesterol compared with FENO (−22% vs. −9%, respectively; $p < 0.001$). There were also significantly greater improvements in triglycerides, high-density lipoprotein cholesterol (HDL-C), total cholesterol, non–HDL-C, and apolipoprotein B with FENO plus EZE compared with FENO. Changes in apolipoprotein A-I and high-sensitivity C-reactive protein were similar between groups. Overall, FENO plus EZE was well tolerated during the extension study. The proportion of patients with consecutive elevations of alanine aminotransferase/aspartate aminotransferase ≥3 times upper limit of normal were similar between the FENO plus EZE (1.2%) and FENO (1.7%) groups. No cases of creatine phosphokinase elevations ≥10 times upper limit of normal or myopathy were observed in either group.

CONCLUSIONS Long-term, 48-week co-administration of FENO plus EZE was well tolerated and more efficacious than FENO in patients with mixed hyperlipidemia. (J Am Coll Cardiol 2006;47: 1584–7) © 2006 by the American College of Cardiology Foundation

The cholesterol absorption inhibitor ezetimibe (EZE) effectively lowers low-density lipoprotein cholesterol (LDL-C) by inhibiting the intestinal absorption of dietary and biliary cholesterol without affecting absorption of triglycerides or fat-soluble vitamins (1). Fibrates have favorable effects on triglycerides, high-density lipoprotein cholesterol (HDL-C), and LDL particle size (2). Recently in patients with mixed hyperlipidemia, 12-week co-administration of fenofibrate (FENO) plus EZE was well tolerated and produced significant improvements in lipid profiles compared with either FENO or EZE alone (3). Thus, in the short term, the co-administration of FENO plus EZE, through their complementary mechanisms of action, provides another therapeutic option for treating patients with mixed hyperlipidemia. The present study examined the long-term safety and efficacy of co-administered FENO plus EZE in patients with mixed hyperlipidemia over 48 weeks.

METHODS

Study design. Study design and results for the 12-week base study were published previously (3). For the base study, mixed hyperlipidemia was defined as a baseline LDL-C level of 130 to 220 mg/dl inclusive (100 to 180 mg/dl for patients with type

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Abbreviations and Acronyms

AE = adverse experience
ALT = alanine aminotransferase
AST = aspartate aminotransferase
CPK = creatine phosphokinase
EZE = ezetimibe
FENO = fenofibrate
HDL-C = high-density lipoprotein-cholesterol
hs-CRP = high-sensitivity C-reactive protein
LDL-C = low-density lipoprotein-cholesterol
TC = total cholesterol
ULN = upper limit of normal

2 diabetes) and a baseline triglyceride level of 200 to 500 mg/dl inclusive. After completing the 12-week base study, which compared EZE 10 mg, FENO 160 mg, FENO 160 mg plus EZE 10 mg, and placebo, patients continued into the 48-week double-blind extension study unless there was a condition that would interfere with the patient's ability to participate. Patients in the FENO plus EZE and FENO groups continued on their respective base study treatment, and those in the EZE and placebo groups were switched to FENO plus EZE and FENO, respectively. All patients were instructed to continue following the National Cholesterol Education Program (NCEP) Step I or comparable diet throughout the study. Follow-up visits were conducted at weeks 6, 12, 24, 36, and 48 of the extension study.

Safety assessment. Safety and tolerability were evaluated by adverse experiences (AEs), laboratory measurements (specifically alanine aminotransferase [ALT], aspartate aminotransferase [AST], and creatine phosphokinase [CPK] levels), and physical examination findings for only the 48-week extension study. Results were not combined with the 12-week base study. The study investigators assessed the potential relationship of all AEs to drug treatment while blinded to treatment assignment (Appendix). The AEs of clinical interest that resulted in discontinuation included: consecutive, unexplained elevations of CPK ≥10 times the upper limit of normal (ULN) or ALT/AST ≥3 times ULN; myopathy (muscle symptoms accompanied by CPK ≥10 times ULN); persistent elevations in serum creatinine >1.8 mg/dl or >30% above the baseline value from base study for patients with baseline creatinine levels >1.0 mg/dl; persistent elevations in creatinine >50% above the baseline value of base study for patients with baseline creatinine levels ≤1.0 mg/dl. Beginning at week 12 of the extension, if the LDL-C concentration was >15 mg/dl above the patient's NCEP Adult Treatment Panel III risk-specific LDL-C target as established at baseline, the patient was discontinued for lack of efficacy.

Efficacy assessments. The primary efficacy variable was percent change in LDL-C from baseline of the base study to study end point in the extension. Secondary efficacy end points included percent change from baseline to study end point in total cholesterol (TC), HDL-C, triglycerides, non–HDL-C, apolipoprotein B, apolipoprotein A-I, and high-sensitivity C-reactive protein (hs-CRP).

Laboratory measurements. A central laboratory performed all clinical laboratory analyses of safety and efficacy variables as described previously (3).

Statistical analyses. Inferential testing was limited to a pre-specified number of safety parameters, including myopathy, persistent ALT and/or AST elevations ≥3 times ULN, persistent CPK elevations ≥10 times ULN, planned or performed cholecystectomy (pooled end point including performed cholecystectomy or diagnosed cholecystitis, cholangitis, or cholelithiasis), and serum creatinine ≥1.5 mg/dl. Proportions of patients were compared between treatments with the Fisher exact test. Given the differences in average duration of exposure to active therapy between groups in the present study, examining the crude incidence rates may be misleading. Therefore, adjusted incidence rates per 1,000 patient-years were calculated for the pre-specified safety parameters listed above based on cumulative patient-years available for each treatment (i.e., adjusted incidence rate = number of events/exposure [expressed in 1,000 patient-years]). The efficacy analysis was an all-patients-treated approach with an end point defined as percent change from baseline to the average of all measurements available throughout extension. A parametric analysis of covariance (ANCOVA) model with terms for treatment and baseline triglyceride values was used to compare each efficacy variable between treatment groups. Because triglycerides and hs-CRP were not normally distributed, a non-parametric ANCOVA was used to assess between-group differences. Least-squares mean or median differences between treatment groups with corresponding 95% CIs were summarized.

Table 1. Baseline* Summary of Patient Demographics, Lipid Parameters, and hs-CRP

Study Variable	FENO (n = 236)	FENO + EZE (n = 340)
Age, yrs	52.9 (10.4)	54.1 (9.5)
Patients ≥65 yrs, n (%)	34 (14.4)	53 (15.6)
Gender, n (%)		
Male	139 (58.9)	192 (56.5)
Female	97 (41.1)	148 (43.5)
Body mass index	29.3 (4.4)	29.5 (4.6)
Type 2 diabetes, n (%)	33 (14.0)	60 (17.6)
Metabolic syndrome, n (%)	138 (59.0)	190 (55.9)
LDL-C, mg/dl	164.1 (27.9)	159.7 (27.7)
HDL-C, mg/dl	41.9 (9.5)	41.7 (8.8)
Triglycerides,† mg/dl	277.0 (86.5)	275.0 (101.6)
TC, mg/dl	264.4 (33.5)	259.9 (32.2)
Non–HDL-C, mg/dl	222.6 (31.8)	218.2 (31.0)
Apo B, mg/dl	171.3 (25.0)	167.8 (24.5)
Apo A-I, mg/dl	151.0 (28.5)	149.1 (25.7)
hs-CRP,† mg/l	3.0 (4.0)	2.5 (3.1)

*Baseline values as recorded in the base study (reference 3). Data are expressed as mean (standard deviation [SD]) or frequency unless otherwise indicated. †Values are median (robust SD for median).

Apo = apolipoprotein; hs-CRP = high-sensitivity C-reactive protein; EZE = ezetimibe; FENO = fenofibrate; HDL-C = high-density lipoprotein-cholesterol; hs-CRP = high-sensitivity C-reactive protein; LDL-C = low-density lipoprotein-cholesterol; TC = total cholesterol.

Table 2. Disposition of Patients Entered Into the 48-Week Extension Study

	FENO (n = 236)	FENO + EZE (n = 340)
Patient completed	87 (36.9)	230 (67.6)
Patient discontinued	149 (63.1)	110 (32.4)
Due to lack of efficacy*	120 (50.8)	82 (24.1)
Due to clinical adverse experience	7 (3.0)	5 (1.5)
Due to laboratory adverse experience	7 (3.0)	10 (2.9)
Due to other reasons†	15 (6.4)	13 (3.8)

Data are expressed as n (%). *Lack of efficacy was defined as LDL-C >15 mg/dl above NCEP ATP III risk-specific LDL-C goal at week 12 or later during the extension. †Other reasons include patients who withdrew consent, moved, deviated from protocol, or were lost to follow-up.

NCEP ATP III = U.S. National Cholesterol Education Program Adult Treatment Panel III; other abbreviations as in Table 1.

RESULTS

Of the 587 patients who completed the 12-week base study, 576 patients continued into the 48-week extension study (N = 340 for FENO plus EZE and N = 236 for FENO; Table 1). During the extension phase, a greater proportion of participants in the FENO group discontinued treatment compared with those in the FENO plus EZE group, primarily because of the failure to meet the LDL-C efficacy criterion (Table 2). Thus, average exposure to study treatment was less in the FENO group (212.3 days) compared with the FENO plus EZE group (271.3 days).

The FENO plus EZE resulted in significantly greater percent reductions from baseline to average extension end point in LDL-C, TC, triglycerides, non–HDL-C, and apolipoprotein B compared with FENO (Table 3). The percent increase in HDL-C, but not apolipoprotein A-I, was significantly greater with FENO plus EZE versus FENO. Reductions in median hs-CRP levels were not different between treatments.

The FENO plus EZE was well tolerated during the 48-week extension study. Both groups were similar with regard to incidence of treatment-related AEs and discontinuations because of treatment-related AEs, respectively (Table 4). Five patients had treatment-related serious AEs in the extension study: three in the FENO group (angioneurotic edema, pancreatitis, polyarthropathy) and two in the FENO plus EZE group (cholangitis, cholecystitis). A patient on FENO plus EZE died in the extension study from a cerebral hemorrhage that the investigator reported was definitely not caused by study treatment.

Table 4. Safety and Tolerability Summary for 48-Week Extension Study

Number (%) of Patients With	FENO (n = 236)	FENO + EZE (n = 340)
One or more AEs	145 (61.4)	229 (67.4)
Treatment-related AEs	38 (16.1)	47 (13.8)
SAEs	14 (5.9)	23 (6.8)
Treatment-related SAEs	3 (1.3)	2 (0.6)
Deaths	0 (0.0)	1 (0.3)
Discontinuations due to AEs	14 (5.9)	15 (4.4)
Discontinuations due to treatment-related AEs	13 (5.5)	13 (3.8)
Discontinuations due to SAEs	2 (0.9)	3 (0.8)
Discontinuations due to treatment-related SAEs	2 (0.9)	2 (0.6)
AEs of interest		
ALT and/or AST ≥3 times ULN consecutive	4/235 (1.7)	4/337 (1.2)
CPK ≥10 times ULN	0/235	0/337
Myopathy	0	0
Planned or performed cholecystectomy	1 (0.4)	4 (1.2)
Serum creatinine ≥1.5 mg/dl	21/235 (8.9)	36/338 (10.7)

AEs = adverse experiences; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CPK = creatine phosphokinase; SAEs = serious adverse experiences; ULN = upper limit of normal; other abbreviations as in Table 1.

No patient experienced CPK elevations ≥10 times ULN or myopathy. The proportion of patients with consecutive elevations of ALT and/or AST ≥3 times ULN was low and similar between treatment groups (Table 4). The proportion of patients with planned or performed cholecystectomy was not significantly different between treatments (Table 4). To account for differences in exposure to treatments, rates of planned or performed cholecystectomy were adjusted for exposure (expressed in 1,000 patient-years) and were still not signifi-

Table 3. Comparison of the Lipid and hs-CRP Effects of FENO and FENO Plus EZE With Regard to Percent Change From Baseline Values in the Base Study* to the End Point Values in the Extension Study

	Extension Study		
Parameter	FENO (n = 235)	FENO + EZE (n = 337)	p Value
LDL-C	−8.6 (−10.6 to −6.5)	−22.0 (−23.7 to −20.3)	<0.001
HDL-C	17.8 (15.9 to 19.8)	20.9 (19.2 to 22.5)	0.02
Triglycerides†	−41.8 (−44.9 to −38.7)	−46.0 (−48.2 to −43.8)	0.002
TC	−13.6 (−15.0 to −12.1)	−23.2 (−24.4 to −22.0)	<0.001
Non–HDL-C	−19.4 (−21.2 to −17.6)	−31.6 (−33.1 to −30.1)	<0.001
Apo B	−16.2 (−18.5 to −13.9)	−25.2 (−27.1 to −23.3)	<0.001
Apo A-I	7.8 (5.5 to 10.1)	10.1 (8.2 to 12.0)	0.12
hs-CRP†	−21.1 (−29.0 to −13.1)	−25.3 (−33.1 to −17.5)	0.46

*Baseline values were recorded at the beginning of the base study (reference 3); data are expressed as least-squares mean percent change (95% CI). †Median percent change (95% CI); for apolipoproteins B and A-I, n = 217 for FENO and n = 321 for FENO + EZE; for hs-CRP, n = 221 for FENO and n = 326 for FENO + EZE.

Abbreviations as in Table 1.

cantly different between FENO plus EZE and FENO groups (15.9 per 1,000 patient-years [95% CI 4.3 to 40.7] vs. 7.3 per 1,000 patient-years [95% CI 0.2 to 40.6], respectively). The proportion of patients with serum creatinine ≥1.5 mg/dl was not significantly different between groups (Table 4). The results of all other measures of safety did not suggest any clinically meaningful differences between treatment groups.

DISCUSSION

Co-administration of FENO plus EZE provided superior lipid-altering effects compared with FENO during the 48-week extension study. In the present study, FENO plus EZE produced an incremental LDL-C reduction of 13.5% compared with FENO. This was consistent with the incremental reduction observed for FENO plus EZE versus FENO in the base study (3) and also that observed with EZE plus statin versus statin monotherapy (4). Improvements in TC, non–HDL-C, TG, HDL-C, and apolipoprotein B were also greater in the co-administration group. The results from the extension study were generally consistent with those from the base study, and the small differences in efficacy between studies (TG and HDL-C) may be because the extension study was not randomly assigned and was imbalanced.

The safety profile for long-term co-administration of FENO plus EZE was similar to that of FENO in this study. Groups did dramatically differ in the overall rate of discontinuations, which was mainly attributable to an imbalance in the number of patients who discontinued because of the protocol-specified lack of LDL-C efficacy criterion used in the extension, which was more than double in the FENO group versus the FENO plus EZE group. This imbalance was related to the greater lipid efficacy of FENO plus EZE compared with FENO. As a result of this difference, patients in the FENO plus EZE group averaged approximately 8.5 more weeks of treatment exposure than those in the FENO group.

No clinically important elevations in CPK or cases of myopathy were observed in either treatment group during the extension. The incidence of elevated ALT and/or AST levels ≥3 times ULN was low and was not different between treatment groups. Fenofibrate increases cholesterol excretion into the bile, which may lead to cholelithiasis (5). Ezetimibe has inconsistent effects on biliary cholesterol in animal models (6). There seems, however, to be no evidence, based on short-term clinical study data available to date, that EZE monotherapy increases the risk of gallstones in patients with primary hypercholesterolemia (1,7,8). In this study, most randomized patients had numerous risk factors, including hyperlipidemia, obesity, age, female gender, and type 2 diabetes, that would predispose them to an increased risk for gallstones (9). Patients were excluded from the present study for a history of gallbladder disease and not previously having been treated with cholecystectomy. The proportion of patients with performed or planned cholecystectomy was not significantly different between groups when expressed as either the proportion of patients with events or the incidence rates adjusted for group differences in patient exposure to treatments. This study was, however, not designed to assess infrequently occurring AEs such as cholecystectomy, and only a much larger, longer-term study could conclusively assess these infrequent biliary AEs.

Although modest increases in the incidence of serum creatinine level ≥1.5 mg/dl were found in both treatment groups, the proportion of patients with these elevated creatinine levels did not differ between groups. The increase in both groups might have been anticipated, because FENO is known to increase creatinine levels (5). The overall safety profile of co-administered FENO plus EZE in this longer-term 48-week study was consistent with the findings in the shorter 12-week base study (3). Furthermore, considering the greater mean duration of treatment exposure for patients in the FENO plus EZE group compared with those in the FENO group in this study, the comparable safety findings between treatment groups support co-administration of FENO plus EZE as a well-tolerated therapy.

In summary, the long-term FENO plus EZE therapy was a more effective treatment option than FENO, and was well-tolerated for up to 48 weeks of treatment for patients with mixed hyperlipidemia in this study.

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REFERENCES

1. 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;24:729–41.
2. Fazio S, Linton MF. The role of fibrates in managing hyperlipidemia: mechanisms of action and clinical efficacy. Curr Atheroscler Rep 2004; 6:148–57.
3. Farnier M, Freeman M, Macdonell G, et al. Efficacy and safety of the co-administration of ezetimibe with fenofibrate in patients with mixed hyperlipidaemia. Eur Heart J 2005;26:897–905.
4. Davidson MH, Ballantyne CM, Kerzner B, et al. Efficacy and safety of ezetimibe co-administered with statins: randomised, placebo-controlled, blinded experience in 2382 patients with primary hypercholesterolemia. Int J Clin Pract 2004;58:746–55.
5. Product Information: TRICOR (fenofibrate tablets). North Chicago, IL: Abbott Laboratories, February 2003.
6. Product Information: ZETIA (ezetimibe). North Wales, PA: Merck/Schering-Plough Pharmaceuticals, March 2005.
7. Dujovne CA, Ettinger MP, McNeer JF, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002;90: 1092–7.
8. Bays HE, Moore PB, Drehobl MA, et al. Effectiveness and tolerability of ezetimibe in patients with primary hypercholesterolemia: pooled analysis of two phase II studies. Clin Ther 2001;23:1209–30.
9. Sama C, Labate AM, Taroni F, Barbara L. Epidemiology and natural history of gallstone disease. Semin Liver Dis 1990;10:149–58.

APPENDIX

For a list of the extension study investigators, please see the online version of this article.