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Lipoprotein effects of combined ezetimibe and colesevelam hydrochloride versus ezetimibe alone in hypercholesterolemic subjects: a pilot study

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Abstract

Two drug classes act in the intestine to lower cholesterol. Ezetimibe inhibits cholesterol absorption, whereas bile acid–binding resins enhance cholesterol excretion via enhanced conversion to bile acids. Combining these 2 classes may be beneficial, but cholestyramine binds ezetimibe, and the combined effect of colesevelam hydrochloride and ezetimibe was little studied. The aim of the study was to determine if adding colesevelam HCl to ezetimibe provides additional lowering of low-density lipoprotein– and apolipoprotein B–containing lipoproteins or alters ezetimibe levels. Twenty subjects with low-density lipoprotein cholesterol (LDL-C) levels of 130 mg/dL or higher were enrolled and taught a National Cholesterol Education Program Step I diet. At a second baseline visit, lipoproteins were measured and subjects were randomly allocated to (1) ezetimibe 10 mg daily with placebo colesevelam HCl twice daily (E) or (2) ezetimibe 10 mg daily with 1.875 g colesevelam HCl twice daily (E + C). Lipoproteins were measured 6 and 12 weeks after initiating treatment. Baseline characteristics (mean ± SD) were statistically indistinguishable in E vs E + C: LDL-C (mg/dL), 167 ± 26 and 158 ± 27; triglyceride, 134 ± 75 and 140 ± 67; and BMI, 29.4 ± 4.9 and 27.8 ± 6.6 kg/m^2, respectively. Percent changes after 12 weeks in E vs E + C were as follows: LDL-C, −24 ± 12 vs −30 ± 11 (P = .102); triglyceride, −19 ± 34 vs 36 ± 85 (P = .054; at 6 weeks, P = .009); total cholesterol, −19 ± 9 vs −15 ± 8 (P = .50); non–high-density lipoprotein cholesterol, −25 ± 10 vs −21 ± 11 (P = .70); apolipoprotein B, −31 ± 14 vs −22 ± 14 (P = .41). Plasma ezetimibe levels at 12 weeks were 21% lower in E + C vs E, a nonsignificant difference (P = .54). In conclusion, in the short term, colesevelam HCl may not consistently add cholesterol-lowering benefit to ezetimibe. This observation requires confirmation.

1. Introduction

The intestine is an important organ in cholesterol regulation and is an important target for dietary and drug management of hypercholesterolemia. Two medication classes act in the intestine, the bile acid–binding resins and the cholesterol absorption inhibitors.

Bile acid–binding resins enhance cholesterol excretion by inhibiting bile acid reabsorption and increasing cholesterol conversion into bile acids [1]. The older bile acid–binding resins have limited use because of their bulk and nonspecific binding of other drugs. Nonetheless, cholestyramine diminished coronary artery disease incidence on the order of 20% in a high–cardiovascular disease risk, primary prevention setting [2,3]. The newer resin, colesevelam hydrochloride (WelChol, Sankyo Pharma Inc, Parsippany, NJ), has greater affinity for bile acids, requires only one tenth the dose of the older resins, yields better low-density lipoprotein lowering, and has less nonspecific binding of concomitant medications (Fig. 1).

Ezetimibe is the first of a new class of cholesterol absorption inhibitors (Fig. 1). Low-density lipoprotein levels are lowered an average of 18% [4-6]. Ezetimibe acts by inhibiting the intestinal cholesterol transporter, NPC1L1 [7]. This transporter resembles a lysosomal cholesterol transport protein defective in Niemann-Pick disease, a childhood disorder of lysosomal cholesterol storage [8].

Previous studies have shown that cholestyramine, the original bile acid–binding resin, binds ezetimibe and decreases its absorption [9,10]. As a result, ezetimibe is recommended to be taken at a different time than bile acid–binding resin [10]. However, binding of ezetimibe by colesevelam HCl has not been studied. The effect of

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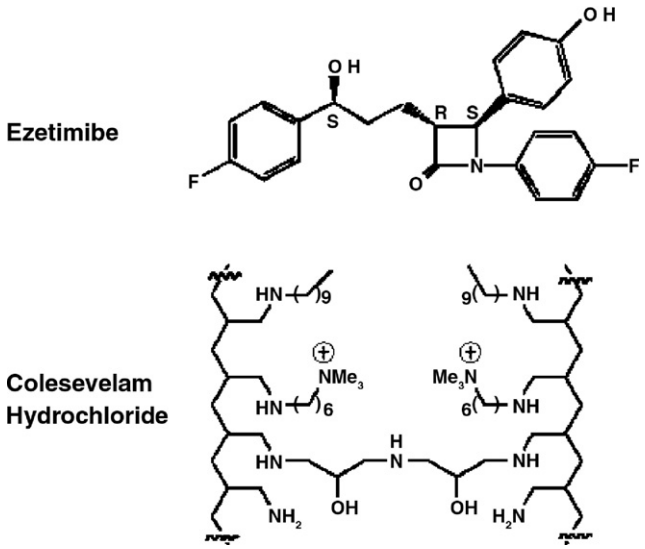

Fig. 1. Structural formulas for ezetimibe and colesevelam.

combined colesevelam HCl–ezetimibe administration has not been extensively studied, but a beneficial effect of combined drug has been observed in an open-label, crossover design study and in a retrospective lipid clinic chart review [11,12]. The present study addresses the questions: (*a*) does ezetimibe given with colesevelam HCl lower low-density lipoprotein cholesterol (LDL-C) more than ezetimibe given alone and (*b*) does colesevelam administration reduce plasma ezetimibe levels?

2. Methods

2.1. Study subjects

Study participants were recruited from public advertising and clinic records. The study protocol and advertising were reviewed and approved by the University of Washington Human Subjects Review Committee. Men and women aged 21 to 80 years were eligible with fasting LDL-C levels equal to or exceeding 130 mg/dL [13] at the initial screening visit. Eligible fasting plasma triglyceride levels were less than 350 mg/dL at the initial screening visit.

Subjects were ineligible if they had a clinical diagnosis of diabetes or had a fasting plasma glucose level of more than 125 mg/dL at the initial screening visit. Also ineligible were subjects who had coronary heart disease, congestive heart failure, blood pressure of more than 150/90, untreated hyper- or hypothyroidism, nephrotic syndrome or proteinuria on dipstick, taking lipid-altering drugs in the past 4 weeks, any concurrent illness that would prevent successful study participation, recent history of drug or alcohol abuse, swallowing or intestinal motility disorders, cancer diagnosis within 5 years except nonmelanoma skin cancer, unstable or cyclic hormone replacement therapy, pregnancy or lactation, or prior study participation within 30 days.

2.2. Study design

The study was double blind, randomized, and parallel in design consisting of 4 study visits over a 4-week screening period and a 12-week treatment interval. In addition, one subject was crossed over in a double-blind manner, receiving ezetimibe, colesevelam HCl placebo for 6 weeks, then ezetimibe, colesevelam HCl for 6 weeks. This subject is included in the table of characteristics of subjects studied, in the results of subjects at 6 weeks in the ezetimibe group, and separately in the narrative results.

Initial eligibility was established by a telephone contact with the study coordinator. If eligible, the subject was sent a consent form to review and given an appointment for a clinic visit after an overnight fast.

At visit 1, the consent form was explained to the subject and the questions were answered. After signing the consent form, vital signs were obtained including body weight, and a brief physical examination was also performed to rule out exclusionary disease states. Blood was drawn for a Cholestech (Cholestech, Haywood, CA) estimation of cholesterol, triglyceride, high-density lipoprotein cholesterol (HDL-C), calculated LDL-C, and glucose. A urinalysis was done to rule out urinary tract infection and clinically significant proteinuria. A baseline aspartate aminotransferase (AST) was also obtained. A diet history was obtained, and subjects were counseled on a National Cholesterol Education Program Step I diet [14] and instructed to maintain this level of intake throughout the study.

At visit 2 (baseline), subjects had a derived lipoprotein quantification, a medication and symptoms review, and vital signs were again obtained. Adherence to the National Cholesterol Education Program Step I diet was reviewed. Subjects were randomly assigned to their medication using a predetermined randomization code. Subjects were given a 6-week supply of ezetimibe 10 mg once daily at bedtime (Merck-Schering Plough, North Wales, PA) and colesevelam HCl placebo (3 capsules twice per day with meals) (Sankyo Pharma, Parsippany, NJ) or ezetimibe 10 mg once daily at bedtime and 0.625-g tablets of colesevelam HCl (3 tablets twice per day with meals).

At visit 3 (week 6), subjects returned for a repeat derived lipoprotein quantification, serum AST measurement, recording of vital signs and body weight, review of Step I diet, and medication use and symptom review. Returned medication was counted, and adherence to the assigned medication was calculated as a percentage of the medication dispensed. Then, the second 6-week supply of medication was provided.

At visit 4 (week 12), all of the procedures and measurements were repeated as at visit 3.

2.3. Measurements

Eligibility lipoprotein lipid and glucose measurements were performed at the first visit on the Cholestech LDX Lipid Analyzer using reagent-impregnated pads enclosed in

Table 1
Characteristics of subjects at visit 2

	Ezetimibe	Ezetimibe + colesevelam HCl	*P*
n	10	10	
Total TG (mg/dL)	134 ± 75	140 ± 67	.762
Total C (mg/dL)	254 ± 34	238 ± 33	.290
LDL-C (mg/dL)	167 ± 26	158 ± 27	.290
Non–HDL-C (mg/dL)	194 ± 31	186 ± 37	.677
ApoB (mg/dL)	125 ± 25	121 ± 19	.691
HDL-C (mg/dL)	61 ± 18	52 ± 15	.384
AST (mg/dL)	24.7 ± 3.7	25.0 ± 8.2	.519
Blood pressure, systolic (mm Hg)	115 ± 12	118 ± 18	.623
Blood pressure, diastolic (mm Hg)	72 ± 9	72 ± 7	.731
Weight (kg)	81 ± 13	82 ± 20	1.000
Body mass index (kg/m^2)	29.4 ± 4.9	27.8 ± 6.6	.450
Age (y)	54.6 ± 9.4	57.1 ± 9.1	.495
Men/women	4/6	6/4	

TG indicates triglyceride; C, cholesterol.

a cassette and quantification by reflectance photometry after a 4-minute incubation period. Subsequent lipoprotein measurements were performed in the laboratory of the Northwest Lipid Research Clinic using enzymatic methods for triglyceride and cholesterol and dextran sulfate precipitation of apolipoprotein B (apo B)–containing lipoproteins to permit HDL-C measurement on the supernatant [15]. Lipid measurements were performed on a Hitachi 704 analyzer (Roche Diagnostics, Indianapolis, IN). Low-density lipoprotein cholesterol was calculated by the Friedewald algorithm, which approximates but does not exactly correspond to the direct measurement of LDL by ultracentrifugation [16,17]. Serum AST and apoB measurements were performed in the Department of Laboratory Medicine at the University of Washington (Seattle, WA). Plasma ezetimibe measurements were performed by PPD Development (Richmond, VA) through the assistance of Dr T Kosoglou and Robert P. Clement, PhD, Schering-Plough Research Institute, Kenilworth, NJ. The assay used a liquid chromatography–tandem mass spectrometry method performed before and after enzymatic hydrolysis of the glucuronidated ezetimibe to measure free and total ezetimibe. Glucuronidated ezetimibe was calculated by difference. Extra serum was saved at −70°C for subsequent analyses.

2.4. Statistics

A randomization code was created using a random-number generator. Data were entered into a Microsoft Access database (Microsoft, Redmond, WA). Summary statistics are expressed as means and SDs. Statistical comparisons were performed comparing changes from baseline to weeks 6 and 12 using the Mann-Whitney nonparametric test as the normality of the distributions in this small sample could not be assured. As a practical matter, the conclusions were the same by parametric and nonparametric methods.

3. Results

Baseline characteristics of subjects assigned to ezetimibe plus placebo (E) or ezetimibe plus colesevelam HCl (E + C) are shown in Table 1. Mean body weights were nearly identical in the 2 groups at 81 and 82 kg. Mean body mass indexes were similar and in the overweight range at 29.4 and 27.8 kg/m^2. Mean blood pressures were very similar at 115/72 and 118/72 in the E and E + C groups, respectively. Mean AST levels (visit 1) were 25 U/L in both groups (upper limit of normal, 44 U/L). No glucose value exceeded 110 mg/dL at the visit 1 screen.

Table 2
Changes in lipoproteins from baseline to weeks 6 and 12

n	Ezetimibe (E)		Ezetimibe + colesevelam HCl (E + C)		E vs E + C	
	Baseline to		Baseline to		*P*	
	Week 6	Week 12	Week 6	Week 12	Week 6	Week 12
	9	8	9	9		
(A) mg/dL						
TG	−29 ± 45	−40 ± 57	57 ± 69	42 ± 102	.005	.123
Total C	−43 ± 19	−50 ± 29	−29 ± 20	−34 ± 21	.171	.194
LDL-C	−36 ± 17	−41 ± 24	−41 ± 16	−45 ± 15	.452	.413
Non–HDL-C	−42 ± 17	−49 ± 21	−30 ± 22	−37 ± 21	.157	.176
ApoB	−22 ± 12	−32 ± 13	−16 ±15	−22 ± 14	.536	.412
HDL-C	−0.4 ± 6.0	−0.4 ± 8.2	1.6 ± 5.0	2.4 ± 4.9	.689	.469
(B) %						
TG	−12 ± 31	−19 ± 34	53 ± 61	36 ± 85	.009	.054
Total C	−16 ± 6	−19 ± 9	−12 ± 7	−15 ± 8	.145	.501
LDL-C	−21 ± 8	−24 ± 12	−27 ± 9	−30 ± 11	.102	.102
Non–HDL-C	−22 ± 7	−25 ± 10	−16 ± 11	−21 ± 11	.310	.700
ApoB	−22 ± 13	−31 ± 14	−17 ±15	−22 ± 14	.691	.413
HDL-C	0.6 ± 9.0	0.9 ± 12	3.0 ± 10	5.0 ± 10	.566	.413
(C) Drug adherence (%)						
Ezetimibe	96 ± 4	95 ± 5	95 ± 15	95 ± 10	.67	.67
Colesevelam HCl/placebo	90 ± 13	92 ± 5	92 ± 15	91 ± 11	.44	.54

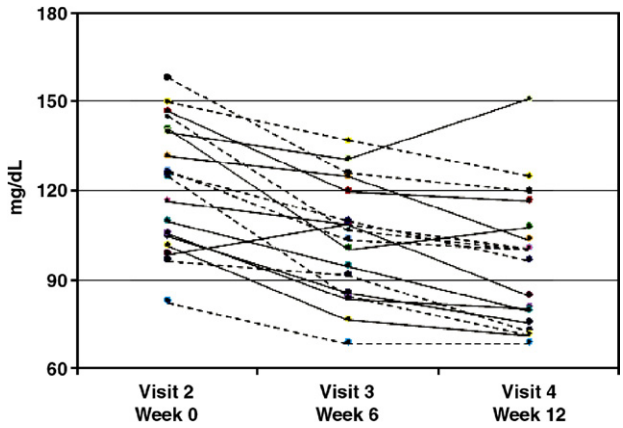

Fig. 2. Plots of individual data points for plasma apoB of subjects assigned to ezetimibe (dashed lines) or ezetimibe and colesevelam HCL (solid lines) at baseline and after 6 and 12 weeks of treatment.

Mean baseline (visit 2) lipid measurements were also statistically indistinguishable. In E and E + C, respectively (mg/dL), mean triglyceride levels were 134 and 140, LDL-C 167 and 158, non–HDL-C 194 and 186, and HDL-C 61 and 52.

Of the subjects participating in the study, 24 were screened, 20 were randomized and 2 dropped out, one from each of the assigned groups. One subject dropped out of the combined medication group because of stomach upset, nausea, and a rash over 3 days of medication taking. A second patient in the ezetimibe only group lost interest and failed to take any significant amount of medication. One subject was crossed over from regimen to the other at 6 weeks.

The lipoprotein effects of the 2 treatments from the visit 2 baseline to weeks 6 and 12 (mg/dL) are shown as absolute changes (Table 2A) and percent changes (Table 2B). Percentage of adherence to the study medication is shown in Table 2C.

Plasma triglyceride levels at weeks 6 and 12 decreased 29 and 40 mg/dL from baseline in E compared to an increase of 57 and 42 mg/dL in E + C ($P < .01$ at week 6). Corresponding percent changes were 12% and 19% below baseline in E and 53 and 36% above baseline in E + C.

Low-density lipoprotein cholesterol reductions were 36 and 41 mg/dL from baseline in E and 41 and 45 mg/dL in E + C. Corresponding percentage of reductions were 21% and 24% in E and 27% and 30% in E + C. The percentage of reduction in E + C was borderline greater than E at both 6 and 12 weeks ($P = .102$ in both instances) (Table 2B).

Total cholesterol levels in E decreased 43 and 50 mg/dL at weeks 6 and 12, respectively, compared to 29 and 34 mg/dL in E + C. Respective percentage reductions were 16% and 19% in E and 12% and 15% in E + C. Corresponding non–HDL-C reductions were 42 and 49 mg/dL in E and 30 and 37 mg/dL in E + C, and percentage of reductions were 22% and 25% in E and 16% and 21% in E + C. Corresponding reductions in apoB levels were 22 and 32 mg/dL in E and 16 and 22 mg/dL in the E + C group, and percentage of reductions were 22% and 31% in E and 17% and 22% in E + C. None of the reductions in total-C, non–HDL-C, or apoB were statistically different between E and E + C at 6 or 12 weeks. The extent of overlapping for apoB-containing lipoproteins in the E and E + C groups is illustrated by measurements of apoB for each individual shown in Fig. 2. No differentiating trend between the 2 groups is apparent.

Mean HDL-C levels decreased by 0.4 mg/dL from baseline in E at both weeks 6 and 12, whereas increasing 1.6 and 2.4 mg/dL in E + C at weeks 6 and 12. The differences between E and E + C were not significant at week 6 ($P = .69$) or week 12 ($P = .47$). Percentage-wise, HDL-C increased from baseline 0.6% and 0.9% in E and 3.0% and 5.0% in E + C at 6 and 12 weeks, respectively, again not significantly different between E and E + C.

The one subject who was crossed over at 6 weeks received ezetimibe first and then combination medication in the second 6-week period. Low-density lipoprotein cholesterol levels at baseline, and 6 and 12 weeks were 156, 120, and 105 mg/dL, representing percentage reductions of 23% and 33%, respectively. Plasma triglyceride levels were low and changed little over the 3 visits: 45, 56, and 62 mg/dL. Corresponding total cholesterol levels declined similarly over the 4 visits: 222, 193, and 179 mg/dL, respectively. For the combined data analysis, this subject is treated as an ezetimibe-treated subject in Table 1 and the 6-week visit in Table 2.

Adherence to study medication in E at 6 and 12 weeks was 96% and 95% for ezetimibe and 90% and 92% for colesevelam HCl placebo. In E + C, adherence was 95% at both 6 and 12 weeks to ezetimibe and 92% and 91% at 6 and 12 weeks to colesevelam HCl.

Total, unconjugated, and conjugated levels of ezetimibe were measured to determine if plasma ezetimibe levels were reduced in association with colesevelam HCl administration (Table 3). Total plasma ezetimibe levels were 21.0% lower at 12 weeks in E + C compared to E, but not significantly ($P = .54$). A similar trend was observed at 6 weeks for total

Table 3
Ezetimibe levels during colesevelam HCl vs placebo treatment

	ng/mL ± SD (n)	
	Week 6	Week 12
Total		
E	46.9 ± 49.4 (9)	36.7 ± 19.5 (9)
E + C	35.5 ± 56.1 (9)	29.0 ± 15.8 (8)
P	.297[a]	.541
Unconjugated		
E	5.3 ± 6.8 (9)	4.0 ± 1.9 (9)
E + C	3.5 ± 2.9 (9)	3.6 ± 2.6 (8)
P	.546[a]	.606
Conjugated		
E	41.3 ± 42.8 (9)	32.7 ± 18.0 (9)
E + C	36.0 ± 54.3 (9)	25.4 ± 14.0 (8)
P	.387[a]	.423

[a] With outliers of more than 100 ng/mL eliminated at week 6, *P* values were 0.195, 0.505, and 0.541 for total, unconjugated, and conjugated ezetimibe levels, respectively, comparing ezetimibe + colesevelam HCl placebo (E) to ezetimibe + colesevelam HCl (E + C).

ezetimibe and at 6 and 12 weeks for the conjugated and unconjugated fractions of ezetimibe. None of the differences between E and E + C were statistically significant.

Because baseline or on-treatment plasma triglyceride levels may influence the response to resin treatment and potentially diminish cholesterol lowering, we examined the relationship of baseline triglyceride to the cholesterol reduction at week 12 in E + C (Fig. 3A). No consistent association between higher baseline triglyceride and lesser cholesterol decrease was observed. However, the one subject with the highest baseline triglyceride levels had a slight increase in total cholesterol level.

The association between triglyceride change and cholesterol change from baseline to week 12 was also examined (Fig. 3B). No association was seen between changes in triglyceride levels of less than 50mg/dL and the extent of cholesterol reduction. However, 2 subjects with triglyceride increments above 150 mg/dL appeared to have a lesser cholesterol reduction (Fig. 3B).

Serum AST levels are depicted in Fig. 4. Excepting one subject, there were no elevations above the reference range at weeks 6 and 12, and no value exceeded 39 U/L (upper limit of normal of 44 U/L). One subject had AST levels at baseline and 6 weeks of 28 and 33 U/L, but an elevation of 165 U/L at week 12 after a trip abroad. The AST measurement returned to 25 U/L 1 month later.

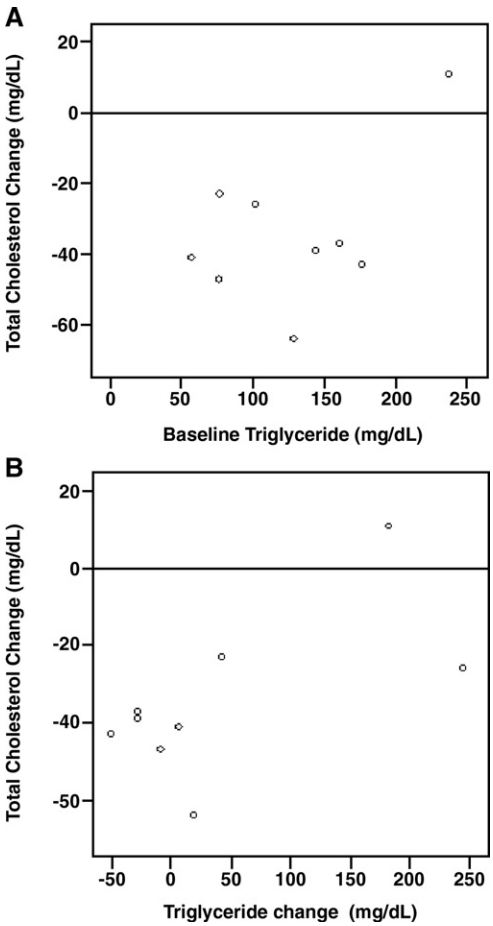

Fig. 3. Plots of the total cholesterol reduction of individual subjects in the ezetimibe plus colesevelam HCl group from baseline to 12 weeks vs the baseline triglyceride level (A) or the change in triglyceride level between baseline and week 12 (B).

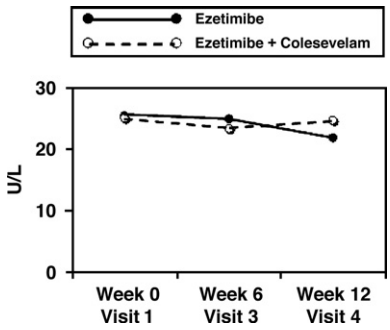

Fig. 4. Serum AST at baseline, week 6, and week 12 for the ezetimibe group (solid line) and ezetimibe–colesevelam HCl combined group (hatched line). Standard deviation values range from 4.0 to 8.3 U/L at weeks 6 and 12 of follow-up (see Table 1). No significant differences were detected between the 2 treatment groups.

4. Discussion

Both the bile acid–binding resins and the cholesterol absorption inhibitor ezetimibe can be used alone or with other agents such as statins or fibric acids to lower cholesterol levels [1,18-20]. In severe cases of hypercholesterolemia or in cases of statin intolerance, combined use of lipid-lowering drugs is necessary. One potentially beneficial combination is ezetimibe combined with a bile acid–binding resin.

The prototype bile acid–binding resin, cholestyramine, binds numerous drugs nonspecifically, including ezetimibe in vitro [9,21]. In vivo, ezetimibe bioavailability is reduced to 45% of control when cholestyramine is given 1 or 13 hours after ezetimibe administration. In addition, cholestyramine reduces enterohepatic recycling of ezetimibe, manifested by diminished plasma ezetimibe peaks after oral ezetimibe administration [21]. It is therefore recommended that ezetimibe be given 1 hour before or 4 hours after taking bile acid–binding resin [10].

Use of cholestyramine has been largely replaced by colesevelam HCl in the management of hypercholesterolemia. Colesevelam HCl is specifically constructed to fit the polar head group of bile acids [22]. The result is a bile acid–binding resin that lowers LDL-C at approximately one tenth the dosage of cholestyramine [1,22] and does not bind 6 concomitant medications, including digoxin [22]. These considerations suggest that colesevelam HCl could be combined with ezetimibe to manage hypercholesterolemia with less potential for concomitant binding of ezetimibe. This is the rationale for this investigation.

The results show a trend toward greater LDL-C lowering with E + C of 27 and 30% at 6 and 12 weeks of treatment

compared to 21% and 24% with E alone between the 2 groups ($P < .102$ at both weeks 6 and 12).

On the other hand, the reductions in total and non–HDL-C levels and apoB were slightly less in E + C compared to E owing to the triglyceride increase in E + C (see discussion below). Because the triglyceride elevation was less at 12 weeks than at 6 weeks, it is possible that the elevations might disappear with time. However, trends toward improving reductions in non-HDL and apoB levels from 6 to 12 weeks were similar in the E and E + C groups.

The present results indicate that the combination of E + C may not yield additional benefits in the short term, such as the 12-week duration of this study. On the other hand, additional benefit is not precluded in the short or long term, as seen in the one subject crossed over from E to E + C at 6 weeks. This subject experienced an additional LDL-C decrease of 15 mg/dL. A recent nonblinded study reported a similar result where LDL-C decreased 36 mg/dL in 6 subjects after colesevelam HCl was added to ezetimibe and 32 mg/dL in 4 subjects after ezetimibe was added to colesevelam HCl [11]. A retrospective chart review study also showed that ezetimibe lowered cholesterol 18% when added to a stable lipid-lowering regimen including colesevelam HCl [12]. Taken together, the results indicate that additional LDL-C lowering can be attained with the addition of colesevelam HCl to ezetimibe treatment in some subjects, but that it may not be consistent and may not extend to reductions in non–HDL-C or apoB levels.

The potential role of triglyceride elevations in combined E + C therapy requires mention. Elevation of plasma triglycerides is a known side effect of the bile acid–binding resin class [1,2]. The greater diversion of cholesterol into the bile acid pool prompts an increase in de novo cholesterol formation and with it an increase in hepatic triglyceride secretion in the form of very low-density lipoprotein. The result is an increase in plasma very low-density lipoprotein cholesterol as well as triglyceride levels, potentially offsetting the reduction in LDL-C. The triglyceride rise with colesevelam HCl added to ezetimibe in the present study is consistent with previous experience with resins alone [1,2], although the observed triglyceride rise is greater than the 5% to 10% observed in large clinical trials of colesevelam HCl [23-25]. Neither high baseline triglyceride levels nor triglyceride increases were consistent predictors of lesser cholesterol decrease in this limited study, although individual cases were suggestive (Fig. 3A and B). Further research is needed to determine if there is a link between triglyceride physiology and the cholesterol response to combined ezetimibe/colesevelam HCl.

Binding of ezetimibe by colesevelam HCl is a possible mechanism of impaired cholesterol lowering in combined therapy. Typically, nonspecific binding of concomitant drug administration is avoided by giving the drug 1 to 2 hours before or 4 hours after resin administration. However, this strategy might not work for ezetimibe. Ezetimibe is recycled through the enterohepatic circulation for at least 24 hours and would be potentially vulnerable to resin binding, regardless of the timing of the administration of colesevelam HCl. In this study, ezetimibe was given at bedtime, consistent with the recommendation for treatment with resin, 4 hours after the evening meal and about 8 hours before the morning meal. In any case, the reduction in ezetimibe levels with concomitant colesevelam HCl treatment was not statistically significant at 19.5% and was less than the 45% reduction seen with cholestyramine administration [9,18].

Apart from the unexpected triglyceride rise observed with the combined drug regimen, both medications were well tolerated and only one subject dropped out of the study for an apparent drug side effect. Minimal difficulty in maintaining adherence to the drug regimen was reported. Similarly, there was no undue rise in transaminase levels in either group attributable to the drug regimens.

The present study is limited by the number of subjects studied and by the lack of assurance that the subjects in the 2 groups might not differ in some respect. Further studies of longer duration and with larger numbers of subjects are needed to address these questions.

In conclusion, colesevelam HCl in combination with ezetimibe for 12 weeks was associated with a borderline lower LDL-C level compared to ezetimibe alone. However, the combined treatment was associated with an increase in triglyceride that was statistically significant, and no further reduction in total cholesterol, non–HDL-C, or apoB levels. The nonstatistically significant ~20% reduction in plasma levels of ezetimibe with combined therapy does not appear to be sufficient to explain the lack of additional cholesterol lowering. More studies are needed to determine if the results of this pilot study are generalizable and the conditions in which combination colesevelam HCl and ezetimibe therapy will be most successful. Among these conditions are simple hypercholesterolemia and the combined hyperlipidemias common in obesity and the metabolic syndrome [1,26,27].

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