Clin. Cardiol. 24, 467–474 (2001)

Low-Dose Combination Therapy with Colesevelam Hydrochloride and Lovastatin Effectively Decreases Low-Density Lipoprotein Cholesterol in Patients with Primary Hypercholesterolemia

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Summary

Background: Colesevelam hydrochloride is a novel, lipid-lowering agent that binds bile acids with high affinity. A multicenter, randomized, double-blind, placebo-controlled, parallel-design study was conducted to assess the efficacy and tolerability of combination low-dose colesevelam and lovastatin treatment in patients with primary hypercholesterolemia.

Hypothesis: Combination therapy with low doses of colesevelam and lovastatin decreases low density (LDL) cholesterol with minimal adverse events.

Methods: Following a 4- to 6-week dietary lead in, 135 patients were randomized into five groups for a 4-week treatment period: placebo, colesevelam 2.3 g at dinner, lovastatin 10 mg at dinner, the combination of colesevelam and lovastatin given at dinner (dosed together), and combination treatment with colesevelam given at dinner and lovastatin administered at bedtime (dosed apart).

Results: Combination colesevelam and lovastatin treatment decreased LDL cholesterol by 34% (60 mg/dl, $p < 0.0001$) and 32% (53 mg/dl, $p < 0.0001$) when colesevelam and lovastatin were dosed together or dosed apart, respectively. Both combination therapies were superior to either agent alone ($p < 0.05$). Decreases in LDL cholesterol exceeded the combined decreases observed for colesevelam alone (13 mg/dl, 7%) and lovastatin alone (39 mg/dl, 22%). Both combination treatments reduced total cholesterol by 21% ($p < 0.0001$) and apolipoprotein B by 24% ($p < 0.0001$). Neither combination treatment significantly altered high-density lipoprotein cholesterol or triglycerides. Adverse side effects were not significantly different among randomized groups.

Conclusions: Combination colesevelam and lovastatin was efficacious and well tolerated, resulting in additive decreases in LDL cholesterol levels whether or not both agents were administered simultaneously.

Key words: hypercholesterolemia, lipid-lowering therapy, bile acid sequestrants, 3-hydroxy-3-methylglutaryl coenzyme A reductase inhibitors, combination lipid-lowering therapy

Introduction

Hypercholesterolemia is recognized as a major risk factor for the development of coronary heart disease (CHD). An estimated 12 million Americans have clinically evident CHD, and more than 500,000 deaths are attributed to CHD.[1] The importance of effective total and low-density lipoprotein (LDL) cholesterol reduction for primary prevention of CHD is well established.[2–5] Evidence from clinical trials also demonstrates that reductions in serum LDL cholesterol reduce morbidity and mortality rates of patients already diagnosed with CHD.[6,7] Because of the persuasive data linking elevated LDL cholesterol with increased CHD risk, the National Cholesterol Education Program (NCEP) has established guidelines for reduction of LDL cholesterol.[8,9] These recommendations place a major emphasis on pharmacologic treatment strategies for lowering LDL cholesterol for primary prevention of CHD and secondary prevention of subsequent coronary events.

This study was funded by GelTex Pharmaceuticals, Inc., Waltham, Mass.

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Received: July 17, 2000
Accepted with revision: September 20, 2000

The NCEP guidelines recommend that the decision to initiate lipid-lowering therapy depends on the LDL cholesterol level, the number of CHD risk factors, and the presence or absence of CHD.[8] Dietary therapy and exercise are initially indicated for the treatment of hypercholesterolemia in patients without CHD. If intensive dietary therapy alone does not result in the desired decrease in LDL cholesterol,[10] addition of a 3-hydroxy-3-methylglutaryl-coenzyme A (HMG-CoA) reductase inhibitor or bile acid sequestrant is recommended. Although these agents when given alone substantially improve plasma lipid profiles, recent studies demonstrate that combination drug therapy is highly effective in allowing patients to achieve lipid-lowering goals.[11-13] Therefore, the use of combination therapy is recommended for the aggressive treatment of hypercholesterolemia in high-risk patients.[8]

Colesevelam hydrochloride (WelChol™, 625 mg/tablet, Sankyo Pharma, Inc., New York, N.Y., USA), or colesevelam, is a novel lipid-lowering agent specifically designed to bind bile acids with high affinity.[14] Binding of bile acids to this polymer results in increased fecal excretion and decreased enterohepatic cycling.[15] Previous studies with related compounds have shown that decreased intestinal absorption of bile acids leads to increased conversion of hepatic intracellular cholesterol to bile salts, a secondary increase in LDL receptor expression, and decrease in plasma LDL cholesterol.[16, 17] Clinical studies by Davidson *et al.* demonstrated that, in patients with moderate primary hypercholesterolemia, colesevelam at a dose of 3.8 g/day decreased serum LDL cholesterol levels by 19%, while exhibiting minimal side effects.[18] However, the effects of colesevelam in combination with other lipid-lowering agents had yet to be characterized.

In the present study colesevelam was administered in combination with a well-defined HMG-CoA reductase inhibitor, lovastatin.[19] The efficacy and safety of low-dose colesevelam (2.3 g/day) in combination with low-dose lovastatin (10 mg/day) on plasma lipids were assessed over a 4-week treatment period. To detect any potential interaction, the two lipid-lowering agents were dosed either together or apart. The goals of this study were to evaluate therapeutic efficacy, potential interactions, and tolerability of low-dose colesevelam and lovastatin when coadministered to patients with moderate primary hypercholesterolemia.

Methods

Study Design

This was a multicenter, randomized, double-blind, placebo-controlled, parallel-design study. Patients entered a 4-week American Heart Association Step I diet lead-in period (total fat ≤ 30% of total calories, saturated fat < 10% of calories, cholesterol < 300 mg/day). A 6-week diet/washout period was required for patients previously taking lipid-lowering drugs. Patients who met the entrance criteria were randomized into one of five groups: placebo, colesevelam 2.3 g at dinner, lovastatin 10 mg at dinner, the combination of colesevelam and lovastatin given at dinner (dosed together), and the combination of the two with colesevelam given at dinner and lovastatin administered at bedtime (dosed apart). Patients were treated for 4 weeks followed by a 2-week washout period. In this study, colesevelam was supplied as capsules containing 375 mg (GelTex Pharmaceuticals, Inc., Waltham, Mass., USA). Lovastatin was supplied as capsules containing 10 mg lovastatin, magnesium stearate, and microcrystalline cellulose. Placebo capsules were identical in appearance to their respective active treatment counterparts and contained magnesium stearate and microcrystalline cellulose.

Patients

Of the 202 patients screened for the study, 135 patients were randomized into the treatment period. Based on a previous colesevelam trial,[18] a sample of 120 randomized patients was expected to provide sufficient power to detect treatment differences in percent change in LDL cholesterol using a 0.05 level of significance. Patients were eligible for inclusion into the study if they met the following criteria: male or female ≥ 18 years of age with moderate hypercholesterolemia (LDL cholesterol ≥ 160 mg/dl, but ≤ 220 mg/dl, and triglycerides ≤ 300 mg/dl) and willingness to adhere to the American Heart Association Step I diet during the study. Patients taking certain drugs such as steroids, thiazide diuretics, or beta blockers were required to be on stable doses for 30 days prior to screening. Patients with a history of dysphagia, swallowing disorders, intestinal motility disorders, or any clinically significant unstable medical condition were excluded. Pregnant and lactating women were excluded from participation and those of childbearing potential were required to use an approved birth control method. Randomization was stratified by baseline LDL cholesterol: ≤ 190 mg/dl versus > 190 mg/dl using mean LDL cholesterol values obtained 1 and 2 weeks prior to randomization. Randomized patients were prohibited from using lipid-lowering medications, other than the study drugs, during the study. Certain other drugs, including nefazadone, ketoconazole, itraconazole, and specific antibiotics were also prohibited because of potential interactions with lovastatin.[20]

Lipid Analyses

A fasting lipid profile, including measurements of total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglycerides, was conducted at each clinic visit. Low-density lipoprotein cholesterol was calculated using the Friedewald equation.[21] Apolipoproteins B and A-1, as well as lipoprotein(a), were measured at randomization and following 28 days of treatment. Assays for total cholesterol, HDL cholesterol, and triglycerides were performed according to the Lipid Standardization Program of the Centers for Disease Control and Prevention and the National Heart, Lung and Blood Institute.[22] Apolipoproteins B, apolipoprotein A-1, and lipoprotein(a) were measured according to standard methods (Behring Diagnostics, Inc., Somerville N.J., USA).[23]

The primary efficacy variable was the mean change in LDL cholesterol from baseline (average of values obtained from measurements conducted 1 week prior to and at randomization) to endpoint (average of values obtained from measurements conducted on Days 21 and 28). Secondary efficacy variables included the mean percent change from baseline to endpoint in LDL cholesterol, the absolute and percent changes from baseline to endpoint in total cholesterol, HDL cholesterol, and triglycerides, and the mean percent change from Day 0 to 28 for apolipoprotein B, apolipoprotein A-1, and lipoprotein(a).

Analyses of lipid variables were completed using valid lipid values. A lipid value was considered valid if the subject had fasted for at least 9 h and had abstained from alcohol for at least 48 h prior to the blood draw. A central laboratory (Medical Research Laboratories, Highland Heights, Ken., USA) was used for all laboratory tests except for lipid profiles performed at screening.

Safety Analyses

Serum chemistry profile and complete blood count including differential and platelet counts were completed at screening, baseline, following 28 days of treatment, and at the end of the 2-week washout. In addition, prothrombin and partial thromboplastin time were analyzed at baseline and at the end of treatment. Physical examinations with vital signs were conducted at screening and Day 28. Information regarding adverse events or side effects experienced by the patients was collected at each clinic visit.

Ethics

The study was carried out in accordance with the U.S. Code of Federal Regulations for clinical studies (21 CFR) and the Declaration of Helsinki concerning medical research in humans. An appropriately constituted Institutional Review Board/Ethics Committee reviewed and approved the protocol and consent form. Before the start of the study, each subject signed an informed consent form.

Statistics

Both intent-to-treat and evaluable populations were analyzed for efficacy variables. The intent-to-treat population was defined as those patients who were randomized, took at least one dose of study medication, and had at least one post-baseline efficacy evaluation. The evaluable population was defined as those patients who completed the study through Day 28, were $\geq 80\%$ compliant to study medications, and did not take any prohibited medications. All tests for main effects were two-sided and conducted at the $\alpha = 0.05$ level of significance.

Absolute and percent changes in each lipid parameter from baseline to endpoint for each treatment group were analyzed using paired *t*-tests. The last observation carried forward rule was applied to endpoint analyses to fill in missing post-baseline observations. Differences in mean absolute and percent changes between groups were analyzed using analysis of variance (ANOVA), and paired comparisons between treatment groups were tested by contrasts from the one-way ANOVA model.

Differences across treatment groups in changes in laboratory parameters were compared using a Kruskal-Wallis test. A Wilcoxon signed-rank test was used to assess the change from baseline to endpoint within each treatment group. The percentage of patients in each treatment group with adverse events was compared using Fisher's exact test.

Results

Patients

Of the 202 screened patients, 135 patients were randomized, and a total of 126 patients completed the study (Fig. 1). The intent-to-treat population treatment groups were comparable with respect to demographic and baseline characteristics (Table I). Overall compliance with the study regimen was high, ranging from 92% in the combination group dose together to 97% in the placebo and combination group dosed apart (data not shown). Treatment groups were well balanced at baseline with respect to LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides (Table II). Since results for the intent-to-treat and evaluable populations were similar, only the results for the intent-to-treat population are presented here.

Lipids

Table II displays values of LDL cholesterol, total cholesterol, HDL cholesterol, and triglycerides at baseline and endpoint, as well as changes with treatment. Treatment with low-dose combination colesevelam and lovastatin decreased LDL cholesterol by 60 mg/dl or 53 mg/dl ($p < 0.0001$), respectively,

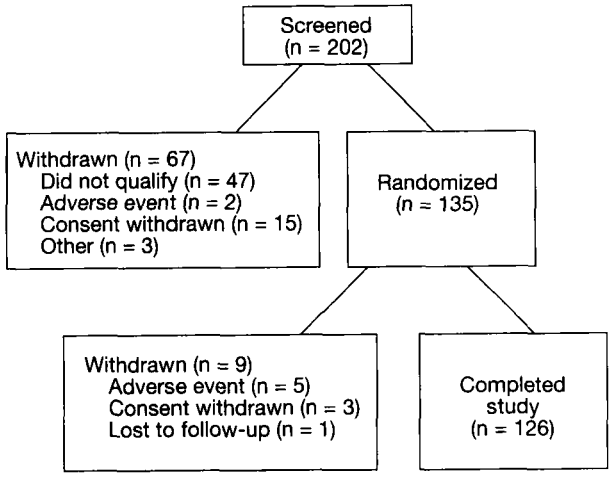

FIG. 1 Disposition of the 131 patients in the intent-to-treat population. Four patients did not have valid lipid measurements and were excluded from the 135 randomized patients.

TABLE I Demographic and baseline characteristics [a]

Variable	Placebo (n = 26)	Colesevelam (n = 29)	Lovastatin (n = 26)	Colesevelam/lovastatin dosed together (n = 27)	Colesevelam/lovastatin dosed apart (n = 23)
Age, years, mean ± SD	57 ± 12	54 ± 12	56 ± 15	63 ± 16	59 ± 12
Male, n (%)	13 (50)	16 (55)	11 (42)	9 (33)	10 (44)
Female, n (%)	13 (50)	13 (45)	15 (58)	18 (67)	13 (56)
Weight, kg, mean ± SD	84 ± 24	84 ± 20	79 ± 19	80 ± 17	80 ± 12
BMI, kg/m^2, mean ± SD	29 ± 7	29 ± 6	28 ± 6	29 ± 5	28 ± 3
Race, n					
Caucasian (%)	22 (85)	23 (79)	22 (85)	23 (85)	22 (96)
Black (%)	3 (11)	4 (14)	1 (4)	4 (15)	1 (4)
Hispanic (%)	0	1 (3)	1 (4)	0	0
Asian (%)	1 (4)	1 (3)	2 (8)	0	0
LDL-cholesterol at baseline, n					
≤ 190 (mg/dl) (%)	22 (85)	22 (76)	22 (85)	20 (74)	18 (78)
> 190 (mg/dl) (%)	4 (15)	7 (24)	4 (15)	7 (26)	5 (22)

[a] No significant differences between treatment groups.
Abbreviations: BMI = body mass index, SD = standard deviation, LDL = low-density lipoprotein.

TABLE II Changes in lipid parameters

Treatment and lipid variable	n	Baseline (mg/dl)	Endpoint (mg/dl)	Absolute change (mg/dl)	% Change
				Mean ± SEM	
LDL-C [a]					
Placebo	26	171 ± 4	172 ± 6	0 ± 4	1 ± 2
Colesevelam	29	172 ± 5	158 ± 5	−13 ± 4 [b]	−7 ± 2 [b]
Lovastatin	26	168 ± 5	129 ± 4	−39 ± 4 [c]	−22 ± 2 [c]
Colesevelam / lovastatin dosed together	27	174 ± 5	115 ± 3	−60 ± 3 [c]	−34 ± 1 [c]
Colesevelam / lovastatin dosed apart	23	169 ± 5	116 ± 7	−53 ± 5 [c]	−32 ± 3 [c]
Total cholesterol [a]					
Placebo	26	256 ± 4	258 ± 6	2 ± 4	1 ± 2
Colesevelam	29	254 ± 6	247 ± 6	−8 ± 4	−3 ± 2
Lovastatin	26	253 ± 6	216 ± 5	−38 ± 4 [c]	−15 ± 2 [c]
Colesevelam / lovastatin dosed together	27	260 ± 5	205 ± 4	−55 ± 4 [c]	−21 ± 1 [c]
Colesevelam / lovastatin dosed apart	23	256 ± 5	202 ± 7	−53 ± 5 [c]	−21 ± 2 [c]
HDL-C					
Placebo	26	51 ± 3	52 ± 3	0 ± 1	1 ± 2
Colesevelam	29	49 ± 2	51 ± 2	2 ± 1 [b]	4 ± 2 [b]
Lovastatin	26	50 ± 3	52 ± 2	1 ± 1	3 ± 2
Colesevelam / lovastatin dosed together	27	51 ± 2	53 ± 2	2 ± 1	3 ± 2
Colesevelam / lovastatin dosed apart	23	56 ± 3	57 ± 4	2 ± 1	3 ± 2
Triglycerides					
Placebo	26	167 ± 14	170 ± 15	3 ± 7	2 ± 4
Colesevelam	29	173 ± 17	188 ± 15	15 ± 9	14 ± 4 [c]
Lovastatin	26	175 ± 14	173 ± 11	−1 ± 9	5 ± 6
Colesevelam / lovastatin dosed together	27	180 ± 15	191 ± 17	12 ± 11	9 ± 7
Colesevelam / lovastatin dosed apart	23	154 ± 12	145 ± 10	−9 ± 8	−3 ± 4

Baseline = average of values obtained from measurements conducted on Days −7 and 0; endpoint = average of values obtained from measurements conducted on Days 21 and 28.
[a] Significant difference among treatment groups ($p < 0.0001$).
[b] Significant change from baseline to endpoint ($p < 0.01$).
[c] Significant change from baseline to endpoint ($p < 0.0001$).
Abbreviations: LDL-C= low-density lipoprotein cholesterol, HDL-C = high-density lipoprotein cholesterol, SEM = standard error of the mean.

depending on whether the agents were dosed together or dosed apart. As shown in Figure 2, the combination of colesevelam and lovastatin dosed apart resulted in a 32% decrease in LDL cholesterol relative to baseline, while combination colesevelam and lovastatin dosed together significantly decreased LDL cholesterol by 34% (both $p < 0.0001$). Upon cessation of treatment, LDL cholesterol values returned to baseline (Fig. 3).

Analysis of absolute mean and percent change by 1-way ANOVA with factor for the various treatments showed significant differences between the individual treatment groups. All active treatment groups displayed statistically significant decreases in LDL cholesterol relative to placebo ($p < 0.05$). The reductions in LDL cholesterol produced by the two combination treatment regimens were significantly different from either treatment alone ($p < 0.05$). Moreover, the reduction in LDL cholesterol exceeded the combined decreases observed for low-dose colesevelam alone (13 mg/dl, 7%) and low-dose lovastatin alone (39 mg/dl, 22%). Thus, LDL cholesterol was reduced by an additional 10–12% in patients who received the low-dose combination of colesevelam and lovastatin compared with lovastatin alone.

Analogous to the effects observed for LDL cholesterol, combination therapy decreased total cholesterol by 21% compared with baseline ($p < 0.0001$), irrespective of the timing of dosing. Total cholesterol levels were not significantly changed in patients treated with colesevelam alone, while patients treated with lovastatin alone exhibited a 14% decrease in total cholesterol, relative to baseline ($p < 0.0001$) (Table II). Both combination treatment regimens produced additional reductions in total cholesterol that differed significantly from those obtained by colesevelam or lovastatin alone ($p < 0.05$).

Mean HDL cholesterol levels increased significantly only in the colesevelam treated group (5%, $p < 0.01$) (Table II). There were no statistically significant changes in serum triglyceride concentrations for any treatment group, with the exception of colesevelam alone, nor were there significant differences in absolute or percent change for triglycerides among treatment groups (Table II). A statistically significant increase in the percent change of triglycerides, from baseline to endpoint, was observed in patients treated with colesevelam alone ($p = 0.0013$). However, contrast tests revealed no significant differences between placebo and colesevelam alone with regard to the percent change in endpoint triglyceride levels.

Apolipoproteins and Lipoprotein(a)

As shown in Table III, apolipoprotein B levels decreased significantly for each active treatment group, with the exception of the colesevelam alone group, compared with baseline values ($p < 0.0001$). Apolipoprotein A-1 levels increased significantly, relative to baseline, in each active treatment group ($p < 0.05$), with the exception of the combination colesevelam/lovastatin dosed apart group. There were no statistically significant changes in lipoprotein(a) for any treatment groups relative to baseline (data not shown).

Safety Evaluation

The number of patients experiencing side effects did not differ among treatment groups. At least one side effect was experienced by 50 to 68% of patients (data not shown). Side effects occurring in > 10% of patients are presented in Table IV. Five patients discontinued treatment due to adverse events (one patient in the colesevelam group; two patients in colesevelam and lovastatin dosed together; two patients in colesevelam dosed apart). Adverse events related to patient discontinuance included one patient with epigastric pain, one patient with esophageal reflux and diarrhea, one patient with

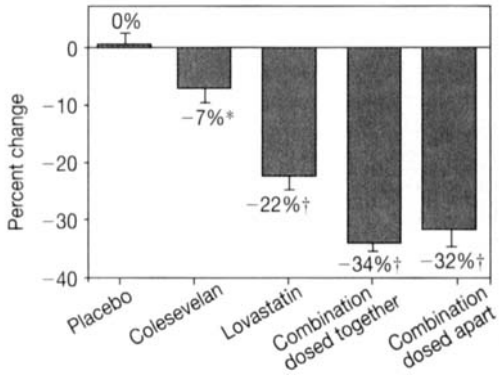

FIG. 2 Percent reduction in low-density lipoprotein (LDL) cholesterol concentrations from baseline (mean of Days −7 and 0) to endpoint (mean of Days 21 and 28) for patients who received either placebo, 2.3 g colesevelam, 10 mg lovastatin, 2.3 g colesevelam and 10 mg lovastatin dosed together, or 2.3 g colesevelam and 10 mg lovastatin dosed apart. Error bars indicate standard error of the mean. *Significant change from baseline to endpoint ($p < 0.01$). †Significant change from baseline to endpoint ($p < 0.0001$).

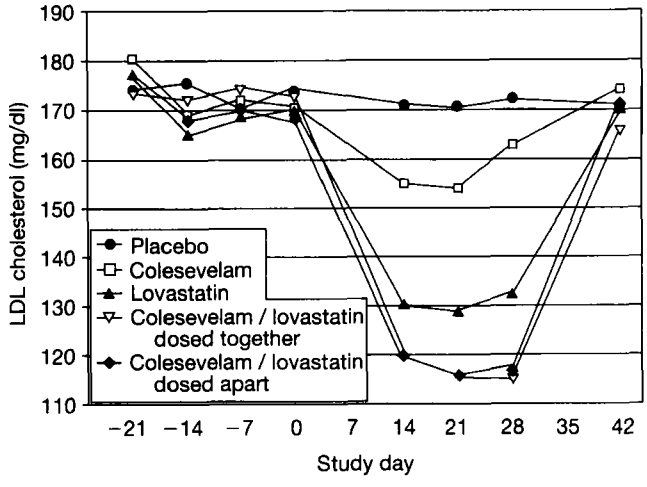

FIG. 3 Low-density lipoprotein (LDL) cholesterol concentrations throughout the study for patients who received either placebo (closed circles), 2.3 g colesevelam (open squares), 10 mg lovastatin (closed triangles), 2.3 g colesevelam and 10 mg lovastatin dosed together (open triangles), or 2.3 g colesevelam and 10 mg lovastatin dosed apart (closed diamonds).

TABLE III Changes in serum apolipoproteins A-1 and B

Treatment and lipid variable	n	Baseline (mg/dl)	Endpoint (mg/dl)	Absolute change (mg/dl)	% Change
			Mean ± SD		
Apolipoprotein B [a]					
Placebo	23	162 ± 19	162 ± 21	0 ± 15	0 ± 9
Colesevelam	28	159 ± 21	153 ± 23	−6 ± 18	−3 ± 11
Lovastatin	25	166 ± 23	138 ± 20	−28 ± 19 [c]	−16 ± 10 [c]
Colesevelam / lovastatin dosed together	25	164 ± 19	124 ± 19	−40 ± 20 [c]	−24 ± 10 [c]
Colesevelam / lovastatin dosed apart	23	158 ± 22	121 ± 29	−37 ± 14 [c]	−24 ± 10 [c]
Apolipoprotein A − 1 [a]					
Placebo	23	154 ± 31	153 ± 30	−1 ± 14	0 ± 10
Colesevelam	28	147 ± 25	158 ± 27	11 ± 12 [c]	8 ± 8 [c]
Lovastatin	25	151 ± 27	158 ± 26	7 ± 13 [b]	5 ± 9 [b]
Colesevelam / lovastatin dosed together	25	159 ± 21	166 ± 23	7 ± 14 [b]	5 ± 9 [b]
Colesevelam / lovastatin dosed apart	23	160 ± 32	166 ± 33	6 ± 15	4 ± 9

[a] Baseline = Day 0, endpoint = Day 28.
[b] Significant change from baseline to endpoint ($p < 0.05$).
[c] Significant change from baseline to endpoint ($p < 0.0001$).
Abbreviation: SD = standard deviation.

TABLE IV Side effects occurring in >10% of patients [a]

Variable	Placebo (n = 26)	Colesevelam (n = 29)	Lovastatin (n = 26) n (%)	Colesevelam/lovastatin dosed together (n = 29)	Colesevelam/lovastatin dosed apart (n = 25)
Headache	3 (12)	3 (10)	5 (19)	0	5 (20)
Infection	1 (4)	3 (10)	2 (8)	1 (3)	1 (4)
Pain	0	3 (10)	1 (4)	1 (3)	0
Diarrhea	2 (8)	1 (3)	4 (15)	2 (7)	2 (8)
Constipation	1 (4)	3 (10)	0	2 (7)	1 (4)
Myalgia	0	0	3 (12)	2 (7)	0

[a] There were no significant differences between treatment groups.

upset stomach, and two patients with nausea. Headache was the most commonly reported side effect, while diarrhea was the most commonly reported gastrointestinal side effect. There were no clinically significant changes in chemistry or hematology laboratory values, including liver function tests, or vital signs (data not shown). No patient developed hepatic enzyme elevations above 3× the upper limit of normal. No serious adverse events occurred during the treatment period and there were no deaths during the study.

Discussion

In this multicenter, randomized, double-blind, placebo-controlled, parallel-design study, the lipid-lowering effects of low-dose colesevelam (2.3 g/day) and low-dose lovastatin (10 mg/day) in combination were evaluated in patients with moderate primary hypercholesterolemia. Several notable findings were observed: (1) low-dose combination treatments with colesevelam and lovastatin produced additive decreases in LDL cholesterol that were superior to either agent alone, (2) the efficacy of low-dose combination colesevelam and lovastatin therapy was similar if the drugs were administered together or apart, and (3) adverse events were not significantly different between active treatment groups and placebo. In this study, coadministration of colesevelam and lovastatin was well tolerated and efficacious for reducing serum LDL cholesterol levels in patients with primary hypercholesterolemia.

Previous reports have demonstrated the effectiveness of combination therapies in decreasing cholesterol levels in hypercholesterolemic patients who fail to achieve therapeutic targets using dietary and/or single drug treatments.[11–13] Fur-

thermore, combination lipid-lowering therapy has been shown to decrease clinical events associated with the progression of atherosclerosis.[24–27] In this study, the coadministration of low-dose colesevelam with lovastatin resulted in decreases of 32–34% for LDL cholesterol, 21% for total cholesterol, and 24% for apolipoprotein B (Tables II and III). Since lovastatin alone caused a 22% decrease in LDL cholesterol, the incremental reduction contributed by colesevelam amounted to an additional 10–12% decrease in LDL cholesterol levels.

Another important finding in the current study was that varied dosing intervals for the combination therapy yielded similar decreases in LDL cholesterol, suggesting that colesevelam did not interfere with the absorption or activity of lovastatin. Indeed, pharmacokinetic studies evaluating serum levels of lovastatin and its hydroxyacid metabolites show that lovastatin pharmacokinetics are similar when given alone or coadministered with colesevelam (unpublished data, GelTex Pharmaceuticals, Inc.). This observation is also supported by the lack of clinically significant interactions when colesevelam was coadministered with six other drugs in separate studies.[28] In contrast, cholestyramine and colestipol may alter the absorption of HMG-CoA reductase inhibitors such that current dosing recommendations are that these agents be administered 1 h after or 4 to 6 h prior to other medications.[29–32] Thus, these data indicate that colesevelam does not interact significantly with lovastatin in the gastrointestinal tract, a property that would allow for implementation of convenient dosing regimens.

The relative benefit of combination therapy is typically classified as less than additive, additive, or synergistic.[33] In the current study, low doses of colesevelam and lovastatin showed greater efficacy in lowering LDL cholesterol than would be predicted based on the effect elicited by each agent alone, indicating that coadministration produced an apparently greater than additive effect. Since the dose-related LDL cholesterol-lowering effects elicited by HMG-CoA reductase inhibitors obeys a log-linear relationship, a 7% reduction in LDL cholesterol is achieved with each doubling of the dose.[34] By adding colesevelam to lovastatin, an additional 10–12% reduction in LDL cholesterol was achieved, equivalent to a 2- to 4-fold increase in the dose of the lovastatin.[34] Therefore, when colesevelam is used in combination with an HMG-CoA reductase inhibitor, there is a significant dose-sparing effect.

The additive lipid-lowering properties of colesevelam and lovastatin are most likely the result of complementary mechanisms of action. Colesevelam enhances fecal bile acid excretion, an effect that presumably results in increased hepatic de novo synthesis of bile acids.[15, 16] Utilization of cholesterol in the bile acid synthetic pathway would lead to a compensatory increase in LDL receptor expression and enhanced clearance of LDL cholesterol.[17] In contrast, lovastatin exerts its therapeutic effects by inhibiting HMG-CoA reductase, resulting in decreased hepatic cholesterol synthesis and a secondary increase in LDL receptors.[19, 35] The ability to intervene in the cholesterol metabolic pathway at two distinct points makes cotherapy with colesevelam and lovastatin inherently attractive.

Side effects occur with all lipid-lowering agents and may decrease patient compliance and lead to discontinuation of drug therapy.[36–38] Previous studies have shown that colesevelam was well tolerated by patients.[18, 39] In a recent 24-week safety study involving 494 patients randomized into five treatment groups, the incidence of adverse events in patients treated with colesevelam, at doses between 2.3 and 4.5 g/day, was not significantly different than placebo.[39] Furthermore, an integrated analysis of seven placebo-controlled trials with 1,350 patients showed that adverse events were comparable between colesevelam treatments and placebo groups.[40] In the current study, colesevelam treatment did not increase significantly the number of side effects, including those of gastrointestinal origin, compared with placebo control. Colesevelam and/or lovastatin treatment did not increase significantly hepatic enzyme levels compared with baseline values, a finding that may be related to the low dosages utilized in these studies. These data suggest that additional monitoring beyond that required for lovastatin alone is not necessary. The reason colesevelam displays minimal side effects is unclear but may be partly due to high affinity binding to bile acids.[14] Furthermore, being a hydrogel, colesevelam forms a soft gelatinous-like material that may minimize the potential for gastrointestinal irritation or side effects. In the present study, compliance with each study medication was over 90%, indicating that colesevelam and lovastatin in combination were well tolerated by patients.

Previous studies have established the benefit of aggressive lipid-lowering in the primary prevention of CHD and/or secondary prevention of acute coronary events.[2–7] In the current study, low-dose coadministration of colesevelam and lovastatin caused additive reductions in LDL and total cholesterol levels, irrespective of the time of dosing. Colesevelam and lovastatin combination therapy was also well tolerated by patients. Thus, colesevelam represents a novel lipid-lowering agent that, in combination with lovastatin, is efficacious with excellent gastrointestinal tolerability.

Acknowledgments

This study was supported by GelTex Pharmaceuticals, Inc., Waltham, Mass. Drs. Davidson, Toth, Weiss, McKenney, Hunninghake, and Isaacsohn received research grants from GelTex Pharmaceuticals. Drs. Burke and Donovan are employed by GelTex Pharmaceuticals, the developer of colesevelam hydrochloride. Drs. Hunninghake and Davidson have also served as consultants to GelTex Pharmaceuticals.

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