Randomized Crossover Study of Gemfibrozil Versus Lovastatin in Familial Combined Hyperlipidemia: Additive Effects of Combination Treatment on Lipid Regulation

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The most appropriate therapy for combined hyperlipidemia remains to be determined. We compared the lipid-regulating effects of gemfibrozil and lovastatin in 30 patients with familial combined hyperlipidemia (FCHL) in a randomized, double-blind, placebo-controlled crossover study including 8-week courses of one drug followed by a washout period and a crossover phase to the alternate drug. After completion of the trial, open-label combination therapy was given for up to 12 months. Lovastatin was more efficacious than gemfibrozil in the reduction of total cholesterol (23% *v* 9%, $P < .001$) and low-density lipoprotein (LDL) cholesterol (28% *v* 2%, $P < .001$), whereas gemfibrozil surpassed lovastatin in the reduction of triglycerides (48% *v* 0%, $P < .001$) and very–low-density lipoprotein (VLDL) cholesterol (50% *v* 19%, $P = .005$) and the increase of high-density lipoprotein (HDL) cholesterol (18% *v* 4%, $P = .005$). Lovastatin caused a greater decline in total apolipoprotein B (apo B) and LDL apo B than gemfibrozil, whereas VLDL apo B decreased only after gemfibrozil therapy. Drug-induced changes in lipoprotein composition indicated that gemfibrozil reduced both the number and size of VLDL particles and lovastatin decreased the number of LDL particles. Combined treatment was safe and had additive effects on lipids, causing significant ($P < .001$) reductions in total cholesterol (32%), triglycerides (51%), LDL cholesterol (34%), and apo B (26%) and an increase in HDL cholesterol (19%). Target LDL cholesterol levels were achieved only in 11% of patients given gemfibrozil alone and triglycerides decreased to target levels in 22% after lovastatin alone, whereas combined therapy normalized both lipid fractions in 96% of patients. Thus, in FCHL, gemfibrozil has no effect on LDL cholesterol levels but favorably influences the putative atherogenic alterations of lipoprotein composition that are related to hypertriglyceridemia. Conversely, lovastatin markedly decreases LDL cholesterol but has little effect on triglyceride-rich lipoproteins. Combination treatment safely corrects all of the lipid abnormalities in most patients.

FAMILIAL COMBINED HYPERLIPIDEMIA (FCHL) is a common genetic dyslipidemia with a prevalence of about 1% among the general population, and is frequently associated with premature coronary artery disease.[1-3] FCHL is characterized by variable expression of hypercholesterolemia and hypertriglyceridemia in both affected individuals and family members.[1] Patients with FCHL commonly show elevations of low-density lipoprotein (LDL) cholesterol and triglycerides; overproduction of very–low-density lipoprotein (VLDL) apolipoprotein B (apo B) is incriminated as the underlying metabolic defect.[2,4] FCHL is inherited as an autosomal dominant disorder,[1-5] but the genetic basis is complex.[6] Mutations in the apo AI-CIII-AIV gene cluster[7] or the lipoprotein lipase gene[8] have been found in some families, and a strong linkage to chromosome 1q21-q23 has recently been described in FCHL families of the genetically homogeneous Finnish population.[9] However, variable expression of the lipid phenotype suggests multigenic etiology. On the other hand, phenotype changes with time in the same individual indicate an important influence of life-style factors; phenotypic expression is also variably influenced by age, gender, hormonal status, and the amount of visceral fat, underlining the metabolic complexity of this genetically heterogeneous disorder.[10]

Key components of FCHL imparting an increased cardiovascular risk are hypertriglyceridemia and its metabolic consequences: low levels of high-density lipoprotein (HDL) cholesterol, accumulation of triglyceride-rich lipoproteins, small and dense LDL subclasses, enhanced postprandial lipemia, and prothrombotic changes of the coagulation system.[11] Because, in addition, they show elevated LDL cholesterol levels, patients with combined hyperlipidemia are predicted to have a higher cardiovascular risk than patients with isolated hypercholesterolemia.[12,13]

The therapy for FCHL should aim to decrease both cholesterol and triglyceride levels. Dietary therapy alone often is inadequate to normalize lipid levels, and hence, pharmacologic intervention is necessary in many patients. However, the most appropriate therapy remains to be determined. Nicotinic acid would be the drug of choice because it decreases LDL cholesterol and triglycerides and increases HDL cholesterol, but it often has limiting side effects.[14] Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase such as lovastatin are effective to reduce LDL cholesterol but have modest effects on elevated triglyceride and low HDL cholesterol levels,[15] whereas the fibrate gemfibrozil decreases triglycerides and increases HDL cholesterol but has only a small effect on LDL cholesterol in the presence of hypertriglyceridemia.[16] Nevertheless, the cardiovascular risk in patients with combined hyperlipidemia can be favorably altered by gemfibrozil treatment.[12,13]

The US guidelines for the treatment of hyperlipidemia in

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adults define specific target levels of LDL cholesterol, while hypertriglyceridemia plays little part in the algorithms for diagnosis and management.[17,18] Even a recent conference focusing on triglycerides[19] did not address the target levels for therapy in so-called borderline hypertriglyceridemia, ie, a triglyceride level of 200 to 500 mg/dL (2.3 to 5.7 mmol/L). In contrast, European guidelines[20-22] take into account triglycerides in risk equations and suggest that therapy should aim at reducing them to less than 200 mg/dL (2.3 mmol/L).

In a randomized double-blind crossover trial, we compared the effects of gemfibrozil and lovastatin on serum lipids and lipoproteins in patients with FCHL to determine which is most effective as a single agent to attain target lipid levels according to current guidelines. After completion of the controlled trial, the efficacy and safety of combination therapy with the two drugs were assessed in an open study.

SUBJECTS AND METHODS

Subjects and Study Protocol

Outpatients with FCHL attending the Lipid Clinic of our tertiary-care university-affiliated medical center were enrolled in the study if they met the following criteria: age less than 70 years; LDL cholesterol greater than 150 mg/dL (3.9 mmol/L) and triglycerides between 200 and 500 mg/dL (2.3 to 5.7 mmol/L) while on a low–saturated-fat diet; serum apo B greater than 130 mg/dL (upper-normal limit of our reference population, 2 SD greater than the mean of 97 ± 16.5 mg/dL); families with at least four adult first-degree relatives of known lipid profile and in whom half or more show hyperlipidemia present as variable lipoprotein phenotypes (either LDL cholesterol >150 mg/dL [3.9 mmol/L], triglycerides >200 mg/dL [2.3 mmol/L], or both); absence of hypercholesterolemic children in the family; a positive family history of premature atherosclerosis (before age 60 years); and an absence of the apo E2/2 phenotype. Other exclusion criteria were hepatic, renal, or endocrine disease, diabetes mellitus (fasting blood glucose >140 mg/dL [7.8 mmol/L], or blood glucose 2 hours after a 75-g glucose oral load >200 mg/dL [11.1 mmol/L] in subjects with fasting levels between 110 [6.1 mmol/L] and 140 mg/dL [7.8 mmol/L]), myocardial infarction within the past 6 months, unstable angina, and alcohol or drug abuse. Premenopausal women had to use nonhormonal contraception.

The trial was designed to compare two drugs, gemfibrozil and lovastatin, for their effects on serum lipids, lipoproteins, and apo AI and B in patients with FCHL. This was a randomized, double-blind, placebo-controlled crossover study divided into five consecutive periods over 30 weeks. The first period (week −6 to day 0) was a run-in period of dietary treatment. The second period (day 0 to week 4) was a baseline placebo phase. At week 4, blood was taken for lipoprotein analysis, and patients meeting lipid criteria for entry were randomly assigned by a random number table method to receive daily either gemfibrozil 1.2 g together with placebo matching lovastatin or lovastatin 40 mg along with placebo matching gemfibrozil during the third period (weeks 4 to 12). This was followed by a 4-week placebo washout period (weeks 12 to 16), at the end of which patients were switched to the alternative drug, again under double-blind conditions according to a preestablished sequence of the randomization codes (weeks 16 to 24). Lipoprotein determinations and safety biochemistry profiles obtained at the end of each placebo period were compared with those obtained at the end of ensuing active treatment periods. The protocol was approved by the institutional review board, and all patients provided written informed consent.

After completion of the controlled trial, patients were offered open-label combination treatment with both drugs. Thorough information was provided about the risk of myopathy and remedial action in the event of symptoms, and they were scheduled for outpatient visits with blood tests for lipid and safety profiles at 3, 6, and 12 months.

The dietary goals were 35% of energy as fat (10% saturated fatty acids, 20% monounsaturated fatty acids, and 5% polyunsaturated fatty acids) and less than 300 mg cholesterol per day.[23] Alcohol was prohibited for the duration of the study. Throughout the controlled study, dietary instructions were reinforced and caloric intake was adjusted to maintain a constant body weight by 2-week interviews with a registered dietitian.[24] During the open phase of the study, dietary supervision was performed at scheduled outpatient visits.

Analytical Methods

Fasting concentrations of cholesterol and triglycerides in serum and in the VLDL fraction obtained by centrifugation were measured by enzymatic methods. HDL cholesterol was determined after precipitation of apo B–containing lipoproteins with phosphotungstate/magnesium. HDL_3 cholesterol was isolated from whole serum by the dextran sulfate/$MgCl_2$ precipitation method,[25] and HDL_2 cholesterol was calculated by subtraction from total HDL cholesterol. For separation of lipoproteins, 2-mL aliquots of serum were covered with 2 mL NaCl (d 1.006) and centrifuged at 105,000× *g* for 18 hours at 15°C. Cholesterol, triglyceride, and apo B concentrations and apo E phenotype were determined in the supernatant fraction containing VLDL. LDL cholesterol was obtained by subtraction of HDL cholesterol and VLDL cholesterol from total cholesterol. Apo AI and B concentrations were measured by immunoturbidimetry[26]; LDL apo B was calculated by subtraction of VLDL apo B from total apo B. Serum lipoprotein (a) [Lp(a)] levels were measured by immunoturbidimetry (Incstar Lp(a) SPQ Test System; Incstar, Stillwater, MN). Apo E phenotypes were determined in the VLDL fraction by an acrylamide gel isoelectric focusing method.[24] No lipoprotein fractionation or Lp(a) measurements were made during open-label combined drug therapy, when LDL cholesterol was calculated by the Friedewald equation (LDL cholesterol [mg/dL] = total cholesterol − HDL cholesterol − triglycerides/5).

For comparison of lipoprotein composition, 35 control subjects defined as normolipidemic by current guidelines[17-22] who were age- and sex-matched to patients entering the active treatment phase were concurrently studied (Table 1).

Table 1. Clinical Characteristics and Lipid and Lipoprotein Values at Baseline in the FCHL Patient and Reference Control Groups

Characteristic	FCHL	Control
No. of subjects	35	35
Sex ratio (men/women)	26/9	25/10
Age (yr)	53 ± 2 (33-69)	53 ± 2 (32-69)
Body mass index (kg/m^2)	27.5 ± 2.8 (22.1-32.7)	26.3 ± 1.7 (20.2-33.0)
Coronary heart disease (n)	15 (33%)	0
Hypertension (n)	10 (29%)	4 (11%)
Total cholesterol	292 ± 9 (230-447)	189 ± 3 (128-221)
Triglycerides	290 ± 11 (175-459)	92 ± 6 (48-188)
VLDL cholesterol	57 ± 3 (7-89)	13 ± 1 (3-29)
VLDL triglycerides	163 ± 6 (100-255)	38 ± 4 (10-86)
LDL cholesterol	200 ± 7 (151-326)	119 ± 4 (76-149)
HDL cholesterol	37 ± 2 (21-68)	57 ± 2 (36-82)
Apo B	180 ± 7 (132-286)	97 ± 3 (67-131)
Apo AI	141 ± 4 (102-166)	157 ± 4 (114-203)

NOTE. Lipid, lipoprotein, and apolipoprotein values are the mean ± SE in mg/dL (range). To convert cholesterol from mg/dL to mmol/L, multiply by 0.026; for triglyceride values, multiply by 0.011.

Statistics

The efficacy analysis included all patients with data both at baseline and on treatment, and was based on percent changes from baseline. Between-treatment comparisons of lipids, lipoproteins, and apolipoproteins were performed by ANOVA; the model included effects due to treatment, period, sequence, and patient as random effects.[27] To adjust for baseline differences in lipid values, an analysis of covariance was performed for the assessment of changes from baseline with the effects due to treatment, period, sequence, and patient as random effects and baseline values as a covariate. The results of inferential analyses are presented as the adjusted mean ± SE.

Spearman correlation coefficients were used to assess the association between LDL cholesterol and LDL apo B levels. Chi-square statistics with Yates' correction when necessary were used to evaluate differences in target lipid levels with the two drugs. Differences between lipoprotein levels after completion of the controlled trial and during open-label combined therapy were analyzed by one-way ANOVA.

Version 3.1 of the SPSS/PC+ software (SPSS, Chicago, IL) was used for descriptive analysis, and version 6.08 of the SAS software (SAS Institute, Cary, NC) was used for inferential analysis.

RESULTS

Baseline Characteristics

Of 52 patients enrolled in the trial, 17 were excluded during the first placebo period (14 did not meet predefined lipid criteria, and three withdrew for personal reasons). Clinical characteristics and lipid and lipoprotein values for 35 patients who entered the active treatment period are shown in Table 1. Reference values from 35 control subjects are shown for comparison. Apo E phenotypes in FCHL patients were distributed as follows: one E3/2, three E4/2, 22 E3/3, and nine E4/3.

Withdrawals and Adverse Events

Of 35 patients entering the active treatment period, five withdrew and 30 completed the two double-blind phases. Reasons for withdrawal were noncompliance with medication in two patients, adverse events during active drug treatment in two patients (rash during gemfibrozil treatment and abdominal pain during lovastatin), and pill overdose during the second placebo phase in one patient.

All 35 patients who entered the double-blind treatment phase were included in the evaluation of safety. The study medications were well tolerated. Adverse events that were regarded as possibly, probably, or definitely associated with drug treatment but were not a reason for discontinuation were as follows: one (3%) during gemfibrozil treatment (abdominal pain) and three (9%) during lovastatin treatment (diarrhea in two and a slight elevation of serum alanine aminotransferase in one). Creatine kinase levels remained in the normal range for both drug regimens.

Effects on Serum Lipids and Lipoproteins

For each drug relative to its own placebo baseline, neither order nor carryover effects from the previous active treatment phase at crossover were observed. Table 2 shows the lipoprotein data after each placebo baseline period and each active drug period for the two crossover intervention sequences. There were significant changes from the placebo baseline for each drug and between the two drugs (Fig 1). Gemfibrozil produced a marked reduction in triglycerides and VLDL lipid, a moderate reduction in total cholesterol, and no change in LDL cholesterol. On the other hand, lovastatin had no effect on total and VLDL triglycerides, induced a moderate reduction of VLDL cholesterol, and markedly decreased total cholesterol and LDL cholesterol. Treatment with gemfibrozil, but not lovastatin, increased total HDL cholesterol, and this was at the expense of both the HDL_2 and HDL_3 subfractions (29% and 17%, respectively, $P = .002$ and $P = .003$, respectively). Apo AI increased nonsignificantly after treatment with gemfibrozil and lovastatin (5% and 6%, respectively). The effects on Lp(a) differed between the drugs, with gemfibrozil therapy having none and lovastatin increasing Lp(a) by 22% (Fig 1).

Gemfibrozil and lovastatin decreased the total cholesterol to HDL cholesterol ratio to a similar extent (21% and 24%, respectively, $P < .001$ for both drugs), while the LDL cholesterol to HDL cholesterol ratio was decreased more with lovastatin (29%, $P < .001$) than with gemfibrozil (14%, $P = .002$).

Effects on Apo B Lipoproteins

Baseline levels of total apo B were approximately twice the reference values (Table 1). VLDL apo B and LDL apo B levels were also higher in FCHL in comparison to control values (14 ± 1 *v* 7 ± 1 and 166 ± 7 *v* 90 ± 3 mg/dL, respectively), while the LDL cholesterol to apo B ratio was lower (1.22 ± 0.03 *v* 1.34 ± 0.04, respectively). Changes after drug treatment are shown in Fig 2. Levels of total apo B and LDL apo B were

Table 2. Lipid and Lipoprotein Values (mg/dL) After Placebo and Active Drug Treatment for Each Intervention Period in 30 Patients With FCHL Completing the Trial

	Gemfibrozil-Lovastatin Group (n = 15)				Lovastatin-Gemfibrozil Group (n = 15)			
Parameter	Placebo	Drug	Placebo	Drug	Placebo	Drug	Placebo	Drug
Total cholesterol	289 ± 11	252 ± 10	285 ± 11	230 ± 9	295 ± 10	220 ± 7	283 ± 12	259 ± 12
Triglycerides	296 ± 18	153 ± 15	278 ± 25	259 ± 22	284 ± 15	272 ± 32	289 ± 32	144 ± 13
VLDL cholesterol	60 ± 4	27 ± 4	54 ± 6	47 ± 7	54 ± 4	41 ± 4	51 ± 4	24 ± 4
VLDL triglycerides	170 ± 10	86 ± 10	164 ± 17	158 ± 16	156 ± 7	155 ± 14	155 ± 12	76 ± 10
LDL cholesterol	198 ± 11	184 ± 10	192 ± 12	148 ± 7	201 ± 9	134 ± 6	191 ± 10	190 ± 9
HDL cholesterol	35 ± 2	41 ± 2	35 ± 2	35 ± 2	39 ± 2	41 ± 2	40 ± 3	44 ± 3
HDL_2 cholesterol	8 ± 1	12 ± 2	9 ± 1	11 ± 2	9 ± 1	11 ± 2	10 ± 2	10 ± 2
HDL_3 cholesterol	22 ± 1	28 ± 2	25 ± 2	23 ± 2	29 ± 2	30 ± 2	29 ± 3	31 ± 2
Apo B	177 ± 9	152 ± 8	180 ± 11	147 ± 7	183 ± 9	133 ± 6	177 ± 9	163 ± 9
Apo AI	134 ± 4	138 ± 6	136 ± 4	141 ± 5	147 ± 6	153 ± 6	149 ± 8	153 ± 7
Lp(a)	24 ± 4	26 ± 5	27 ± 6	31 ± 5	28 ± 7	31 ± 9	30 ± 8	29 ± 6

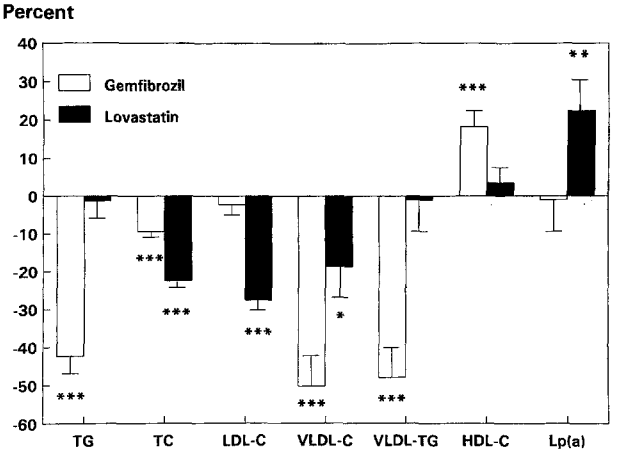

Fig 1. Percentage changes from baseline for lipids and lipoproteins in 30 patients with FCHL after treatment with gemfibrozil or lovastatin. TG, triglycerides; TC, total cholesterol; LDL-C, LDL cholesterol; VLDL-C, VLDL cholesterol; HDL-C, HDL cholesterol. *P = .01, **P = .003, ***P < .001, baseline v treatment values. Differences between the effects of gemfibrozil and lovastatin were significant for all lipid and lipoprotein values (P = .030 for Lp(a), P = .005 for VLDL cholesterol and HDL cholesterol and P < .001 for triglycerides, total cholesterol, LDL cholesterol, and VLDL triglyceride).

decreased by both drugs, but lovastatin was more potent than gemfibrozil. LDL cholesterol and LDL apo B were significantly (P < .001) correlated at baseline (R^2 = .74) and after treatment (R^2 = .84 with gemfibrozil and R^2 = .78 with lovastatin). Gemfibrozil, but not lovastatin, significantly decreased VLDL apo B (Fig 2). The drugs had opposite but marginal effects on the LDL cholesterol to apo B ratio.

The VLDL cholesterol to apo B ratio was abnormally high at baseline in comparison to control values (4.90 ± 0.22 v 2.17 ± 0.44, respectively), as is characteristic of FCHL,[2,4] and was decreased significantly by both drugs: 34% ± 4% (P < .001) by gemfibrozil and 22% ± 5% (P = .001) by lovastatin. On the other hand, the VLDL triglyceride to apo B quotient, which was also elevated at baseline in comparison to reference values (11.64 ± 0.50 v 6.25 ± 0.44, respectively), indicating large triglyceride-enriched VLDL particles, was reduced significantly (P < .001) by 27% ± 5% after gemfibrozil, but was not affected by lovastatin therapy (3% ± 5% reduction).

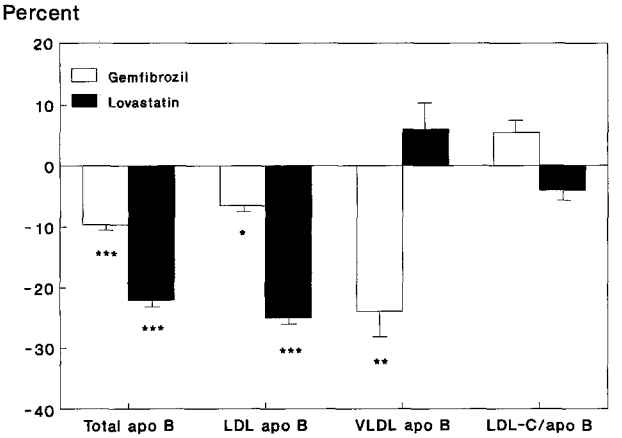

Fig 2. Effect (percentage change from baseline) of treatment with gemfibrozil or lovastatin on apo B in total serum and in apo B–containing lipoproteins and the LDL cholesterol to apo B ratio in 30 patients with FCHL. LDL-C, LDL cholesterol. *P = .009, **P = .002, ***P < .001, baseline v treatment values. Differences between the effects of gemfibrozil and lovastatin were significant for total apo B (P < .001), LDL apo B (P < .001), and VLDL apo B (P = .005).

Effectiveness of Single-Drug Treatment

The proportion of patients attaining target lipid levels according to the Spanish Atherosclerosis Society guidelines (LDL cholesterol <150 mg/dL [3.9 mmol/L], triglycerides <200 mg/dL [2.3 mmol/L], and HDL cholesterol >35 mg/dL [0.9 mmol/L])[21] differed for each drug. Because of the crossover design, not all 30 patients had LDL cholesterol greater than 150 mg/dL (3.9 mmol/L) or triglycerides greater than 200 mg/dL (2.3 mmol/L) before each specific treatment period. Seventeen and nine patients had HDL cholesterol less than 35 mg/dL (0.9 mmol/L) prior to gemfibrozil and lovastatin therapy, respectively. Gemfibrozil and lovastatin therapy reduced LDL cholesterol to less than target levels in three of 28 patients (11%) and 19 of 28 (68%), respectively (P < .001); the respective numbers for target serum triglycerides were 20 of 27 patients (74%) and six of 27 (22%) (P = .001). On the other hand, gemfibrozil therapy increased HDL cholesterol levels above 35 mg/dL (0.9 mmol/L) in 10 of 17 patients (59%) who had low baseline levels, whereas this occurred in one of nine (11%) on lovastatin (P = .036).

The triple lipid abnormality of LDL cholesterol and triglycerides above and HDL cholesterol below desired levels was corrected only in three patients (10%), two receiving gemfibrozil and one given lovastatin.

Safety and Efficacy of Combined Gemfibrozil—Lovastatin Therapy

Combination drug therapy was offered to 27 patients who were still dyslipidemic after the trial. Of 15 patients completing the study in each group (Table 2), 13 each initiated combination therapy, that is, patients on gemfibrozil received lovastatin, 40 mg daily and those on lovastatin received gemfibrozil 1.2 g daily. One patient refused combined therapy because of a fear of side effects. Another patient developed abdominal pain when gemfibrozil was added to lovastatin, and stopped treatment. The remaining 25 patients completed 12 months of combined therapy without interruption; dyspeptic symptoms that did not warrant discontinuation of treatment were reported by three. There were neither side effects on striated muscle nor increases in the serum concentration of creatine kinase, and alanine aminotransferase serum levels remained within normal limits in all patients.

Table 3 shows the lipid changes induced by combination therapy in comparison to the preceding single-drug treatment. Because there were no differences in lipid values in measurements at 3, 6, and 12 months by one-way ANOVA, the on-treatment data have been averaged. Addition of gemfibrozil to lovastatin was effective to reduce triglycerides and increase HDL cholesterol, whereas adding lovastatin to gemfibrozil led to significant reductions of total cholesterol, LDL cholesterol, and apo B. Averaged lipid values on combined therapy were

Table 3. Effect of Adding the Alternate Drug in Combination Therapy on the Lipid Profile and Serum Apolipoprotein Levels in Patients With FCHL Previously Treated With Lovastatin or Gemfibrozil as Monotherapy

Lipids (mg/dL)	Lovastatin + Gemfibrozil (n = 12)	Gemfibrozil + Lovastatin (n = 13)
Total cholesterol		
Single drug	232 ± 10	255 ± 10
Combination	195 ± 8†	194 ± 6‡
Triglycerides		
Single drug	266 ± 21	146 ± 13
Combination	143 ± 16‡	140 ± 12
LDL cholesterol		
Single drug	140 ± 8	191 ± 9
Combination	129 ± 5	128 ± 5‡
HDL cholesterol		
Single drug	35 ± 2	43 ± 2
Combination	42 ± 2*	43 ± 2
Apo B		
Single drug	142 ± 7	167 ± 8
Combination	134 ± 6	130 ± 5‡
Apo AI		
Single drug	141 ± 5	150 ± 7
Combination	144 ± 6	152 ± 7

NOTE. Combination treatment values are the average of data at 3, 6, and 12 months after adding the alternate drug.

*P = .024, †P = .009, ‡P < .001 *v* single-drug values by 1-way ANOVA.

similar in the two treatment arms (Table 3). The overall result of combination gemfibrozil-lovastatin therapy was a normalization of the lipid profile in 17 (68%) patients: LDL cholesterol less than 150 mg/dL (3.9 mmol/L) in all cases, triglycerides less than 200 mg/dL (2.3 mmol/L) in all except one patient (96%), and HDL cholesterol greater than 35 mg/dL (0.9 mmol/L) in 17 patients (68%). This group included 14 patients with established coronary heart disease, of whom 10 (71%) achieved LDL cholesterol levels less than 130 mg/dL (3.4 mmol/L), thus meeting current standards for secondary prevention.

A comparison of lipid values after combination drug therapy to the averaged placebo baseline values (Table 2) for these 25 patients showed the benefit of this treatment modality for all lipid fractions, with significant ($P < .001$) reductions of total cholesterol (32%), triglycerides (51%), LDL cholesterol (34%), and apo B (26%) and increased HDL cholesterol (19%), whereas apo AI increased nonsignificantly (5%).

DISCUSSION

In this study, 30 patients with FCHL completed a crossover trial comparing gemfibrozil and lovastatin as lipid-modulating agents. Gemfibrozil therapy effectively decreased serum triglycerides and VLDL lipid and increased HDL cholesterol, but had no effect on elevated levels of LDL cholesterol. Lovastatin, on the other hand, was efficacious to reduce LDL cholesterol and, to a lesser extent, VLDL cholesterol, while having no effect on total and VLDL triglyceride or HDL cholesterol levels. Monotherapy with either drug was ineffective to correct all of the lipoprotein abnormalities in most patients. On the other hand, concomitant gemfibrozil-lovastatin therapy subsequently for up to 1 year combined the specific lipid-modulating properties of the two drugs and normalized the lipid profile without side effects in the majority of patients.

Few studies have compared the hypolipidemic effects of fibrates and HMG CoA reductase inhibitors in patients with combined hyperlipidemia, with overall results similar to those of our study regarding the effects on total cholesterol and LDL cholesterol.[28-32] However, HMG CoA reductase inhibitor–induced alterations in VLDL differed from those reported here in two of three trials where lipoprotein fractionation was performed.[28,30,31] Vega and Grundy[28] and Bredie et al[30] observed similar reductions in VLDL cholesterol after gemfibrozil and HMG CoA reductase inhibitors (lovastatin and simvastatin, respectively), whereas lovastatin had a small effect on VLDL cholesterol in our study. A reason for this discrepancy may be the fact that these investigators[28,30] isolated VLDL and remnant particles together ($d < 1.019$ g/mL) instead of isolating VLDL alone ($d < 1.006$ g/mL) as we did. The small impact of lovastatin on VLDL would be explained by a lack of contamination with denser remnant particles that can be cleared rapidly from the circulation by upregulation of LDL receptors.[33] Recently, the new HMG CoA reductase inhibitor atorvastatin has been shown to significantly reduce both cholesterol-rich and triglyceride-rich lipoproteins in patients with combined hyperlipidemia.[34]

In this study, lovastatin failed to reduce serum triglyceride or to increase HDL cholesterol, in contrast to the effects of gemfibrozil therapy. A 7% to 30% reduction of the serum triglyceride concentration and a 4% to 18% increase in HDL cholesterol have been reported in patients with combined hyperlipidemia treated with HMG CoA reductase inhibitors.[28-32] Thus, with the possible exception of atorvastatin,[34] these agents appear to have an inconsistent effect on high triglyceride and low HDL cholesterol levels. The HDL cholesterol–increasing effect of gemfibrozil was at the expense of the HDL_2 subfraction and, to a lesser extent, the HDL_3 subfraction. This effect is consistent with increased activities of both lipoprotein and hepatic lipase induced by the drug.[16] However, whereas total HDL cholesterol levels have been shown clearly to be negatively associated with the risk of ischemic heart disease,[35] the relative importance of HDL_2 and HDL_3 in this association is still uncertain.[36-38]

Elevated total apo B and LDL apo B levels, a characteristic feature of FCHL,[2,6] were significantly decreased by gemfibrozil and to a greater extent by lovastatin. On the other hand, only gemfibrozil reduced VLDL apo B (Fig 2). Because all apo B–containing lipoproteins have one molecule of apo B per particle, it is clear that lovastatin markedly reduced the number of LDL particles, but not VLDL, while gemfibrozil had the opposite effect. Such changes are consistent with decreased VLDL apo B secretion induced by gemfibrozil[16] and enhanced LDL apo B catabolism through upregulation of hepatic LDL receptors caused by lovastatin.[15]

In patients with hypertriglyceridemia, VLDL catabolism is abnormally slow, so there is a sustained period during which the circulating lipid-transfer proteins act on VLDL, catalyzing the transfer of triglycerides to LDL and HDL in exchange for cholesterol, resulting in compositional abnormalities of all three lipoprotein classes.[39,40] Besides low HDL cholesterol, other consequences of hypertriglyceridemia that impart an increased

risk of coronary heart disease[12] are the accumulation of both large triglyceride-rich VLDL[41] and small dense LDL particles.[42] Characteristically, small dense LDL have a decreased cholesterol to apo B ratio[43] and an enhanced susceptibility to oxidation.[44]

Although we did not perform lipoprotein subfractionation studies, from the compositional data for the VLDL fraction and the low cholesterol to apo B ratio in LDL, it can be inferred that these abnormalities were present at baseline in our patients. As reported in FCHL,[2,4] VLDL particles had a high lipid to apo B ratio. Gemfibrozil therapy partially reversed these alterations, indicating less particle enrichment with cholesterol and triglycerides and smaller VLDL more easily converted to LDL, a probable reason why the drug has little effect on LDL levels. Studies of the effects of gemfibrozil on VLDL subspecies in hypertriglyceridemic subjects have shown a predominant reduction of the large subfractions.[45,46] As reported for bezafibrate,[39] the decreased VLDL mass induced by gemfibrozil shortens the exposure of LDL and HDL to the action of lipid-transfer proteins, resulting in normalization of their composition.[47] Indeed, the increased HDL cholesterol with unchanged apo AI levels as observed after gemfibrozil treatment suggests cholesterol enrichment of HDL. However, there was only a small insignificant increase of the LDL cholesterol to apo B quotient. Small dense LDL have been reported either to persist[32,46,48] or to decrease[49,50] in the presence of significant triglyceride reductions after gemfibrozil therapy in hypertriglyceridemic subjects. At any rate, correction by fibrates of the lipoprotein compositional changes associated with hypertriglyceridemia, in theory, could have antiatherogenic potential despite the inefficacy in LDL cholesterol–lowering. As recently shown in the BECAIT Study,[51] bezafibrate reduced the angiographic progression of atherosclerosis even though LDL cholesterol was not reduced.

As inferred from the changes in the VLDL triglyceride to apo B ratio, lovastatin therapy was less efficacious than gemfibrozil to ameliorate VLDL composition. Recently, Gianturco et al[52] have reported that lovastatin reduces the number of large VLDL particles in hypertriglyceridemic patients. On the other hand, the abnormally low LDL cholesterol to apo B ratio, an indirect measure of the predominance of atherogenic small LDL particles,[43] was not affected by lovastatin treatment. In patients with combined hyperlipidemia, HMG CoA reductase inhibitors have been reported either to leave unchanged[32,53] or to reduce[54] small, dense LDL; apparently, the number of denser LDL particles declines only in patients in whom elevated triglyceride levels are reduced by drug therapy.[55]

In this study, gemfibrozil treatment had no effect on serum Lp(a) levels; in contrast, lovastatin induced a modest increase. Whereas no substantial Lp(a) changes have been reported after gemfibrozil therapy, the results of treatment with HMG CoA reductase inhibitors have been inconclusive, as both unchanged and increased levels have been observed.[56]

The inability of monotherapy to correct all of the lipid abnormalities in patients with mixed hyperlipidemia has prompted the utilization of combination treatment with fibrates and statins in this situation.[57] Both classes of drugs, by selectively targeting one aspect of the altered lipid profile, add their specific effects to normalize the three main lipid alterations characteristic of combined hyperlipidemia: high LDL cholesterol, high triglycerides, and low HDL cholesterol. Extending the findings of prior reports of short-term fibrate-statin therapy in small series of patients with mixed hyperlipidemia,[58-60] the results of coadministration of gemfibrozil and lovastatin for up to 1 year in patients with FCHL show how the effects of both drugs are combined to substantially modify lipid and lipoprotein values and attain target levels despite the severity of baseline dyslipidemia. While an alleged accentuated risk of muscle damage mandates close supervision of patients given fibrate-statin combinations,[57] standard doses of gemfibrozil plus medium doses of lovastatin were well tolerated in our patients. Our observations, together with recent reports of the safety and substantial benefit of long-term treatment with fibrate-statin combinations in large series of patients,[61,62] suggest this is the best therapeutic approach in patients with mixed hyperlipidemia. Monotherapy with atorvastatin holds promise in this situation,[34] but more clinical experience is needed.

In summary, the results of this study indicate that in patients with FCHL displaying elevated serum levels of apo B–containing lipoproteins and reduced HDL cholesterol concentrations, gemfibrozil favorably influences VLDL and HDL, whereas lovastatin has its major effect on LDL. However, the abnormal lipid profile is normalized only in a minority of patients after either therapy. This goal is safely achieved when giving combined treatment with both drugs. Given the increasing clinical experience with the safe use of fibrate-statin combination therapy, this can be regarded as the treatment of choice for patients with highly atherogenic dyslipidemia such as FCHL.

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