

ORIGINAL ARTICLE

Inhibition of Microsomal Triglyceride Transfer Protein in Familial Hypercholesterolemia

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ABSTRACT

BACKGROUND

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Patients with homozygous familial hypercholesterolemia have markedly elevated cholesterol levels, which respond poorly to drug therapy, and a very high risk of premature cardiovascular disease. Inhibition of the microsomal triglyceride transfer protein may be effective in reducing cholesterol levels in these patients.

METHODS

We conducted a dose-escalation study to examine the safety, tolerability, and effects on lipid levels of BMS-201038, an inhibitor of the microsomal triglyceride transfer protein, in six patients with homozygous familial hypercholesterolemia. All lipid-lowering therapies were suspended 4 weeks before treatment. The patients received BMS-201038 at four different doses (0.03, 0.1, 0.3, and 1.0 mg per kilogram of body weight per day), each for 4 weeks, and returned for a final visit after a 4-week drug washout period. Analysis of lipid levels, safety laboratory analyses, and magnetic resonance imaging of the liver for fat content were performed throughout the study.

RESULTS

All patients tolerated titration to the highest dose, 1.0 mg per kilogram per day. Treatment at this dose decreased low-density lipoprotein (LDL) cholesterol levels by 50.9% and apolipoprotein B levels by 55.6% from baseline ($P < 0.001$ for both comparisons). Kinetic studies showed a marked reduction in the production of apolipoprotein B. The most serious adverse events were elevation of liver aminotransferase levels and accumulation of hepatic fat, which at the highest dose ranged from less than 10% to more than 40%.

CONCLUSIONS

Inhibition of the microsomal triglyceride transfer protein by BMS-201038 resulted in the reduction of LDL cholesterol levels in patients with homozygous familial hypercholesterolemia, owing to reduced production of apolipoprotein B. However, the therapy was associated with elevated liver aminotransferase levels and hepatic fat accumulation.

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HOMOZYGOUS FAMILIAL HYPERCHOLESTEROLEMIA is caused by loss-of-function mutations in both alleles of the low-density lipoprotein (LDL) receptor gene.¹⁻³ Patients with the disease have plasma cholesterol levels of more than 500 mg per deciliter (12.9 mmol per liter); if untreated, patients have cardiovascular disease before 20 years of age and generally do not survive past 30 years of age.¹⁻³ Patients with homozygous familial hypercholesterolemia also have a poor response to conventional drug therapy,¹⁻³ which generally lowers LDL cholesterol levels through up-regulation of the hepatic LDL receptor. The current standard of care for these patients is LDL apheresis. This procedure can transiently reduce LDL cholesterol levels by more than 50%^{4,5} and may delay the onset of atherosclerosis,⁶⁻⁸ but it must be repeated frequently (every 1 to 2 weeks) and is not widely available. Thus, new therapies are needed for patients with homozygous familial hypercholesterolemia, as well as for other patients with severe refractory hypercholesterolemia who are candidates for LDL apheresis.

A potentially effective therapy for homozygous familial hypercholesterolemia would be to reduce LDL production. The microsomal triglyceride transfer protein is responsible for transferring triglycerides onto apolipoprotein B within the liver in the assembly of very-low-density lipoprotein (VLDL), the precursor to LDL.⁹ In the absence of functional microsomal triglyceride transfer protein, as in the rare recessive genetic disorder abetalipoproteinemia, the liver cannot secrete VLDL, leading to the absence of all lipoproteins containing apolipoprotein B in the

plasma.¹⁰⁻¹² Thus, the pharmacologic inhibition of microsomal triglyceride transfer protein might be a strategy for reducing LDL production and plasma LDL cholesterol levels.

Preclinical studies in animal models lacking LDL receptors have shown that the inhibition of microsomal triglyceride transfer protein significantly reduces serum cholesterol levels.^{13,14} We evaluated the cholesterol-lowering efficacy of the microsomal triglyceride transfer protein inhibitor BMS-201038 in patients with homozygous familial hypercholesterolemia and determined the mechanism of cholesterol reduction, the tolerability, and the effects on hepatic fat, using magnetic resonance imaging (MRI).

METHODS

STUDY PATIENTS

Six patients with homozygous familial hypercholesterolemia (three men and three women), 18 to 40 years of age, were enrolled in and completed the study. A diagnosis of homozygous familial hypercholesterolemia was suspected on clinical grounds and was confirmed by genetic analysis. Exclusion criteria were major surgery in the previous 3 months, congestive heart failure, history of liver disease or aminotransferase levels of more than three times the upper limit of the normal range, a serum creatinine level of more than 2.5 mg per deciliter (221 μ mol per liter), cancer within the past 5 years, or history of alcohol abuse or drug abuse. Two patients had known, clinically significant cardiovascular disease; both had undergone prosthetic-valve replacement and were receiving anticoagulation therapy. Our study was

Table 1. Baseline Characteristics of the Study Patients.

Patient No.	Sex	Age yr	Weight kg	Body-Mass Index*	Cardiovascular Disease†	LDL-Receptor Gene Mutations
1	F	18	56.1	24.3	Absent	delEx3-6/delEx3-6
2	F	18	59.0	25.3	Absent	1877delA/?
3	M	35	85.4	27.7	Present	652delGGT/652delGGT
4	F	40	77.3	30.1	Present	Ser156Leu/Ser156Leu
5	M	22	60.1	18.5	Absent	Cys660Xaa/Cys660Xaa
6	M	21	64.0	23.2	Absent	Cys660Xaa/Cys660Xaa

* The body-mass index is the weight in kilograms divided by the square of the height in meters.

† Patients 3 and 4 had symptomatic coronary artery disease that was confirmed by coronary angiography. Patients 1, 2, 5, and 6 had no symptoms of cardiovascular disease and were regularly evaluated with the use of noninvasive testing (and, if appropriate, coronary angiography), without evidence of obstructive coronary disease.

Table 2. Lipid and Lipoprotein Levels at Baseline, after Receipt of One of Four Doses of BMS-201038 for 4 Weeks, and after the 4-Week Washout Period.*

Measure	Patient No.						Percent Change from Baseline	P Value
	1	2	3	4	5	6		
Total cholesterol (mg/dl)								
Baseline	756	837	903	684	711	1212		
0.03 mg	660	840	717	717	684	1248	-4.8±9.9	0.29
0.1 mg	627	858	585	774	648	1086	-9.3±16.6	0.23
0.3 mg	482	714	591	504	424	891	-29.8±9.2	<0.001
1.0 mg	284	410	443	340	236	379	-58.4±8.6	<0.001
Washout	993	1053	1023	714	714	738	6.0±25.1	0.58
LDL cholesterol (mg/dl)								
Baseline	480	789	609	637	534	636		
0.03 mg	505	748	585	668	442	597	-3.7±8.3	0.32
0.1 mg	558	753	483	718	481	403	-7.1±20.1	0.42
0.3 mg	348	642	498	436	387	478	-24.7±5.3	<0.001
1.0 mg	224	383	403	301	201	306	-50.9±9.3	<0.001
Washout	804	883	858	518	559	478	13.6±35.4	0.39
VLDL cholesterol (mg/dl)								
Baseline	256	21	270	12	153	549		
0.03 mg	135	69	114	15	220	627	34.4±103.3	0.45
0.1 mg	48	84	75	24	138	642	42.3±142.4	0.50
0.3 mg	108	48	57	29	28	372	3.3±103.7	0.94
1.0 mg	34	5	18	8	14	44	-78.7±23.1	<0.001
Washout	153	138	138	162	129	216	273.6±535.1	0.27
Triglycerides (mg/dl)								
Baseline	285	130	362	82	233	605		
0.03 mg	248	84	279	110	416	502	4.1±43.5	0.83
0.1 mg	194	68	139	113	105	658	-24.9±39.7	0.19
0.3 mg	200	87	148	88	126	340	-34.1±22.8	0.02
1.0 mg	51	56	102	46	69	206	-65.2±13.3	<0.001
Washout	226	119	210	234	135	288	3.3±90.6	0.93

approved by the institutional review board and the General Clinical Research Center of the University of Pennsylvania and was monitored by the Office of Human Research of the University of Pennsylvania. The study protocol was fully explained to all six patients, each of whom provided written, informed consent.

STUDY PROTOCOL

The authors designed the study and generated, held, and analyzed the data. The study drug, BMS-201038, was provided by Bristol-Myers Squibb.

This was an open-label study to evaluate the safety, tolerability, and efficacy of BMS-201038 for the treatment of patients with homozygous familial hypercholesterolemia. During an initial screening visit, the eligibility of the six patients was verified, their health status was evaluated, and a very-low-fat diet was initiated. All lipid-lowering treatments, including apheresis, were suspended at least 4 weeks before the baseline visit and continued to be suspended until the study was completed. No other drug treatment was suspended. BMS-201038 was administered,

Table 2. (Continued.)

Measure	Patient No.						Percent Change from Baseline	P Value
	1	2	3	4	5	6		
Apolipoprotein B (mg/dl)								
Baseline	315	273	342	240	303	387		
0.03 mg	306	354	336	300	330	396	10.2±14.0	0.13
0.1 mg	276	336	288	276	225	375	-3.2±18.8	0.70
0.3 mg	228	312	273	216	213	330	-14.7±16.0	0.08
1.0 mg	112	149	216	121	91	127	-55.6±13.5	<0.001
Washout	324	345	432	324	282	312	10.7±21.7	0.28
HDL cholesterol (mg/dl)								
Baseline	20	27	24	35	24	27		
0.03 mg	20	23	18	34	22	24	-10.4±9.0	0.04
0.1 mg	21	21	27	32	29	41	9.9±25.6	0.39
0.3 mg	26	24	36	39	9	41	11.6±43.5	0.54
1.0 mg	26	22	22	31	21	29	-2.2±18.0	0.77
Washout	36	32	27	34	26	44	29.9±33.4	0.08
Apolipoprotein A-I (mg/dl)								
Baseline	68	79	83	76	62	30		
0.03 mg	67	67	63	80	77	95	34.2±90.9	0.40
0.1 mg	69	64	79	80	65	74	22.4±61.5	0.41
0.3 mg	78	70	80	88	64	94	38.7±86.2	0.32
1.0 mg	62	64	64	67	49	44	-6.1±26.4	0.59
Washout	100	81	82	96	76	104	57.3±94.4	0.20

* Plus-minus values are means ±SD. To convert values for cholesterol to millimoles per liter, multiply by 0.02586. To convert values for triglycerides to millimoles per liter, multiply by 0.01129. P values are for the levels during the study versus those at baseline.

beginning at the baseline visit, at four increasing doses — 0.03, 0.1, 0.3, and 1.0 mg per kilogram of body weight per day — each for 4 weeks. The patients returned to the General Clinical Research Center every 7, 14, and 28 days after the start of a new dose, and 28 days after the last dose of the study drug, for safety and pharmacodynamic evaluations.

The most recent Common Terminology Criteria for Adverse Events of the National Cancer Institute (initially version 2 and subsequently version 3) were used to assign a severity grade to all adverse events. According to protocol, if a patient had a confirmed grade 3 (severe) adverse event, the dose was decreased to 1.5 times the previous dose for 4 weeks (with visits at 7, 14, and 28 days during that period). If there was no evidence of adverse events of grade 3 or higher during that period, the dose was increased to the next-high-

est dose and treatment proceeded per protocol. Adverse events were judged by one of the investigators as not related to treatment with the study drug, unlikely to be related, possibly related, probably related, or definitely related, and these judgments were reviewed by a data and safety monitoring board.

DIET

All patients received detailed dietary counseling by a registered dietitian at the screening visit and at all subsequent visits until after the study drug was discontinued. The patients were advised to consume a diet containing less than 10% of energy from total dietary fat while consuming adequate calories to maintain weight or promote growth. All patients received a standard multivitamin that supplied 100% of the reference dietary intake for all vitamins and minerals.

MRI OF THE LIVER

MRI of the liver was conducted at baseline, after 4 weeks at each dose, and at 4 weeks after drug withdrawal, with the use of chemical-shift MRI techniques that have been shown to evaluate fat content of the liver accurately.^{15,16} All quantitative MRI measurements of hepatic fat content were performed by a single radiologist, who was unaware of the patients' clinical status and liver-function results.

LABORATORY ANALYSIS

Blood was drawn at each visit, after a 12-hour fast. A standard metabolic panel, complete blood count, and standard urinalysis were also performed at each visit. Plasma lipid and lipoprotein analyses were performed in a lipid laboratory standardized by the Centers for Disease Control and Prevention. Total cholesterol, high-density lipoprotein (HDL) cholesterol, and triglyceride levels were measured enzymatically on an autoanalyzer (Cobas Fara II, Roche Diagnostic Systems) with reagents from Sigma Chemical Co. VLDL and LDL cholesterol levels were determined with the use of beta-quantification and the standard Lipid Research Clinics protocol as modified by Cole et al.¹⁷ Levels of apolipoproteins B and A-I were measured with the use of reagents from Wako Chemicals USA, and Lp(a) lipoprotein levels were measured with reagents from Diasorin on a Cobas Fara II autoanalyzer. Levels of lipoprotein subclasses were determined with the use of proton nuclear magnetic resonance spectroscopy, as previously described.¹⁸

KINETICS STUDIES

Before the study began, three patients (Patients 4, 5, and 6) had participated in a kinetics study to investigate the metabolism of lipoproteins containing apolipoprotein B in patients with homozygous familial hypercholesterolemia.¹⁹ To investigate in vivo the mechanism of action of BMS-201038, we repeated the kinetic study in these patients at the end of the 4-week period at the highest dose (1.0 mg per kilogram per day), using identical methods (endogenous labeling with deuterated leucine).

STATISTICAL ANALYSIS

Statistical comparisons were performed with SAS software (version 8.2, SAS Institute). Continuous variables that were not normally distributed, such

as fasting triglyceride levels, were appropriately transformed to meet the assumptions of subsequent statistical tests. Continuous variables were analyzed using paired t-tests for changes over time or the Wilcoxon signed-rank test, as appropriate. Percentages were analyzed using the chi-square test or Fisher's exact test when expected cell counts were less than 5. For within-patient comparisons over time, we used McNemar's test, along with matched odds ratios and 95% confidence intervals. All P values were calculated from two-tailed tests, and P values less than 0.05 were considered to indicate statistical significance.

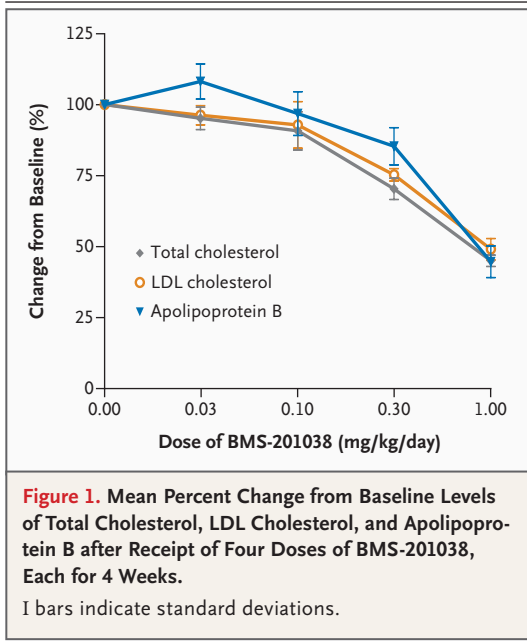
RESULTS**STUDY PATIENTS**

The characteristics of the six study patients at screening are shown in Table 1. Four patients (Patients 1, 3, 5, and 6) were found to be negative for the LDL receptor on the basis of homozygosity for known loss-of-function LDL-receptor mutations.^{1,2} A fifth (Patient 2) was found to be receptor-negative on the basis of phenotype and LDL-receptor activity in skin fibroblasts. The sixth patient (Patient 4) was found to have a defective LDL receptor on the basis of her LDL-receptor mutation.

EFFECTS OF BMS-201038 ON PLASMA LIPID AND LIPOPROTEIN LEVELS

The mean doses of BMS-201038 at each of the four titration steps were 2.0, 6.7, 20.1, and 67.0 mg per day. Table 2 shows the changes in lipid and lipoprotein levels during the study (additional lipoprotein results are available in Table A in the Supplementary Appendix, available with the full text of this article at www.nejm.org). The mean total cholesterol level was 851 mg per deciliter (22.0 mmol per liter) at baseline. After 4 weeks of receiving the 0.3-mg-per-kilogram dose, the mean level was reduced to 601 mg per deciliter (15.5 mmol per liter), a 29.8% reduction from the baseline level ($P<0.001$). After 4 weeks of receiving the 1.0-mg-per-kilogram dose, the mean level was reduced to 349 mg per deciliter (9.0 mmol per liter), a 58.4% reduction from baseline ($P<0.001$).

The mean LDL cholesterol level was 614 mg per deciliter (15.9 mmol per liter) at baseline. After 4 weeks at the 0.3-mg-per-kilogram dose, the mean level was reduced to 465 mg per deciliter (12.0 mmol per liter), a 24.7% reduction from the

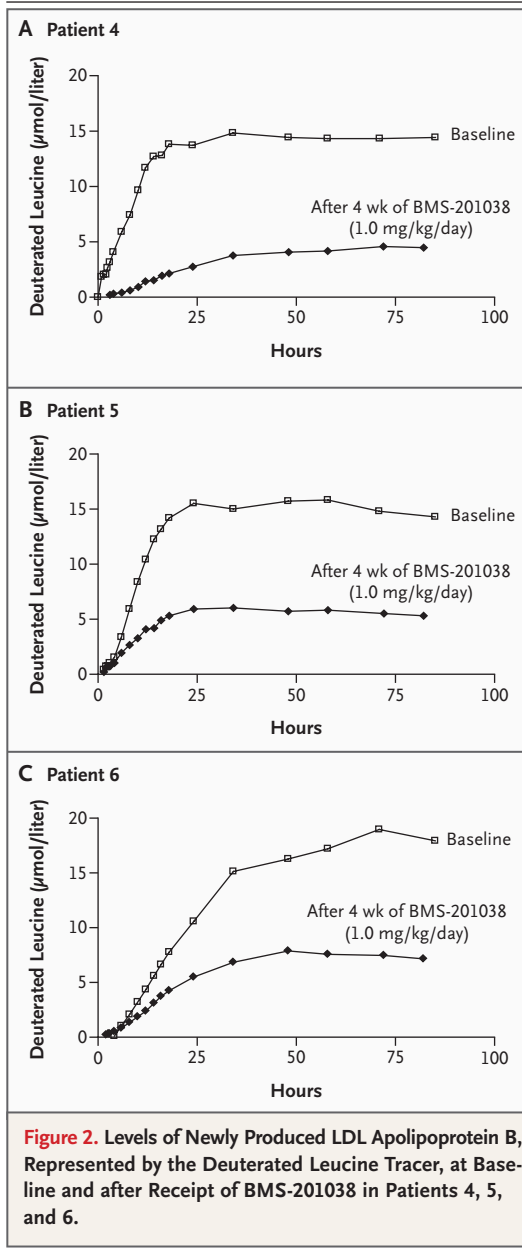


baseline level ($P < 0.001$). At the 1.0-mg-per-kilogram dose, the mean level was further reduced to 303 mg per deciliter (7.8 mmol per liter), a 50.9% reduction from the baseline level ($P < 0.001$).

The mean triglyceride level was 283 mg per deciliter (3.2 mmol per liter) at baseline and was reduced to 165 mg per deciliter (1.9 mmol per liter) after 4 weeks at the 0.3-mg-per-kilogram dose, a 34.1% reduction from the baseline level ($P = 0.02$). After 4 weeks at the 1.0-mg-per-kilogram dose, the mean level was further reduced to 88 mg per deciliter (1.0 mmol per liter), a 65.2% reduction from the baseline level ($P < 0.001$).

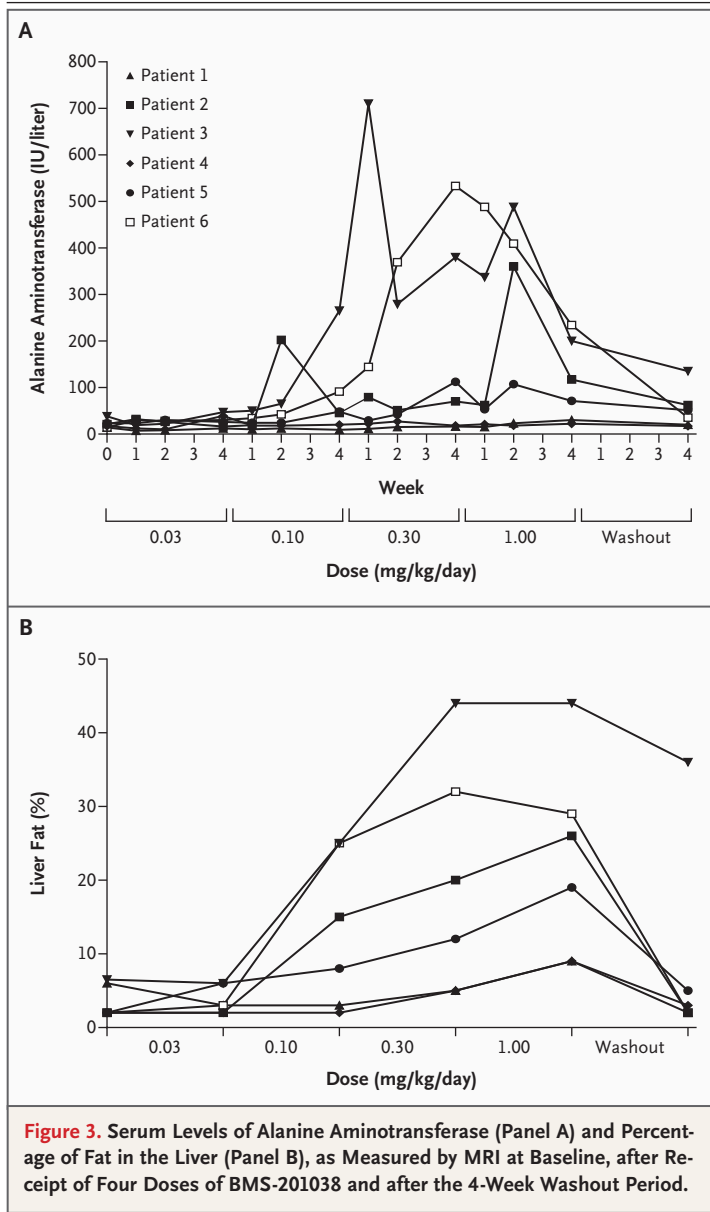
The mean apolipoprotein B level was 310 mg per deciliter at baseline and, after 4 weeks at the 0.3-mg-per-kilogram dose, was reduced to 262 mg per deciliter, a 14.7% reduction from the baseline level ($P = 0.08$). After 4 weeks at the 1.0-mg-per-kilogram dose, the mean level was further reduced to 136 mg per deciliter, a 55.6% reduction from the baseline level ($P < 0.001$).

Despite a range of lipid levels at baseline, similar percent reductions were observed during the study in all the patients (Fig. 1). There were no clinically significant changes in the plasma levels of HDL cholesterol, apolipoprotein A-I, or Lp(a) lipoprotein. Lipoprotein subclass levels, measured by nuclear magnetic resonance spectroscopy, were consistent with the plasma lipid and apolipoprotein levels (see Table A in the Supplementary Appendix). Thus, inhibition of the



microsomal triglyceride transfer protein markedly reduced plasma levels of apolipoprotein B-containing lipoproteins across the spectrum.

Lipoprotein kinetics studies, using endogenous labeling with deuterated leucine, were performed in three of the six patients before the trial began and again during the 4 weeks at the highest dose of BMS-201038 (1.0 mg per kilogram). As compared with the pretreatment (baseline) kinetic data, the rate of production of LDL apolipoprotein B during those 4 weeks at 1.0 mg per kilogram was reduced by approximately 70% (Fig. 2). This finding



shows that the mechanism of the reduction in LDL cholesterol levels induced by the microsomal triglyceride transfer protein is reduced production of apolipoprotein B.

SAFETY AND TOLERABILITY

A list of all adverse events reported during the study is given in Table B in the Supplementary Appendix. No patients withdrew from the study owing to an adverse event. Adverse events judged to be possibly or probably drug-related included primarily gastrointestinal adverse events, particularly increased stool frequency. Five of the six pa-

tients reported one or more episodes of increased stool frequency of mild or moderate intensity. All episodes were transient and in many cases were temporally linked to consumption of a relatively high-fat meal. The average caloric intake from fat during the entire study was 16.7%, but the range was less than 10% to approximately 30%, and fat intake may have influenced the gastrointestinal tolerability of the drug. By the end of the 4 weeks at 1.0 mg per kilogram of BMS-201038 per day, there was a trend toward a decrease in body weight as compared with baseline (mean [\pm SD] decrease, $4.4 \pm 2.9\%$; $P=0.06$). Weight rebounded to baseline values after the 4-week washout period.

We observed elevated liver aminotransferase levels (Fig. 3A, and Table C in the Supplementary Appendix) in four of the six patients. In addition, hepatic fat (Fig. 3B) increased substantially in four patients in response to treatment with BMS-201038. Two patients (Patients 1 and 4) did not have elevated aminotransferase levels and had only minimal increases in hepatic fat (less than 10%). In two other patients (Patients 2 and 5), the elevation in aminotransferase levels was dose-dependent, and the hepatic fat content was 18 to 24%. In Patients 3 and 6, aminotransferase levels were elevated substantially, and the hepatic fat content increased to more than 30% at the highest dose. In particular, Patient 3 had a confirmed grade 3 elevation in aminotransferase level 1 week after titration to the 0.3-mg-per-kilogram dose. As per protocol, the dose was reduced to 0.15 mg per kilogram for 4 weeks, with a consequent decrease in aminotransferase levels, and was then titrated back up to 0.3 mg per kilogram. The patient then completed 4 weeks of treatment at both the 0.3-mg-per-kilogram and 1.0-mg-per-kilogram doses. Aminotransferase and hepatic fat levels returned to baseline levels 4 weeks after the therapy was ceased in all the patients except Patient 3, in whom they did not return to the normal range until 14 weeks after cessation of therapy.

DISCUSSION

In this study, we showed that treating patients who have homozygous familial hypercholesterolemia with the microsomal triglyceride transfer protein inhibitor BMS-201038 was highly effective in reducing plasma LDL cholesterol levels, with a reduction of more than 50% at the highest dose. Plasma levels of all other apolipoprotein B-con-

taining lipoproteins were similarly reduced by inhibition of the microsomal triglyceride transfer protein. We also established that the mechanism of this reduction in LDL cholesterol is a markedly reduced rate of production of LDL apolipoprotein B. Thus, inhibition of microsomal triglyceride transfer protein is effective in lowering plasma levels of atherogenic apolipoprotein B-containing lipoproteins in patients lacking functional LDL receptors.

Because the microsomal triglyceride transfer protein is expressed in the intestine and is required for chylomicron assembly and secretion,⁹ inhibition of the protein could cause steatorrhea. For this reason, we instructed patients in this study to follow a diet containing less than 10% of energy from fat. In addition, we devised a dose-titration strategy that might allow the intestine to accommodate the increasing inhibition of microsomal triglyceride transfer protein. Under these conditions, all six patients tolerated the drug up to the highest dose (1.0 mg per kilogram per day), with relatively minor gastrointestinal side effects. The few episodes of frequent stools were dose-related, transient, and temporally associated with consumption of a relatively high-fat meal. Patients with abetalipoproteinemia, who completely lack microsomal triglyceride transfer protein, learn early in life to consume a fat-restricted diet in order to avert steatorrhea.^{10,20-22} Thus, it may be possible to minimize the gastrointestinal side effects of microsomal triglyceride transfer protein inhibition through dietary fat restriction, dose titration and, when necessary, reduction of the dose.

Accumulation of liver fat is likely to be intrinsically linked to the mechanism of action of microsomal triglyceride transfer protein inhibitors, and such accumulation could present a serious barrier to the clinical use of this class of agents. In our small study, we noted substantial variability among the six patients, in whom responses ranged from no elevation of aminotransferase levels and minimal changes in hepatic fat content in two patients to substantial elevation of aminotransferase levels and increases in hepatic fat content to more than 30% in two others. Of the latter patients, one had marked hypertriglyceridemia, and the other revealed that he had been drinking a substantial amount of alcohol during the study.

Thus, these patients had metabolic perturbations associated with increased hepatic triglyceride synthesis that might have predisposed them to greater increases in hepatic fat. In five of the six patients, hepatic fat content returned to baseline levels 4 weeks after the drug was withdrawn, but it did persist in the sixth patient.

The clinical significance of hepatic fat accumulation and the probability of its evolution to fibrotic liver disease are still debated, but substantial elevation of aminotransferase levels and hepatic steatosis are potentially serious adverse events that should not be underestimated. Studies of long-term therapy with microsomal triglyceride transfer protein inhibitors, under carefully monitored conditions, will be required to fully determine the safety of this approach.

In summary, the microsomal triglyceride transfer protein inhibitor BMS-201038 was effective in reducing the levels of atherogenic apolipoprotein B-containing lipoproteins by reducing their production in patients with homozygous familial hypercholesterolemia. These results establish proof of concept for microsomal triglyceride transfer protein inhibition in such patients and provide support for further clinical investigation of this therapy. However, our small study showed major effects on aminotransferase and hepatic fat levels. The effects of long-term inhibition of the microsomal triglyceride transfer protein on the liver will need to be carefully studied to determine the safety of this approach.

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Dr. Szapary reports being an employee of and having equity interest in Wyeth; Dr. Gregg, being an employee of and having equity interest in Bristol-Myers Squibb and holding patents on microsomal triglyceride transfer protein inhibitors (including BMS-201038) and the use of microsomal triglyceride transfer protein inhibitors to lower plasma lipid and lipoprotein levels; Dr. Rader, receiving lecture fees, consulting fees, and grant support from Bristol-Myers Squibb, as well as from other companies that manufacture lipid-lowering drugs, and having equity interest in Aegerion Pharmaceuticals, which holds the license to develop BMS-201038; and Ms. Bloedon, serving as a consultant for Aegerion Pharmaceuticals. No other potential conflict of interest relevant to this article was reported.

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