Effect of Simvastatin in Addition to Chenodeoxycholic Acid in Patients With Cerebrotendinous Xanthomatosis

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The effects of combination therapy with chenodeoxycholic acid (CDCA) and simvastatin on serum cholestanol, low-density lipoprotein (LDL) cholesterol, and lathosterol levels were investigated in seven adult patients with cerebrotendinous xanthomatosis (CTX) who were on long-term treatment with CDCA. The patients were treated with a combination of CDCA 750 mg daily and an increasing dose of simvastatin from 10 mg to 40 mg daily for a period of 6 months. We found a significant effect of this combination therapy compared with CDCA alone in terms of decreasing the serum cholestanol and LDL cholesterol levels, particularly with a daily dose of 40 mg simvastatin. The mean cholestanol level decreased from 9.27 μmol/L (baseline) to 6.69 μmol/L (40 mg simvastatin), while the mean LDL cholesterol level decreased from 5.08 mmol/L (baseline) to 3.04 mmol/L (40 mg simvastatin). No side effects were reported, and there were no effects on the clinical condition, cerebral magnetic resonance imaging (MRI), visual evoked potentials, and electroencephalographic features. We conclude that a combination of 750 mg CDCA and 40 mg simvastatin daily is effective to further reduce serum cholestanol, LDL cholesterol, and lathosterol in adult CTX patients treated with long-term CDCA. Whether this combination treatment will be effective for the long-term prevention of neurological deterioration and atherosclerosis remains to be established.

CEREBROTENDINOUS XANTHOMATOSIS (CTX) is a rare autosomal recessive lipid-storage disease characterized by abnormal bile acid synthesis due to a deficiency of the mitochondrial enzyme sterol 27-hydroxylase.[1] This deficiency leads to reduced synthesis of cholic acid and almost no production of chenodeoxycholic acid (CDCA). The absence of the negative-feedback mechanism of cholic acid and CDCA on 7α-hydroxylase—the rate-limiting enzyme in bile acid synthesis—leads to increased flux through the part of the bile acid synthesis pathway upstream of the metabolic block. Via the metabolite 7α-hydroxycholesterol, this results in excessive production of cholestanol, which accumulates in many tissues.[2] Via 24- and 25-hydroxylation, bile alcohols are produced in CTX that are excreted in the bile and urine. In CTX patients, cholesterol synthesis is also increased, perhaps because of the reduced feedback inhibition of beta hepatic hydroxymethylglutaryl coenzyme A (β-HMG-CoA) reductase in the liver by bile acids.[2] Ballantyne et al[3] found an enhanced fractional clearance of low-density lipoprotein (LDL), most likely due to increased activity of hepatic receptors for LDL. The biochemical diagnosis is made on the basis of elevated bile alcohol levels in urine and elevated serum cholestanol levels.[4,5] The clinical spectrum of CTX is characterized by premature bilateral cataracts, followed by neurologic and neuropsychiatric abnormalities and formation of tendon xanthomas. Premature atherosclerosis is observed in many CTX patients.[2]

Since 1975, CDCA has been commonly used as a therapy for CTX.[6] After starting CDCA therapy, there is a considerable decrease in the serum cholestanol level and a sharp decline in the excretion of bile alcohols in the urine. Long-term CDCA treatment is effective for CTX.[7] However, many patients deteriorate neurologically despite CDCA therapy.[8-12] The exact pathogenesis of this neurological deterioration is still unknown. In the literature, comprising one trial and seven case studies, there is limited information about the effect of β-HMG-CoA reductase inhibitors in CTX patients.[13-20]

To investigate whether the combination of CDCA and a β-HMG-CoA reductase inhibitor would reduce serum cholestanol levels to a greater extent than CDCA treatment alone, we administered a combination of CDCA and an increasing dose of simvastatin to seven adult CTX patients for a period of 6 months in a self-controlled trial. All had been receiving long-term (at least 7 years) CDCA treatment. The aim of this study was to evaluate the efficacy and tolerance of simvastatin in these patients, particularly the effects on serum cholestanol, cholesterol, high-density lipoprotein (HDL) and LDL cholesterol, and lathosterol levels. We also monitored the clinical condition, tendon xanthoma size, cerebral magnetic resonance imaging (MRI) scan features, electroencephalographic characteristics, and visual evoked potentials (VEPs) before and after combination therapy.

SUBJECTS AND METHODS

Seven adult CTX patients who had been treated with 750 mg CDCA daily for a period of 7 to 13 years were included in a self-controlled trial. The biochemical diagnosis of the patients was established by elevated plasma cholestanol levels or elevated urinary bile alcohol excretion. Moreover, analysis of the sterol 27-hydroxylase gene showed mutations on both alleles that have been described previously.[21-24] Clinical and biochemical features of the patients at the time of diagnosis are listed in Table 1.

Owing to the rarity of this disease, a randomized controlled trial was not possible. Pregnant or breast-feeding women and patients with active liver disease or an unexplained elevation of serum transaminase were excluded, as were patients with concurrent use of immunosuppressive drugs, nicotinic acid, or fibric acid derivatives.

Therapy with simvastatin was started at 10 mg daily for a period of 4 weeks. The dose of simvastatin was then doubled for another period of 4 weeks, after which the daily simvastatin dose was increased once more by 10 mg for a 4-week period. Ultimately, a daily dose of 40 mg was

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Table 1. Clinical and Biochemical Characteristics of the Patients at the Time of Diagnosis, Duration of CDCA Therapy Before Entering the Trial, and Radiologic and Neurophysiologic Features Before and After the Trial Medication

Characteristic	Patient						
	A	B	C	D	E	F	G
Sex	Female	Male	Male	Female	Female	Male	Male
Age (yr)	51	44	54	47	46	58	40
Age at diagnosis (yr)	44	37	41	34	40	46	33
Duration of CDCA therapy (yr)	7	7	13	13	7	11	7
Major systemic signs							
Cataract	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Achilles tendon xanthomas	Yes	Yes	Yes	Yes	No	Yes	Yes
Neurologic signs							
Epilepsy	+	+	−	+	−	+	−
Dementia	+	+	+	++	−	+	−
Corticospinal tract	++	++	++	++	−	++	++
Cerebellar	+	−	+	++	−	++	−
Polyneuropathy	+	+	+	+	−	+	+
Biochemistry at diagnosis							
Serum cholestanol (3.3-12.5 μmol/L)	33	83	229	299	55	124	NA
Serum cholesterol (4.7-6.5 mmol/L)	2.4	3.9	5.0	5.0	5.1	5.3	NA
CCR (0.08%-0.21%)	1.3	2.1	4.6	6.0	1.1	2.3	NA
Urine bile alcohol excretion	++	++	++	++	++	++	++
MRI findings							
T2 hyperintensity (demyelination)	+	+	+	++	NA	++	+
General atrophy	+	+	++	++	NA	++	−
Achilles tendon xanthoma size (cm^3)							
Left (before/after)	28.2/27.5	28.8/29.4	108.8/99.5	32.9/29.3	NA	104.0/90.8	22.5/33.8
Right (before/after)	0/0	24.9/26.0	142.9/136.7	11.2/7.3	NA	153.6/136.3	53.5/56.4
EEG findings							
Diffuse slowing	+/NC	+/NC	++/NC	+/NC	NA	++/NC	+/NC
Paroxysmal discharges	−/NC	−/NC	+/NC	−/NC	NA	+/NC	+/NC
VEP findings							
Delayed P 100	Yes/NC	Yes/NC	Yes/NC	Yes/NC	NA	Yes/NC	Yes/NC

Abbreviations: −, absent; + → ++, mild → moderate; NA, not available; NC, no change after simvastatin treatment.

used for 3 months. After each 4-week period, the patients were evaluated clinically and biochemically. Then, simvastatin treatment was stopped while CDCA was continued; over the following 3 months, a biochemical analysis was performed after each 4-week period. After completing the trial, the patient reverted to the medication regimen that was used before the trial, until the trial data were fully evaluated. The study was approved by the ethics committee, and informed consent was obtained from each subject.

Biochemical and Technical Studies

Tests for liver and renal function, creatine kinase, glucose, hemoglobin, and leukocyte and thrombocyte counts were performed. Serum cholestanol and cholesterol levels were measured according to the method of Koopman et al[25] using capillary gas chromatography on a CP Sil 19 CB column (Chrompack, Middleburg, The Netherlands). The lathosterol level, a parameter of endogenous cholesterol synthesis, was measured according to the method of Wolthers et al[4] using capillary gas chromatography on a CP Sil 5 column. Urinary excretion of bile alcohols was measured using capillary gas chromatography essentially according to the method of Wolthers et al[5] and expressed per millimole of creatinine. To avoid methodological differences in analyzing the serum samples for cholestanol, cholesterol, and lathosterol, the samples were frozen (−20°C) and analyzed within one analytical run. The same procedure was followed for urine samples.

Before and after 6 months of combination therapy, the following investigations were performed in six of seven patients: cerebral MRI (performed on 1.5 T including T_1- and T_2-weighted axial images), electroencephalogram (EEG), checkerboard and flash visual evoked potentials (VEPs), and electrocardiogram. Also, the volume of Achilles tendon xanthomas was measured with a sagittal T_1-weighted MRI before and after combination therapy.

Statistics

Statistical analyses were performed for serum cholestanol, cholesterol (including HDL and LDL cholesterol), and lathosterol levels and the following parameters: serum cholestanol to cholesterol ratio (CCR), LDL/HDL cholesterol ratio, percentage of LDL and HDL in total cholesterol (%LDL and %HDL), and serum lathosterol to cholesterol ratio (LCR). Differences in any of the parameters between the successive doses of simvastatin and baseline were examined by two-sided paired Student *t* tests. Afterward, separate two-way ANOVAs (mixed model) were performed on the increasing doses, repeated maximum doses, repeated washout measurements for serum cholestanol, total cholesterol, LDL cholesterol, and lathosterol levels, followed by a multiple comparison of all pairwise differences according to the method of Scheffé.[26] Changes in the mean volume of xanthomas on both Achilles tendons before and after simvastatin therapy were examined by the two-sided paired Student *t* test.

Differences were considered to statistically significant at a P value of .05 or less.

RESULTS

Patients and Technical Investigations

All patients showed premature bilateral cataracts combined with neurological signs and symptoms (Table 1). Before

entering the trial, six patients had white-matter lesions on MRI, and five patients had mild to moderate cerebral atrophy. In six patients, the EEG revealed diffuse slowing, and paroxysmal discharges were observed in three patients. The VEP showed prolonged conduction times in these six patients.

All of the patients completed the trial. No side effects of simvastatin were reported, and there was no increase in serum creatine kinase or transaminase. After 6 months of simvastatin therapy, there were no changes in the clinical condition, EEG, VEP, or the original abnormalities on cerebral MRI. A reduction in the tendon xanthoma volume was noted in patients C and F, whereas the volume increased in one patient (case G). The mean volume of the bilateral Achilles tendon xanthomas was 59 cm^3 before simvastatin therapy and 56 cm^3 after 6 months; this mean reduction was not significant ($P = .36$).

Serum Lipids

The raw data for serum cholestanol, cholesterol, LDL cholesterol, and lathosterol are shown per monthly assessment in Fig 1. The mean values are connected by the line. In Table 2, the effects of simvastatin on all lipid parameters are shown.

Before starting the trial medication, cholestanol levels were less than the upper-normal level of 12.5 μmol/L in all patients except patient G (13.3 μmol/L). Generally, there was a significant decrease in serum cholestanol, cholesterol, LDL cholesterol, and lathosterol compared with the baseline levels with each successive dose of simvastatin. This effect was most prominent at a daily dose of 30 mg or 40 mg simvastatin. Regarding HDL cholesterol, a significant increase was found at daily doses of 20 and 40 mg simvastatin. Similar results were observed with respect to the LDL/HDL ratio, %LDL, %HDL, and LCR. The CCR remained essentially unchanged. Withdrawal of simvastatin resulted in an immediate change in serum cholestanol, cholesterol, LDL cholesterol, and lathosterol levels, and there was no further significant deviation from baseline. An ANOVA on the measurements from the first phase with increasing doses (including the first month with a dose of 40 mg) showed that serum cholestanol decreased significantly with simvastatin doses of 30 mg ($P = .02$) and 40 mg ($P = .007$) as compared with baseline levels. Serum cholesterol, LDL cholesterol, and lathosterol decreased significantly with all simvastatin doses of 10 to 40 mg ($P \leq .01$, $P \leq .002$, and $P \leq .04$, respectively). No significant differences were found between the doses. An ANOVA on the measurements from the maintenance phase of 40 mg simvastatin (over a period of 3 months) did not show any significant shifts in the serum levels of these parameters. An ANOVA on the measurements after withdrawal of simvastatin only showed a significantly lower level of

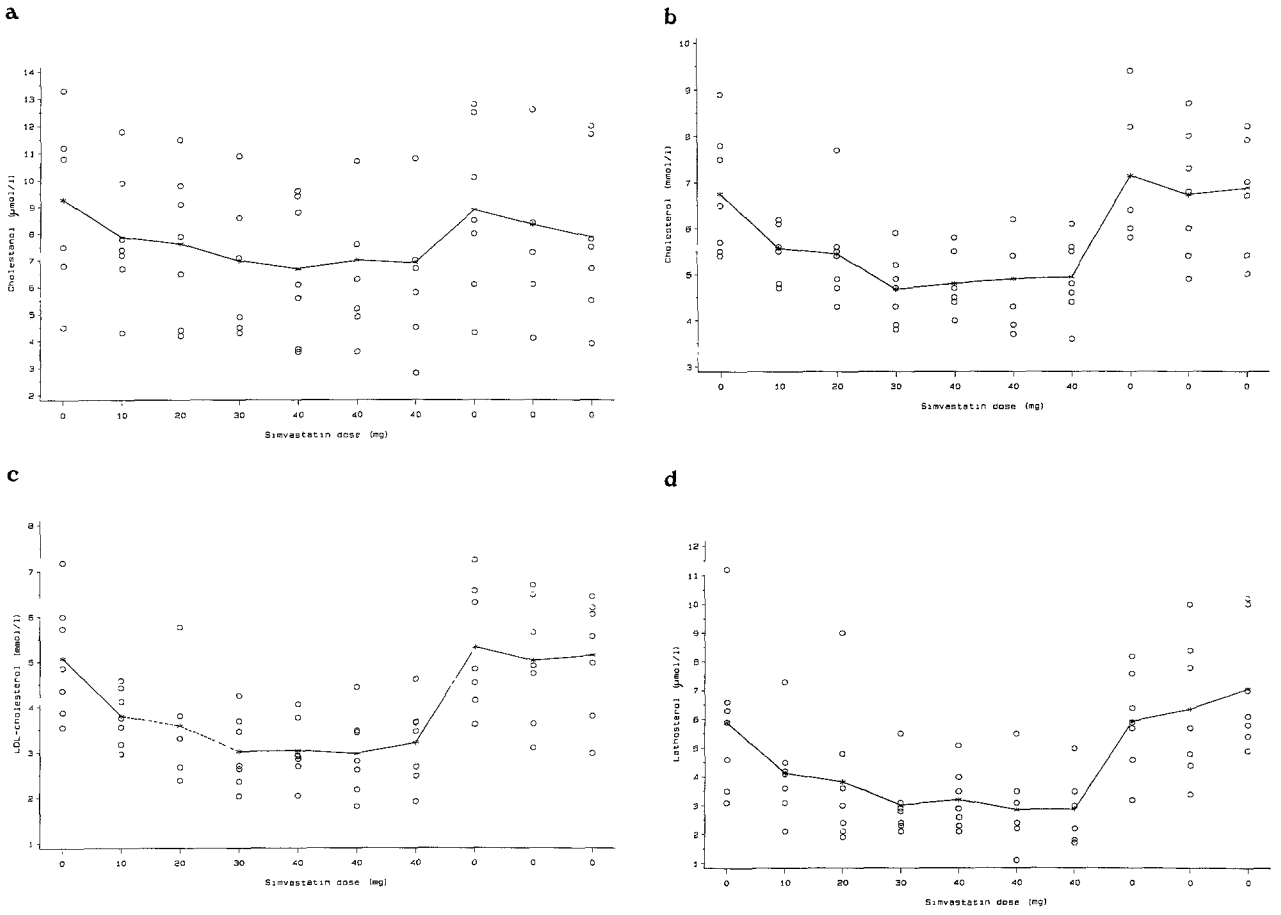

Fig 1. Serum lipid levels during combination therapy and washout of simvastatin. Each dose level was administered for 1 month. a, cholestanol (μmol/L); b, cholesterol (mmol/L); c, LDL cholesterol (mmol/L); d, Lathosterol (μmol/L).

Table 2. Mean Plasma Lipid Levels and Lipid Ratios During Successive Months of Gradually Increasing Doses of Simvastatin Followed by Withdrawal in Seven CTX Patients on Long-Term CDCA Treatment

		Simvastatin Dose									
Parameter	Reference Range	0 mg	10 mg	20 mg	30 mg	40 mg	40 mg	40 mg	0 mg	0 mg	0 mg
Cholestanol	3.3-12.5 μmol/L	9.27	7.87	7.63‡	6.99†	6.69‡	7.00†	6.91†	8.90	8.34	7.87*
Cholesterol	4.7-6.5 mmol/L	6.76	5.57†	5.44‡	4.67‡	4.80‡	4.90§	4.94‡	7.14	6.73	6.87
HDL cholesterol	0.95-1.70 mmol/L	1.18	1.32	1.35‡‖	1.20	1.29†	1.40*	1.29†	1.26	1.16	1.23
LDL cholesterol	<4.7 mmol/L	5.08	3.80†	3.59§‖	3.02§	3.04§	2.98§	3.22‡	5.32	5.03	5.14
LDL/HDL cholesterol ratio		3.98	2.76†	2.18§‖	2.40‡	2.20§	2.02§	2.21§	3.92	3.95	3.81
%HDL cholesterol		17.7	23.8†	26.0‡‖	26.3‡	27.2§	28.8§	27.0§	18.1	17.7	18.5
%LDL cholesterol		74.6	68.1†	65.1‡‖	63.8§	62.8§	60.2‡	64.1§	73.9	73.9	73.8
CCR		0.134	0.139	0.140	0.147	0.139	0.143	0.140	0.127	0.126	0.114
Lathosterol¶		5.9	4.1†	3.8‡	3.0‡	3.2‡	2.9‡	2.9‡	5.9	6.4	7.1
LCR		0.86	0.74*	0.67†	0.64†	0.66†	0.57‡	0.59‡	0.83	0.96	1.02

NOTE. Baseline values (0 mg) were compared with the mean levels using paired Student *t* tests.

*$.05 < P \leq .10$.

†$.01 < P \leq .05$.

‡$.001 < P \leq .01$.

§$P \leq .001$.

‖n = 5; in 2 of 7 patients, these results could not be obtained.

¶Normal values[4]: normal subjects (n = 22), 5.70 ± 2.47 μmol/L; untreated CTX patients (n = 13), 26.05 ± 11.03 μmol/L; CTX patients on CDCA treatment (n = 13), 6.34 ± 4.06 μmol/L.

cholestanol in the last (third) month relative to the first ($P = .03$).

It is to be expected that the distribution of the lipid parameters will be more or less skewed to the right. This was true of the data except for cholestanol, cholesterol, CCR, and %LDL cholesterol. However, substitution of the paired *t* tests by signed-rank tests only showed minor deviations in the results. A similar conclusion could be drawn after performing the ANOVAs using square root transformation.

During CDCA therapy and combination therapy, there was no measurable urinary bile alcohol excretion (data not shown).

DISCUSSION

In seven adult CTX patients treated with long-term CDCA, we found a significant reduction in serum cholestanol, LDL cholesterol, and lathosterol levels with a combination of 750 mg CDCA and 30 or 40 mg simvastatin daily. During combination therapy, no clinical effects or changes in the Achilles tendon xanthoma size, EEG, VEP, or cerebral MRI were observed. This was not unexpected, because the duration of combination therapy was short in relation to the disease duration in these patients. Besides, most of the patients were in an advanced stage of CTX and probably had irreversible neurological damage.

According to the literature, several compounds have been administered to CTX patients, eg, cholestyramine, but these led to increased levels of cholestanol.[6] Ursodeoxycholic acid, cholic acid, and taurocholic acid also were given to CTX patients.[27] Since 1975, CDCA has been used as a therapy for CTX[6] and has proven to be biochemically and clinically effective.[7,28,29] After starting CDCA therapy, there is a considerable decrease in serum cholestanol, often with a slight increase in serum cholesterol.[7] This effect is accompanied by a sharp decline in the excretion of bile alcohols in the urine of CTX patients.[5,30] There is obviously a long washout period for cholestanol, a compound with a large body distribution volume. In most of our patients, we found a gradual decline in serum cholestanol during the first 2 years of CDCA therapy. In two of our patients, we increased the dose of CDCA to 1,000 mg/d, without any further effect on the serum choletanol level (data not shown).

The most effective inhibitor of cholestanol production is a combination of CDCA and a β-HMG-CoA reductase inhibitor. Salen et al[14] showed that β-HMG-CoA reductase inhibitor therapy without CDCA does not effectively decrease the serum cholestanol level and the production of bile alcohols.

In the literature, there is limited information about the effect of β-HMG-CoA reductase inhibitors on CTX patients. Only one trial has been reported in which pravastatin in combination with CDCA was administered to seven patients.[13] There are also some case reports using lovastatin,[14] simvastatin,[15] both lovastatin and simvastatin,[16] pravastatin,[18,20] and mevinolin.[17,19] In the study by Kuriyama et al,[13] CTX patients treated with CDCA alone did not have any significant further reduction in serum cholestanol when pravastatin (10 mg daily) was added for a period of 6 or 7 months. However, their serum lipid spectrum became more antiatherogenic with the combination therapy. This antiatherogenic effect, ie, a decrease in LDL cholesterol with an increase in HDL cholesterol, was also found in our patients. In all of these reports,[13-20] β-HMG-CoA reductase inhibitor therapy was started soon after the diagnosis was established. To our knowledge, no trials have been performed after long-term treatment with CDCA. The results of that trials were reported may therefore have been influenced by the cholestanol washout that always occurs in CTX patients during the first 2 years of CDCA therapy. Therefore, there is doubt as to whether the cholestanol changes observed in these studies were caused by β-HMG-CoA reductase inhibitor therapy. To avoid this cholestanol washout bias in our study, we included CTX patients who were treated with CDCA alone for at least 7 years. We believe that combination therapy would be clinically beneficial to CTX patients in the earlier stages of the disease, because a further decrease of the already normal serum

cholestanol level will facilitate the long-term washout of cholestanol from the central nervous system.[28] In addition, a reduction in LDL cholesterol will reduce the risk of premature atherosclerosis in CTX patients. Since premature atherosclerosis is part of the clinical spectrum of CTX, this is an important finding. In our patients, we observed a significant decrease in serum cholestanol with the combination of CDCA and simvastatin.

Theoretically, increased LDL receptor expression induced by simvastatin could lead to a decrease in serum cholestanol and LDL cholesterol through an increase in tissue uptake of cholestanol. If this is true, simvastatin treatment potentially could have negative effects. However, studies in mice[31] and in patients with familial defective apolipoprotein B-100[32] present evidence that the major LDL-lowering effect of simvastatin is associated with decreased LDL synthesis rather than enhanced LDL receptor clearance. We did not observe any negative side effects (liver function parameters, EEG, or tendon xanthoma volume changes) during simvastatin treatment. We found a sharp decrease in serum lathosterol levels, reflecting effective inhibition of endogenous cholesterol synthesis.[4] For these reasons, we do not believe that LDL receptor upregulation plays a significant role in decreasing cholestanol levels in our patients.

During the maintenance phase with 40 mg simvastatin daily, there was no further decrease in serum cholestanol, LDL cholesterol, and lathosterol levels. After withdrawal of simvastatin, serum cholestanol, LDL cholesterol, and lathosterol returned to baseline levels within 1 month. Therefore, it is unlikely that a 10-mg daily dose of simvastatin for 4 weeks had any significant effect on the decrease in cholestanol at higher doses. No effect was found on the urinary excretion of bile alcohols, but the amount excreted was already minimal during CDCA therapy.

Our patients did not report any adverse effects of simvastatin during the 6-month treatment period, but long-term evaluation in a larger group of CTX patients is needed to establish the potential side effects. In the literature, one patient experienced rhabdomyolysis during simvastatin therapy, but she also had a mitochondrial enzyme deficiency.[33]

We conclude that in adult CTX patients on long-term CDCA treatment, a combination of 750 mg CDCA and 30 or 40 mg simvastatin daily effectively reduces serum cholestanol, LDL cholesterol, and lathosterol levels. Whether this combination treatment will be effective for the long-term prevention of neurologic deterioration and severe atherosclerosis without the occurrence of side effects remains to be established.

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