

Simvastatin: a new therapeutic approach for Smith-Lemli-Opitz syndrome

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Abstract The Smith-Lemli-Opitz syndrome (SLOS) is caused by deficient Δ^7 -dehydrocholesterol reductase, which catalyzes the final step of the cholesterol biosynthetic pathway, resulting in low cholesterol and high concentrations of its direct precursors 7-dehydrocholesterol (7DHC) and 8DHC. We hypothesized that *i)* 7DHC and 8DHC accumulation contributes to the poor outcome of SLOS patients and *ii)* blood exchange transfusions with hydroxymethylglutaryl (HMG)-CoA reductase inhibition would improve the precursor-to-cholesterol ratio and may improve the clinical outcome of SLO patients. First, an *in vitro* study was performed to study sterol exchange between plasma and erythrocyte membranes. Second, several exchange transfusions were carried out *in vivo* in two SLOS patients. Third, simvastatin was given for 23 and 14 months to two patients. The *in vitro* results illustrated rapid sterol exchange between plasma and erythrocyte membranes. The effect of exchange transfusion was impressive and prompt but the effect on plasma sterol levels lasted only for 3 days. In contrast, simvastatin treatment for several months demonstrated a lasting improvement of the precursor-to-cholesterol ratio in plasma, erythrocyte membranes, and cerebrospinal fluid (CSF). Plasma precursor concentrations decreased to 28 and 33% of the initial level, respectively, whereas the cholesterol concentration normalized by a more than twofold increase. During the follow-up period all morphometric parameters improved. The therapy was well tolerated and no unwanted clinical side effects occurred. **■** This is the first study in which the blood cholesterol level in SLOS patients is normalized with a simultaneous significant decrease in precursor levels. There was a lasting biochemical improvement with encouraging clinical improvement. Statin therapy is a promising novel approach in SLOS that deserves further studies in larger series of patients.—Jira, P. E., R. A. Wevers, J. de Jong, E. Rubio-Gozalbo, F. S. M. Janssen-Zijlstra, A. F. J. van Heyst, R. C. A. Sengers, and J. A. M. Smeitink. **Simvastatin: a new therapeutic approach for Smith-Lemli-Opitz syndrome.** *J. Lipid Res.* 2000. 41: 1339–1346.

Supplementary key words cholesterol biosynthesis • Smith-Lemli-Opitz syndrome • simvastatin • exchange transfusion

The Smith-Lemli-Opitz syndrome (SLOS) is caused by a deficient Δ^7 -dehydrocholesterol reductase activity, the final

enzyme of the cholesterol biosynthetic pathway. Low cholesterol and high concentrations of its direct precursors 7-dehydrocholesterol (7DHC) and its isomer, 8-dehydrocholesterol (8DHC), in blood and tissues are the biochemical hallmarks of the syndrome (1–3). Plasma sterol concentrations generally correlate with syndrome severity and outcome (3). Δ^7 -Sterol reductase activity in the liver of SLOS patients is markedly decreased (4). The human Δ^7 -sterol reductase gene has been characterized and assigned to chromosome 11q12-13. Mutations in this gene cause SLOS (5–7). Cholesterol fulfills an essential role in embryogenesis, during which it functions as a transporter molecule for sonic hedgehog signaling proteins required for correct morphogenesis. Without sufficient cholesterol their transport and function are impaired (8, 9). These findings may explain the phenotypic consequences of the Δ^7 -reductase deficiency as observed in SLOS: microcephaly, a distinctive facies, cleft palate, various organ malformations, syn/polydactyly, and genital abnormalities.

It is still a matter of debate whether the low cholesterol or the increased concentration of precursors or both is the most harmful component in growth and development of these patients. On the basis of experience with familial hypobetalipoproteinemia (10), in which plasma cholesterol in heterozygotes is as low as in some SLOS cases, without any clinical effect, we hypothesized that the cholesterol precursors 7DHC and 8DHC may be toxic. Both precursors are structurally similar to cholesterol (differing only in having an extra double bond in the cholesterol B-ring) and therefore may interfere with the important role of cholesterol. Cholesterol is the precursor of steroid hormones; therefore, a reduction of the availability of cholesterol or incorporation of precursors by adrenal and testicular cells may reduce or interfere with normal synthesis of

Abbreviations: BAEP, brainstem auditory evoked potential; BBB, blood-brain barrier; CSF, cerebrospinal fluid; DHC, dehydrocholesterol; EEG, electroencephalogram; HMG, hydroxymethylglutaryl; MRI, magnetic resonance imaging; SLOS, Smith-Lemli-Opitz syndrome.

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corticosteroids and androgens. Steroid hormones also affect a wide variety of behavioral and psychological states. In SLOS abnormal bile acid profiles already have been documented (11). Furthermore, some enzyme systems accepting cholesterol as substrate have also been shown to accept 7DHC and 8DHC as a substrate (12).

So far, therapeutic trials in SLOS patients used dietary supplementation of cholesterol with or without bile acids. The concentration of plasma cholesterol could be increased to subnormal levels in some patients. The concentrations of the precursors 7DHC and 8DHC, however, were only marginally influenced in patients and animal experiments, and clinical improvement until now was in general disappointing (13–19).

We here report the results of a study performed to investigate *i*) the *in vitro* exchange kinetics of cholesterol and precursors between plasma and erythrocyte membranes, *ii*) the *in vivo* effect of exchange transfusions in SLOS patients, and *iii*) the effect of simvastatin (hydroxymethylglutaryl [HMG]-CoA reductase inhibitor) on cholesterol and precursor levels in two young unrelated SLOS patients. The exchange transfusions aimed simultaneously to remove precursors while supplying additional cholesterol from the donor blood. Simvastatin inhibits *de novo* production of precursors at the level of HMG-CoA reductase in the cholesterol biosynthetic pathway (Fig. 1).

CLINICAL AND LABORATORY INVESTIGATIONS

Subjects

In the Pediatric Clinic (University Hospital Nijmegen, Nijmegen, The Netherlands) two patients with SLOS were treated with exchange transfusions and simvastatin. Parents were informed about the aim of the study, study protocol, and potential side effects. Informed parental consent was obtained on behalf of both patients for the application of repeated exchange transfusions and for the use of simvastatin as an investigational drug, based on previously published evidence of the safety and efficacy of statins in children. The consent to participate in the study was strictly voluntary and could be renounced at any time by the parents without disadvantage for further medical care of their child.

Patient A Patient A, a girl, first child of healthy unrelated parents, was born after an uneventful pregnancy. A cesarean section was performed at 38⁺⁴ weeks gestational age because of breech position. Apgar scores were 8 and 10 after 1 and 5 min, respectively. Birth weight was 3,520 g (97th percentile), length was 50 cm (75th percentile) and head circumference was 33 cm (50th percentile). The observed facial dysmorphias, ptosis, syndactyly of second and third toes, and failure to thrive gave rise to the suspicion of SLOS. At the age of 2 months she was admitted to our clinic, where the diagnosis was confirmed biochemically. Organ malformations were not present. Brain magnetic resonance imaging (MRI) was normal. Ophthalmological and neurophysiological (electroencephalogram [EEG], brainstem auditory evoked potential [BAEP]) examinations revealed no abnormalities.

Patient B Patient B, a boy, was born after the second pregnancy of unrelated parents. At 37 weeks gestational age he underwent an external cephalic version due to a breech position and was born at 40 weeks. Apgar scores were 10 and 10 after 1 and 5 min, respectively. Birth weight was 2,570 g (5th percen-

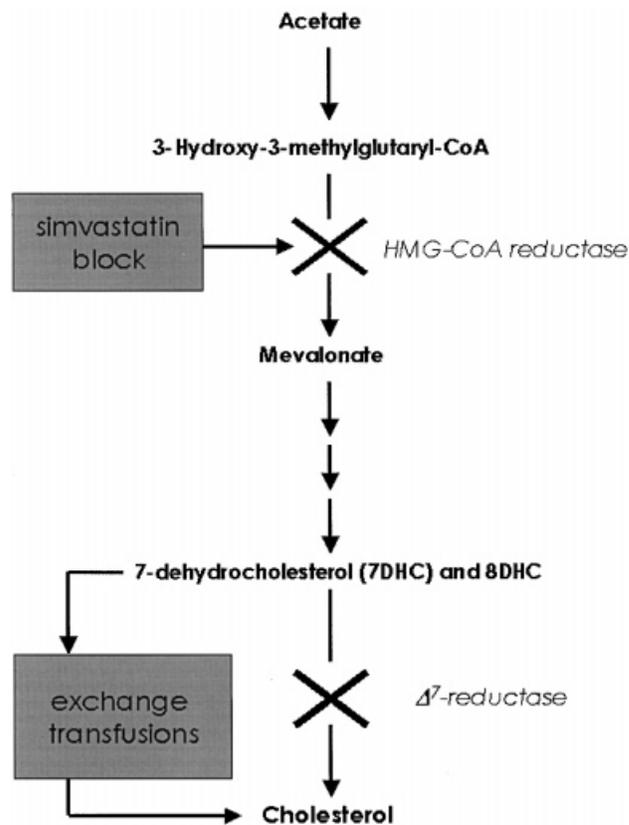


Fig. 1. Cholesterol biosynthetic pathway from acetate. The rate-controlling enzyme is HMG-CoA reductase, whereas the defective enzyme in SLOS syndrome is Δ^7 -reductase.

tile), length was 51 cm (90th percentile), and head circumference was 31.5 cm (25th percentile). He had mild facial dysmorphias, syndactyly of the second and third toe, and failure to thrive. Diagnosis of SLOS was confirmed biochemically in plasma at the age of 5 months. No organ malformations could be detected. MRI of the brain showed normal structures and myelination and the EEG was normal. Ophthalmological examination showed no cataract or other abnormalities.

Biochemical studies

The initial diagnosis and the biochemical effect of our therapeutic approaches on cholesterol and precursors in plasma, erythrocyte membranes, and cerebrospinal fluid (CSF) were investigated by gas chromatography and gas chromatography/mass spectrometry as described previously (12, 20).

In vitro sterol exchange study To study sterol exchange kinetics between plasma and erythrocyte membranes two *in vitro* experiments were designed: *i*) Erythrocytes from patient A were isolated, washed three times with saline, and incubated at 37°C in normal donor plasma. The patient's erythrocytes again were isolated after an incubation time of 0, 20, 40, 60, 120, and 240 min, washed three times with saline, and analyzed; *ii*) similarly, donor erythrocytes were incubated with plasma from patient A and studied after 0, 20, 60, 120, and 360 min of incubation.

In vivo exchange transfusions After surgical insertion of a subclavian venous catheter eight blood exchange transfusions with 800 mL of donor blood were performed in patient A. The 2-h procedures took place on days 1, 4, 11, 39, 40, 148, 150, and 152, in total accounting for eight times her circulating blood volume. In patient B three exchange transfusions were performed, on

days 1, 4, and 7 with 800 mL each, accounting for five times his blood volume.

HMG-CoA reductase inhibition by simvastatin therapy Simvastatin was started on day 20 and gradually increased from 0.2 to 1.0 mg/kg per day (two daily doses) during 23 months in patient A. In patient B the simvastatin dosage was not altered and was maintained at 0.6 mg/kg per day for 14 months. Study methods consisted of baseline hematological investigations and blood chemistry profiles. These were repeated at 2- to 6-week intervals from the start of therapy. Both children received standard pediatric formula without dietary supplementation of cholesterol or bile acids. Patient B was, in addition, treated during the last 3 months with oral cholesterol supplementation (100 mg/kg per day; cholesterol-module available from Nutricia (product code number 18,012; Special Product Service, Zoetermeer, The Netherlands) in combination with simvastatin therapy.

Sterol analysis in plasma, erythrocytes and CSF was carried out before and during therapy. Clinical course, neuromotor development, neuroimaging by MRI, and growth were monitored, scored, and compared with normative data from the Dutch population (21). Informed parental consent was obtained for the application of repeated exchange transfusions and for the use of simvastatin as investigational drugs based on previously published evidence of the safety and efficacy of statins in children (22–29).

RESULTS

Both patients had total cholesterol concentrations below the age-related reference values and 100-fold higher concentrations than the upper reference range limits for 7DHC and 8DHC in plasma, erythrocytes, and CSF before treatment, confirming the diagnosis of SLOS as shown in **Table 1**. Mutation analysis will be reported elsewhere.

Sterol exchange study

SLO erythrocytes were incubated in donor plasma with cholesterol, 7DHC, and 8DHC concentrations of 5,038, 6, and 16 $\mu\text{mol/L}$, respectively. A rapid increase in cholesterol in membranes of SLO erythrocytes in 240 min was observed, from 1,070 to 2,019 $\mu\text{mol/L}$. Simultaneously, the 7DHC + 8DHC concentration in SLO erythrocytes decreased from 1,180 to 613 $\mu\text{mol/L}$, improving the (7DHC + 8DHC)/cholesterol ratio from 1.10 to 0.30 (**Fig. 2**, experiment 1).

In the second incubation normal human donor erythrocytes were incubated in SLO plasma with concentrations of cholesterol, 7DHC, and 8DHC of 1,228, 326, and 274 $\mu\text{mol/L}$, respectively. A significant and rapid increase in the (7DHC + 8DHC)/cholesterol ratio from 0.01 to 0.32 occurred over 6 h (**Fig. 2**, experiment 2). These experiments show that cholesterol, 7DHC, and 8DHC exchange easily and rapidly between plasma and membrane compartments, which encouraged us to proceed in performing exchange transfusions in our two patients. Cholesterol exchange between red cell membrane and serum lipoproteins has been studied previously. In accordance with our observations, these investigators documented a rate constant for movement of cholesterol from erythrocytes to plasma and from plasma to erythrocytes with the half-time for efflux of 4 to 6 h (30, 31).

Exchange transfusions

The effect of exchange transfusion on correcting plasma cholesterol, 7DHC, and 8DHC is prompt as illustrated by the plasma sterol concentrations in the period of

TABLE 1. Sterol effect of simvastatin therapy during a 23- and 14-month period in two young infants with SLO syndrome

	Patient A					Patient B				Controls
	Months of Therapy					Months of Therapy				
	0	3	6	14	23	0	3	6	14	
Age (months)	3	6	9	17	26	10	13	16	24	
Biochemistry										
Plasma										
Cholesterol (mmol/L)	1.338	1.608	2.594	2.916	2.815	1.281	1.567	2.050	3.312	2.600–5.200
7DHC + 8DHC (mmol/L)	0.625	0.289	0.289	0.212	0.172	0.407	0.147	0.178	0.136	<0.01
Ratio ^a	0.47	0.18	0.11	0.07	0.06	0.32	0.09	0.09	0.04	<0.01
Erythrocytes										
Cholesterol (mmol/L)	1.273	1.762	2.700	2.368	2.499	1.846	2.230	2.706	2.997	2.400–3.200
7DHC + 8DHC (mmol/L)	1.547	0.583	0.577	0.372	0.299	1.137	0.388	0.451	0.212	<0.01
Ratio ^a	1.22	0.33	0.21	0.16	0.12	0.62	0.17	0.17	0.07	<0.01
CSF										
Cholesterol (nmol/L)	3,217	2,564	1,938	2,776	—	1,972	—	2,656	2,902	3,500–5,100 ^d
7DHC (nmol/L)	610	340	168	160	—	404	—	276	280	<20
Ratio ^b	0.19	0.13	0.09	0.06	—	0.20	—	0.10	0.10	<0.01
Morphometrics										
Length (cm)	55	62	70	78		65	68	76	83	
SD	–3.2	–1.8	–0.5	–1.2		–6.6	–5.0	–1.9	–1.3	
Weight (kg)	4.11	5.95	7.25	9.75		5.15	6.55	7.20	8.60	
SD ^c	–3.5	–1.9	–1.5	–0.7		–5.6	–3.7	–2.7	–2.4	
Head circumference (cm)	34.0	38.0	40.5	43.2		40.4	42.3	43.2	44.0	
SD ^c	–6.8	–4.7	–3.3	–2.6		–5.2	–4.4	–3.5	–3.5	

^a (7DHC + 8DHC)/cholesterol.

^b 7DHC/cholesterol ratio.

^c Standard deviation below the 50th percentile.

^d Range of values from ref. 18.

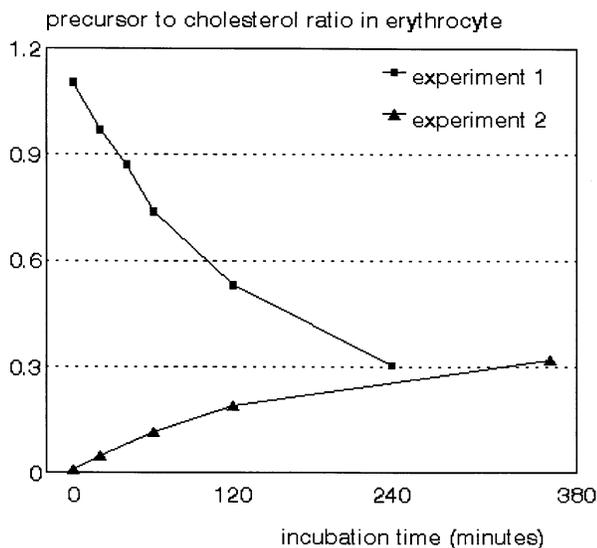


Fig. 2. In vitro sterol exchange kinetics between erythrocyte membranes and plasma. Sterol composition of SLOS erythrocytes incubated in normal plasma (experiment 1) and sterol composition of normal erythrocytes incubated in plasma of an SLOS patient (experiment 2).

three exchange transfusions on days 1, 4, and 11 in patient A (**Fig. 3**). A significant amount of cholesterol could be delivered to the patient. Also, a substantial quantity of precursors could be removed from the patient. The plasma precursor-to-cholesterol ratio improved significantly. The beneficial effect on the plasma levels lasted for only 3 days (**Fig. 3**).

The patient total body/tissue cholesterol uptake from donor blood, calculated from initial donor blood concentrations and the concentrations in the remaining exchanged blood in patient A during the exchange transfusions on days 148, 150, and 152, was 1.7 g (0.4 + 0.6 + 0.7 g, respectively). For patient B, cholesterol uptake was 1.9 g (0.6 + 0.6 + 0.7 g, respectively) during his three exchange transfusions. This body cholesterol delivery of 300–400 mg/kg, achieved by donor cholesterol uptake through three exchange transfusions in both patients, is substantial when seen from the perspective of a normal daily cholesterol synthesis of 8.3–14.5 mg/kg documented in healthy children (32, 33). The mean amount of plasma precursors (7DHC + 8DHC) for both patients removed by one exchange transfusion is 53 mg (variation, 32–92 mg).

Unfortunately, the effect of a single exchange transfusion on the plasma sterol levels was limited to 2–3 days. Also, repeated exchange transfusions did not result in a lasting change in either the plasma cholesterol or the plasma precursor concentrations (**Fig. 4**). This limited effect motivated us to evaluate the effect of HMG-CoA reductase inhibition by simvastatin therapy for several months.

Simvastatin effect

Patients A and B were treated with simvastatin for 23 and 14 months, respectively. Precursor levels decreased

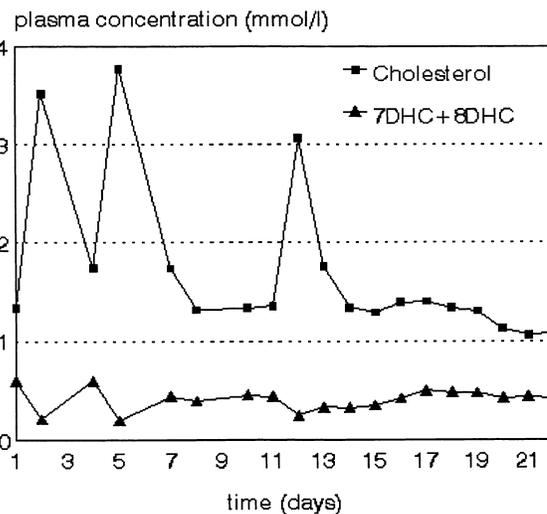


Fig. 3. Effect of the first three exchange transfusions (days 1, 4, and 11) on plasma cholesterol (solid squares) and precursor (solid triangles) concentration in time in patient A.

significantly to 28 and 33% of the initial (pretreatment) level in plasma, in erythrocyte membranes, and CSF (Table 1 and **Fig. 4**). Surprisingly, an increase and finally a normalization of the plasma cholesterol concentration (>2.6 mmol/L) was observed after several months. As mentioned earlier, patients did not receive cholesterol supplementation during the simvastatin treatment period (except for the last 3 months for patient B). The plasma (7DHC + 8DHC)/cholesterol ratio finally decreased from 0.47 to 0.06 in patient A and from 0.32 to 0.04 in patient B. Although promising, it is important to note that despite the significant reduction in precursor plasma level and the increase in cholesterol plasma level with this therapy, the (7DHC + 8DHC)/cholesterol ratio was still above normal. The 7DHC/8DHC ratio in the plasma of both patients remained unchanged during treatment (0.82–1.42), uninfluenced by the decrease in total precursor values. In erythrocyte membranes the 7DHC/8DHC ratio was significantly higher (1.66–2.78) compared with plasma. These data suggest that erythrocyte membranes incorporate 7DHC more readily than 8DHC.

During the months of treatment cholesterol precursor concentrations decreased in the CSF of both patients, improving the precursor-to-cholesterol ratio as illustrated in Table 1. During treatment, brain-specific proteins (neuron-specific enolase, S-100, and myelin basic protein) and neurotransmitter metabolites (homovanillic acid [HVA], 5-hydroxyindoleacetic acid [5-HIAA], and 3-methoxy-4-hydroxy-phenylethyleneglycol [MHPG]) in the CSF of both patients remained in the normal range (results not shown). The blood–brain barrier (BBB) function was intact both before and during the therapy period. Simvastatin supplementation therapy was well tolerated. Neuromuscular complications were not observed. Plasma enzymatic activity of aminotransferases and creatine kinase remained in the normal range. No cataract developed.

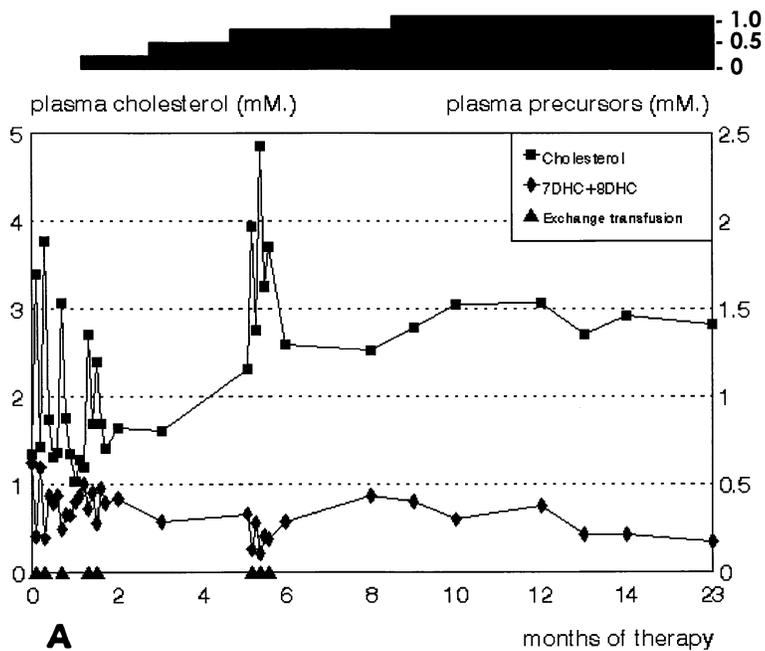
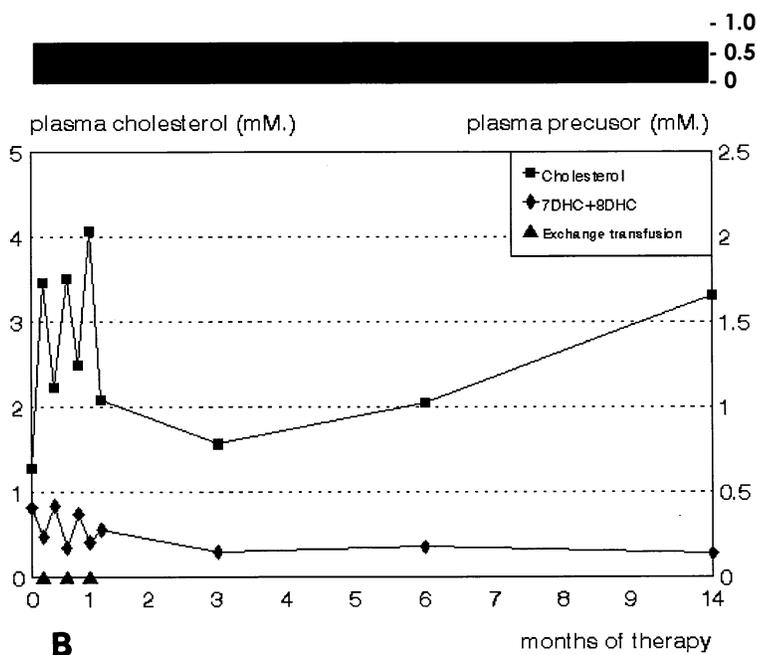


Fig. 4. Effect of exchange transfusions (solid triangles) and simvastatin on plasma cholesterol (solid squares) and precursor (solid diamonds) levels (mmol/L) in patient A (A) and patient B (B). Simvastatin dosage is illustrated by the black bars, which represent oral simvastatin dosage in milligrams per kilogram per day.



Patient outcome

Mental, motor, and social development of both patients shows constant improvement. At the age of 17 months (patient A) and 24 months (patient B), the neuromotor assessment of both patients, as determined by the Hoskins-Squires test (34), and cognitive skills corresponded to 11 and 14 months, respectively. Weight, length, and head circumference during treatment are shown in Table 1. Eating behavior, however, was unchanged. Patient A received a percutaneous gastrostomy after prolonged nasogastric tube feeding while patient B is eating orally with substantial effort of his parents. By the age of 2½ years both patients walked with help and started to communicate by word expression.

Our results suggest that simvastatin therapy may repre-

sent a simple, effective, and safe way to reduce accumulated cholesterol precursors while improving cholesterol plasma levels in patients with SLOS.

DISCUSSION

Our therapeutic approach aimed at a fast supply of cholesterol and removal of a substantial amount of precursors by blood exchange therapy. Thereafter use of simvastatin was aimed at blocking the cholesterol biosynthesis pathway as a way to avoid the formation of large amounts of the cholesterol precursors 7DHC and 8DHC, which may be potentially harmful to patients. Both aims were met in our first patient, where we accomplished a significant re-

duction in the plasma levels of 7DHC and 8DHC as published earlier (35). We were encouraged by this biochemical response and decided to continue therapy, using simvastatin as the only medication. Also, a second patient was included to confirm our findings. In this second patient three exchange transfusions were carried out for rapid supplementation of cholesterol and removal of part of the precursor load. The patient received simvastatin without dietary cholesterol for 11 months. As in our first patient the precursor levels in plasma, erythrocytes, and CSF declined significantly, fully confirming our findings in the first patient. This is the first time that a therapeutic approach has succeeded in normalizing plasma cholesterol levels with simultaneous significant reduction of cholesterol precursor levels in plasma. We believe that our therapeutic approach is superior to the approach of dietary cholesterol with or without bile acid supplementation (14–18). In 11 SLOS patients, treated with cholesterol and bile acids, the mean cholesterol-to-total sterol ratio in plasma only increased from 55% to 72% (17). In 6 other SLOS patients treated with cholesterol and bile acids this ratio did not exceed 60% (18). These data are comparable to our own experience with 2 other SLOS patients treated with cholesterol and bile acid supplementation for more than 1 year. In these patients there was no significant decline in plasma precursor levels and only a temporary and limited increase in plasma cholesterol that never reached normal levels. The cholesterol-to-total sterol ratios were unchanged during therapy and remained below 79 and 68%. In contrast, the two patients in this study reached cholesterol-to-total sterol ratios of 94 and 96%.

The gradual disappearance of cholesterol precursors 7DHC and 8DHC under statin therapy is relatively easy to understand. The statin blocks the *de novo* synthesis of the precursors at the level of HMG-CoA reductase. The simultaneous rise in plasma cholesterol is unexpected. It is difficult to understand because our patients did not receive extra cholesterol supplementation. Simvastatin may influence the expression level of the deficient Δ^7 -reductase. Such an effect was described for the combination of cholestyramine and lovastatin in rats (36). Moreover, Shefer et al. (37) showed an upregulation of the Δ^7 -reductase in human fibroblasts in cholesterol-deficient medium supplemented with lovastatin.

We observed in both patients an impressive improvement in all morphometric parameters (Table 1). In most of the described SLOS patients the head circumference, height, and weight stay below the third percentile, even during conventional therapy (15–18). Whether growth and developmental progress are, in fact, the result of therapy and relate to the biochemical corrections, or might have occurred otherwise, is difficult to prove. Data derived from rats, however, support the view that oxidized 7DHC derivatives play a role in embryo toxicity and growth retardation (38). Confirmation with a larger group of patients over a longer period of time is needed. Studies of cholesterol metabolism ultimately will result in more understanding of the origin and metabolism of cholesterol that is used in growth, development, and myelin in the CNS in children.

A small number of studies demonstrated the efficacy and safety of statin therapy in childhood. Pediatric studies showed that statins were well tolerated by children with familial hypercholesterolemia (22–26), nephrotic syndrome (27, 28), and Niemann–Pick disease type C (29). One study, however, in which an attempt was made to reduce mevalonate accumulation by administering simvastatin to two children with mevalonate kinase deficiency (39), documented impressive acute adverse effects. In adults the use of simvastatin did not show any significant adverse effects on brain activity measured by EEG, evoked potentials, mood, sleep, or cognitive performance (40). The beneficial effects of simvastatin used in our study without any unwanted clinical side effects encouraged us to proceed to use this therapy in our patients. Of course, a careful clinical follow-up of the patients is required to prevent any complications in liver function or other unwanted side effects of the drug. It remains to be established whether simvastatin use will also work to the same extent in other, perhaps more severely affected SLOS patients. Further studies will also be required in new SLOS cases to find out whether the initial exchange transfusions really are required. The transfusions have a relatively high clinical risk. When a similar effect of statin use on plasma cholesterol and precursor levels can be found without exchange transfusions this approach would of course be preferred. Also, it remains to be established in further studies whether dietary cholesterol supplementation therapy with simultaneous statin use can add to the success of statin use.

Brain is the most cholesterol-rich organ in the body. Cholesterol in the human brain, developing sheep brain, and rat pup brain is made locally from glucose, acetate, or polyunsaturated fatty acids (41–43). Sterols formed in the brain by the mevalonate pathway have an active and independently regulated biosynthesis. Cholesterol is not imported from peripheral blood across the BBB by lipoprotein uptake (44, 45). Even during fetal brain development, including the time before closure of the BBB, lipoproteins circulating through the central nervous system are not used as a source of cholesterol, but are synthesized locally (45–48). In our two treated patients we demonstrated that precursor concentrations are highly increased and that cholesterol concentrations in CSF are decreased in comparison with controls. Dietary supplementation of cholesterol alone, in SLOS, will not influence an impaired (7DHC + 8DHC)/cholesterol ratio in the central nervous system. In line with previously described evidence (41–48) the only way to reduce cerebral accumulation of cholesterol precursors in SLOS individuals is by means of local inhibition of brain cholesterol biosynthesis. Statins with lipophilic properties (simvastatin and lovastatin) cross the BBB (49) and are potential inhibitors of cerebral cholesterol precursor accumulation in SLOS. The half-life for cholesterol calculated in rat brain studies was found to be about 5–6 months (43, 46, 47). Elimination of brain cholesterol precursors is therefore not expected to be a rapid process. This could explain why in our patients the sterol improvement in plasma and erythrocyte membranes was faster and superior to the correction observed in CSF.

In conclusion, simvastatin therapy reduced 7DHC and 8DHC and normalized cholesterol concentrations in two children with SLOS and was well tolerated without side effects. Blocking the de novo synthesis of cholesterol precursors reduced accumulation of these intermediates in plasma, membranes, and CSF. Biochemical and clinical follow-up was 23 and 14 months, respectively, and we are encouraged to explore the long-term beneficial effects of this new treatment strategy in these and other SLOS patients. ■

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