Effect of CS-514 on Type III and Type III-like Hyperlipoproteinemia*

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Introduction

Type III hyperlipoproteinemia (HLP) is an uncommon lipid disorder in which the plasma cholesterol and triglyceride levels are elevated due to an increase in chylomicron remnants, very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL)¹⁾. The concentration of low density lipoprotein (LDL) is usually reduced because of its 'hypercatabolism'^{2,3)} and apolipoprotein (apo) E abnormalities have been reported in this disease⁴⁾.

CS-514 is a newly introduced inhibitor of the rate-limiting enzyme of cholesterol biosynthesis, 3-hydroxy-3-methylglutaryl coenzyme A (HMG CoA) reductase, administration of which caused significant decrease in plasma cholesterol of hypercholesterolemic subjects⁵⁻¹⁰⁾. Plasma triglyceride was also decreased by this drug in Type IIb subjects^{11,12)}. Since overproduction of IDL can also play a major part in its accumulation in this lipid disorder¹³⁾, we examined the effects of CS-514 on the lipoprotein profile in Type III HLP.

Subjects and Methods

Two subjects were studied. Patient 1 showed typical characteristics of Type III HLP¹⁾ (Table 1). Gel isoelectric focusing of his VLDL demonstrated apo E-III deficiency⁴⁾. The lipoprotein profile of patient 2 was not typical of Type III HLP, but her whole plasma showed a 'broad- β band' on paper electrophoresis¹⁴⁾. In addition, an abnormal accumulation of the Sf 20-60 fraction was found even after strict diet control. Therefore, patient 2 can be classified as 'Type III-like HLP'. Both patients had no evidence of an aggravating cause for their hyperlipidemia (patient 1 had diabetes but under excellent control by diet), and they received no medications known to affect plasma lipid levels before CS-514 treatment. After 4 weeks of lipid lowering diet 20 mg per day of CS-514 were administered. Blood was withdrawn with EDTA before and 3 months after the beginning of the treatment.

The lipoprotein separation procedure has been described previously¹⁵⁾. The suitability of this separation procedure (VLDL: Sf 60-400, IDL₁: Sf 20-60, IDL₂: Sf 12-20) in Type III HLP has been discussed by Reardon et al.¹³⁾ and by Packard et al.³⁾ Cholesterol and triglyceride in plasma and each lipoprotein fraction were measured enzymatically. Isoelectric focusing of VLDL fraction was done according to Utermann et al.⁴⁾

Results

Both subjects responded well to CS-514 therapy. Plasma cholesterol and triglyceride fell during therapy and the fall was accompanied by a reduction in the lipid content in the Sf 20-400 range (Table 1). This accounted for most the decrease in

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Table 1 Effects of CS-514 on lipoprotein profile of Type III and Type III-like HLP subjects

(mg/dl)

	Age	Month	VLDL Sf 60-400		IDL ₁ Sf 20-60		IDL ₂ Sf 12-20		LDL Ch	HDL Ch	Total	
			Ch	Tg	Ch	Tg	Ch	Tg			Ch	Tg
Case 1	63	0	145	320	193	453	31	37	50	26	525	1,377
(male)		3	59	140	35	49	44	32	60	40	379	300
Case 2	43	0	92	476	70	312	5	25	35	23	258	1,245
(female)		3	19	91	37	171	13	3	40	35	166	413

0 month: before CS-514 treatment, 3 month: after the treatment.

Ch: cholesterol, Tg: triglyceride.

The mean value of each parameter of normolipidemic healthy subjects by this separating procedure has been reported by us¹⁵⁾.

total lipids in plasma. On the other hand, LDL-cholesterol as well as HDL-cholesterol increased in both cases from one month after treatment. These effects persisted for at least 6 months. The rise in the LDL fraction was also seen in one of our Type IV HLP subjects after CS-514 treatment (data not shown).

Discussion

Type III HLP is a primary lipid transport disorder which responds dramatically to diet and drug treatment¹⁾. The present cases, however, showed persistent dyslipoproteinemia after diet restriction. Not only defective catabolism of the remnant but also oversynthesis of such a lipoprotein is responsible for this disease²⁾. Therefore, the effect of an inhibitor of cholesterol biosynthesis on this lipid disorder was examined in this study.

CS-514 is a potent inhibitor of HMG CoA-reductase. We and others have previously reported the clinical safety and efficacy of this drug⁷⁻¹⁰⁾. Both subjects here showed a good response to CS-514, suggesting that overproduction of abnormal lipoproteins can be one of the cause of Type III HLP.

Although the cholesterol per triglyceride ratio in the Sf 20-400 fraction of subject 2 before treatment was not typical of Type III, the appearance of a broad- β band on electrophoresis, increased lipid concentration of the Sf 20-400 fraction and the suppressed LDL-cholesterol level indicate that a lipoprotein disorder similar to Type III was present in this case.

Suppression of LDL-cholesterol in both cases before treatment could be explained by 'LDL hypercatabolism'²⁾. 'Paradoxical rise' in LDL-choles-

terol after fibrates may not be surprising since earlier studies observed this phenomenon in hypertriglyceridemic subjects^{16,17)}. However, it is perhaps surprising that this increase in the cholesterol-rich fraction occurred after treatment with an inhibitor of cholesterol biosynthesis. A similar result was obtained from one of our Type IV HLP subjects (data not shown). The precise mechanisms for this phenomenon are not known. But it is possible that the drug caused the hepatic release of lipoprotein particles which are subject to degradation by lipase. It is known that such a kind of drug can accelerate LDL catabolism through induction of LDL-receptor activity by suppressing intracellular cholesterol biosynthesis¹⁸⁾. The rise in LDL-cholesterol after the treatment also suggests that the hypercatabolism of LDL in these cases had already been at the maximum rate and therefore the drug could not enhance this catabolic rate. Thus, our results indicate that CS-514 accelerates the VLDL-LDL cascade.

East et al.¹⁹⁾ reported the effect of mevinolin on a Type III subject. However, his LDL-cholesterol decreased after treatment. This might be due to an absence of LDL hypercatabolism. It is very difficult to explain the reason for this discrepancy since they did not show at which fraction IDL was included.

Interestingly, an inhibitor of endogenous cholesterol synthesis suppressed plasma lipids in Type III HLP patients in much the same way as did fibrates in those with hypertriglyceremia¹⁷⁾. But these two kinds of drugs are apparently different in their effects on lipoprotein metabolism including lipoprotein lipase activity. This unique effect of CS-514 warrants further study.

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Summary

We examined the effects of CS-514, a newly introduced inhibitor of cholesterol biosynthesis, on lipoprotein metabolism of Type III and Type III-like hyperlipoproteinemia (HLP). Two subjects were studied. Case 1 showed typical lipoprotein abnormalities of Type III HLP with apoprotein (apo) E-III deficiency and Case 2 demonstrated broad- β band on paper electrophoresis and increased concentration of intermediate density lipoprotein without apo E abnormality. LDL-cholesterol level was low in both cases. After 3 months of CS-514 treatment, they showed decreased cholesterol and triglyceride concentration in plasma.

This was accompanied by a reduction in the lipid content of Sf 20–400 range. On the other hand, LDL-cholesterol rose in both cases.

Since it is unlikely that inhibition of cholesterol biosynthesis causes suppression of LDL-receptor activity, the rise in LDL-cholesterol after the treatment may indicate the accelerated conversion of VLDL-remnant to LDL. Thus, it is speculated that CS-514 can enhance the VLDL-LDL cascade by producing lipoprotein particles which are subject to degradation by lipoprotein lipase.

Key words: CS-514, Type III hyperlipoproteinemia, VLDL-LDL cascade, IDL.