Correspondence

Severe Decrease in Serum HDL-Cholesterol During Combination Therapy of Bezafibrate and Pioglitazone

Fibrate often produces a rise in HDL-cholesterol (C) mediated by the increased expression of apolipoprotein A-I by the activation of peroxisome proliferator-activated receptor (PPAR) α . It is also well known that pioglitazone increases HDL-C by activation of PPAR γ . Many diabetic patients with hypertriglyceridemia receive combination therapy of fibrate and pioglitazone; however, there have been a very small number of reports describing a severe decrease in serum HDL-C with this combination therapy^{1, 2}. We encountered a profound decrease in HDL-C with combination therapy of bezafibrate and pioglitazone in a man aged 61 who had type 2 diabetes mellitus, hyperlipidemia, and impaired renal function. Initial serum levels of total cholesterol (TC), triglycerides (TG), HDL-C, and creatinine (Cre) were 257 mg/dL, 217 mg/dL, and 38 mg/dL, and 1.6 mg/dL, respectively, in October 2000 before starting the combination therapy. He suffered from diarrhea, nausea, appetite loss, and general fatigue for 7 days before admission to our hospital on June 27, 2005. Until admission, he was taking 400 mg/day of bezafibrate and 15 mg/day of pioglitazone. Serum HDL-C levels with this combination therapy were around 10 mg/dL. On the admission day, serum fasting levels of TC, TG, HDL-C, glucose, HbA1c, blood urea nitrogen (BUN), Cre, albumin, and hemoglobin were 114 mg/dL, 207 mg/dL, 4 mg/dL, 104 mg/dL, 3.8%, 30 mg/dL, 3.2 mg/dL, 3.1 g/dL, and 8.2 g/dL, respectively. On the 14th hospital day after stopping both bezafibrate and pioglitazone, HDL-C increased to 16 mg/dL, and on the 28th hospital day HDL-C returned to 35 mg/dL (Fig. 1), and serum levels of TC, TG, BUN, Cre, albumin, and hemoglobin were 173 mg/dL, 77 mg/dL, 72 mg/dL, 3.2 mg/dL, 3.7 g/dL, and 8.4 g/dL, respectively.

One of the causes of the decrease in HDL-C on admission was insufficient food intake and poor general condition; however, taking such conditions into consideration, his 4 mg/dL HDL-C level was too low. The precise mechanism of fibrate-, pioglitazone-, or this combination-induced hypo-HDL-cholesterolemia is, as yet, unclear in the literature. However, it is supposed that polymorphisms in the promoter regions of several genes regulated by PPAR α and/or PPAR γ involved in the HDL metabolic pathway may contribute to the HDL-C level at baseline and may account for dramatic change in HDL metabolism^{3, 4}. Further-

Fig. 1. Lipid pattern in relation to the combination therapy of bezafibrate and pioglitazone.

more, since this patient had decreased renal function when starting bezafibrate, which should be prescribed very carefully in patients with decreased renal function because of its renal excretion and renal impairment, the serum concentration of bezafibrate may increase.

It is unclear whether the profound decrease in HDL-C in this case occurred by bezafibrate, or pioglitazone, or their combination. However, it would be advisable to ensure that HDL-C has been documented before starting fibrate and/or pioglitazone and that HDL-C is rechecked shortly after beginning these drugs.

References

- 1) Ebcioglu Z, Morgan J, Carey C, and Capuzzi D: Paradoxical lowering of high-density lipoprotein cholesterol level in 2 patients receiving fenofibrate and a thiazolidinedione. *Ann Intern Med*, 2003; 139:W80
- 2) Sarker A, Semple RK, Dinneen AF, O'Rahilly S, and Martin SC: Severe hypo- α -lipoproteinemia during treatment with rosiglitazone. *Diabetes Care*, 2005; 27:2577-2580
- 3) Vu-Dac N, Schoonjans K, Laine B, Fruchart JC, Auwerx J, and Staels B: Negative regulation of the human apolipoprotein A-I promoter by fibrates can be attenuated by the interaction of the peroxisome proliferator-activated receptor

with its response element. *J Biol Chem*, 1994; 269:31012-31018

- 4) Vu-Dac N, Chopin-Delannoy S, Gervois P, Bonnelye E, Martin G, Fruchart JC, Laudet V, and Staels B: The nuclear receptors peroxisome proliferator-activated receptor alpha and Rev-erbalpha mediate the species-specific regulation of apolipoprotein A-I expression by fibrates. *J Biol Chem*, 1998; 273:25713-25720

Hiroaki Senba

Mikihiko Kawano

Masanobu Kawakami

Department of Comprehensive Medicine,
Jichi Medical University, Omiya Medical Center,
Saitama, Japan.