Fibrates

Shun ISHIBASHI

Division of Endocrinology and Metabolism, Department of Internal Medicine, Jichi Medical University, Japan,

ishibash@jichi.ac.jp

Abstract

Epidemiological and genetic studies have shown that hypertriglyceridemia is an independent risk factor of ischemic heart disease and ischemic stroke. Clinical trials have shown that gemfibrozil significantly reduced CV events (Helsinki Heart Study and VA-HIT). However, gemfibrozil is not widely used because of the concern of adverse interaction with statins. Although fenofibrate can be safely used in combination with statins, it did not significantly reduce CV events when used on top of simvastatin (ACCORD-LIPID). Subgroup analysis showed significant reduction of CV events in patients with dyslipidemia (high TG and low HDL-C). The limitation of these classical fibrates can be ascribed to their adverse effects on plasma levels of creatinine and homocysteine, which are considered to be atherogenic. Fenofibrate also frequently increases liver enzymes. To circumvent the limitations, a new type of fibrate, pemafibrate, was developed. Since pemafibrate potently and selectively activates PPARα, it belongs to a novel category named as selective PPARα modulator (SPPARMα). Drug-drug interactions with any statins were negligible. Since pemafibrate was primarily excreted into bile, theoretically it can be safely used in patients with impaired kidney function, which is contraindication for other fibrates. Pemafibrate 0.2mg BID was more efficacious than fenofibrate 100mg QD in patients with dyslipidemia with remarkably low incidence of adverse effects. The increasing effects on plasma levels of creatinine and homocysteine were negligible. Moreover, pemafibrate significantly decreased liver enzymes such as ALT, gGT and ALP. Pemafibrate significantly decreased HOMA-R, while fenofibrate did not. Since the increasing effects of pemafibrate on plasma FGF21 levels were more pronounced than those of fenofibrate, FGF21 might mediate a part of the favorable metabolic effects of pemafibrate. Similar efficacy and safety were demonstrated in dyslipidemic patients with type 2 diabetes mellitus as well as in those taking various types of statins. Currently, the multinational outcome trial (PROMINENT) is underway.

Keywords

Triglyceride, dyslipidemia, HDL, PPARα, fibrates, pemafibrate, diabetes