Fenofibrate May Prevent Amputation in Type 2

BY MARY ANN MOON

Fenofibrate use is associated with a lower risk of amputation in patients with type 2 diabetes, particularly in those who have no known large-vessel disease.

This effect appears to be unrelated to fenofibrate's antihypertensive effects or lipid-lowering activity. The drug's ability to decrease amputation risk also occurs regardless of patients' level of glycemic control and background use of ACE inhibitors or angiotensin-receptor blockers, "strongly suggesting that [fenofibrate's] effects are additive to other measures," wrote Dr. Kushwin Rajamani of the University of Sydney and his associates.

The Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study was designed to assess whether long-term lipid-lowering therapy with fenofibrate could reduce adverse macrovascular and microvascular outcomes. The FIELD researchers previously found that the drug reduces the need for laser therapy for diabetic retinopathy, "beyond what could be expected from a moderate observed reduction in blood pressure."

In this portion of the study, which was funded in part by Laboratoires Fournier SA (now part of Solvay Pharmaceuticals), maker of fenofibrate, patients aged 50-75 years were randomly assigned to receive once-daily micronized fenofibrate (4,895 subjects) or matching placebo (4,900 subjects) and were followed at 4- to 6-month intervals for a median of 5 years.

A total of 115 patients had lower-limb amputations due to diabetes, including 47 patients who required more than 1 amputation. The amputation rate was significantly lower among patients taking fenofibrate than among those taking placebo (39% vs. 61%).

There were 190 lower-limb amputations in all. Significantly fewer amputations occurred in patients taking fenofibrate than in those on placebo (73 vs. 117).

Fenofibrate's beneficial effect emerged just after 1.5 years of treatment and increased over time. It was most striking among patients without known large-vessel disease who required minor amputations (below the ankle) thought to be related to microvascular disease.

In contrast, the reduction in amputation risk was nonsignificant among patients with known large-vessel disease who required major amputations (above the ankle) thought to be related to atherosclerosis of the major arteries.

"The number of patients needed to treat with fenofibrate over 5 years to prevent at least 1 amputation in 1 patient is 197, but is 25 for someone with previous foot ulcer and albuminuria," the researchers wrote (Lancet 2009;373:1780-8).

The drug's protective effect against amputation was similar between patients who were taking ACE inhibitors and those who were not, as well as between patients who were taking angiotensin-receptor blockers and those who were not. The protective effect also did not differ between patients with good versus poor glycemic control, nor between patients with and without dyslipidemia.

Fenofibrate's mechanism of action in preventing amputations is not known. The drug is thought to improve endothelial-dependent vascular reactivity, reduce markers of endothelial dysfunction and inflammation, reduce viscosity, decrease angiogenesis, decrease tissue ischemia, inhibit oxidative stress, and exert neuroprotective effects, the investigators said. Fenofibrate is indicated by the Food and Drug Administration as adjunctive therapy to diet for the reduction of LDL cholesterol, total cholesterol, triglycerides, and apo B in adults with primary hypercholesterolemia or mixed dyslipidemia.

In an accompanying editorial, Dr. Sergio Fazio and Dr. MacRae F. Linton of Vanderbilt University, Nashville, said that fenofibrate's ability to improve wound healing may be key. This effect would set fibrates apart from the many agents that have so far been unable to reduce amputations in people with diabetes, they noted (Lancet 2009;373:1740-1).

Dr. Fazio and Dr. Linton have received honoraria for lectures from Merck, Schering-Plough, GlaxoSmithKline, Abbott, and Astra-Zeneca, as well as clinical trial support from Merck, Schering-Plough, ISIS, Genzyme, and AstraZeneca. ■