Fenofibrate Cuts Retinopathy in Diabetic Patients

Those who were treated with the drug also had less progression of albuminuria and fewer amputations.

BY MITCHEL L. ZOLER
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ORLANDO — Treatment with fenofibrate led to a substantial drop in the need for laser treatments for retinopathy in a controlled trial of nearly 10,000 patients with type 2 diabetes.

Physicians should "consider using fenofibrate on all patients with diabetes, even patients already on a statin and at their target lipid levels, to further reduce their risk and microvascular complications," Dr. Anthony C. Keech said at an industry-sponsored press briefing during the annual scientific sessions of the American Heart Association.

"Having a new tool to deal with [diabetic retinopathy] is very exciting. It's exciting to use it to treat patients, and it opens a whole new area of research," commented Dr. Virgil Brown, who is professor of internal medicine at Emory University, Atlanta.

The benefits of fenofibrate for microvascular disease of diabetes appeared to extend beyond its significant effect on retinopathy. Patients treated with fenofibrate also had less progression of albuminuria, and fewer amputations, Dr. Keech and his associates reported.

"The results were very clear-cut. It's very hard to make a coherent argument not to use fenofibrate" in patients with diabetes, said Dr. Keech, professor of medicine, cardiology, and epidemiology at the University of Sydney. "This is a unique finding in a lipid-modifying drug. We don't see the effect with statin treatment."

Dr. Frank Sachs, professor of medicine at Harvard Medical School, Boston, agreed. "It would be very easy to recommend fenofibrate for any diabetes patient with the earliest sign of retinopathy. That might be the first step in trying to translate these findings to clinical recommendations," he commented.

The new retinopathy findings came from a prespecified, tertiary analysis in the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) trial, which involved 9,795 patients with type 2 diabetes at 63 centers in Australia, New Zealand, and Finland. The study's primary end point was the rate of cardiovascular events—cardiovascular deaths, nonfatal myocardial infarctions, strokes, and coronary revascularization procedures—during 5 years of follow-up. Treatment with 200 mg daily of micronized fenofibrate cut this rate by 11%, compared with placebo, an effect that was not statistically significant (Lancet 2005;366:1849-61).

In the analysis of retinopathy end points, the 4,895 patients on fenofibrate had a 3.4% rate of all laser eye treatments, compared with a 4.9% rate in 4,900 placebo patients, a 37% relative risk reduction that was highly significant. The relative risk of a first laser treatment was cut by about 30% in all patients, including those who developed macular edema and those with proliferative retinopathy.

The results were released by the Lancet on the same day as the briefing (Lancet 2007 [Epub doi:10.1016/S0140-6736(07)61607-9]).

The trial was initially sponsored by Laboratories Fournier; the company, which owned the rights to fenofibrate, was acquired by Solvay Pharmaceuticals in 2005. Fenofibrate (Tricor) is marketed in the United States by Abbott under license from Solvay, and it is marketed as Lipanthyl everywhere else by Solvay. Dr. Keech has served on an advisory board for Solvay and Abbott, and receives travel support from those companies to attend meetings. He is also listed on a patent application for fenofibrate.

Treatment with fenofibrate cut the rate of laser treatments in patients with no history of retinopathy and in patients who had retinopathy when they started the study, although the reduction was not statistically significant among the patients who already had retinopathy before starting treatment.

The trial also included an ophthalmologic substudy with 1,012 patients, in which serial retinal photography was used to assess patients in more detail. In this subgroup, treatment with fenofibrate slowed development of a two-step progression of retinopathy on the Early Treatment Diabetic Retinopathy Study scale among patients with pre-existing retinopathy: There was a 3% progression rate among patients treated with fenofibrate, compared with a 15% rate among patients treated with placebo, a statistically significant difference. Among patients with no retinopathy at baseline, the rate of two-step progression was virtually the same in the two treatment groups.

The primary end point for this substudy was the overall rate of two-step progression of retinopathy among all patients. The rate was 12.3% in the placebo group and 9.6% in the fenofibrate group, a difference that was not statistically significant.

The safety profiles of fenofibrate and placebo were similar during 5 years of treatment.

Several weaknesses in the study's design were noted in an editorial by Dr. Rafael Simó and Dr. Cristina Hernández, of the Diabetes Research Unit at Vall d'Hebron University Hospital, Barcelona, that accompanied the printed version of the new report. Retinal photographs were not routinely collected for all patients in the FIELD trial, which makes it impossible to confirm the retinal status of most patients (Lancet 2007 Nov. 6 [Epub doi:10.1016/S0140-6736(07)61608-0]).

Also, they said, the criteria used to perform laser therapy were not defined in the study protocol, and therefore they probably varied among the study centers. The number of patients in the retinal substudy was small, making it impossible to draw definitive conclusions based on 5 years of follow-up. Finally, there is no clear explanation of how fenofibrate affects diabetic retinopathy.

Possible mechanisms include documented anti-inflammatory effects of fenofibrate, the drug's inhibitory effect on endothelial cell migration, and the drug's reduction of apoptosis in retinal endothelial cells, said Jean-Charles Fruchart, Ph.D., head of the department of atherosclerosis at the Pasteur Institute of Lille, France, during the press briefing. The retinopathy effect did not appear to be mediated by an effect on blood pressure or glycemic control, because fenofibrate had little or no effect on these.

Additional evidence of beneficial effects of fenofibrate on microvascular disease in patients with diabetes comes from observations of the drug's effect on renal function and neuropathy. Progression of albuminuria occurred in 11% of placebo patients and 9% of those on fenofibrate, a 15% relative risk reduction, Dr. Keech said. And regression of albuminuria occurred in 9% of patients treated with fenofibrate and 8% of placebo patients, a 14% relative increase.

In addition, amputations were lowered from a 1.5% rate with placebo to a 0.9% rate with fenofibrate, a relative risk reduction of 38% that was statistically significant. The amputation rate was reported by Dr. Keech and his associates in a separate report during the American Heart Association's meeting. ■

40 mg of Lisinopril Daily Is Ideal for Diabetic Nephropathy

BY MIRIAM E. TUCKER
Senior Writer

AMSTERDAM — In type 1 diabetic patients with diabetic nephropathy, 40 mg/day of lisinopril appears to be the ideal dose for renoprotection, Dr. Katrine J. Schjoedt said in a poster presentation at the annual meeting of the European Association for the Study of Diabetes.

Angiotensin converting enzyme inhibitors such as lisinopril are considered first-line agents for renoprotection in patients with type 1 diabetes who have nephropathy, because these drugs reduce albuminuria in addition to lowering blood pressure. The currently recommended 20 mg/day dose of lisinopril is based on the drug's blood pressure–lowering effect; the optimal dose for renoprotection has not been established, said Dr. Schjoedt of the Steno Diabetes Center, Gentofte, Denmark.

To evaluate whether additional renoprotective effects could be obtained with higher doses of lisinopril, 56 type 1 diabetic patients with diabetic nephropathy were taken off all ongoing antihypertensive therapy and put on fixed doses (median 60 mg/day) of slow-release furosemide for the entire study. After a 2-month washout period, the patients were randomized to receive 20, 40, or 60 mg/day of lisinopril for 2 months.

The 49 patients who completed the trial had a mean age of 49 years and a diabetes duration of 33 years; two-thirds of them were men. At baseline, they had a mean blood pressure of 142/74 mm Hg, a mean urinary albumin excretion rate of 362 mg/24 hours, and a mean estimated glomerular filtration rate of 75 mL/min per 1.73 m^2.

The mean urinary albumin excretion rate fell by 71% from baseline with 40 mg lisinopril, by 70% with 60 mg, and by 63% with 20 mg. All of the reductions from baseline were significant. The 40-mg group and the 60-mg group both had significant reductions in urinary albumin excretion rate, compared with the 20-mg group, but the difference between the 60-mg and 40-mg groups was not significant.

High doses of lisinopril offer additional renoprotection. Ultrahigh doses offer no additional benefit.

DR. SCHJOEDT

"High [40 mg] doses of lisinopril offer additional renoprotection in comparison to the currently recommended dose [20 mg]. Ultrahigh [60 mg] doses do not offer any further beneficial effect," Dr. Schjoedt remarked.

All three dose groups also had significant reductions in blood pressure from baseline: Systolic pressure fell by 10, 13, and 12 mm Hg and diastolic pressure fell by 6, 8, and 7 mm Hg with lisinopril doses of 20, 40, and 60 mg/day, respectively. In addition, there was a dose-dependent reduction in estimated glomerular filtration rate, from 75 mL/min per 1.73 m^2 at baseline to 69, 68, and 67 mL/min per 1.73 m^2 with lisinopril doses of 20, 40, and 60 mg/day, respectively.

Adverse events leading to study dropout were an increase in plasma creatinine in two patients (one on the 20-mg dose and one on the 60-mg dose), high blood pressure in one patient in the 60-mg group, mild dizziness in two patients (on 40 mg and 60 mg), mild diarrhea in one (on 40 mg), and restless legs in one (on 20 mg). There were dose-dependent decreases in hemoglobin (down to 7.8 mmol/L with the 60- and 40-mg doses, compared with 8.3 mmol/L at baseline), and a significant increase in hemoglobin A_{1c} in the 60-mg group (rising to 8.9%, compared with 8.6% at baseline).

Nonetheless, Dr. Schjoedt concluded, "high doses of lisinopril are generally well tolerated and safe." ■