Preop Glycemic Control Decreases Infection Risk

**BY SHERRY BOSCHERT**

San Francisco Bureau

Three different regimens of a new extended-release version of metformin, including two once-a-day regimens, were as effective as immediate-release metformin in reducing hemoglobin A1c levels in adults with type 2 diabetes, Dr. Sherwyn Schwartz reported.

A double-blind, phase III trial randomized 770 patients to 24 weeks of treatment, and 706 patients with efficacy data were included in an intent-to-treat analysis. Patients on antihyperglycemic agents stopped the medications for 6 weeks before all patients began metformin at 1,000 mg once daily. Treatment was started over 2-3 weeks to assigned regimens of immediate-release metformin (Glucophage) at 1,500 mg/day, of extended-release metformin (Glumetza) in dosages of once-daily 1,000 mg/day, the same dose but bid, or once-daily 2,000 mg/day.

All groups showed significant reductions in hemoglobin A1c (HbA1c) levels by week 12. Levels continued declining until week 20, and were maintained until the end of the study at week 24, said Dr. Schwartz, an endocrinologist in a group practice in San Antonio, and his associates (Diabetes Care 2006;29:759-64). The study was funded by Depomed Inc., which makes Glumetza.

The reductions in mean HbA1c levels were similar to results from clinical trials of Glucophage and of another extended-release metformin product (Glucophage XR, by Bristol-Myers Squibb). Glumetza is the first extended-release metformin formulation, however, to show equal efficacy in daily or twice-daily dosing, Dr. Schwartz said.

Among secondary end points in the current study, all treatment groups significantly reduced fasting plasma glucose concentrations to a comparable extent. The reductions were maintained in all groups, with a significantly greater drop in the 2,000-mg group.

In the trial, 529 patients who completed the protocol switched to the once-daily 2,000 mg dose of Glumetza in an open-label extension study. The decreases in HbA1c from the randomized trial were maintained in the 24-week extension study. Each of the Glumetza regimens in the randomized trial produced greater decreases in HbA1c than did Glucophage in several subgroups: in women, in patients 65 years or older, in non-Caucasians, and in patients with a body mass index (kg/m2) of 30 or greater. The daily 2,000 mg dose provided the greatest efficacy, with some subgroups achieving HbA1c levels of less than 7% (in previously untreated patients and in those aged 65 years or older).

Other studies have reported that the effects of metformin monotherapy are independent of age, ethnicity, and body weight. "Our results indicate that the 2,000 mg/day dose may be more effective in some patient populations," Dr. Schwartz said.

There was a trend for triglyceride levels to increase slightly in patients on Glumetza (similar to trends in previous trials of extended-release metformin formulations), an effect not seen with Glucophage. The reason for this and its clinical significance are unclear.

Metformin is known to cause gastrointestinal side effects, including abdominal discomfort, nausea, and diarrhea. The overall incidence of adverse events was similar between groups. Patients in the Glumetza groups were less likely to report nausea during the first week of treatment. There was no increase in adverse events seen in the 2,000 mg/day Glumetza group.

Patients in the twice-daily drug regimen groups took 500 mg in the morning and 1,000 mg in the evening. All study drugs and placebo pills were taken after a meal. Reasons for those who stopped treatment were similar between groups, except that fewer patients in the Glumetza 2,000 mg group stopped because of lack of efficacy compared with the Glucophage group (2% vs. 8%). Reasons included withholding of consent, lack of efficacy, and loss to follow-up.

Simvastatin Increases Blood Flow, Intraocular Pressure

**BY MARY ANN MOON**

Contributing Writer

Simvastatin increases retinal blood flow and decreases intraocular pressure in healthy subjects, making it a potential treatment for diabetic retinopathy and glaucoma, according to Dr. Taji Nagaoka of Asahikawa (Japan) Medical College and associates.

Noting that long-term statin use has been reported to reduce the risk of retinal ischemic diseases, the researchers assessed the effect of simvastatin on the retinal circulation and on intraocular pressure in 12 healthy volunteers. The subjects were nonsmoking Japanese men aged 19-23 years. They were examined 90 minutes after a single 20-mg dose of the drug on one occasion and after taking a placebo on a separate occasion. They also underwent similar assessments after taking daily doses of either simvastatin or placebo for 1 week.

Retinal blood flow increased significantly, by 20% in the retinal arteries and by 23% in the retinal veins, after 1 week of simvastatin therapy. Intraocular pressure decreased significantly, from 14.3 mm Hg at baseline to 12.6 mm Hg after a single dose of the drug and to 12.4 mm Hg after 1 week of therapy. Plasma nitrite/nitrate levels also rose by 60% after 1 week on simvastatin.

In contrast, all retinal measurements remained unchanged after administration of the placebo.

Comparable Efficacy With Once-Daily, Extended-Release Metformin

**BY KATE JOHNSON**

Montreal Bureau

Diabetic patients with good preoperative glycemic control had significantly decreased both the incidence and severity of postoperative infections, with good glucose control decreasing both the incidence and severity of postoperative infections, according to a retrospective analysis of data from the Veterans Affairs National Surgical Quality Improvement Program.

"If the association is confirmed in other studies, strategies to improve glycemic control prior to elective surgery can be employed to decrease infections and improve overall outcomes for diabetic surgical patients," wrote Dr. Annika S. Dronge of Yale University, New Haven, Conn., and her colleagues. They noted limitations of their study, including the fact that all subjects came from a single Veterans Affairs hospital and were predominantly male, making generalizability of the findings uncertain.

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This is the first study to show that simvastatin increases retinal blood flow, "predicting who improved in nitric oxide," the investigators said (Arch. Ophthalmol. 2006;124:665-70).

The increase appears to be exerted mainly on the intracellular level, they added. A previous study involving six subjects suggested that statins might improve hard exudates and microaneurysms in diabetic retinopathy. "Although the findings in the present study are obtained from healthy men whose pharmacologic response to simvastatin may be different from that of patients with diabetes, the increased retinal blood flow associated with treatment with simvas- tatin may be a potential therapy for diabetic retinopathy," Dr. Nagaoka and associates said.

Similarly, another study recently reported that statin use appears to reduce the risk for glaucoma but did not measure intraocular pressure. In the present study, we document for the first time . . . that the intraocular pressure was slightly but significantly decreased by simvastatin," they added.

"Further study among more subjects is needed to examine the effects of age, sex, and systemic disorders such as hyperlipidemia, hypertension, and diabetes mellitus, on the retinal circulation that are associated with systemic administration of simvas- tatin," they said.

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