Liraglutide Helps Reduce Body Weight, HbA_{1c}

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ROME — The investigational, once-daily, human glucagon–like peptide-1 analog, liraglutide, produced a 1.5 percentage point drop in hemoglobin A_{1c}, as well as significant drops in body weight and blood pressure, in a study of patients with type 2 diabetes who were also taking metformin and rosiglitazone.

The findings of this 26-week phase IIIA randomized, placebo-controlled trial of 533 patients were reported by Dr. Bernard Zinman at a press briefing held during the annual meeting of the European Association for the Study of Diabetes.

The LEAD (Liraglutide Efficacy and Action in Diabetes) 4 trial, sponsored by Novo-Nordisk, comprised 533 subjects with a mean age of 55 years, mean body mass index of 33.5 kg/m^2, and mean HbA_{1c} of 8.3%. All had been previously treated with at least one oral glucose-lowering agent. Dosages were titrated up to 8 mg of rosiglitazone and 2,000 mg of metformin therapy. The patients were then randomized to liraglutide (either 1.2 mg or 1.8 mg) injected once daily, or to placebo, said Dr. Zinman, professor of medicine at the University of Toronto and director of the diabetes center at Mount Sinai Hospital, Toronto.

The proportions of patients taking liraglutide who achieved an HbA_{1c} of less than 7.0% were 58% of those on the 1.2-mg dose and 54% of those on the 1.8-mg dose.

At 26 weeks, HbA_{1c} levels had dropped from baseline by a statistically significant 1.5 percentage points in both the 1.2-mg and 1.8-mg liraglutide groups, to 7.0% and 7.1%, respectively, compared with a drop of just 0.5 percentage point (to 7.9%) in the placebo group.

The proportions who achieved an HbA_{1c} of less than 7.0% were 58% of those on the 1.2-mg dose and 54% of those on the 1.8-mg dose, compared with just 28% of the placebo group.

More than a third of both groups (36% of those on the 1.2-mg dose and 37% of those on the 1.8-mg dose) achieved HbA_{1c} levels of 6.5% or less.

Fasting plasma glucose (FPG) levels also dropped significantly with both liraglutide doses (by 2.2 mmol/L with 1.2 mg and by 2.4 mmol/L with 1.8 mg) to final FPG levels of 7.7 mmol/L and 7.6 mmol/L, respectively. The FPG drop in the placebo subjects was just 0.4 mmol/L (to 9.5 mmol/L).

Body weight dropped by 1.02 kg with the 1.2-mg dose and by 2.02 kg with the 1.8-mg dose, both statistically significant changes.

Mean systolic blood pressure levels were reduced by 6.7 mm Hg with the 1.2-mg dose and by 5.6 mm Hg with the 1.8-mg dose, compared with just 1.1 mm Hg with placebo, which were also statistically significant differences.

No major hypoglycemic episodes were reported during the study. Minor hypoglycemia (defined as less than 3.1 mmol/L), occurred in 9% of the 1.2-mg group, 8% of the 1.8-mg group, and 5% of the placebo group. The rate of 0.64 events per subject per year that was seen in the 1.8-mg group was statistically significant, compared with the 0.17 rate seen in the placebo group.

Nausea was the most common adverse event reported, occurring in 29% of the 1.2-mg group and 40% of the 1.8-mg group, compared with just 9% with placebo. Nausea occurred early in the treatment regimen and returned to placebo levels after 16 weeks.

On May 23, 2008, Novo Nordisk submitted a New Drug Application to the Food and Drug Administration in the United States, as well as a marketing authorization application to the European Medicines Agency for the approval of liraglutide for the treatment of type 2 diabetes. If approved, liraglutide would be the first human-derived GLP-1 analog.

Exenatide (Byetta), the GLP-1 mimetic currently on the market, is derived from the salivary gland of a lizard.

Novo-Nordisk has completed a head-to-head comparison study that compares liraglutide with exenatide, both combined with metformin and sulfonylurea. Those results will be presented this month at the Canadian Diabetes Association annual meeting in Quebec.

Dr. Zinman is a consultant for Novo Nordisk Inc. ■