ABSTRACT

Although it is well known that lowering A1c (also known as glycated hemoglobin) is associated with a marked reduction in the occurrence of complications in patients with type 2 diabetes, A1c is not well controlled in most of these patients in the United States. Follow-up data from the National Health and Nutrition Examination Survey showed that only 37% of people with type 2 diabetes achieved an A1c of less than 7% in 2000. The frequent occurrence of suboptimal A1c control with present therapies has led to investigations of possible approaches to increase glucagon-like peptide-1 (GLP-1) receptor activation, one method of improving glycemia in patients with type 2 diabetes. These approaches include agents that are analogs of GLP-1; oral dipeptidyl peptidase-IV (DPP-IV) inhibitors that act to prolong the activity of endogenous GLP-1; and a synthetic version of the naturally occurring peptide exendin-4 (exenatide), which exhibits GLP-1 receptor binding in vitro equivalent to that of GLP-1. Liraglutide (NN2211), a long-acting, acylated GLP-1 analog currently in regulatory investigational trials, has exhibited significant reduction of A1c versus placebo at certain dosages. CJC-1131, another GLP-1 analog, also has been associated with improvement in A1c compared to placebo. Vildagliptin (NVP-LAF237), a long-acting DPP-IV inhibitor, has been associated with significant decreases in A1c from baseline compared to placebo; a glycemic benefit maintained out to 52 weeks in an open-label extension trial. Exenatide is a 39-amino acid peptide structurally identical to native exendin-4 and resistant to inactivation by DPP-IV. In clinical trials involving patients with type 2 diabetes previously treated with metformin, a sulfonylurea, or the combination of metformin and a sulfonylurea, addition of exenatide produced significant reductions in A1c, weight loss, and improvement in β-cell function. This review summarizes clinical trial data on efficacy, safety, tolerability, and other effects for each of these incretin-related agents. (Adv Stud Med. 2005;5(10E):S1074-S1078)

Data from an epidemiologic analysis of the United Kingdom Prospective Diabetes Study showed that in people with type 2 diabetes, reduction of A1c (also known as glycated hemoglobin) was associated with a marked decrease in the occurrence of micro- and macrovascular complications. Yet despite this information, A1c is not well controlled in most people with type 2 diabetes in the United States. Data from the National Health and Nutrition Examination Survey III in 1994 showed that only 44% of people with type 2 diabetes achieved an A1c of less than 7%. In the year 2000, this number actually decreased to 37%. Recently at a meeting of the American Association of Clinical Endocrinologists, a report was issued on the state of diabetes health showing that in a study of 157,000 Americans in 39 states, 66% of individuals with type 2 diabetes were above the American College of Endocrinology (ACE) goal for glycemic control of 6.5% or less. In every state studied, more than 50% of the population studied was
above the ACE goal. Present therapies are associated with a number of challenges that contribute to suboptimal control. In people with type 2 diabetes, these challenges include difficulty in attenuating the postprandial rise in glycemia, the association of most therapies with a progressive loss of glycemic control over time that appears related to a progressive decline in β-cell function,4 and the association of most antihyperglycemic treatments with weight gain.

Glucagon-like peptide-1 (GLP-1) has a number of antihyperglycemic actions, including enhancement of glucose-dependent insulin secretion, inhibition of postprandial glucagon secretion, slowing of gastric emptying, and enhancement of satiety. GLP-1 levels are decreased in people with type 2 diabetes, and infusing GLP-1 improves glycemia in patients with type 2 diabetes. However, because GLP-1 is rapidly inactivated after administration, continuous infusion, which is not a desirable option, would be required for GLP-1 to serve as a therapeutic agent. There has been active investigation of other possible approaches to increasing GLP-1 receptor activation, such as analogs of GLP-1, a synthetic version (exenatide) of the naturally occurring peptide exendin-4, and oral dipeptidyl peptidase-IV (DPP-IV) inhibitors. Trial results to date with these agents taken as a group indicate they have antihyperglycemic efficacy with mild to moderate side effects and the absence of weight gain. Exenatide, recently approved by the US Food and Drug Administration (FDA), actually has been associated with significant weight loss. Furthermore, GLP-1–related treatment may offer the potential of preserving or enhancing β-cell function and/or β-cell mass. This paper discusses certain aspects of the clinical trial results with these GLP-1–related therapies.

**Glucagon-like Peptide-1 Analogs**

Liraglutide (NN2211) is a long-acting, acylated GLP-1 analog currently in regulatory investigational trials. In one 12-week, double-blind, randomized, parallel-group, placebo-controlled trial of liraglutide involving 193 outpatients with type 2 diabetes, A1c decreased in all but the lowest liraglutide dosage group.6 In the 0.75-mg liraglutide group, A1c decreased by 0.75 percentage points compared to placebo (P <.0001). In this study, liraglutide was associated with a very low incidence of hypoglycemia and no consistent effect on body weight. At certain doses, slight weight loss was seen, whereas at other doses there was no change in weight. The incidence of nausea seemed to increase with increasing doses of liraglutide. Other observed gastrointestinal events (e.g., diarrhea, vomiting, and constipation) in this study were mild and transient, generally resolving in 1 to 3 days.

A 12-week, randomized, double-blind, placebo-controlled phase II clinical study of CJc-1131, another GLP-1 analog, assessed effects of once-daily dosing on glycemic control in patients with type 2 diabetes who were inadequately controlled, despite treatment with metformin alone or in combination with a sulfonylurea.7 Treatment with CJc-1131 was associated with a mean -1.1% greater A1c change from baseline (7.93%) than placebo (P <.0001). CJc-1131 treatment also was associated with a mean placebo corrected weight loss of 0.9 kg. Nausea was the only major side effect.

**Dipeptidyl Peptidase-IV Inhibitors**

Vildagliptin (NVP LAF237) is a long-acting DPP-IV inhibitor that prolongs the activity of endogenous GLP-1. DPP-IV is a widely expressed enzyme that has postproline and postalanine peptidase activity and, as a result, both inactivates and activates peptides. Its substrates in the gut endocrine system are not solely GLP-1. Others include gastrin-releasing peptide, glucose-dependent insulinotropic peptide, glucagon-like peptide-2, and peptide YY. In a 12-week, placebo-controlled study of vildagliptin in metformin-treated patients with type 2 diabetes, A1c decreased (-0.6% ± 0.1%) from a mean baseline of 7.7%, whereas A1c did not change in the placebo group.a An open-label extension of this trial demonstrated maintenance of the glycemic benefit out to 52 weeks with vildagliptin, whereas there was further loss of glycemic control in the placebo group. Vildagliptin was associated with a low incidence of hypoglycemia and appeared to be weight neutral (in the 12-week core study, body weight decreased 0.4 ± 0.2 kg in patients receiving vildagliptin plus metformin, whereas body weight in the placebo group decreased by 0.5 ± 0.2 kg; in the extension study weight change [-0.2 kg] was the same in both groups). Tolerability of vildagliptin was comparable with placebo.

Another DPP-IV inhibitor, MK-0431, also is entering late-stage clinical development. In 2 dose-ranging studies, treatment of patients with type 2 diabetes for 12 weeks resulted in placebo-corrected reductions in A1c, of 0.4% to 0.8%. Changes in weight were not observed in the 2 studies.a,b
EXENATIDE

Exenatide (synthetic exendin-4) is a 39-amino acid peptide that is structurally identical to native exendin-4. GLP-1 receptor binding with exenatide is equivalent to GLP-1. Exenatide is rapidly absorbed after subcutaneous injection, is resistant to inactivation by DPP-IV, is suited for twice-daily injection, and recent ly received FDA approval for treatment of patients with type 2 diabetes who had not achieved adequate glycemic control, despite treatment with metformin and/or a sulfonylurea.

Exenatide has been shown to improve β-cell function and lower glucose. In a study of 12 patients with type 2 diabetes who had previously been treated with diet or oral agents, the injection of exenatide was associated with a marked increase in insulin secretion and a resultant fall in glycemia. But as is characteristic of GLP-1–related compounds, as glucose levels approached the normal range, there was an attenuation of insulin secretion. The glucose-dependent insulin secretion with this agent should reduce the risk for hypoglycemia.

In individuals who do not have diabetes, intravenous glucose results in a very rapid first-phase insulin secretion followed by more prolonged, second-phase insulin secretion. Patients with type 2 diabetes receiving intravenous glucose display an attenuation or absence of this first-phase insulin response. Fehse et al studied 13 subjects with type 2 diabetes and compared them to 12 healthy subjects with normal glucose tolerance. Treatment of patients with type 2 diabetes with exenatide increased insulin (P < .005) and C-peptide areas under the curve (P < .005) during the first (0–10 min) and second (10–120 min) phases after intravenous glucose by 2- to 4-fold relative to placebo. Exenatide-treated patients with type 2 diabetes had a secretory pattern similar to healthy subjects, in contrast to patients with type 2 diabetes treated with placebo who had blunted first-phase insulin secretion compared to healthy control subjects. This study thus demonstrated the ability of exenatide to acutely improve β-cell function and restore and enhance the first-phase insulin response of patients with type 2 diabetes.

Exenatide versus placebo injected subcutaneously was compared to placebo in patients with type 2 diabetes being treated with diet and/or oral antidiabetic agents. One hundred nine patients were assigned to 1 of 3 exenatide regimens or placebo for 28 days. After 28 days of exenatide treatment, all 3 treatment groups showed significant reductions in serum fructosamine (P ≤ .004), A1c (P ≤ .006), and attenuation of the postprandial rise in plasma glucose (P ≤ .004) compared to placebo. There was no change in body weight from day 1 to day 28.

Three phase III pivotal trials of 30 weeks’ duration compared exenatide versus placebo in patients with type 2 diabetes who had not achieved glycemic control, despite treatment with metformin, a sulfonylurea, or the combination of metformin and a sulfonylurea. There were 336 and 377 patients in the first 2 studies respectively, and 733 in the third, with a 2-to-1 randomization in favor of exenatide. Intent-to-treat A1c results from these trials (Figure 1) in individuals with a baseline A1c ranging from 8.2% to 8.7% showed an approximate 1% decrease in A1c compared to placebo in all 3 trials. Weight loss was seen in each of the 3 studies, with a mean weight loss of approximately 2 kg across the studies (Figure 2). The greatest weight loss occurred in the group of patients in whom exenatide was added to metformin. These trials also assessed the percentage of patients achieving A1c of 7% or below. In the metformin trial, 46% of patients receiving exenatide 10 µg twice daily achieved an A1c of 7% or below. In the sulfonylurea trial, 41% of patients at the highest dosage of exenatide (10 µg twice daily) achieved an A1c of 7% or below. In the trial comparing exenatide and placebo in patients not at goal, despite receiving a combination metformin and sulfonylurea therapy—individuals who would be expected to have more advanced type 2 diabetes—34% of patients receiving exenatide 10 µg twice daily achieved an A1c of 7% or below.

A 52-week open-label extension of each of the 3 trials also was completed. All patients, irrespective of treatment during the 30-week trial, were initially treated with exenatide 5 µg twice daily for the first 4 weeks of the open-label extension, and then were advanced to 10 µg twice daily. Upon receiving exenatide, patients who previously had been in the placebo cohort had a rapid decrease of A1c similar to that observed with exenatide treatment in the first 30 weeks. Mean A1c reductions from baseline were very similar at 82 weeks (at least -1.1%) for all 3 original study treatment groups. For patients receiving 10 µg exenatide twice daily for 82 weeks, 51% achieved an A1c of 7% or below at 82 weeks.

Placebo-treated subjects in the initial trial, upon
receiving exenatide in the extension, showed a significant decrease of weight similar to that observed with exenatide treatment in the first 30 weeks. Mean body weight reductions mediated by exenatide during the first 30 weeks were sustained and appeared to be progressive through 82 weeks with a mean weight loss of approximately 10 lbs compared with baseline. Preliminary 2-year data demonstrate that these effects on glycemic control and weight appear to persist.

In the 30-week trial in which metformin-treated patients with type 2 diabetes were randomized to exenatide 5 or 10 µg twice daily or placebo, the reported incidence of hypoglycemia was no greater for exenatide than for placebo-treated subjects. This low incidence of hypoglycemia is what would be anticipated for an agent producing glucose-dependent insulin secretion. When exenatide was added to patients treated with sulfonylurea alone or sulfonylurea plus metformin, an increase in hypoglycemia compared to placebo was observed. However, exenatide subjects also had achieved a significantly lower A1c, and there were no episodes of serious hypoglycemia and only 1 episode of severe hypoglycemia (requiring the assistance of another person) in these studies.

Other adverse events in the 30-week trials that were more frequent in exenatide than in placebo-treated subjects were mostly gastrointestinal in nature. Nausea, the most frequent side effect, was mostly mild to moderate in intensity. Only 3% of exenatide and 1% of placebo-treated patients discontinued the study because of nausea. The incidence of nausea decreased over time. In contrast, as noted earlier in this article, weight loss with exenatide continued to progress over time, and weight loss also was seen in subjects without nausea, indicating that weight loss was not primarily caused by nausea.

CONCLUSIONS

Glucagon-like peptide-1 appears to be deficient in people with type 2 diabetes, and enhancing GLP-1 receptor activation can improve glycemic control, especially after meals. GLP-1 analogs, DPP-IV inhibitors, and synthetic exendin-4 (exenatide) have been in development, and exenatide has recently received FDA approval. Trial results to date indicate these agents are effective in lowering blood glucose with mild-to-moderate side effects and are not associated with the weight gain seen with most antihyper-
glycemic therapies. Indeed, exenatide therapy is associated with significant weight loss. These agents also may offer the potential to preserve or enhance β-cell function and even β-cell mass. Further studies that attempt to elucidate these potential β-cell effects are eagerly anticipated.

REFERENCES