New Approaches in the Treatment of Type 2 Diabetes Mellitus: Focus on Synthetic Exendin-4

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Diabetes mellitus (DM) represents a group of heterogeneous metabolic diseases characterized by persistent hyperglycemia and various acute and chronic complications. It results from impaired insulin secretion, insulin action, or both.1 A recent national survey discovered that there are approximately 16.9 million adults aged 20 years or older who have DM. Diabetes was the sixth leading cause of deaths in the U.S. in 1999.2 In addition, the prevalence of DM has increased from 4.9% in 1990 to 7.3% in 2000, representing a 49% increase. The direct and indirect costs of diabetes are nearly $100 billion annually.3 Acute manifestations of DM range from relatively mild polyuria, polydipsia, weight loss, and blurred vision to life-threatening manifestations, such as hyperglycemic ketoacidosis and nonketotic hyperosmolar syndrome. However, chronic complications of DM are primarily responsible for morbidity and mortality associated with this disease. By affecting the brain, eyes, heart, kidney, and nervous system, DM can lead to serious complications, such as cerebrovascular disease, blindness, cardiovascular disease, end-stage renal disease, peripheral vascular disease, and neuropathy.1,2

The two most common types of DM are type 1 and type 2, with the latter accounting for about 90% to 95% of all diagnosed cases.2 Patients with type 1 DM exhibit complete absence of insulin resulting from dysfunction and/or destruction of pancreatic β-cells, whereas patients with type 2 DM demonstrate insulin resistance, leading to chronic overproduction of insulin and exhaustion of pancreatic β-cells.

Recent years have witnessed the introduction of novel hypoglycemic agents with a variety of therapeutic mechanisms. Compared to older drugs, these agents allow better glycemic control and have a more favorable safety profile in the treatment of DM, particularly type 2 diabetes. Nevertheless, diabetes is a progressive and increasingly prevalent disease that urgently requires new therapeutic modalities to establish adequate glycemic control and prevent disastrous complications.4 In January 1999, Amylin Pharmaceuticals, Inc. filed an investigational new drug application with the Food and Drug Administration (FDA), and presently is conducting phase III clinical trials of its new class antidiabetic agent, AC 2993 (synthetic exendin-4) that might become an important addition to the armamentarium for the treatment of type 2 DM. Synthetic exendin-4 displays similar properties to the mammalian hormone glucagon-like peptide-1 (GLP-1), but has prolonged duration of action compared to GLP-1.

PHARMACOLOGY

Synthetic exendin-4 is a 39 amino acid peptide that shares several antidiabetic actions of GLP-1, a natural hormone synthesized in intestinal endocrine cells. The biological activities of GLP-1 include stimulation of glucose-dependent insulin secretion and insulin biosynthesis, inhibition of glucagon secretion and gastric emptying, and reduction in food intake.5 Natural exendin-4 was isolated from venom of the Gila monster lizard (Heloderma suspectum). The name exendin is derived from the fact that this group of peptides was isolated from an exocrine gland and was subsequently shown to have endocrine actions.5 Exendin-4 shows 53% amino acid similarity to GLP-1 and is a GLP-1 receptor agonist.6 In animal models, synthetic exendin-4 has been shown to stimulate insulin secretion in the presence of hyperglycemia, but not during periods of hypoglycemia. It has also been shown to modulate gastric emptying to slow the entry of ingested nutrients into the bloodstream. Chronic administration of synthetic exendin-4 reduced food consumption in obese animals, leading to decreased body weight. Most notably, administration of exendin-4 resulted in lowering of blood glucose to near-normal concentrations.8-11 Another biological function of exendin-4 that might prove useful in treating DM in the future is its ability to stimulate both replication and neogenesis of pancreatic β-cells.12

As mentioned before, GLP-1 has a short duration of action, thus making it impossible to achieve adequate therapeutic levels. Therefore, a stable synthetic compound with similar antidiabetic properties but a longer duration of action is desirable.

PHARMACOKINETIC AND PHARMACODYNAMIC PROPERTIES

The pharmacokinetic and pharmacodynamic properties of AC2993 have not been extensively studied. In animal models, the drug is biologically active when administered via oral, sublingual, pulmonary, transcutaneous, or nasal routes; however, most of the human studies were conducted utilizing subcutaneous injections.13 Amylin Pharmaceuticals, Inc. conducted a number of studies that demonstrated certain pharmacodynamic parameters of AC2993. During a single-blind, dose-rising, placebo-controlled study, eight male patients with type 2 DM received three or four subcutaneous doses ranging from 0.1 to 0.4 mcg/kg at 48-hour intervals. There was a dose-dependent decrease of plasma glucose concentrations compared to placebo, suggesting a linear relationship between the dose of AC2993 and its...
EFFICACY AND SAFETY

The efficacy and safety of AC2993 have been tested in a number of clinical trials. The majority of trials involved patients with type 2 DM and investigated the role of AC2993 in the treatment of diabetes.

In a randomized, single-blind, placebo-controlled, two-period crossover study, Buse, Koller and colleagues evaluated the efficacy, safety, and tolerability of AC2993 in 24 patients with type 2 DM previously treated by diet, oral hypoglycemic agents (OHA), or insulin. Fourteen days prior to randomization, OHA therapy was discontinued and patients were stabilized with a single injection of insulin NPH at bedtime. Patients were randomized to two groups: the first group received 0.1 mg/kg subcutaneous injection of AC2993 twice daily and the second group received a placebo in a similar manner. The duration of treatment for both groups was five days. After the two- to three-day washout period, patients were crossed over to the other treatment. Liquid meal challenge (Sustacal 7 Kcal/kg) was given to all patients 10 minutes after the morning injection on days one and five.

On day five, the mean change in five-hour time-weighted post-prandial plasma glucose concentration from fasting values was $-7.7\pm5.1$ mg/dL for AC2993 compared to $67.2\pm7.9$ mg/dL for the placebo groups ($P<0.0001$). The three-hour post-prandial plasma glucon concentration area-under-the-curve (AUC) decreased by 23% for AC2993 groups compared to placebo ($P=0.0123$). There was a 24% suppression of peak post-prandial triglyceride concentrations compared to placebo ($P=0.0001$). The rate of gastric emptying was evaluated by administration of 20 mg/kg of acetaminophen along with a meal. The five-hour mean total acetaminophen concentration was decreased by 57% in the AC2993 groups compared to the placebo groups.

There were no safety issues identified. The most common side effects were mild headache, nausea, vomiting, and mild hypoglycemic symptoms.

Another study evaluated the dose-response relationship for the AC2993’s reduction in plasma glucose, and determined its effect on post-prandial plasma glucagon concentrations and on the rate of gastric emptying at doses of 0.1 mg/kg or less.

AC2993 was administered in a single-blind, placebo-controlled, crossover study, 14 patients with type 2 DM were studied following withdrawal of OHA for 10 to 14 days. Six subjects randomly received subcutaneous injections of placebo, 0.01 and 0.1 mcg/kg of AC2993, while eight subjects received placebo, 0.02, 0.05, and 0.1 mg/kg of AC2993 in a similar manner. Study medication was administered following an overnight fast; injections were given 10 minutes prior to ingestion of a standardized Sustacal meal (7 Kcal/kg). The rate of gastric emptying was assessed by oral acetaminophen test. Plasma glucagon concentrations were measured by Radio Immune Assay (RIA).

Plasma glucose concentrations were reduced in a dose-dependent fashion with responses ranging from a 42.0±7.9 mg/dL increment above basal for placebo compared to a 30.5±8.6 mg/dL decrement below basal with 0.1 mg/kg of AC2993 with a median effective dose (ED$_{50}$) of 0.038 mcg/kg. The meal-associated increment in plasma glucagon concentrations was reduced by 58%, 50%, and 47% with 0.02, 0.05, and 0.1 mcg/kg of AC2993, respectively, with an ED$_{50}$ of 0.017 mcg/kg. The rate of gastric emptying was significantly delayed with AC2993, reducing AUC for acetaminophen up to 53.0±8.8% ($P<0.0005$) with ED$_{50}$ of 0.048 mcg/kg. No safety issues were identified. The most common side effects were mild gastrointestinal symptoms.

In a 28-day, four-arm, multicenter, triple-blind, placebo-controlled, parallel-group study, Fineman et al. evaluated the effectiveness of AC2993 in improving glycemic control among 109 patients with type 2 DM who were inadequately controlled with sulfonylureas or metformin alone or in combination. Patients were continued with their medications throughout the study. Patients received subcutaneous injections of placebo and/or AC2993 in the following dosing schedules: placebo three times a day, AC2993 0.08 mcg/kg twice daily at breakfast and dinner (BD), AC2993 0.08 mcg/kg twice daily at breakfast and bedtime (BS), and AC2993 0.08 mcg/kg at breakfast, dinner, and bedtime (BDS). Twice-daily treatment groups received placebo as a third injection to maintain the study blinding. A standardized breakfast meal was given to patients at baseline (day one) and on day 28.

At day 28, mean serum fructosamine concentrations, reflecting average blood glucose control over two to three weeks, were significantly ($P<0.010$) reduced ($-45.8$ – $39.9$, and $-46.9$ mol/L for the BD/BS arm, and the BDS arm, respectively) compared to placebo ($-5.7$ mol/L).

Similarly, significant ($P<0.006$) reductions in mean glycosylated hemoglobin (HbA$_1c$) were observed after AC2993 treatment ($-1.1\pm0.1$, $-0.7\pm0.1$, and $-1.0\pm0.1$ for BD/BS, and BDS, respectively) compared to placebo ($-0.3\pm0.1$); moreover, reductions in glycosylated hemoglobin (HbA$_1c$) of 0.5% or greater were achieved by 90% of the AC2993 patients compared to 33% of the placebo patients. There were statistically significant reductions in post-prandial plasma glucose concentrations with AC2993 treatment ($-79\pm10$, $-57\pm12$, and $-60\pm11$ mg/dL for BD/BS and BDS, respectively) compared to placebo ($-10\pm10$ mg/dL). There was neither a significant difference in fasting plasma glucose concentrations, nor were there significant changes in body weight between the groups. The most common treatment-emergent adverse reaction was nausea (28.4% were mild or moderate in...
intensity; 2.5% were severe). Four patients (3.7%) withdrew from the study because of nausea.

ONGOING TRIALS

From the end of 2001 through the beginning of 2002, Amylin Pharmaceuticals, Inc., initiated three phase III studies in the company’s “AC2993: Diabetes Management for Improving Glucose Outcomes” (AMIGO) development program.19 These studies are designed to demonstrate AC2993’s ability to improve glucose control in people with type 2 DM who do not achieve target blood glucose levels with metformin and/or sulfonylureas. All studies will follow a similar design whereby study participants will be randomized into three groups—two on AC2993, and one on placebo. Those on the drug will receive an introductory 5-mcg dose of AC2993 for one month, given by subcutaneous injection twice daily, at breakfast and at dinner. This will be followed by six months of exposure to doses of either 5 or 10 mcg given twice a day, at breakfast and at dinner. Participants who complete the study will be given the opportunity to enter an open-label extension. The first and second studies will each involve 400 patients who are not adequately controlled on metformin or sulfonylureas alone, respectively. The third study will involve 800 patients who are not adequately controlled on metformin/sulfonylureas combination. The company hopes to release results of these studies by the end of this year.

In May 2000, Amylin Pharmaceuticals, Inc., signed an agreement with Alkermes, Inc., for the development, manufacture and commercialization of an injectable long-acting formulation of AC2993 (AC2993 LAR) by utilizing Alkermes’ patented Medisorb injectable sustained-release drug-delivery technology. The goal of the work under this agreement is to develop a formulation that would allow once-a-month administration of AC2993 for the treatment of type 2 DM. In August 2001, the company announced results from the first phase I study of AC2993 LAR. This initial safety study in healthy volunteers was designed to investigate multiple long-acting release formulations of AC2993. Sustained plasma concentrations of AC2993 were measured for greater than 30 days in all formulations tested. The study also showed that AC2993 LAR was well-tolerated. In June 2002, the company initiated the AC2993 LAR phase II development program. Preliminary results from the first phase II study are expected before the end of 2002.20

CONCLUSION

Several clinical trials have demonstrated that subcutaneous injections of AC2993 (synthetic exendin-4) resulted in dose-dependent insulin secretion, suppression of postprandial glucagon secretion, a decrease in gastric emptying, and a possible reduction of food intake in patients with type 2 DM. Moreover, the drug demonstrated a decrease of HbA1c and fructosamine in patients who are inadequately controlled with metformin and/or sulfonylureas, thus providing improved glycemic control. In the majority of trials, the most commonly observed adverse effect was nausea, which was mild in nature. Currently, Amylin Pharmaceuticals, Inc., is conducting phase III trials to obtain an additional efficacy and safety data; the company is also working on the development of a once-a-month formulation of the drug. However, at this point, there is a need for additional data in order to determine if AC2993 can be a useful addition to the armamentarium for the treatment of type 2 DM.

REFERENCES

3. AACE Diabetes Guidelines, Endocr Pract. 2002;8(Suppl. 1).