

# Exenatide and GLP-1: Novel Treatments for Type 2 Diabetes

A GLP-1 medication would be the first drug to stimulate insulin secretion without causing hypoglycemia or weight gain.

BY KATHLEEN DUNGAN, MD; AND JOHN B. BUSE, MD, PHD

**G**lucagon-like peptide-1 (GLP-1) is produced by the proglucagon gene in L-cells of the small intestine in response to nutrients.<sup>1</sup> It is an incretin – a gut hormone – that is responsible for the greater insulin response to oral versus IV glucose.<sup>2</sup> Its major mechanism of action occurs through stimulation of glucose-dependent insulin release from the pancreatic islets. In addition to its insulinotropic effects, GLP-1 is thought to exert glucose-lowering effects by slowing gastric emptying,<sup>3</sup> inhibiting inappropriate glucagon release,<sup>4</sup> stimulating beta-cell proliferation<sup>5</sup> and differentiation,<sup>6</sup> as well as improving satiety<sup>7</sup> (Table 1).

In type 2 diabetes, GLP-1 levels are decreased,<sup>8</sup> insulin secretion is delayed and diminished and gastric emptying is paradoxically accelerated.<sup>9</sup> Glucagon levels are also inappropriately elevated in the fasting state and lack normal post-prandial suppression.<sup>10</sup> Agents that increase GLP-1 activity may help to correct these abnormalities. In clinical trials, GLP-1 effects are evident regardless of the duration or severity of diabetes.<sup>11</sup> Modulating GLP-1 levels and GLP-1 activity through administration of the native hormone, analogues and mimetics, or by inhibiting its degradation, has become a major focus of investigation to develop treatments for type 2 diabetes.

GLP-1 binds to a seven-transmembrane G-protein-coupled receptor of a subfamily that includes receptors for secretin, vasoactive intestinal peptide (VIP) and gastric inhibitory peptide.<sup>12</sup> The receptor is found on pancreatic periductal and beta-cells, as well as the kidney, heart, stomach and brain.<sup>13</sup> Glucagon-like peptide receptor (GLP-1R) knockout mice have fasting hyperglycemia and abnormal glucose tolerance but are not obese.<sup>14</sup>

GLP-1 exhibits a relatively short half-life of 1 to 2 minutes

that necessitates continuous infusion to achieve steady-state in pharmacologic studies.<sup>15</sup> This is attributed to N-terminal degradation by the enzyme dipeptidyl peptidase IV (DPP-IV).<sup>1</sup> Mice lacking DPP-IV exhibit reduced food intake, improved insulin sensitivity and attenuated decline in beta-cell mass.<sup>16</sup> Current research focuses on agents that increase GLP-1 via inhibition of DPP-IV and on GLP-1 analogues that are resistant to DPP-IV degradation.

## EXENDIN-4

Exendin-4 is a naturally occurring component of Gila monster (*Heloderma suspectum*) saliva.<sup>17</sup> It has 53% homology with mammalian GLP-1,<sup>17</sup> and a key difference in its C-terminus (Figure 1) makes exendin-4 resistant to DPP-IV.<sup>18</sup> Interestingly, exendin-4 is transcribed via a gene

TABLE 1. GLP-1

Target Organ	Effect of GLP-1
Liver	Reduces hepatic glucose output by inhibiting glucagon release
CNS	Promotes satiety
Stomach	Slows gastric emptying
Pancreatic beta-cell	Stimulates glucose-dependent insulin secretion, promotes beta-cell regeneration
Pancreatic alpha-cell	Inhibits glucagon's secretion



Figure 1. Amino acid sequences of exendin-4, mammalian GLP-1 and Gila monster GLP-1.

that is distinct from the Gila monster GLP-1 gene, and therefore likely serves a unique function for the Gila monster. There are some differences between exendin-4 and GLP-1, suggesting that not all of exendin-4's action is mediated by the GLP-1 receptor.<sup>19,20</sup>

In vitro, exendin-4 has been shown to bind to the GLP-1 receptor of rat islets.<sup>21</sup> Exendin-4 exhibits dose dependent augmentation of insulin secretion. In vivo, the insulinotropic effects are suppressed as the plasma glucose approaches 4 mmol/L (72 mg/dL).<sup>22</sup> Like GLP-1, exendin-4 slows gastric emptying and seems to effect satiety through centrally mediated mechanisms. Exendin-4 has been shown to cross the blood-brain barrier in mice<sup>23</sup> and bind receptors in the hypothalamus and thalamus in a pattern identical to that for GLP-1.<sup>24</sup> Exenatide, a synthetic form of the naturally occurring reptilian hormone exendin-4, is the first GLP-1 based therapy to be submitted to the FDA. It could become available for clinical use as early as the summer.

### PHASE 1 AND 2 HUMAN STUDIES

Studies of exenatide's acute effects were performed by Egan et al.<sup>22</sup> Hyperglycemic clamps demonstrated fourfold potentiation of insulin response with a 1-hour exenatide infusion. This effect persisted several hours beyond the cessation of the infusion, demonstrating its prolonged half-life. Basal glucagon levels fell and glucose clearance increased in healthy volunteers and those with diabetes. Insulin levels dropped after stopping the glucose infusion, substantiating that the insulinotropic effect was glucose-dependent. A longer study showed a significant reduction in HbA1c from 9.1% to 8.3% after 1 month of therapy.<sup>25</sup> Several studies have examined the effect of exenatide on insulin sensitivity; apparent increases in insulin sensitivity are confounded by the effects of ameliorating glucotoxicity as well as by alterations in gastric emptying and changes in insulin and glucagon secretion.<sup>26</sup>

Kolterman et al.<sup>27</sup> reported a blinded, placebo-controlled, crossover study where exenatide resulted in significant reductions in postprandial glucose, glucagon, insulin and gastric emptying rates after 5 days of therapy. Effects are likely independent of exenatide's insulinotropic effects, as they are evident in insulin requiring type 2 diabetic patients as well as C-peptide negative patients with type 1 diabetes.<sup>27,28</sup>

A randomized, triple-blind, placebo-controlled trial, per-

formed at 24 sites, treated 109 type 2 diabetes (HbA1c 8% to 11%) patients concomitantly with sulfonylurea, metformin or both over 28 days.<sup>29</sup> HbA1c dropped significantly by 0.9%. There were also significant reductions in postprandial but not fasting glucose. The homeostasis model assessment, an indicator of beta-cell function, was significantly

increased following therapy. There was no significant effect of therapy on body weight, lipids, vital signs or laboratory parameters. Nausea was reported in 31% of patients, most of which was mild to moderate and declined substantially after the first week. Hypoglycemia was observed only in patients who were simultaneously treated with sulfonylureas.

As noted above, exenatide has shown weight-loss benefits. Healthy humans demonstrated a significant reduction in caloric consumption (19%) despite no difference in reported satiety or nausea.<sup>30</sup>

GLP-1 may have beneficial cardiac effects that are of interest in diabetes management. Patients with coronary artery disease treated with GLP-1 have shown improved endothelial dysfunction.<sup>31</sup> In a dog heart failure model, there was improvement in left ventricular hemodynamics, including a 57% increased cardiac output and increased myocardial glucose uptake.<sup>32</sup>

### PHASE 3 TRIALS

The efficacy and safety of exenatide has been demonstrated in three separate phase 3 studies, termed the AMIGOs (AC-2993 – Diabetes Management for Improving Glucose Outcomes) (Table 2).

The first was a triple-blinded, placebo-controlled trial of 377 type 2 diabetes patients from 101 sites who were on a maximally effective dose of sulfonylurea monotherapy.<sup>33</sup> Patients underwent randomization to one of four treatment arms; they received either 5 or 10 µg exenatide twice daily or one of two placebo arms of equivalent volumes.

A 4-week dose escalation period was used in the 10-µg

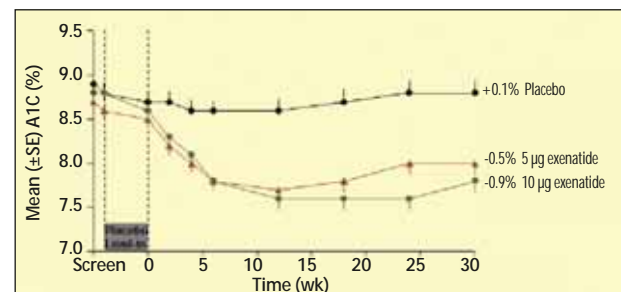


Figure 2. Effects of sulfonylurea plus exenatide on HbA1c. ITT, n = 377 (Placebo, n = 123; 5 µg exenatide, n = 125; 10 µg exenatide, n = 129).  $P < .0001$  for reduction from baseline (pairwise comparison to placebo) in both exenatide arms for weeks 6 to 30.

arm. Results were analyzed in an intention-to-treat manner. At 30 weeks, HbA1c decreased by 0.86% in the 10- $\mu$ g arm and 0.46% in the 5- $\mu$ g arm (Figure 2). A total of 34.2% in the 10- $\mu$ g arm and 26.7% in the 5- $\mu$ g arm were able to reach a HbA1c of <7%, with larger reductions occurring in those with higher baseline HbA1c levels.

Nausea was observed approximately twice as commonly in patients treated with exenatide, but was generally mild to moderate intensity and waned over the first few weeks of therapy; rarely was nausea or vomiting dose limiting. Withdrawal due to nausea was low; 4% in the 10- $\mu$ g arm and 2% in the 5- $\mu$ g arm. Furthermore, body weight decreased significantly at 30 weeks, on average by 1.6 kg in the 10- $\mu$ g group (Figure 3). Weight loss was not related to the incidence of nausea. Antiexenatide antibodies were reported in 41% but there was no predictive effect on overall glycemic control.

**IDENTICAL TO INSULIN**

Full publication of studies 112 and 115 that randomized patients to exenatide or placebo on the background of metformin or metformin plus sulfonylurea are not available. Preliminary abstract publications suggest that the HbA1c lowering efficacy of exenatide in the context of metformin therapy is identical to insulin but with greater weight loss. Perhaps more importantly, the rate of hypoglycemia in the metformin study was identical when patients were treated with exenatide or placebo, suggesting that the increased rates of hypoglycemia seen with exenatide plus sulfonylurea is likely mediated by sulfonylurea. Open-label extension studies to 52 weeks have demonstrated sustained improvement in HbA1c and weight.

**AUGMENTATION OF BETA-CELL MASS**

The progressive loss of beta-cell function and mass is an early feature of type 2 diabetes and may lead to insulin dependence.<sup>35</sup> Intervening early in the course of diabetes or perhaps in the prediabetic state to stimulate beta-cell dif-

ferentiation and/or reduce apoptosis could theoretically halt the progression of the disease. In vitro, exenatide stimulates islet cell differentiation.<sup>36,37</sup> In rats undergoing partial pancreatectomy, exenatide treatment was associated with a 40% expansion of beta-cell mass.<sup>38</sup> The most dramatic results are seen in the intrauterine growth retarded rat, in which exenatide has prevented the development of diabetes by rescuing the otherwise inevitable 80% reduction in beta-cell mass.<sup>39</sup> By 18 months, untreated rats were dead while those treated with 6 days of exenatide were indistinguishable from normal rats.

**FUTURE DIRECTIONS**

Other GLP-1 analogues that are resistant to DPP-IV degradation have shown similar results to that of exenatide and GLP-1 in preliminary studies.<sup>40</sup> In addition, a long-acting formulation of exenatide given once a month is being developed.<sup>41</sup> DPP-IV inhibitors have the theoretical advantage of oral administration. A 12-week randomized, double-blinded, placebo-controlled study of 107 patients with type 2 diabetes on a stable dose of metformin monotherapy resulted in a significant 0.6% drop in HbA1c.<sup>42</sup> Of these GLP-1-based therapies, exendin-4 (in the form of exenatide) may reach the market this summer.

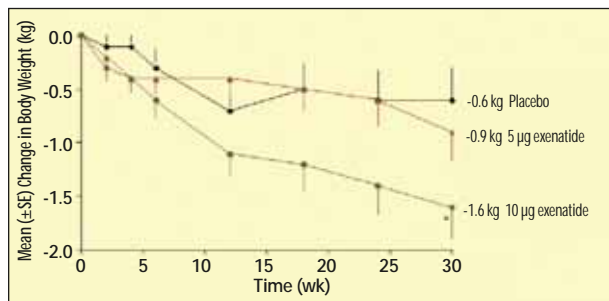
**CONCLUSION**

GLP-1 based therapy would be a novel and complementary approach to diabetes management for many reasons. A GLP-1 based medication would be the first antidiabetic agent to stimulate insulin secretion without causing hypoglycemia or weight gain. In fact, therapies are generally associated with moderate weight loss. Thus, GLP-1 based treatments may be preferred over secretagogues or insulin. Such treatment could be used as a bridge to insulin therapy or to reduce insulin requirements of insulin resistant patients in order to avoid weight gain.

Although GLP-1 based therapies have not been studied in patients with renal or hepatic insufficiency, its safety pro-

**TABLE 2. EXENATIDE US CLINICAL TRIALS: SUMMARY OF SELECTED OUTCOMES**

	Study 113 Sulfonylurea (max dose)	Study 112 Metformin	Study 115 Metformin plus Sulfonylurea
Change in HbA1c (placebo adjusted)	down 1.0%	down 0.9%	down 1.0%
Weight change (placebo adjusted)	down 0.3 to 1.0 kg	down 1.3 to 2.5 kg	down 0.7 kg
Nausea placebo vs 10 mcg	7% vs 51%	23% vs 45%	21% vs 49%
Severe nausea placebo vs 10 mcg	2% vs 5%	2% vs 4%	1% vs 3%
Hypoglycemia placebo vs 10 mcg	3% vs 36%	5% vs 5%	13% vs 28%



**Figure 3.** Effects of sulfonylurea plus exenatide on HbA1c. ITT, n = 377 (Placebo, n = 123; 5 µg exenatide, n = 125; 10 µg exenatide, n = 129) \*P < .05.

file may make it the preferred agent in these patients. GLP-1 based treatment would also provide for entirely novel mechanisms of action including suppression of the inappropriately elevated glucagon levels and rates of gastric emptying in patients with diabetes. They may also promote beta-cell regeneration and thus theoretically halt diabetes progression, though this has not been studied in humans.

Exenatide's injectable route of delivery and its potential side effects of nausea and vomiting may be the main barriers to widespread use. However, slow dose-escalation has been shown to reduce these side effects.<sup>43</sup> Further studies are needed to determine its long-term efficacy, effects on weight and its potential for beta-cell recovery. ■

*Kathleen Dungan, MD, is from the division of endocrinology, department of medicine, at the University of North Carolina School of Medicine. John B. Buse, MD, PhD, is in the divisions of endocrinology and general medicine and clinical epidemiology, department of medicine, at the University of North Carolina School of Medicine.*

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