Drugs 2005; 65 (12): 1693-1695
0012-6667/05/0012-1693/$39.95/0

Exenatide
A Viewpoint by Julio Rosenstock

Dallas Diabetes and Endrocrine Center at
Medical City, Dallas, Texas, USA

Roger Unger's visionary article in *The New England Journal of Medicine* almost 35 years ago postulated that a pharmacological means of suppressing glucagon secretion to appropriate levels would "increase the effectiveness of available insulin, markedly reduce insulin requirements and perhaps improve control of the diabetic state".[1]

Exenatide, a glucagon-like peptide-1 (GLP-1) mimetic, represents the first pharmacological tool for regulating glucagon secretion, hailing the 'rediscovery' of glucagon suppression as a target for controlling postprandial hyperglycaemia in type 2 diabetes mellitus. GLP-1-related interventions result in glucose-dependent insulinotropic and glucagon-suppressing actions with robust postprandial effects.

Exenatide challenges our current treatment paradigm for type 2 diabetes, which has traditionally consisted of lifestyle and nutritional changes combined with oral antidiabetic agents, with or without insulin. Indeed, multiple combinations of two or three oral antidiabetic agents have failed over the years to sustain optimal glycaemic control because of the multifactorial nature of type 2 diabetes and the inexorable decline in β-cell function. Supplementation with new insulin analogues is often needed to attain glycaemic targets, but weight gain and hypoglycaemia remain major barriers to successful insulin therapy. Developing the full therapeutic potential of the GLP-1 derivatives may overcome these treatment obstacles in type 2 diabetes.

The main highlights of the GLP-1 story are:

- stimulation of insulin secretion in a glucose-dependent manner occurring mainly during hyperglycaemia;
- suppression of inappropriate postprandial hyperglucagonaemia, also in a glucose-dependent manner, without affecting the physiological defensive response to hypoglycaemia;
- delay of gastric emptying and possible reduction of food intake because of fullness and apparent increased satiety;
- presumptive preservation of β-cell mass and function based on experimental evidence in animal models showing reduced apoptosis and increased neogenesis.

Arguably, the suppression of glucagon is the clinical benefit that deviates most markedly from traditional therapies that have failed to control postprandial hyperglycaemia. Indeed, this property may explain the robust improvements of postprandial glucose levels that have been demonstrated in trials of GLP-1-related compounds (e.g. the mimetic exenatide extensively discussed in this review, the GLP-1 analogue liraglutide and the dipeptidyl peptidase IV [DPP-IV] inhibitors) compared with those of conventional agents. Most oral DPP-IV agents have shown glycosylated haemoglobin (HbA_{1c}) reductions from baseline ranging from 0.6–0.7% with no weight gain, whereas injectable exenatide exhibited slightly higher HbA_{1c} reductions in the 0.8–0.9% range, with a weight loss of 1.6–2.8kg in combination with a sulfonylurea and/or metformin. Although this weight loss is relatively modest, it is noteworthy in view of the concomitant improvement in HbA_{1c}.

Furthermore, the relevance of these HbA_{1c} improvements clearly depends on the baseline HbA_{1c} level. For example, the reduction of 1.1% becomes clinically meaningful when the baseline HbA_{1c} is 8.2%, as demonstrated in the study comparing exenatide with insulin glargine, wherein both compounds were associated with similar reductions in HbA_{1c} levels but with contrasting effects on weight. Presumably, this HbA_{1c} reduction will have an even greater impact if patients are treated earlier when baseline HbA_{1c} levels are lower. Alternatively, reaching HbA_{1c} targets in patients with higher baseline levels will tend to favour the use of insulin, which has a greater glucose-lowering potential if titrated properly and consistently.

Of note, the frequency of nausea with exenatide in the registration trials was as high as 45–50% and vomiting was 12–14%, but these adverse effects tended to dissipate over time and were not a major issue during the clinical trials, largely owing to a well structured support system featuring consistent communication and educational reassurance to en-

sure compliance. However, it still remains to be seen how the gastrointestinal adverse effect profile will impact the use of exenatide in the 'real world' without such support systems. Further long-term controlled studies to elucidate the positioning and efficacy of exenatide versus basal insulin, with close assessment of the hypoglycaemia risks, weight changes and gastrointestinal adverse effects, are clearly warranted. Highly needed are studies to explore the optimal potential combination of these two compounds: basal insulin glargine controlling nocturnal and fasting hyperglycaemia and exenatide correcting postprandial hyperglycaemia.

The most critical test of the potential of GLP-1 compounds to transform diabetes care will come when near-normal glycaemia is sustained long enough to substantiate the claim of β-cell preservation. To date, the *post hoc* data in selected populations of exenatide responders or completers are not sufficient to support this claim. The vision of using exenatide or other novel GLP-1-related agents to preserve β-cells, and thereby prevent progression or even development of type 2 diabetes, can only be realised with carefully controlled long-term studies in pre-diabetes or early type 2 diabetes. ▲

Reference

1. Unger RH. Glucagon physiology and pathophysiology. N Engl J Med 1971 Aug 19; 285 (8): 443-9