Exenatide for the Treatment of Type 2 Diabetes Mellitus

Summary

Exenatide is a glucagon-like peptide-1 agonist. It is being investigated as an add-on therapy for patients with type 2 diabetes mellitus who are taking oral antidiabetic drugs.

Evidence indicates that exenatide reduces glycosylated hemoglobin and plasma glucose levels when compared with placebo.

Limitations of the therapy include the need for twice daily injections and potentially dose-limiting nausea and vomiting.

Long-term studies are required to determine the effects of exenatide on disease-related morbidity and mortality.

The Technology

Exenatide is the first in a new drug class known as incretin mimetics, which are being investigated for the treatment of type 2 diabetes mellitus (T2DM). Exenatide is being co-developed by Amylin Pharmaceuticals (San Diego CA) and Eli Lilly and Company (Indianapolis IN). Exenatide, which is a glucagon-like peptide-1 (GLP-1) agonist, helps to regulate blood glucose in several ways, including enhancement of insulin secretion, suppression of glucagon secretion, delay in gastric emptying and reduction of food intake.

Regulatory Status

Exenatide has not been approved for use in Canada. In the US, the Food and Drug Administration granted approval for the use of exenatide as an adjunctive therapy in patients with T2DM who are taking oral hypoglycemic agents (OHAs), such as metformin, sulfonylurea or a combination of the two, but who have not achieved adequate glycemic control. Exenatide has not yet been approved for use in Europe.

Patient Group

T2DM is characterized by insulin resistance and progressive pancreatic beta-cell failure, which lead to chronic hyperglycemia. Long-term complications include diseases of the heart, blood vessels, kidneys, nerves and eyes. The reported prevalence of diabetes in Canada is 4.8% of the adult population, but the prevalence could be higher as many cases are undiagnosed. The cumulative incidence from 1994 to 1998 was 1.4%. T2DM occurs in 90% of patients with diabetes.

Current Practice

Treatment for T2DM comprises lifestyle modification (diet, exercise) and therapy with OHAs and insulin. It is recommended that glycemic control be kept close to normal [glycosylated hemoglobin (A1C) level <7.0%]. Many patients do not achieve the recommended level of control. Typically, pharmacologic therapy is initiated using one or two OHAs from different classes. If glycemic targets are unreached in six months to 12 months, a different OHA or insulin may be added.

The Evidence

Eight randomized controlled trials (RCTs) comparing the efficacy of exenatide with placebo in patients with T2DM were located (Table 1). Their design varied from single- to triple-blinded.
Table 1: Efficacy of exenatide in patients with T2DM

<table>
<thead>
<tr>
<th>Study</th>
<th>Participants</th>
<th>Intervention</th>
<th>A1C reduction</th>
<th>PG reduction (mmol/L)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Fineman et al.</td>
<td>109 patients, metformin and/or SU, mean A1C&gt;9%</td>
<td>Exenatide 0.08 µg/kg sc bid or tid versus placebo for 28 days</td>
<td>bid 0.7% to 1.1%; tid 1.0%; placebo 0.3%; (p≤0.006 for all groups)</td>
<td></td>
</tr>
<tr>
<td>Kolterman et al.; Study A</td>
<td>24 patients, diet, OHA or insulin:OHA</td>
<td>Exenatide 0.1 µg/kg sc bid versus placebo for 5 days</td>
<td>NA</td>
<td>Postprandial: 0.1 µg/kg†; (p&lt;0.05)†</td>
</tr>
<tr>
<td>Kolterman et al.; Study B</td>
<td>13 patients, diet or OHA</td>
<td>Exenatide 0.05, 0.1 or 0.2** (µg/kg sc)</td>
<td>NA</td>
<td>Fasting: all doses§ (p&lt;0.0001)</td>
</tr>
<tr>
<td>Kolterman et al.; Study A</td>
<td>8 patients, diet and/or OHA</td>
<td>Exenatide 0.1, 0.2, 0.3 or 0.4** (µg/kg sc)</td>
<td>NA</td>
<td>Postprandial: all doses§ (p&lt;0.05)†</td>
</tr>
<tr>
<td>Kolterman et al.; Study B</td>
<td>Part 1: 6 patients; Part 2: 8 patients,</td>
<td>Part 1: Exenatide 0.01, 0.1** (µg/kg sc); Part 2: Exenatide 0.02, 0.05 or 0.1** (µg/kg sc)</td>
<td>NA</td>
<td>Part 1: postprandial 0.1 µg/kg† NS§; Part 2: postprandial all doses§ (p&lt;0.05)†</td>
</tr>
<tr>
<td>Buse et al.</td>
<td>377 patients, SU, mean A1C=8.6%</td>
<td>Exenatide 5 or 10 (µg sc bid) versus placebo for 30 weeks</td>
<td>10 µg 0.86%; 5 µg 0.46%; placebo 0.12% increase; (p≤0.0002 for all groups)</td>
<td></td>
</tr>
<tr>
<td>Maksoud et al.</td>
<td>15 patients, diet or SU, mean A1C=8.5%</td>
<td>Exenatide 0.4 µg/m² sc bid or 0.2 µg/m² sc qid versus placebo for 24 hours</td>
<td>NA</td>
<td>Fasting: 10 µg 0.6 (p&lt;0.05)§; 5 µg NS; placebo 0.4 increase</td>
</tr>
<tr>
<td>Taylor et al.</td>
<td>24 patients, diet and/or metformin</td>
<td>Exenatide 0.2, 0.4, 0.6 or 0.8 (µg/kg) daily sc infusions (23 hours) versus placebo</td>
<td>NA</td>
<td>23-hour average: 0.2 µg 2.2; 0.4 µg 2.5; 0.6 µg 2.9; 0.8 µg 3.3; no p values</td>
</tr>
<tr>
<td>Kendall et al.</td>
<td>733 patients, metformin and SU, mean A1C=8.5%</td>
<td>Exenatide 5 or 10 (µg sc bid) versus placebo for 30 weeks</td>
<td>5 µg 0.60%; 10 µg 0.80%; placebo 0.20% increase; (p&lt;0.0001 for both groups)†</td>
<td></td>
</tr>
<tr>
<td>DeFronzo et al.</td>
<td>366 patients, metformin, mean A1C=8.2%</td>
<td>Exenatide 5 or 10 (µg sc bid) versus placebo for 30 weeks</td>
<td>5 µg 0.40%; 10 µg 0.78%; placebo 0.08% increase; (p&lt;0.002 for both groups)†</td>
<td></td>
</tr>
</tbody>
</table>

A1C=glycosylated hemoglobin; bid=twice daily; OHA=oral hypoglycemic agents; NA=not assessed; NS=not significant; PG=plasma glucose; qid=four times daily; sc=subcutaneous; SU=sulfonylurea; tid=three times daily. *Results not listed for a given exenatide regimen were not assessed and/or not reported; †compared with placebo; ‡actual values not reported; **single dose versus placebo.
OHAs were continued in most trials, but were stopped before study drug administration in others.

Overall, the studies indicate that compared with placebo, exenatide is associated with clinically significant improvements in blood glucose levels. At the recommended target dose of 10 µg bid, A1C reductions ranged from 0.78% to 0.86%, and the reduction in postprandial plasma glucose was 3.0 mmol/L. Some studies suggest that there are beneficial effects on beta-cell function and gastric emptying. Reduction in fasting plasma glucose and positive changes in insulin profiles, glucagon secretion and body weight were reported in some RCTs, but they were unconfirmed in others. Some of the RCTs are published in abstract or poster form only, which limits interpretation of the results.

Preliminary comparative data from a study of >500 participants also suggest that exenatide is equivalent to insulin glargine at reducing A1C.

**Adverse Effects**

Gastrointestinal reactions (nausea, vomiting, diarrhea) and headache were the most commonly reported adverse effects in clinical trials. The incidence of mild or moderate nausea in two studies was reported to be 46% and 49% for exenatide versus 5% and 21% for placebo respectively.

Mild or moderate hypoglycemia occurred in 28% to 36% of patients on exenatide, compared with 3% to 13% of patients on placebo. This adverse event was observed more frequently in individuals receiving exenatide with concomitant sulfonylurea therapy as compared with those taking sulfonylurea alone. One episode of severe hypoglycemia associated with exenatide (in combination with sulfonylurea) was reported.

**Administration and Cost**

A progressive dose increase starting with 5 µg twice daily for one month followed by a maintenance dose of 10 µg twice daily reduces the nausea that is associated with exenatide. This approach is endorsed in the US product monograph. In the US, exenatide is supplied in pre-filled pens containing a 5 µg or a 10 µg dose. The drug needs to be refrigerated.

No pricing information for exenatide is available in Canada. In the US, the 30-day wholesale supply price varies from $145.00 to $172.50, depending on dosage. Canadian pricing may differ due to unique regulatory contexts.

**Concurrent Developments**

A long-acting formulation of exenatide that would allow weekly to monthly subcutaneous injection is in phase II development. The manufacturer is planning long-term studies to evaluate the efficacy of exenatide in the preservation of beta-cell function.

Many other GLP-1-based compounds are under development. Data that are based on patients with T2DM are limited.

**Rate of Technology Diffusion**

Compared with oral insulin secretagogues and insulin, exenatide may be less likely to cause hypoglycemia based on its glucose-dependent activity. This remains to be demonstrated in studies comparing exenatide to other antidiabetic drugs, including insulin, rather than placebo alone. Also, exenatide appears to have a lower risk of causing weight gain than many other antidiabetic drugs, and it may be associated with weight loss.

The limitations of the current exenatide formulation include the need for twice daily injections and potentially dose-limiting nausea and vomiting. Data from RCTs regarding clinically relevant outcomes such as morbidity and mortality are lacking, as they are with most new antidiabetic agents.

**Implementation Issues**

Exenatide may offer an alternative to insulin therapy or it may delay the use of insulin in...
patients with T2DM who have not achieved adequate glycemic control with OHAs. The benefits of therapy with exenatide versus insulin have yet to be clearly demonstrated in controlled trials.

The cost of exenatide and the lack of information about its effect on diabetic complications, including the utilization of other antidiabetic medications, will influence its implementation.3

References