Treatment options for type 2 diabetes: introducing the incretin-based therapies

AH Barnett*

Introduction
Despite the availability of numerous treatments for patients with type 2 diabetes (T2DM) continues to lead to serious complications, including cardiovascular disease (CVD), stroke, amputation, blindness, renal impairment and premature death.1,2 This poor prognosis may be related to worsening glucose control and the high prevalence of other CVD risk factors, such as hypertension, dyslipidaemia and obesity.1,2

Pharmacological treatment of T2DM aims to achieve fasting plasma glucose (FPG) levels <6.0mmol/L and glycated haemoglobin (HbA1c) levels <6.5–7%.1,2 Metformin is widely recommended as first-line therapy, particularly in overweight patients, because of its efficacy, weight neutrality and evidence for vascular protection. Other agents, including insulin secretagogues and acarbose, may be considered as first-line therapy in selected patients.1,2

In most patients, glycaemic control deteriorates over time because of progressive worsening of pancreatic β-cell function; as a result, intensification of therapy becomes necessary and many patients ultimately require insulin.1,2 Adverse effects of treatment include weight gain with insulin, insulin secretagogues and glitazones; gastrointestinal side effects with metformin and acarbose; hypoglycaemia with sulphonylureas and insulin; and peripheral oedema with glitazones.1,2

New therapies for T2DM are needed that can maintain glycaemic control and improve other CVD risk factors and which may preserve or enhance β-cell function. This article discusses new therapies derived from the incretin system – an important physiological mechanism in insulin β-cell function. This article focuses on GLP-1.

The incretin system: the key to a new treatment approach

The incretin response
Oral administration of glucose in healthy humans causes a greater stimulation of insulin secretion than intra-venous administration of a similar glucose load. The augmented insulin response to oral glucose is termed the incretin response and is reported to be reduced or abolished in patients with T2DM.3,4 The incretin response is mediated by two peptides – glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide-1 (GLP-1); glucose-dependent insulinotropic polypeptide (GIP)

Actions of GLP-1
In contrast to GIP, patients with T2DM remain responsive to GLP-1.3 Pharmacological treatment with GLP-1 therefore has the potential to restore the incretin response and improve glucose control in these patients. Administration of native GLP-1 to patients with T2DM increases glucose-dependent stimulation of insulin secretion, inhibits glucagon secretion, suppresses appetite, produces weight loss and delays gastric emptying.3,4 In preclinical studies in animal models, GLP-1 receptor agonists increased β-cell

ABSTRACT
In type 2 diabetes mellitus (T2DM), glycaemic control is often difficult to maintain and current treatments can produce adverse effects. The incretin-based therapies – dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 (GLP-1) agonists – improve glycaemic control when added to conventional therapies and are well tolerated, with a low incidence of hypoglycaemia. In addition, the GLP-1 agonists reduce body weight and systolic blood pressure and improve surrogates of β-cell function. Incretin-based therapies may be appropriate for selected patients with T2DM when first-line therapy does not maintain glycaemic control, particularly where weight gain or hypoglycaemia are a concern.

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KEY WORDS
type 2 diabetes; incretin-based therapies; liraglutide; exenatide; glucagon-like peptide-1 (GLP-1); glucose-dependent insulinotropic polypeptide (GIP)

Table 1 summarises the actions of both peptides. GIP makes an important contribution to the incretin response and has other potentially beneficial actions, but patients with T2DM have markedly reduced sensitivity to it.4 Consequently, interest has concentrated on GLP-1.

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mass. Many of the effects of GLP-1 would be beneficial in T2DM, but its rapid inactivation by DPP-4 means that it would need to be administered by continuous intravenous infusion to demonstrate beneficial pharmacological levels. The problem of the rapid degradation of GLP-1 can be overcome by inhibition of DPP-4 or by providing stable GLP-1 receptor agonists. Positive clinical trial data have led to regulatory approval of drugs from both classes, with more under development.

**Incretin-based therapies**

**DPP-4 inhibitors**

**Sitagliptin**

Sitagliptin is licensed for use at a dose of 100mg once daily, added to oral agents in patients with T2DM. Once-daily sitagliptin monotherapy improves glycaemic control (0.79–0.94% reductions in HbA1c compared with placebo). Sitagliptin plus metformin reduces HbA1c by 1.6–2.1% versus 1.0–1.3% for metformin alone and by 0.8% for sitagliptin alone compared with placebo. Sitagliptin significantly reduces HbA1c (by approximately 0.5–1.0%) and fasting and postprandial glucose when combined with metformin, glimepiride (with or without metformin) and pioglitazone. Several of these studies also demonstrated improvements in surrogate measures of pancreatic β-cell function and some lipid parameters. Sitagliptin added to metformin gives similar reductions in HbA1c as add-on therapy with rosiglitazone. In another trial, addition of sitagliptin to metformin over 52 weeks was non-inferior to glipizide plus metformin, with both treatments yielding reductions in HbA1c of 0.67% compared with baseline. These trials indicate that sitagliptin is weight-neutral compared with placebo. Sitagliptin is generally well tolerated, with slightly higher rates of constipation, nasopharyngitis, urinary tract infections, hypertension and dizziness compared with placebo.

**Vildagliptin**

Vildagliptin is licensed for use at a dose of 50mg once or twice daily, as dual oral therapy in patients with T2DM. In a placebo-controlled trial, vildagliptin significantly reduced HbA1c by 0.7–0.9%. In a comparative study, vildagliptin and rosiglitazone monotherapy decreased HbA1c by 1.1% and 1.3%, respectively, over 24 weeks; body weight increased with rosiglitazone but did not significantly change with vildagliptin. In drug-naive patients, vildagliptin produced a smaller reduction in HbA1c than metformin over one year. Significant weight loss was observed with metformin but not with vildagliptin, but vildagliptin had better gastrointestinal tolerability. In another study of drug-naive patients with mild hyperglycaemia, vildagliptin (50mg/day) over two years attenuated the progressive loss of glycaemic control compared with placebo plus lifestyle counselling. Vildagliptin does not appear to affect gastric emptying.

Initial combination therapy with vildagliptin and pioglitazone over 24 weeks reduced HbA1c from baseline by 1.7–1.9% and was significantly more effective than either agent alone. In other trials, addition of vildagliptin to a sulphonylurea, metformin or pioglitazone significantly reduced HbA1c. In patients inadequately controlled on metformin alone, addition of vildagliptin reduced HbA1c to the same degree as add-on pioglitazone (0.9% and 1.0%, respectively), while pioglitazone resulted in a greater reduction in FPG. Pioglitazone was associated with significant weight gain. Clinical trials indicate that vildagliptin is weight-neutral. These studies also reported improvements in surrogate measures of β-cell function with vildagliptin.

Vildagliptin was generally well tolerated in these trials. Its most common adverse effects included headache, nasopharyngitis, dizziness, back pain, peripheral oedema and arthralgia. Vildagliptin had no consistent effects on body weight, blood pressure or lipid profiles in these studies.

**GLP-1 receptor agonists**

Two classes of GLP-1 receptor agonist have been developed: exendin-based therapies and human GLP-1 analogues. Exendin-based therapies are derived from biologically active peptides isolated from the salivary glands of a lizard; human GLP-1 analogues are based on modification of the native human peptide.

**Exenatide**

Exenatide, a synthetic exenin-based therapy, is presently the only marketed GLP-1 agonist and is licensed for patients with T2DM at 5–10µg twice daily in combination with metformin and/or sulphonylureas. It is identical to exendin-4, a peptide isolated from the salivary glands of the lizard Heloderma suspectum (the Gila monster). It is approximately 50% homologous with human GLP-1, is a potent GLP-1 receptor agonist, and is resistant to DPP-4. Exenatide has a half-life of 2.4 hours. Exenatide 10µg twice daily has been investigated in patients with glycaemia not adequately controlled by metformin, sulphonylureas, glitazones or metformin plus sulphonylureas. Exenatide reduced HbA1c by approximately 1%, reduced fasting and postprandial plasma glucose, and was associated with sustained reductions of approximately 1.5–3kg in body weight. Exenatide monotherapy is as effective as insulin glargine and biphasic insulin aspart for glycaemic control.

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**Table 1. Actions of GIP and GLP-1**

<table>
<thead>
<tr>
<th>Action</th>
<th>GIP</th>
<th>GLP-1</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stimulation of glucose-induced insulin secretion</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibition of gastric emptying</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Inhibition of glucagon secretion</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Inhibition of food intake and weight gain</td>
<td>Yes</td>
<td>Yes</td>
</tr>
<tr>
<td>Promotion of expansion of β-cell mass</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Secretion in patients with T2DM</td>
<td>Normal</td>
<td>Normal</td>
</tr>
<tr>
<td>Sensitivity of patients with T2DM to peptide</td>
<td>Reduced</td>
<td>Retained</td>
</tr>
</tbody>
</table>

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14. These trials indicate that sitagliptin is weight-neutral compared with placebo. Sitagliptin is generally well tolerated, with slightly higher rates of constipation, nasopharyngitis, urinary tract infections, hypertension and dizziness compared with placebo.
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control and, in contrast to the weight gain associated with insulin, it leads to weight loss. A once-weekly formulation of exenatide, currently in development, provides greater reductions in HbA1c (1.9% vs 1.5%) and FPG (2.3mmol/L vs 1.4mmol/L) than the twice-daily formulation, with similar reductions in body weight (approximately 4kg).

Exenatide has been reported to improve β-cell function and postprandial insulin responses and to reduce blood pressure. A comparative trial reported significantly better improvements in postprandial glycaemic control with exenatide than sitagliptin.

The most common adverse effects of twice-daily exenatide reported in the trials described above were nausea, hypoglycaemia (mostly when combined with a sulphonylurea) and vomiting, reported in approximately 35–60%, 5–35% and 10–15% of patients, respectively. These side effects are generally mild to moderate but can occasionally lead to treatment discontinuation. Approximately 40–50% of patients develop antibodies to exenatide. However, in controlled studies about 6% of patients developed high titres of antibodies; approximately half of these patients had no apparent glycaemic response to exenatide.

**Liraglutide**

Liraglutide, a human GLP-1 analogue, is in advanced clinical development but is not yet licensed. Liraglutide is 97% homologous with native human GLP-1, differing only by one amino acid substitution and the addition of a fatty acyl side chain. These modifications render liraglutide resistant to DPP-4 and promote binding of liraglutide to serum albumin. The half-life of liraglutide is approximately 11–15 hours, permitting once-daily subcutaneous injection. Liraglutide has been investigated in the phase III Liraglutide Effect and Action in Diabetes (LEAD) studies. LEAD-3 compared liraglutide monotherapy with glimepiride monotherapy. Liraglutide 1.2 and 1.8mg/day decreased HbA1c by 0.84% and 1.14%, respectively, versus 0.51% for glimepiride; both differences were statistically significant. Liraglutide also reduced postprandial glucose.

Patients receiving liraglutide, 1.2 and 1.8mg/day, lost approximately 2.0 and 2.5kg of weight, respectively; those on glimepiride experienced an increase of approximately 1kg. LIRAGLUTIDE-4 was a placebo-controlled trial of liraglutide on a background regimen of metformin plus rosiglitazone. In LEAD-1, LIRAGLUTIDE-2 and LEAD-3, liraglutide was compared with placebo and an active comparator agent, each added to background oral therapy. The following results were observed.

- Liraglutide 1.2 or 1.8mg/day significantly reduced HbA1c compared with placebo or rosiglitazone (each added to a sulphonylurea); the higher dose also significantly reduced FPG compared with both comparators.
- Liraglutide 1.8mg/day significantly reduced HbA1c and body weight compared with placebo or rosiglitazone (each added to a sulphonylurea); the higher dose also significantly reduced FPG compared with both comparators.
- Liraglutide 1.8mg/day significantly reduced HbA1c and body weight compared with placebo or insulin glargine (each added to metformin plus sulphonylurea).

**Table 2. Mean changes in HbA1c (%) with liraglutide and control regimens (C1 and C2) in the LEAD trials**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Liraglutide 1.2mg/day</th>
<th>Liraglutide 1.8mg/day</th>
<th>C1</th>
<th>C2</th>
</tr>
</thead>
<tbody>
<tr>
<td>LEAD-1&lt;sup&gt;39&lt;/sup&gt;</td>
<td>-1.08</td>
<td>-1.13</td>
<td>+0.23</td>
<td>-0.44</td>
</tr>
<tr>
<td>Liraglutide vs</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + sulphonylurea</td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Rosiglitazone + sulphonylurea (C2)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + metformin vs</td>
<td>-1.0</td>
<td>-1.0</td>
<td>+0.1</td>
<td>-1.0</td>
</tr>
<tr>
<td>Placebo + metformin + glitazone (C1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + metformin vs</td>
<td>-0.84</td>
<td>-1.14</td>
<td>-0.51</td>
<td>–</td>
</tr>
<tr>
<td>Placebo + metformin + glitazone (C1)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + sulphonylurea vs</td>
<td>-1.48</td>
<td>-1.48</td>
<td>-0.54</td>
<td>–</td>
</tr>
<tr>
<td>Placebo + metformin + metformin + glitazone (C2)</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + sulphonylurea vs</td>
<td>–</td>
<td>-1.33</td>
<td>-0.24</td>
<td>-1.09</td>
</tr>
<tr>
<td>Placebo + metformin + metformin + glitazone (C2)</td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Placebo + sulphonylurea + metformin vs</td>
<td>–</td>
<td>-1.12</td>
<td>-0.79</td>
<td>–</td>
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<tr>
<td>Placebo + sulphonylurea + metformin + metformin (C1)</td>
<td></td>
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</tbody>
</table>

LEAD, Liraglutide Effect and Action in Diabetes.
greater reduction in postprandial glucose was also seen.38

In these trials, liraglutide reduced HbA1c by approximately 1–1.5% (Table 2) and enabled more patients to reach HbA1c targets of <7% or ≤6.5%.38–41 Liraglutide was associated with weight reductions of approximately 1–2.5kg as opposed to weight gains of approximately 2kg with rosiglitazone,39 1.5kg with insulin glargine41 and 1kg with glimepiride.40 LEAD-6 compared liraglutide once daily with exenatide twice daily (both added to metformin and/or a sulphonylurea).42 Liraglutide was associated with significantly greater reductions in HbA1c (1.1% vs 0.8%) and FPG (1.61 vs 0.6mmol/L) and with more patients reaching HbA1c targets of <7% and ≤6.5%. Mean weight fell by approximately 3kg in both groups. Nausea was reported by 25.5% of patients receiving liraglutide and by 28% receiving exenatide. Liraglutide improved surrogate measures of β-cell function,43 reduced systolic blood pressure by approximately 2.7–4.5mmHg,44 and suppressed postprandial hunger and energy intake.45 The latter effect may be related to the delay of gastric emptying. Weight loss associated with liraglutide has been reported to improve quality of life.46

Antibodies against liraglutide develop in 9–12% of patients.37,41

**Table 3. Summary of efficacy and safety of incretin-based therapies**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Status</th>
<th>Approved dosing schedule</th>
<th>Improved glycaemic control?</th>
<th>Weight reduction?</th>
<th>Improved surrogates of pancreatic β-cell function?</th>
<th>Other benefits</th>
<th>Adverse effects reported in clinical trials</th>
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<tr>
<td><strong>DPP-4 inhibitors</strong></td>
<td></td>
<td></td>
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<tr>
<td>Sitagliptin</td>
<td>Approved (USA and EU)</td>
<td>100mg once daily</td>
<td>Yes</td>
<td>No</td>
<td>Yes8,10,12–14</td>
<td>Improved lipid profiles8,11,13,14</td>
<td>Mild hypoglycaemia</td>
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<td>Gastrointestinal disorders</td>
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<td>Somnolence</td>
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<td>Peripheral oedema</td>
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<tr>
<td>Vildagliptin</td>
<td>Approved (EU only)</td>
<td>50mg once or twice daily</td>
<td>Yes</td>
<td>No</td>
<td>Yes21–25</td>
<td>Enhanced pancreatic α-cell sensitivity15</td>
<td>Mild hypoglycaemia</td>
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<tr>
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<td>Nervous system disorders</td>
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<td><strong>GLP-1 agonists</strong></td>
<td></td>
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</tr>
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<td>Exenatide</td>
<td>Approved (USA and EU)</td>
<td>5 or 10µg twice daily</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes29,32</td>
<td>Reduced systolic and diastolic blood pressure32,33</td>
<td>Nausea</td>
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<td></td>
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<td></td>
<td></td>
<td></td>
<td></td>
<td>Improved lipid profiles8,33</td>
<td>Vomiting</td>
</tr>
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<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>Slowed gastric emptying43</td>
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<td></td>
<td></td>
<td>Improved postprandial insulin response37,38</td>
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<tr>
<td>Liraglutide</td>
<td>Phase III</td>
<td>0.6, 1.2 and 1.8mg once daily in clinical trials</td>
<td>Yes</td>
<td>Yes</td>
<td>Yes</td>
<td>Reduced systolic blood pressure37,44</td>
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<td></td>
<td></td>
<td></td>
<td>Reduced postprandial glucose40</td>
<td>Diarrhoea</td>
</tr>
<tr>
<td></td>
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<td></td>
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<td>Reduced postprandial hunger and energy intake</td>
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<td></td>
<td></td>
<td></td>
<td>Low immunogenicity37,38</td>
<td>Hypoglycaemia (rare except when given with sulphonylurea)</td>
</tr>
</tbody>
</table>

**Incretin-based therapies’ role in the management of T2DM**

The UK National Institute for Health and Clinical Excellence (NICE) guidelines for the management of T2DM state that exenatide can be considered for selected obese patients with inadequate glycaemic control after a trial of metformin and sulphonylureas.2 A NICE statement on newer agents for glucose control in T2DM, presently under review, may include addition of a DPP-4 inhibitor as a second-line therapy for selected patients with unsatisfactory glycaemic control, specifically where there is a high risk of hypoglycaemia and/or for patients in whom hypoglycaemia should be avoided at all
Key points

- To maintain glycaemic control in patients with type 2 diabetes mellitus (T2DM), intensive therapy may be required; but this may increase the risks of weight gain and hypoglycaemia.
- The incretin-based therapies – DPP-4 inhibitors and GLP-1 agonists – represent a new approach to the management of T2DM.
- Incretin-based therapies improve glycaemic control when added to conventional agents and are associated with a low incidence of hypoglycaemia. The GLP-1 agonists reduce body weight and DPP-4 inhibitors are weight-neutral.

Costs. The American Diabetes Association/European Association for the Study of Diabetes algorithm includes GLP-1 agonists in combination with metformin as second-line therapy. For all patients, clinical judgement and individualisation of therapy are required.

Incretin-based therapies represent a new approach for the management of T2DM. Clinical trials clearly demonstrate that they improve glycaemic control, either alone or in combination with conventional agents (see Table 3). GLP-1 agonists may confer somewhat greater reductions in HbA1c than DPP-4 inhibitors and appear to have more consistent evidence for weight loss and reduction of food intake. Oral administration of DPP-4 inhibitors may be more acceptable to some patients than injection of GLP-1 agonists. Both classes are well tolerated. The low risk of hypoglycaemia with these agents is an important advantage over many conventional treatments. On current evidence, incretin-based therapies are a reasonable choice when metformin alone does not achieve glycaemic control or is poorly tolerated or contraindicated. Avoidance of hypoglycaemia is particularly important in certain groups, including people who hold heavy goods vehicle or public service vehicle licences, the elderly living alone, and patients with a history of significant hypoglycaemia on sulphonylureas. It is particularly important to avoid further weight gain in patients who in addition to T2DM have other health problems associated with obesity (e.g. sleep apnoea, polycystic ovarian syndrome). Early introduction of GLP-1 agonists may preserve β-cell function and maintain insulin secretion, and may improve long-term outcomes. Physicians and patients need to be educated about these important potential benefits. Further clinical trials will confirm the clinical role of these agents.

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Conflict of interest statement

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