Incretin-based Therapies for Type 2 Diabetes—Comparisons Between Glucagon-like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors

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Abstract
Type 2 diabetes exerts a huge toll on both morbidity and mortality, despite an expanding range of antiglycemic drugs and epidemiological evidence highlighting the benefits of effective glycemic control. Incretin-based agents offer important benefits, including a meal-dependent mode of action that may protect against hypoglycemia, and weight loss—in contrast to other antihyperglycemic drugs that cause weight gain. There are now two glucagon-like peptide-1 (GLP-1) receptor agonists and three dipeptidyl peptidase-4 (DPP-4) inhibitors approved for the management of type 2 diabetes in the US. Clinical trials have established the efficacy of incretin-based agents in controlling fasting and post-prandial blood glucose levels as well as glycosylated hemoglobin (HbA1c), both as monotherapy (including as first-line pharmacological treatment) and in combination with other antihyperglycemic treatments. GLP-1 receptor agonists and DPP-4 inhibitors have different mechanisms of action, which may explain their inconsistent efficacy results in direct comparator trials; for example, lixisenatide has better efficacy than sitagliptin. However, GLP-1 receptor agonists can cause transient nausea in some patients. There is also evidence of different effects of individual agents within the same class; for example, lixisenatide has shown superior efficacy to exenatide when added to metformin and/or sulfonylurea. Lixisenatide is not cleared through renal mechanisms, unlike sitagliptin and saxagliptin. Isolated cases of pancreatitis led to concerns about a putative link with incretin-based therapies. However, the data currently available do not support a mechanistic or epidemiological link, although there does appear to be an increased risk of pancreatitis in people with diabetes that is independent of incretin-based treatment. Ongoing studies aim to extend our longer-term understanding of these agents, and hence, allow us to develop an optimal approach to patient management.

Keywords
Dipeptidyl peptidase-4, exenatide, fasting plasma glucose, glucagon-like peptide-1, incretin, linagliptin, lixisenatide, saxagliptin, sitagliptin, type 2 diabetes

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Incretin-based therapies now include two classes: glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors. However, there are important differences between individual agents, even within these classes. This article will discuss mechanisms of action (MOA), efficacy and safety data, and effects on body weight, highlighting differences and similarities between GLP-1 receptor agonists and DPP-4 inhibitors, and the clinically relevant advantages both classes of incretins may provide compared with more established drugs.

**Glucagon-like Peptide-1 Receptor Agonists and Dipeptidyl Peptidase-4 Inhibitors**

All incretin-based therapies approved to date are for glycemic control in addition to diet and exercise for adults with type 2 diabetes, either as monotherapy or in combination with metformin, sulfonylureas, or thiazolidinediones. Sitagliptin and saxagliptin, and exenatide are also approved for use in combination with insulin and insulin glargine, respectively. The US Food and Drug Administration (FDA) approved the first GLP-1 receptor agonist, exenatide, twice daily, in April 2005, and the first commercial DPP-4 inhibitor, sitagliptin, in October 2006. Two additional DPP-4 inhibitors, saxagliptin and linagliptin, received FDA approval in July 2009 and May 2011, respectively. The FDA approved liraglutide, a once-daily GLP-1 receptor agonist with 97% homology to native GLP-1, in January 2010.

**Mechanisms of Action**

The endogenous incretins, glucose-dependent insulin peptide (GIP) and GLP-1, are released from the gut in response to food intake. Both stimulate insulin secretion and promote beta-cell proliferation. GLP-1, but not GIP, also inhibits glucagon secretion, gastric emptying, food intake, and weight gain. Some, but not all, individuals with type 2 diabetes have reduced GLP-1 secretion and a normal response to GIP, so increasing GLP-1 activity offers multiple potential benefits. In contrast, GIP secretion is normal in type 2 diabetes, but the response to GIP is blunted.

GLP-1 receptor agonists act directly on GLP-1 receptors in pancreatic beta-cells, and deliver more sustained activity than endogenous GLP-1 because they resist breakdown by the enzyme DPP-4 and can be dosed to pharmacological levels. DPP-4 inhibitors slow DPP-4-catalyzed breakdown of both GLP-1 and GIP, and can double endogenous GLP-1 levels. This may explain the higher efficacy and weight loss seen with GLP-1 receptor agonists compared with DPP-4 inhibitors. The importance of increasing GIP levels in the mechanism of DPP-4 inhibitor activity is unclear, as target cells have an impaired response to GIP in type 2 diabetes.

Some evidence suggests that these differences between the physiological effects of GLP-1 receptor agonists and DPP-4 inhibitors would predict superior outcomes for the former. Both drug classes act by increasing GLP-1 levels, but GLP-1 receptor agonists allow direct supplementation to pharmacologically active levels, while DPP-4 inhibitors offer less potential to achieve GLP-1 levels far above physiological levels via their mode of action (i.e., reducing degradation of endogenous GLP-1). Sitagliptin can double or triple plasma GLP-1 concentrations following an oral glucose tolerance test. GLP-1 levels were similar after a 25 mg or 200 mg dose of sitagliptin, suggesting that any dose–response relationship had leveled out below 30 nM. Plasma concentrations of liraglutide can increase in a dose-dependent manner to around 13,000 pmol/l, with no evidence of a plateau.

DPP-4 inhibitors have an additional effect on GIP, which also stimulates insulin secretion and suppresses glucose. The importance of increasing GIP levels in the mechanism of DPP-4 inhibitor activity is unclear; however, target cells have an impaired response to GIP in type 2 diabetes, and patients show smaller increases in insulin and less suppression of glucose than non-diabetic individuals. Studies have linked GIP with increased glucagon levels, in contrast with GLP-1, which suppresses glucagon.

A recent publication revealed that combining GIP with GLP-1 impairs the latter’s glucagon-lowering efficacy in patients with type 2 diabetes.

**Efficacy in Non-comparative Trials**

**Dipeptidyl Peptidase-4 Inhibitors**

Randomized controlled trials (RCTs) have shown significant but modest improvements in both HbA1c and fasting plasma glucose (FPG) with the three approved DPP-4 inhibitors—sitagliptin, saxagliptin, and linagliptin—from baseline versus placebo (see Table 1). These drugs appear to have little impact on body weight, and are generally well tolerated (see later sections).

**Sitagliptin**

An 18-week, placebo-controlled study of sitagliptin monotherapy reported significantly reduced post-prandial peaks from baseline versus placebo following a meal tolerance test (subset n=150; total randomized population n=521; mean diabetes duration 4.5 years). Placebo-subtracted changes in three-hour area under the curve (AUC) over 18 weeks were -6.7 and -7.6 mmol/hour l1 for sitagliptin 100 mg and 200 mg once daily, respectively (both p<0.001). Sitagliptin demonstrated non-inferiority to metformin as monotherapy in 1,050 treatment-naive patients over 24 weeks. Long-term double-blind follow-up studies revealed similar glycemic control for sitagliptin monotherapy and metformin monotherapy for up to two years.

Sitagliptin demonstrated additive efficacy when combined with metformin in a study of 1,091 patients with type 2 diabetes (mean diabetes duration 4.5 years), of whom 50% had received no oral hypoglycemic agent for at least eight weeks before randomization. This study compared sitagliptin monotherapy, metformin monotherapy, combined sitagliptin/metformin, and placebo over 24 weeks. Combining sitagliptin with metformin seemed more effective than increasing the metformin dose to improve efficacy—including improving HbA1c and both fasting and post-meal glucose levels.

Double-blind extensions of 30 and 54 weeks confirmed the efficacy of this combination for up to two years.

A 24-week trial in 701 metformin-treated patients with a mean diabetes duration of 6.2 years also reported significant improvements in post-meal glucose with 100 mg sitagliptin compared with placebo (two-hour AUC, p<0.001). Sitagliptin showed non-inferiority to glipizide as an adjunct to ongoing metformin treatment in a 52-week study that included 1,172 patients (average known type 2 diabetes disease duration 5.8 years). At two years’ extended follow-up, least squares mean changes in HbA1c were -0.54 % and -0.51 % with sitagliptin and glipizide, respectively, per
Table 1: Clinical Trial Efficacy Data for Marketed Dipeptidyl Peptidase-4 Inhibitors in the Treatment of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Indication, Administration</th>
<th>Effect of Treatment from Baseline versus Placebo on:</th>
<th>Body Weight</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HbA1c</td>
<td>FPG</td>
<td></td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Sitagliptin versus placebo plus pioglitazone for 24 weeks</td>
<td>-0.7 % versus -0.54 % (p=0.001)</td>
<td>-17.7 mg/dl versus -11.0 mg/dl (p=0.001)</td>
<td>+1.8 kg versus +1.5 kg</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 or 200 mg monotherapy versus placebo for 18 weeks</td>
<td>-0.48 % and -0.36 % versus 0.12 % (both p&lt;0.001)</td>
<td>-12.6 mg/dl (p&lt;0.001) and -10.8 mg/dl (p&lt;0.01) versus 7.2 mg/dl</td>
<td>-0.6 kg and -0.2 kg versus -0.7 kg</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>100 mg or placebo plus metformin for 24 weeks</td>
<td>-0.67 % versus -0.02 % (p&lt;0.001)</td>
<td>-16.2 mg/dl versus 9.0 mg/dl (p&lt;0.001)</td>
<td>Small decreases were observed (0.6–0.7 kg)</td>
</tr>
<tr>
<td>Sitagliptin</td>
<td>Sitagliptin 100 mg qd Metformin 500 mg bid Metformin 1,000 mg bid Sitagliptin 50 mg + metformin 500 mg bid Sitagliptin 50 mg + metformin 1,000 mg bid versus placebo</td>
<td>-0.66 %, -0.82 %, -1.13 %, -1.40 %, and -1.90 % versus +0.17 % (all p&lt;0.001)</td>
<td>-17.5 mg/dl, -27.3 mg/dl, -29.3 mg/dl, -47.1 mg/dl, and -63.9 mg/dl versus +5.8 mg/dl (all p&lt;0.001)</td>
<td>Significant weight loss in all groups (p=0.05) except sitagliptin group, which showed no change</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 mg, 5 mg, or 10 mg plus metformin versus metformin alone for 24 weeks</td>
<td>-0.59 %, -0.69 %, and -0.58 % versus +0.13 % (all p&lt;0.0001)</td>
<td>-14.31 mg/dl, -22.03 mg/dl, and -20.50 mg/dl versus +1.24 mg/dl (all p&lt;0.0001)</td>
<td>Mean changes from baseline at Week 24: -1.43 kg, -0.87 kg, and -0.53 kg versus -0.92 kg for metformin alone</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>5 mg or 10 mg plus metformin or saxagliptin 10 mg alone versus metformin alone for 24 weeks</td>
<td>-2.5 % and -2.5 % versus -1.7 % and -2.0 % (all p&lt;0.0001 versus monotherapy)</td>
<td>-60 mg/dl and -62 mg/dl versus -31 mg/dl and -47 mg/dl (all p&lt;0.001)</td>
<td>Mean changes from baseline at Week 24: -1.8 kg, -1.4 kg, and -1.1 kg for the saxagliptin groups versus -1.6 kg for metformin alone</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 mg or 5 mg in combination with glyburide 7.5 mg versus glyburide 10 mg alone for 24 weeks</td>
<td>-0.54 % and -0.64 % versus +0.08 % (both p&lt;0.0001)</td>
<td>-7.0 mg/dl and -10.0 mg/dl versus +1.0 mg/dl (p=0.0218 and p=0.002)</td>
<td>+0.7 kg and +0.8 kg versus +0.3 kg with up-titrated glyburide (both p&lt;0.05)</td>
</tr>
<tr>
<td>Saxagliptin</td>
<td>2.5 mg or 5 mg plus thiazolidinedione versus placebo plus thiazolidinedione for 24 weeks</td>
<td>-0.66 % and -0.94 % versus -0.30 % (both p&lt;0.001)</td>
<td>-14.4 mg/dl (p=0.0053) and -18.0 mg/dl (p=0.0005) versus -3.6 mg/dl</td>
<td>+1.3 kg and +1.4 kg versus +0.9 kg</td>
</tr>
<tr>
<td>Linagliptin</td>
<td>2.5 mg, 5 mg, 10 mg, or placebo for 28 days</td>
<td>-0.31 %, -0.37 %, and -0.28 % placebo-corrected mean change (p&lt;0.025)</td>
<td>-19.2 mg/dl, -21.4 mg/dl, and 16.6 mg/dl versus 3.2 mg/dl (p&lt;0.025)</td>
<td>+0.9 kg to -1.6 kg for treatment groups versus -1.8 kg for placebo</td>
</tr>
</tbody>
</table>

Bid = twice daily; DPP-4 = dipeptidyl peptidase-4; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; qd = once daily.

Protocol population (n=504). A 30-week RCT in 1,035 patients with type 2 diabetes showed that sitagliptin was non-inferior to glimepiride, and an 18-week study in 273 patients found no difference between sitagliptin and glimepiride alone for 24 weeks (both p<0.05) except saxagliptin group, which showed no change.

Evidence also supports the efficacy of saxagliptin as an adjunct to insulin in patients with long-standing type 2 diabetes (mean disease duration 12–13 years). Adding saxagliptin to ongoing insulin treatment in 641 patients with type 2 diabetes significantly reduced HbA1c compared with placebo (-0.6 % versus 0.0 %, p<0.001) over 24 weeks. FPG and two-hour PPG also fell significantly in saxagliptin-treated patients, with placebo-adjusted mean changes of -14.4 mg/dl and -36.0 mg/dl, respectively (p<0.001).
A 24-week RCT of saxagliptin monotherapy in 401 antihyperglycemic drug-naive patients revealed significant reductions in HbA1c (placebo-adjusted change: -0.62 % and -0.65 % with saxagliptin 2.5 mg and 5.0 mg, respectively [both p<0.0001 versus placebo]), FPG (placebo-adjusted change: -1.49 mg/dl with saxagliptin 2.5 mg and 5.0 mg, respectively [p<0.05 versus placebo]), and two-hour PPG (-38.88 mg/dl, respectively, with saxagliptin 2.5 mg [significance not tested] and 5.0 mg [p<0.05 versus placebo]).

In a study of 743 patients whose type 2 diabetes was inadequately controlled by ongoing metformin treatment (mean diabetes duration 6.5 years), adding saxagliptin to metformin significantly improved HbA1c values, the percentage of patients with HbA1c values ≤7.0 %, and both fasting and post-prandial glucose levels (all p<0.0001 from baseline versus placebo). A second RCT revealed the efficacy and safety profile of saxagliptin with metformin as a first-line antihyperglycemic regimen for patients with relatively recent diagnoses of type 2 diabetes and inadequate glycemic control (n=1,306, mean disease duration 1.4–2 years). Both fasting and post-prandial glucose parameters fell even more significantly after 24 weeks of combination therapy versus either drug as a single agent (all p<0.0002). According to a 52-week study in 858 patients, saxagliptin is non-inferior to glipizide as an adjunct to inadequate metformin treatment, with a between-group difference in HbA1c reduction of 0.06 %.

A 76-week study in 1,306 treatment-naive patients with type 2 diabetes has also shown the sustained long-term additive efficacy of saxagliptin with metformin as initial combination therapy for up to 76 weeks. HbA1c fell by 2.31 % and 2.33 % with metformin plus saxagliptin 5 mg or 10 mg, respectively, compared with 1.79 % with metformin alone and 1.55 % with saxagliptin 10 mg monotherapy (p<0.0001 for combinations versus monotherapies).

In 768 randomized patients, adding saxagliptin to a submaximal dose of glyburide was linked with significantly improved HbA1c, and both fasting and post-challenge plasma glucose after 24 weeks, compared with increasing the glyburide dose (p<0.00218). Mean disease duration was 6.8–7.1 years; patients entered the study with inadequate glycemic control on submaximal doses of sulfonylurea.

According to a 24-week RCT in 565 patients with type 2 diabetes, saxagliptin can also significantly reduce HbA1c and fasting and post-prandial glucose levels when added to a thiazolidinedione. Patients had insufficient glycemic control (HbA1c >7.0 % to ≤10.0 %) with ongoing pioglitazone or rosiglitazone treatment (mean disease duration 5.1–5.3 years). A 52-week extension to this study reported significant HbA1c reductions from baseline versus placebo with both 2.5 mg and 5.0 mg saxagliptin. Placebo-subtracted changes in HbA1c were -0.39 % and -0.89 % with 2.5 mg and 5.0 mg saxagliptin, respectively (p<0.0019 and p<0.0001) in the 360 patients who completed the full 76-week follow-up.

Linagliptin

A phase III RCT including 503 patients with type 2 diabetes, who were either treatment-naive or had received one oral antihyperglycemic drug, showed the significant benefits of linagliptin monotherapy over 24 weeks. Linagliptin-treated patients experienced placebo-corrected reductions in HbA1c (0.69 %), FPG (23.4 mg/dl), and PPG (57.6 mg/dl) [all p<0.0001]. Treatment differences in HbA1c, FPG, and PPG were similar with linagliptin as an add-on to metformin in a 24-week study of 701 patients with type 2 diabetes. Placebo-corrected changes were -0.64 %, -21.6 mg/dl, and -66.6 mg/dl for HbA1c, FPG, and PPG, respectively (all p<0.0001). Another study, including 333 patients with inadequate glycemic control with metformin alone, showed similar results after 12 weeks of linagliptin 5 mg or glimepiride treatment (0.75 % and 0.9 % placebo-corrected HbA1c reductions, respectively [p<0.001]). Mean type 2 diabetes disease duration was 6.2–8.2 years. Neither study reported significant body weight changes in the linagliptin treatment groups.

In another study, patients randomized to an initial combination regimen of linagliptin plus pioglitazone had treatment differences of -0.51 % and -14.22 mg/dl in HbA1c and FPG, respectively (both p<0.0001). A 24-week RCT in 1,058 patients whose type 2 diabetes was inadequately controlled with metformin plus sulfonylurea treatment also linked add-on linagliptin with significant improvements in glycemic control. Placebo-adjusted changes in HbA1c and FPG were -0.62 % and -12.6 mg/dl, respectively (both p<0.0001).

**Glucagon-like Peptide-1 Receptor Agonists**

Data from non-comparative trials regarding the efficacy of GLP-1 receptor agonists is summarized in Table 2.

**Exenatide Twice Daily**

A 24-week RCT revealed significant (and dose-dependent) improvements in HbA1c and daily mean post-prandial glucose peaks in treatment-naive patients with two years’ type 2 diabetes disease duration receiving first-line antihyperglycemic exenatide treatment twice daily after failed glycemic control using diet and exercise (HbA1c -0.7 % and -0.9 % versus -0.2 % [all p<0.003]; FPG: -17.46 mg/dl and -18.72 mg/dl versus -5.22 mg/dl [p=0.029 for 5 μg and 10 μg exenatide twice daily versus placebo, respectively]).

Investigators demonstrated the efficacy of exenatide twice daily as an add-on to existing oral agents in three simultaneous 30-week Phase III studies in the US (total randomized population: 1,447). Patients with poor glycemic control with metformin experienced significant improvements in HbA1c and both fasting and post-prandial glucose levels after 30 weeks of treatment with 5 μg or 10 μg exenatide twice daily. HbA1c values fell by 0.4 % and 0.78 % with 5 μg and 10 μg exenatide twice daily, respectively, compared with a 0.08 % increase in the placebo group (p<0.001 overall). Similar HbA1c reductions were seen in sulfonylurea-treated patients receiving 5 μg and 10 μg exenatide twice daily: 0.46 % and 0.86 %, respectively, versus a 0.12 % increase with a sulfonylurea alone (p<0.0002 pairwise comparisons). The third study also demonstrated consistent HbA1c lowering when exenatide twice daily was added to metformin plus sulfonylurea combination therapy: 0.55 % and 0.77 % decreases were seen with 5 μg and 10 μg exenatide twice daily, respectively, compared with a 0.23 % increase with placebo (p<0.001). Post-prandial glucose AUC fell significantly more with exenatide twice daily than with placebo (p<0.01). Mean diabetes duration ranged from 4.9 to 9.4 years for all three 30-week studies.

In another study, exenatide twice daily was shown to improve both HbA1c and fasting plasma glucose as well as post-prandial glucose values over the
### Table 2: Clinical Trial Efficacy Data for Marketed Glucagon-like Peptide-1 Receptor Agonists in the Treatment of Type 2 Diabetes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Dosage, Comparators, Follow-Up</th>
<th>Change from Baseline in Study Drug and Comparator Groups in:</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>HbA1c FPG Body Weight</td>
<td></td>
</tr>
</tbody>
</table>
| Exenatide bid           | 5 µg or 10 µg monotherapy versus placebo for 24 weeks | -0.7 % and -0.9 % versus -0.2 % (both p<0.001, versus placebo) | -2.8 kg and -3.1 kg versus -1.4 kg (both p<0.005) | Moreno et al., 2008
db           |
|                         |                                 | For fasting serum glucose: -17.46 mg/dl and -18.72 mg/dl versus -5.22 mg/dl (both p<0.05) |           |
| Exenatide bid           | 5 µg or 5 µg for four weeks followed by 10 µg versus placebo plus SU for 30 weeks | -0.46 % and -0.86 % versus +0.12 % (p<0.002) | -5.4 mg/dl and -10.8 mg/dl versus +7.2 mg/dl (p<0.05 for 10 µg exenatide versus placebo) | Buse et al., 2004
db           |
|                         |                                 | -0.9 kg and -1.6 kg versus -0.6 kg for placebo (p<0.05 for 10 µg exenatide versus placebo) |           |
| Exenatide bid           | 5 µg or 5 µg for four weeks followed by 10 µg versus placebo plus metformin for 26 weeks; total 30 weeks | -0.4 % and -0.78 % versus +0.08 % (p<0.002) | -7.2 mg/dl and -10.8 mg/dl versus +14.4 mg/dl (p<0.005 for both) | DeFronzo et al., 2009
db           |
|                         |                                 | -1.6 kg and -2.8 kg versus -0.3 kg (p<0.05 and p<0.001 versus placebo, respectively) |           |
| Exenatide bid           | 5 µg or 5 µg for four weeks followed by 10 µg versus placebo plus metformin for 26 weeks; total 30 weeks | -0.55 % and -0.77 % versus +0.23 % (p<0.001) | -10.8 mg/dl and -9.0 mg/dl versus +14.4 mg/dl (p<0.0001) | Kendall et al., 2005
db           |
|                         |                                 | -1.6 kg and -1.6 kg versus -0.9 kg (p<0.01 and placebo, respectively) |           |
| Exenatide bid           | 10 µg versus placebo, in combination with TZD with or without metformin for 16 weeks | -0.89 % versus +0.09 % with placebo (p<0.001) | -28.62 mg/dl versus +1.80 mg/dl with placebo (p<0.001) | Zinman et al., 2007
db           |
|                         |                                 | -2.15 kg versus +0.14 kg with placebo (p<0.001) |           |
| Liraglutide             | 1.2 mg or 1.8 mg monotherapy versus glimepiride 8 mg, 52 weeks double-blind with 52-week extension | -0.84 % and -1.14 % versus -0.51 % on glimepiride (p<0.0014 and p<0.0001, respectively) at 52 weeks. Significantly greater reductions from baseline at two years for both doses versus glimepiride, using ITT or completer analyses. Larger HbA1C reductions occurred in previously drug-naive subgroup (-1.4 % in two-year completers) compared with entire trial population | Significant weight reductions at 52 weeks and 104 weeks: -2.1 kg and -2.7 kg versus +1.1 kg (p<0.0001 for both doses versus glimepiride after 104 weeks) | LEAD-3, Garber et al., 2009, 2011
db           |
|                         |                                 | -15.12 mg/dl and -29.16 mg/dl versus -5.22 mg/dl at 52 weeks (p<0.027 and p<0.0001 versus glimepiride, respectively) |           |
| Liraglutide             | 0.6 mg, 1.2 mg, or 1.8 mg once daily versus glimepiride 4 mg or placebo, all in combination with metformin for 26 weeks | -0.7 %, -1.0 %, and -1.0 % versus -1.0 % and +0.1 % (p<0.0001 for all active treatments versus placebo) | -1.8 kg, -2.6 kg, and -2.8 kg versus +1.0 kg and -1.5 kg (p<0.0001 for all liraglutide doses versus glimepiride; p=0.01 for 1.2 mg and 1.8 mg liraglutide versus placebo) | LEAD-2, Nauck et al., 2009
db           |
|                         |                                 | -19.8 mg/dl, -28.8 mg/dl, and -30.6 mg/dl versus -23.4 mg/dl and +7.2 mg/dl (all liraglutide doses p<0.0001 versus placebo) |           |
| Liraglutide             | 0.6 mg, 1.2 mg, or 1.8 mg versus rosiglitazone 4 mg/day or placebo, all in combination with glimepiride for 26 weeks | -0.6 %, -1.1 %, and -1.1 % versus -0.4 % and +0.2 % (p<0.0001 for 1.2 mg and 1.8 mg liraglutide versus both rosiglitazone and placebo; 0.6 mg liraglutide non-inferior to rosiglitazone) | +0.7 kg, +0.3 kg, and -0.2 kg versus +2.1 kg and -0.1 kg (all liraglutide doses p<0.0001 versus rosiglitazone) | LEAD-1, Marre et al., 2009
db           |
|                         |                                 | -12.96 mg/dl, -28.26 mg/dl, and -28.62 mg/dl versus -15.84 mg/dl and +18.18 mg/dl (all liraglutide doses p<0.0001 versus placebo; 1.2 mg and 1.8 mg liraglutide versus placebo) |           |
| Liraglutide             | 1.2 mg or 1.8 mg versus placebo, all in combination with metformin 1 g and rosiglitazone 4 mg for 26 weeks | -1.5 % and -1.5 % versus -0.5 % on placebo (p<0.0001) | -1.9 kg and -2.0 kg versus +0.6 kg on placebo (p<0.0001) | LEAD-4, Zinman et al., 2009
db           |
|                         |                                 | -39.6 mg/dl and -43.2 mg/dl versus -7.2 mg/dl (p<0.0001) |           |
| Liraglutide             | 1.8 mg versus insulin glargine or placebo, all in combination with metformin and glimepiride for 26 weeks | -1.33 % versus -1.09 % and -0.24 % on insulin glargine or placebo, (p<0.0015 and p<0.0001, respectively) | -27.90 mg/dl versus +9.54 mg/dl on insulin glargine or placebo, respectively (p<0.0001 versus placebo) | LEAD-5, Russell-Jones et al., 2009
db           |
|                         |                                 | -18 kg versus +1.6 kg and -0.42 kg on insulin glargine and placebo, respectively (p<0.0001 versus both) |           |

*Bid = twice daily; FPG = fasting plasma glucose; GLP-1 = glucagon-like peptide-1; HbA1C = glycated hemoglobin; ITT = intention-to-treat; LEAD = Liraglutide effect and action in diabetes; SU = sulfonylurea; TZD = thiazolidinedione.*
Liraglutide

The extensive Liraglutide effect and action in diabetes (LEAD) program of six clinical trials, with a total randomized population of 4,456 patients with type 2 diabetes, has established the efficacy, tolerability, and safety of liraglutide as part of various combination regimens with sulfonylureas, metformin, or thiazolidinedione or as a monotherapy (see Table 2 and Figure 1).52–54

Liraglutide monotherapy significantly reduced HbA1c compared with glimepiride in 746 patients with inadequate type 2 diabetes control and mean disease duration between 5.2 and 5.6 years (LEAD-3 trial, p<0.0014 for liraglutide 1.2 mg and 1.8 mg versus glimepiride 8 mg).54,55

The superiority of liraglutide monotherapy over glimepiride was sustained until the end of a 52-week open-label extension (two year follow-up).55 The monotherapy trial yielded comparable FPG and PPG reductions with liraglutide or glimepiride (both superior to placebo) at 52 weeks, but FPG was lower after two years of liraglutide therapy compared with glimepiride (p=0.0001 and p=0.0015 for 1.8 mg and 1.2 mg doses, respectively).55,56 Liraglutide 1.8 mg was also associated with significantly lower PPG than glimepiride after two years (p=0.0105).54

In the LEAD-2 trial, combining liraglutide with metformin yielded significant HbA1c reductions versus placebo over 24 weeks: -0.8 % (95 % confidence interval [CI] -1.0 to -0.6), -1.1 % (95 % CI -1.3 to -0.9), and -1.1 % (95 % CI -1.3 to -0.9) with 0.6 mg, 1.2 mg, and 1.8 mg doses, respectively. Liraglutide was non-inferior to glimepiride as an add-on therapy to metformin. Mean daily PPG values fell by 30.6 mg/dl, 41.4 mg/dl, and 45.0 mg/dl with liraglutide 0.6 mg, 1.2 mg, 1.8 mg, and glimepiride, respectively, compared with -10.8 mg/dl in the placebo group (p=0.001). This study included 1,091 patients with poorly controlled type 2 diabetes; mean disease duration was seven to eight years.56

The 26-week LEAD-1 study linked liraglutide (0.6 mg, 1.2 mg, or 1.8 mg per day) with significant HbA1c and FPG reductions versus placebo (p<0.0001). Liraglutide 1.2 mg and 1.8 mg also showed significantly greater efficacy than rosiglitazone (p<0.0001 and p=0.006 for HbA1c and FPG, respectively, versus placebo). Mean daily PPG values fell by 45.0 mg/dl and 48.6 mg/dl with liraglutide 1.2 mg and 1.8 mg, respectively (p=0.043 and p=0.0022) and by 32.4 mg/dl with liraglutide 0.6 mg (p<0.0001), versus rosiglitazone.57

Liraglutide has also shown efficacy in patients with prolonged disease duration (mean duration nine or more years) whose glycemic control is poor despite combination therapy.58,59 The LEAD-4 trial compared liraglutide combined with metformin and rosiglitazone with placebo in 533 patients. HbA1c, FPG, and PPG values all fell significantly from baseline in liraglutide-treated patients over 26 weeks (p<0.0001, p<0.0001, and p<0.001, respectively, versus placebo).60 Mean PPG values decreased by 46.8 mg/dl and 48.6 mg/dl with liraglutide 1.2 mg and 1.8 mg, respectively, compared with -14.4 mg/dl in the placebo group.60

Adding liraglutide to combined metformin plus a sulfonylurea significantly improved HbA1c, FPG, and PPG versus placebo (p<0.0001) in the LEAD-5 study of 581 patients with poorly controlled type 2 diabetes. Both FPG and PPG fell even more significantly with liraglutide versus placebo (treatment differences -37.44 mg/dl and -33.12 mg/dl, respectively, both p<0.0001). This study also linked liraglutide with significantly better HbA1c control than the active comparator, insulin glargine (p=0.0015).61 These results should be interpreted with caution because an intensive treat-to-target approach might have produced more effective insulin glargine dosing. The patient-driven titration in this study was, however, consistent with real-life clinical experience (mean daily insulin glargine dose 24 International Units [IU] at end of study).62

**Incretin-based Therapies for Type 2 Diabetes**

**Head-to-head Trials of Incretin-based Therapies**

Data from some head-to-head trials of incretin-based therapies in type 2 diabetes are summarized in Table 3. A few trials have directly compared individual incretin-based agents.53,55,64 A preliminary two-week comparison in 95 patients showed that exenatide twice daily produced greater reductions in post-prandial glucose and triglycerides than sitagliptin (p<0.0001, p=0.0118, respectively).64 An eight-week cross-over RCT also reported significantly greater reductions in mean 24-hour and post-prandial glucose values with exenatide twice daily than with sitagliptin.65
**Diabetes Management**

Table 3: Head-to-head Clinical Trial Data for Incretin-based Therapies

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Effect of Treatment on:</th>
<th>Adverse Effects and Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>HbA1c</strong></td>
<td>FPG</td>
<td></td>
</tr>
<tr>
<td>Liraglutide 1.8 mg qd versus exenatide 10 μg bid for 26 weeks</td>
<td>Liraglutide lowered mean HbA1c (-1.12 % [SE 0.08] versus -0.79 % [SE 0.08], p&lt;0.0001)</td>
<td>Both well tolerated, but less persistent nausea with liraglutide (estimated treatment rate ratio 0.448, p&lt;0.0001) and only minor hypoglycemia (1.93 versus 2.60 events for liraglutide and exenatide, respectively, per patient per year, p=0.0131)</td>
</tr>
<tr>
<td>Test switching from exenatide 10 μg bid to liraglutide 1.8 mg qd or remaining on liraglutide qd for 26 weeks</td>
<td>Switch to liraglutide further reduced HbA1c (-0.32 %, p=0.0001)</td>
<td>Switch to liraglutide well tolerated, with minor hypoglycemia (1.30 episodes per patient per year) or nausea (3.2 %) versus 1.5 % in those continuing liraglutide</td>
</tr>
<tr>
<td>Exenatide 5 μg bid then 10 μg bid versus sitagliptin 100 mg qam for two weeks</td>
<td>Reduction similar with both treatments (-15 mg/dl versus -19 mg/dl)</td>
<td>Exenatide reduced body weight more than sitagliptin (-0.8 kg, p&lt;0.0001) Mild to moderate gastrointestinal adverse events with both treatments</td>
</tr>
<tr>
<td>Liraglutide 1.2 mg or 1.8 mg qd versus sitagliptin 100 mg qd for 26 weeks</td>
<td>Liraglutide lowered HbA1c more than sitagliptin (-1.24 % and -1.50 %, respectively, versus -0.90 %, both p&lt;0.0001)</td>
<td>Weight loss greater with both doses of liraglutide than with sitagliptin (-2.86 kg and -3.38 kg, respectively, versus -0.96 kg, p&lt;0.0001) Nausea more common with liraglutide, similar frequency of minor hypoglycemia for all groups</td>
</tr>
<tr>
<td>Participants continued the above treatment of liraglutide 1.2 mg or 1.8 mg qd versus sitagliptin 100 mg qd in a 26-week extension</td>
<td>Liraglutide lowered HbA1c more than sitagliptin (-1.29 % and -1.51 % versus -0.88 %, both p&lt;0.0001)</td>
<td>Weight loss greater with liraglutide than with sitagliptin (-2.78 kg and -3.68 kg versus -1.16 kg, p&lt;0.0001) Minor hypoglycemia (8.1 %, 8.3 %, and 6.4 % with liraglutide 1.2 mg, liraglutide 1.8 mg, and sitagliptin, respectively). Gastrointestinal side effects (including nausea) more frequently seen with liraglutide, declined after several weeks</td>
</tr>
<tr>
<td>Exenatide 2 mg qw versus liraglutide 1.8 mg qd</td>
<td>Liraglutide lowered HbA1c more than exenatide qw (-1.48 % [SE 0.05] versus -1.28 % [SE 0.05])</td>
<td>Weight loss greater with liraglutide than with exenatide qw (-3.58 kg versus -2.68 kg) Minor hypoglycemia (10.8 % and 8.9 % with exenatide qw and liraglutide, respectively). Gastrointestinal side effects and withdrawal due to adverse events lower with exenatide qw</td>
</tr>
</tbody>
</table>

AE = adverse event; Bid = twice daily; FPG = fasting plasma glucose; HbA1c = glycosylated hemoglobin; NA = not available; qam = every morning; qd = once daily; qw = once weekly; SE = standard error.

Other studies have compared liraglutide directly with exenatide twice daily, and liraglutide directly with sitagliptin. The LEAD-6 trial (n=464) reported superior results for liraglutide over exenatide twice daily in HbA1c reduction (-1.12 % versus -0.79 %, respectively, p=0.0001). The patients treated with liraglutide also reported significantly higher overall treatment satisfaction compared with the exenatide group (p=0004). Patients who switched from exenatide twice daily to liraglutide in the 14-week extension phase gained further improvements in HbA1c. Mean A1C further decreased from 7.2 % at Week 26 to 6.9 % at Week 40 (p=0.0001) after switching from exenatide to liraglutide, but remained similar with continued liraglutide (7.0 % to 6.9 %, p=0.1222). Figure 2 illustrates some of the therapeutic benefits of switching from exenatide twice daily to liraglutide in this study.

Liraglutide 1.8 mg or 1.2 mg was linked with decreases of 1.50 % and 1.24 % in HbA1c levels, respectively, from baseline in a 26-week trial of 665 metformin-treated patients, compared with a 0.90 % reduction with sitagliptin 100 mg (both liraglutide doses p<0.0001 versus sitagliptin). A 26-week extension study revealed sustained efficacy of liraglutide versus sitagliptin, with significantly greater HbA1c reductions from baseline at 52 weeks. Estimated mean treatment differences after one year were -0.40 % and -0.63 % with liraglutide 1.2 mg and 1.8 mg, respectively, versus sitagliptin (p=0.0001 for both comparisons). Adding 1.8 mg liraglutide to metformin increased overall treatment satisfaction scores, which were significantly higher in the liraglutide groups than in the sitagliptin group (4.35 versus 2.96 point increase with liraglutide versus sitagliptin, respectively, p=0.03), and this difference was maintained at 52 weeks (4.3 versus 3.0 point increase, respectively, p=0.03). In the trial to compare the efficacy and safety of exenatide once weekly versus liraglutide in patients with type 2 diabetes (DURATION-6), both treatment groups showed robust glycemic lowering with related weight loss. Reductions in HbA1c and weight loss were greater with daily liraglutide injections, while gastrointestinal (GI) side effects and withdrawals due to adverse events were significantly lower with exenatide once weekly.
Incretin-based Therapies for Type 2 Diabetes

Safety Profiles of Incretin-based Therapies

In clinical trials, adverse events (AEs) occurring with GLP-1 receptor agonists and DPP-4 inhibitors have been predominantly mild to moderate, with incidences generally similar to those seen with placebo.20–40,43–60,62–64 All three approved DPP-4 inhibitors are associated with increased rates of nasopharyngitis (up to 6.9 %) and headache (up to 6.5 %).6–8 Other AEs in clinical trials included upper respiratory tract infections (up to 6.3 % and 7.7 % with sitagliptin and saxagliptin, respectively).6,8 Typical AEs in GLP-1 receptor agonist-treated patients are GI AEs, such as nausea, vomiting, and diarrhea.5,9 Post-marketing surveillance has identified a few rare but serious AEs in patients receiving incretin-based therapy, including severe hypoglycemia when incretin-based therapy is used in combination with either sulfonylureas or insulin, and pancreatitis. Thyroid C-cell tumors (see ‘Thyroid C-cell Tumor’ section on page 91) with GLP-1 receptor agonists were identified in rodent studies, but human relevance has not been established. Some DPP-4 inhibitors have warnings about rare, severe hypersensitivity reactions.6–8

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin

Phase III clinical trial data linked sitagliptin monotherapy with fewer GI AEs than metformin (11.6 % versus 20.7 %, respectively).20 Diarrhea and nausea occurred significantly more often in patients taking metformin than in patients taking sitagliptin (3.6 % versus 10.9 % [p<0.001] and 1.1 % versus 3.1 % [p=0.032], respectively).20 Adding sitagliptin to metformin had little impact on AEs, which tended to increase with rising metformin dose, at up to two years’ follow-up.21–23

Saxagliptin

Saxagliptin 2.5 mg, 5.0 mg, and 10 mg doses all had similar AE frequencies than placebo in a phase III monotherapy trial.6 Similarly, AE rates were similar across study groups in trials of saxagliptin in combination regimens with metformin, glyburide, or thiazolidinedione.26,29,31,32 AE rates in extension studies remained similar for up to 76 weeks in patients receiving thiazolidinedione as monotherapy or 2.5 mg or 5.0 mg saxagliptin, and in patients receiving saxagliptin monotherapy, metformin monotherapy, or a combined regimen of saxagliptin and metformin.26,32

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**Linagliptin**
Linagliptin showed an overall incidence of AEs that was comparable to that observed with placebo in the monotherapy trials, with the most frequent AEs reflecting those observed with other DPP-4 inhibitors.

**Glucagon-like Peptide-1 Receptor Agonists**

**Exenatide**
Only one treatment-emergent AE—nausea—was significantly higher with exenatide twice daily monotherapy versus placebo (8% versus 0% in the exenatide and placebo groups, respectively [p=0.010]). The main AEs in exenatide twice-daily trials were GI AEs that were mild to moderate in intensity; the results also suggested that GI side effects were dose-dependent. In one trial of exenatide twice daily 10 μg in combination with a thiazolidinedione, there were 19 (15.7%) withdrawals for AEs (mainly nausea and/or vomiting) with exenatide versus two (1.8%) withdrawals for AEs with placebo. In that study, most AEs were mild to moderate. Starting exenatide twice daily therapy at the higher dose one week before titrating to the higher exenatide twice daily dose of 10 μg, instead of the recommended one month.

**Liraglutide**
As with exenatide, the most common AEs in liraglutide-treated patients were GI. Incidences in the six LEAD studies ranged from 10.5% to 44% for nausea, 4.4% to 17% for vomiting, and 4% to 18.7% for diarrhea. GI side effects were generally mild to moderate and often transient; for example, one study reported 216 vomiting events in the first four weeks with liraglutide, compared with only 65 events during the subsequent 22 weeks. Direct comparator studies have compared the tolerability and safety profiles of liraglutide against those of both sitagliptin and exenatide twice daily. Nausea was more common in liraglutide-treated patients versus sitagliptin, but it was also more transient and affected less than 4% of patients in all treatment groups by the end of the study. The LEAD-6 study reported no major hypoglycemic episodes with liraglutide, with minor hypoglycemic event rates of 1.932 versus 2.600 events per patient per year with liraglutide versus exenatide twice daily, respectively (rate ratio=0.55, p=0.013). Initial nausea incidences were similar with both agents but, by Week 26, only 3% of patients taking liraglutide were affected compared with 9% of patients taking exenatide twice daily.

**Hypoglycemia**
When incretin-based agents are used as monotherapy, the incidence and severity of hypoglycemia is low and generally similar to those observed with placebo, but the hypoglycemia risk may increase with combination regimens, particularly when sulfonylureas or insulin are included.

**Sitagliptin**
RCTs have reported hypoglycemia incidences of up to 3% for sitagliptin monotherapy with no apparent increased hypoglycemia risk for the drug in combination with metformin or pioglitazone. Sitagliptin has been linked with significantly less hypoglycemia than glipizide (50 episodes in 29 [4.9%] patients versus 657 episodes in 187 [32%] patients receiving sitagliptin and glipizide, respectively). Adding sitagliptin to insulin doubled hypoglycemia rates compared with placebo (16% versus 8%).

**Saxagliptin**
Confirmed hypoglycemic episodes were rare in both saxagliptin monotherapy studies, affecting up to 0.6% of subjects. Fewer saxagliptin-treated patients experienced hypoglycemia compared with glipizide as an adjunct to metformin treatment over 52 weeks (3.0% versus 36.3%; p<0.0001). Confirmed hypoglycemia events remained rare after 76 weeks of treatment with saxagliptin plus thiazolidinedione.

**Linagliptin**
There was no excess of hypoglycemic episodes with linagliptin monotherapy versus placebo and no patient required third-party intervention. Hypoglycemia affected three patients (0.6%) taking metformin plus linagliptin and five patients (2.8%) in the metformin plus placebo group. A trial comparing linagliptin versus placebo or glimepiride reported no hypoglycemic events for linagliptin or placebo, but three patients (5%) experienced hypoglycemia in the glimepiride group.

**Exenatide Twice Daily**
RCTs revealed no significant increase in the incidence of hypoglycemia in patients taking exenatide twice daily as monotherapy, or taking exenatide combined with metformin, thiazolidinediones, or metformin plus thiazolidinediones. Adding exenatide twice daily to a sulfonylurea may increase the incidence of hypoglycemia (reported incidences of 14% and 36% for a sulfonylurea combined with exenatide twice daily 5 μg or 10 μg, respectively, compared with 3% for a sulfonylurea alone). The incidence of hypoglycemia also increased when exenatide twice daily was added to a sulfonylurea plus metformin (19.2%, 27.8%, and 12.6% for exenatide twice daily 5 μg, 10 μg, and placebo, respectively).

**Liraglutide**
Major hypoglycemic episodes were extremely rare in liraglutide studies, and occurred in most cases with a concomitant sulfonylurea, while minor hypoglycemia affected between 3–26% of liraglutide-treated patients. Rates of minor hypoglycemia were significantly higher in patients taking 1.2 mg or 1.8 mg liraglutide than in patients taking rosiglitazone in one study, and significantly lower than with glimepiride or exenatide twice daily in three other studies.

**Pancreatitis**
A small number of patients treated with incretin-based therapies have developed acute pancreatitis during clinical trials, and post-marketing surveillance reports have led to FDA warnings about the risk of acute pancreatitis with exenatide twice daily, sitagliptin, saxagliptin, and liraglutide. Pancreatitis has also been reported during linagliptin clinical trials. However, a causal link between incretin-based therapies and pancreatitis has not been established. Large-scale analyses of healthcare databases and pooled clinical trial data suggest that the risk of pancreatitis in patients with type 2 diabetes receiving incretin-based therapy is comparable to that of patients with type 2 diabetes not receiving incretin-based agents. The incidence of pancreatitis was three times higher in individuals with type 2 diabetes than in people without diabetes.
to confirm any link between GLP-1 receptor agonists and pancreatitis, further investigation.

Compared with the high levels of GLP-1 receptors in C-cells of rodents, human C-cells have barely detectable levels of GLP-1 receptors. However, long-term clinical trial data are needed to clarify what effect incretin-based therapy may have on pancreatitis risk. However, incretin-based therapies should not be used in patients with risk factors for pancreatitis (e.g., gallstones, excessive alcohol use, high triglycerides) and should be discontinued if pancreatitis is suspected. Diagnosis of pancreatitis should be confirmed by established criteria, not by raised levels of pancreatic enzymes alone.

**Thyroid C-Cell Tumor**

GLP-1 receptor agonist treatment may cause the development of thyroid C-cell hyperplasia and neoplasia in rodents. However, long-term clinical trials of sufficient size and duration to allow conclusions to be drawn regarding cancer and incretin therapeutics have not yet been completed. Liraglutide has received a black box warning against its use by established criteria, not by raised levels of pancreatic enzymes alone.

**Impact on Body Weight**

Studies have linked GLP-1 receptor agonists with progressive and sustained weight loss, although DPP-4 inhibitors are typically weight neutral; other studies have reported weight gain or weight loss. However, a meta-analysis of 13 DPP-4 inhibitor trials identified a small weight increase compared with placebo, so the precise effect of these drugs on body weight remains unclear.

A meta-analysis of eight GLP-1 receptor agonist studies revealed a -2.37 kg weighted mean difference (WMD) versus comparators, with a WMD of -1.44 kg for exenatide twice daily versus placebo. In the LEAD trial program, placebo-subtracted body weight losses were 0.1 kg, 1.3 kg, 2.6 kg, and 1.38 kg with liraglutide, respectively. Comparator-subtracted weight losses were 2.3 kg versus rosiglitazone (p<0.0001), 3.3-3.8 kg versus glimepiride (p=0.0038), and 3.4 kg versus insulin glargine.

In the LEAD-3 trial, liraglutide monotherapy produced dose-dependent and sustained weight loss for two years. Estimated treatment differences versus glimepiride were -3.24 kg and -3.78 kg for 1.2 mg and 1.8 mg liraglutide, respectively (both p<0.0001). Exenatide twice daily was also linked with dose-dependent weight loss with no plateau up to the end of a 30-week RCT (placebo-subtracted weight loss at study end: 1.0 kg [p<0.05 versus placebo]). In a direct comparator trial, the difference in weight loss between exenatide twice daily and liraglutide (2.87 kg versus 3.24 kg, respectively) was non-significant after 26 weeks. Weight loss continued in a 14-week extension to this study—a further 0.4 kg in patients continuously receiving liraglutide and 0.9 kg in patients who switched from exenatide twice daily to liraglutide at 26 weeks.

Weight loss with GLP-1 receptor agonists could, in theory, be related to nausea, which is one of the most common side effects of this therapeutic class. Nausea was largely transient, however, and declined sharply after the first few weeks, while weight loss was sustained throughout follow-up in clinical studies. Patients with no nausea, or no GI side effects lasting more than one week, can also lose weight while taking a GLP-1 receptor agonist.

It seems likely that weight loss with GLP-1 receptor agonists is due to enhanced recognition of satiety, leading to reduced food intake.
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Post-meal increases in endogenous GLP-1 are linked with increased blood supply to the prefrontal cortex and hypothalamus in humans, an indication of neuronal activity in areas controlling satiety and food intake. Clinical data also support reduced calorie intake during GLP-1 receptor agonist therapy.

Potential Cardioprotection

GLP-1 receptor agonist therapy may exert a cardioprotective effect in type 2 diabetes. A database study of 39,275 patients treated with exenatide twice daily and 381,218 patients receiving other antihyperglycemic drugs linked GLP-1 therapy with reduced cardiovascular events (hazard ratio [HR]: 0.81, p=0.01), reduced hospital admissions for cardiovascular events (HR: 0.88, p=0.02), and reduced all-cause hospital admissions (HR: 0.94, p<0.001). Robust clinical trial data are required to confirm whether incretin-based therapies are cardioprotective in type 2 diabetes; several studies are under way (see Table 4).

Comparison of Incretin-based Therapies

DPP-4 inhibitors have rapidly gained position among the oral antidiabetic treatments. This is due to their ease of use, lack of any increase in weight, minor hypoglycemia risk, apparently benign AE profile, and good tolerability. The GLP-1 receptor agonists exenatide twice daily and liraglutide also offer a low hypoglycemia risk and a good tolerability/safety profile. Unlike the DPP-4 inhibitors, the two approved GLP-1 receptor agonists are injected but, although this might appear to be less convenient or attractive for patients, they offer the added benefit of long-term sustained weight loss. Indeed, an assumed patient preference for oral treatments may reflect prescriber perceptions rather than actual patient preferences. RCT data revealed significantly higher overall treatment satisfaction with liraglutide than with sitagliptin, despite the latter having an oral mode of administration.

Pharmacokinetic Considerations

Both sitagliptin and saxagliptin are primarily eliminated via the kidney; therefore, dose reductions are required in patients with moderate or severe renal impairment (saxagliptin has not been studied in patients receiving dialysis). This is highly relevant for the type 2 diabetes population, of whom about 40 % have chronic kidney disease (CKD) according to data from the Fourth National Health and Nutrition Examination Survey (NHANES IV); also, elderly patients may have normal serum creatinine levels but ‘concealed’ impaired glomerular filtration. In contrast, the kidney accounts for only 5 % of linagliptin excretion, so no dose adjustments are required in patients with renal impairment. Linagliptin clearance is via the liver, so drugs that induce cytochrome P450, isozyme CP3A4, or P-glycoprotein (P-gp) are likely to reduce linagliptin exposure to subtherapeutic levels. Linagliptin should not be used in patients who require CP3A4 or P-gp inducers such as rifampin.

No dose adjustments in patients with renal impairment are required for either exenatide twice daily or liraglutide, although both drugs should be used with caution in this population. Exenatide is not recommended in patients with severe renal impairment or end-stage renal disease (ESRD), and physicians should be cautious about giving exenatide twice daily doses of 5 μg or more to patients with moderate renal impairment. Current advice is to use liraglutide with caution in patients with renal impairment, following post-marketing reports of raised serum creatinine, acute renal failure, or worsening of chronic renal failure. A meta-analysis of the six LEAD phase III RCTs concluded that the efficacy and safety profile of liraglutide was unaffected by mild renal impairment.

Both GLP-1 receptor agonists and DPP-4 inhibitors are novel classes of drugs, and careful long-term monitoring and post-marketing surveillance for any unexpected AEs are required. Further data are required to confirm whether GLP-1 receptor agonists or DPP-4 inhibitors do increase pancreatitis risk. In the meantime, it seems prudent to assume that, if there is a causative link, it may be a class effect, and caution should be used when prescribing GLP-1 receptor agonists or DPP-4 inhibitors, particularly in patients with pre-existing pancreatitis.

Implications of Clinical Trial Data

Typical considerations for most patients with type 2 diabetes would be efficacy, hypoglycemia, impact on body weight, and common AEs. Incretin-based therapies have shown minimal risk of hypoglycemia when used as monotherapy. Combining DPP-4 inhibitors or GLP-1 receptor agonists with other antihyperglycemic agents such as sulfonylureas has been linked with increased hypoglycemia rates, but reducing sulfonylurea doses may mitigate this risk.

DPP-4 inhibitors appear to be weight neutral, while GLP-1 receptor agonists are linked with long-term weight loss, which is an attractive characteristic for both physicians and patients that could optimize treatment adherence. GI side effects such as nausea may prove limiting for some patients, but clinical trials have demonstrated that nausea declines rapidly during the first few weeks of liraglutide treatment. LEAD-6 study data suggest that nausea may subside earlier with liraglutide than with exenatide twice daily. Interestingly, 382 patients with type 2 diabetes who participated in an online survey ranked efficacy (measured by HbA1c) as the most important of four factors determining preference for a hypothetical GLP-1 receptor agonist, ahead of nausea, hypoglycemia, and dosing schedule; 96 % of patients preferred the product profile of liraglutide to the product profile of exenatide twice daily, based on clinical trial data.

Both liraglutide and exenatide twice daily have shown superior efficacy (including HbA1c reductions) compared with sitagliptin in direct comparator trials. Within the GLP-1 receptor agonist class, the phase III LEAD-6 trial revealed significantly greater HbA1c reduction and treatment satisfaction for liraglutide versus exenatide twice daily. Results of a meta-analysis of seven trials (n=4,625) were consistent with the head-to-head comparator studies: 40 % and 32 % of patients receiving liraglutide 1.8 mg or 1.2 mg, respectively, achieved a pre-specified composite endpoint of HbA1c <7.0 % without weight gain or hypoglycemia. The same composite endpoint occurred in 6–25 % of comparators, including 25 % with exenatide twice daily and 11 % with sitagliptin.

Discussion

Type 2 diabetes is a complex disease that involves multiple, interrelated metabolic processes. Patients are often overweight and have other cardiovascular risk factors such as dyslipidemia. Tight glycemic control is achievable using maximized doses of...
Incretin-based Therapies for Type 2 Diabetes

antihyperglycemic drugs, but weight gain is a common side effect of many of these treatments that, in turn, increases cardiovascular risk. Incretin-based therapies offer effective glycemic control, and could offer additional cardioprotective benefits. Clinical studies have consistently reported weight loss with the GLP-1 receptor agonists exenatide and lixisenatide. Reducing body weight offers potential metabolic improvements in addition to glycemic control.

Adherence to treatment is crucial for effective disease management in type 2 diabetes, and achieving good adherence to treatment can be a major challenge. It seems logical to assume that regular self-injection might be a barrier to adherence, and expect oral antihyperglycemic drugs to be more acceptable to patients than injectable agents. Evidence suggests, however, that patient satisfaction with treatment is more strongly linked to efficacy than to the mode of administration. Rapid and sustained weight reduction, as reported in liraglutide clinical trials, may also encourage adherence.

Ongoing trials continue to investigate the impact GLP-1 receptor agonists and DPP-4 inhibitors have on cardiovascular disease and other comorbidities associated with diabetes that may result from weight loss alone, or weight loss in combination with other cardioprotective effects.

The MOA of these agents is glucose-dependent, so their effect is attenuated with normoglycemia, potentially minimizing the risk of hypoglycemia. Clinical trials have confirmed that there is a relatively low risk of severe hypoglycemic episodes using incretin-based agents, although this risk does increase when an incretin-based agent is used in combination with a sulfonylurea.

Incretin-based therapies offer effective control of both FPG and PPG, and hence HbA1c, with acceptable tolerability. The risk of serious hypoglycemic episodes is low, except for combination therapies with a sulfonylurea, in which case the benefit of lowering the sulfonylurea dose is recommended. The two currently available GLP-1 receptor agonists are linked with weight loss; DPP-4 inhibitors are generally described as weight neutral, although this remains unclear. Trials are under way to clarify whether therapy with GLP-1 receptor agonists or DPP-4 inhibitors exhibit a direct cardioprotective effect. There are concerns about potential rare, serious AEs such as pancreatitis, although no causative link has yet been established. Patients with risk factors such as a history of pancreatitis should not receive these agents until further data become available. For most patients with type 2 diabetes, however, GLP-1 receptor agonists and DPP-4 inhibitors offer a useful addition to current therapeutic options.

Future Developments

GLP-1 receptor agonists and DPP-4 inhibitors are incretin-based agents characterized by glucose-dependent actions. This allows them to have differential potency of glycemic effects, depending on ambient glucose levels. The clinical differences between the two classes of agents highlight the potential for new therapies with different targets. The need for daily injections could make GLP-1 receptor agonists less appealing to some patients than oral formulations. However, this is balanced by a more potent glucose-lowering effect than DPP-4 inhibitors as well as beneficial weight loss effects. Developing oral formulations or once-weekly (or less frequent) injectable formulations could make these therapies more convenient.

Accumulating evidence in recent years supports the potential for incretin-based therapies to improve prognoses for patients whose diabetes is poorly controlled by other medications. Incretin-based agents may, in future, be used even earlier in the treatment of type 2 diabetes. They may also prove valuable in the management of type 1 diabetes.

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