Choosing GLP-1 Receptor Agonists or DPP-4 Inhibitors: Weighing the Clinical Trial Evidence

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The management of patients with type 2 diabetes has become more complex in recent years. Although the foundational use of metformin and lifestyle interventions has simplified clinicians' selection of initial therapy for most patients, the progressive nature of type 2 diabetes means that, eventually, pharmacological agents in addition to metformin will be required for successful glycemic management. It is at this juncture that treatment has become more complex because of the diverse treatment options now available, as reflected in the most recent American Diabetes Association/European Association for the Study of Diabetes[1] and American Association of Clinical Endocrinologists/American College of Endocrinology[2,3] guidelines.

Among the changes from previous guidelines, it is noteworthy that incretin-based therapies (i.e., glucagon-like peptide-1 [GLP-1] receptor agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors) have become fundamental treatment options, with GLP-1 receptor agonists having higher status in both sets of guidelines. GLP-1 receptor agonists and DPP-4 inhibitors, which each act in distinct ways on the incretin system to regulate glucose homeostasis, represent unique treatment approaches for type 2 diabetes.

Selecting Among GLP-1 Receptor Agonists and DPP-4 Inhibitors

There are numerous factors to consider when selecting among the treatment options for type 2 diabetes, including the five incretin-based therapies. These include mechanisms for regulating glucose homeostasis, magnitude of A1C reduction, effects on fasting plasma glucose (FPG) and postprandial glucose (PPG) levels, effects on pancreatic β-cell function, nonglycemic effects, safety and tolerability (especially with regard to hypoglycemia), effects on weight, ease of use, and cost. To gain insight into these considerations, the subsequent discussion will focus on seven published prospective clinical trials comparing incretin-based therapies.

IN BRIEF

Comparative trials show that there are important differences between and among the glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors with respect to glycemic lowering, weight effects, and effects on systolic blood pressure and the lipid profile. Nausea, diarrhea, headaches, and dizziness are common with both of the available GLP-1 receptor agonists. Upper respiratory tract infections, nasopharyngitis, and headaches are common with the DPP-4 inhibitors. Ongoing safety evaluations should provide a clear picture regarding long-term safety.

Review of Prospective, Head-to-Head Incretin Trials

Objectives and methods

A search of PubMed in May 2011 identified seven clinical trials that provide head-to-head comparison of two incretin-based therapies.[4–10] Each of these trials randomized patients who had inadequate glycemic control with metformin-based therapy. The trials are summarized in Table. 1.

Review of these trials allows for a better understanding of the similarities and differences among the GLP-1 receptor agonists (exenatide and liraglutide) and DPP-4 inhibitors (sitagliptin and saxagliptin). Outcomes of the trials are summarized in Table 2. The DPP-4 inhibitor linagliptin was not included in any of these clinical trials but is briefly discussed at the end of this article.

Glucose-lowering efffects

The results of the clinical trials demonstrated significantly greater reductions in A1C with liraglutide compared to exenatide, and both GLP-1 receptor agonists caused greater reductions than those observed with sitagliptin.[4–7,9] For example, after 26 weeks, Buse et al.[4] observed that significantly more patients achieved the target A1C level of < 7.0% in the liraglutide group (54%) than in the exenatide group (43%; $P = 0.0015$). The treatment difference was greatest for patients

Table 1. Goals and Methods of Head-to-Head Incretin Clinical Trials

	Exenatide Versus Liraglutide (LEAD-6)[4]	Exenatide Versus Liraglutide (LEAD-6 extension)[5]	Exenatide Versus Sitagliptin[6]	Liraglutide Versus Sitagliptin (1860-LIRA-DPP-4 and extension)[7,8]	Exenatide Versus Sitagliptin[9]	Sitagliptin Versus Saxagliptin[10]
Primary Endpoint	Change in A1C from baseline to week 26	Change in A1C from week 26 to week 40	Change in FPG and PPG over 2 weeks	Change in A1C from baseline to week 26, then to week 52	Unadjusted 6-hour PPG excursion at 4 weeks	Change in A1C from baseline to week 18
Design	26-week, randomized, open-label, active-comparator, parallel-group, multinational	14-week extension	5-week randomized, double-blind, crossover, multicenter	26-week, randomized, open-label, active-comparator, parallel-group, multinational; extension phase to 52 weeks	4-week, single-center, randomized, open-label, active comparator, 3-arm parallel group	18-week, multicenter, randomized, double-blind, non-inferiority
Patients (*n*)	464	389	61	665	48	801
Age (years)	18–80	—	18–70	18–80	35–70	≥ 18
Baseline A1C (%)	7.0–11.0	—	7.0–11.0	7.5–10.0	7.0–10.0	6.5–10.0
Baseline BMI (kg/m^2)	≤ 45	—	25–45	≤ 45	21.0–39.9	—
Baseline treatment	Stable, maximally tolerated doses of metformin, SU, or both for at least 3 months	Stable, maximally tolerated doses of metformin, SU, or both for at least 3 months	Stable treatment with metformin	Stable treatment with metformin ≥ 1,500 mg/day for at least 3 months	Stable treatment with metformin with or without SU or insulin glargine/detemir/NPH with or without stable dose of metformin for at least 3 months	Stable treatment with metformin 1,500–3,000 mg/day for at least 8 weeks

continued on p. 5

with a baseline A1C level ≥ 10%, but was unaffected by baseline BMI or previous glucose-lowering therapy. FPG was reduced significantly more with once-daily liraglutide (−29 mg/dl) compared with twice-daily exenatide (−11 mg/dl; $P < 0.0001$). However, the patient-measured PPG was reduced significantly more with exenatide than with liraglutide after breakfast (estimated treatment difference [ETD] 24 mg/dl; $P < 0.0001$) and after dinner (ETD 18 mg/dl; $P = 0.0005$), whereas the ETD after lunch was not statistically significant.

In the 14-week extension phase,[5] patients switched from exenatide to liraglutide experienced further significant reductions in A1C (−0.3%; $P < 0.0001$) and in FPG levels (−16 mg/dl; $P < 0.0001$) compared to levels at 26 weeks. The 26-week levels were stable in patients who remained on liraglutide.

Although 2 weeks of treatment with twice-daily exenatide and once-daily sitagliptin resulted in

Table 1. Goals and Methods of Head-to-Head Incretin Clinical Trials, *continued from p. 4*

	Exenatide Versus Liraglutide (LEAD-6)[4]	Exenatide Versus Liraglutide (LEAD-6 extension)[5]	Exenatide Versus Sitagliptin[6]	Liraglutide Versus Sitagliptin (1860-LIRA-DPP-4 and extension)[7,8]	Exenatide Versus Sitagliptin[9]	Sitagliptin Versus Saxagliptin[10]
Treatment	Baseline treatment (SU could be reduced up to 50%) plus: • Exenatide 5 µg BID × 4 weeks, then 10 µg BID × 22 weeks or • Liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 1 week, then 1.8 mg QD × 24 weeks	Baseline treatment (SU could be reduced up to 50%) plus: • Exenatide-treated patients switched to liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 1 week, then 1.8 mg QD × 12 weeks or • Liraglutide-treated patients continued	• Exenatide 5 µg BID × 1 week, then 10 µg BID × 1 week • Sitagliptin 100 mg QAM × 2 weeks	• Liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 25 weeks • Liraglutide 0.6 mg QD × 1 week, then 1.2 mg QD × 1 week, then 1.8 mg QD × 24 weeks • Sitagliptin 100 mg/day • Same treatment continued to week 52	• Baseline SU was discontinued • Insulin treatment switched to insulin glargine to achieve FPG ≤ 100 mg/dl • Exenatide 5 µg BID × 2 weeks, then 10 µg BID × 2 weeks or • Sitagliptin 100 mg QD • Metformin + insulin glargine	• Sitagliptin 100 mg QD or • Saxagliptin 5 mg QD

1860-LIRA-DPP-4, 1860-Liraglutide-Dipeptidyl Peptidase-4 trial; BID, twice daily; FPG, fasting plasma glucose; LEAD-6, Liraglutide Effect and Action in Diabetes-6 trial; QAM, every morning; QD, every day; SU, sulfonylurea

similar reductions in FPG (−15 vs. −19 mg/dl; $P = 0.3234$), DeFronzo et al.[6] observed that PPG reduction was significantly greater with exenatide (−112 mg/dl) compared to sitagliptin (−37 mg/dl; $P < 0.0001$). Furthermore, patients who crossed over from sitagliptin to 2 weeks of exenatide achieved a further PPG decrease of 76 mg/dl compared to an increase of 73 mg/dl for those who crossed over from exenatide to sitagliptin.

After 26 weeks of treatment, Pratley et al.[7] observed an A1C reduction of 1.2% with liraglutide, 1.2 mg daily; 1.5% with liraglutide, 1.8 mg daily; and 0.9% with sitagliptin, 100 mg daily ($P < 0.0001$ vs. each liraglutide dose). FPG decreased significantly more in the group taking 1.2 mg of liraglutide (−34 mg/dl) and in the group taking 1.8 mg of liraglutide (−39 mg/dl) compared to sitagliptin (−15 mg/dl; $P < 0.0001$).

After 52 weeks, A1C and FPG reductions from baseline were similar to those observed after 26 weeks in all three groups.[8]

A 4-week open-label trial[9] compared the addition of exenatide or sitagliptin to baseline treatment with a stable dose of metformin and insulin glargine to achieve an FPG ≤ 100 mg/dl. At the end of treatment, the unadjusted 6-hour PPG excursion in the add-on exenatide (606 mg/dl/hour) and sitagliptin (612 mg/dl/hour) groups was significantly smaller than in the group treated with metformin and glargine (728 mg/dl/hour; $P < 0.05$ vs. both exenatide and sitagliptin). A1C decreased significantly from baseline in all three groups ($P < 0.05$), with a significantly greater reduction in the exenatide group compared to the metformin-plus-glargine group ($P < 0.05$).

An 18-week non-inferiority trial[10] compared the addition of sitagliptin, 100 mg daily, and saxagliptin, 5 mg daily, to metformin, 1,500–3,000 mg daily. A1C decreased 0.6% in patients treated with sitagliptin and 0.5% in those treated with saxagliptin, indicating that saxagliptin was noninferior to sitagliptin as add-on therapy to metformin.

The results of these seven head-to-head clinical trials are consistent with the results of clinical trials that have compared a GLP-1 receptor agonist or a DPP-4 inhibitor to another glucose-lowering

Table 2. Outcomes of Prospective Trials[4–10]

	Exenatide Versus Liraglutide		Exenatide Versus Liraglutide		Exenatide Versus Sitagliptin		
	E 10 µg BID	L 1.8 mg QD	E 10 µg BID → L 1.8 mg QD	L 1.8 mg QD	E 5 µg BID × 1 week, then 10 µg BID × 1 week	S 100 mg QD	E 5 µg BID × 1 week, then 10 µg BID × 1 week → S 100 mg QD
A1C (%)							
Baseline	8.1	8.2	7.2	7.0	—	—	—
Change	−0.8	−1.1¶	−0.3	−0.1	—	—	—
FPG (mg/dl)							
Baseline	171	176	160	147	178	178	—
Change	−11	−19¶	−16[3]	−4	−15	−19	
PPG (mg/dl)							
Baseline	—	—	—	—	245	245	133
Change	—	—	—	—	−112¶	−37	72
Δ Weight (kg)	−2.9	−3.2	−0.9[3]	−0.4	−0.8†	−0.3	—
Δ Pancreatic β-cell function							
Fasting insulin (pmol/L)	−1.38	12.43*	NC	NC	—	—	—
Fasting C-peptide (nmol/L)	−0.02	0.05	NC	NC	—	—	—
Fasting proinsulin:insulin ratio	−0.02	0.00	NC	NC	—	—	—
HOMA-B (%)	2.74	32.12¶	14.5[2]	—	—	—	—
HOMA-IR (%)	—	—	NC	NC	—	—	—
Δ Blood pressure (mmHg)							
Systolic	−2.0	−2.5	−3.8[3]	−2.2	—	—	—
Diastolic	−2.0	−1.1	NC	NC	—	—	—
Δ Lipids (mg/dl)							
Total cholesterol	−4	−8	—	—	—	—	—
LDL cholesterol	−16	−17	—	—	—	—	—
HDL cholesterol	−2	−2	—	—	—	—	—
Triglycerides	−20	−36*	—	—	—	—	—

E, exenatide; Gl, glargine; HOMA-B, homeostasis model assessment of β-cell function; HOMA-IR, homeostasis model assessment of insulin resistance; L, liraglutide; NC, data not reported but authors indicated no significant change from baseline to study end; S, sitagliptin; Sa, saxagliptin; —, data not reported

*P values between two agents: *P ≤ 0.05; †P ≤ 0.01; ‡P ≤ 0.005; §P ≤ 0.001; ¶P ≤ 0.0001*

P value compared to baseline: [1]P < 0.05; [2]P = 0.001; [3]P < 0.0001

[a]At the end of 26 weeks

[b]At the end of 52 weeks

[c]Unadjusted 6-hour PPG excursion (AUC $BG_{0\text{-}6\ hours}$)

Liraglutide Versus Sitagliptin				Exenatide Versus Sitagliptin			Sitagliptin Versus Saxagliptin	
S 100 mg QD → E 5 µg BID × 1 week, then 10 µg BID × 1 week	L 1.2 mg QD	L 1.8 mg QD	S 100 mg QD	E 5 µg BID × 2 weeks, then 10 µg BID × 2 weeks	S 100 mg QD	Gl	S 100 mg QD	Sa 5 mg QD
— —	8.4 −1.2¶[a] −1.3¶[b]	8.4 −1.5¶[a] −1.5¶[b]	8.5 −0.9[a] −0.9[b]	8.4 −1.8[l]	7.9 −1.5[l]	7.9 −1.2[l]	7.7 −0.6	7.7 −0.5
—	182 −34¶[a] −31¶[b]	178 −39¶[a] −37¶[b]	180 −15[a] −11[b]	94 12[l]	96 12[l]	94 −5	160 −16	160 −11
209 −76	— —	— —	— —	606[c*]	612[c*]	728	—	—
—	−2.9¶[a] −2.8¶[b]	−3.4¶[a] −3.7¶[b]	−1.0[a] −1.2[b]	−0.9*[l]	0.1	0.4	−0.4	−0.4
—	5.12[a] −0.6[b]	1.29[a] 1.63[b]	−6.77[a] −2.27[b]	—	—	—	−3 µmol/L	−0.5 µmol/L
—	0.09‡[a] 0.05[b]	0.09§[a] 0.09[b]	−0.04[a] 0.01[b]	—	—	—	−0.01	−0.05
—	−0.08*[a] −0.07‡[b]	−0.10[a] −0.09§[b]	−0.03[a] −0.01[b]	—	—	—	—	—
—	27.23¶[a] 22.58§[b]	28.70¶[a] 25.76§[b]	4.18[a] 3.98[b]	—	—	—	13	11
—	−1.06[a] −1.27[b]	−1.50[a] −1.36*[b]	−0.94[a] −0.41[b]	—	—	—	—	—
—	−0.55[a] −0.37[b]	−0.72[a] −2.55[b]	−0.94[a] −1.03[b]	—	—	—	—	—
—	−0.71[a] −0.53[b]	0.07*[a] −0.87[b]	−1.78[a] −1.47[b]	—	—	—	—	—
— — — — —	−1[a] 0[b] 3[a] 4[b] 0[a] 0[b] −17[a] −9[b]	−7*[a] −4[b] 2[a] 4[b] 0[a] 0[b] −38[a] −30[b]	−1[a] −1[b] 5[a] 7[b] 0[a] 0[b] −36[a] −20[b]	−9† −12†[l] −2 —	−11† −11†[l] −2 —	12[l] 4 3 —	— — — —	— — — —

agent.[11–17] That is, as monotherapy or when added to single- or multiple-agent glucose-lowering regimens, GLP-1 receptor agonists are associated with an A1C reduction of 0.5–1.5%, which is greater than the A1C reduction of 0.5–1.0% from DPP-4 inhibitors. A significantly greater reduction is observed with liraglutide compared to exenatide.

Similarly, the GLP-1 receptor agonists are associated with greater reductions in FPG and PPG compared to DPP-4 inhibitors. The FPG reduction with liraglutide is significantly greater than that with exenatide; conversely, the PPG reduction with exenatide is significantly greater than that with liraglutide.

Weight effects

The results of the seven incretin-based clinical trials have generally demonstrated the same benefits observed in comparative trials with other glucose-lowering agents. More specifically, depending on background glucose-lowering therapy, a weight loss of 1–4 kg is generally observed in patients treated with a GLP-1 receptor agonist,[12,18–20] whereas DPP-4 inhibitors are weight neutral.[13,21–23]

In the 26-week trial by Buse et al.,[4] weight losses of 2.9 and 3.2 kg were observed with exenatide and liraglutide, respectively ($P = 0.2235$). In the 14-week extension phase,[5] those switched from exenatide to liraglutide experienced an additional weight loss of 0.9 kg ($P < 0.0001$) compared to 0.4 kg for those who remained on liraglutide ($P = 0.0089$).

In the comparison of liraglutide with sitagliptin by Pratley et al.,[7] a weight loss of 2.9 kg was observed in the group taking liraglutide, 1.2 mg; a loss of 3.4 kg in the group taking liraglutide, 1.8 mg; and a loss of 1.0 kg in the sitagliptin group ($P < 0.0001$ vs. both liraglutide dose groups). During the next 26 weeks, body weight stabilized in all three groups such that, after 52 weeks, the decrease in weight from baseline was 2.8, 3.7, and 1.2 kg, respectively (all $P < 0.0001$).[8]

In the crossover comparison of exenatide with sitagliptin,[6] patients treated with exenatide for 2 weeks before the crossover lost 0.8 kg, and those treated with sitagliptin lost 0.3 kg ($P = 0.0056$). The difference between the exenatide and sitagliptin groups may have been the result of a significant difference in the caloric intake as shown during an ad libitum meal (i.e., exenatide group −134 kcal vs. sitagliptin group +130 kcal; $P = 0.0227$).

Thus, although the weight-neutral effect of DPP-4 inhibitors is an important benefit compared to many other glucose-lowering agents, the weight loss associated with GLP-1 receptor agonists may be particularly beneficial.

Effects on cardiovascular markers

Cardiovascular markers (i.e., blood pressure and blood lipids) have generally shown greater improvements with use of GLP-1 receptor agonists compared to DPP-4 inhibitors. The reduction in systolic blood pressure has ranged from 1 to 7 mmHg with the GLP-1 receptor agonists, whereas the reduction in diastolic blood pressure has been similar to placebo.[4,11,12,19,20,24–26] Data from the DPP-4 inhibitors are limited.[13,27]

Exenatide, 10 mg twice daily, and liraglutide, 1.8 mg daily, caused similar reductions in systolic blood pressure during 26 weeks (−2.0 vs. −2.5 mmHg, respectively; $P = 0.6409$),[4] with further reductions of 3.8 mmHg for patients switched from exenatide to liraglutide and 2.2 mmHg for patients who continued on liraglutide (P = NS) for an additional 14 weeks.[5] Smaller reductions were observed with diastolic blood pressure.[4] Comparison of sitagliptin, 100 mg, and liraglutide, 1.2 or 1.8 mg, showed reductions in systolic blood pressure of < 1 mmHg after 26 weeks.[7]

With regard to the lipid profile, the greatest impact is on triglyceride levels, although improvements in LDL and HDL cholesterol may be observed.[11–13,19,20,24–27] Compared to sitagliptin, exenatide resulted in a significantly greater reduction in triglycerides ($P = 0.0118$),[6] whereas liraglutide resulted in a similar reduction (liraglutide at 1.2 mg dose, −17 mg/dl; liraglutide at 1.8 mg dose, −38 mg/dl; and sitagliptin at 100 mg dose, −36 mg/dl; P = NS).[7] Compared to exenatide, triglycerides were reduced significantly more with liraglutide, 1.8 mg daily (−20 vs. −36 mg/dl; $P = 0.0485$) after 26 weeks.[4]

Although the effects on these cardiovascular markers do not qualify these agents as primary therapy and the true clinical significance is unknown, the risk of cardiovascular disease is not worsened and might be reduced.

Safety and Tolerability

Clinical trial results and clinical experience to date reveal that GLP-1 receptor agonists and DPP-4 inhibitors are characterized by good safety and tolerability profiles. There are, however, some issues with which clinicians should become familiar before initiating therapy with a GLP-1 receptor agonist or a DPP-4 inhibitor. In addition, safety and tolerability should be assessed at every patient follow-up visit.

Hypoglycemia risk

Hypoglycemia is a major treatment concern of clinicians and their patients with type 2 diabetes. Because of their glucose-dependent mechanism of action (i.e., they stimulate insulin secretion only during hyper-

glycemia), incretin-based therapies have a low hypoglycemia risk. However, the risk of hypoglycemia does increase when a GLP-1 receptor agonist or a DPP-4 inhibitor is combined with a sulfonylurea.

In the 26-week trial by Buse et al.,[4] severe hypoglycemia requiring the assistance of another person occurred in 2 of the 231 patients treated with exenatide and a sulfonylurea; no cases were observed in patients treated with liraglutide. Minor hypoglycemia (blood glucose < 56 mg/dl successfully self-treated) occurred in 34% of patients treated with exenatide and 26% of those treated with liraglutide. In patients concomitantly treated with a sulfonylurea, 42% experienced an episode of minor hypoglycemia with exenatide and 33% had minor hypoglycemia with liraglutide.

No patients experienced major hypoglycemia in the crossover trial of exenatide and sitagliptin,[6] although one exenatide patient experienced moderate hypoglycemia (blood glucose 39 mg/dl). Similarly, no major hypoglycemia was observed in the comparison of exenatide with sitagliptin as add-on therapy to metformin plus insulin glargine.[9]

In the comparison of liraglutide and sitagliptin,[7] one patient treated with liraglutide, 1.2 mg, experienced an episode of major hypoglycemia (blood glucose 65 mg/dl). In this trial, the event rates for minor hypoglycemia were 0.178 episodes per participant-year with liraglutide, 1.2 mg; 0.370 episodes per participant-year with liraglutide, 1.8 mg; and 0.106 episodes per participant-year with sitagliptin.

No major hypoglycemia occurred in the comparison of sitagliptin to saxagliptin as add-on therapy to metformin; hypoglycemia occurred in 3% of patients in each group.[10]

These trials confirm earlier observations that incretin-based therapies are associated with a very low incidence of hypoglycemia, most of which is mild or moderate in nature.

Other adverse events

Nausea

The most commonly observed adverse event with GLP-1 receptor agonists is transient nausea, which may be the result of delayed gastric emptying. Such nausea occurs in up to 57% of patients treated with exenatide[11] and 29% of those treated with liraglutide.[12]

Although nausea resolves within 6–8 weeks in most patients, the incidence and severity can be reduced using a dose-escalation strategy. For exenatide, treatment should be initiated with 5 mg twice daily given within 60 minutes before a meal. If necessary to further lower blood glucose, the dose can be increased to 10 mg twice daily after 1 month.[28] Liraglutide should be initiated without regard to meals at a dose of 0.6 mg daily and increased to 1.2 mg daily 1 week later. If necessary, the dose may be increased subsequently to 1.8 mg daily.[29]

Using these dose-escalation strategies, Buse et al.[4] reported 28% of patients treated with exenatide and 26% of those treated with liraglutide experienced nausea and that the nausea was of shorter duration with liraglutide ($P < 0.0001$). In the crossover trial,[6] 34% of patients treated with exenatide and 12% of those treated with sitagliptin experienced nausea.

In the 26-week trial by Pratley et al.,[7] 21–27% of patients treated with liraglutide and 5% of those treated with sitagliptin experienced nausea. During the 26-week extension phase,[8] the incidence of nausea was similar in all three groups, ranging from 1 to 3% of patients.

Unspecified adverse gastrointestinal events were experienced by 56% of patients treated with exenatide and 19% of those treated with sitagliptin, both as add-on therapy to metformin plus insulin glargine.[9]

Acute pancreatitis

Perhaps the most concerning issue to arise with exenatide, liraglutide, and sitagliptin is acute pancreatitis, most of which has been described in postmarketing reports. Determining that these cases are treatment-related has been difficult; in fact, symptoms have resolved despite continuing therapy.[12]

Acute pancreatitis was not observed in any of the four comparative incretin-based trials.[4–7] Buse et al.[4] observed pancreatitis in one patient treated with liraglutide who successfully continued therapy. The pancreatitis was judged to be chronic and unrelated to liraglutide, which is possible given that patients with type 2 diabetes have a 2.8 times greater risk of pancreatitis than those without diabetes.[30]

To clarify the possible association between incretin-based therapies and acute pancreatitis, the U.S. Food and Drug Administration (FDA) has required the manufacturers of exenatide, liraglutide, sitagliptin, saxagliptin, and linagliptin to conduct additional investigations.[31–37] In the meantime, exenatide, liraglutide, and sitagliptin should not be prescribed for patients with a history of pancreatitis or risk factors such as cholelithiasis, hypertriglyceridemia, or alcohol abuse.[28,29,38]

Ongoing safety investigations

In addition to those already noted, the FDA has required further postmarketing investigations to clarify the long-term safety of GLP-1 receptor agonists and DPP-4 inhibi-

tors. One investigation relates to a possible association with medullary thyroid cancer[32] based on postmarketing reports with exenatide[33] and rodent studies with liraglutide.[34] In its review of liraglutide, the FDA determined that there is a low risk for humans because the rodent changes occurred at drug exposure levels many times those anticipated in humans.[32]

Additional investigation has shown that there is a GLP-1 receptor–mediated mechanism for these changes in rodents leading to C-cell hyperplasia in rats and, to a lesser extent, in mice.[39] On the other hand, GLP-1 receptor expression in thyroid C-cells has been shown to be low in humans and monkeys, such that 20 months of liraglutide treatment at more than 60 times human exposure levels did not lead to C-cell hyperplasia in monkeys. In addition, patients exposed to liraglutide for 2 years had levels of calcitonin, a biomarker for medullary thyroid cancer, that remained at the lower end of the normal range.

Thyroid cancer was not observed in the four comparative incretin-based trials. The manufacturer of exenatide is required to carry out an epidemiological study,[33] whereas the manufacturer of liraglutide must conduct animal studies and maintain a 15-year registry.[34] In the meantime, liraglutide is contraindicated in people with a personal or family history of medullary thyroid cancer.[29]

The FDA has also required additional investigation regarding the cardiovascular safety of liraglutide,[34] saxagliptin,[36] and linagliptin[40] because new standards regarding cardiovascular safety for all glucose-lowering agents were implemented by the FDA after completion of clinical trials for these three agents. Although phase II and phase III trials of liraglutide met the new standard for ruling out an unacceptable increase in cardiovascular risk, more stringent post-approval criteria were not met.[32] Other FDA-mandated investigations are ongoing for all five incretin-based therapies.[33–36,40]

Use in renal impairment

The differing clearance pathways of the incretin-based therapies have important implications with respect to dosing and use in patients with renal impairment. Renal clearance of liraglutide and linagliptin is minor; therefore, dosage adjustment is not necessary in patients with renal impairment, although caution is advised.[29,31] Approximately 24% of saxagliptin is eliminated in urine as an unchanged drug; therefore, reducing the dose to 2.5 mg daily is recommended in patients with a creatinine clearance < 50 ml/minute.[37] Exenatide and sitagliptin are eliminated predominately via the kidneys. Consequently, the dose of sitagliptin should be reduced to 50 mg daily in patients with a creatinine clearance of 30–49 ml/minute and to 25 mg daily in those with a creatinine clearance < 30 ml/minute.[38] For exenatide, caution is advised when the agent is used in patients with a creatinine clearance of 30–50 ml/minute, and exenatide is contraindicated in patients with a creatinine clearance < 30 ml/minute.[28]

Linagliptin Information

Linagliptin, approved by the FDA in May 2011, has been evaluated as add-on therapy to metformin.[41,42] In a 24-week trial, patients with an A1C level of 7.0–10.0% were randomized to linagliptin, 5 mg daily (n = 524), or placebo (n = 177).[41] From a mean baseline of 8.0–8.1%, A1C decreased to 7.6% with linagliptin and increased to 8.3% with placebo ($P < 0.0001$). Similarly, FPG decreased from a baseline of 169 to 158 mg/dl with linagliptin and increased from 166 to 180 mg/dl with placebo ($P < 0.0001$). Two-hour PPG decreased 49 mg/dl in the linagliptin group and increased 18 mg/dl in the placebo group. Body weight decreased 0.4 kg in the linagliptin group and 0.5 kg in the placebo group. Hypoglycemia (blood glucose ≤ 70 mg/dl) was experienced by 0.6% of patients treated with linagliptin and 2.8% of those treated with placebo; none of the hypoglycemia episodes required assistance.

General Recommendations

Consistent with current expert panel guideline recommendations, GLP-1 receptor agonists and DPP-4 inhibitors are useful in the management of patients with type 2 diabetes over the spectrum of A1C levels, including drug-naive patients as well as those treated with other glucose-lowering therapy. GLP-1 receptor agonists are preferred over DPP-4 inhibitors because of the greater reductions in blood glucose and A1C and the weight loss observed in most patients treated with a GLP-1 receptor agonist.

Because of their low risk of hypoglycemia, GLP-1 receptor agonists and DPP-4 inhibitors may be particularly valuable in patients with hypoglycemia unawareness or in other patients for whom hypoglycemia is a major concern.

Improvements in blood pressure and lipids make GLP-1 receptor agonists and DPP-4 inhibitors especially helpful in patients with preexisting cardiovascular disease. Because they are not appropriate as primary therapy for cardiovascular risk reduction, other measures are needed to achieve target blood pressure and lipid levels.

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