Incretin-Based Therapies for Type 2 Diabetes Mellitus: Current Status and Future Prospects

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Incretin-based therapies encompass two new classes of antidiabetic drugs: glucagon-like peptide-1 (GLP-1) receptor agonists (e.g., liraglutide, exenatide, and exenatide long-acting release), which are structurally related to GLP-1, and the dipeptidyl peptidase-4 (DPP-4) inhibitors (e.g., sitagliptin and saxagliptin), which limit the breakdown of endogenous GLP-1. To evaluate the safety and effectiveness of incretin-based therapies for the treatment of type 2 diabetes mellitus and the role of these therapies in clinical practice, a MEDLINE search (January 1985–November 2009) was conducted. Relevant references from the publications identified were also reviewed. Of 28 studies identified, 22 were randomized controlled trials. Data show that these therapies affect insulin secretion in a glucose-dependent manner, achieving clinically meaningful reductions in hemoglobin A_{1c} levels, with very low rates of hypoglycemia. In addition, reductions in body weight have been observed with GLP-1 receptor agonists, which also exert a pronounced effect on systolic blood pressure. Various human and animal studies show that GLP-1 improves β-cell function and increases β-cell proliferation in vitro, which may slow disease progression. Thus, incretin-based therapies represent a promising addition to the available treatments for type 2 diabetes.

Key Words: type 2 diabetes, incretin-based therapies, glucagon-like peptide-1, GLP-1, dipeptidyl peptidase-4, DPP-4.

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The increasing prevalence of diabetes mellitus is an acknowledged world health crisis that is both a major contributor to patient morbidity and mortality and a huge economic burden.[1] The complex pathophysiology of type 2 diabetes makes effective treatment problematic. Hyperglycemia is associated with an increased risk of microvascular complications, sensory neuropathy, myocardial infarction, stroke, macrovascular mortality, and all-cause mortality.[2] Type 2 diabetes is also linked causally with obesity—in itself a global health crisis—which independently increases the risk of serious cardiovascular comorbidities.[1] Hypertension, also often associated with type 2 diabetes, can further increase cardiovascular risk.

The global economic impact of diabetes, due to premature death and complications from the disease, is considerable. At least $232 billion were spent on treatment and prevention of diabetes worldwide in 2007, with three quarters of that

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amount spent in industrialized countries on the treatment of long-term complications and on general care, such as efforts to prevent micro- and macrovascular complications.[3] The indirect costs of the disease must also be included in any discussion of its burden. In 2007, it was estimated that disability, lost productivity, and premature death due to diabetes cost the United States economy alone $58 billion.[1]

Treatment Potential for Type 2 Diabetes Mellitus

Insulin resistance and impaired insulin secretion both contribute to the development of type 2 diabetes, with the shift from normal to impaired glucose tolerance and then to diabetes, accompanied by a 40% decrease in insulin sensitivity and a 3–4-fold deterioration in insulin secretion due to loss of β-cell capacity (50–80%).[4, 5] However, if impaired glucose tolerance is diagnosed early enough, overt type 2 diabetes can be prevented or at least delayed, with lifestyle interventions aimed at reducing calorie intake and body fat[6, 7] or through drug treatment[7] to normalize glycemic control. Once type 2 diabetes has been diagnosed, weight loss alone can greatly improve both glycemic control and patients' cardiovascular risk profiles.[8] The effects are interrelated: glycemic control, coupled with effective management of additional risk factors, benefits cardiovascular prognosis.[9]

Despite treatment guidelines that recommend early, aggressive intervention,[10, 11] many patients fail to reach targets for glycemic control (~43% of patients in the United States have hemoglobin A_{1c} [A1C] levels ≥ 7%),[12] with minority groups having greater disease prevalence.[13, 14]

Many factors contribute to the failure to manage type 2 diabetes successfully. The most fundamental of these are the necessary lifestyle modifications, which, if not implemented at the time of diagnosis, may result in further decline in glycemic control and hasten the need for pharmacotherapy. Other factors include psychosocial and economic influences and shortcomings in the efficacy and tolerability profiles of many available antidiabetic drugs.

Goals of Therapy and Limitations of Current Treatments

To successfully improve patient outcomes and minimize the risk of complications and their cost, treatment should ideally address deteriorating β-cell function, A1C, and fasting plasma glucose (FPG) and postprandial plasma glucose (PPG) levels simultaneously, without increasing risk of hypoglycemia, weight gain, or cardiovascular disease contributors. Adequate glycemic control is essential, as reduction of A1C levels can decrease the risks of microvascular and macrovascular complications and mortality associated with type 2 diabetes.[2] For every 1% reduction in A1C, a 37% decrease in risk for microvascular complications ($p<0.0001$) and a 21% decrease in risk of death related to diabetes ($p<0.0001$) have been observed.[2] An ideal treatment would reduce cardiovascular risk factors as well as control blood glucose levels.

Current guidelines for type 2 diabetes from the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD) advocate a stepwise escalation of intervention, starting with lifestyle modification and metformin[15]; however, sulfonylureas, a common second-line intervention in type 2 diabetes treatment regimens, are limited by a failure of β-cell function that underlies the progression of the disease. Although β-cell function cannot be measured directly in humans, several indicators can be used to monitor its decline. These include the homeostatic model assessment of β-cell function (HOMA-B), which yields an estimate from fasting plasma insulin and glucose concentrations,[16] and the proinsulin:insulin ratio. The HOMA-B results have shown that established oral antidiabetic drug therapies such as metformin, sulfonylureas, and thiazolidinediones can improve β-cell function during the first year of treatment when they are given as initial treatment in patients with newly diagnosed type 2 diabetes; however, β-cell function declines progressively thereafter.[4, 17, 18] The A1C level parallels these changes in β-cell function, decreasing in the first year of therapy and then increasing progressively, highlighting the need for therapies that can sustain improvements in β-cell function.[19]

Insulin therapy is necessary once β-cell secretory capacity becomes insufficient; however, alternative antihyperglycemic drugs—the incretin-based therapies—are now available that may offer advantages over conventional oral antidiabetic drug therapies. These incretin-based agents were included in the 2009 recommendations of an American Association of Clinical Endocrinologists–American College of Endocrinology consensus panel,[20] which suggested that patients with A1C levels of 7.6–9.0% be treated with dual therapy with metformin

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(unless contraindicated) plus, in order of preference, glucagon-like peptide-1 (GLP-1) receptor agonists, dipeptidyl peptidase-4 (DPP-4) inhibitors, glinides, or sulfonylureas. The panel emphasized the lower risk of hypoglycemia with GLP-1 receptor agonists and DPP-4 inhibitors compared with glinides and sulfonylureas, but preferred GLP-1 receptor agonists over DPP-4 inhibitors because of their greater potential for lower PPG level and substantial weight loss. For patients requiring triple therapy, metformin, a GLP-1 receptor agonist, and a third oral antidiabetic drug—a thiazolidinedione, a sulfonylurea, or a glinide—are recommended.

Incretin-Based Therapies

Physiologic Effects of Glucagon-Like Peptide-1

The "incretin effect" describes the phenomenon whereby a glucose load delivered orally produces a much greater insulin secretion than the same glucose load administered intravenously.[21] This effect is mediated by two incretin hormones secreted by intestinal cells.[22] Glucose-dependent insulinotropic polypeptide (GIP) was identified first,[22] followed by GLP-1.[23] It is now thought that healthy individuals may derive up to 70% of their prandial insulin secretory response from the incretin effect.[24] Under normal conditions, the incretin peptides are secreted as needed, in response to ingested nutrients, and have a short plasma half-life due to degradation by the ubiquitous DPP-4 enzyme.[25]

In people with type 2 diabetes, pancreatic responsiveness to GLP-1 is impaired,[26] but the insulin-secretory response can be restored with pharmacologic doses of human GLP-1.[27] Further studies in vitro and in animals show that GLP-1 promotes β-cell neogenesis and preservation[28–30] and inhibits β-cell apoptosis.[30, 31] Also, GLP-1 has potentially beneficial effects on cardiac function: it has been shown to be cardioprotective in ischemia-reperfusion models in rats in vivo,[32] and to reduce blood pressure in Dahl salt-sensitive rats.[33] In humans, GLP-1 improves left ventricular function as well as endothelial function in patients with high cardiac risk.[34, 35] Along with these benefits, GLP-1 has been shown to slow the rate of gastric emptying in humans[36] and to reduce appetite.[37] These effects are particularly important, since type 2 diabetes is often associated with obesity and excessive caloric intake. It is clear that drugs acting through the physiologic GLP-1 pathways might have important ancillary benefits for the treatment of type 2 diabetes.

A key feature of GLP-1 action is the glucose-dependent stimulation of insulin secretion and concomitant suppression of glucagon. When patients with type 2 diabetes are infused with human GLP-1, insulin levels return toward basal levels when normal FPG concentrations are reached, despite ongoing infusion of GLP-1.[38] Continuous subcutaneous GLP-1 infusion for 6 weeks also reduced A1C by 1.3% and FPG by 77 mg/dl, slowed gastric emptying, and reduced appetite and body weight by 1.9 kg.[39] Therefore, GLP-1 and therapies that activate GLP-1 receptors only stimulate increases in insulin secretion when glucose levels are elevated and, as a result, carry a very low risk of hypoglycemia (Figure 1) unless combined with a sulfonylurea or insulin.

Unfortunately, therapeutic use of human GLP-1 is not practical due to its rapid degradation by DPP-4 enzyme,[25] with an elimination half-life of

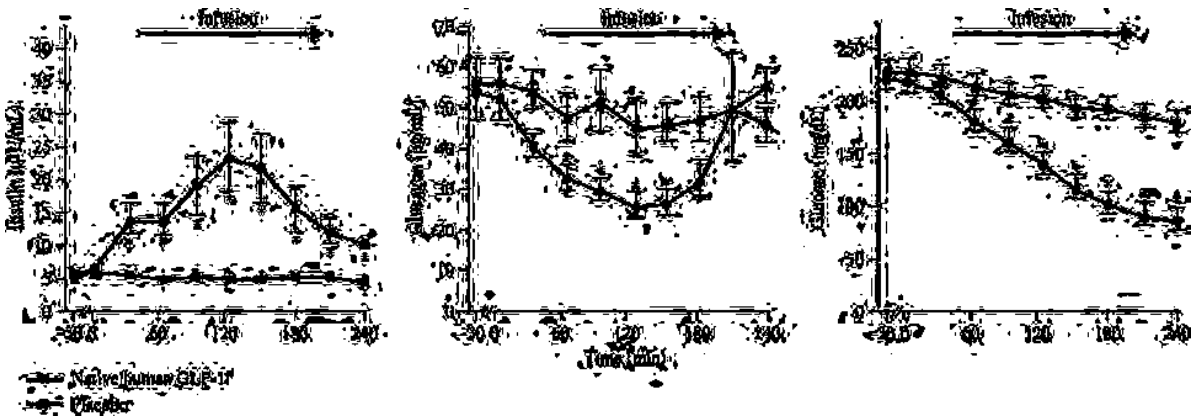

Figure 1. Effects of glucagon-like peptide-1 (GLP-1) or placebo infusion on insulin, glucagon, and glucose levels. *p<0.05. (From reference 38 with permission.)

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about 2 minutes.[27] As a result, two alternative approaches to harnessing the therapeutic potential of the incretin system have been pursued—GLP-1 receptor agonists and DPP-4 inhibitors.

Two Alternative Approaches

The GLP-1 receptor agonists are designed to fulfill the role of native GLP-1 while exhibiting resistance to degradation by DPP-4, and are present for therapeutic use at supraphysiologic levels (equivalent to 6–10-fold normal GLP-1 levels). These drugs include exenatide (available since 2005), exenatide long-acting release (LAR), which is undergoing regulatory review by the U.S. Food and Drug Administration (FDA); and liraglutide, which is available in the United States, Europe, and Japan. Other drugs (AVE-0010 bid/ZP10, albiglutide, and taspoglutide/R1583) have recently entered phase III trials; their data will not be reviewed.

The DPP-4 inhibitors act to impair the activity of the DPP-4 enzyme, thereby increasing the half-life of endogenous GLP-1. Compared with the GLP-1 receptor agonists, DPP-4 inhibitors produce modestly elevated levels of GLP-1 and exert their effects principally through interaction with receptors on afferent nerves rather than through receptors on target organs.[40] The first of these drugs to enter the market was sitagliptin, which was approved in the United States in 2006. A second DPP-4 inhibitor, vildagliptin, has been approved for use in Europe; however, since its manufacturer is not pursuing approval in the United States, vildagliptin will not be discussed in detail. Saxagliptin has received recent European Medicines Agency and FDA approval, but U.S. approval of alogliptin has been delayed because of the requirement for an additional cardiovascular study. In December 2008, the FDA issued the recommendation that all therapies for the treatment of type 2 diabetes should provide evidence that they do not increase the risk of cardiovascular events. Hence, alogliptin will not be reviewed.

To identify relevant literature on the incretin-based therapies, a MEDLINE search (January 1985–November 2009) was performed by using the following key words: type 2 diabetes, incretin, GLP-1, DPP-4, liraglutide, exenatide, sitagliptin, and saxagliptin. Relevant references from the publications identified during this search were also reviewed. All studies that were published in the English language and that evaluated the safety and efficacy of incretin-based therapies were analyzed. Priority was given to randomized clinical trials and retrospective studies in clinical settings.

Pharmacology

Glucagon-Like Peptide-1 Receptor Agonists

Exenatide. This drug is a recombinant peptide based on exendin-4, which is found in the saliva of *Heloderma suspectum* (i.e., Gila monster lizard). Exenatide shares 53% of its amino acid sequence identity with human GLP-1 and functions as a full agonist of the GLP-1 receptor.[41] It is, however, more resistant to degradation by DPP-4 enzyme, due to the presence of a glycine residue on the penultimate NH_2 group.[42]

Studies investigating the pharmacokinetic profile of exenatide show that it reaches peak plasma levels at about 2 hours after subcutaneous injection, has a plasma half-life of 3–4 hours, and provides glucose reduction over 5–7 hours.[43, 44] This means that exenatide requires twice-daily dosing (0–60 min before breakfast and dinner) and exerts its predominant effect on PPG levels.[44] A new drug application for a long-acting (slow-absorption) formulation requiring once-weekly dosing (exenatide LAR) was submitted in May 2009. In March 2010, a response letter was issued by the FDA requesting the finalization of the product labeling, risk evaluation and mitigation strategy, and clarification of existing manufacturing processes. Preliminary data indicate that exenatide LAR may have better efficacy than twice-daily exenatide.[45] Exenatide is renally excreted,[46] and although no dosage adjustment is needed in cases of mild or moderate renal impairment, exenatide is not recommended for use in patients with severe renal impairment (creatinine clearance < 30 ml/min) or end-stage renal disease ([ESRD] i.e., chronic, irreversible renal failure). This advice follows the finding that single doses of exenatide 5 µg caused gastrointestinal adverse effects in patients with ESRD who were receiving dialysis.[47] Gastrointestinal adverse events in these patients may worsen renal function. In November 2009, the FDA issued guidance advocating caution when starting or uptitrating exenatide in patients with moderate renal impairment (creatinine clearance 30–50 ml/min).[48]

Elimination of exenatide is not dependent on hepatic function, however, and it is therefore not expected to interact with hepatically metabolized drugs as a result of competition for liver

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enzymes. One way in which exenatide and other GLP-1 receptor agonists might interact with other drugs is through their effects on gastric motility and, hence, absorption kinetics. Studies examining the possibility of such an effect on digoxin, warfarin, and a statin do not suggest that their kinetics will be altered to a clinically meaningful extent by concomitant exenatide.[49–51]

Liraglutide. This GLP-1 receptor agonist is rather different from exenatide in its structure (Figure 2). It is an analog of human GLP-1 with 97% primary amino acid sequence identity, but with a fatty acid side chain attached through a glutamic acid linker.[52] This fatty acid structure enables reversible plasma albumin binding, which may contribute to the drug's partial resistance to DPP-4 degradation and its subsequent prolonged action.[53] The primary mechanism for prolonging the action of liraglutide, however, is thought to be through slowed absorption due to the self-association (as heptameric aggregates) of liraglutide molecules within the injection depot.[53] These heptamers are thought to be too large to pass through capillary membranes readily, so absorption is delayed pending the dissociation of liraglutide through dilution at the absorption site. Although liraglutide is partially resistant to DPP-4 degradation, elimination studies show that it is nevertheless degraded almost completely into small molecules by this enzyme and by endopeptidases, as with endogenous GLP-1.[54, 55] This means that its elimination is not dependent on hepatic or renal function, which may prove to be clinically advantageous.

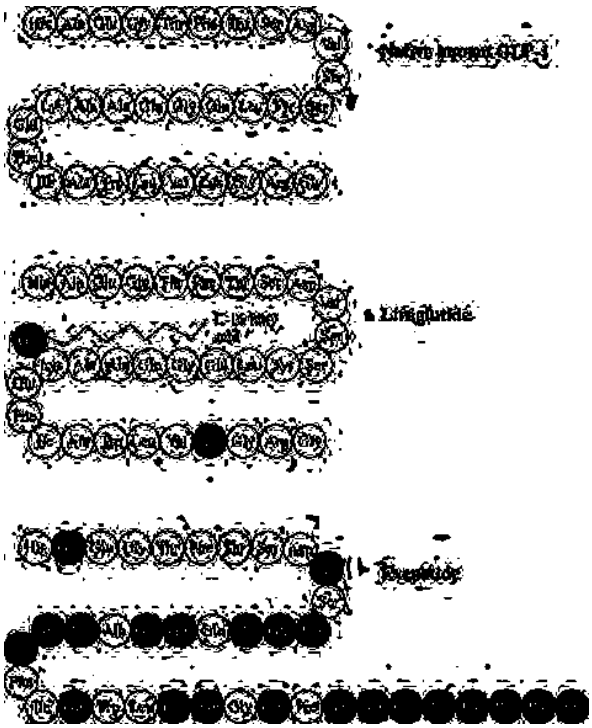

Figure 2. The structures of native glucagon-like peptide-1 (GLP-1), liraglutide, and exenatide. (From reference 52 with permission.)

Studies that investigated the pharmacokinetic profile of liraglutide have shown that it reaches peak plasma levels 9–12 hours after dosing by subcutaneous injection, with a subsequent mean elimination half-life of 11–15 hours.[56] Steady state is reached after 3 days, and therapeutic plasma liraglutide concentrations are observed for up to 24 hours after a single injection. These characteristics make liraglutide compatible with once-daily administration, and it may be possible to choose the dosing time without regard to meals.[56, 57] As with exenatide, drug-drug interaction studies have been performed to investigate liraglutide's potential to affect the kinetics of drugs that are sensitive to gastric transit time due to their absorption properties. Again, it was concluded that the effect of liraglutide on atorvastatin, lisinopril, digoxin, and griseofulvin was unlikely to be clinically relevant.[58]

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin. This drug is an orally absorbed small molecule that produces at least 80% inhibition of DPP-4 activity for 12 hours at doses of 50 mg or more, and for 24 hours at doses of 100 mg or more.[59] Therefore, the recommended dosage is 100 mg once/day. Compared with placebo, sitagliptin results in at least a 2-fold increase in postprandial GLP-1 levels, both after single doses and at steady state, reducing postprandial glycemia and not causing hypoglycemia.[59, 60] Steady state is reached after about 2 days. Inhibition of glucagon secretion is also seen with DPP-4 inhibition, but this class of drugs does not seem to affect gastric motility to the extent of the GLP-1 receptor agonists, possibly because of the relatively modest increase in GLP-1 signal that DPP-4 inhibition alone induces.[61] This might also account for the observation that weight tends to remain unchanged rather than reduced in response to DPP-4 inhibition. It is also worth noting that the DPP-4 enzyme degrades other peptides besides the incretins, including cytokines and chemokines,[61] and inhibition of

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this process might account for some of the adverse effects seen with DPP-4 inhibitors, which are elaborated on below.

Sitagliptin is primarily (79%) eliminated unchanged by the kidney. This process involves active tubular excretion, so dosage adjustment is recommended in patients with renal impairment to ensure that plasma sitagliptin levels do not accumulate.[62] Dosing should be reduced to 50 mg once/day in patients with moderate renal insufficiency and to 25 mg once/day in cases of severe renal impairment or ESRD. Only about 16% of sitagliptin undergoes hepatic metabolism; hence, its pharmacokinetics have been shown to be unaffected by mild-to-moderate hepatic failure.[63] Drug interactions are not anticipated to be a problem with sitagliptin, and studies have shown that it does not alter the kinetics (to a clinically relevant extent) of other antidiabetic drugs, simvastatin, warfarin, digoxin, and oral contraceptives,[64, 65] although a possible cytochrome P450 (CYP) interaction with lovastatin has been reported.[66] The concomitant use of cyclosporine produced only modest changes in the pharmacokinetics of sitagliptin.[65]

Saxagliptin. This is the second small-molecule once-daily DPP-4 inhibitor to become available in the United States. The pharmacokinetic and pharmacodynamic properties of saxagliptin have been investigated in two 2-week studies of a wide range of doses given once/day in both healthy subjects (40–400 mg)[67] and patients with type 2 diabetes (2.5–50 mg).[67] The level of DPP-4 inhibition with saxagliptin 24 hours after dosing was 50% of predose levels in the 2.5-mg group, and 79% of predose levels in the 400-mg group. Doses of 150 mg or greater provided the same level of inhibition, and no dose-related adverse events, including hypoglycemia, were observed during the study. All doses of saxagliptin increased postprandial levels of intact GLP-1 by 1.5–3 times compared with placebo, but there was no dose-related trend in this effect.[68] The recommended dosage is therefore 2.5 or 5 mg/day.

Saxagliptin is extensively metabolized in the liver by the CYP system, and its primary metabolite is active and has about 50% of the DPP-4 inhibitory potency of the parent compound. Both the parent and the metabolite are renally excreted,[69] and accumulation can occur in patients with renal impairment, necessitating a daily dose limit of 2.5 mg. Although some accumulation can occur with hepatic impairment, dosage adjustment does not appear necessary in patients with hepatic impairment but healthy renal function.[70]

Because of its hepatic metabolism, exposure to saxagliptin is potentially affected by inducers or inhibitors of the CYP system. However, dosage adjustments are not considered necessary to compensate for increased elimination caused by inducers such as rifampin, nor to avoid accumulation due to moderate inhibitors such as amprenavir, aprepitant, erythromycin, fluconazole, fosamprenavir, grapefruit juice, and verapamil. The daily dose of saxagliptin should be limited to 2.5 mg when used concomitantly with strong CYP inhibitors such as ketoconazole.[70]

Efficacy and Safety: Clinical Studies

The reviewed clinical studies investigating the efficacy and safety of incretin-based therapies are summarized in Table 1[45, 71–85] and Table 2.[86–93]

Glucagon-Like Peptide-1 Receptor Agonists

Exenatide. Pivotal phase III efficacy and safety data for exenatide were derived from three key Diabetes Management for Improving Glucose Outcomes (AMIGO) trials in patients with type 2 diabetes who were inadequately controlled with either a sulfonylurea,[72] metformin,[73] or a sulfonylurea plus metformin[75] (Table 1). In each of these trials, twice-daily exenatide was shown to reduce A1C significantly, by approximately 0.9% from baseline over the 30-week trial period compared with placebo.[72, 73, 75] These large, well-designed studies (double- or triple-blind, placebo-controlled, 30-wk trials with well-matched treatment and placebo groups) provided proof of the ability of exenatide to achieve significant A1C reductions over the time period studied. A pooled analysis of trial data plus two 52-week extension studies, which were completed by 314 of 1446 patients in an intent-to-treat group from the 30-week randomized trials, found that the reductions in A1C were sustained (–1.1% over 2 yrs).[94] The same analysis showed that 48% of patients achieved A1C less than 7%, and that FPG level was reduced by 25.2 mg/dl. It should be noted that the 48% of patients reaching an A1C less than 7.0% were those with baseline A1C values above 7.0%. The subgroup with a baseline A1C of 9.0% or greater showed a mean ± SD reduction in A1C from baseline of 2.0 ± 0.2%, compared with 0.8 ± 0.1% for the subgroup with baseline A1C less than 9.0%.[94] Although this was an open-label noncontrolled trial, these results suggest that the

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Table 1. Summary of Randomized Controlled Trials of the Glucagon-Like Peptide-1 Receptor Agonists

Study Duration	Population	Treatment Groups	Change in A1C (%)	Change in Weight (kg)	Change in SBP (mm Hg)
Exenatide					
24 wks[71]	232 drug-naïve patients, A1C 7.8%, weight 86 kg	Exenatide 5 µg b.i.d. Exenatide 10 µg b.i.d. Placebo	–0.7 –0.9 –0.2	–2.8 –3.1 –1.4	NA
30 wks (AMIGO 2)[72]	377 patients taking a sulfonylurea, A1C 8.6%, weight 96 kg	Exenatide 5 µg b.i.d. Exenatide 10 µg b.i.d. Placebo	–0.46 –0.86 +0.12	–0.9 –1.6 –0.6	
30 wks (AMIGO 1)[73]	336 patients taking metformin, A1C 8.2%, weight 100 kg	Exenatide 5 µg b.i.d. Exenatide 10 µg b.i.d. Placebo	–0.4 –0.8 +0.1	–1.6 –2.8 –0.3	
2 x 16-wk periods (crossover design)[74]	138 patients taking metformin or a sulfonylurea, A1C 8.95%, weight 84.8 kg	Exenatide 10 µg b.i.d. Titrated insulin glargine	–1.36 –1.36	–2.2 (exenatide vs glargine)	
30 wks (AMIGO 3)[75]	733 patients taking metformin + a sulfonylurea, A1C 8.5%, weight 98 kg	Exenatide 5 µg b.i.d. Exenatide 10 µg b.i.d. Placebo	–0.6 –0.8 +0.2	–1.6 –1.6 –0.9	
26 wks[76]	551 patients taking metformin + a sulfonylurea, A1C ~8.25%, weight 88 kg	Exenatide 10 µg b.i.d. Titrated insulin glargine	–1.11 –1.11	–2.3 +1.8	
52 wks[77]	501 patients taking metformin + a sulfonylurea, A1C 8.6%, weight ~84 kg	Exenatide 10 µg b.i.d. Titrated premix insulin analog	–1.04 –0.89	–2.5 +2.9	
52 wks[78]	69 patients taking metformin, A1C 7.5%, weight ~91 kg	Exenatide to 20 µg t.i.d. Titrated insulin glargine	–0.8 –0.7	–3.6 +1.0	
15 wks[45]	45 patients taking metformin (60%) or implementing dietary changes, A1C 8.5%, weight 106 kg	Exenatide LAR 0.8 mg q wk Exenatide LAR 2.0 mg q wk Placebo	–1.4 –1.7 +0.4	–0.0 –3.8 –0.0	
30 wks[79]	295 patients implementing dietary changes and exercise treated with metformin, a sulfonylurea, a thiazolidinedione, or any combination of 2 of these agents; A1C 8.3%, weight 102 kg	Exenatide LAR 2.0 mg q wk Exenatide 10 µg b.i.d.	–1.9 –1.5	–3.7 –3.6	
Liraglutide					
52 wks (LEAD 3)[80]	746 patients naïve to oral antidiabetic drugs, A1C 8.2%, weight 92.6 kg	Liraglutide 1.2 mg q.d. Liraglutide 1.8 mg q.d. Glimepiride 8 mg q.d.	–0.84 –1.14 –0.51	–2.05 –2.45 +1.12	–2.1 –3.6 –0.7
26 wks (LEAD 1)[81]	1041 patients taking a sulfonylurea, A1C 8.4%, weight 81.6 kg	Liraglutide 0.6 mg q.d. Liraglutide 1.2 mg q.d. Liraglutide 1.8 mg q.d. Placebo Rosiglitazone 4 mg/day	–0.60 –1.08 –1.13 +0.23 –0.44	+0.72 +0.32 –0.23 –0.10 +2.11	–0.9 –2.6 –2.8 –2.3 –0.9
26 wks (LEAD 2)[82]	1091 patients taking metformin, A1C 8.4%, weight 88.6 kg	Liraglutide 0.6 mg q.d. Liraglutide 1.2 mg q.d. Liraglutide 1.8 mg q.d. Glimepiride	–0.69 –0.97 –1.00 –0.98	–1.78 –2.58 –2.79 +0.95	–0.6 –2.8 –2.3 +0.4
26 wks (LEAD 4)[83]	533 patients taking metformin + a thiazolidinedione, A1C 8.5%, weight 97.0 kg	Liraglutide 1.2 mg q.d. Liraglutide 1.8 mg q.d. Placebo	–1.48 –1.48 –0.54	–1.02 –2.02 +0.60	–6.7 –5.6 –1.1
26 wks (LEAD 5)[84]	581 patients taking metformin + a sulfonylurea, A1C 8.2%, weight 85.4 kg	Liraglutide 1.8 mg q.d. Placebo Insulin glargine	–1.33 –0.24 –1.09	–1.81 –0.42 +1.62	–4.0 –1.4 +0.5
26 wks (LEAD 6)[85]	464 patients taking metformin, a sulfonylurea, or both; A1C 8.2%, weight 93 kg	Liraglutide 1.8 mg q.d. Exenatide 10 µg b.i.d.	–1.12 –0.79	–3.24 –2.87	–2.51 –2.00

A1C = hemoglobin A_{1c}; SBP = systolic blood pressure; NA = not applicable; LAR = long-acting release.

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Table 2. Summary of Randomized Controlled Trials of the Dipeptidyl Peptidase-4 Inhibitors

Study Duration	Population	Treatment Groups	Change in AIC (%)	Change in Weight (kg)
Sitagliptin				
18 wks[86]	521 patients naïve to oral antidiabetic drugs, A1C 8.1%	Sitagliptin 100 mg q.d.	–0.60 vs placebo	
		Sitagliptin 200 mg q.d.	–0.48 vs placebo	
		Placebo		
24 wks[87]	741 patients either treated with or naïve to oral antidiabetic drugs, A1C 8.0%	Sitagliptin 100 mg q.d.	–0.79 vs placebo	–0.2
		Sitagliptin 200 mg q.d.	–0.94 vs placebo	–0.1
		Placebo		–1.1
24 wks[88]	701 patients treated with metformin, A1C 8.0%	Sitagliptin 100 mg q.d.[a]	–0.65 vs placebo	
		Placebo[a]		
		Pioglitazone		
		Rescue therapy permitted (metformin)		
24 wks[89]	175 patients treated with a thiazolidinedione, A1C 8.1%	Sitagliptin 100 mg q.d.	–0.70 vs placebo	
		Placebo		
		Metformin		
		Rescue therapy permitted (pioglitazone)		
24 wks[90]	1091 patients naïve to oral antidiabetic drugs, A1C 8.8%	Sitagliptin 100 mg q.d.	–0.83 vs placebo	
		Sitagliptin 100 mg q.d. + metformin 1000 mg q.d.	–1.57 vs placebo	
		Sitagliptin 100 mg q.d. + metformin 2000 mg q.d.	–2.07 vs placebo	
		Metformin 1000 mg q.d.	–0.99 vs placebo	
		Metformin 2000 mg q.d.	–1.30 vs placebo	
		Placebo		
30 wks[91]	190 patients treated with metformin, AIC 9.2%	Sitagliptin 100 mg q.d.	–1.0 vs placebo	
		Placebo		
Saxagliptin				
12 wks[92]	Low-dose group: 338 patients naïve to oral antidiabetic drugs, A1C 7.9%	Saxagliptin 2.5 mg q.d.	–0.72	–0.94
		Saxagliptin 5 mg q.d.	–0.90	–0.23
		Saxagliptin 10 mg q.d.	–0.81	–1.28
		Saxagliptin 20 mg q.d.	–0.74	–0.11
		Saxagliptin 40 mg q.d.	–0.80	+0.51
		Placebo	–0.27	–1.03
6 wks[92]	High-dose group: 85 patients naïve to oral antidiabetic drugs, A1C 7.8%	Saxagliptin 100 mg q.d.	–1.09	–0.20
		Placebo	–0.36	–0.85
24 wks[93]	743 patients treated with metformin. A1C 8.1%	Saxagliptin 2.5 mg q.d.	–0.73 vs placebo	–1.5
		Saxagliptin 5 mg q.d.	–0.83 vs placebo	–0.9
		Saxagliptin 10 mg q.d.	–0.72 vs placebo	–0.5
		Placebo		–1.0

A1C = hemoglobin A_{1c}.
[a]Change in systolic blood pressure was –0.6 mm Hg for sitagliptin 100-mg group and –0.6 mm Hg for placebo group.

initial glycemic control achieved with exenatide over a 30-week period is sustainable in the long term.

Data from studies that used the once-weekly formulation (exenatide LAR) suggest that its efficacy is at least comparable to that of twice-daily exenatide. In a 15-week, placebo-controlled phase II trial in 45 patients, exenatide 0.8 mg or 2.0 mg/week reduced mean A1C by 1.4% and 1.7%, respectively ($p<0.0001$ vs placebo for both doses),[45] enabling 36% and 86% of patients to achieve an A1C of 7% or less. In another open-label, 30-week, phase III study in 295 patients previously managed with dietary changes and exercise and/or oral antidiabetic drugs, exenatide LAR 2 mg once/week achieved a greater reduction in A1C (–1.9%) than exenatide 10 µg twice/day (–1.5%, $p=0.002$), as well as greater reductions in FPG level (42 vs 25 mg/dl, $p<0.0001$).[79]

Exenatide was also found to significantly reduce body weight during the AMIGO trials, by up to 2.8 kg from baseline in patients who were also receiving metformin,[73] and by up to 3.1 kg

from baseline (vs 1.4 kg with placebo) in a more recent study of drug-naïve patients.[71] These reductions in weight are apparently unrelated to nausea (a common adverse effect with this therapy), as patients who did not experience this adverse effect also lost weight.[73] Body weight reductions were further observed in studies that used exenatide LAR.[45, 79]

Although blood pressure was not an end point in the AMIGO trials (it was monitored as a laboratory safety measurement), a subsequent open-label study reported significant reductions in systolic blood pressure (–6.3 mm Hg over 82 wks).[95] This study was limited by its open-label design and lack of a placebo group, but it supports a clinically meaningful effect of exenatide on systolic blood pressure that should be verified in randomized trials. In a group of 73 patients with meal tests at baseline and week 30, improvements in β-cell function were shown for exenatide by using model-based β-cell function parameters that relate insulin secretion to glucose concentration.[96] At week 30, the model-predicted insulin secretion rate at a reference glucose concentration had increased by 72% and 40% with doses of 10 and 5 µg, respectively, but had decreased by 21% with placebo ($p=0.015$ and 0.045 for 10 and 5 µg, respectively, vs placebo).[96] This prediction of an upward shift of the β-cell dose-response with exenatide treatment appears to be supported by more recent trials that showed improvements in β-cell function versus placebo as measured by HOMA-B.[71, 97]

Exenatide monotherapy resulted in significant increases in HOMA-B from baseline compared with placebo after 24 weeks of treatment (28–32% vs 6%).[71] In an open-ended, open-label clinical trial, patients treated with exenatide in combination with metformin and/or a sulfonylurea for more than 3 years experienced significant and sustained improvement in HOMA-B over time (+17.7%, $p<0.0001$ vs baseline).[96] In a further 1-year study comparing exenatide with insulin glargine, hyperglycemic clamp-derived measures of β-cell function were significantly improved with exenatide (first- and second-stage glucose-stimulated C-peptide secretion increased 1.52- and 2.85-fold, respectively, $p<0.0001$).[78]

The most frequently reported adverse events during the AMIGO trials were nausea, vomiting, and diarrhea. Nausea, reported at a rate of 50%, was associated with a dropout rate of around 5%[72, 73, 75] (higher overall than in trials of liraglutide), and the frequency and severity of all gastrointestinal adverse effects appeared to be reduced over time. Although gradual dosage escalation has been shown to decrease nausea, higher doses were still associated with a higher rate of nausea over 30 weeks (unlike other gastrointestinal adverse events such as vomiting and diarrhea, which do not appear to be so dose dependent).[73] Low-titer antiexenatide antibodies, which did not affect glycemic control, were detected in 38% of patients during the AMIGO 1 trial.[73] An additional 6% of patients had higher titer antibodies and, in half of these patients (3% of all exenatide-treated patients in AMIGO), the glycemic response to exenatide was decreased.[47] Hypoglycemia occurred rarely, and no severe episodes were reported. The frequency of administration-site reactions with twice-daily exenatide treatment during the AMIGO studies has not been reported. In the phase II study of once-weekly exenatide LAR, however, injection-site bruising occurred more frequently with exenatide LAR than placebo (13% and 7% in lower and higher dose groups, respectively, vs 0% in placebo group).[45]

Although exenatide has been shown to be generally well tolerated in clinical trials and in clinical use,[98] the FDA has recently updated its Information for Healthcare Professionals to reflect 30 new cases of acute pancreatitis associated with the use of exenatide.[99] Patients with type 2 diabetes have a 3 times greater risk for developing pancreatitis than the general population,[100] and that conditions commonly associated with diabetes such as obesity, hypertriglyceridemia, and gallstones are well known risk factors for developing pancreatitis. The frequency of cases associated with exenatide does not appear to exceed that associated with diabetes, so these adverse events are not necessarily causally related. Nevertheless, patients should be monitored for signs of pancreatitis. If pancreatitis is suspected, exenatide should be discontinued, confirmatory tests performed, and appropriate treatment begun.

Liraglutide. The Liraglutide Effect and Action in Diabetes (LEAD) program of phase III studies investigated liraglutide use as monotherapy or in combination with one or two oral antidiabetic drugs versus placebo and active comparators, all in combination with background therapy (Table 1).[80–85] The A1C level was the primary outcome measure in all LEAD trials: mean reductions of up to 1.5% were seen after 26 weeks' treatment with liraglutide 1.8 mg added to metformin plus

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rosiglitazone,[83] and reductions of around 1% were seen for liraglutide added to either glimepiride or metformin (statistically greater than that seen with placebo and background therapy).[81, 82] When liraglutide monotherapy was investigated in a subgroup of previously drug-naïve patients over 52 weeks, reductions in A1C seen within the first 8–12 weeks of trial start were still evident at the end of the trial (–1.6% with liraglutide 1.8 mg after 52 wks).[80] Of these previously drug-naïve subjects, 62% had A1C levels less than 7.0% at the end of the trial.

Changes in weight from baseline observed during the LEAD trials are summarized in Table 1.[80–84] Significant weight reductions versus placebo were observed with liraglutide in combination with metformin, metformin plus rosiglitazone, and metformin plus a sulfonylurea. Patients receiving liraglutide 1.8 mg in combination with metformin lost a mean weight of 2.8 kg during the LEAD 2 trial, significantly more than the loss seen with metformin alone (–1.5 kg, $p<0.05$).[82] Liraglutide monotherapy also resulted in significant weight reductions compared with glimepiride during the LEAD 3 trial (–2.5 vs 1.1 kg, $p=0.0001$).[80] Improvements in HOMA-B of 27–35% from baseline were seen across the LEAD program with liraglutide 1.8 mg (LEAD 1, 2, 4, and 6).[81–83, 85] There were significant reductions in systolic blood pressure (–2.1 to –6.7 mm Hg) with liraglutide 1.2 or 1.8 mg—the recommended clinical doses—across the LEAD studies; these preceded significant weight loss, suggesting that the mechanism is independent of the effect of liraglutide on body weight.[79–84] These trials were large and well designed (double-blind, placebo-controlled studies of 26 or 52 weeks with well-matched treatment and placebo groups). They provide evidence of the efficacy of liraglutide to achieve good glycemic control over the medium (26 wks) and long terms (52 wks), and of clinically meaningful reductions in body weight and systolic blood pressure achieved with liraglutide treatment.

No major hypoglycemic episodes (defined as those requiring third-party assistance or medical intervention) were reported during LEAD 2, 3, or 4,[80, 82, 83] and only nine major events were reported in the entire LEAD program with liraglutide 1.8 mg, all in patients also using glimepiride.[80] The frequency of minor hypoglycemia was also low: 0.17–1.93 events/patient-year.[80–85] There was a small but increased risk of hypoglycemic events when liraglutide was taken with a sulfonylurea (1 event/subject every second year), but when compared with the rate of hypoglycemic events reported with insulin regimens (e.g., 12 events/subject-year with the prandial insulin regimen[101]), this rate is relatively low.

As with exenatide, the most common adverse effect of liraglutide is nausea, which led to withdrawal in 1–9% of patients receiving the 1.8-mg dose during the LEAD program. During the LEAD trials, the frequency of nausea with liraglutide ranged from 10.5% when combined with a sulfonylurea to 40% with a thiazolidinedione.[81, 83] In comparison, the frequency of nausea and/or vomiting reported with metformin is approximately 25%.[102] As with exenatide, nausea with liraglutide can be limited by gradual dosage titration.[103] Pooled data from three LEAD studies (LEAD 1, 4, and 5) found that 8.6% of patients developed antibodies to liraglutide, with no negative effect on A1C.[81, 82, 84] The clinical significance of this finding remains unclear. The frequency of administration-site reactions, where reported, has been low in studies with liraglutide.[80, 84]

To date, the only available head-to-head comparison between incretin-based therapies is between liraglutide and exenatide.[85] In the 26-week LEAD 6 trial, liraglutide 1.8 mg/day (233 patients) or exenatide 10 µg twice/day (231 patients) was given in combination with maximally tolerated doses of metformin, with or without sulfonylureas. Liraglutide resulted in a significantly greater reduction in A1C compared with exenatide (1.12% vs 0.79%, $p<0.0001$) and 54% and 43% of liraglutide- and exenatide-treated patients, respectively, achieved the A1C target of less than 7.0% ($p=0.0015$). Liraglutide and exenatide treatments each resulted in weight loss (–3.24 and –2.87 kg, respectively), whereas minor hypoglycemia was less frequent (1.93 vs 2.60 events/patient-year, $p=0.01$) and nausea less persistent with liraglutide. During a 14-week extension study in which patients receiving exenatide switched to liraglutide, there were further improvements in glycemic control, weight gain, and β-cell function.[104]

Dipeptidyl Peptidase-4 Inhibitors

Sitagliptin. In clinical trials of sitagliptin, the greatest reductions in A1C were seen when it was introduced as combination therapy with metformin to previously oral antidiabetic drug–naïve patients, suggesting that these agents have an additive effect (Table 2).[90] When used as monotherapy in this same population, however, the A1C reduction was more modest (–0.6 to –0.9%),[86, 87] and the

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lower the patient's A1C at baseline, the less marked the A1C reduction.

Sitagliptin monotherapy is generally weight neutral.[81–83] Reductions in weight from baseline of 0.1–0.6 kg have been reported with sitagliptin as monotherapy or in combination with metformin.[86, 87] With the exception of one study in which placebo resulted in greater reductions in weight from baseline compared with sitagliptin monotherapy,[87] these changes were not significantly different from those observed with placebo. An increase in weight from baseline was observed with sitagliptin in combination with pioglitazone (+1.5 kg), not significantly different from that observed in the placebo group (+1.8 kg).[89]

The effect of sitagliptin on blood pressure in patients with type 2 diabetes was reported in only one of the studies reviewed here (Table 2). In this study, a nonsignificant reduction of 0.6 mm Hg in systolic blood pressure was observed in both the sitagliptin and placebo groups, both in combination with metformin.[88] Patients treated with sitagliptin, or a combination of metformin and sitagliptin, have shown improvements in β-cell function as measured by proinsulin:insulin ratio and HOMA-B.[90] For example, 88 patients with mean ± SD baseline HOMA-B of 40.8% ± 33.1% improved to 58.4% ± 54.5%, a least-squares mean change of 18.1% (95% confidence interval 7.3–28.9%).[90]

All of these studies were large and well designed (randomized, double-blind, and with placebo or active control) and therefore provide strong evidence of the efficacy of sitagliptin to achieve clinically meaningful reductions in A1C with no weight gain and with improvements in HOMA-B. It is worth noting that all of the studies investigating sitagliptin treatment as monotherapy were of relatively short duration (12–24 wks), and it is therefore unknown whether the ability of sitagliptin monotherapy to control glycemia will be sustained in the long-term. However, improvements in glycemic control with sitagliptin in combination with metformin have been sustained for at least 52 weeks.[105]

Saxagliptin. This DPP-4 inhibitor has been investigated in two large clinical studies (Table 2).[92, 93] In one study in which saxagliptin was added to metformin, adjusted-mean, placebo-subtracted differences in A1C after 24 weeks of treatment with doses of 2.5, 5, and 10 mg were 0.73%, 0.83%, and 0.72%, respectively (all $p<0.0001$).[93] All of these doses of saxagliptin also significantly reduced FPG levels compared with placebo (all $p<0.0001$). Relative to placebo, saxagliptin was not associated with any increase in the frequency of hypoglycemia and was found to be weight neutral. In the other study, patients were randomly assigned to receive saxagliptin monotherapy at either a high dose for 6 weeks or a low dose for 12 weeks. In the low-dose cohort, saxagliptin reduced A1C by 0.7–0.9% versus placebo (0.3% reduction) from an average baseline of 7.9%, and was weight neutral.[92]

Saxagliptin monotherapy resulted in weight changes from baseline of –1.3–0.5 kg.[92] These changes were not dose dependent (Table 2) and did not differ significantly from the change in weight from baseline observed with placebo (–1.0 kg). When combined with metformin, saxagliptin treatment resulted in weight reductions from baseline of 0.5–1.5 kg. These reductions did not differ significantly from the reduction observed with placebo (–1.0 kg).[93]

The effect of saxagliptin on blood pressure has not been reported in any of the studies reviewed. Compared with placebo, treatment with saxagliptin monotherapy resulted in significant increases in HOMA-B from baseline of 16.9–24.7% after 12 weeks.[92] Saxagliptin in combination with metformin also resulted in increases in HOMA-B (16.5–18.1%), although these changes did not differ significantly from those observed with placebo in combination with metformin (4.9%).[93] Adverse events were similar across all treatment groups, and the frequency of confirmed hypoglycemia was very low with saxagliptin treatment. Although both studies were large and well designed (randomized, double-blind, placebo-controlled), additional studies of longer duration are needed to confirm the safety and efficacy of saxagliptin in the long-term.

Safety. The risk of hypoglycemia is low with the DPP-4 inhibitors, with only sporadic events reported except when they were used with sulfonylureas. Safety concerns that have emerged from published trials include a relative excess of urinary tract infections (3.2%) and nasopharyngitis (6.4%) versus comparators (2.4% and 6.1%, respectively), and there have been some post-marketing reports of serious hypersensitivity reactions, including anaphylaxis and angioedema, and exfoliative skin conditions, including Stevens-Johnson syndrome.[106] This suggests that DPP-4 inhibitors may have some effect on the immune system, since DPP-4 is expressed on lymphocyte cells and degrades some cytokines.[42]

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Benefits

Incretin-based therapies have been shown to improve glycemic control, as assessed by A1C levels. Although all of these treatments achieved significant reductions in A1C levels when given as monotherapy, the benefit appears to be greater when they are combined with traditional therapies (Tables 1 and 2). As new additions to the range of available antidiabetic drugs, the place of incretin-based therapies in the continuum of care is still evolving. However, based on the evidence accumulated so far, they offer a number of novel benefits in addition to clinically meaningful A1C reductions. Key among these is a glucose-dependent mechanism of action that minimizes the risk of hypoglycemic episodes and makes initiation and dose escalation easier.

The two available incretin-based therapy subclasses appear different in a number of ways, although it must be stressed that these observations arise from indirect comparisons; no studies were found that directly compared GLP-1 receptor agonists and DPP-4 inhibitors. For example, the extent of A1C reduction seen in trials of GLP-1 receptor agonists is greater than that seen with DPP-4 inhibitors, and GLP-1 receptor agonists also offer advantages in terms of reducing body weight and blood pressure. The weight-loss effect is particularly significant considering the weight gain typically seen with existing therapies (e.g., insulin, sulfonylureas, and thiazolidinediones).[18, 107] Unlike the GLP-1 receptor agonists, no member of the DPP-4 inhibitors subclass appears to have any positive impact on weight loss. The differing mode of action may play a role in this, since DPP-4 inhibitors do not raise GLP-1 concentrations to the supraphysiologic levels achieved by GLP-1 receptor agonist treatment.[61] In addition, the DPP-4 enzyme acts on peptides other than GLP-1 (including GIP, which is therefore also elevated). The GIP has been shown to stimulate lipogenesis,[108] an action that may partially offset the weight-reducing properties mediated by GLP-1 as a result of DPP-4 inhibition. Although they do not have a weight-sparing effect, the DPP-4 inhibitors do appear to be weight neutral, unlike sulfonylureas, thiazolidinediones, or insulin.

The GLP-1 receptor agonists also improve measures of β-cell function,[71, 81–83, 85] an effect also seen with some DPP-4 inhibitors.[90, 92, 93] Data from the United Kingdom Prospective Diabetes Study (UKPDS) show that β-cell function—already reduced by approximately 50% at the time of type 2 diabetes diagnosis—continues to deteriorate over time regardless of treatment (dietary changes and exercise, metformin, or sulfonylurea). By contrast, insulin sensitivity remains unchanged.[4] Thus, decline in β-cell function may be the key factor in the development of diabetes and subsequent disease progression. Improvements in β-cell health seen with incretin-based therapies could lead to modification of the progression of type 2 diabetes. However, long-term studies are necessary to confirm that this is the case and to establish whether or not improvements in β-cell function are associated with improved glycemic control and reduced micro- and macrovascular complications.

Dosing and Administration

Exenatide was the first GLP-1 receptor agonist to be approved, and its U.S. label covers its use as an adjunctive therapy for patients with type 2 diabetes in combination with metformin, sulfonylureas, or thiazolidinediones; in combination with metformin plus a sulfonylurea; or in combination with metformin plus a thiazolidinedione. It has also recently been approved by the FDA for use as monotherapy. It is administered twice/day up to 1 hour before breakfast and the evening meal, by means of subcutaneous injection in the thigh, abdomen, or upper arm from a prefilled pen containing either a 5- or 10-µg dose. The 5-µg dose is used initially for at least 1 month in order to ensure patient tolerability and can subsequently be increased to 10 µg (twice/day) to provide improved glycemic control, but doses over 10 µg are not recommended. There is no need to adjust the metformin dosage when exenatide is added to metformin; however, when exenatide is added to a sulfonylurea, a reduction in the sulfonylurea dosage should be considered in order to counter a relatively increased risk of hypoglycemia. This relatively increased risk has also been seen with liraglutide and DPP-4 inhibitors in combination with a sulfonylurea.[81] The exenatide dosage does not need to be adjusted in patients with mild renal impairment, but with moderate renal impairment, escalation from the 5-µg to the 10-µg dose should be monitored closely. Exenatide is not recommended for use in patients with ESRD or severe renal impairment.

In contrast to exenatide, liraglutide was dosed once/day independently of meals in clinical trials, although administration time should be consistent from day to day. It was similarly administered from a prefilled pen device and has been tested in

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three treatment doses (0.6, 1.2, and 1.8 mg), with the 0.6-mg dose used for dose initiation to minimize the risk of nausea. During the LEAD trials, the liraglutide dose was escalated weekly until the allocated dose was reached. Considerably fewer patients treated with liraglutide during the LEAD program developed antibodies than did exenatide-treated patients during the AMIGO trials (up to 13% vs up to 43%),[73, 81, 83, 84, 94] and none showed a resulting nonresponse to the drug. A further difference between liraglutide and exenatide is that liraglutide treatment is unlikely to require dosage adjustment in patients with mild-to-severe renal impairment because it is not cleared by glomerular filtration.[109]

Sitagliptin is approved for use as monotherapy, as combination therapy with one oral antidiabetic drug (metformin, a sulfonylurea, or a thiazolidinedione) or two oral antidiabetic drugs (metformin plus a sulfonylurea, or metformin plus a thiazolidinedione), and as combination therapy with insulin with or without metformin. When sitagliptin is used in combination with a sulfonylurea or insulin, a lower dose of these agents may be required to reduce the risk of hypoglycemia.[65] Sitagliptin is dosed as 100 mg once/day and is also available in a combination sitagliptin-metformin tablet. Saxagliptin is approved for use either as monotherapy or as combination therapy with metformin, a sulfonylurea, or a thiazolidinedione and is dosed as 5 mg once/day. Patients with mild renal impairment do not require any dosage adjustment, but a dosage reduction to 2.5 mg once/day is recommended for patients with moderate or severe renal insufficiency or ESRD. A reduced dosage of 2.5 mg once/day is also recommended when saxagliptin is coadministered with strong CYP 3A4/5 inhibitors. Saxagliptin is eliminated by both renal and hepatic pathways. However, in patients with hepatic impairment, the differences in pharmacodynamic characteristics of saxagliptin were not clinically meaningful compared with healthy individuals. Therefore, no dosage adjustment is recommended for patients with hepatic impairment.[70]

Place in Therapy

Despite the encouraging results with exenatide, in clinical practice it is most often used as add-on therapy—probably because of cost considerations and its subcutaneous route of administration. A recently published ADA-EASD consensus statement advised considering GLP-1 receptor agonists as a second-line intervention after metformin in patients for whom hypoglycemia is particularly undesirable, or in those for whom promotion of weight loss is a major consideration.[15] The DPP-4 inhibitors were not included in the ADA-EASD algorithm, but a recent publication by the American Association of Clinical Endocrinologists has recommended the use of DPP-4 inhibitors as monotherapy if A1C levels are 6.5–7.5%, and, as with GLP-1 receptor agonists, they can be used as dual or triple therapy in a stepwise manner.[20]

There are few reports on the cost-effectiveness of these newer therapies compared with the more traditional type 2 diabetes treatments. A 2008 review implied that although newer diabetes treatments with a favorable overall metabolic profile could be considered a cost-effective approach to managing diabetes, a direct cost analysis between treatments is clearly needed.[110]

Conclusion

Drugs for the treatment of type 2 diabetes have typically been associated with certain trade-offs, most commonly among efficacy, hypoglycemia, weight gain, and convenience. The net result is that patients endure suboptimal glycemic control that increases their risk of developing complications as the disease progresses. In addition, existing treatments do not directly target the β-cell, the health of which is at the root of the disease. The availability of novel and potentially highly efficacious glucose-dependent therapies that work through the incretin system is an exciting development. The GLP-1 receptor agonists and DPP-4 inhibitors achieve clinically meaningful reductions in A1C with a low risk of hypoglycemia and, in some cases, significant improvements in β-cell function as assessed by HOMA-B. These improvements in glycemic control are further accompanied by weight and systolic blood pressure reductions in the case of GLP-1 receptor agonists, and no weight gain with DPP-4 inhibitors. Meal-independent dosing (with the exception of exenatide, which should be administered within 60 min before the morning and evening meals) and simple administration and dosage adjustment also make the incretin-based therapies attractive options for treatment of type 2 diabetes, although more studies are needed to confirm the long-term efficacy and safety of these agents.

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