CME SERIES: VOL. 4

article insights™

A nutshell analysis of medical journal articles for family physicians

volume 4

Integrating Incretin Therapies into Clinical Practice

Primary Care Education Consortium

about article insights™

Article Insights™ CME Series are educational activities that provide practical pearls to the primary care physician (PCP) on various therapeutic areas treated and managed by PCPs. Each activity includes a reprint of an article that has recently been published in a specialty journal as well as a Question and Answer interview between two PCPs on the important "take-away" points of the article reprint.

In this edition of **Article Insights™ CME Series**, Dr. Brunton will interview Dr. Morales on how PCPs may apply the findings in the journal article, "Overview of Glucagon-like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors for Type 2 Diabetes" by Richard E. Pratley, MD, to better manage diabetes in their patients.

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learning objectives

After reviewing this activity, the reader will be better able to:

- Compare the efficacy and safety among the glucagon-like peptide-1 analogs and dipeptidyl peptidase-4 inhibitors
- Identify patients with type 2 diabetes mellitus for whom a glucagon-like peptide-1 analog or dipeptidyl peptidase-4 inhibitor would be an appropriate treatment option

target audience

Primary care physicians and clinicians who have an interest in treating patients with diabetes.

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Dr. Brunton is on the advisory boards for Amylin, Eli Lilly and Company, Novo Nordisk Inc., and Takeda Pharmaceuticals.

Dr. Morales is on the advisory board and speakers' bureau for Novo Nordisk Inc.

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Clinical Practice Recommendations for AAFP EB CME Designation
1. Practice Recommendation: Incretin mimetics mimic the antidiabetic or glucose-lowering actions of naturally occurring human hormones called incretins. The incretins can be used to stimulate insulin production in response to elevated levels of blood glucose, as well as to inhibit the release of glucagon after meals, slow the rate at which nutrients are absorbed, and increase satiety.

Evidence-Based Source: American Association of Clinical Endocrinologists

Website of Supporting Evidence: http://www.aace.com/pub/pdf/guidelines/DMGuidelines2007.pdf

Strength of Evidence: Consensus guidelines

2. Practice Recommendation: If glycemic goals are not achieved at the end of 2 to 3 months of therapy, initiate a more intensive regimen and persistently monitor and titrate therapy over the next 2 to 3 months until all ACE/AACE glycemic goals are achieved.

Evidence-Based Source: American Association of Clinical Endocrinologists

Website of Supporting Evidence: http://www.aace.com/pub/pdf/guidelines/DMGuidelines2007.pdf

Strength of Evidence: Grade A: Homogeneous evidence from multiple well-designed randomized controlled trials with sufficient statistical power. Homogeneous evidence from multiple well-designed cohort controlled trials with sufficient statistical power ≥1 conclusive level-of-evidence category 1 publications demonstrating benefit>>risk

3. Practice Recommendation: Given the emerging relationship between postprandial hyperglycemia and the development of macrovascular disease, it may be more prudent to address both fasting and postprandial abnormalities simultaneously with the understanding that therapies targeting postmeal glucose concentrations will become more effective as HbA1c levels are reduced.

Evidence-Based Source: American Association of Clinical Endocrinologists

Website of Supporting Evidence: http://www.aace.com/pub/pdf/guidelines/DMGuidelines2007.pdf

Strength of Evidence: Grade C: Evidence based on clinical experience, descriptive studies, or expert consensus opinion. No conclusive level-of-evidence category 1 or 2 publication; ≥1 conclusive level- of-evidence category 3 publications demonstrating benefit >> risk. No conclusive risk at all and no conclusive benefit demonstrated by evidence.

Medium
Text publication in the form of a reprint article with a corresponding question and answer analysis by physicians.

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Overview of Glucagon-like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors for Type 2 Diabetes

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Overview of Glucagon-like Peptide-1 Analogs and Dipeptidyl Peptidase-4 Inhibitors for Type 2 Diabetes

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Abstract and Introduction

Abstract

Context: Impairment of incretin activity is now recognized as integral to the metabolic derangement underlying type 2 diabetes. Glucoregulatory agents that target the incretin system have recently been developed, and the place of these drugs in the treatment of type 2 diabetes can be assessed based on a growing body of clinical data.

Evidence Acquisition: A PubMed search was conducted to identify clinical studies of incretin therapies in type 2 diabetes. Article reference lists were also searched for relevant information, and supplemental material such as conference abstracts, drug prescribing information, and treatment guidelines were included as appropriate.

Evidence Synthesis: Two classes of therapies target the incretin system. The first, glucagon-like peptide-1 (GLP-1) agonists (exemplified by exenatide and liraglutide), have demonstrated considerable efficacy in clinical trials, reducing hemoglobin A1c (HbA1c) by up to 1.3%, decreasing fasting and postprandial glucose concentrations, reducing weight by approximately 3.0 kg, and improving cardiovascular risk factors. The second class, the dipeptidyl peptidase-4 inhibitors (such as sitagliptin and vildagliptin) rely on production of endogenous GLP-1 and act by reducing its turnover. The dipeptidyl peptidase-4 (DPP-4) inhibitors produce modest reductions in HbA1c (< 1%) compared with GLP-1 agonists and are generally weight-neutral. Neither GLP-1 agonists nor DPP-4 inhibitors cause hypoglycemia unless used with other agents known to increase risk.

Conclusions: GLP-1 agonists and DPP-4 inhibitors provide a valuable new treatment option for patients with type 2 diabetes and may be associated with a wider range of therapeutic benefits than older drugs.

Introduction

The current pandemic of diabetes mellitus and projections for future growth in the prevalence of the disease threaten to create a global public health crisis. In the United States alone, 20.8 million (9.6%) persons aged 20 years and older and 8.6 million (10.3%) of those aged 60 years and older have diabetes. In addition, approximately 54 million people are estimated to have prediabetes.[1] From 1995 to 2025, the number of individuals with diabetes is likely to rise by 42% (from 51 million to 72 million) in developed countries and by 170% (from 84 million to 228 million) in developing countries.[2] Type 2 diabetes accounts for between 90% and 95% of these cases.[3] The chronic complications of diabetes are frequent, severe, progressive, and expensive. These complications -- which prominently include macrovascular disease (coronary heart disease, stroke, and peripheral arterial disease), microvascular disease (nephropathy, neuropathy, retinopathy), as well as heart failure and periodontal disease -- are responsible for a reduction in life expectancy of 12 years for men and 19 years for women in addition to considerable morbidity.[3] Of patients with diabetes, 65% die of heart disease or stroke.[1] Patients with diabetes are 2 to 4 times more likely to have coronary heart disease or peripheral arterial disease and, among patients < 55 years of age, are at a 10-fold increased risk for stroke.[4-6] Microvascular complications from diabetes are an additional important cause of morbidity and disability.

Diabetes is the leading cause of end-stage renal disease, accounting for approximately 44% of new cases.[1] It is also the leading cause of blindness in working-age adults; approximately 55% of patients with type 2 diabetes have evidence of retinopathy within 15 years of diagnosis.[1] Evidence from clinical trials provides clear, compelling evidence that intensive treatment of type 2 diabetes -- which represents > 90% of cases in the United States -- can profoundly reduce the risk for the development and progression of chronic complications. Given the impact of diabetes on both the individual and the healthcare system together with the projected exponential growth of the population with diabetes, it is clear that the availability of a broad spectrum of effective, safe antidiabetic agents is becoming increasingly important.

This review will examine the latest additions to the therapeutic armamentarium for type 2 diabetes: the incretin-modifying therapies, including glucagon-like peptide-1 (GLP-1) agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, with a view to how these agents can fit into the increasingly complex treatment regimens for type 2 diabetes. In the context of current therapy, in which many patients and prescribers are unwilling to initiate insulin therapy because of the complexity of treatment, requirement for additional teaching, and risk for hypoglycemia and weight gain, GLP-1 agonists offer an effective alternative to oral antidiabetic drugs without the risk for weight gain associated with many of the commonly used oral drugs. Indeed, GLP-1 agonists have consistently elicited weight reductions in clinical trials. Furthermore, GLP-1 agonists are associated with a low risk for hypoglycemia unless combined with a secretagogue or insulin.[7-9] The characteristics of GLP-1 agonists make them a viable alternative (or addition) to oral antidiabetic agents and/or insulin.

Conventional View of the Progression of Type 2 Diabetes

Type 2 diabetes is a progressive metabolic disorder that is typified by functional defects in multiple organs. Prominent abnormalities include progressive pancreatic islet dysfunction, characterized by both qualitative and quantitative abnormities in insulin secretion from beta-cells and unrestrained glucagon secretion from alpha-cells, insulin resistance in muscle and adipose tissue, and dysregulated hepatic glucose production. Clinically, type 2 diabetes progresses from asymptomatic insulin resistance and islet defects to mild postprandial hyperglycemia and to frank diabetes that requires pharmacologic intervention. The conventional view of the progression of type 2 diabetes has focused primarily on insulin resistance and progressive beta-cell failure resulting in insulin deficiency.

Insulin acts to reduce blood glucose by signaling peripheral tissues to increase glucose uptake; it also promotes glycogen formation from glucose (glycogenesis) in the liver and inhibits secretion of glucagon from pancreatic alpha-cells.[10] Glucagon acts as a counterbalancing force by enhancing hepatic glucose production. Under normal physiologic conditions, glucagon sustains plasma glucose under fasting conditions.[10]

Beyond Insulin and Glucagon The Role of Amylin and Incretin Hormones

Apart from insulin resistance and deficiency, glucose homeostasis is also influenced by amylin and incretin hormones. Amylin, a beta-cell hormone like insulin, was first identified in 1987.[10] Amylin is secreted in response to nutrient stimuli and works together with insulin to suppress glucagon secretion. It is also involved in the regulation of gastric emptying, thereby influencing the rate of glucose appearance in the circulation.[10] As with insulin, there are both qualitative and quantitative abnormalities in the secretion of amylin in type 2 diabetes.

The incretin hormones, glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) are now widely recognized as important contributors to the maintenance of glucose homeostasis. These gut-produced hormones were first hypothesized to exist when it was noted that ingested glucose elicits a larger and longer-lasting insulin response compared with intravenous glucose, suggesting that a mechanism existed within the gut that enhanced insulin release in response to meals.[11,12]

Two incretin hormones were later identified: GIP and GLP-1. Levels of these hormones were shown to rise rapidly shortly after nutrient intake and then fall precipitously shortly thereafter as a result of inactivation by the enzyme DPP-4. Of the two incretin hormones, GLP-1 is secreted in greater concentrations and is generally considered more physiologically relevant in humans (Figure).[13] GLP-1 has been shown to enhance glucose-dependent insulin secretion, suppress postprandial glucagon secretion from pancreatic alpha-cells, slow gastric emptying, and reduce food intake and body weight. GLP-1 may also preserve and/or enhance beta-cell mass, by promoting beta-cell proliferation, and by decreasing beta-cell apoptosis.[14] In addition to its effects on the core defects in type 2 diabetes, GLP-1 also appears to have direct effects on other tissues. For example, GLP-1 has been shown to reduce blood pressure and triglyceride levels, and also may have a protective effect on the vasculature and kidneys.[15-20]

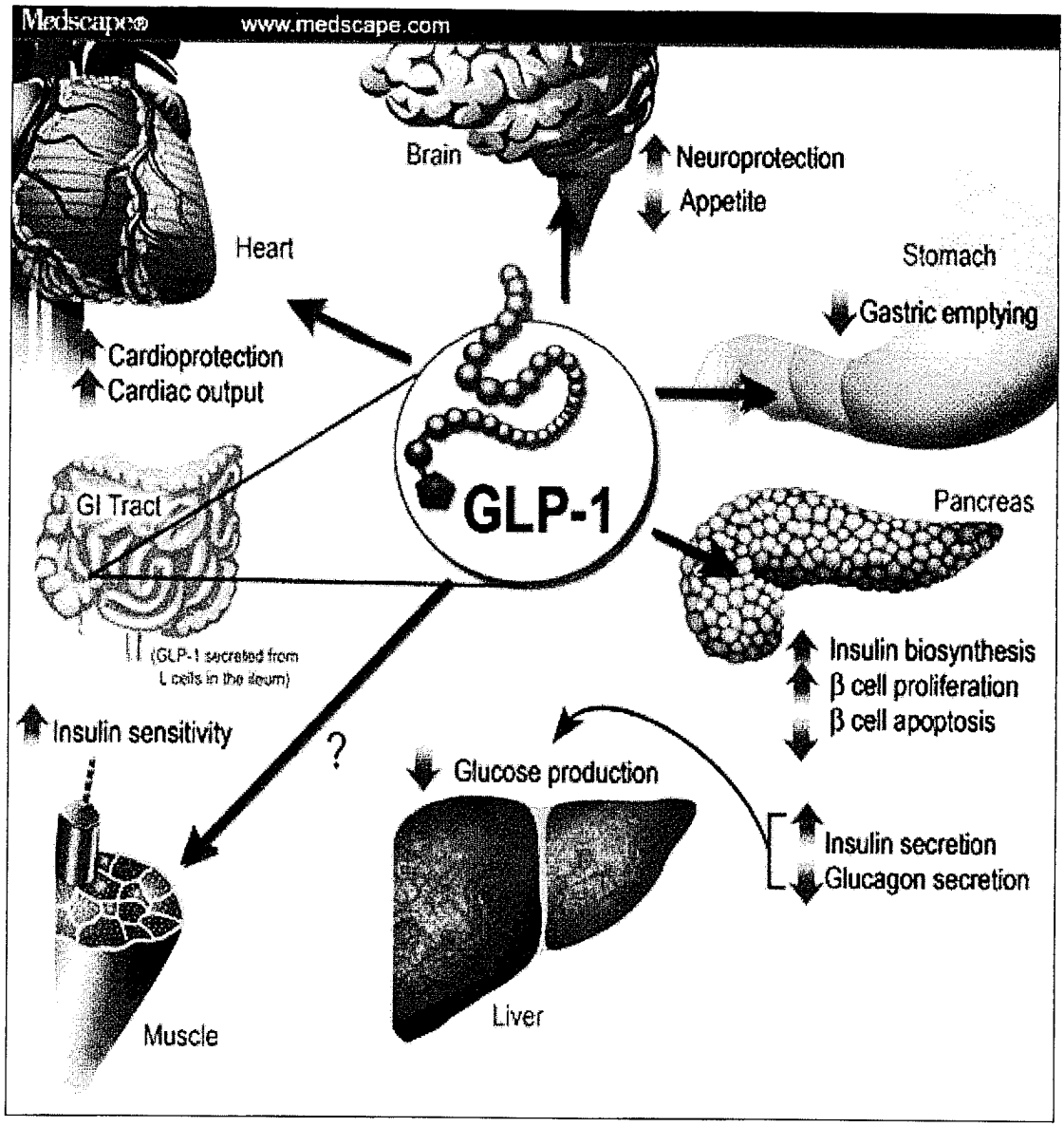

Figure.

Figure: Physiology of glucagon-like peptide-1 (GLP-1) secretion and action on GLP-1 receptors in different organs and tissues. *GI = gastrointestinal.* Modified with permission from Drucker DJ. The biology of incretin hormones. Cell Metab. 2007;3:154.

As with insulin, glucagon, and amylin, derangements in GLP-1 function appear to contribute to the development of hyperglycemia. Type 2 diabetes is characterized by a marked blunting of the incretin effect, which is caused, at least in part, by decreased secretion of GLP-1.[21] This blunting of the incretin effect results in defective glucose-stimulated insulin secretion, reduced glucose clearance, increased levels of glucagon, and quicker gastric emptying.[22]

Initial evidence for the efficacy of supplementing incretin activity in patients with diabetes came from studies in which exogenous, native GLP-1 was administered by continuous intravenous or subcutaneous infusion. In these studies, exogenous GLP-1 normalized beta-cell responsiveness to glucose,[23] restored insulin response in patients with type 2 diabetes,[24] and reduced daytime plasma glucose levels to near normal.[25]

Although highly effective, the administration of native GLP-1 is limited because of the rapid degradation of native GLP-1 by DPP-4. Because continuous infusion of native GLP-1 is both expensive and impractical for the large majority of patients with type 2 diabetes, research has focused on developing compounds that could either mimic the activities of GLP-1 while being less susceptible to degradation by DPP-4 or that could limit turnover of endogenous GLP-1 by inhibiting DPP-4.

Limitations of Current Antidiabetic Agents

Collectively, the literature summarized above indicates that glucose homeostasis is governed by a complex interplay among insulin, glucagon, amylin, and incretin hormones. In addition to insulin replacement, a broad range of oral and injectable therapies is available, including insulin secretagogues and sensitizers, amylin analog, biguanides, and alpha-glucosidase inhibitors. Although all of these agents control hyperglycemia to varying degrees (with reductions in A1c ranging from about 0.5% to 1.5%), some are limited by adverse effects including weight increases (sulfonylureas, glinides, thiazolidinediones, and insulin) that may counteract the therapeutic gains elicited by these treatments as well as increased risk of hypoglycemia (sulfonylureas, glinides, amylin analog, and insulin). All of these antidiabetic agents are subject to declining efficacy with disease progression. Moreover, none of these therapies address the changes in incretin production, which is now known to constitute an integral part of the core defects underlying type 2 diabetes.

Perhaps the most important recent advances in the treatment of type 2 diabetes have been the development of GLP-1 agonists, which act by supplementing and/or replacing the activity of endogenous incretins, and DPP-4 inhibitors, which work by indirectly increasing levels of intact, physiologically active endogenous GLP-1 and GIP-1.

The GLP-1 Agonists Role in Type 2 Diabetes

Glucagon-like peptide-1 agonists represented the first advance in addressing defects in incretin secretion. The first of these agents, exenatide, is a naturally occurring peptide GLP-1 agonist originally identified in the venom of the Gila monster (*Heloderma suspectum*).[26] Exenatide has only 53% homology to the human GLP-1 amino acid sequence; as such, it is relatively more resistant to DPP-4 (with a half-life of 2.4 hours rather than 2-3 minutes for native GLP-1).[27] Owing to an enhanced pharmacokinetic profile, exenatide is more pharmacologically potent than native GLP-1.[28] A once-daily human GLP-1 analog, liraglutide, is in late clinical development; additional GLP-1 agonists, including a long-acting formulation of exenatide, are in phase 2 and 3 trials.

Exenatide: Synthetic Exendin-4

Exenatide has been studied extensively in humans and is currently approved as adjunctive therapy to improve glycemic control in patients with type 2 diabetes who are taking metformin, a sulfonylurea, a thiazolidinedione, or a combination of metformin and either a sulfonylurea or a thiazolidinedione, and who have not achieved adequate glycemic control.[27] It is administered initially as a 5-microgram (mcg) twice-daily injection within 60 minutes of the morning and evening meals and is usually titrated to 10 mcg twice daily as tolerated.[27] The Table summarizes outcomes in clinical trials of exenatide.[8,9,24,29-43]

Three 30-week, double-blind, placebo-controlled trials enrolling a total of 1446 patients have been conducted to evaluate the safety and efficacy of exenatide in patients with type 2 diabetes whose glycemic control was inadequate with metformin alone, a sulfonylurea alone, or metformin in combination with a sulfonylurea.[8,9,29] All of these trials were similarly designed: after a 4-week placebo lead-in period, patients were randomized to treatment with exenatide 5 mcg twice daily, exenatide 10 mcg twice daily (titrated from 5 mcg twice daily), or placebo before the morning and

evening meals, in addition to their existing antidiabetic agent(s).[8,9,29] The primary outcome measure for all trials was glycemic control as assessed by change in hemoglobin A1c (HbA1c). Regardless of the underlying oral antidiabetic therapy, patients who were randomized to treatment with exenatide experienced significant but modest incremental reductions in HbA1c. In the 5-mcg twice-daily groups, HbA1c reductions ranged from -0.40% when used with a sulfonylurea to -0.60% when used with the combination of metformin and a sulfonylurea, compared with no change or small gains in the placebo groups.[8,9] In patients who received the 10-mcg twice-daily dosage of exenatide, reductions in HbA1c ranged from -0.78% when combined with metformin alone to -0.86% when combined with a sulfonylurea. Small but consistent reductions in fasting glucose levels of approximately 7.0 to 10.0 mg/dL were also seen in the exenatide 5 mcg and 10 mcg groups; in the 2 studies that reported postprandial glucose levels, reductions of up to 34% were observed.[29,44] Notably, progressive weight losses of up to -2.8 kg were noted in all studies at the 10-mcg twice-daily dose.[8,9,29]

Across all studies, gastrointestinal side effects were relatively frequent, particularly during the early weeks of the trial with the 10-mcg dosage of exenatide. In the sulfonylurea add-on trial, nausea was reported in 51% of patients who received exenatide 10 mcg twice daily, compared with only 7% of those who received the sulfonylurea alone.[9] Similarly, nausea was more frequent when exenatide 10 mcg was used with metformin (45% vs 23%) and when used in combination with metformin plus a sulfonylurea (48.5% vs 20.6%).[29,44] Nausea was, however, mostly mild to moderate and generally decreased with increasing duration of treatment. The incidence of hypoglycemia (primarily mild to moderate) was higher among patients who received exenatide 10 mcg g twice daily in combination with a sulfonylurea (36% vs 3%) or the combination of metformin and a sulfonylurea (27.8% vs 12.6%), but the incidence was similar in patients who received exenatide plus metformin or metformin alone.[9,29,44]

Exenatide, like many nonhuman peptide therapeutics, appears to elicit an immune response. In the trials summarized, detectable antibodies to exenatide developed in a substantial percentage of patients (approximately 40% to 50%).[9,29,44] Although anti-exenatide antibodies did not influence glycemic response in these trials, it is noted in the exenatide prescribing information that high-titer anti-exenatide antibodies develop in between 6% and 9% of patients; in 3% to 9% of these patients, the glycemic response to exenatide is attenuated.[27]

Exenatide is not recommended in patients with severe renal insufficiency (creatinine clearance < 30mL/minute) or end stage renal disease. In patients with end-stage renal disease on dialysis, exenatide 5 mcg has been poorly tolerated because of gastrointestinal side effects.[27]

Long-term extension studies of the exenatide/metformin study[29] and a report of patients enrolled in all 3 trials who were overweight[45] indicate that long-term exenatide treatment provides incremental reductions in HbA1c of up to 1.3% (when combined with metformin) and up to -1.1% in overweight patients after 82 weeks.[30,45] Notably -- and unlike most weight-loss agents -- continued progressive reductions in weight were observed in both studies. As is well known, long-term extensions are likely to enroll patients who experience good results during earlier study phases, and these data should be interpreted with caution.

Exenatide has also been compared with biphasic insulin aspart and insulin glargine.[46,47] In these studies, exenatide was non-inferior to insulins in HbA1c reductions and appeared to provide better postprandial glucose control, as well as weight reductions. However, the design of these trials has elicited some concern, as insulin therapy was not optimized in a manner consistent with other trials.[48]

Long-acting Exenatide

A once-weekly, long-acting formulation of exenatide (exenatide LAR) is in phase 3 clinical development, with a projected availability of 2009 to 2010. Although data are limited, phase 2 clinical trials indicated that exenatide LAR (at dosages of 0.8 and 2.0 mg) produced mean HbA1c reductions from baseline of 1.4% and 1.7%, respectively, and mean fasting plasma glucose

reductions from baseline of 43.2 and 39.6 mg/dL, respectively. Relatively high rates of nausea (up to 27%) with low rates of hypoglycemia were reported with exenatide LAR as was frequent injection-site bruising (Table). Also, by the end of the study, 67% of subjects had anti-exenatide antibodies.[32]

Apart from mentioning that subcutaneous injections were administered by study personnel each week, few details were provided on the injection device. In practical terms, exenatide LAR is likely to be most useful in patients with demonstrated tolerance to the shorter-acting formulation because the long half-life of this drug may extend the adverse effects of treatment in exenatide-naive patients.

Liraglutide: A Human GLP-1 Analog

Once-daily liraglutide represents an approach to GLP-1 agonist therapy that is distinct from exenatide. Unlike exenatide, liraglutide is nearly identical to native human GLP-1, with only a single amino acid substitution and the addition of a glutamate-spaced acyl side chain to distinguish it from the native peptide. These minor substitutions have a dramatic effect on turnover, extending the time to maximum concentration to 9 to 12 hours and the half-life to around 13 hours after subcutaneous administration.[28,49] These pharmacokinetic improvements permit 24-hour glycemic control with a once-daily injection of the drug. Early dose-ranging studies provided initial evidence for the efficacy of liraglutide.[50,51] More recent phase 2 trials have evaluated the effects of liraglutide at clinically relevant dosages.[52] The table summarizes outcomes in phase II trials of liraglutide.

A phase 2 trial evaluated the effects of liraglutide monotherapy in patients who have not achieved glycemic control despite treatment with an oral antidiabetic agent.[52] Enrolled patients were either on diet with HbA1c 7.5% to 10% or on oral antidiabetic monotherapy with HbA1c 7.0% to 9.5%. At 1.90 mg once daily, liraglutide was associated with HbA1c reductions of 1.74% compared with placebo after 14 weeks of treatment; nearly half of patients who received liraglutide at the 2 highest dosages (1.25 or 1.90 mg once daily) achieved American Diabetes Association targets for postprandial control.[52] Fasting plasma glucose levels were significantly reduced vs placebo by 61.3 and 79.3 mg/dL with liraglutide 1.25 and 1.90 mg once daily, respectively ($P < .0001$). Liraglutide resulted in significant dose-dependent reductions in body weight of up to 3 kg at the end of treatment. Notably, the difference in the incidence of any gastrointestinal adverse event between patients in the liraglutide groups (29% to 37%) and the placebo group (23%) appears lower than that observed with exenatide.[52] Consistent with the fact that liraglutide has high homology with native GLP-1, anti-liraglutide antibodies have not been detected.[52]

Beyond Glycemic Control and Weight: Pleiotropic Effects of GLP-1 Agonists

Beyond their effects on glycemic control and weight, both exenatide and liraglutide have demonstrated pleiotropic effects that may enhance their therapeutic effect in patients with type 2 diabetes. The extension studies summarized above found marked improvements in lipid profiles for exenatide, with substantial reductions in apolipoprotein B (ApoB) (-5.2 mg/dL), triglycerides (-73 mg/dL), and increased high-density lipoprotein cholesterol (+4.5 mg/dL), together with small reductions in total cholesterol and low-density lipoprotein cholesterol. In addition, exenatide appears to be associated with substantial improvements in systolic and diastolic blood pressure, averaging -6.3/-4.1 mm Hg after 82 weeks of long-term treatment.[30] These improvements may, in part, be the result of the weight loss experienced by patients who remained on treatment in the extension studies. Much shorter-term phase 2 studies of liraglutide have also found substantial reductions in triglycerides of 22%, and reductions in blood pressure of about -7.9/2-3 mm Hg.[52]

The observation that improvements in triglycerides and blood pressure occur after relatively short periods of treatment with liraglutide suggests that GLP-1 has direct effects that are not simply the result of weight loss. In addition, these studies have demonstrated reductions in emerging markers of cardiovascular risk and inflammation, including plasminogen activator inhibitor type 1,

brain natiuretic peptide, and C-reactive protein.[53] The changes in cardiovascular risk factors seen with the GLP-1 agonists are particularly important given the substantially elevated risk for morbidity and mortality from cardiovascular disease seen in patients with type 2 diabetes.

In addition to cardiovascular effects, GLP-1 agonists appear to enhance beta-cell function. In preclinical studies, exenatide has been shown to inhibit beta-cell apoptosis and preserve function[54-56] and to improve beta-cell function in humans by up to 50%.[33] After 30 weeks of therapy with exenatide 10 mcg twice daily, insulin secretion rates were shown to increase by up to 72%.[56] Similarly, preclinical studies suggest that liraglutide has a positive effect on beta-cell function.[57-59] Liraglutide 1.9 mg/day increased beta-cell secretory capacity by up to 114% and increased first-phase insulin secretion by up to 118%.[60] In another study using a validated beta-cell model to evaluate liraglutide effects during conditions of normal living, insulin secretion was significantly increased from 189 to 322 pmol/minute/m^2 ($P < .005$).[61] Whether the improvements observed in clinical studies are the direct effects of GLP-1 agonists on beta-cell function or are a result of improved glycemia remains to be elucidated.

The DPP-4 Inhibitors Role in Type 2 Diabetes

The DPP-4 inhibitors represent the first oral therapies targeted at increasing endogenous incretin levels. As the name suggests, these agents function by inhibiting the essential enzyme DPP-4, extending the physiologic half-life of endogenous GLP-1 and GIP by preventing their degradation. These agents are entirely dependent on secretion of endogenous incretins; thus, they may be best employed early in type 2 diabetes before substantial impairments in incretin secretion become apparent.

Sitagliptin

One DPP-4 inhibitor, sitagliptin, was approved in 2006 and is currently marketed in most countries worldwide. A fixed-dose combination of sitagliptin with metformin is also currently available. A second DPP-4 inhibitor, vildagliptin, has been approved in Europe but not in the United States. A broad range of DPP-4 inhibitors are currently in clinical development.

In the United States, sitagliptin is indicated as an adjunct to diet and exercise to improve glycemic control in patients with type 2 diabetes as monotherapy and in combination with metformin, glimepiride, pioglitazone, or metformin + glimepiride. It is also indicated as initial therapy in combination with metformin.[62] The recommended dose of sitagliptin is 100 mg once daily; in patients with moderate or severe renal insufficiency, the dose must be reduced to 50 mg and 25 mg once daily, respectively.[62]

Sitagliptin monotherapy (100 and 200 mg) provides significant ($P < .001$) reductions in HbA1c of 0.79% and 0.94%, respectively, and reductions in plasma fasting glucose of -17.1 to -21.3 mg/dL among drug-naive patients.[43] These benefits are accompanied by few hypoglycemic adverse events, even at the unapproved 200-mg dose. In general, sitagliptin is very well tolerated; slightly higher rates of certain adverse events, including constipation, nasopharyngitis, urinary tract infection, hypertension, and dizziness compared with placebo were seen in trials.[43] However, in postmarketing studies, more severe skin reactions, including some cases of Stevens-Johnson syndrome, have been reported. The relationship of these events to sitagliptin treatment is uncertain, however. In contrast to exenatide and liraglutide, sitagliptin does not appear to elicit meaningful changes in body weight.

Addition of sitagliptin in patients inadequately controlled on metformin or pioglitazone monotherapy also yields reductions in HbA1c of up to 0.65% to 0.70%, without an increased risk for gastrointestinal adverse events.[44,47] In head-to-head comparisons, sitagliptin plus metformin was non-inferior to the combination of glipizide 5 to 20 mg/day plus metformin in terms of HbA1c, and also provided small weight losses (-1.5 kg) compared with weight gain with glipizide (1.1 kg), with a clinically significant between-treatment difference of -2.5 kg ($P < .001$).[63] It is notable that in previous studies, relative to placebo, sitagliptin has been generally shown to have a weight-

neutral effect as both monotherapy and as add-on therapy to metformin.[44,64] Sitagliptin and metformin combination therapy is associated with significant incremental reductions in HbA1c over initiation of either agent alone, without a substantial increase in adverse events.[65]

Vildagliptin

Vildagliptin is currently under investigation in the United States but was recently approved in Europe for the treatment of type 2 diabetes. Vildagliptin yields HbA1c reductions of approximately 1.0% compared with 1.4% with metformin after 1 year of treatment, with neutral effects on body weight and much lower rates of adverse events than metformin (primarily related to major reductions in the incidence of gastrointestinal adverse events compared with metformin).[46] Vildagliptin has also been shown to provide HbA1c reductions similar to those seen with the thiazolidinedione rosiglitazone (-1.1% vs -1.3%, respectively) while remaining weight-neutral compared with increases of 1.9 kg among patients who received rosiglitazone.[66]

Vildagliptin has also been studied in combination with pioglitazone. In a 24-week trial, vildagliptin 100 mg administered once daily with pioglitazone 30 mg yielded HbA1c reductions of -1.9%, with significant changes in fasting plasma glucose (-50 mg/dL) and overall weight gain (2.1 kg).[42] Another trial that tested vildagliptin (50 or 100 mg/day) as add-on therapy for patients poorly controlled with pioglitazone (45 mg/day) yielded incremental improvements in HbA1c, with small gains in weight (Table).[43]

DPP-4 inhibitors, like GLP-1 agonists, have been shown to improve beta-cell function and insulin sensitivity. In a 12-week study that examined the effects of vildagliptin on meal-related beta-cell function and insulin sensitivity in metformin-treated patients with type 2 diabetes, insulin secretion correlated with changes in HbA1c and increased with the addition of vildagliptin.[67] Sitagliptin 100 or 200 mg has also demonstrated improvements in homeostasis model assessment of beta-cell function vs placebo after 24 weeks of monotherapy in patients with type 2 diabetes.[43] As with GLP-1 agonists, the mechanism by which DPP-4 inhibitors improve beta-cell function requires further study.

Safety of DPP-4 Inhibitors

DPP-4 inhibitors have proven to be generally safe and well tolerated in clinical trials. Because sitagliptin is primarily excreted via renal elimination, the dosage must be adjusted in patients with moderate-to-severe renal insufficiency or end-stage renal disease.[62] A systematic meta-analysis suggests increased risks for nasopharyngitis and urinary tract infections, as well as an increased frequency of headache with short-term use of sitagliptin.[68] DPP-4 is also involved in multiple physiologic processes, with substrates beyond incretins that include, but are not limited to, certain neuropeptides, growth factors, and chemokines.[69] Whether DPP-4 plays an important physiologic role in the processing of these peptides remains to be determined. Although there have not been adverse events attributable to alterations in these off-target hormones, the potential long-term effects of chronic DPP-4 inhibition must be monitored carefully.

How Should Incretin-Targeted Therapies Be Used in the Clinic

The number of therapies available for type 2 diabetes has increased significantly over the last decade, which translates into more therapeutic options and complexity in making treatment decisions.

Although the 2007 American Diabetes Association guidelines do not contain specific guidance on the use of exenatide or sitagliptin, the American Association of Clinical Endocrinologists

guidelines for the management of diabetes provide recommendations on the use of incretin-targeted therapies in patients with type 2 diabetes.[3] According to these guidelines, exenatide (in combination with a sulfonylurea, metformin, a sulfonylurea plus metformin, or a thiazolidinedione) is a therapeutic option for patients with type 2 diabetes who have not achieved glycemic goals with oral therapy alone.[3] Exenatide is not recommended for use in patients with end-stage renal disease or severe renal impairment. The DPP-4 inhibitor, sitagliptin, is recommended as initial monotherapy and as part of combination therapy with metformin, glimepiride, pioglitazone, or metformin + glimepiride. It can also be given as initial therapy in combination with metformin; dose reductions are required in patients with moderate or severe renal insufficiency.

Conclusions: Integrating Incretin-Modifying Therapies Into Clinical Practice

Given the multiple therapeutic options available to treat type 2 diabetes, where do DPP-4 inhibitors and GLP-1 agonists fit into the overall treatment paradigm? Because the mechanism of action of DPP-4 inhibitors is dependent on endogenous incretin secretion, which may be impaired in patients with type 2 diabetes, DPP-4 inhibition achieves active GLP-1 levels that are, at best, in the high physiologic range. Moreover, DPP-4 inhibitors produce only minor increases in fasting active GLP-1 levels; their predominant effects are seen post-prandially. Thus, DPP-4 inhibitors lower A1c levels by only a modest degree. Nevertheless, because these drugs are orally available, given once daily, extremely well tolerated and, to date, have had a good safety profile, they will likely become important agents in the treatment paradigm for type 2 diabetes. Until long-term data are available, it is plausible to assume that DPP-4 inhibitors will work best early in the course of diabetes, given their dependence on endogenously produced GLP-1. They can work well as monotherapy for patients who are metformin intolerant or in those with renal insufficiency in whom metformin is contraindicated. Their weight-neutral action and low risk for hypoglycemia also make them appropriate monotherapy in patients for whom the weight gain and risk for hypoglycemia associated with sulfonylureas is undesirable. Likewise, their complementary mechanism of action and low risk for hypoglycemia is ideal in combination with either metformin or thiazolidinediones. Finally, DPP-4 inhibitors are well suited for treating elderly patients with type 2 diabetes because of their low risk for hypoglycemia as well as their tolerability profile and lack of significant drug-drug interactions.[70]

In contrast to DPP-4 inhibitors, GLP-1 agonists do not rely on endogenous incretin secretion, and pharmacologic levels of GLP-1 activity are achieved only after injection. Whereas the efficacy of exenatide is limited by its relatively short half-life and consequent minor effects on fasting glucose levels, longer-acting GLP-1 agonists, such as liraglutide, exenatide-LAR, and other molecules in development have robust effects on fasting glucose levels and may potentially provide superior efficacy to exenatide and most oral agents. In addition, an important attribute of members of this class is their ability to promote weight loss. Counterbalancing these benefits, all GLP-1 agonists must be given as injections, and the incidence of adverse events, particularly nausea, is higher. GLP-1 agonists are appropriate treatment for patients with type 2 diabetes when given in combination with oral agents such as metformin, sulfonylureas, and thiazolidinediones. They may be particularly beneficial in obese patients with type 2 diabetes because of the weight loss promoted by these agents, which can be substantial, and other ancillary benefits such as reducing blood pressure and improving lipid profiles. If further clinical studies of long-acting GLP-1 agonists confirm this initial impression of superior efficacy, these drugs could achieve widespread use as second-line, or even first-line treatments to bring more patients with type 2 diabetes to goal.

Table. Comparison of Incretin-Targeted Therapies

Therapy	Baseline HbA1c	ΔHbA1cvs Baseline	Δ Body Weight vs Baseline	Most Common Adverse Events
Exenatide*				
Added to metformin[29,30]	8.2% (30 weeks) 8.1% (82 weeks)	-0.8% (30 weeks) -1.3% (82 weeks)	-3.0 kg (30 weeks) to -5.3 kg (82 weeks)	Nausea (45%) Nausea (14%)
Added to sulfonylurea[9]	8.6%	-0.9% (30 weeks)	-1.6 kg (30 weeks)	Nausea (51%) Mild-to-moderate hypoglycemia (36%)
Added to metformin And sulfonylurea[8]	8.5%	-0.8% (30 weeks)	-1.6 kg (30 weeks)	Nausea (49%) Mild-to-moderate hypoglycemia (28%)
Added to thiazolidinedione[31]	7.9%	-0.9% (16 weeks)	-1.75 kg (16 weeks)	Nausea (40%) Vomiting (13%)
Monotherapy (LAR), 0.8 mg or 2.0 mg[32]	8.3%	-1.7% (15 weeks)	-3.8 kg (15 weeks)	Mild-to-moderate nausea (19% and 27%, respectively) Gastroenteritis (19% and 13%, respectively) Hypoglycemia (25% and 0%, respectively)
Liraglutide*				
Monotherapy[52]	8.5%	-1.4% (14 weeks)	-2.99 kg (14 weeks)	Diarrhea (21%) Nausea (7.3%)
Added to metformin[33]	9.5%	-0.8%† (5 weeks)	-2.2 kg (5 weeks)	Nausea (35.3%)
Sitagliptin*				
Monotherapy[34]	8.0%	-0.6%	Neutral	Few adverse events
Added to metformin[35]	8.0%	-0.7%	Neutral	Few adverse events
Added to pioglitazone[36]	8.1%	-0.8%	+1.8 kg	Few adverse events
Added to glimepiride + metformin[37]	8.3%	-0.6%	+0.8 kg (24 weeks)	Hypoglycemia (16.4%)
Vildagliptin*				
Monotherapy[38]	8.7%	-1.0%	Neutral	Few adverse events
Added to insulin[39]	8.4%	-0.5%	+1.3 kg (24 weeks)	Hypoglycemia (22.9%)
Added to metformin[40]	8.4%	-0.9%	+0.2 kg (24 weeks)	Few adverse events
Added to glimepiride[41]	8.6%	-0.6%	+1.3 kg (24 weeks)	Asthenia (5.9%) Nasopharyngitis (5.9%) Upper respiratory tract infection (5.3)
Initiated with pioglitazone[42]	8.8%	-1.9%	Neutral	Few adverse events
Added to pioglitazone[43]	8.7%	-1.0%	+2.7 kg	Edema (7%) UTI (5.1%)

*Data given for 10-mcg dosage (exenatide) or for highest dosage used in a particular trial that does not exceed the currently indicated dosage, or for the highest dosage employed in a clinical trial (investigational agents). All values are approximate.

†Reduction is given relative to metformin alone, not baseline.
LAR = long-acting release; HbA1c = hemoglobin A1c; UTI = urinary tract infection

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CME Series: volume 4

Integrating Incretin Therapies into Clinical Practice

In this fourth issue of Article Insights, Javier Morales, MD, expands on the article by R.E. Pratley, MD, using case studies to identify patients who are candidates for a glucagon-like peptide-1 analog or dipeptidyl peptidase-4 inhibitor and clinical pearls regarding their use.

Question 1

Dr. Brunton: Among the treatments that have recently become available for type 2 diabetes mellitus (T2DM), the incretin hormones offer some unique advantages.

Dr. Morales: The incretin hormones, ie., glucagon-like peptide-1 (GLP-1) receptor agonists and dipeptidyl peptidase-4 (DPP-4) inhibitors, act upon the incretin system, which is impaired in patients with T2DM. The GLP-1 receptor agonists act directly on the GLP-1 receptor and are able to achieve supraphysiologic levels, whereas the DPP-4 inhibitors act indirectly by inhibiting the degradation of endogenous GLP-1, thereby raising GLP-1 to physiologic levels. The incretin hormones regulate glucose homeostasis through several mechanisms, including stimulating insulin production in response to elevated levels of blood glucose and inhibiting the release of glucagon during meals. The GLP-1 receptor agonists also slow the rate at which nutrients are absorbed and increase satiety. (1) Both as monotherapy and when added to other agents, the glucagon-like peptide-1 receptor agonists generally lower A1C by 0.5-1.5% and dipeptidyl peptidase-4 inhibitors by 0.5-0.8%. However, comparing the effects of agents within or between the GLP-1 receptor agonists and DPP-4 inhibitors is difficult because of a lack of published head-to-head trials and differences in study populations and methodologies. GLP-1 receptor agonists promote weight loss; DPP-4 inhibitors are weight neutral. The incretin hormones also lower blood pressure and produce beneficial effects on the lipid profile. (2,3) Preliminary data suggest that they also improve ß-cell function. (4-6) The effects of the GLP-1 receptor agonists and DPP-4 inhibitors on morbidity and mortality await investigation.

Question 2

Dr. Brunton: What generally have we seen with respect to safety and tolerability?

Dr. Morales: The GLP-1 receptor agonists and DPP-4 inhibitors have generally demonstrated good safety and tolerability profiles over the course of several months of therapy. For example, the incidence of symptomatic hypoglycemia has been less than 5% in most clinical trials. The GLP-1 receptor agonists exenatide and liraglutide (investigational) cause nausea and/or vomiting in about half of patients, with improvement generally after 6 to 8 weeks. Initiating exenatide, for example, with a dose of 5 mcg for a month helps mitigate the nausea. There have been more than 30 post-marketing reports of acute pancreatitis thought to be caused by exenatide. (7) With respect to the DPP-4 inhibitors, there have been very rare post-marketing reports of sitagliptin causing serious hypersensitivity and allergic reactions. (8) Vildagliptin (investigational) has been observed to cause skin reactions and elevated liver enzymes. (9)

Question 3

Dr. Brunton: Because the GLP-1 receptor agonists and DPP-4 inhibitors are unique among the available treatments for T2DM, it might be helpful to our colleagues to learn more about them in the context of some case vignettes.

Dr. Morales: Our first case is RB, an overweight (BMI 28 kg/m2) 46-year-old female with a normal lipid profile but impaired fasting glucose (fasting plasma glucose 118 mg/dL). Physical exam reveals blood pressure 124/78 mm Hg (118/72 mm Hg 1 year ago) and a normal eye exam. RB's 72-year-old mother was diagnosed with T2DM 14 years ago and has suffered a minor stroke. Initial treatment for RB was lifestyle modification, which reduced her BMI

to 25 kg/m2 over 16 months. Laboratory tests from a few days ago show her fasting plasma glucose (FPG) to be 139 mg/dL and 2-hour postprandial glucose (PPG) 203 mg/dL. Her A1C is 7.8%.

Question 4

Dr. Brunton: Given RB's fasting and postprandial glucose levels, she clearly meets the criteria for T2DM. In addition to intensifying lifestyle modification, how else should she be managed?

Dr. Morales: Drug therapy is needed, especially given her family history. The A1C target is as close to normal as possible, and certainly under 7%. For most patients including RB, the glycemic goals have not changed in light of the ACCORD, ADVANCE, and VADT trials. On the other hand, for a patient with established cardiovascular disease or additional cardiovascular risk factors, there may be no benefit by reducing the A1C to less than 7%, at least in terms of cardiovascular risk. We'll know more when the full results of these trials are released. In the meantime, I think we should follow the lead of the American Diabetes Association (10,11) and the American Association of Clinical Endocrinologists (12), which separately recommended not modifying the glycemic goals outlined in their respective guidelines pending the results of the analyses.

Since the ADA recommends starting with metformin at the time of diagnosis, this is the preferred treatment. In addition to its ability to lower the blood glucose levels to the target range, metformin is attractive because it is available orally, is inexpensive, and is weight neutral, which is especially important in the case of RB. Alternatives such as the alpha-glucosidase inhibitors and DPP-4 inhibitors are unlikely to achieve this A1C target. A glinide, sulfonylurea, thiazolidinedione, or GLP-1 receptor agonist should provide the needed glucose control as monotherapy. Of these, a GLP-1 receptor agonist would be preferred because of its ability to promote weight loss. However, exenatide, the only commercially available GLP-1 receptor agonist, is not currently indicated as initial therapy.

Question 5

Dr. Brunton: Does ß-cell preservation play a role in selecting a treatment?

Dr. Morales: Yes, we'd like to avoid further loss of pancreatic ß-cells. As we learned from the United Kingdom Prospective Diabetes Study (UKPDS), patients with T2DM have only about half of their ß-cell function remaining at the time of diagnosis. Recent evidence suggests that only 20% of ß-cell function may remain at the time of diagnosis. (13) The UKPDS also demonstrated that durable glycemic control is not achieved with metformin for more than 3 years in more than half of the patients, which suggests that it has no significant effect on preserving ß-cell function. (14) On the other hand, thiazolidinediones have been shown to preserve ß-cell function (15), and emerging evidence in rodent and in vitro models indicates that a GLP-1 receptor agonist or a DPP-4 inhibitor enhance ß-cell function. Clinical studies in humans of the GLP-1 receptor agonists and DPP-4 inhibitors show improvement in the first- and second-phase insulin response (16), an increase in the fasting insulin level (3,17-19), improvement in the homeostasis model of assessment (4,20), among other measures. Since we are limited to these indirect measures of ß-cell function and the trials have involved patients treated for only up to 2 years, with a return to baseline after discontinuation, we must view the data as preliminary. However, this preliminary evidence suggesting improvement of ß-cell function would make GLP-1 receptor agonist or DPP-4 inhibitor even better choices.

Question 6

Dr. Brunton: How soon would you modify therapy for RB if she is not at goal?

Dr. Morales: First, the dose of metformin should be titrated every 1 to 2 weeks based on tolerability and self monitoring of blood glucose (SMBG) to the maximum effective dose of 2000 mg per day. According to the American Diabetes Association, the timing and frequency of SMBG in patients with T2DM treated only with oral agents is not known. (21) However, one multi-disciplinary panel of diabetes experts concluded that SMBG should probably be done at least once a day (22) until glycemic control is achieved. It's important to remember that the American College of Endocrinology/American Association of Clinical Endocrinologists recommends individualized treatment regimens based on the presenting A1C in treatment-naïve patients or the current A1C in treated patients, and they stress the need to advance therapy if the A1C goal is not met within 3 months. (23) If the patient is not at goal after another 3 months, therapy should be intensified by adding another agent.

Question 7

Dr. Brunton: Would metformin have been your choice if RB was obese, with a BMI of 34 kg/m²?

Dr. Morales: In that case, I would prefer a drug that promotes weight loss instead of being weight neutral. This leaves only 2 options, an amylin analog (pramlintide), which must be used in combination with insulin, or a GLP-1 receptor agonist, which is not indicated as initial therapy. Although a GLP-1 receptor agonist is administered subcutaneously, weight loss is a significant benefit that reduces both the physician and patient's barriers to the use of an injectable. As we learned from the Diabetes Attitudes, Wishes, and Needs (DAWN) study (24), these barriers to injectable agents are important to address beginning at the time of diagnosis. The transition to injection therapy for diabetes management has been made easier as a consequence of the introduction of the GLP-1 receptor agonists, especially since there is a weight benefit and a low risk of symptomatic hypoglycemia.

Question 8

Dr. Brunton: Given the progressive loss of ß-cell function in T2DM, most patients require combination drug therapy within a few years of diagnosis. What role do the GLP-1 receptor agonists and DPP-4 inhibitors play in these patients?

Dr. Morales: In addition to being effective as monotherapy, both the GLP-1 receptor agonists and DPP-4 inhibitors have been shown to further lower blood glucose when added to existing therapy. Our second patient is a 58-year-old male diagnosed with T2DM 6 years ago. Since his initial A1C was 8.9%, glimepiride was initiated along with lifestyle management. His A1C decreased to 7.8% over the next 15 months. Because his A1C rose to 8.4% over the next year, pioglitazone was added and titrated to 45 mg once daily. His A1C decreased about 1%, but again began to rise so that now 3 years later (6 years after diagnosis), his A1C is 8.1%. During this time, his BMI has remained relatively stable at about 30 kg/m2. It's unfortunate that during this entire 6 years following diagnosis of T2DM, he has never been at goal. This might be due to concerns about hypoglycemia or weight gain, as well as injections, which can serve as barriers to intensifying therapy both on the physician's and patient's parts.

Question 9

Dr. Brunton: This patient presents a common dilemma because of the progressive ß-cell loss and weight issue.

Dr. Morales: Yes, so our choices are very limited because we want to avoid a secretagogue because of the loss of ß-cell function. The 5-year incidence of monotherapy failure has been shown to be 34% with a sulfonylurea compared to 21% for metformin and 15% for a thiazolidinedione. (25) At the same time, a drug is needed that can lower the A1C by more than 1%. This leaves us with metformin, a GLP-1 receptor agonist, or insulin. Since insulin promotes weight gain, it would not be an ideal choice. Metformin would be a somewhat better choice since it is weight neutral. The best choice would be a GLP-1 receptor agonist since it promotes weight loss in most patients. It should be emphasized that the dose of a sulfonylurea should be reduced by 50% to 75% when a GLP-1 receptor agonist is added to avoid hypoglycemia from the sulfonylurea. In this patient's case, I would probably discontinue the glimepiride within a few weeks of initiating the GLP-1 receptor agonist since it is my impression that the contribution of the glimepiride to lowering the blood glucose is negligible.

Question 10

Dr. Brunton: Although it is good that the patient has not gained weight while on sulfonylurea therapy, I am surprised that there was no change in his weight since he was diagnosed.

Dr. Morales: I agree, although it's important to remember that patients respond differently. This is a good time to talk with the patient about further lifestyle modification with referral to a diabetes educator or nutritionist. I would particularly focus on his eating at mealtime. How long does it take for him to feel full? Does he continue to eat after beginning to feel full? How many calories does he consume at mealtime? If any of these is an issue, a GLP-1 receptor agonist would again be a good choice since it promotes early satiety and reduces caloric intake in healthy subjects and patients with T2DM. (26,27)

Question 11

Dr. Brunton: Gastrointestinal side effects due to a GLP-1 receptor agonist are not uncommon. How should they be managed?

Dr. Morales: Nausea is the most likely, occurring in about half of patients. First, I would start with a low dose, eg. exenatide 5 mcg twice daily, for the first month and educate the patient that the frequency and severity generally peak by 8 weeks after starting therapy, decreasing thereafter. (28) Second, if the nausea persists and is troublesome and I have determined that the GLP-1 receptor agonist is the cause, I instruct the patient to take the dose of the GLP-1 receptor agonist just prior to or at the end of the meal. This may, however, reduce the magnitude of the glycemic reduction, especially the postprandial glucose. Alternatively, the total daily dose can be cut in half for two weeks or so. For example, if the dose of exenatide is 5 mcg twice daily, 5 mcg once daily can be given. If the dose is 10 mcg twice daily, 5 mcg twice daily can be given. However, the patient should be instructed to seek immediate medical attention should severe abdominal pain persist since acute pancreatitis has been reported, although it is rare. (7,29)

Question 12

Dr. Brunton: Would you have considered a DPP-4 inhibitor for this patient if the A1C had been lower?

Dr. Morales: The fact that the DPP-4 inhibitors are administered orally is an advantage, so I would have considered them if the A1C had been 7.5-7.8% or less since they generally lower the A1C 0.5% to 0.8%, although a larger decrease may be seen when the A1C is high. Although there have been no published head-to-head trials, the A1C lowering effect of the DPP-4 inhibitors appears to be less than the GLP-1 receptor agonists, which is probably due to the fact that the DPP-4 inhibitors work indirectly via endogenous GLP-1 and glucose-dependent insulinotropic polypeptide (GIP), whereas the GLP-1 receptor agonists act directly on the GLP receptor. This also may explain why the GLP-1 receptor agonists promote early satiety and reduce caloric intake, but the DPP-4 inhibitors don't. (26,27)

Question 13

Dr. Brunton: Cardiovascular risk reduction is an important treatment objective in patients with T2DM. Most glucose-lowering agents lower cardiovascular risk primarily by improving glycemic control. How does this influence treatment decisions?

Dr. Morales: Cardiovascular risk is a critical factor to consider, and must be factored into the overall management plan. Our third case is a 37 year-old obese male diagnosed with T2DM 2 years ago based upon a FPG of 185 mg/dL. Lifestyle modification lowered his A1C from 9.1% to 8.7% and his BMI from 41 to 39 kg/m2 after 1 year. Metformin was added and titrated to 2000 mg in divided doses daily. Seven months after initiating metformin, his A1C was 8.4%, while his fasting plasma and postprandial glucose levels ranged from 158-183 mg/dL and 196-229 mg/dL, respectively. Now 3 months later, his A1C is 8.3%. His physical examination revealed grade I retinopathy and blood pressure 134/84 mm Hg. His lipid profile was elevated (total cholesterol 218 mg/dL, LDL-cholesterol 136 mg/dL, HDL-cholesterol 47 mg/dL, and triglyceride 176 mg/dL).

Question 14

Dr. Brunton: Among his several problems, which would you address next?

Dr. Morales: Obesity is the central problem and must be addressed aggressively, although it may take some time before an acceptable weight can be achieved. There is evidence of retinopathy and his blood pressure is elevated, and his lipid profile is not at goal. However, because both his fasting and postprandial glucose levels are significantly elevated, I would address his glucose control and obesity initially. Because postprandial glucose contributes more to the A1C level as the A1C level declines, especially below 8.4%, simultaneously addressing fasting and postprandial glucose hyperglycemia may be prudent because therapies that target postprandial glucose will become more effective as the A1C level is reduced.

Question 15

Dr. Brunton: If we limit the drug treatment options to drugs that promote weight loss because of his obesity, only pramlintide or a GLP-1 receptor agonist are options. Pramlintide must be used in combination with insulin. Would you please compare the combination of pramlintide and insulin versus a GLP-1 receptor agonist?

Dr. Morales: The combination of pramlintide plus insulin would be expected to lower A1C, as well as both the fasting and postprandial glucose levels, from its current level to the target level of less than 7%. Exenatide alone probably wouldn't achieve an A1C less than 7% since it generally lowers A1C 0.5-1.0%. Liraglutide monotherapy might achieve the target level since it generally lowers A1C 0.5-1.5%. Preliminary evidence indicates that the addition of exenatide to insulin further lowers A1C, with a small percentage of patients achieving glycemic control while discontinuing insulin. (30,31) Insulin causes weight gain, although pramlintide alone promotes weight loss. The combination generally causes little or no weight gain. A GLP-1 receptor agonist promotes 1-4 kg weight loss. Both pramlintide and GLP-1 receptor agonist promote early satiety. Pramlintide, insulin, and GLP-1 receptor agonist all require injection, which emphasizes the importance of patient education regarding the injection devices and ultra-fine needles. While liraglutide is administered once daily, the others require multiple daily injections. Symptomatic hypoglycemia is more likely with insulin, while gastrointestinal side effects are common with pramlintide and GLP-1 receptor agonists. Taking all of these factors into account for this patient, a GLP-1 receptor agonist would be my initial choice.

Question 16

Dr. Brunton: Would you favor one GLP-1 receptor agonist over the other?

Dr. Morales: I think there are some important differences, although while exenatide is commercially available, liraglutide is under review by the US Food and Drug Administration. First, exenatide requires twice daily administration, liraglutide once daily, and exenatide LAR once weekly. Second, acute pancreatitis has been reported, although rarely, with exenatide but not liraglutide. Third, our clinical impression has been that liraglutide provided greater reduction in the blood glucose than exenatide. This has now been shown in an as yet unpublished head-to-head trial involving 464 patients with T2DM inadequately controlled with metformin, sulfonylurea, or both. Patients were randomized to either exenatide or liraglutide. Exenatide 5 mcg twice daily was administered for 4 weeks followed by 10 mcg twice daily for the duration. Liraglutide was administered once daily, 0.6 mg for 1 week followed by 1.2 mg for 1 week, then 1.8 mg for the duration. At the end of 26 weeks, the addition of liraglutide caused a significantly greater reduction in the A1C than exenatide (1.1% vs 0.8%, respectively; $P<0.0001$) from a baseline of 8.2% and 8.1%, respectively. More liraglutide patients achieved an A1C less than 7% compared with exenatide (54% vs 43%, respectively; $P=0.0015$). Also, the fasting plasma glucose level was reduced 29 mg/dL in the liraglutide group and 11 mg/dL in the exenatide group ($P<0.0001$).

Question 17

Dr. Brunton: If you were to also consider his hypertension and hyperlipidemia, would your treatment approach change?

Dr. Morales: No, I would still favor a GLP-1 receptor agonist since it improves blood pressure (independent of weight loss) and lipid profile, although not to goal. The systolic and diastolic blood pressures are reduced up to 5 mm Hg and 2 mm Hg, respectively, with exenatide (32), and the systolic blood pressure up to 8 mm Hg with liraglutide. (3,33) Both exenatide and liraglutide also reduce total and LDL-cholesterol and triglycerides, and raise HDL-cholesterol. (3,34,35) Although a GLP-1 receptor agonist should not be used with the intent to control blood pressure or lipid reduction, these benefits may be advantageous in this patient in addition to primary therapy for these disorders, such as a statin, aspirin, angiotensin converting enzyme inhibitor, or angiotensin receptor blocker.

Question 18

Dr. Brunton: Do you have any final comments regarding the role of the GLP-1 receptor agonists and DPP-4 inhibitors in the management of T2DM?

Dr. Morales: Both the GLP-1 receptor agonists and DPP-4 inhibitors exert their glycemic lowering effects by multiple, mostly unique mechanisms; consequently, they work well as monotherapy or in combination with other agents. The

weight loss promoted by the GLP-1 receptor agonists is a major benefit. The low incidence of symptomatic hypoglycemia observed with both the GLP-1 receptor agonists and DPP-4 inhibitors makes them especially useful in older adults. The beneficial effects on blood pressure and the lipid profile add to the value of the GLP-1 receptor agonists and DPP-4 inhibitors. However, the improvement of ß-cell function may be the most significant benefit, which awaits further investigation.

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