Medscape

CME

Incretin Replacement Therapy: A New Treatment Tool for Type 2 Diabetes: Shifting Paradigms in Diabetes Therapy: Applying Theory to Clinical Practice

Shifting Paradigms in Diabetes Therapy: Applying

This activity is supported by an educational grant from

Theory to Clinical Practice , Presented by Om Ganda, MD

Drug Therapy in Type 2 Diabetes

Type 2 diabetes is a progressive disease. The A1C level of a person with type 2 diabetes can worsen over time, evolving from the need for 1 oral therapy to 2, or to more, eventually moving on to insulin or a combination of oral medications and insulin. This is a manifestation of the beta-cell deficiency -- a key underlying component in the pathogenesis of type 2 diabetes -- that starts early on and progresses with time.

While fasting hyperglycemia is always on the radar screen, postprandial hyperglycemia is often overlooked, because patients tend not to check postprandial blood glucose levels often. There are times when a patient's blood glucose self-monitoring report may indicate good fasting blood glucose levels, yet their A1C is still high. In this situation, the patient should routinely check postprandial glucose levels, since A1C really reflects the total of fasting preprandial plus postprandial levels.

Aggressive therapy, particularly with insulin or sulfonylureas, can help achieve better outcomes but also heightens the risk of hypoglycemia. This risk can sometimes be an impediment to pursuing the aggressive goals that are ideal. In addition, most pharmacologic therapies that improve glycemia also tend to cause weight gain. This includes insulin, sulfonylureas, and thiazolidinediones (TZDs). In addition to these treatments that cause weight gain, a typical diet of a person with type 2 diabetes might also be a contributing factor.

Characteristics of Specific Classes of Drug Therapy

Sulfonylureas, such as glimepiride or glipizide, may provide up to a 1% to 2% reduction in A1C at the initiation of therapy,[43] although this effect will not be maintained indefinitely. Other insulin secretagogues, such as nateglinide and repaglinide, provide similar A1C reductions when correctly dosed.[44] The effect of metformin is dose-dependent, with a maximum dose achieving up to a 2% reduction in A1C.[45]

Rosiglitazone and pioglitazone, the 2 available TZDs, do not always provide the same degree of A1C reduction in monotherapy as sulfonylureas and metformin, depending on the stage of diabetes in which they are introduced. However, they are often quite effective, even as monotherapy, in earlier stages.[46]

Another class of therapy, the alpha-glucosidase inhibitors (acarbose and miglitol), if tolerated, are well-suited to improve postprandial hyperglycemia but have a modest effect on reducing A1C in monotherapy.[47] They are typically used as adjunctive therapy.

Studies show that A1C levels rise an average of 0.2% to 0.3% yearly, regardless of whether the patient is treated with diet alone, a sulfonylurea, or metformin.[6,48] This correlates with progressive loss of beta-cell function over time in most people with type 2 diabetes. It is not surprising, therefore, that most monotherapies will eventually fail to optimally control A1C levels, and combination approaches are routinely required. All pharmacologic therapies will be more effective and last longer when combined with medical nutrition therapy and appropriately prescribed physical activity. It is important to emphasize to patients that medications are not a substitute for a proper diet.

New and Emerging Treatments for People With Type 2 Diabetes

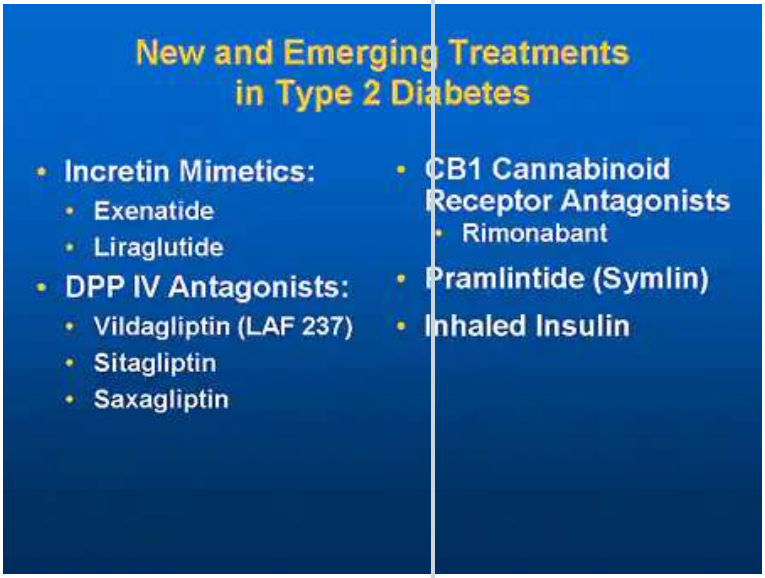
Several newly available or emerging treatments in development for people with type 2 diabetes are based on new approaches to treating the disease.

Incretin mimetics are glucagon-like peptide-1 (GLP-1) agonists. Exenatide is the one GLP-1 agonist currently approved by the U.S. Food and Drug Administration (FDA). Another GLP-1 agonist in development is liraglutide, which is a GLP-1 analog.

Dipeptidyl peptidase-IV (DPP-IV) antagonists inhibit the breakdown of GLP-1 by blocking the action of the DPP-IV enzyme and therefore raise GLP-1 (and GIP) levels 2- to 3-fold. These agents have been called incretin enhancers. Sitagliptin is the first of the DPP-IV inhibitors to have received FDA approval. Vildagliptin has completed phase 3 trials and is under review by the FDA at this writing. Other DPP-IV inhibitors are also in development.

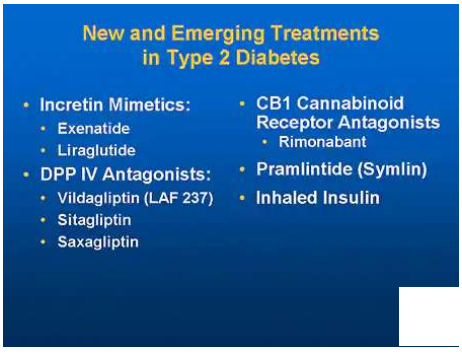
Rimonabant is a selective cannabinoid-1 receptor blocker. Placebo-controlled

[CLOSE WINDOW]



Slide 1.

New and Emerging Treatments in Type 2 Diabetes



phase 3 trials demonstrated that the addition of rimonabant to a hypocaloric diet resulted in sustained weight loss and improvements in cardiometabolic risk factors, including waist circumference, high-density lipoprotein (HDL)-cholesterol, triglycerides, glucose and measures of insulin resistance. Rimonabant has completed phase 3 clinical trials and at this writing is before the FDA.

Pramlintide, a synthetic analog of another islet hormone, amylin, represents a fifth class of therapy. Pramlintide reduces gastric emptying, suppresses glucagon and enhances satiety, and is FDA-approved for use as an adjunct to meal time insulin in people with type 1 and type 2 diabetes who have failed to achieve glycemic control, despite optimal insulin therapy.[49]

Finally, the first inhaled insulin was recently approved by the FDA.[50] Taken together, all of these new therapeutic options -- whether they are available now or in the near future -- have created a new sense of excitement and optimism in the field of diabetes care.

A New Treatment Target: Replacement of Incretin Function in the Clinical Setting

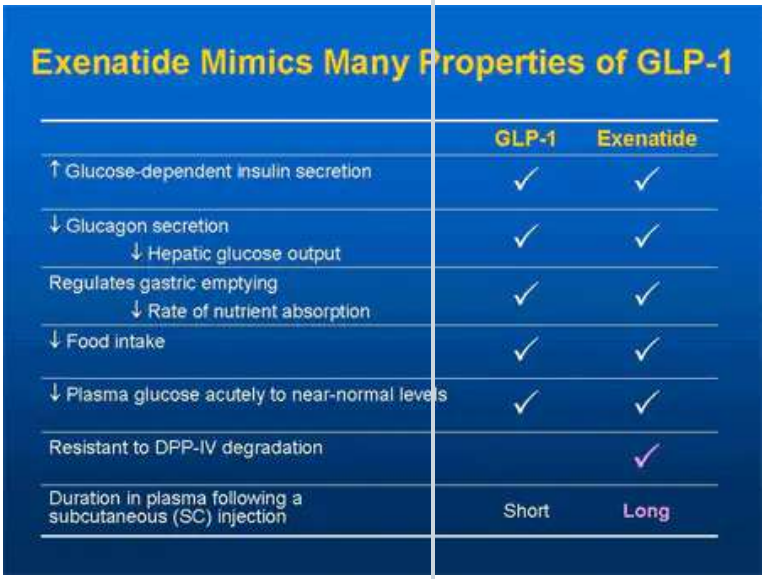
Exenatide is the first incretin-related therapy available for patients with type 2 diabetes. It is a synthetic version of a serendipitously discovered naturally occurring peptide from the saliva of the Gila monster, a type of lizard that lives in the southwest United States. This protein is similar to GLP-1, and has profound effects on stimulating insulin and inhibiting glucagon secretion, both in a glucose dependent manner. Exenatide also slows gastric emptying and enhances satiety. While human GLP-1 and this protein are not identical, there is an approximate 50% homology of various amino acids between the 2. This is sufficient in that, when administered, exenatide binds to GLP-1 receptors as if it were GLP-1.

Natural GLP-1 is degraded by DPP-IV within a few minutes. Exenatide, however, is resistant to DPP-IV inactivation because of an amino-acid substitution at position 2. Following injection, exenatide is measurably in plasma for up to 10 hours, making it suitable for twice a day administration by subcutaneous injection.[51,52]

In studies, exenatide has been shown to cause robust, glucose-dependent insulin secretion in response to a meal. Like GLP-1, it has also been shown to suppress glucagon secretion, delay gastric emptying and enhance satiety. In fact, exenatide appears to mimic most of the key antihyperglycemic properties of GLP-1.

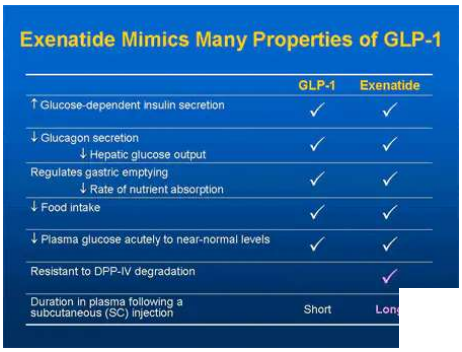
Animal studies have shown exenatide to increase expression of key beta-cell function genes and insulin biosynthesis and processing, as well as to augment beta-cell mass. Exenatide has also been demonstrated to improve first-phase insulin response and reduce the proinsulin-to-insulin ratio, both of which serve as indices of improved beta-cell function.[53-56]

[CLOSE WINDOW]



Slide 2.

Exenatide Mimics Many Properties of GLP-1

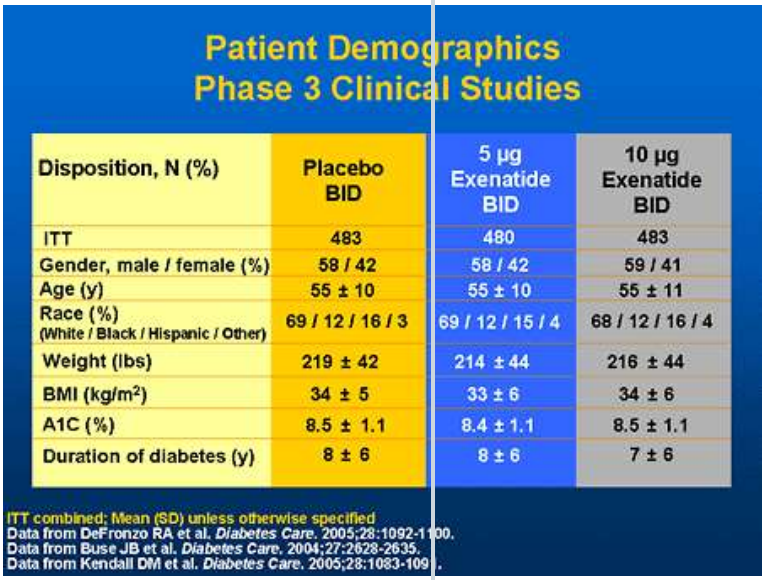


Clinical Trials of Exenatide

Three pivotal clinical trials were conducted to support the approval of exenatide. These randomized, double-blind, placebo-controlled, multicenter studies, called the AMIGO studies, recruited patients with type 2 diabetes who had not achieved adequate glycemic control despite treatment with metformin, a sulfonylurea, or the combination of metformin and a sulfonylurea. Patients were randomized to receive either placebo or exenatide after a 4-week placebo lead-in period.

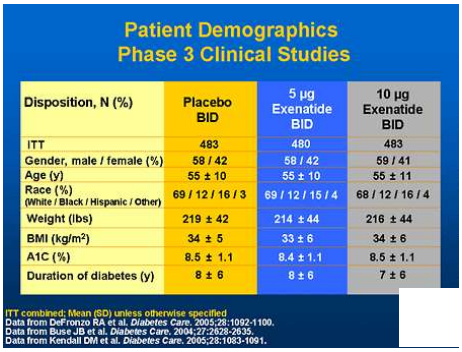
In these trials, one group received exenatide 5 micrograms (mcg) twice daily by subcutaneous injection, a second group received exenatide 10 mcg twice daily, and a third group received the corresponding placebo injection twice daily. Patients were well matched between groups in terms of gender, age, race, weight, body mass index (BMI), baseline A1C levels, and duration of diabetes.[53-55]

[CLOSE WINDOW]



Slide 3.

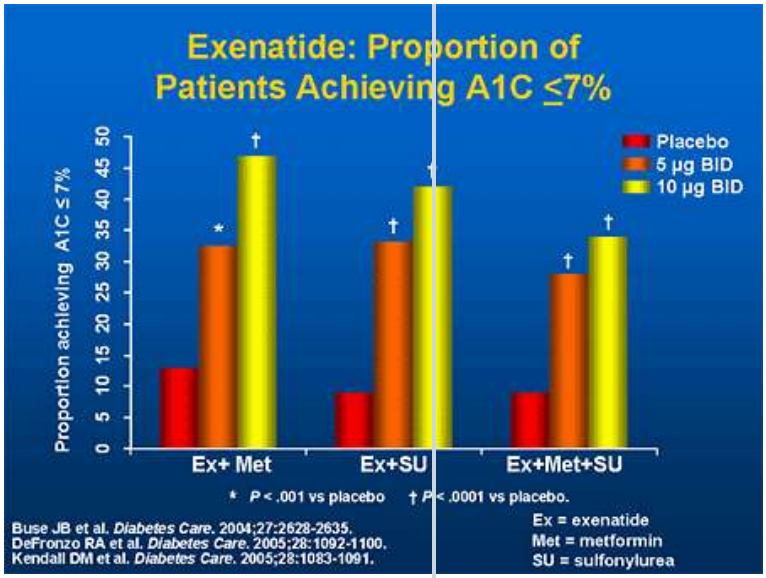
Patient Demographics: Phase 3 Clinical Studies



Exenatide produced a dose-dependent response across these trials, with 5 mcg twice daily providing a modest reduction in A1C in combination with the oral regimen, while 10 mcg produced an approximately 1 percentage point average reduction in A1C compared with placebo. In the arm that received exenatide 10 mcg twice daily in combination with oral agents, approximately 35% to 45% of patients achieved an A1C goal of less than/equal to 7.0%.

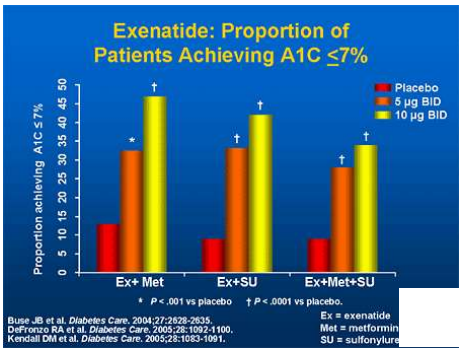
[CLOSE WINDOW]

Therefore, the current recommendation is to use exenatide at that dose, although it is also recommended that therapy be initiated at the 5-mcg twice daily dose for 1 month to reduce the occurrence of gastrointestinal side effects.[53-55]



Slide 4.

Exenatide: Proportion of Patients Achieving A1C 7%



Weight Loss and Nausea With Exenatide

One frequent, and welcomed, effect of exenatide is a reduction in body weight. After adding exenatide, the group that was on metformin alone lost about 3 kg of body weight at 30 weeks, while the sulfonylurea group (who normally might have gained some weight on sulfonylurea alone) experienced a 1.5- to 2-kg weight reduction. Patients receiving metformin and a sulfonylurea in combination along with exenatide lost an average of 2 kg. Weight loss of up to 10 kg has been documented, but it varies from person to person.[53-55]

Moreover, recently published findings have shown progressive weight loss continuing for 82 weeks. The A1C decrease from baseline to week 30 [0.9-0.1% (mean SE)] was maintained to week 82 (1.1-0.1%), with 48% of patients achieving A1C 7% at week 82. Decreased body weight from baseline at week 30 (2.1+/-0.2kg) was further decreased at week 82 (4.4+/-0.3kg).[57] As in the 30-week data set, subjects with higher BMIs lost

more weight and weight loss was greater in those who had exenatide added to metformin alone. In this study, the relationship between nausea and weight were assessed by Pearson correlation analysis, which found that the reduction in body weight was not likely to be driven by the direct effect of nausea (r ¼ 0.11).

An American Diabetes Association (ADA) Scientific Sessions poster in June 2006 revealed that a 2 open label year completer population had reductions from baseline A1C, FPG, and body weight: -1.1+/-0.1% ($P < .05$) and -25.2+/-2.8mg/dL, ($P < .05$) (mean+/-SE) and -4.7+/-0.3kg, ($P < .05$) (mean+/-SE), demonstrating further durability of glycemic effects and progressive weight loss.[58]

People with type 2 diabetes recognize that if therapy with an oral antidiabetes medication fails to achieve glycemic targets, they may need to start insulin therapy, which they also know can lead to weight gain. Thus, even though exenatide is also an injectable (twice daily) medication, people with type 2 diabetes may be more willing to take it before starting insulin therapy because of the added weight-loss benefit. However, it is not a substitute for insulin in insulin-requiring patients.

The one prominent, unwelcome side effect of exenatide is nausea. This was seen uniformly across the clinical trials, although most episodes were mild-to-moderate in intensity and generally intermittent. Nausea tended to be more frequent at the initiation of treatment and decreased over the course of several weeks. Overall, the incidence of severe nausea was low (1% for placebo, 4% for exenatide) and the dropout rate was relatively small (3%) compared with the placebo group.[59,60]

When exenatide was added to metformin, the incidence of hypoglycemia was not more common than with placebo. Hypoglycemia occurred more frequently than with placebo when exenatide was given to patients who were also on sulfonylurea therapy. Only 1 episode of the hypoglycemia was called severe (requiring the assistance of another individual) in these trials. In clinical practice, physicians may consider reducing the dose of sulfonylurea when starting exenatide.

At present, exenatide is not approved for use in combination with TZDs. However, a study examining the use of exenatide in combination with TZDs has recently been reported at the June 2006 Scientific Sessions of the ADA. Exenatide added to the regimen of patients not at goal despite treatment with a TZD alone or in combination with metformin decreased A1C by -0.8+/-0.9% from a baseline of 7.9+/-0.9% (treatment effect, -0.9%, $P < .0001$). Exenatide was associated with decreased body weight from baseline compared to PBO (-1.5+/-3.1kg vs -0.2+/-2.6kg respectively, $P < .001$).

Hypoglycemia rates were similar between exenatide and placebo treatments. As in other studies, the most common adverse event was mild to moderate nausea.

Studies of Glucagon-Like Peptide-1 Analogs and Insulin

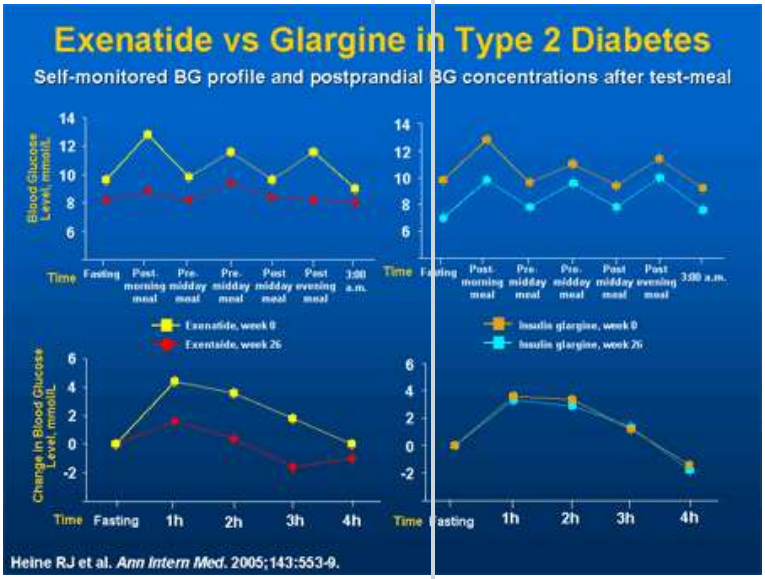
Another study of exenatide compared its effects with insulin glargine in more than 500 patients who previously had not achieved goal glycemia on oral agents. Patients had similar characteristics in both groups in terms of BMI, mean fasting glucose, A1C levels, and years of diabetes duration at baseline. In this trial, A1C levels after 6 months in both groups were comparably reduced. However, in the patients who received glargine insulin, weight increased approximately 1 kg, while weight was reduced by more than 2 kg in those who received exenatide.[61]

At the outset of therapy, blood glucose monitoring revealed that patients were experiencing fairly significant postprandial hyperglycemia after each meal. However, after 6 months of exenatide treatment, postprandial glycemia levels were significantly reduced. Meanwhile, in the glargine group, the postprandial response did not change with treatment.[61]

However, the fasting blood glucose level was reduced with insulin more than it was in patients in the exenatide group. These findings indicate that basal insulin excels at lowering fasting glucose, while exenatide appears superior at lowering postprandial blood glucose.[61]

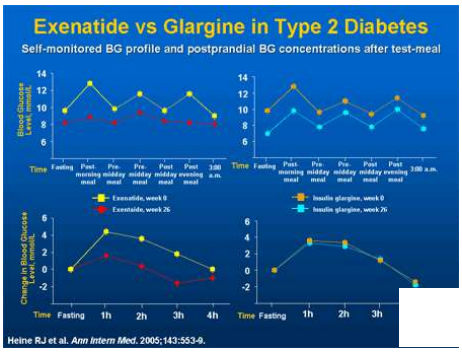
In this trial, a similar side-effect profile was observed, with a fairly high incidence of nausea (57.1% exenatide vs 8.6% insulin glargine) when all levels of severity were considered. Vomiting was also more common among exenatide patients compared with insulin glargine (17.4% vs 3.7%, respectively). The number of hypoglycemic events per patient per year was similar, probably

[CLOSE WINDOW]



Slide 5.

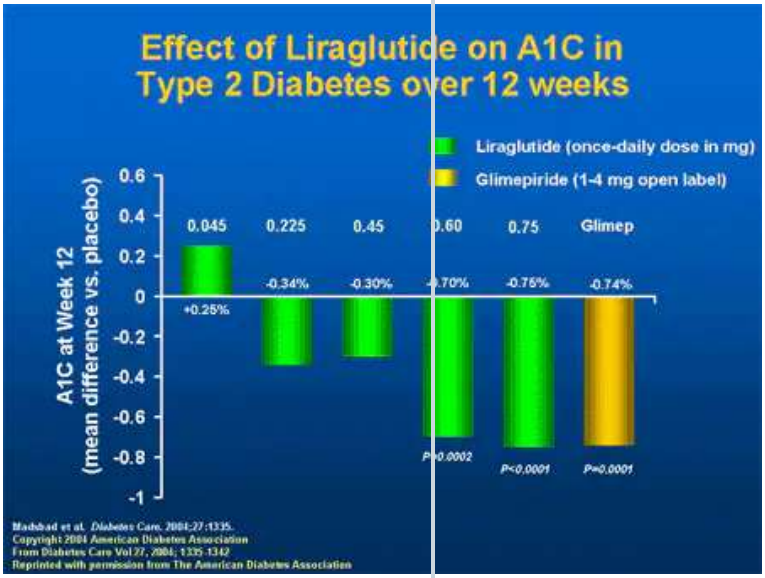
Exenatide vs Glargine in Type 2 Diabetes



because a basal insulin regimen alone was used.[61]

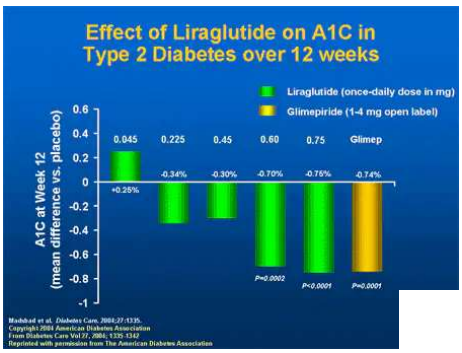
Another GLP-1 agonist is liraglutide, which appears to have an even longer half-life so it may be available as a once-daily therapy if and when it is approved. One 12-week study that compared liraglutide with glimepiride demonstrated a dose-dependent effect with the .60-mg and .75-mg dose of liraglutide resulting in a significant A1C reduction.[62]

[CLOSE WINDOW]



Slide 6.

Effect of Liraglutide on A1C in Type 2 Diabetes Over 12 Weeks



Dipeptidyl Peptidase-IV Antagonists

As stated earlier, GLP-1 is released in response to a meal and is then inactivated by the DPP-IV enzyme. The concept behind DPP-IV inhibitors is to allow the endogenous GLP-1 to remain in circulation for a longer period. This is a different approach to enhancing GLP-1 receptor activation than administering a synthetic GLP-1 agonist, such as exenatide.

DPP-IV inhibitors are oral, rather than injectable, agents like exenatide or one of the GLP-1 agonists. DPP-IV inhibitors produce a 2- to 3-fold increase

in circulating levels of active GLP-1 and GIP and as a result enhance insulin secretion and inhibit glucagon release both in a glucose dependent way.

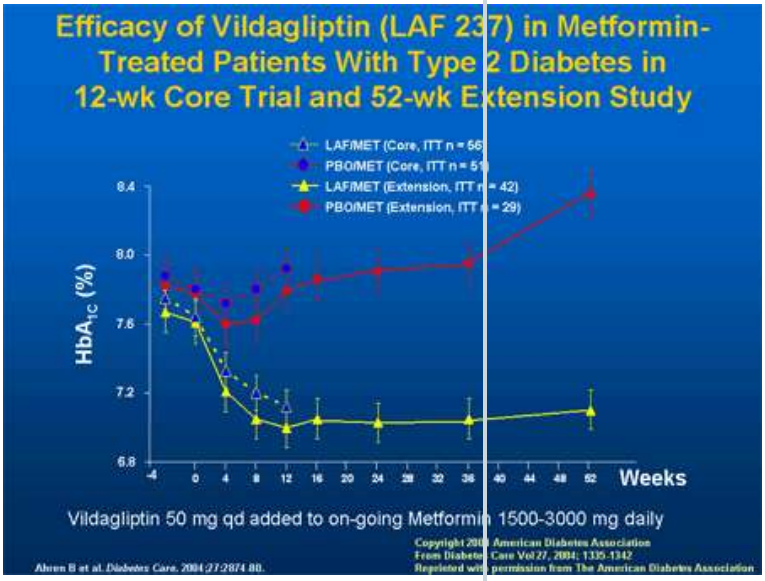
Investigations to date with DPP-IV inhibitors indicate that they are weight neutral. Their use is not associated with weight loss, as has been demonstrated with exenatide but there is not weight gain as has been observed with insulin, insulin secretagogues or thiazolidinediones. DPP-IV inhibitors have been associated with a low incidence of hypoglycemia or gastrointestinal side effects.[63] Preliminary long-term studies of DPP-IV inhibitors suggest a durable effect on glycemia and improvement in some parameters of beta-cell function (see: www.glucagon.com).

Initial Studies of Dipeptidyl Peptidase-IV Inhibitors

One short-term study of people with type 2 diabetes previously on a diet-based therapy who were given the DPP-IV inhibitor vildagliptin demonstrated a reduction in glucose levels. It also found that insulin levels remained unaffected despite the reduced glycemia, indicating an improved insulin response. GLP-1 levels increased and glucagon levels decreased.[64] This study validated the concept of DPP-IV inhibition.

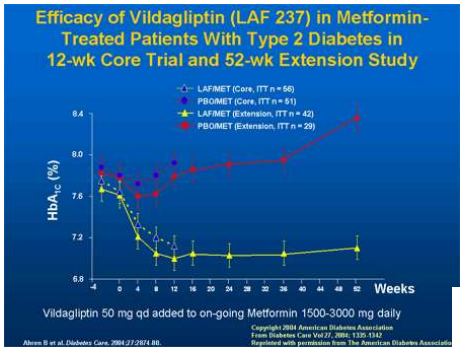
In a separate 12-week study, vildagliptin was studied in patients who were already receiving metformin. During this study, A1C levels decreased modestly but significantly in patients on this combination, while they stayed the same or rose slightly in patients receiving metformin plus placebo. Patients were then followed in an open-label extension phase for up to 1 year. In the patients receiving placebo plus metformin, A1C levels continued to rise during that period, while in those receiving vildagliptin plus metformin, the A1C reductions were maintained.[65] The A1C in vildagliptin-treated subjects was 1.1 {+/-} 0.2% ($P < .0001$) lower than in placebo patients after 1 year. Overall tolerability in vildagliptin studies has been generally comparable to placebo.

[CLOSE WINDOW]



Slide 7.

Efficacy of Vildagliptin (LAF 237) in Metformin-Treated Patients With Type 2 Diabetes in 12-Wk Core Trial and 52-Wk Extension Study



Sitagliptin, another DPP-IV inhibitor, is the first agent in this class to have received FDA approval. In a 24-week study, sitagliptin demonstrated placebo-subtracted reductions in A1C, FPG and PPG of 0.8%, 17 mg/dL and 47 mg/dL, respectively.[66] The addition of sitagliptin to ongoing metformin therapy for 24 weeks produced a significant ($P <$ .001) placebo-subtracted decrease in A1C (-0.65%), FPG (-25.4 mg/dL), and 2-hour post-meal PG (-50.6 mg/dL).[67] In another study sitagliptin added to pioglitazone resulted in placebo-subtracted reductions in A1C (-0.70%, $P <$ .001) and FPG (-17.7 mg/dL, $P <$ .001).[68]

Incidence of adverse reactions with sitagliptin in these trials was similar to placebo. Sitagliptin is indicated as monotherapy and in combination with metformin or thiazolidinediones. The usual recommended dose is 100 mg once daily.[69]

Summary

Insulin resistance, prediabetes, and type 2 diabetes have reached epidemic proportions. However, studies indicate that progression from prediabetes to type 2 diabetes can be prevented or at least delayed. Insulin resistance and a relative insulin secretory defect are key elements of the pathogenesis of type 2 diabetes. In addition, GLP-1 deficiency is another key component in diabetic pathophysiology, contributing to the insulin secretory deficit, as well as an excess of plasma glucagon and postprandial hyperglycemia. Addressing the GLP-1 deficiency is a new and physiologic approach to therapy that might help more people with type 2 diabetes get to goal.

Incretin mimetics offer a new approach in the management of type 2 diabetes. Exenatide is the first agent in this class to be available and is administered via injection twice a day. It has been approved for patients who

have suboptimal glycemic control in spite of receiving a sulfonylurea and/or metformin therapy. In addition to improving glycemic control, exenatide has the unique benefit of causing weight loss that appears to be prolonged based on initial studies. Other GLP-1 agonists are in varying stages of clinical development.

DPP-IV inhibitors can be considered insulin enhancers. They raise GLP-1 levels 2- to 3-fold. These agents appear to be weight neutral and have an incidence of adverse reactions that has been similar to placebo in clinical trials. Sitagliptin is the first of the DPP-IV inhibitors to receive FDA approval. At this writing, vildagliptin is awaiting an FDA approval decision and other DPP-IV agents are currently undergoing clinical trials.

Despite the promise of new therapies that have recently entered the market or are on the horizon, it is important to recognize that achieving glycemic control is only one of the goals for patients with type 2 diabetes. Evidence-based strategies have demonstrated that the burden of complications can be reduced not only by lowering A1C but also by attempting to achieve near normal lipid levels, particularly by getting LDL cholesterol to less than 100 mg/dL in people with diabetes, with a value of less than 70 mg/dL being a therapeutic option in any patient with documented cardiovascular disease.

In addition, the current target blood pressure goal of less than 130/80 mm Hg should be pursued in all patients with diabetes. Antiplatelet therapy is also often beneficial. Therefore, the introduction of these promising new therapies offers clinicians the possibility of achieving recommended goals in more of their patients. These approaches should be undertaken in combination not only with existing oral antidiabetes medications as indicated, but also with other proven cardiovascular risk-reduction strategies, including lifestyle reduction and pharmacologic therapy, as needed.

References

Close