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Abstract

Type 2 diabetes mellitus (T2DM) has traditionally been managed with oral medications. However, in the last few years, subcutaneous glucagon-like peptide-1 (GLP-1) receptor agonists have risen to fame. These agents serve as a reliable addition to current monotherapy. GLP-1 receptor agonists offer a significant reduction in hemoglobin A1C (HbA1c), fasting plasma glucose, and have the added benefit of weight loss. They work primarily by enhancing glucose-dependent insulin secretion while inhibiting glucagon secretion. The available GLP-1 agonists are Byetta® (exenatide), Victoza® (liraglutide), and Bydureon™ (exenatide extended-release). Studies suggest that they are similar in safety and efficacy, with the longer acting GLP-1 receptor agonists, liraglutide and extended-release exenatide, proving to be slightly more efficacious in terms of HbA1c and weight reduction. All three products have unique half-lives, dosing schedules, efficacies, side effects and contraindications.

Introduction

GLP-1 Receptor Agonists and Their Role in Therapy

Glucagon-like peptide-1 (GLP-1) receptor agonists have made a prominent appearance in the management of type 2 diabetes mellitus (T2DM) over recent years. Byetta® (exenatide), Victoza® (liraglutide), and once-weekly Bydureon™ (extended-release exenatide) are the only GLP-1 agonists currently on the market. By acting as an agonist on the GLP-1 receptor, they increase insulin secretion by pancreatic beta cells and inhibit glucagon secretion from pancreatic alpha cells.[1] GLP-1 agonists have become a popular treatment option in T2DM for their glucose and body weight lowering properties.[2] Both the American Association of Clinical Endocrinologists (AACE) and American Diabetes Association (ADA) guidelines recommend GLP-1 agonists as add-on therapy for those who do not achieve adequate control on oral monotherapy.[3,4]

GLP-1 is an incretin hormone secreted by the ileum, colon and rectum. GLP-1 is produced within minutes of ingesting food and is rapidly degraded by dipeptidyl peptidase-4 (DPP-4). The GLP-1 receptor is a G-protein coupled receptor found primarily on pancreatic alpha and beta cells. Activation of the GLP-1 receptor in the pancreas results in increased insulin secretion from beta cells and suppressed glucagon secretion from alpha cells via a second messenger signal transduction system involving cyclic adenosine monophosphate.[5] The existence of incretins was first realized when physicians noted that ingested glucose correlated to a larger and more prolonged increase in insulin compared to intravenous glucose. As seen in Table 1, GLP-1 receptor agonists also slow gastric emptying, increase satiety and acutely increase disposal of glucose in the periphery. Also, long-term use leads to pancreatic beta cell proliferation and an increase in overall insulin synthesis.[2] In patients with T2DM, the incretin effect is impaired and incretin hormone activity is reduced, thus interfering with post-prandial insulin production.[1] This is a very important finding since the incretin effect contributes to nearly two-thirds of insulin secretion in those with normal glucose tolerance. Endogenous GLP-1 undoubtedly plays a significant role in glucose homeostasis following oral glucose consumption. Endogenous GLP-1 is rapidly metabolized by DPP-4, resulting in a half-life of only one to two minutes. Therefore, much attention has been given to understanding the pharmacokinetic properties of GLP-1 receptor agonists and making them more resistant to DPP-4 degradation as a way of prolonging their half-lives.[1,6]

Clinical trials have compared the addition of either a GLP-1 agonist or insulin to oral monotherapy in those patients with inadequately controlled T2DM.[7,8,9] These studies show that adding a GLP-1 receptor agonist to oral monotherapy lowers HbA1c as much or even greater than the addition of insulin.[7,8,9]

In addition, GLP-1 agonists do not cause hypoglycemia and actually promote weight loss;[6] as such, they are used in par-

Table 1. Why Choose GLP-1 Receptor Agonists.[1,2,3,4]

Actions of GLP-1 Agonists	Advantages	Disadvantages
ACUTE • Enhances glucose-dependent insulin secretion • Inhibits glucagon secretion • Slows rate of gastric emptying • Increases satiety • May increase glucose disposal in the periphery **CHRONIC** • Stimulates insulin synthesis • Increases beta cell proliferation • Promotes resistance to apoptosis	• Weight Loss • Limited hypoglycemia • Large decrease in HbA1c	• Gastrointestinal side effects • Route of administration (injection) • High Cost • Possible acute pancreatitis • C-cell hyperplasia/ medullary thyroid tumors (liraglutide and extended-release exenatide) • Long-term safety unknown

ticular in patients at high risk of hypoglycemia or when weight loss is deemed appropriate.[10] Although GLP-1 receptor agonists do not cause hypoglycemia, they may increase the frequency of sulfonylurea-induced hypoglycemia when given in combination. Physicians should therefore consider reducing the sulfonylurea dose when initiating GLP-1 receptor agonist therapy.[11] A review article by Marre and Penfornis suggests that there may be a benefit to using GLP-1 agonists as an initial treatment for T2DM due to possible protective effects on pancreatic beta cells in addition to positive effects on cardiovascular markers, including high-density lipoprotein (HDL) levels, triglyceride levels, and diastolic blood pressure.[1]

Available Options

Byetta® (exenatide) was the first incretin mimetic to be introduced to the market in April 2005.[12] Exenatide is a synthetic form of exendin-4, which is a natural GLP-1 present in the saliva of the Gila monster.[1] It is 53 percent homologous to human GLP-1, but has a half-life of 2.4 hours as compared to the one to two minute half-life of endogenous GLP-1. Byetta® is administered subcutaneously (SQ) twice-daily, up to 60 minutes prior to breakfast and dinner (with at least six hours between the two doses), due to its ability to reduce postprandial glucose (PPG) concentrations for approximately five to eight hours.[13,14] Exenatide appears to be well-tolerated. The frequent adverse effect is nausea, which tends to subside or become less severe as treatment progresses.[11] To combat the gastrointestinal side effects, doses are initiated at 5 mcg twice-daily and titrated up to 10 mcg twice-daily in accordance with tolerability.[1,15] Exenatide is renally eliminated, therefore the product is not recommended in individuals with a CrCl < 30 mL/min.[13]

Another side effect of exenatide is immunogenicity. Anti-exenatide antibodies are reported to develop in 61 percent of patients after a 26 week administration period. High levels of anti-exenatide antibodies in patients were found to be associated with smaller mean HbA1c reductions.[16]

Victoza® (liraglutide) was approved by the Food and Drug Administration (FDA) in January 2010.[12] Liraglutide is 97 percent homologous to native human GLP-1 with only an amino acid substitution of arginine for lysine at position 35 and the addition of a fatty acid chain at position 26. These minor modifications from endogenous GLP-1 increase half-life by promoting protein binding and facilitating self-association into heptamers, thus slowing absorption and preventing DPP-4 degradation.[13,17] The extended half-life of 11 to 15 hours allows for once-daily dosing.[17] Victoza® may be administered without respect to food.[18]

Liraglutide use is contraindicated in patients with a personal or family history of medullary thyroid carcinoma or in patients with multiple endocrine neoplasia syndrome type 2. Unlike exenatide, decreased renal function has proven to have little effect on the pharmacokinetics of liraglutide, but because it is a relatively new drug caution should still be used when treating renally impaired patients.[18]

A study of the immunogenicity of liraglutide has shown the development of anti-liraglutide antibodies in 8.3 percent of patients using liraglutide 1.8 mg after a 26 week period. The presence of anti-liraglutide antibodies does not change the glycemic response to liraglutide, as evidenced by similar reductions in HbA1c in patients with and without the antibodies.[16] Although these antibodies do not seem to alter the efficacy, 40 percent of those patients developing antibodies have developed infections, most commonly upper respiratory tract infections.[18,19] The six Liraglutide Effect and Action in Diabetes (LEAD-6) trials included investigations comparing the immunogenic responses of both exenatide and liraglutide. They reported a greater immunogenic response with exenatide compared to liraglutide and concluded that this effect was due to the greater difference between amino acid sequences between exenatide and endogenous human GLP-1.

Once-weekly exenatide (Bydureon™) was approved in January 2012.[12] Bydureon™ contains the same active ingredient as the original exenatide twice-daily (Byetta®) formulation. The extended-release characteristics come from the drug being encapsulated in microspheres of medical grade poly-(D,L-lactide-co-glycolide). The exenatide-containing microspheres slowly degrade in the body following SQ injection and release the drug in a sustained-release manner. This provides for a low initial release rate while maintaining consistent therapeutic levels over a dosing interval. Bydureon™ comes as a dry powder and must be reconstituted by the patient. Both twice-daily exenatide and liraglutide come as solutions that are ready for injection. Unlike the twice-daily product, once-weekly exenatide can be taken at any time of day without regard to meals.[20] As with Victoza®, Bydureon™ is contraindicated in patients with a personal or family history of medullary thyroid carcinoma.[21]

Literature Review

Recent trials have shown that both once-weekly exenatide and once-daily liraglutide are superior to twice-daily exenatide when added to the treatment regimen of inadequately controlled type 2 diabetics.[3,19,22] Two leading studies comparing efficacy of the different GLP-1 agonists are detailed below. The first is the LEAD-6 trial, which compared exenatide administered twice-daily (Byetta®) and liraglutide (Victoza®).[19] The second is the DURATION-1 trial, which compared exenatide administered twice-daily (Byetta®) and exenatide administered once-weekly (Bydureon™).[22]

Exenatide twice-daily versus liraglutide once-daily (Byetta® versus Victoza®)[19]

Changes in HbA1c from baseline were measured in a 26 week randomized, open-label, active comparator, parallel-group, multinational trial comparing liraglutide 1.8 mg SQ once-daily to exenatide 10 μg SQ twice-daily.[19] Inclusion criteria included age between 18 and 80 years, diagnosis of T2DM, HbA1c between 7 and 11 percent, body mass index (BMI) of 45 kg/m^2 or less and no history of impaired liver or renal function, clinically significant cardiovascular disease, retinopathy or maculopathy requiring acute treatment, uncontrolled hypertension (as described by being ≥ 180/100

mmHg), or cancer, as well as having been on stable treatment with maximally tolerated doses of metformin, sulfonylurea, or both for at least three months with no previous use of insulin, exenatide or liraglutide.

After randomization, participants underwent a two-week liraglutide dose escalation period or a four-week exenatide dose escalation period followed by a 22 to 24 week maintenance period. During the maintenance period, dose reduction was not allowed and any participants who had intolerance to the required study doses were removed from the study. Exenatide was administered zero to 60 minutes before breakfast and dinner (or before each of the two main daily meals that are at least six hours or more apart), and liraglutide participants were encouraged to take liraglutide at the same time each day.

The primary efficacy endpoint was the difference in HbA1c from baseline to 26 weeks. Secondary efficacy endpoints included the proportion of patients reaching HbA1c targets, changes in fasting plasma glucose, self-measured seven-point plasma glucose profiles, β-cell function, glucagon, blood pressure and lipid profiles. Safety variables included adverse events, vital signs, electrocardiogram, biochemical and hematological measures and patient reported hypoglycemic episodes.

A total of 464 participants were randomly assigned to each treatment group. Withdrawal rates were not significantly different between the two treatment groups; the most common reason for withdrawal was adverse events. There were no statistically significant differences in baseline therapy, BMI, nationality or age. There was a statistically significant difference of race between the two treatment groups; however, it is possible that this significance was due to the small number of non-Caucasian participants in the study. The decrease in HbA1c values from baseline to week 26 was significantly greater in the liraglutide group. The proportion of participants achieving HbA1c targets was also significantly higher in the liraglutide group. Both the amount and proportion of participants experiencing weight loss were similar between the groups. Overall treatment satisfaction was reported to be significantly better in the liraglutide group; however, liraglutide was found to have more serious adverse events despite having an overall lower frequency of adverse events. The incidence of nausea was initially found to be similar between the groups, but was lower with liraglutide at week 26.[19]

It is important to note that despite these positive results, the open-label design may have affected the outcome by creating bias in the study and possibly affecting patient expectations and adherence to therapy. Additionally, the study was not properly powered to assess differences between treatments for rare clinical safety adverse events. Another issue is that the majority of participants were Caucasian. This makes it difficult to extrapolate the data to a more varied population, even though there were no significant differences in baseline characteristics of the participants. Even with the limitations to the trial, it provides a direct comparison of efficacy and safety between liraglutide and exenatide over a 26-week period. Although additional studies are needed to investigate long-term clinical benefits of liraglutide, the results show that once-daily liraglutide provides a significantly greater reduction in HbA1c and treatment satisfaction compared to twice-daily exenatide. Liraglutide was also associated with lower incidence of nausea (3 percent of treatment group) compared to exenatide (9 percent of treatment group).

Exenatide once-weekly versus twice-daily (Bydureon™ versus Byetta®)[22]

Efficacy, safety and tolerability of once-weekly and twice-daily formulations of exenatide were compared in a 303 subject randomized, comparator-controlled, open-label trial. Inclusion criteria were age of at least 16 years and diagnosis of T2DM that had been treated for at least two months prior to screening. Following the lead-in, the 295 patients remaining were divided into a 2 mg once-weekly exenatide group and a twice-daily 10 μg exenatide group. During the trial, patients self-administered exenatide after proper training. Patients did not receive instruction on nutritional or caloric restriction during the course of the study.[22]

The study tested the hypothesis that the change in HbA1c from baseline achieved with once-weekly exenatide is non-inferior to that of twice-daily exenatide at the end of 30 weeks of treatment. Secondary endpoints included safety and tolerability, analysis of fasting and PPG concentrations, body weight, fasting glucagon, fasting lipids, blood pressure, and exenatide pharmacokinetics. The proportion of patients achieving target HbA1c concentrations of 7.0 percent or less, 6.5 percent or less, and 6.0 percent or less was also recorded during the study.

Withdrawal rates during the 30 week assessment, as well as baseline demographics, were not found to be statistically significant between the groups. Both treatment groups had significant reductions in HbA1c by week six with the mean reduction being significantly greater with exenatide once-weekly after ten weeks. This trend continued through the remainder of the study. The mean difference of HbA1c levels from baseline was 1.9 for once-weekly dosing and 1.5 in twice-daily dosing. This reduction was found to be statistically significant for both groups. The HbA1c reductions were consistent across all treatment background therapies for patients in both groups, and did not notably vary with sex or age. It was also found that once-weekly dosing yielded a greater proportion of patients achieving a HbA1c level of less than 7.0 percent compared to the twice-daily dosing. Both groups experienced significant reductions in body weight. The most common adverse events in once-weekly dosing were nausea and injection site pruritus, while the most common adverse effects in twice-daily dosing were nausea and vomiting. The incidence of nausea was found to be significantly less in the once-weekly dosing. The authors concluded that both treatment regimens significantly reduced baseline HbA1c and body weight at the end of the 30 week treatment. The significantly greater reduction in HbA1c observed for once-weekly exenatide was thought to be due in part to the continuous exposure of exenatide resulting in greater sup-

pression of fasting glucagon and a corresponding reduction in fasting glucose levels. It is also possible that the open-label study biased the patients' expectations and adherence to therapy, although this bias could have potentially affected both forms of treatment. Despite this limitation, the reduction in HbA1c is consistent with a previous double-blind placebo controlled study of extended-release exenatide conducted by Kim et al. in 2007.[24]

Cost-effectiveness

As these medications are relatively new to the market and are available as brand-only products, many may question the cost-effectiveness of such treatment. According to a 2011 article coming out of Europe, the improved life-expectancy, reduced complication rates, and improved quality of life seen with liraglutide make it a cost-effective choice in comparison to twice-daily exenatide, despite the slightly higher lifetime cost.[25] There are no published studies on the cost-effectiveness of once-weekly exenatide. Despite an increased price, Bydureon™ offers even further improvements in clinical outcomes (weight loss and decreased HbA1c) and therefore may be a cost-effective alternative.

Pharmacist Counseling

Patients using GLP-1 agonists for the treatment of T2DM should be aware of their gastrointestinal side effects. Nausea, the most common side effect, typically peaks within eight weeks of treatment and usually resolves in 14 to 16 weeks.[10] Vomiting, diarrhea or decreased appetite may also occur. Those experiencing increased urination, severe abdominal pain, difficulty swallowing, breathing problems, hypoglycemia, or persistent nausea, diarrhea or dizziness should contact their physician. Patients should be counseled on the dosing regimen of their particular therapy. Diet, exercise, glucose monitoring and regular lab testing should be a part of the treatment regimen for all T2DM patients. If a patient misses a dose of Byetta® or Victoza®, they should skip that dose and take the next dose at the normally scheduled time. Doses should not be doubled. [14,18] If a dose of Bydureon™ is missed, it should be taken as soon as possible unless the next regularly scheduled dose is less than three days away. In other words, two doses of Bydureon™ should not be administered within a three day period.[21]

The Future and Investigational Drugs

A once-monthly formulation of exenatide is currently being developed. Phase 3 clinical trials are currently in consideration, although side effects and dosing concerns have been raised.[12] There are several other GLP-1 agonists in the late stages of development. These include lixisenatide, dulaglutide, albiglutide and taspoglutide. Albiglutide is unique in that it is a recombinant GLP-1/albumin conjugate. It is conjugated with albumin to yield a longer half-life than Victoza® and Byetta®.[2]

Conclusion

Since the introduction of Byetta® in 2005, GLP-1 receptor agonists have become an increasingly popular therapy option in the maintenance of T2DM. The class has a great deal to offer with proven efficacy in lowering fasting plasma glucose and HbA1c as well as minimal side effects and weight loss. Although all three products are similar in their safety and efficacy profiles, studies suggest that liraglutide and extended-release exenatide are more effective in lowering HbA1c and body weight compared to twice-daily exenatide. Extended release exenatide offers the additional benefit of only being administered once-weekly perhaps improving patient compliance and improved drug-related outcomes. The GLP-1 receptor agonists have demonstrated significant therapeutic benefits when added to the medication regimen of type 2 diabetics inadequately controlled on initial monotherapy options.

Table 2. Approved GLP-1 Agonists.[11,14,15,18,19,21,22,23]

	Exenatide (Byetta®)	Exenatide (Bydureon™)	Liraglutide (Victoza®)
Half-life	2.4 hours	2.4 hours, with sustained release of drug from microspheres	11-15 hours
Dosing Interval	BID	Once-weekly	QD
Decrease in HbA1c	0.8-1.1	1.9	1.1-1.6
Decrease in Fasting BG (mmol/L)	1.16	2.12	1.82
Side effects	Nausea (lessens with time) Headache Diarrhea Anti-exenatide antibodies Pancreatitis	Nausea (lessens with time) Headache Diarrhea Anti-exenatide antibodies Pancreatitis	Nausea (lessens with time) Headache Diarrhea Anti-liraglutide antibodies Infections Pancreatitis
Black Box Warnings	None	Dose and duration dependent thyroid C-cell tumors observed in animal studies	Dose and duration dependent thyroid C-cell tumors observed in animal studies
Weight-loss (lbs.)	4.5	5.3	5

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