Weekly Exenatide Therapy: A Real-World Comparison of Incretin Therapies

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Abstract

Background: Traditional diabetes therapies have been associated with weight gain, hypoglycemia, and/or high secondary failure rates. Glucagon-like peptide-1 (GLP-1) analog use is associated with a minimal risk of hypoglycemia, a persistent average weight loss of 2 to 3 kg, and sustained efficacy even after 3 years of use. Presently, 3 GLP-1 analogs are commercially available in the United States. **Objective:** To evaluate the real-world clinical utility of once weekly exenatide in type 2 diabetes mellitus (T2DM) patients who previously received once or twice daily GLP-1 therapy. **Methods:** In this pre-post observational study, electronic medical records (EMRs) were reviewed to identify patients meeting all study criteria. Data collected included baseline patient demographic information, duration of diabetes, disease states, medications, pertinent laboratory data, blood pressure, height, weight, and reported adverse drug events. Primary (changes in A1C and percentage of patients reporting adverse effects of therapy) and secondary (percentage of patients with A1C of <7% and changes in weight, blood pressure, and lipids) outcomes were evaluated using appropriate statistical analysis. **Results:** EMRs of 78 patients met all study criteria. Baseline patient demographic information included an average age of 61 ± 12 years, an average duration of T2DM of 14 ± 6 years, 59% of patients were male, and 93.6% were Caucasian. The baseline average body mass index was 39 ± 9.2 , and mean A1C was $7.47 \pm 1.45\%$. After a minimum of 3 months (average = 5.6 months) switchover, there were significant decreases in A1C (-0.35% ; $P = .0067$) and weight (-1.6 kg; $P = .0151$). There were no significant changes in blood pressure or lipid levels. Two patients (2.5%) discontinued once weekly exenatide due to adverse reactions. **Conclusion:** Once weekly exenatide was generally well tolerated and significantly reduced A1C levels and body weight in patients with T2DM when switched from a shorter-acting GLP-1 analog.

Keywords

diabetes mellitus, exenatide, liraglutide, incretin mimetic, GLP-1 analog

Introduction

Diabetes affects almost 26 million Americans, with an estimated additional 79 million Americans with prediabetes.¹ Type 2 diabetes mellitus (T2DM) represents about 95% of diabetes cases and is often associated with obesity, hypertension, and dyslipidemia, abnormalities that contribute to the microvascular and macrovascular complications often seen with the disease. Traditional diabetes therapies such as insulin, sulfonylureas, and/or metformin have been associated with weight gain, hypoglycemia, and/or high secondary failure rates, characteristics that may also be associated with increased cardiovascular risk.²

Glucagon-like peptide-1 (GLP-1) analogs are a relatively new class of diabetes medication that act by multiple mechanisms, including stimulation of insulin secretion and inhibition of glucagon secretion in glucose-dependent manners, slowing

of gastrointestinal motility thereby blunting postprandial hyperglycemia, and increased satiety resulting in a reduction of food intake.^{3,4} In vitro studies and animal models have identified GLP-1 analogs' ability to increase β -cell proliferation.^{5,6}

Clinical use of GLP-1 analogs is associated with a minimal risk of hypoglycemia, a persistent average weight loss of 2 to 3 kg, and sustained efficacy even after 3 years of

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use.^{7,8} GLP-1 analog use has also been associated with improved lipid profiles, lower blood pressure, and decreased weight, all surrogate markers for cardiovascular risk.⁹⁻¹¹ In addition, GLP-1 therapy is associated with greater reductions in hemoglobin A1C and body weight compared with the dipeptidyl peptidase-4 inhibitors.^{12,13} Longer-acting GLP-1 analogs have been associated with better glycemic control and patient tolerability compared with the use of shorter-acting GLP-1 analogs.^{7,14,15} Significant improvements in overall treatment satisfaction have been reported in patients switched from twice-daily to weekly therapy.¹⁶ Alternatively, once daily liraglutide and once weekly exenatide (unlike twice daily exenatide) have box warnings regarding use in patients with personal or family history of medullary thyroid carcinoma and in patients with personal or family history of multiple endocrine neoplasia syndrome type 2. The Food and Drug Administration is also investigating reports of pancreatic toxicity with all incretin therapies.

Historically, twice daily exenatide use has been associated with A1C reductions of 0.8% to 1.5%. Liraglutide use has been associated with A1C reductions of 1% to 1.5%, and weekly exenatide with A1C reductions of 1.3% to 1.9%. The DURATION-1 and DURATION-5 studies demonstrated significantly greater glucose control with weekly exenatide compared with twice daily therapy. In the head-to-head DURATION-6 study, liraglutide use was associated with a 1.5% A1C reduction, compared with 1.3% with weekly exenatide, but was associated with roughly twice the incidence of gastrointestinal side effects and study dropout rate.¹⁷

The goal of this study was to assess the efficacy and safety of once weekly exenatide in patients with T2DM previously receiving once or twice daily GLP-1 therapy.

Methods

Research Design and Data Collection

This is a pre-post observational study that assessed the efficacy and tolerability of once weekly exenatide in a group of T2DM patients from a private endocrinology practice who were switched from once daily liraglutide or twice daily exenatide. The study protocol was approved by the Albany College of Pharmacy and Health Sciences Institutional Review Board. A computerized text search of the medication and problem lists of patient electronic medical records (EMRs) was used to identify potential subjects. Search terms included exenatide, liraglutide, type 2 diabetes, Byetta, Victoza, and Bydureon. Individual records of identified patients were reviewed to ascertain if all applicable study criteria were met. Inclusion criteria included age between 18 and 95 years, documented diagnosis of T2DM, use of twice daily exenatide or daily liraglutide for a

minimum of 3 months prior to switch, and use of weekly exenatide for a minimum of 3 months. Exclusion criteria included patients with any additions or deletions of other diabetes medications (other than allowance of downward titration of insulin doses) and patients receiving medications for weight loss.

A data collection form was used to collect the following patient information: baseline patient demographic information (age, gender, race), duration of diabetes, medical history, current medications, laboratory data (A1C, cholesterol profile), blood pressure, height, weight, and reported adverse drug events. Drug efficacy was evaluated by a comparison of A1C levels, weight, blood pressure, and cholesterol profiles of patients on daily liraglutide or twice daily exenatide therapy with subsequent values 3 months or greater after initiation of once weekly exenatide. Drug safety was evaluated by review of documented reports of drug side effects.

Primary outcomes were changes in A1C and the percentage of patients reporting adverse effects of therapy. Secondary outcomes included percentage of patients achieving an A1C of <7%, change in weight, changes in systolic and diastolic blood pressures, and changes in lipid parameters (total cholesterol, low-density lipoprotein cholesterol, high-density lipoprotein cholesterol, and triglycerides). A subset evaluation of patient response based on original GLP-1 analog was also performed.

Statistical Analysis

Statistical analysis was completed by using paired and 1-sample *t* tests, as appropriate. *P* values <.05 were considered statistically significant.

Results

The computerized text search of EMRs identified 78 patients who met all study criteria. The study population baseline demographics are listed in Table 1. Overall, this was a primarily middle-aged, morbidly obese, Caucasian population, with an average duration of diabetes of 14 years. At baseline, 98.7% of patients were receiving lipid lowering agents and 91% were receiving antihypertensive therapy, while 55.1% of patients in the study received insulin at baseline (including 33.3% who were on basal insulin only and 21.8% who received basal and prandial insulin). A history of microvascular complications were documented in 56.4% of the study population while 32% of patients had a history of macrovascular disease. At baseline, two thirds of the study population previously received twice daily exenatide (88.5% at 10 µg BID) while one third were taking liraglutide (92.3% at 1.8 mg daily) at baseline. The average duration of previously received GLP-1 therapy was 39

months (47 months for twice daily exenatide and 16 months for liraglutide). Patients were switched from their previous GLP-1 therapy for compliance reasons, and in the hopes of improved tolerability and/or increased efficacy.

In addition to their GLP-1 mimetic therapy, patients in this study received an average of 1.8 ± 0.8 other diabetes medications (median = 2, range = 0-4). Table 1 lists the different classes of diabetes medications used by the study population. Use of insulin secretagogue therapy was uncommon; in contrast, two thirds of the population received concomitant metformin and almost half received pioglitazone.

Patients in this study received an average of 1.9 ± 1.1 blood pressure medications (median = 2, range = 0-5) and 1.5 ± 0.7 lipid-lowering medications (median = 1, range = 1-4). Over 92% of patients received an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker therapy, while 95% were on statin therapy. Overall, blood pressure and lipids at baseline were very well controlled (Table 1).

The average duration of weekly exenatide use at the time of follow-up was 5.6 months (range = 3-9 months). At this time, there was a significant 0.35% ($P = .0067$) reduction in A1C (Figure 1). There was no statistically significant difference in the percentage of patients achieving an A1C of less than 7% (46.5% vs 53.5%). There was a significant 1.6 kg ($P = .0151$) weight loss at follow-up compared with baseline. Subgroup analysis found no differences in A1C or weight response based on original GLP-1 analog therapy. No significant differences were found between the 2 groups regarding blood pressure or lipids. Table 2 lists the change, 95% confidence intervals, and p values for all study primary and secondary outcomes analyses.

At baseline, 43 of 78 patients were receiving insulin therapy including 26 patients who used once daily basal insulin only. Overall, patients used an average of 62 ± 80 units of insulin per day, via an average of 1.9 ± 1.3 doses (median = 1 dose, range = 1-5 doses) per day. Overall, there were no significant changes in insulin use with the change of incretin therapy ($P = .3212$ for change in total short-acting insulin dose and $P = .2798$ for change in long-acting insulin dose). A subgroup analysis did identify a trend of a decrease in long-acting insulin doses in the group originally receiving twice daily exenatide and a trend of increased long-acting insulin dose in the group originally receiving liraglutide; however, neither proved statistically significant.

Two of the 78 patients (2.6%) discontinued weekly exenatide due to adverse reactions. One patient reported a rash while there was no documentation of the specific adverse effect in the second case. There were no reports of pancreatitis, acute renal, or hypoglycemic events.

Table 1. Patient Demographics and Baseline Characteristics.

Patient population (n)	78
Mean age (years)	61 ± 12
Mean duration of T2DM (years)	14 ± 6
Gender (%)	
Male	59
Female	41
Race (%)	
Caucasian	93.6
African American	3.8
Asian	2.7
BMI (kg/m^2)	39 ± 9.2
Disease states/DM complications (%)	
Hypertension	91
Dyslipidemia	98.7
Microvascular disease	56.4
Macrovascular disease	32
Diabetes medications (%)	
Metformin	62.8
Sulfonylurea	7.7
Meglitinide	2.6
Thiazolidinedione	47.4
Insulin	55.1
Hypertensive medications (%)	
ACEI	43.6
ARB	48.7
Diuretic	42.3
Calcium channel blocker	21.8
Beta-blocker	26.9
Aldosterone antagonist	2.6
Alpha-/beta-blocker	2.6
Lipid medications (%)	
Statin	94.9
Fibrate	6.4
Niacin	15.4
Bile acid sequestrant	6.4
Ezetimibe	14.1
Fish oil	12.8
A1C (%)	7.47 ± 1.45
BP (mm Hg)	
SBP	121 ± 8
DBP	72 ± 4
Cholesterol (mg/dL)	
TC	150 ± 36
TG	139 ± 102
HDL-C	53 ± 17
LDL-C	69 ± 28

Abbreviations: A1C, glycosylated hemoglobin; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BMI, body mass index; BP, blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; T2DM, type 2 diabetes mellitus; TC, total cholesterol; TG, triglycerides.

Table 2. Primary and Secondary Outcomes.

Primary Outcomes	Change, 95% CI	P values
Change in A1C	-0.35 (0.10, 0.60)	.0067
% of patients reporting adverse effects	2.6%	
Secondary Outcomes	Change, 95% CI	P values
% of patients with A1C <7%,	-8.4 (-24.9, 8.0)	.4014
Change in weight	1.6 (0.3, 2.9)	.0151
Change in blood pressure		
SBP	11 (-2.7, 2.5)	.9656
DBP	0.8 (-1.0, 2.5)	.3841
Changes in lipid parameters		
TC	2.2 (-4.9, 9.3)	.5378
LDL-C	2.0 (-4.4, 8.4)	.5361
HDL-C	-1.5 (-3.9, 1.0)	.2355
TG's	8.6 (-11.8, 29.0)	.4039

Abbreviations: A1C, glycosylated hemoglobin; BP, blood pressure; DBP, diastolic blood pressure; HDL-C, high-density lipoprotein cholesterol; LDL-C, low-density lipoprotein cholesterol; SBP, systolic blood pressure; TC, total cholesterol; TG, triglycerides.

Figure 1. A1C at baseline and follow-up.

Discussion

This is the first reported observational study regarding the real-world safety and efficacy of switching patients from a shorter acting GLP-1 analog to a once-weekly GLP-1 analog. Patients receiving weekly exenatide demonstrated significantly improved glycemic control and weight loss compared with when taking shorter-acting agents. Unequivocal evidence exist that microvascular and neurological complications of type 1 and type 2 diabetes can be prevented and their progression slowed with improved glycemic control.¹⁸⁻²¹ For example, the United Kingdom Prospective Diabetes Study demonstrated a 37% decline in risk for microvascular complications and a 21% reduction in risk for any diabetes-related end point and diabetes-related death for every 1% decrease in A1C.²²

This study demonstrated that patients receiving twice daily exenatide or once daily liraglutide had a further 0.35% reduction in A1C when switched to once weekly exenatide therapy. A subanalysis found no differences in A1C response based on original GLP-1 analog therapy. Drucker and colleagues found an additional A1C reduction of 0.33% with weekly exenatide compared to twice daily therapy in a 30-week study.¹¹ In contrast, Buse et al reported a 0.21% greater A1C reduction with once daily liraglutide in the only published head-to-head study with once weekly exenatide.¹⁷ To date, randomized controlled studies have reported A1C reductions ranging from 1% to 1.5% with liraglutide and 1.3% to 1.9% with weekly exenatide. The additional A1C lowering seen in our results could be reflective of this range in typical glycemic response, or perhaps it reflects the potential benefit of a more convenient dosing regimen when used in a real-world (ie, nonresearch) setting. While compliance was not evaluated in this study, less missed doses using a medication with a more convenient dosing regimen could explain the improved results demonstrated in this study.

This study found no greater percentage of patients reaching an A1C of less than 7% at follow-up (53.5%) compared to baseline (46.5%). Drucker et al reported that a significantly greater percentage of patients receiving once weekly exenatide achieved an A1C of less than 7% compared with patients receiving the twice daily formulation.¹¹ Likewise, Buse et al reported that significantly more patients treated with once daily liraglutide (60%) compared with patients treated with once weekly exenatide (53%; $P = .0011$) achieved an A1C of less than 7%.¹⁷ These studies were in incretin-naïve patients, however, whereas patients in this study had been receiving incretin therapy for an average of more than 3 years. A larger study population and a longer duration of follow-up might possibly have demonstrated a

statistically significant difference in the percentage of patients achieving an A1C of less than 7%.

GLP-1 mimetics are often used in the management of T2DM because of their efficacy and low risk of hypoglycemia. They are also chosen for their beneficial effects on weight. Rather than the weight gain commonly seen with insulin, sulfonylurea, and thiazolidinedione therapies, studies involving GLP-1 mimetics have reported an average weight loss of 2 to 3 kg.^{7,11,15} This study demonstrated a significant additional mean 1.6 kg weight loss in patients switched from shorter-acting GLP-1 agents to weekly exenatide ($P = .015$). The reason for this additional weight loss is unknown. Comparison studies of twice daily versus once weekly exenatide and daily liraglutide versus twice daily exenatide have demonstrated comparable effects on weight loss, while Buse et al reported an additional mean 0.9 kg weight loss in the liraglutide group compared with weekly exenatide in the DURATION-6 study.¹⁷ Perhaps improved compliance with a weekly regimen resulted in the further weight loss. Regardless, weight loss is generally regarded as a positive effect with the potential of improving cardiovascular risk.

No significant changes in lipid levels or blood pressure were seen in this study. DURATION-6 found that patients receiving liraglutide once daily and exenatide once weekly had comparable improvements in blood pressure and lipid levels.¹⁷ Clinically significant differences in lipid and blood pressure levels were reported in the second stage of the DURATION-1 study when patients were switched from twice daily to weekly exenatide therapy.⁷ The fact that our study population was not GLP-1 drug naïve and the overall excellent control of lipids and blood pressure at baseline may explain the lack of effect seen in this study. Improved metabolic control could potentially result in improved cardiovascular outcomes. The effect of weekly exenatide (Exenatide Study of Cardiovascular Event Lowering [EXSCLE], ClinicalTrials.gov NCT01144338) and daily liraglutide (Liraglutide Effect and Action in Diabetes: Evaluation of Cardiovascular Outcome Results [LEADER], NCT01179048) on cardiovascular events is currently being examined in prospective, long-term outcomes studies.

Overall, weekly exenatide therapy was well tolerated, with only 2 patients (2.6%) discontinuing therapy. The highest incidence of side effects related to GLP-1 analog therapy is typically gastrointestinal in nature. Controlled clinical trials have demonstrated that weekly exenatide is associated with approximately half of the gastrointestinal side effects compared with liraglutide, which has approximately half the rate of gastrointestinal side effects compared with twice daily exenatide therapy. One must keep in mind that patients in this study represented a highly select patient population as participants had already demonstrated the ability to tolerate shorter-acting GLP-1 analog therapy. One of the 2 discontinuations of weekly exenatide was due to a reported rash at the site of injection. This adverse is thought to be due to the poly-(D,L-lactide-co-glycolide) component of the slow release formulation.²³

Though weekly exenatide therapy is not approved for use with insulin, 55% of our study population was concurrently receiving insulin therapy. Several studies have evaluated the addition of twice daily exenatide to basal insulin therapy and have reported reductions in insulin doses.²⁴⁻²⁸ While there appeared to be a slight decrease in mean long-acting insulin dose for patients who received twice daily exenatide at baseline (40.2 ± 23.3 units to 38.6 ± 24.6 units) and a slight increase in mean basal insulin dose for patients who received liraglutide at baseline (46.8 ± 52.7 units to 48.6 ± 42.1 units), these differences were not statistically significant. In general, longer-acting GLP-1 analogs have greater effects on fasting blood sugars compared to shorter-acting agents, which demonstrate greater effects on postprandial glucose levels.⁷

There are several limitations to this study. First, cause and effect cannot be established as this was not a prospective study. For example, this study did not control for diet, exercise, or frequency of glucose monitoring, all of which could affect glucose control. Second, the sample size was small; significant changes in other outcomes may have been demonstrated with a larger sample size. Third, this study did not assess patient compliance. Greater convenience with subsequent improved compliance in a real-world (nonstudy) setting with a once weekly therapy could mean less missed doses compared with once or twice daily therapies, and could potentially explain the beneficial changes in A1C and weight reported in this study. Fourth, this study consisted of a relative homogenous patient population, consisting of a predominately white (93.6%), middle-aged (61 ± 12 years old) population of patients with long-standing (14 ± 6 years) diabetes. It is possible that the results demonstrated here may not be reflective of other, more diverse patient populations. Fifth, the relatively short duration of follow-up, especially for patients with 3-month follow-ups, may underestimate the results seen in this switch study. Weekly exenatide contains exenatide encapsulated in microspheres of a dissolvable matrix, which release active drug slowly and continuously into the circulation following subcutaneous injection. Plasma exenatide concentrations rise over time with steady-state levels reached only after approximately 6 to 7 weeks.²⁹ Finally, as data were collected by review of EMR, only documented adverse effects were captured. It is possible that more adverse effects occurred than were reported.

In summary, patients switched to longer-acting incretin mimetic therapy demonstrated improvement in glycemic and weight control compared with when they were receiving once or twice daily incretin therapy. Overall, therapy was well tolerated with a 2.6% discontinuation rate.

Conclusion

In this pre-post observational study, once weekly exenatide was associated with additional A1C and weight reductions in patients originally managed with shorter acting GLP-1 analogs. Overall, once weekly exenatide was well tolerated.

Based on these results, it is possible that other patients currently receiving once or twice daily GLP-1 therapy may see additional improvements in A1C and weight if switched to weekly GLP-1 therapy.

Authors' Note

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Declaration of Conflicting Interests

The author(s) declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: Michael P. Kane, PharmD, FCCP, BCPS, BCACP, received an investigator-initiated grant from Bristol Myers Squibb Company, makers of Bydureon, for the conduction of this study. Robert S. Busch, MD, has received speaking honoraria from Bristol Myers Squibb. Sara J Micale, PharmD, Shahab Khatounabadi, Gary Bakst, MD, Jill M. Abelseth, MD, and Robert A. Hamilton, PharmD, MPH, report no relevant conflicts of interest.

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