REVIEW

The Clinical Efficacy and Safety of Glucagon-Like Peptide-1 (GLP-1) Agonists in Adults with Type 2 Diabetes Mellitus

Kira R. Brice and Maria K. Tzefos

Wingate University School of Pharmacy, Campus Box 3087, Wingate, NC 28174, USA.
Corresponding author email: k.brice@wingate.edu

Abstract

Objective: To review the efficacy and safety of glucagon-like peptide-1 (GLP-1) agonists to determine their role in type 2 diabetes mellitus (T2DM).

Data sources: A Medline search was conducted using the keywords exenatide, liraglutide, glucagon-like peptide-1, type 2 diabetes mellitus, hyperglycemia, pharmacokinetics, pharmacology and safety.

Study selection: All identified articles written in English were evaluated with priority given to controlled, randomized trials including human data. References of identified published trials were reviewed for additional trials to be included in the review.

Data synthesis: Exenatide and liraglutide are GLP-1 agonists approved for the treatment of T2DM. Several randomized, active and placebo controlled trials examining the efficacy and safety of exenatide and liraglutide both as monotherapy and in combination therapy have been conducted. Both agents have demonstrated improved glycemic control in addition to weight loss and increased beta-cell function. The most common adverse effects are gastrointestinal in nature and appear to be transient.

Conclusion: It appears exenatide and liraglutide are safe and effective in the treatment of T2DM and may exhibit effects that make them preferred over other anti-diabetic medications.

Keywords: type 2 diabetes mellitus, glucagon-like peptide-1, exenatide, liraglutide

Introduction

Type 2 diabetes mellitus (T2DM) is characterized by elevated blood glucose (BG) levels related to decreased insulin secretion and increased insulin resistance. Aggressive management of BG has been shown to reduce the risk of diabetes-related complications; however, many patients still do not reach target BG and hemoglobin A1c (A1c) values.[1,2] Glucagon-like peptide-1 (GLP-1) has been studied more frequently as a novel treatment option for T2DM due to its role in glucose homeostasis and insulin secretion. GLP-1 is an incretin hormone released from the intestine in response to ingestion of food.[3–5] The release of GLP-1 causes increased glucose-dependent insulin secretion, decreased glucagon secretion and slowed gastric emptying in healthy patients; however, these effects are blunted in patients with T2DM potentially contributing to hyperglycemia.[3,4,6,7]

In trials examining the potential of GLP-1 as a treatment option, it was found that administration of exogenous GLP-1 in patients with T2DM lowered fasting plasma glucose (FPG) and increased insulin and c-peptide levels.[8–10] Furthermore, once normal FPG levels were reached, glucose stabilized while insulin and c-peptide decreased.[8] This observation indicated a glucose-dependent response and reduced risk for hypoglycemia. While these trials showed promise, the duration of effect on BG, insulin and c-peptide after a single subcutaneous (SC) injection was limited to only 240, 120 and 180 minutes, respectively.[10] This limited effect is attributed to degradation of GLP-1 by the enzyme, dipeptidyl peptidase IV (DPP-IV) which rapidly breaks down both endogenous and exogenous GLP-1 within minutes.[3,11] The rapid degradation of GLP-1 limited its utility as a treatment option as multiple injections or a continuous infusion would be required to produce a consistent effect. As this may not be practical for chronic use, the development of new molecules that mimic GLP-1 or the modification of the native GLP-1 hormone was needed to reduce DPP-IV degradation and extend the half-life.

The discovery of exendin-4 was a breakthrough in the development of GLP-1 therapy. Exendin-4 is a molecule that was found to have similar effects to GLP-1 but was resistant to DPP-IV degradation. This molecule became the active ingredient in the first available incretin mimetic, exenatide (Byetta®).[11] A second agent, liraglutide (Victoza®), took advantage of modifications to native GLP-1 that resulted in an increased half-life of the GLP-1 molecule.[11] This review will examine the clinical efficacy and safety of the two approved GLP-1 agonists, exenatide and liraglutide (clinical trials summarized in Table 1).

Clinical Pharmacology
Exenatide

Exenatide exhibits its glucose lowering effects by stimulating insulin secretion and decreasing glucagon secretion in a glucose dependent fashion. Other effects include delayed gastric emptying, increased satiety, and reduced food intake.[12] Exenatide is a synthetic form of the 39-amino acid peptide exendin-4.[12] Fifty-three percent of exendin-4 amino acid sequence overlaps with that of human GLP-1.[12] In vitro trials have shown exenatide to bind and activate the pancreatic GLP-1 receptor.[12,13] Clinical trials assessing the pharmacokinetics and pharmacodynamics of exenatide observed dose-dependent increases in concentrations following SC administration.[12,13] Maximum concentrations (C_{max}) were observed between 2–3 hours with a C_{max} of 211 mg/mL, and a mean half life ranged between 3.3 to 4.0 hours.[12,13] Post-prandial glucose (PPG) concentrations were reduced for about 5–8 hours following SC injection, which lends to the recommendation for exenatide to be dosed twice daily (BID).[12,13] Exenatide is primarily eliminated renally and is not recommended in patients with end-stage renal disease (ESRD) or severe renal impairment (creatinine clearance [CrCl] <30 ml/min).[12,13] Further, it does not appear that race, age, body mass index (BMI), or gender affects the pharmacokinetic properties of exenatide.[13]

Liraglutide

Similarly to exenatide, liraglutide decreases FPG and PPG, increases insulin secretion rates, and increases insulin concentrations in a glucose-dependent response.[14–20] In addition, liraglutide has also been shown to improve β-cell function, decrease glucagon levels, and delay gastric emptying.[14–18,20–23]

Liraglutide is a GLP-1 analog that is 97% homologous to native GLP-1; however, it contains modifications including an amino acid substitution of arginine for lysine at position 35 and the addition of a fatty acid chain at position 26.[24] These modifications can increase the half-life of the molecule by delaying

Table 1. Summary of exenatide and liraglutide randomized controlled trials.

Study	# of pts (n)	Study duration	Baseline therapy	Intervention	Change in A1c (%)	Patients reaching A1c < 7% (%)	Change in body weight (kg)
Exenatide							
Moretto[31]	232	24 wks	Drug-naive	Exenatide 5 mcg BID	−0.7	48	−2.8
				Exenatide 10 mcg BID	−0.9	46	−3.1
				Placebo	−0.2	29	−1.4
Buse[32]	377	30 wks	SU	Exenatide 5 mcg BID	−0.46	33	−0.9
				Exenatide 10 mcg BID	−0.86	41	−1.6
				Placebo	+0.12	9	−0.6
DeFronzo[33]	336	30 wks	Metformin ≥ 1500 mg/day	Exenatide 5 mcg BID	−0.40	32	−1.6
				Exenatide 10 mcg BID	−0.78	46	−2.8
				Placebo	+0.08	13	−0.3
Kendall[34]	733	30 wks	Metformin ≥ 1500 mg/day + max dose SU	Exenatide 5 mcg BID	−0.6	27	−1.6
				Exenatide 10 mcg BID	−0.8	34	−1.6
				Placebo	+0.2	9	−0.9
Zinman[35]	233	16 wks	Pioglitazone 30 mg or rosiglitazone 4 mg ± Metformin	Exenatide 10 mcg BID	−0.98	62	−1.75
Heine[36]	551	26 wks	Metformin + SU	Placebo	+0.09	16	−0.24
				Exenatide 10 mcg BID	−1.11	46	−2.3
				Titrated insulin glargine	−1.11	48	+1.8
Nauck[37]	501	52 wks	Metformin + SU	Exenatide 10 mcg BID	−1.04	32	−2.5
				Titrated biphasic insulin aspart	−0.89	24	+2.9
Barnett[38]	138	2 × 16 wks	Metformin or SU	Exenatide 10 mcg BID	−1.36	37.5	1st period: −2.0 2nd period: −2.2
				Titrated insulin glargine	−1.36	39.8	1st period: +1.0 2nd period: +2.3
Liraglutide							
LEAD-3[23]	746	52 wks	Monotherapy	Liraglutide 1.2 mg	−0.84	43	Not reported
				Liraglutide 1.8 mg	−1.14	51	
				Glimepiride 8 mg	−0.51	28	
LEAD-1 SU[40]	1041	26 wks	Glimepiride 2–4 mg daily	Liraglutide 0.6 mg	−0.6	24	+0.7
				Liraglutide 1.2 mg	−1.08	35	+0.3
				Liraglutide 1.8 mg	−1.13	42	−0.2
				Rosiglitazone 4 mg	−0.44	22	+2.1
				Placebo	+0.2	8	−0.1
LEAD-2[41]	1087	27 wks	Metformin 1000 mg BID	Liraglutide 0.6 mg	−0.69	28	−1.8[d]
				Liraglutide 1.2 mg	−0.97	35.3	−2.6[d]
				Liraglutide 1.8 mg	−1.0	42.4	−2.8[d]
				Glimepiride 4 mg	−0.98[c]	36.3	+1.0
				Placebo	+0.09	10.8	−1.5
Lira-DPP4[21]	665	26 wks	Metformin at least 1500 mg/day	Liraglutide 1.2 mg	−1.24	2.75 (OR)[a]	−2.86
				Liraglutide 1.8 mg	−1.5	4.5 (OR)[a]	−3.38
				Sitagliptan 100 mg	−0.9		−0.96

(Continued)

Table 1. (*Continued*)

Study	# of pts (n)	Study duration	Baseline therapy	Intervention	Change in A1c (%)	Patients reaching A1c < 7% (%)	Change in body weight (kg)
LEAD-4[22]	533	26 wks	Metformin 2 gm/day + Rosiglitazone 8 mg	Liraglutide 1.2 mg Liraglutide 1.8 mg Placebo	−1.5 −1.5 −0.5	57.5 53.7 28.1	−1.0 −2.0 +0.6
LEAD-5[42]	581	26 wks	Metformin 2 gm/day + glimepiride 4 mg/day	Liraglutide 1.8 mg Insulin glargine (titrated) Placebo	−1.33 −1.09 −0.24	Not reported	−1.8 +1.6 −0.42
LEAD-6[43]	464	26 wks	Max dose Metformin, SU or both	Liraglutide 1.8 mg Exenatide 10 mcg BID	−1.12 −0.79	54 43	−3.24 −2.87

Abbreviations: A, Odds ratio when compared to sitagliptan therapy; BID, twice daily; SU, sulfonylurea; TID, three times daily; TZD, thiazolidinedione.

absorption and increasing binding to albumin.[25] Following SC injection, liraglutide is absorbed slowly with an absolute bioavailability of 55% and reaches C_{max} in 8–14 hours.[19,24,26] C_{max} and area under the curve (AUC) increase proportionally with increasing doses.[19,24,26] Liraglutide is highly protein bound and has a small volume of distribution of 0.07 L/kg.[19,24] The terminal elimination half-life was found to be 13 hours on average with a range of 11–15 hours which allows for once daily dosing.[19,24,26] It is suspected that liraglutide is metabolized and reabsorbed endogenously as only 6% and 5% of liraglutide or metabolites were recovered in the urine and feces, respectively.[24,27] The pharmacokinetic properties of liraglutide were unaffected by age, sex, renal function, or hepatic function.[28–30]

Clinical Efficacy
Exenatide

Exenatide has been studied in several clinical trials as monotherapy and in combination with other oral antidiabetic drugs (OAD) and insulin therapies. Moretto et al evaluated the use of exenatide monotherapy in patients with a mean A1c of 7.8%. All patients initiated exenatide 5 mcg/BID and either remained on 5 mcg/BID or increased to 10 mcg/BID after 4 weeks. At the end of the 24 week study both exenatide treatment arms resulted in statistically significant A1c reductions (−0.7% with 5 mcg/BID and −0.9% with 10 mcg/BID group) compared to placebo ($P \leq 0.001$).[31] A significant dose-dependent improvement in A1c was observed within the treatment groups ($P = 0.024$).[31] Baseline FPG in all treatment groups at initiation of study ranged from 154–166 mg/dl. Significant decreases in FPG was observed in the 5 mcg (−17.5 mg/dl, $P = 0.029$) and the 10 mcg (−18.7 mg/dl, $P = 0.016$) compared to placebo (−5.2 mg/dl).[31] Further, reductions in mean daily PPG excursion was significantly greater in the exenatide treated patients compared to placebo (−21.3 mg/dl with 5 mcg, $P < 0.001$; −24.7 mg/dl with 10 mcg, $P < 0.001$; placebo −8.3 mg/dl).[31] Significant body weight reductions were reported with 5 mcg (−2.8 kg, $P = 0.004$) and 10 mcg (−3.1 kg, $P < 0.001$) exenatide compared to placebo.[31] Additionally, homeostasis model assessment of β-cell function (HOMA-B) values were significantly increased from baseline by 32% in the 5 mcg group ($P = 0.002$) and

28% in the 10 mcg group ($P = 0.010$) compared with placebo.[31] Systolic blood pressure (SBP) decreased by −3.7 mmHg in both the 5 mcg and 10 mcg exenatide groups ($P = 0.037$) with no statistically significant decrease in diastolic blood pressure (DBP).[31] No statistically significant change in lipid parameters was observed in this monotherapy study.[31]

Three 30 week clinical trials evaluated the use of exenatide in combination with either metformin, sulfonylurea, or combination of metformin plus sulfonylurea, versus placebo in patients with poor glycemic control (baseline A1c 8.2%–8.5%).[32–34] In all 3 trials subjects were randomized to initiate exenatide 5 mcg/BID in combination with current OAD therapy for 4 weeks or placebo.[32–34] After 4 weeks, subjects continued 5 mcg/BID, titrated to 10 mcg/BID, or placebo for the remaining 26 weeks of study.[32–34] Similar results were reported in the exenatide versus placebo added to metformin or sulfonylurea treatment groups. Significant A1c reductions of 0.40 to 0.46% in the 5 mcg groups and 0.78%–0.86% with the 10 mcg groups compared to an increase in A1c in the placebo groups of 0.8%–0.12% ($P < 0.001$ vs. placebo).[32,33] The combination of exenatide with metformin plus sulfonylurea resulted in A1c reductions of 0.6 and 0.8% in the 5 mcg and 10 mcg groups, respectively, whereas there was a slight increase in A1c of 0.2 in the placebo group ($P < 0.0001$ vs. placebo).[34] Modest reductions in FPG were noted in all three of the aforementioned clinical trials, with 5.4–9.0 mg/dl decrease in the 5 mcg groups and 10.8 mg/dl decrease in the 10 mcg group compared to 14.4 mg/dl increase in the placebo group (+14.4 mg/dl).[32–34] In the exenatide versus placebo added to sulfonylurea clinical trial statistical significant FPG reductions was seen only compared to the 10 mcg exenatide group ($P < 0.05$ vs. placebo).[32] Post-prandial glucose was measured after a mixed meal tolerance test in a subset of subjects in some of the exenatide clinical trials. The pooled data indicates dose-dependent reductions in PPG.[13] Mean 2-hour PPG changes after 30 weeks of exenatide BID therapy were −63 mg/dl (5 mcg), −71 mg/dl (10 mcg) and +11 mg/dl with placebo.[13] Greater reductions in PPG were seen in these trials compared to FPG reflecting the glucose-dependent insulinotropic effects of exenatide. Greater reductions in weight loss were reported in all exenatide treatment groups compared to placebo throughout the 30 week study duration.[32–34] Overall, results from these clinical trials assessing the use of exenatide BID in combination with metformin, sulfonylurea, or both metformin plus sulfonylurea have shown statistical significance, with A1c reductions at the max effective dose of exenatide 10 mcg/BID ranging from 0.78%–0.86% with only 34%–46% of patients reaching American Diabetes Association (ADA) recommended A1c goal of <7%. The clinical significance of these results appear to indicate that the addition of exenatide to other antihyperglycemics may be most beneficial in getting patients to glycemic targets when A1c < 8.0%. Additionally, exenatide was studied as add-on therapy to thiazolidinediones (TZD), pioglitazone or rosiglitazone, in patients with sub-optimal control of T2DM. In this 16-week trial patients on TZD therapy (with or without metformin) were randomized to receive either exenatide 10 mcg/BID or placebo. Patients included in this study had a mean A1c of 7.9% and a mean BMI 34.0 kg/m^2.[35] A 0.98% reduction in A1c was seen in the exenatide group compared to a 0.09% increase in the placebo group ($P < 0.001$).[35] Moreover, exenatide reduced FPG by 28.6 mg/dl compared to a 1.80 mg/dl increase in FPG in the placebo group ($P < 0.001$).[35] As previously discussed in prior trials, exenatide greater reductions in PPG were seen compared to FPG with a 31.7 mg/dl reduction post-morning meal and a 30.27 mg/dl reduction post-evening meal.[35] These changes in glycemic control resulted in 67% of patients reaching ADA recommended A1c goal of <7% compared to 16% in the placebo group.[35] It is important to point out that the mean A1c goal was under 8% and closer to 7% at initiation of exenatide therapy and that the noteworthy reduction in PPG may be the reason why these patients reached their goals. Other effects noted in this trial was a greater reduction in body weight in the exenatide group compared to the placebo group (−1.75 kg vs. −0.24 kg, respectively).[35] HOMA-B values significantly increased by 19% in the exenatide group compared to a 6% decrease in the placebo group. This suggests that exenatide may potentially exhibit a disease-modifying effect.

Clinical trials have also assessed the efficacy of exenatide compared to insulin glargine or biphasic insulin aspart. Differences in A1c reductions between exenatide and insulin regimens were below the pre-specified non-inferiority margin of 0.4%, meaning

that exenatide demonstrated non-inferiority to titrated insulin glargine and biphasic aspart regimens in regards to A1c changes.[36–38] Similar A1c reductions of 1.11% and 1.36% were observed in both the exenatide and insulin glargine groups.[36,38] Additionally, similar effects were seen in the exenatide and biphasic insulin aspart groups with a reduction in A1c by 1.04% vs. 0.89%, respectively.[37] Insulin regimens reduced FPG by 30.6–73.8 mg/dl which was significantly greater than exenatide (25.2 to 52.2 mg/dl); however, greater reductions in PPG were seen in the exenatide treatment arms.[36–38] As expected with insulin therapy, patients treated with either insulin glargine or biphasic insulin aspart experienced weight gain during the trial whereas exenatide treated patients had significant weight reductions.[36–38] Between exenatide BID and insulin glargine group treatment differences were reported as −4.1 kg (95% CI, −4.6 kg to −3.5 kg) and −2.2 kg (95% CI, −2.8 kg to −1.7 kg).[36,38] In the trial evaluating exenatide BID and biphasic insulin aspart, between treatment group differences were reported as −5.5 kg (95% CI −5.9 to 5.0 kg, $P < 0.001$).[37] In view of the overall similar improvements in A1c reduction with both exenatide and insulin, consideration may be given to initiating exenatide as add-on therapy prior to insulin given the advantage of weight reduction with exenatide.

Finally, patients from three open-label extension trials were enrolled in one open-ended open-label clinical trial in order to assess exenatide's effects over a 3 year period. Patients continued exenatide 10 mcg/BID plus metformin and/or sulfonyulureas for the 3 year study duration. A1c reductions of 1.0% were maintained for the 3 year duration with 46% of patients attaining ADA recommended A1c goal of <7%.[39] Furthermore, weight reduction changes continued, −5.3 kg at 3 years.[39] Although this trial was limited by its open-label and uncontrolled design, it does suggest that continued treatment with exenatide results in continued improvement in glycemic control and weight reduction.

Liraglutide

Liraglutide has been studied as monotherapy and in combination with other anti-diabetic agents in patients with T2DM by the Liraglutide Effect and Action in Diabetes (LEAD) and Lira-DPP4 study groups.

Liraglutide monotherapy was examined in patients with T2DM previously managed by diet and exercise alone or OAD monotherapy at up to half the maximum dose. Following discontinuation of current therapy, subjects were randomized to receive liraglutide 1.2 mg, liraglutide 1.8 mg or glimeperide 8 mg daily and were followed for 52 weeks. Liraglutide 1.2 mg/daily and 1.8 mg/daily reduced A1c by 0.84% and 1.14%, respectively from an average baseline A1c of 8.3%. Compared to the 0.51% reduction in A1c seen with glimeperide 8 mg/daily, both doses of liraglutide showed significantly greater reductions in A1c and resulted in significantly higher proportions of patients reaching an A1c goals of both <7% and <6.5%.[23] Patients previously controlled by diet and exercise as opposed to OAD therapy had larger decreases in A1c throughout the trial.[23] Although this information is not reported, this effect may be related to lower baseline A1c values in those previously taking OAD. FPG levels decreased by 15 and 25 mg/dl for liraglutide 1.2 mg and 1.8 mg, respectively, which was significantly greater than glimepiride (−5 mg/dl).[23] In addition to improved glycemic control, subjects receiving liraglutide also experienced a significant weight loss of 2–3 kg compared to a weight gain of 1–2 kg with glimepiride ($P < 0.0001$) as well as a significant decrease in SBP of 2.1 and 3.6 mmHg with liraglutide 1.2 mg and 1.8 mg, respectively compared to 0.7 mmHg with glimeperide.[23] Based on these results, it appears liraglutide may be a better option for monotherapy than glimeperide.

Several trials evaluating liraglutide as part of combination therapy with a variety of OADs in patients previously uncontrolled on OAD therapy have been conducted. In these trials liraglutide lowered the mean A1c between 0.8% and 1.5%, depending on the dose and other therapies used in combination.[21,22,40–43] The LEAD-1 trial compared liraglutide 0.6 mg, 1.2 or 1.8 mg daily to rosiglitazone 4 mg daily, all in combination with glimeperide. Liraglutide 0.6 mg, 1.2 mg and 1.8 mg daily showed a mean decrease in A1c of 0.8%, 1.3%, and 1.4%, respectively ($P < 0.0001$ for all doses) compared to placebo. Liraglutide 1.2 mg and 1.8 mg also decreased A1c significantly greater than rosiglitazone (−0.7%, $P < 0.0001$).[40] Maximal reduction in FPG was seen by week 2 and was maintained throughout the trial. FPG was significantly reduced by 47 mg/dl for both

liraglutide 1.2 and 1.8 mg compared to placebo (18 mg/dl, $P < 0.0001$) and rosiglitazone (18 mg/dl, $P < 0.006$).[40] PPG were reduced by 45 mg/dl and 49 mg/dl with liraglutide 1.2 mg and 1.8 mg which again was significant when compared to both placebo (7 mg/dl, $P < 0.0001$) and rosiglitazone (32 mg/dl, $P < 0.0022$).[40] Weight loss was seen only in subjects receiving liraglutide 1.8 mg daily (−0.2 kg) and placebo (−0.1 kg) however, compared to the 2.1 kg weight gain in the rosiglitazone group there was still a significant difference ($P < 0.0001$).[40] While there were minimal changes in blood pressure (BP) there was no significant difference between treatment groups.

Two 26 week trials have examined liraglutide in combination with metformin. The first, the LEAD-2 study, compared liraglutide 0.6 mg, 1.2 mg, or 1.8 mg daily, glimeperide 4 mg daily and placebo all in combination with metformin. In this study, liraglutide 0.6 mg decreased A1c by 0.7% while liraglutide 1.2 mg, liraglutide 1.8 mg and glimeperide all decreased mean A1c by 1%. A1c reductions in all treatment groups were significant when compared to placebo.[41] FPG decreased by up to 30 mg/dl with liraglutide 1.8 mg which was significant when compared to placebo but not when compared to glimeperide (−23 mg/dl). PPG was self-monitored and was reduced similarly by 1.2 mg (−41 mg/dl), liraglutide 1.8 mg (−47 mg/dl) and glimeperide 4 mg (−45 mg/dl) all of which were significant when compared to placebo. Weight loss was dose-dependent with reductions of 1.8 kg, 2.6 kg and 2.8 kg seen with liraglutide 0.6, 1.2 and 1.8 mg, respectively. All reductions were significant when compared to the 1 kg weight gain seen in the glimeperide group and reductions in the 1.2 and 1.8 mg groups were significant when compared to weight loss in placebo group (−1.5 kg).[41] While DBP did not change in this study, SBP was reduced by 2–3 mmHg in liraglutide 1.2 and 1.8 mg groups which was significant when compared to an increase in SBP with glimeperide ($P = 0.128$, $P = 0.0467$, respectively).[41] The second study, conducted by the Lira-DPP-4 study group, compared liraglutide 1.2 mg, liraglutide 1.8 mg and sitagliptan 100 mg all in combination with metformin. Liraglutide 1.2 mg and 1.8 mg were shown to reduce mean A1c significantly better than sitagliptan (1.24%, 1.5% and 0.9%, respectively).[21] In a sub-group analysis, it was suggested those with a baseline A1c > 9%

experienced a greater reduction in A1c. FPG was lowered by 34 mg/dl and 39 mg/dl by liraglutide 1.2 mg and 1.8 mg which was significant compared to the lowering seen by sitagliptan (15 mg/dl).[21] Changes in PPG were not reported. A significantly greater weight loss was seen in subjects receiving liraglutide 1.2 mg (−2.86 kg) and liraglutide 1.8 mg (−3.38 kg) compared to those receiving sitagliptan (−0.96 kg). In addition, significant decreases in waist circumferences were also seen with liraglutide. Minimal decreases in BP were seen in all groups but were not significantly different among treatments. There were no significant differences in lipid panels among treatment groups.[21] These two trials suggest that in combination with metformin, liraglutide has similar glycemic control with glimeperide and superior glycemic control when compared to sitagliptan. Again, its other effects on weight loss and BP make it a viable second-line option.

The LEAD-4 study compared liraglutide 1.2 and 1.8 mg daily to placebo all in combination with metformin and rosiglitazone. Liraglutide 1.2 mg and 1.8 mg when used in combination with metformin and rosiglitazone reduced mean A1c by 0.9% and −1.1% respectively when compared to placebo ($P < 0.0001$) and led to over 50% of patients being at A1c goal of <7%.[22] FPG was lowered by up to 44 mg/dl with liraglutide which was significantly greater than placebo.[22] Weight loss of 1 and 2 kg seen in the liraglutide 1.2 and 1.8 mg, respectively were both significant when compared to the 0.6 kg weight gain in the placebo group ($P < 0.0001$). SBP was significantly reduced by 5.6 mmHg and 4.5 mmHg by liraglutide 1.2 mg and liraglutide 1.8 mg, respectively which was significant when compared to placebo. No significant differences were seen in DBP. This study also found a significant decrease in low-density lipoprotein (LDL) cholesterol and triglycerides in the liraglutide 1.2 mg group, but no other differences were seen in the lipid panel.[22] This study suggests that liraglutide may add benefit as a third-line agent in addition to metformin and rosiglitazone but more clinical trials are needed to compare liraglutide to other OADs in this combination.

Lastly, two 26 week trials, LEAD-5 and LEAD-6, studied the effects of liraglutide when used in combination with metformin and a sulfonylurea. The LEAD-5 study compared liraglutide 1.8 mg

daily, insulin glargine daily and placebo all in combination with metformin and glimeperide. The insulin glargine dose was titrated by the subjects for the first 8 weeks and by investigators thereafter. Liraglutide 1.8 mg/daily significantly reduced mean A1c by 1.09% when compared to placebo ($P < 0.0001$) and by 0.24% when compared to insulin glargine ($P = 0.0015$).[42] Despite the difference in A1c reductions, FPG and PPG reductions were similar between liraglutide (−28 mg/dl and 32.5 mg/dl) and insulin glargine (−28 mg/dl and −28 mg/dl).[42] Weight decreased by an average 1.8 kg in the liraglutide group, 0.4 kg in the placebo group and increased by an average 1.6 kg in the insulin glargine group. Weight loss with liraglutide was significantly decreased when compared to both insulin and placebo.[42] SBP was reduced in the liraglutide group by 4 mmHg which was significant when compared to insulin but not when compared to placebo. This difference was seen prior to weight changes so it is unlikely this is related to weight loss. No differences in DBP were seen.[42] While, this study suggests larger decreases in A1c values, there was no difference in BG values.[42] In addition, it is difficult to determine if insulin dose was appropriately titrated based on information provided. The LEAD-6 study compared liraglutide 1.8 mg daily to exenatide 10 mcg/BID in combination with metformin, a sulfonylurea or both. In this study, liraglutide decreased A1c by 0.33% when compared to exenatide 10 mcg/BID ($P < 0.0001$).[43] While liraglutide lowered FPG to a significantly greater extent than did exenatide (−28.8 mg/dl vs. −10 mg/dl, $P < 0.0001$), exenatide significantly lowered PPG when compared to liraglutide.[43] It should be noted however, that PPG readings were self-monitored by subjects. Weight loss of 3.24 kg and 2.87 kg was similar in both liraglutide and exenatide groups. SBP and DBP was decreased by 2–2.5 mmHg and 1–2 mmHg, respectively which was similar in both groups. Reductions in triglycerides and free fatty acids were significantly greater in the liraglutide group. Treatment satisfaction as measured by the Diabetes Treatment Satisfaction Questionnaire was significantly better in liraglutide group ($P = 0.0004$).[43] Overall, this study suggests that liraglutide and exenatide may be safely added to metformin and sulfonylurea combinations; however, it appears liraglutide may have a slight benefit with regard to A1c reductions.

Some trials showed that liraglutide in combination with a sulfonylurea or metformin had larger decreases in A1c in patients previously on monotherapy compared to combination therapy.[40,41] This may be related to study design as patients were not necessarily on medications used in the study prior to enrollment. Patients' previous therapies were stopped and study medications started for a 2–3 week titration period prior to starting liraglutide; therefore; the effect of the medications used in combination versus the effect of liraglutide is uncertain. Furthermore, maximum decreases in A1c were seen at 12–16 weeks; however, some trials showed a slight increase in A1c after that time.[40–42] Although changes in A1c remained significant at 26 and 52 weeks, long-term effect is unknown as there are no trials extending past 1 year.

Safety
Exenatide
Most common adverse effects (AEs) observed in clinical trials were mild to moderate gastrointestinal (GI) effects with the most common frequent events reported as nausea (33%–57%) and vomiting (10%–20%).[31–38] Incidence of GI effects were reported most frequently at initiation of therapy (0–8 weeks) and decreased over time.[31–38] All incidences of hypoglycemia were reported as mild to moderate in intensity with no severe hypoglycemia reported and no patient withdrawals from study trials attributed to hypoglycemia.[31–38] In the non-sulfonylurea treatment groups the incidence of hypoglycemia was 4.5%–5.2% in the 5 mcg treatment group and 3.8%–10.7% in the 10 mcg group compared to 1.3%–7.1% incidence in the placebo group.[31,33] It is important to note a higher hypoglycemia incidence of 27.8%–35.7% was observed in patients receiving concomitant sulfonylurea (with or without metformin) and exenatide therefore lowering the sulfonylurea dose may be warranted when using this combination.[32,34] In trials comparing the safety of exenatide to insulin glargine or biphasic aspart, incidence of hypoglycemia was similar between treatment groups; however, lower rates of nocturnal hypoglycemia were reported in patients treated with exenatide.[36–38] Low titers of anti-exenatide antibodies were identified in 27%–49% of patients in clinical trials reviewed.[31–38] Although, some trials identified antibodies in almost half of patients receiving exenatide, they did not appear to affect glycemic control or the incidence of AEs.[31–38]

Heine et al stratified A1c results by the presence of antibodies and found no significant difference in mean A1c reduction between the groups (positive antibody −1.04% versus −0.96% negative antibody).[36]

Liraglutide

The most common AEs reported with liraglutide were GI related and included nausea, abdominal pain, decreased appetite, diarrhea and vomiting and affected 10%–40%, 27%, 3%–10%, 7%–19% and 4%–17% of patients, respectively. GI events increased with dose and were found to be transient, typically resolving after 4 weeks.[15,21–23,40–43] Other common AEs were headache and dizziness which occurred in 7%–11% and 5%–6% of patients, respectively;[21,40,43] however, this was similar to placebo in placebo-controlled trials.

Severe hypoglycemia requiring third party assistance, was rare but occurred in two patients also receiving glimepiride.[23,42] Minor hypoglycemia (plasma glucose <55 mg/dl) occurred in 3%–27% patients.[21–23,42,43] Hypoglycemia occurred significantly less when compared to glimepiride but significantly more when compared to placebo or rosiglitazone.[23,40,41]

Pancreatitis has been reported but was rare. All patients recovered and some continued on liraglutide therapy without further incidence.[23,40,41,43] In clinical trials, 4%–13% of patients receiving liraglutide developed anti-liraglutide antibodies; however, their presence had no effect on clinical safety or efficacy.[22,40,42] Benign thyroid C-cell adenomas were seen in mice trials; however, incidence was dose-dependent and occurred with doses leading to 10–45 times the human exposure concentrations. Four cases of thyroid C-cell hyperplasia have been seen in human clinical trials in patients using liraglutide compared to one case in the comparator groups.[24] Increased detection may be related to mandatory calcitonin monitoring in clinical trials; however, caution should be used in patients at risk for or with a history of thyroid carcinoma.

Drug Interactions of GLP-1 Agonists

There are no drugs that are contraindicated for use with exenatide or liraglutide; however, it is important to note that due to decreased gastric emptying, the rate and extent of absorption for oral drugs may be impacted.[13,18] Therefore, for drugs that may be dependent on peak concentrations (eg, antibiotics) or have a narrow therapeutic index, caution should be used when initiating exenatide or liraglutide. The prescribing information for exenatide does recommend administering drugs dependent on peak concentrations at least 1 hour before exenatide dose.[13] A study examining the pharmacokinetics of liraglutide with griseofulvin, atorvastatin, lisinopril, and digoxin showed minor changes in pharmacokinetic properties but no clinically significant differences in overall absorption.[44]

Although trials assessing the effects of exenatide with concomitant warfarin therapy did not find any significant alteration in international normalized ratio (INR), post-marketing reports have suggested a potential drug interaction with concomitant use of warfarin, enhancing its anticoagulant effect.[13,45] Prescribing information describes reports of elevated INR sometimes accompanied by bleeding. It is recommended to increase monitoring of INR at the time of initiation or change in dose of exenatide therapy.

Finally, clinical trials have reported increased severity of hypoglycemia when exenatide and liraglutide are used in combination with sulfonylureas and may also be a risk with other insulin secretogogues.[13,24] Dose reduction of concomitant insulin secretagogues when initiating GLP-1 agonist therapy may reduce the risk of hypoglycemia.[13,24]

Dosage and Administration of GLP-1 Agonists

Exenatide is a SC injection available in 5 mcg (1.2-mL) and 10 mcg (2.4-mL) pre-filled pens. It is recommended to initiate 5 mcg/BID 60 minutes before morning and evening meals for one month to reduce the incidence of GI effects.[13] Following one month and based on clinical and safety response, the dose can be titrated to the maximum dose of 10 mcg/BID.[13] Liraglutide is a SC injection administered using a 3-mL pre-filled pen that can deliver doses of 0.6, 1.2, and 1.8 mg. Based on pharmacokinetic trials which showed BG lowering effects up to 24 hours post-administration, liraglutide can be administered once daily and without regard to food.[17,24] Liraglutide should be initiated at 0.6 mg/daily for one week then titrated to 1.2 mg/daily to reduce GI effects. If optimal BG control is not obtained, liraglutide can be increased to a maximum dose of 1.8 mg/daily.[24]

Recommended injection sites include thigh, abdomen, and upper arm.[13,24] Due to the risk of hypoglycemia, it is recommended to decrease the dose of concomitant sulfonylureas.[13,24] This precaution should also be

considered with other insulin secretogogues if used in combination with exenatide or liraglutide.[13,24] No dosing adjustments recommended with metformin or TZD. Dosing adjustments are not recommended with mild to moderate renal impairment; however, exenatide should not be used in cases of severe renal impairment (CrCl < 30 ml/min) or ESRD.[13] The pen should be stored in the refrigerator prior to first use then may be stored at room temperature for up to 30 days.[13,24]

Place in Therapy
Patient preference

Approval of new drug classes has increased the options for the management of T2DM. This can make choosing the most appropriate therapy difficult for health care providers and patients. The established OAD and insulin therapies have shown to be effective in attaining good glycemic control; however, most of the available agents result in weight gain, which can be frustrating for the patient. This is especially true for overweight or obese patients, where one of the priorities in managing T2DM is weight loss. Due to this favorable benefit, GLP-1 agonists are being favored as add-on therapy to existing OAD and prior to insulin. Some of the limiting factors with the use of GLP-1 agonists include the cost compared to some of the available agents, such as metformin and sulfonylureas, and that they are administered subcutaneously.

Differences between exenatide and liraglutide may impact selection of one agent over another. The once-daily dosing and flexibility of being able to use liraglutide at any time of day without regard to meals compared to exenatide which must be taken BID before meals may be an appealing option for most patients. The dosing and administration of liraglutide may especially be appealing to patients with T2DM who are already on multiple medications. LEAD-6 is the only head-to-head trial comparing exenatide BID to liraglutide which suggested that A1c and FPG reductions were greater with liraglutide compared to exenatide; however, PPG reductions were greater with exenatide.[43] Weight loss in both groups was similar. Both medications were well tolerated, but nausea was less persistent and hypoglycemia less frequent with liraglutide.[43] Liraglutide may provide more significant improvements in glycemic control with better tolerance compared to exenatide which may lead to better compliance and continued use by patients.

Therapeutic recommendations

Several factors should be taken into account when selecting an appropriate antihyperglycemic agent, including effectiveness of glucose-lowering, reductions in long term complications, safety/tolerability, ease of use, and cost.[46] Other effects such as reduction in body weight, impact on hypertension and lipids that may impact cardiovascular disease risk factors should also be taken into account when selecting an agent.[46] The ADA and American Association of Clinical Endocrinologist/American College of Endocrinology (AACE/ACE) consensus panels have published treatment recommendations for glycemic control in T2DM. Both have identified GLP-1 agonists as tier 2 or add-on therapies, following metformin, sulfonylurea, and insulin.[46,47] For most cases, GLP-1 agonists are considered appropriate add-on therapies to other OADs such as metformin; however, in some clinical settings it may be appropriate to use a GLP-1 agonist sooner. Obese patients may benefit from GLP-1 therapy, known for its weight reduction properties, compared to the risk of weight gain with sulfonylureas and/or insulin. Additionally, patients with hazardous jobs where hypoglycemia may impact performance, a GLP-1 agonist, with a lower risk of hypoglycemia compared to sulfonylureas and/or insulin may be preferred. It is important to note the primary goal in diabetes treatment is individualized glycemic control and reaching the ADA's recommended A1c goal of <7% in appropriate patients. In the trials reviewed here the estimated A1c reduction with GLP-1 therapies as monotherapy is about 0.9%–1.1% therefore they may not be appropriate in patients with A1c > 8.0%. Higher A1c reductions have been observed in combination with other antihyperglycemics. This further supports the idea that GLP-1 agonists should not be recommended as monotherapy but as a potential therapeutic approach in combination with other antihyperglycemic agents. Its use in combination with insulin has not been FDA approved; however, on-going clinical trials are assessing the efficacy and safety of the combination. Furthermore, the lack of outcome data with GLP-1 agonists supports the placement of these agents as second tier after metformin initiation, which has positive outcome data available.

Conclusion

Management of T2DM continues to be a significant challenge to healthcare providers and there is a growing

need for new treatment options in order to meet patients varying needs. Many of the available T2DM therapies present their own limitations including weight gain, fluid retention and hypoglycemia. Exenatide and liraglutide have been shown to be effective in reducing A1c, FPG, and PPG in patients with T2DM similar to and better than several other classes of antidiabetic medications including insulin glargine. In addition to glycemic control, these agents have also demonstrated benefits in weight loss which provides a therapeutic advantage over available treatment options and especially favorable for obese/overweight patients with T2DM. In general, exenatide and liraglutide were well tolerated with most patients experiencing GI AEs. These agents were also associated with low levels of hypoglycemia, making this a potentially good option in patients with a high risk of hypoglycemia and/or occupations that may be impacted by the incidence of hypoglycemia. While GLP-1 agonists have shown improvements in numerous markers, such as BP, the impact of these improvements has not been determined to improve long-term complications of T2DM. The potential of these agents is great; however, additional data is needed in order to fully elucidate these agents appropriate place in therapy and impact on clinical practice.

Abbreviations

A1c, hemoglobin A1c; ADA, American Diabetes Association; AE, adverse effects; AUC, area under the curve; BID, twice daily; BG, blood glucose; BMI, body mass index; C_{max}, maximum concentrations; CrCl, creatinine clearance; DPP-IV, dipeptidyl peptidase IV; DBP, diastolic blood pressure; ESRD, end-stage renal disease; FDA, Food and Drug Administration; FPG, fasting plasma glucose; GI, gastrointestinal; GLP-1, Glucagon-like peptide-1; HOMA-B, homeostasis model assessment of β-cell function; INR, international normalized ratio; LDL, low density lipoprotein; LEAD, Liraglutide Effect and Action in Diabetes; OAD, oral antidiabetic drugs; PPG, postprandial plasma glucose; SBP, systolic blood pressure; SC, subcutaneous; T2DM, Type 2 diabetes mellitus; TZD, thiazolidinediones.

Disclosures

This manuscript has been read and approved by all authors. This paper is unique and is not under consideration by any other publication and has not been published elsewhere. The authors and peer reviewers of this paper report no conflicts of interest. The authors confirm that they have permission to reproduce any copyrighted material.

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