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REVIEW

Recent results of exenatide use as adjunctive therapy in the treatment of patients with type 2 diabetes

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Abstract: Exenatide is a GLP-1 receptor agonist approved for use in type 2 diabetes mellitus. In clinical trials, significant reductions in serum glucose and weight were demonstrated for exenatide with primary glycemic effects of the twice daily formulation on prandial glucose control. In this paper, we review recent research with exenatide as adjunctive therapy in type 2 diabetes mellitus. In particular, studies demonstrate ongoing benefit on glycemic control and weight reduction with continued therapy up to 82 weeks duration and efficacy as adjunctive therapy for patients taking metformin, thiazolidinediones, and/or a sulfonylurea and as compared to sitagliptin and various insulin formulations. Compared to insulin, exenatide likely has greatest benefit for those patients who are overweight or who need improved prandial glucose control. The new long-acting release formulation of exenatide has demonstrated slightly improved efficacy compared to the twice daily formulation as well as a reduction in gastrointestinal side effects. Emerging research is further exploring novel benefits of exenatide as adjunctive DM therapy, effects on prandial glycemic control, markers of hepatic inflammation, alternative dosage forms including intra-nasal administration, and effects on beta cell function.

Keywords: exenatide, diabetes, GLP-1

Background

The prevalence of diabetes mellitus is conservatively estimated at 23 million individuals in the United States.[1] Weight gain is directly correlated with insulin resistance and predisposes to the development of type 2 diabetes mellitus (T2DM), so it is not surprising that the increasing incidence of this disorder mirrors the epidemic rise in obesity among US citizens. Health care costs related to the treatment of diabetes and its complications are staggering, estimated at US$116 billion annually.[1] The development of diabetes associated microvascular complications can be reduced by the improvement in hyperglycemia associated with the condition.[2,3] Since 1995, therapeutic options for the treatment of T2DM have grown considerably. Unfortunately this increase in pharmacologic choices has not translated into an improvement in individual glycemic targets associated with a reduction in diabetic microvascular complications.[4] One of the hurdles to improving hyperglycemia is patient adherence to a prescribed medical regimen. Often patients cite a reluctance to gain weight, a common side effect of many available hypoglycemic medications. Therapies that effectively reduce blood glucose and are weight neutral or can promote weight loss are highly sought.

Insulin secretion is more pronounced in response to an oral glucose stimulus compared to a calorically equivalent intravenous glycemic bolus, a phenomenon termed the incretin effect.[5] This effect, presumed to be the result of a coordinated

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interplay between gut hormones and pancreatic islet cells, can account for up to 70% of postprandial insulin production. Many intestinal hormones can stimulate insulin secretion, however studies suggest that two gut hormones, glucagon like peptide 1 (GLP-1) and glucose dependent insulinotropic polypeptide (GIP) are predominantly responsible for the incretin effect(6). Specifically GLP-1 and GIP are secreted following a meal, augment insulin secretion, and their insulinotropic effect is only seen during times of hyperglycemia. Interference with incretin hormone activity is associated with reduced insulin secretion and hyperglycemia.[7,8] The actions of incretin hormones would suggest an ideal pharmacologic agent for the treatment of hyperglycemia. Despite these factors, administration of GIP to individuals with T2DM has little hyperglycemia ameliorating effect even when given in supraphysiologic doses.[9] Studies have shown that hyperglycemia down regulates GIP receptors on the beta cell thus reducing the potential for GIP as a therapeutic agent.[10] In comparison, GLP-1 administration to individuals with T2DM is associated with a response predicted by the administration of an incretin hormone and has been intensely studied as a therapeutic agent in T2DM.

GLP-1 is derived from cleavage of the larger polypeptide, proglucagon, the precursor to related compounds, GLP-2, glucagon, oxyntomodulin and glicentin.[11] Production and secretion of GLP-1 occurs in the enteroendocrine L-cells of the jejunum and ileum. GLP-1 plasma levels are low in the fasting state but rise significantly in response to meal ingestion.[12] Certain nutrient types can be more stimulatory, however the exact factors leading to GLP-1 production and secretion are still not known.[12,13]

GLP-1 administration to individuals with and without DM is associated with an augmentation of insulin secretion and activity[14] as well as a concomitant inhibition of post-meal glucagon production.[15] This coordinated islet cell hormone production is ideally suited to reduce meal-induced hyperglycemia. Even more salutary is that this function is glucose dependent, predominating only during times of elevated serum glucose, therefore GLP-1 is less likely to induce hypoglycemia. Beyond its glucose regulatory effect, GLP-1 has exhibited CNS appetite control, promoting satiety and decreased GI motility.[16] Individuals with T2DM or impaired glucose tolerance exhibit reduced GLP-1 serum levels in response to a meal.[17,18] Moreover GLP-1 secretion post prandially is inversely correlated with the degree of insulin resistance.[19] In summary, GLP-1 promotes glucose dependent insulin secretion, decreases post-meal glucagon production, inhibits gastric motility, promotes satiety and is deficient in those with T2DM, making it an ideal pharmacologic agent. Enthusiasm for this concept waned with the realization that GLP-1 is rapidly metabolized following secretion in sera. GLP-1 is inactivated by cleavage at the position 2 alanine residue by the endopeptidase dipeptidyl peptidase 4 (DPP 4).[20,21] DPP 4 removes two amino acids from the N-terminus residue of GLP-1, a process that inactivates the insulinotropic effect. DPP 4 is secreted from capillary endothelial cells and can quickly and effectively metabolize GLP-1. The half-life of endogenous GLP-1 is 1 to 2 minutes.[21] Clearly any attempt to utilize these agents pharmacologically would mandate the abrogation of DPP 4 metabolism.

Exendin 4 is a naturally occurring 39 amino acid GLP-1 receptor agonist originally isolated in the saliva of the Gila Monster (*Heloderma suspectum*).[22] The peptide has 53% homology with mammalian GLP-1 with similar incretin hormone physiology.[22,23] The compound is more resistant to DPP 4 metabolism and therefore has a much longer half-life. Exenatide (Byetta®; Amylin Pharmaceuticals, Inc., and Lilly USA, LLC), a synthetic analogue of exendin 4, was approved by the FDA for use in the treatment of T2DM on April 28, 2005.[24] Exenatide has a half-life of 2 hours when administered subcutaneously. Clinical trials designed to evaluate the glycemic effects of exenatide, either as a solo agent or in combination with other hypoglycemic medications, have proven its efficacy to lower serum glucose and promote weight loss. Exenatide is administered as a 5 μg or 10 μg dose subcutaneously twice daily.

Among individuals with poorly controlled T2DM on maximal sulfonylurea or metformin therapy, or the combination, exenatide administered in 5 μg or 10 μg subcutaneous twice daily dosing was associated with a significant hemoglobin A_{1c} (HbA_{1c}) reduction and weight loss compared to placebo at 30 weeks.[25–27] Those individuals randomized to receive 10 μg twice daily, experienced an average HbA_{1c} reduction of 0.9% with an associated average weight loss of 1.6 kg. Approximately 40% of the individuals with a baseline HbA_{1c} of 8.3% attained HbA_{1c} values $\leq$7% at study closure. Overall exenatide was well tolerated with the most common side effect being nausea that occurred in a significant minority of individuals but was self limited in the vast majority. Due to the gastrointestinal side effects, it is recommended that exenatide be initiated at a 5 μg twice daily dose with titration to 10 μg twice daily after one month. In some individuals, gastrointestinal side effects may be limited by administration 10 to 15 minutes prior to a meal. Hypoglycemia was rare in these studies, was most often associated with concomitant sulfonylurea use and abrogated by a decrease in sulfonylurea

dosing. A summary of the initial clinical trial experience with exenatide can be found in Table 1.

Since the initial release of exenatide, research has continued to explore the long-term effects, efficacy as adjunctive therapy, and to further tease out any pharmacokinetic distinctions in special populations or drug interactions. The following is a summary of the clinical trial research evaluating long-term use and comparative efficacy of exenatide published in the last three years since publication of the initial exenatide trials and its release to the US market.

Methods

Data sources

A MEDLINE search (January 2006–April 2009) was conducted with the key words exenatide and Byetta for clinical trials limited to human research published in English. Follow-up searches were performed using key author names. References of identified articles were used for additional citations. BIOSIS Previews and the American Diabetes Association 2008 Scientific Abstracts were used for published abstract information.

Study selection and data extraction

Clinical trials (prospective, randomized, controlled trials) evaluating the safety and efficacy of exenatide as adjunctive therapy for T2DM in adults and children were selected. Data presented at 2008 diabetes scientific meetings of the American Diabetes Association and the American Association of Clinical Endocrinologists and available in abstract format were included for timeliness and are outlined in the 'Emerging Research' section.

Results

There were 8 (exenatide) adjunctive therapy clinical trials published between January 1, 2006 and April 30, 2009, including one major report of continuation of the initial three exenatide clinical trials.[25–27] Three abstracts were published in 2008 presenting clinical trial research.

Clinical trials

In the last 3 years, exenatide has been evaluated in open label extension trials, as a once weekly formulation, as adjunctive therapy with metformin, sulfonylureas, and/or thiazolidinediones, and as compared to sitagliptin and insulin.

Extension studies

Several studies[28–30] have reported the results stemming from an interim (82 week) evaluation of extension of therapy in the three initial multicenter, double-blind, placebo controlled efficacy trials.[25–27] The most recent report details findings from a 24-month pooled interim analysis of this real world extension of exenatide, highlighting the effects on HbA_{1c}, liver function, and weight.[31] Following completion of the 30-week clinical trials,[25–27] 974 subjects opted to continue open label use of exenatide, however, 453 were excluded due to site closure or late enrollment. Of the 521 remaining subjects considered to be the 2-year eligible intention to treat group, 283 subjects completed the full 2 years of treatment for

Table 1 Summary of initial exenatide clinical trials

Study	SFU + exenatide or placebo[25]		Met + exenatide or placebo[26]		Met/SFU + exenatide or placebo[27]	
	Exenatide 10 μg bid	Placebo	Exenatide 10 μg bid	Placebo	Exenatide 10 μg bid	Placebo
Subjects (N)	129	123	113	113	241	247
HbA_{1c} decrease (avg)	–0.86% ($P < 0.001$)	+0.12%	–0.78% ($P < 0.002$)	+0.08%	–0.8% ($P < 0.0001$)	+0.2
≤7% HbA_{1c} (%)	41% ($P \leq 0.0002$)	8.8%	46% ($p < 0.01$)	13%	34% ($P < 0.0001$)	9%
Wt loss (Avge kg)	–1.6 ($P < 0.05$), baseline 97 kg	–0.6	–2.8 ($P < 0.001$), 100 kg baseline	–0.3	–1.6 ($P < 0.01$), 98 kg baseline	–0.9
Nausea (%)	51%	7%	45%	23%	49%	21%
Mild to moderate hypoglycemia < 60 mg/dL	36%	3%	5%	5%	28%	13%
Severe hypoglycemia	0%	0%	0%	0%	0%	0%

Abbreviations: SFU, sulfonylurea; Met, metformin

the interim analysis (238 withdrew from study due to adverse event 9%, loss of glucose control 3%, loss to follow-up 5%, administrative, investigator decision or protocol violation 14%, or withdrawal of consent 15%). The initial reduction in HbA_{1c} (–0.9%) seen in the pooled analysis of the 3 clinical trials was sustained at 2 years (–1.1%, $P < 0.001$, 2-year completer population) and was significantly lower than baseline. In addition, weight reduction (mean [SD]) was progressive with continuation therapy (–2.1 kg [0.2] at 30 weeks to –4.7 kg [0.3] at 2 years, $P < 0.001$, and BMI reduction of 1.6 kg/m^2 [0.1], $P < 0.001$, vs baseline for 2-year completer population). Of note, subjects with slightly elevated ALT at baseline (mean 38 (SEM 1) IU/mL, 53% of the sample) had a significant mean reduction from baseline (–11 (SEM 1) IU/mL, $P < 0.05$), with 39% achieving a normal ALT by 104 weeks. These findings support the ongoing use of exenatide for diabetes and weight control, and highlight a potential therapeutic option for those who are overweight with elevated ALT, to improve liver function.

Once weekly formulation

The use of exenatide may be deferred by some patients taking oral diabetes medications in an effort to avoid the use of injections. Recent research has explored the option of a once weekly formulation of exenatide as a less frequently administered alternate to twice daily injections. In a phase 2, placebo comparison study, long-acting release (LAR) exenatide (0.8 mg and 2 mg) was studied in adults with T2DM (N = 45, baseline HbA_{1c} 8.3% to 8.6% across groups) with or without metformin (n = 27 using metformin).[32] By week 2, exenatide levels had achieved the desired minimal concentration for effect (50 pg/mL). Fasting plasma glucose was significantly reduced at week 15 (–43.2 ± 16.2 and –39.6 ± 9 mg/dL as computed from mmol/L reported for the 0.8 mg and 2 mg groups, respectively, $P < 0.001$ vs placebo). The magnitude of postprandial glucose excursion was reduced by a factor of 4 for the 2 mg exenatide LAR group compared to placebo. HbA_{1c} was reduced by 1.4% (±0.3) and 1.7% (±0.3) for the 0.8 (N = 16) and 2 mg (N = 15) dose groups, respectively, with 36% of subjects in the 0.8 mg group and 86% in the 2 mg group achieving $HbA_{1c} \leq 7\%$ at week 15, compared with 0% of placebo subjects (N = 14). Additionally, patients in the 2 mg group achieved a 3.8 kg weight loss (±1.4 kg) or 3.5% of baseline body weight at 15 weeks ($P < 0.05$). Body weight was unchanged from baseline for the 0.8 mg and placebo LAR groups. In a study reported by Drucker and colleagues, LAR exenatide 2 mg given subcutaneously (SC) once weekly was compared to 10 µg exenatide SC twice daily in an open-label, non-inferiority study in 295 people with T2DM either naïve to treatment or on 1 or more antidiabetic medications.[33] At 30 weeks, the once weekly exenatide group had a greater reduction in HbA_{1c} (–1.9% vs –1.5%, $P = 0.0023$) and a greater proportion of patients achieved an $HbA_{1c} < 7\%$ (77% in weekly group vs 61% in BID group, $P = 0.0039$). Fasting plasma glucose was reduced to a greater extent (–41.4 [SE 3.6] mg/dL vs –25.2 [3.6], $P < 0.0001$), for once weekly and twice daily, respectively. Weight loss was similar for the two treatment groups. Nausea, the most common side effect seen with the twice daily formulation currently available, was reported by 26.4% of subjects receiving the once weekly formulation as compared to 34.5% of the twice daily group with vomiting rates of 10.8% for once weekly and 18.6% for twice daily administration. Injection site pruritus was reported to a much greater extent (17.6% vs 1.4%) by the group receiving the once weekly formulation. The improved reduction in HbA_{1c} seen with the weekly formulation is likely related to the longer duration of action allowing for ongoing incretin supplementation rather than the shorter, burst supplementation provided by the twice daily formulation which has a half-life of 2 hours resulting in loss of coverage between doses. Patient reported side effects (eg, nausea or bloating) are also less likely with the weekly formulation, possibly related to reduction of daily peak effects.[34] The use of a once weekly formulation presents a promising new option for those who may benefit from incretin therapy.

Adjunctive therapy comparative trials

Exenatide has recently been evaluated as adjunctive therapy with metformin, thiazolidinediones, sulfonylureas, or combinations of these and compared with insulin and sitagliptin (Table 2). Overall, the addition of exenatide is beneficial with greatest potential in those who are overweight or with prandial glucose excursions not responding to oral therapy or insulin.

Exenatide vs insulin

Whether to initiate exenatide or insulin in an individual with uncontrolled T2DM is a decision based on several factors including the need for weight loss, needs for prandial versus basal glucose control, co-morbidities (eg, exenatide contraindication if motility disorders) and patient acceptance of injection therapy. From a pharmacologic standpoint, basal insulin and exenatide therapies are quite different. The usual first step in insulin therapy in T2DM, basal insulin, targets overall control, as measured by fasting plasma glucose,

Table 2 Comparative studies of exenatide as adjunctive therapy in adults with type 2 diabetes mellitus

Primary investigator	Comparator to exenatide[a]	Adjunctive DM tx	Trial design	Subjects combined baseline characteristics	Outcomes	Results	Of note…
Davis[36]	Insulin (patient's pre-study regimen)	Metformin and/or SFU	16-week, open-label, 2:1 randomized replacement of insulin with exenatide	N = 51, 53 yrs, BMI 34, HbA_{1c} 8.1%, DM × 11 yrs	HbA_{1c} increase < 0.5%	HbA_{1c} changes not sig. different between groups; 62% exenatide vs 81% insulin-treated patients maintained glycemic control	Hypoglycemia incidence 39% exenatide and 38% insulin, primarily during daytime and in those using a SFU
Barnett[37]	Insulin glargine titrated to fasting serum glucose 100 mg/dL	Single agent using either metformin or SFU	2 × 16-week, open label, cross-over, non-inferiority, randomized	N = 138, 54.9 yrs, BMI 31, HbA_{1c} 8.9%, DM × 7.4 yrs, 55.1% metformin, 44.9% SFU	Change in HbA_{1c}	HbA_{1c} reduction 1.36% both groups, both significantly lower than baseline ($P < 0.001$)	Exenatide produced lower 2-h PPG excursions than insulin ($P < 0.016$). Nausea greater for exenatide (42.6% vs 3.1%), however, hypoglycemia was no different between groups
Nauck[38]	Biphasic insulin aspart (Blasp) 70/30 titrated to fasting glucose <126 mg/dL and 2 hour postprandial <180 mg/dL	Metformin and SFU	52-week, open label, noninferiority trial	N = 446, 58.5 yrs, BMI 30, HbA_{1c} 8.6%, DM duration × 10 yrs	HbA_{1c} difference < 0.4% between groups	Exenatide demonstrated non-inferiority to premixed insulin	Withdrawal rate 21% exenatide vs 10% insulin due to protocol violations and adverse events
Bergenstal[39]	Blasp 70/30 fixed dose of 12 units once daily before supper or 12 units twice daily given before breakfast and supper	Metformin and SFU	24-week, open label, randomized 1:1:1	N = 372, > 18 yrs of age, HbA_{1c} 10.2%, DM duration 9 yrs	HbA_{1c}, FPG, safety	HbA_{1c} reduction 0.91% bid group, reduction 0.67% qd group. HbA_{1c} < 6.5% achieved by 25% bid vs 8% exenatide, $P = 0.0004$	Hypoglycemia 56%, 61%, and 29%, daily Blasp, bid Blasp, and exenatide, respectively. Weight +2.85 kg, +4.08 kg, −1.96 kg for daily insulin, bid insulin, and exenatide, respectively
Glass[40]	Glargine or biphasic insulin aspart (Blasp)	Metformin and SFU	Pooled, post-hoc analysis of 2	N = 1047	HbA_{1c}, weight	22% achieved 5% or more weight loss; 3.2% achieved 10% or more; 73.3% averaged 3 kg weight loss on exenatide vs 2% at least 5 kg weight loss; 0.2% at least 10% weight loss; and 75.9% mean 3 kg gain for insulin group	Similar glycemic control between groups
Schwartz[41]	Placebo	Metformin with (37%) or without (63%) a TZD	2-week, randomized, double-blind, 2-arm, parallel-group, placebo-controlled	N = 30, 63% female, 53 yrs, BMI 34, HbA_{1c} 8%, DM duration 8.7 yrs, 60% Hispanic, White 33%, Black 7%	Glucose over 24-h, pre- and postprandial triglycerides and fatty acids	24-h mean glucose 126 mg/dL (±3.6) and 157 mg/dL (±5.4) for exenatide and placebo, respectively ($P < 0.001$); all 2-h postprandial points significantly reduced for exenatide; triglyceride increases were significantly lower post-meal after 2 weeks of exenatide; no effect of free fatty acids	Exenatide titration occurred during the 2-week study phase

(*Continued*)

Table 2 (*Continued*)

Primary investigator	Comparator to exenatide[a]	Adjunctive DM tx	Trial design	Subjects combined baseline characteristics	Outcomes	Results	Of note…
Zinman[42]	TZD	with or without metformin	16-week, placebo run-in (SC saline twice daily × 2 weeks), randomized, double-blind, placebo-controlled trial	N = 233, 19%–23% TZD alone and 77%–80% TZD plus metformin, 56 yrs, BMI 34, HbA_{1c} 7.9%, 65% male	HbA_{1c} (primary), FPG, body weight, beta cell function, insulin sensitivity	HbA_{1c} reduction 0.98% (0.74%–1.21% CI reduction); FPG reduction 30.5 mg/dL (CI 21–40 reduction); weight reduction 1.5 kg (CI 0.88–2.15 reduction)	16% vs 2% discontinuation in the exenatide group for adverse events (40% nausea vs 15% placebo)
DeFronzo[43]	Sitagliptin	metformin	Double-blind, randomized, cross-over trial	N = 61, BMI 33, HbA_{1c} 8.5%, 2-h postprandial 245 mg/dL, 54% female	2-h PPG, FPG, insulin and glucagons secretion, gastric emptying, and caloric intake	2 h postprandial 133 (±6 mg/dL) vs 208 (±6 mg/dL), $P < 0.0001$; FPG reduction no difference; improved insulin secretion ($P = 0.02$), reduced PP glucagons ($P = 0.001$); slowed gastric emptying ($P < 0.0001$); reduced total calorie intake ($P = 0.02$, n = 25 evaluated)	Calorie intake increased in the sitagliptin group (increase of 130 ± 97 kcal exenatide) vs reduction of 134 ± 97 kcal exenatide)

[a]Exenatide dosed at 5 μg bid once monthly, then 10 μg bid.

Abbreviations: Biasp, biphasic insulin aspart; BMI, body mass index; SFU, sulfonylurea; TZD, thiazolidinedione; FPG, fasting plasma glucose; PPG, postprandial glucose.

whereas exenatide has a greater impact on reducing prandial glucose excursions. Ideally, decisions about which product to initiate should be made with the specific needs for glucose control in mind. This point is reinforced by an earlier 2005 study comparing the addition of exenatide or insulin glargine in 551 subjects suboptimally controlled on metformin and a sulfonylurea.[35] In this comparison, no difference in HbA_{1c} reduction (1.11% both groups) was demonstrated between treatments; however, exenatide had a greater effect on postprandial glucose excursions than insulin glargine, which reduced fasting glucose to a greater extent. In a more recent study, Davis and colleagues investigated the substitution of exenatide for insulin in a 16-week study in adults with T2DM (BMI $>$ 27 but $<$ 40 kg/m^2) using oral antidiabetic agents plus insulin.[36] In this trial, patients using some level of insulin (NPH, glargine, ultralente, a mix product, or multiple insulin formulations) were included. A 2:1 randomization resulted in 33 subjects switched from their insulin to exenatide (5 μg bid × 4 weeks, then 10 μg bid × next 12 weeks) and 16 subjects continuing their insulin regimen. All subjects continued previous oral antidiabetic medications. In the intention to treat analysis, 62% of subjects switched to exenatide maintained glycemic control (HbA_{1c} increase $<$0.5%) as compared to 81% of the insulin treated group. Subjects in the exenatide group (n = 18) who had the greatest improvement were those using less insulin, having shorter diabetes duration, higher c-peptide levels, and on insulin for shorter duration. Of the 11 exenatide-treated subjects who did not maintain glycemic control, 5 discontinued exenatide prior to completing the study period, primarily due to loss of glucose control. Overall, the differences in glycemic control between the two groups were not statistically significant. Gastrointestinal adverse events were reported in higher frequency for the exenatide. In particular, 79% of exenatide subjects reported a treatment-emergent adverse event (48.5% nausea) compared to 56% of the insulin group (31.3% headache, 12.5% nausea). Incidence of hypoglycemia was similar between groups (39% exenatide and 38% insulin), primarily occurring during the daytime and in those using a sulfonylurea. Although this study suggests the possibility of replacing insulin with exenatide, it is difficult to fully assess the benefit of this approach given the high drop-out rate in the exenatide group. In addition, the inclusion of all insulin use in this study clouds the ability to discern the true benefit of substitution therapy given that the action of twice daily exenatide, the formulation used in the study, is directed more at prandial control than basal.

In an open-label crossover study comparing exenatide to titrated glargine in 138 adults with previously uncontrolled

diabetes on metformin (55.1%) or a sulfonylurea (44.9%), Barnett and colleagues found that both exenatide and glargine were associated with similar reductions in HbA_{1c} (−1.36% each medication, $P < 0.001$) with no significant difference in the proportion of patients achieving the American Diabetes Association (ADA) target HbA_{1c} <7%.[37]

In a multi-country randomized trial, biphasic insulin aspart (ie premixed insulin, 70/30) twice daily was compared to twice daily exenatide in a 52-week non-inferiority study (n = 501, intention to treat) in overweight or obese patients (BMI baseline 30.4 kg/m^2) suboptimally controlled (HbA_{1c} greater than or equal to 7% but less than or equal to 11%) on metformin and a sulfonylurea.[38] Following randomization, subjects in the exenatide group were titrated to 10 µg twice daily exenatide over 1 month. Premixed insulin aspart was initiated for the comparator group by investigators and then titrated on an as needed basis to achieve optimal glycemic control, however, a forced titration was not used to guide dosing. Results demonstrated non-inferiority of the exenatide to premixed insulin (HbA_{1c} −1.04% ± 0.07% exenatide and −0.89% ± 0.06% biphasic insulin aspart, $P = 0.067$). A secondary finding was a significant reduction in weight with mean change from baseline of −2.5 kg and +2.9 kg for exenatide and premixed insulin, respectively, resulting in a between group difference at week 52 (−5.4 kg, $P < 0.001$).

A second comparison of exenatide to 70/30 biphasic insulin aspart was recently published by Bergenstal et al.[39] In this study, adult subjects taking metformin and a sulfonylurea with $HbA_{1c} > 8\%$ were randomized to either once or twice daily biphasic aspart or exenatide (1:1:1, N = 372). Glycemic control was significantly improved in the two groups using biphasic aspart as compared to those receiving exenatide (HbA_{1c} difference of −0.91%, CI −1.23% to −0.59% for biphasic aspart twice daily; −0.67% reduction, CI −0.99% to −0.34% biphasic aspart once daily) although hypoglycemia was less frequent for the exenatide study group (56%, 61%, 29% for biphasic aspart once daily, twice daily, and exenatide, respectively). Weight gain of 2.85 to 4.08 kg occurred in the insulin groups with an average weight loss of 1.96 kg in the exenatide group. Of note, the baseline HbA_{1c} was 10.2% in this trial with mean duration of diabetes of almost 9 years, indicating the potential for greater need or benefit from insulin over exenatide therapy for these subjects.

In addition to effects on HbA_{1c}, weight change has been evaluated in insulin comparative trials. In a pooled post-hoc analysis of two multicenter, randomized, open-label trials (N = 1047) comparing exenatide to insulin (glargine or biphasic insulin aspart) in individuals using metformin and a sulfonylurea, weight loss (a secondary outcome of these trials) was achieved in the exenatide group (73% averaging 3 kg loss, 22% achieving 5% or more weight loss) as compared to the insulin group in which 76% of subjects gained weight (mean 3 kg) with only 2% achieving 5% or more weight loss.[40] This study highlights the potential benefit of weight loss in exenatide users, however, strict interpretation is difficult given the post-hoc design.

Exenatide vs oral DM therapies

In patients using oral antihyperglycemic therapies for T2DM, exenatide is an adjunctive therapy option to add to pre-existing metformin therapy with or without a sulfonylurea. Recently, exenatide has been studied as adjunctive therapy to metformin with or without a thiazolidinedione (TZD), TZD monotherapy, and compared with sitagliptin, a DPP-4 inhibitor. A 2-week study of exenatide titrated to 10 µg twice daily in adults (N = 17) vs placebo (N = 13), added to metformin (63%) or metformin plus a thiazolidinedione (37%) further explored exenatide as adjunctive therapy.[41] After the 2-week treatment period, 24-hour glucoses averaged 126 mg/dL (±3.6) and 157 mg/dL (±5.4) in the exenatide and placebo groups, respectively. Significant differences ($P \leq 0.001$) between groups were noted for 2-hour postprandial values at all meal times (119 vs 216, 158 vs 213, and 122 vs 204 mg/dL), with triglyceride excursions significantly reduced after morning and evening meals for the exenatide group. This study highlights the impact on postprandial glucose of this therapy when used as an adjunct. In a randomized, placebo-controlled evaluation of exenatide adjunctive therapy with thiazolidinedione (TZD) treatment for 16 weeks in 233 subjects (ages 21 to 75 years, stabilized on TZD for at least 4 months) from Canada, Spain, and the United States using either metformin or no other therapy, HbA_{1c} was reduced by an additional 0.98% (95% CI −1.21% to −0.74%).[42] In addition to HbA_{1c} reduction with adjunctive therapy, weight reduction of a mean of 1.75 kg (CI −2.15 to −0.88 kg) or 1.8% reduction occurred in the exenatide group. Of note, 16% of the subjects in the exenatide group discontinued treatment as compared to 2% in the placebo group due to adverse events, primarily due to nausea (40% exenatide vs 15% placebo). In a 2-week crossover trial, exenatide was compared to sitagliptin as adjunctive therapy to metformin with significantly improved exenatide efficacy on all measures including postprandial glucose lowering (mean 133 ± 6 exenatide vs 208 ± 6 sitagliptin mg/dL, $P < 0.00001$), increased insulin secretion, reduced postprandial glucagon secretion, reduced postprandial triglycerides,

slower gastric emptying, and reduced calorie intake.[43] Given the more targeted action of exenatide at mimicking glucagon-like peptide(GLP-1) compared with sitagliptin which impairs breakdown of GLP-1, these results are to be expected.

Beta cell function

Research on exenatide suggests a beneficial effect on first and second phase insulin secretion.[44] Two recent studies have explored this potential using measurement and simulation of beta cell function. These studies have been included in this update to provide evidence on the potential benefit of exenatide on beta cell function when used as adjunctive therapy.

In a 52-week study evaluating the effect on beta cell function of the addition of exenatide or insulin glargine to ongoing metformin therapy, change in blood glucose and C-peptide secretion in 60 subjects was measured prior to, at 52-weeks, and after a 4-week off-treatment period.[45] Baseline HbA_{1c} ranged from 7.6% (±0.1) for the exenatide group to 7.4% (±0.1) for the glargine group. Although HbA_{1c} reductions were similar for exenatide and glargine groups (−0.8% ± 0.1% and −0.7% ± 0.2%, respectively, at 52 weeks, $P = 0.55$), parameters of beta cell function were improved in the exenatide group significantly as compared to the glargine group. In particular, first and second phase C-peptide secretion were increased 1.53 (±0.11) and 2.85 ± 0.22 fold, respectively ($P < 0.00001$). Of note, measures of beta cell function returned to pre-treatment levels by 4 weeks after treatment discontinuation, implying a benefit only while drug is present.

A second evaluation used mathematical modeling from data in an exenatide adjunctive therapy investigation to examine the effect of exenatide on predicted insulin secretion and beta cell function in adults with T2DM treated with metformin or metformin and a sulfonylurea.[46] Using data from mealtime blood glucose tests at baseline and week 30 for the model, an increase in insulin secretion was predicted for exenatide 10 µg (72% predicted increase, $P = 0.015$) and a slightly less profound increase predicted for 5 mcg doses (40% predicted increase, $P = 0.045$). These authors suggest the effect of exenatide on improved beta-cell function in their concluding remarks; however, it is difficult to draw specific conclusions given the theoretical nature of the model. This early work suggests a novel benefit of exenatide in those with T2DM not yet seen with other DM medications; however, further research to tease out the specific influence of exenatide on beta cell function and potential recovery is needed.

Emerging research

At the 2008 meetings of the ADA and AACE, new research yet unpublished but available in abstract form highlighted novel dosage forms of exenatide (intranasal),[47] positive effects of exenatide on post-meal metabolism and lipid response,[48] and a beneficial influence of exenatide treatment on liver enzymes.[49]

Summary

Exenatide is a GLP-1 agonist administered as a 5 µg or 10 µg dose subcutaneously twice daily which promotes satiety, post-meal glucagon suppression, and insulin release in response to meals. Collectively, these actions result in improved post-meal hyperglycemia, overall HbA_{1c} control, and some degree of weight loss. In clinical trials of adults with T2DM, significant reductions in serum glucose and weight have been demonstrated for exenatide with primary glycemic effects of the twice daily formulation on prandial glucose control. Based on clinical trials, efficacy of exenatide appears more optimal in those who have not had long diabetes duration and those who have adequate endogenous insulin. Recent research with exenatide demonstrates ongoing benefit on glycemic control and weight reduction with continued therapy up to 82 weeks' duration. Additionally, studies have demonstrated efficacy of exenatide as adjunctive therapy for patients taking metformin, thiazolidinediones, and/or a sulfonylurea. As compared to sitagliptin, exenatide has superior efficacy. Compared with insulin, exenatide likely has greatest benefit for those patients who are overweight or who need improved prandial glucose control; however additional study is warranted to fully distinguish the role of exenatide versus insulin. The new long-acting release formulation of exenatide has demonstrated slightly improved efficacy compared with the twice daily formulation as well as a reduction in gastrointestinal side effects. The influence of exenatide on beta cell recovery requires further investigation; however, the initial studies demonstrate improved insulin secretion in the presence of exenatide. Emerging research is further exploring novel benefits of exenatide as adjunctive T2DM therapy including effects on prandial glycemic control and markers of hepatic inflammation. Additionally, alternative dosage forms including intra-nasal exenatide are under investigation.

Conclusion

Exenatide is an effective option as adjunctive therapy for T2DM in those taking metformin, sulfonylureas, thiazolidinediones, or insulin. The benefit appears greatest for

individuals with inadequate prandial glycemic control or for whom weight reduction is desired. The use of exenatide has been limited by gastrointestinal side effects, cost, and the need for twice daily subcutaneous injection. Gastrointestinal side effects and the need for frequent injections may be abated somewhat with use of the long-acting release, once weekly formulation if it becomes available. Further research on the potential effects of exenatide on beta cell proliferation is needed to distinguish the benefits of therapy on insulin secretion, which has been demonstrated, versus insulin production or beta cell recovery.

Disclosure

The authors declare no conflicts of interest.

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