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The Use of Exenatide in Islet Transplant Recipients with Chronic Allograft Dysfunction: Safety, Efficacy and Metabolic Effects

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Abstract

Background—A current limitation of islet transplantation is reduced long term graft function. The glucagon like peptide-1 (GLP-1) receptor agonist, exenatide (Byetta®, Amylin Pharmaceuticals, CA) has properties that could improve existing islet function, prevent further loss of islet mass and possibly even stimulate islet regeneration.

Methods—This prospective study evaluated the safety, efficacy and metabolic effects of exenatide in subjects with type 1 diabetes mellitus and islet allograft dysfunction requiring exogenous insulin.

Results—Sixteen subjects commenced exenatide, twelve continue (follow-up 214±57 days; range 108-287), four (25%) discontinued medication due to side effects. At six months, exogenous insulin was significantly reduced with stable glycemic control (0.15 ± 0.02 vs. 0.11 ± 0.025 Units/kg/day; $p < 0.0001$); three subjects discontinued insulin from 4, 5 and 9 U/day respectively, two sustained insulin independence with A1c reduction below graft dysfunction criteria. Post-prandial capillary blood glucose was significantly decreased (129.4 ± 3.8 vs. 118.7 ± 4.6 mg/dL; $p < 0.001$), C-peptide and C-peptide/glucose ratio increased significantly by 5th and 6th months of treatment (ratio- 1.09 ± 0.15 vs. 1.52 ± 0.18 ; $p < 0.05$). Weight loss >3 kg occurred in 8/12 (67%) subjects. Stimulation testing demonstrated improved glucose disposal and C-peptide secretion (glucose area under the curve $52,332 \pm 3,219$ vs. $2,072 \pm 1,965$; $p = 0.002$ mg·min⁻¹·dL⁻¹, Mixed Meal Stimulation Index 0.50 ± 0.06 vs 0.66 ± 0.09 ; $P = 0.03$ pMol·mL⁻¹), with marked suppression of glucagon secretion and progressive increase in amylin secretion. Side effects were more frequent/severe compared to published reports in type 2 diabetes, tolerated doses were lower.

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Conclusions—Exenatide was tolerated in this patient population following appropriate dose titration and there appeared to be gradual but sustained positive effects on glycemic control and islet graft function.

Keywords

Islet; Transplant; Function; GLP-1; Safety; Efficacy

Introduction

Islet transplantation is moving into the arena of a clinical therapy for selected individuals with type 1 diabetes mellitus (T1DM) complicated by unstable control and/or hypoglycemia unawareness (1). After six years of islet transplantation in the ‘Edmonton Protocol’ era, a consistent observation has been that while graft function persists, exogenous insulin must be restarted in 80-100% of transplant recipients by 4-5 years to maintain normoglycemia (2-5). While the benefits of more stable control, lack of severe hypoglycemia and improved quality of life remain (6), the graft dysfunction is more often than not progressive.

The causes of the observed graft dysfunction remain to be elucidated and it is likely that multiple variables contribute to this phenomenon (7). Possibilities include: low numbers of islets that survive the transplant procedure resulting in a marginal islet mass at outset; gradual exhaustion of this marginal islet mass due to a relatively high metabolic demand; suboptimal intrahepatic location which may increase metabolic demand while exposing islets to relatively high levels of immunosuppression and other toxins (8-10); immunological losses (allorejection and recurrent autoimmunity) (11-13); and acute/chronic islet toxicity of immunosuppressive drugs (14-15).

In the search for ways to improve islet function and preserve islet mass, the use of incretins [i.e., glucagon-like peptide (GLP-1) and GLP-1 receptor agonists] is appealing. GLP-1, at the level of the β -cell, has demonstrable insulinotropic actions that include stimulation of insulin gene transcription, insulin biosynthesis, and insulin secretion (16-18). GLP-1/mimetics also demonstrate, in various animal models, the ability to act as growth factors, stimulating formation of new pancreatic islets (neogenesis) while slowing β -cell death (apoptosis) (19-22).

Exenatide (Byetta®, Amylin Pharmaceuticals, CA), is a recently FDA approved synthetic GLP-1 receptor agonist. Studies using exenatide, in patients with T2DM, resulted in a significant reduction in A1c, weight and fasting glucose levels at both 30 and 82 weeks of treatment (23-26). Thus, GLP-1 receptor agonists could be of potential benefit to islet transplant recipients with partial function to improve remaining islet function and glycemic control while preserving islet mass over time.

The objective of this prospective trial was to evaluate the feasibility of treatment, side effect profile, efficacy and metabolic effects of exenatide in subjects with T1DM demonstrating islet allograft dysfunction requiring exogenous insulin therapy.

Materials and Methods

Islet transplant recipients were transplanted in islet alone (IA) or islet after kidney (IAK) protocols utilizing an ‘Edmonton-like’ protocol of immunosuppression (3,27). Graft dysfunction warranting insulin therapy was considered present if CBG values were >140 mg/dl (7.8 mmol/L) fasting, or >180 mg/dl (10.0 mmol/L) postprandial on three or more occasions in a single week, or two sequential A1c values were >6.5% (28). Any subject on exogenous

insulin or who met the above criteria of graft dysfunction was eligible for enrollment into the study. Severe gastroparesis, judged clinically, was considered an exclusion criterion. Subjects were counseled as to the risks and benefits of this medication and all enrolled subjects signed an informed consent approved by the institutional review board.

Eligible subjects underwent a baseline visit and follow-up visits at our center at three and six months. Thereafter, they continued their pre-exenatide follow-up schedule at semi-annual intervals. Subjects were educated in the administration and refrigerated storage of the medication. During protocol follow-up, graft function was continuously evaluated using fingerstick capillary blood glucose (CBG) values, laboratory glucose, C-peptide, basal insulin and A1c levels (5,28). Each follow-up visit included history and physical, (including height, weight, BMI), nutritional assessment, baseline laboratory testing and stimulation testing. Mixed meal tolerance testing (MMTT) with and without administration of exenatide was performed at three and six months. At baseline, MMTT without exenatide only was performed (5).

Subjects were maintained on their immunosuppressive regimen and commenced on exenatide 5 µg twice a day, either morning and evening or with the two largest meals of the day (except one insulin independent subject who was commenced at 2.5 µg QD due to concern of hypoglycemia). Dose was increased or decreased as tolerated up to three injections and a target total daily dose (TDD) of 30 µg, in an attempt to maximize possibility of islet regeneration. At time of commencement of exenatide, insulin TDD was reduced by 30-40% as per protocol; this included cessation of all meal coverage coincident with exenatide administration, and a variable reduction in basal insulin coverage. Toxicity assessments were done at regular intervals. Immunosuppression levels were closely monitored due to the concern that altered gastric emptying may affect trough levels.

Statistical Analysis

Results are expressed as means±SEM calculated from the 6 months pre exenatide for the baseline value and the means of months 1-4 and 5-6 post treatment values. Exenatide subjects were compared to themselves pre-treatment. For each of the outcomes under consideration, we performed a repeated measures analysis of the data using linear mixed model regression. This method of analysis generalizes linear regression techniques to allow for repeated observations by taking into account the correlation that exists within observations on the same subject to more appropriately estimate variances used for the various tests of significance. Using this approach, we are able to simultaneously estimate differences from baseline at each time point post baseline while appropriately accounting for the correlation of outcomes within each patient. Correlation within subject is modeled by incorporating a random intercept term to the model. Thus, the intercept (which corresponds to baseline value of the outcome under consideration) is assumed to vary randomly among subjects following a normal distribution with some overall population mean and fixed variance. In addition to the effect of time post-exenatide on the outcome measures, we were able to incorporate other factors into the regression models in order to adjust for potential confounding factors such as insulin therapy. Thus for each of the outcome measures, we conducted an analysis using linear mixed models regression that considered the change in the outcome measure from baseline as the dependent variable and time point (month), and insulin therapy as potential explanatory variables.

Safety data is presented in an 'intent to treat' format, i.e. all 16 subjects that started on the medication are included in the analysis. The remaining data of long-term effects of the medication are presented in an "efficacy" format, i.e. only those 12 subjects that continued the medication are analyzed. The primary endpoint of the study was insulin independence. Secondary endpoints included measures of glycemic control and graft function.

Results

Seventeen subjects (six IAK, eleven IA recipients) were evaluated for enrollment into the study. Sixteen met the criteria for exenatide treatment, one IAK subject did not meet inclusion/exclusion criteria due to clinical symptoms of severe gastroparesis. All IAK and nine IA subjects were using exogenous insulin, two IA subjects were insulin independent and qualified through elevation of A1c as previously described (Table 1).

Four subjects (25%, one IA and three IAK subjects) did not tolerate exenatide and discontinued treatment after a mean of 36 ± 12 days (range 16-42), prior to any follow-up visit. Reasons for exenatide discontinuation were general malaise (n=1), exacerbation of gastroparesis (n=1) and nausea (n=2). Twelve subjects continue on the medication, current mean follow-up is 214 ± 16.5 days (range 108-287). Of these twelve subjects, eight continue on exenatide therapy alone, four received supplemental infusions, based on protocol eligibility criteria, when the primary outcome was not achieved; three during the sixth month and one during the seventh month of treatment. Data on these subjects is included up until the day of supplemental infusion. The four supplemental infusions were performed with administration of exenatide 1 hour prior to islet infusion and all resulted in re-achievement of insulin independence. Although these subjects remain on exenatide, data post supplemental infusion was not included.

Exenatide target TDD was 30 μg . Only one subject (6%) achieved the target dose at any time during the initial six months of follow-up, but this was not sustained. Seven subjects (44%) achieved a TDD of ≥ 20 μg at any time during follow-up; currently four subjects (25%) continue to take ≥ 20 μg . At six months, exenatide median TDD was 15 μg (range 2.5-25); subjects took up to four months to achieve their maximum daily dose. There was no obvious reason for the wide range in dosage observed; this was not weight related. Subcutaneous administration was well tolerated by all subjects.

The primary outcome of insulin independence was achieved in 5/16 subjects (31%). Two subjects were insulin independent prior to exenatide treatment and sustained this with a reduction in HbA1c to $< 6.5\%$. Three subjects were using 4, 5 and 9 U/day insulin and all maintained a normal HbA1c off insulin. In one subject, insulin had to be reintroduced after 3 months. Supplemental infusions were performed in four subjects who did not achieve insulin independence after 3 months or who showed little or no response to exenatide. Supplemental infusions were not performed in the remaining 11 subjects due to patient preference, previous supplemental infusion or medical contraindications.

Fifteen out of sixteen subjects (94%) experienced nausea of varying degrees. Four subjects (25%), excluding those who discontinued the medication, required dose reduction and/or prolonged continuation of a lower dose due to side effects (primarily nausea). Of the four subjects who discontinued the medication, nausea was the primary reason in two (Table 2).

Weight was measured at follow up visits only and these occurred at three and six months post onset of treatment. A weight reduction > 3 kg occurred in seven subjects (44%), requiring dose reduction in two. Maximum weight loss was 9.3 kg (13% initial body weight); this subject was trying to lose weight and had begun a diet shortly before starting exenatide. A second subject lost 5 kg in three months (9% initial body weight), exenatide dose was reduced until weight stabilized. In six subjects (38%) there was no significant weight change at three or six months (weight within 1 kg of starting weight). Overall, weight decreased, becoming significant by six months (pre: 65.5 ± 3.1 , 3 months: 64.0 ± 3.4 [diff=1.5, $p=0.052$], 6 months: 62.8 ± 3.43 [diff=2.75, $p=0.024$] kg) (Figure 1A). In general weight loss was more pronounced during the first three months, however continued during the second three months also (see figure 1A) In the twelve subjects who continued taking exenatide, weight loss was more pronounced in the first three months and less pronounced between three and six months suggesting stabilization.

Precise data regarding daily oral intake is being analyzed separately, however most subjects reported anorexia/nausea/early satiety as cause of weight loss.

During exenatide treatment, there were no episodes of severe hypoglycemia, however, 12/16 subjects (75%) experienced mild to moderate hypoglycemia, defined as a CBG reading <54 mg/dL (3.0 mmol/L) or hypoglycemia symptomatology requiring oral intake to treat (Table 3). In 11/12 subjects these events occurred while still taking basal insulin, however one subject (#13) experienced post-prandial hypoglycemia (CBG 46-49 mg/dl) 17 days after all exogenous insulin had been discontinued and this coincided with an increase in exenatide dose from 5-10 μ g twice a day. In all subjects the majority of hypoglycemic events were post-prandial. Overall there was an increase in the frequency of hypoglycemia, (6 months on exenatide: 34 events in 9 subjects [5.67 events/pt/yr] compared with 6 months pre: 29 events in 7 subjects [4.83 events/pt/yr]).

Subsequent results are presented as efficacy data, i.e. data only from the twelve subjects continuing the exenatide long term is considered. Glycemic control was significantly altered during exenatide treatment. Fasting CBG levels increased significantly at all time points following commencement of exenatide, however levels decreased over time as insulin was readjusted upward to restore normoglycemia (pre: 110.0 ± 2.9 , 1-4 months: 120.8 ± 3.0 [diff=10.9; $p < 0.001$], 5-6 months: 113.2 ± 3.1 [diff=3.2; $p < 0.001$] mg/dL). (Figure 2A/D).

Post-meal CBG values demonstrated an immediate reduction, this decreased further and reach statistical significance during months 5-6 (pre: 129.4 ± 3.8 , 1-4 months: 125.5 ± 3.8 [diff=3.84; $p = 0.06$], 5-6 months: 120.6 ± 4.0 [diff=8.8; $p = 0.0004$] mg/dL) (Figure 2B/D). The ability of exenatide to abrogate meal excursions was more clearly evident when data in exenatide-treated subjects, was sub-analyzed comparing post-prandial CBG in meals with/without exenatide (meals without exenatide 152.8 ± 7.8 , with exenatide 119.3 ± 2.1 [$p < 0.001$]) (Figure 2C).

A1c levels rose slightly during the 6 months prior to exenatide treatment (5.97 ± 0.66 to 6.46 ± 0.46 %). Exenatide treatment did not result in any significant change in A1c although levels were slightly lower by months 5-6 (pre: 6.35 ± 0.10 , 1-4 months: 6.38 ± 0.11 [NS], 5-6 months: 6.33 ± 0.13 [NS] %).

Initial iatrogenic reduction in insulin requirements over the first month of exenatide treatment was 46.27% (from 0.15 ± 0.10 to 0.08 ± 0.07 U/kg/day) as recommended in the protocol. Despite titration upwards to re-establish optimal glycemic control, levels remained significantly (28%) reduced post exenatide (pre: 0.15 ± 0.03 , 1-4 months: 0.09 ± 0.03 [diff=0.06, $p < 0.0001$], 5-6 months: 0.12 ± 0.03 [diff=0.04, $p < 0.0001$]) units/kg/day (Figure 1B).

Measures of islet function also improved significantly. Exenatide treatment resulted in a gradual increase in basal C-peptide levels which reached statistical significance during months 5-6 (pre: 1.13 ± 0.14 , 1-4 months: 1.22 ± 0.15 [NS], 5-6 months: 1.58 ± 0.17 [diff=0.46, $p = 0.001$] ng/mL) (Figure 1C). When correcting for basal glucose using C-peptide/glucose ratio (28), the elevation of C-peptide glucose ratio was also significant during months 5-6 levels (pre: 1.08 ± 0.15 , 1-4 months: 1.17 ± 0.16 [NS], 5-6 months: 1.36 ± 0.18 [diff=0.43, $p = 0.001$]) (Figure 1D).

MMTT stimulation testing at three and six months, performed without exenatide administration, demonstrated progressive improvement of the glucose AUC although without normalization of glucose values (pre - $52,332 \pm 3,219$, 3 months - $44,732 \pm 2,418$ [diff=7601, $p = 0.052$], 6 months - $42,072 \pm 1,965$ [diff=10,261, $p = 0.002$] $\text{mg} \cdot \text{min} \cdot \text{dL}^{-1}$) (Figure 3A). C-peptide AUC improved at 6 months, but did not reach statistical significance (pre: 761 ± 71 , 3 months: 707 ± 76 [diff=-54, $p = 0.30$], 6 months: 842 ± 118 [diff=81, $p = 0.35$] $\text{ng} \cdot \text{min} \cdot \text{mL}^{-1}$) (Figure 3B). When glucose levels were taken into consideration using Mixed Meal Stimulation Index, there was significant improvement by 6 months (pre: 0.50 ± 0.06 , 3 months: 0.55 ± 0.07

[diff=0.04, $p=0.31$], 6 months 0.66 ± 0.09 [diff 0.15, $P=0.03$] $\text{pMol}\cdot\text{mL}^{-1}$). There was a pronounced increase in amylin AUC (pre: **3,718** $\pm$ 781, 3 months: **6,787** $\pm$ 942 [diff=3,069, $p=0.004$], 6 months: **7,777** $\pm$ 1,504 [diff=4,060, $p=0.02$] $\text{pg}\cdot\text{min}\cdot\text{dL}^{-1}$) (Figure 3C).

To assess the acute effect of exenatide during a meal, MMTT was also performed with exenatide administration. There was marked suppression of glucose excursion when exenatide was administered (3 months, glucose AUC exenatide negative: **44,732** $\pm$ 2,418, 3 months exenatide positive: **36,635** $\pm$ 1,522 [diff=8,097, $p=0.002$] $\text{mg}\cdot\text{min}\cdot\text{dL}^{-1}$) (Figure 3D) with concomitant suppression of glucagon secretion (3 months, glucagon AUC exenatide negative: **25,681** $\pm$ 2,802, exenatide positive: **18,522** $\pm$ 1,835 [diff=7,159, $p=0.0001$] $\text{pg}\cdot\text{min}\cdot\text{dL}^{-1}$) (Figure 3E). Exenatide administration at time of MMTT resulted in lower C-peptide levels compared to testing without exenatide, although over time, C-peptide levels increased (C-peptide AUC pre: **761** $\pm$ 71, 3 months: **659** $\pm$ 111, 6 months: **771** $\pm$ 86 $\text{ng}\cdot\text{min}\cdot\text{mL}^{-1}$) (Figure 3F).

Discussion

In virtually all recipients with intraportal islet transplants under the ‘Edmonton protocol’ of immunosuppression a progressive graft dysfunction is observed over time (3-5), the etiology of which remains obscure. Future progress in β -cell replacement therapies lies in improving long-term graft function and insulin independence both of which depend on preserving transplanted islets.

The pattern of islet graft dysfunction is a gradual one in most subjects. Glycemic control through CBG testing is usually the earliest indicator. While there may be an elevation of fasting glucose levels, very often it is the coverage of meal excursions that becomes difficult for the lower mass of islets to control (5). Stimulation testing confirms this observation; we have shown that as graft function deteriorates there is progressive elevation of peak glucose, prolonged time to peak glucose, prolonged time to peak C-peptide and ultimately a reduction in peak C-peptide during MMTT, while intravenous glucose tolerance testing demonstrates a reduction/loss of first phase insulin release (29). Concomitantly there is a reduction in basal C-peptide levels, a finding that can be detected earlier if corrected for glucose levels using CPGR (28), elevation of A1c and ultimately exogenous insulin must be introduced to maintain normoglycemia.

There are several possible etiologies for the observed graft dysfunction that may be related to loss of viable islet mass and/or functional islet impairment, as listed in the introduction. The current inability to measure islet mass and the limitation of current immunological monitoring limit our ability to assess the contribution of individual etiologies. It is most likely a combination of multiple variables that contribute (7-15).

While alternative sites for transplantation (30) and strategies for immunosuppression and cytoprotection are being evaluated for *de novo* transplant recipients (31), existing transplant recipients are an excellent group to test strategies for preserving functional islet mass. With the emergence of agents that mimic or increase GLP-1 there is renewed optimism that their use in islet transplantation will result in improved long term islet function. It is clear that if effective, these agents should be introduced at the time of islet transplantation and continued indefinitely, however there is great potential benefit also in subjects with existing allografts, to stabilize or even improve existing graft function.

Explanation of results

It has already been demonstrated that transplanted islets appear to retain the ability to respond to GLP-1 (32). However, prolonged usage in this population has not yet been described.

Following at least 6 months of continuous treatment in this group of 12 subjects, consistent changes in glycemic control were demonstrated.

During the 6 months prior to onset of exenatide treatment there was an overall trend of progressive graft dysfunction with rising insulin requirements, rising glucose and A1c values without a significant change in C-peptide.

Following onset of exenatide treatment, there was an immediate improvement in postprandial CBG values which was sustained. This can be ascribed to the acute effects of exenatide which include decreased gastric emptying, increased satiety, suppression of glucagon secretion, increased glucose dependent insulin secretion and possibly increased peripheral sensitivity to insulin (33). It is not clear which is the predominant effect in this subject group. Decreased gastric emptying likely plays a large role and although not directly measured, anecdotally almost all subjects described getting full quicker and with less food and feeling fuller longer after the meal. Acetaminophen testing is prospectively underway to assess the effect of exenatide on gastric emptying. Suppression of glucagon, as demonstrated in the stimulation tests where exenatide was administered, compared with the paradoxical glucagon elevation in response to a meal typically seen in patients with T1DM and noted during stimulation testing without exenatide, is likely another important contributor to the change in blood glucose levels.

The initial deterioration in fasting CBG values observed can be explained by the pre-emptive reduction in exogenous insulin to avert hypoglycemia. As exogenous insulin was optimally titrated, fasting CBG levels approached baseline. Although the insulin reduction initially was iatrogenic, a significant reduction was sustained at 6 months. It could be considered that acutely, the metabolic effects of exenatide during a meal, replaced the short acting insulin for meal coverage; by preventing higher post prandial glucose excursions, however, it may have allowed for less basal coverage also.

There was no change in A1c levels likely due to the fact that A1c levels were near normal in all patients at onset of exenatide treatment (6.36 ± 0.10 % pre-exenatide) and the effect of exenatide was more that of insulin reduction while maintaining the same glycemic control. There was justified concern of hypoglycemia in subjects on insulin and exenatide, so insulin levels were titrated slowly with the aim of normalizing A1c. Weight reduction pattern was very variable. While the majority subjects did experience weight loss, almost half of the subjects were within 1kg of their starting weight by 6 months. While weight loss is well described in patients with type 2 diabetes (23-26), it was not clear if weight loss would occur in T1DM exenatide-treated subjects since they were of normal weight at baseline. The weight loss seen in the subjects described herein coincided with side effects and was reversed as dose related side effects resolved.

There is a wealth of evidence that GLP-1 and GLP-1 receptor agonists can improve metabolic control (32,34-35), reduce apoptosis (36) and increase islet neogenesis and regeneration in a variety of animal models of diabetes (19-20,37-40). The interesting question remains whether long term administration can increase islet mass in human islet transplant recipients. Since there is no test to assess islet mass at this time only indirect measures can be used (basal C-peptide/CPGR). Both of these measures, basal and stimulated, demonstrated a progressive and persistent increase after 3-4 months of treatment when compared with 6 months prior to exenatide treatment which was statistically significant. Stimulation testing demonstrated a significant reduction in glucose AUC and a trend towards improved C-peptide response despite lower glucose values during a meal challenge. These effects are most likely insulinotropic rather than an increase in islet mass, however treatment in a small group of subjects continues to see if the trend continues to improve. Our findings were similar to those of Ghofaili et al,

although treatment was for a shorter period of time and they did not demonstrate a change in C-peptide levels therefore concluding that there was no trophic effect on islets

Response to exenatide was not uniform across the group. Further evaluation of individual subjects showed that some subjects responded better (n=5) to exenatide than others (n=7). Due to the uniformity of immunosuppressive regimen it was not possible to evaluate individual immunosuppressive drug toxicity. In the responders, however, pre-exenatide, indicators of graft function tended to be better; C-peptide levels (1.4 ± 0.5 vs. 1.1 ± 0.7 ng/ml), C-peptide/glucose ratio (1.4 ± 0.7 vs. 0.9 ± 0.5) and 90 minute glucose from MMTT (199.4 ± 53.5 vs. 248.3 ± 57.0 mg/dl). Additionally, post operative day at time of commencement of exenatide (973.8 ± 325.1 vs. 1281.7 ± 195.0 days) and duration of graft dysfunction (366.6 ± 250.1 vs. 654.1 ± 383.5 days) were lower. None, however, reached statistical significance. Response therefore, may be limited to varying degrees by the marginal residual functional islet mass, ongoing immunological events, continued toxicity/anti-regenerative effects of immunosuppression (tacrolimus and/or sirolimus), or reduction in efficacy of exenatide e.g. by exenatide antibodies.

Lessons learned

The tolerated dose of exenatide in islet allograft recipients with T1DM is lower than that reported in patients with T2DM. At standard doses, side effects were significantly more frequent and resulted in a significantly higher number of subjects that discontinued the medication compared with studies in T2DM (23-26). Nausea was the most frequent side effect, however, there were a higher number of subjects that complained of lower gastrointestinal side effects (diarrhea and constipation) and CNS side effects, namely fatigue, decreased concentration/mood alteration associated with acute injection. In our study population, the side effect frequency and profile suggests a greater sensitivity to exenatide. Despite lower doses, metabolic effects were clearly apparent. Following adequate dose adjustment, all subjects continued to tolerate the medication well. Those that discontinued the medication did so relatively early (mean exenatide duration 36 ± 12 days (range 16-42)).

Reported hypoglycemia secondary to exenatide is rare in patients with T2DM occurring with concomitant sulfonylurea administration. By comparison, in subjects with T1DM and functional transplanted islets there is a significant risk of hypoglycemia. This may be explained by the normal/near-normal fasting glucose levels, dysregulation of transplanted islet in the liver where cessation of insulin secretion may be delayed and glucagon secretion inhibited by exenatide, limiting recovery mechanisms. Hypoglycemia is also exacerbated by the presence of exogenous insulin particularly concomitant meal coverage.

This study is limited by the lack of a randomized control group. It was elected to use subjects as their own controls given the small sample size.

We believe that the overall effect of exenatide administration in islet transplant recipients with graft dysfunction has been a positive one resulting in a reduction in insulin requirements, possible stabilization of graft dysfunction versus improved graft function at a cost of additional injections and the side effects experienced, perhaps the most concerning of which is hypoglycemia. These results are preliminary, and conclusive evidence of increased islet mass will likely take considerable time to gather. Unfortunately several subjects underwent a supplemental infusion and their long term data will not be available, however eight subjects continue on the medication at this time. Those undergoing re-infusion continued taking exenatide in an effort to improve engraftment, their data is under evaluation (42).

While regeneration cannot be proven, there has been no further deterioration in graft function in any recipient suggesting, at the very least, the gradual deterioration previously described may be ameliorated by exenatide. A non-injectable preparation with longer action would likely

be more beneficial while the use of exenatide is better indicated from the time of initial islet transplantation when preservation of islet mass at time of implantation would likely reduce the large islet losses at this time thereby improving acute outcomes (single donor insulin independence) as well as long term graft function.

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Abbreviations

CBG	Capillary Blood glucose (fingerstick)
CPGR	C-peptide/Glucose ratio
GLP-1	glucagon like peptide-1
IA	islet alone transplant recipient
IAK	islet after kidney transplant recipient
MMTT	mixed meal tolerance test
SSI	mixed meal stimulation index
TDD	total daily dose
T1DM	type 1 diabetes mellitus

Figure 1.

Panel A. Weight changes in exenatide subjects. Single measure in each subject at follow up visits demonstrates weight loss during initial 3 months with some stabilization thereafter (mean pre: 65.5 ± 3.1 (n=16 range 48.2-92.3), 3 months: 64.0 ± 3.4 (n=14 range 48.2-91.8) [diff=1.5, $p=0.052$], 6 months: 62.8 ± 3.43 (n=14 range 44.1-92.3) [diff=2.75, $p=0.024^*$] kg

Panel B. Monthly Mean $\pm$ SEM insulin requirements (ins/Day) demonstrate a significant reduction at all time points. Initially reduction is iatrogenic but at the end of 5/6 months of treatment, insulin requirements remain significantly decreased (pre: 0.15 ± 0.03 , 5-6 months: 0.12 ± 0.03 [diff=0.04, $p < 0.0001$]). By comparison, insulin requirements tend to increase over the 6 months prior to exenatide.

Panel C/ D. Exenatide subjects demonstrated a significant increase in C-peptide levels by 5-6 months post treatment compared to baseline (pre: 1.13 ± 0.14 , 1-4 months: 1.22 ± 0.15 [NS], 5-6 months: 1.58 ± 0.17 [diff=0.46, $p=0.001$] mg/dL) and CPGR (pre 1.08 ± 0.15 , 1-4 months: 1.17 ± 0.16 [NS], 5-6 months: 1.36 ± 0.18 [diff=0.43, $p=0.001$]).

Figure 2.

Panel A. In exenatide subjects fasting CBG levels increase significantly at all time points, although values are approaching baseline by 5-6 months (pre: 110.0 ± 2.9 , 1-4 months: 120.8 ± 3.0 [$p < 0.001$], 5-6 months: 113.2 ± 3.1 [$p < 0.001$] mg/dL).

Panel B. In exenatide subjects reduction in postprandial CBG levels is immediate and significant by 6 months (pre: 129.4 ± 3.8 , months 1-4: 125.5 ± 3.8 [$p = 0.06$], months 5-6: 120.6 ± 4.0 [$p = 0.0004$] mg/dL).

Panel C. Sub-analysis of meal excursions demonstrates more clearly the acute effects of exenatide. During months 5-6 of treatment, meal excursions are markedly diminished when exenatide is administered; when exenatide is not administered, excursions are greater than baseline likely secondary to a reduction in TDD insulin. Post meal CBG values (mean $\pm$ SEM): meals without exenatide 152.8 ± 7.8 ; meals with exenatide: 119.3 ± 2.1 [diff = 16.2 $p < 0.001$] mg/dL.

Panel D. In exenatide-treated subject only, chronological changes in preprandial and postprandial CBG levels are shown (mean $\pm$ SEM) during the follow-up period and compared to stable levels prior to initiation of exenatide.

Figure 3.

Panel A. In exenatide subjects levels of glucose during MMTT (without exenatide administration) demonstrated a progressive decrease over time, significant at 6 months (Glucose AUC pre: $52,332 \pm 3,219$, 3 months: $44,732 \pm 2,418$ [diff=7601, $p=0.052$], 6 months: $42,072 \pm 1,965$ [diff=10,261, $p=0.002$] $\text{mg} \cdot \text{min} \cdot \text{dL}^{-1}$).

Panel B. In exenatide subjects CPGR during MMTT (without exenatide administration) demonstrated a progressive increase over time, significant at 6 months (CPGR AUC pre: 469 ± 56 , 3 months: 502 ± 64 [diff=36, $p=0.40$], 6 months: 616 ± 85 [diff=149, $p=0.03$]).

Panel C. In exenatide subjects levels of Amylin during MMTT (without exenatide administration) demonstrated a progressive increase over time, significant at both 3 and 6 months (Amylin AUC pre: $3,718 \pm 781$, 3 months: $6,787 \pm 942$ [diff=3,069, $p=0.004$], 6 months: $7,777 \pm 1,504$ [diff=4,060, $p=0.02$] $\text{mg} \cdot \text{min} \cdot \text{dL}^{-1}$).

Panel D. In exenatide subjects levels of glucose during MMTT (with and without exenatide administration) at 3 months post treatment demonstrated near complete abrogation of the glucose peak following meal ingestion resulting in significant reduction in glucose AUC (Glucose AUC pre: $52,332 \pm 3,219$, 3 months exenatide negative: $44,732 \pm 2,418$, 3 months exenatide positive: $36,635 \pm 1,522$ [diff=8,097, $p=0.002$] $\text{mg} \cdot \text{min} \cdot \text{dL}^{-1}$).

Panel E. In exenatide subjects levels of glucagon during MMTT without exenatide administration demonstrated abnormal elevation of glucagon levels following meal ingestion, while during MMTT with exenatide administration, glucagon secretion was completely inhibited resulting in significant reduction in glucagon AUC (Glucagon AUC pre: $23,865 \pm 3,077$, 3 months exenatide negative: $25,681 \pm 2,802$, 3 months exenatide positive: $18,522 \pm 1,835$ [diff=7,159, $p=0.0001$] $\text{mg} \cdot \text{min} \cdot \text{dL}^{-1}$).

Panel F. In exenatide subjects levels of C-peptide during MMTT with exenatide administration were lower compared to levels during MMTT without exenatide administration although when comparing C-peptide AUC during MMTT with exenatide administration at 3 and 6 months post treatment there was a progressive rise (C-peptide AUC pre: 761 ± 71 , 3 months exenatide positive: 659 ± 111 , 6 months exenatide positive: 771 ± 86 ng·min·mL⁻¹).

Table 1

Patient Demographics and Baseline Metabolic Control

Subject ID	Transplant Type	Age (years)	Weight (Kg)	BMI (Kg/m ²)	Islet infusions (No.)	Insulin Independence (POD)	Graft Dysfunction (POD)	Islet Transplant f/Insulin Requirement (POD)	Exenatide Treatment Onset ***				Max dose Exenatide (µg)	Exenatide Treatment Duration (days)
									Transplant f/Insulin Requirement (Units)	A1c (%)	Requirement (U/Kg/day)			
1	IA	37	67.3	25.1	2	36	1233	1520	5.8	7.2	0.09		15	
2	IA	43	75	24.8	2	42	1440	1514	3	7.2	0.03			41
3	IA	48	62.3	22.5	3	33	296	1455	16.7	6.9	0.23		20	
4	IA	40	92.3	26.8	1	45	679	1401	12.1	6.2	0.13		20	
5	IA	56	76.4	21.6	2	50	1244	1358	0	6.7	0		20	
6	IA	64	86.8	27.5	3	76	118	1348	28	6.1	0.32		10	
7	IA	60	55.5	21.7	2	108	451	1212	7	6.3	0.12		30	
8	IA	52	70.5	22.6	2	40	683	1100	9.9	6.1	0.14		25	
9	IA	38	53.6	20.3	2	53	609	1076	3.4	6.5	0.07		15	
10	IA	53	60	20.7	1	1	658	1066	18.4	6.1	0.31		15	
11	IA	39	47.7	19.6	1	52	491	757	0.5	6.8	0.06		15	
12	IAK	53	64.1	24.1	1	1	281	1027	16.1	6	0.25			42
13	IAK	39	52.7	21.3	2	126	535	989	10	6.8	0.19		15	
14	IAK	54	61.8	20.1	2	48	579	947	8.5	6	0.12			18
15	IAK	45	56.4	22	2	114	308	567	7.9	6.2	0.15		20	
16	IAK	49	55.9	20.8	2	114	441	441	10.9	6.8	0.19			42
Mean±SEM		48.1±2.1	64.9±3.1	22.6±0.6		55.0±9.5	640.3±99.1	1111.1±81.2	9.9±1.8	6.5±0.1	0.2±0.02		18.3±1.6	35.8±5.9

Bold = received a supplemental infusion during exenatide treatment

*** mean 1 month pre-exenatide commencement

‡ never achieved insulin independence

Add demographics of other 4 that started the medication

Table 2

Side effects associated with Exenatide treatment

Side Effect	Total Frequency		Mild (Grade 1)*		Moderate (Grade 2)*		Severe (Grade 3)*		Dose Reduction	
	#	%	#	%	#	%	#	%	#	%
n=16										
Nausea	15	94	10	63	5	31	0	0	7	44
Constipation	3	19	2	13	1	6	0	0	0	0
Diarrhea	5	31	4	25	1	6	0	0	0	0
Fatigue/ weakness	3	19	2	13	1	6	0	0	0	0
Jittery	2	13	2	13	0	0	0	0	0	0
Decreased concentration	3	19	3	19	0	0	0	0	0	0

* NCI criteria (version 3.0B)

Table 3
Hypoglycemic events in islet transplant recipients receiving exenatide treatment

HYPOGLYCEMIA										
Subject	Events Pre Exn	Events Post Exn	Timing of Post Exn Events (#)			POD Exn 1 st Hypo	Relation to Insulin Rx (#)		Exn Dose Range (µg)	
			Pre Meal	Post Meal	Not Meal related		Meal Bolus	Basal Only		No Insulin
1	2	4	0	3	1	18	0	5	N/A	1.25-5
2	1	5	1	3	1	10	0	6	N/A	0-10
3	3	5	1	4	0	100	4*	0	N/A	10
4	None	None								
5	None	None								
6	1	5	0	5	0	6	0	6	N/A	5-10
7	8	5	3	2	0	29	2*	3	N/A	10
8	None	1	0	1	0	6	0	1	N/A	5
9	12	8	1	6	1	0	0	4	N/A	5
10	1	5	1	4	0	2	0	4	N/A	2.5-5
11	None	3	0	3	0	31	1*	3	N/A	2.5
12	None	None								
13	None	4	0	4	0	32	0	0	4	10
14	None	1	0	1	0	7	0	1	N/A	5
15	1	None								
16	2	0	0	1	0	25	0	1	N/A	5

* meal coverage became necessary when exenatide alone was not sufficient to prevent post prandial hyperglycemia.