Published in final edited form as:

Transplantation. 2009 January 15; 87(1): 154. doi:10.1097/TP.0b013e318191ebe9.

Exenatide Use in Islet Transplantation - Reasons to Remain Optimistic

Tatiana Froud^{1,3}, Camillo Ricordi^{1,3}, and Rodolfo Alejandro^{1,2}

¹ University of Miami Miller School of Medicine, Diabetes Research Institute

² University of Miami Miller School of Medicine, Department of Medicine

³ University of Miami Miller School of Medicine, Department of Surgery/Radiology

Keywords

Islet Transplantation; Beta cell function; GLP-1 agonists; Islet graft survival

There is no doubt that six months of follow up is a short duration and not sufficient to evaluate the longer durability of this treatment; however, the primary purpose of this study was to examine the short term effects (efficacy and safety) of exenatide administration in a group of subjects that have clear potential benefits, primarily the re-achievement of insulin independence and possible prevention of further graft loss/improvement of graft mass. While one subject did require reintroduction of insulin, 4/12 subjects taking the medication achieved and sustained insulin independence. Another four subjects went on to have supplemental infusions since they did not achieve insulin independence in the short time frame allocated.

Overall there was a significant reduction in insulin requirements. This was greater between the 1–4 months due, at least in part, to an intentional insulin reduction at the onset of exenatide therapy, to avoid the potential risk of hypoglycemia. Hypoglycemia was shown to be a more frequent complication than anticipated, however did not reach severe proportions. Our theory as to its mechanism, in no contradiction to those published, is that this is due to some excessive insulin secretion, with delayed gastric emptying at the time of nutrient ingestion and suppression of glucagon secretion reducing hepatic glucose production. Perhaps more concerning is the recent awareness of a possible link between hemorrhagic pancreatitis and exenatide. To date we have not experienced this and we are optimistic that coexisting conditions/risk factors, as suggested by Amylin/Lilly (recent communication), may be responsible. Alternative agents that increase GLP-1 levels such as sitagliptin (Januvia™ Merck & Co., Inc. USA) may be as effective with fewer side effects and greater patient acceptance.

Following the positive results in this pilot study, we went on to use exenatide from the time of islet infusion. Our hypothesis, that exenatide will prevent some of the large losses of islets that occurs during infusion and engraftment, while preserving functional islet mass over time was affirmed in subjects undergoing supplemental infusions (re-transplant) for graft dysfunction (see figure). Results were recently presented at the 22nd International Congress of the Transplantation Society in Sydney (1) and show prolonged insulin independence and improved islet function at 18 months compared with historical controls re-transplanted without exenatide (manuscript in press).

Further studies at our institution demonstrate anti-apoptotic, anti-inflammatory and immunomodulatory effects of exenatide during islet isolation and culture, specifically increased PI-9, reduction in tissue factor, activation of Akt and reduction in multiple inflammatory cytokines, which further increase the rationale for the use of the drug (2). It is largely accepted that exenatide has effects that are very beneficial in islet transplantation. Indeed, the NIH Clinical Islet Transplant Consortium reviewed and unanimously approved the randomized prospective trial testing exenatide in islet transplantation. This trial, which we proposed over 2 years ago, is already in progress, with patient enrollment and recruitment well underway and we eagerly anticipate the results.

Acknowledgments

We would like to thank Dr. Rickels for his comments on this publication and are gratified to see that this manuscript has sparked some debate.

References

1. Froud T, Faradji RN, Tharavanij T, et al. Long Term Insulin Independence and Restoration of First Phase Insulin Release after Supplemental Islet Infusion under Exenatide Treatment in Subjects with Islet Graft Dysfunction. *Transplantation* 2008;86(2S) abstract number 245.
2. Cechin SR, Perez-Alvarez I, Ochoa MS, Ricordi C, Fenjves ES. Exenatide (Byetta) Activates Anti-Inflammatory and Anti-Apoptotic Pathways in Human Pancreatic Islets. *Diabetes* 2008;57(S1):A466. abstract number 1678-P.

Durability of Insulin Independence Following Supplemental Infusion

Figure.