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INVITED COMMENTARY

Liraglutide in islet transplantation: from bench to bedside*

Thierry Berney

Department of Surgery, Geneva University Hospitals and University of Geneva School of Medicine, Geneva, Switzerland

Correspondence
Thierry Berney MD, MSc, Division of Visceral and Transplant Surgery, Department of Surgery, Geneva University Hospitals, 4, rue Gabrielle-Perret-Gentil, 1211 Geneva 14, Switzerland. Tel.: +41 22 372 34 04; fax: +41 22 372 77 07; e-mail: thierry.berney@hcuge.ch

*Commentary on ''Liraglutide, a long-acting human glucagon-like peptide 1 analogue, improves human islet survival in culture.'' by Toso *et al.*

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In this issue of Transplant International, Toso *et al.* [1] provide us with data of great translational potential that are likely to be of almost immediate relevance for the field of clinical islet of Langerhans transplantation. In this article, the authors have studied the impact of treatment with liraglutide, a glucagon-like peptide-1 (GLP-1) analogue, both *in vitro* and *in vivo*, on human islet viability and engraftment. They show that short-term culture of human islets in the presence of liraglutide in the culture medium results in a lower rate of islet cell apoptosis and thus, in higher rate of islet recovery after 48 h. Beta-cell function was also improved as demonstrated by higher levels of glucose-stimulated insulin release. Importantly, these beneficial effects could be carried over after transplantation to diabetic immunodeficient mice and even prolonged by *in vivo* treatment of islet recipients for a certain time [1].

Glucagon-like peptide-1 is an intestinal hormone secreted by the L-cells upon oral food intake and responsible for the ''exendin effect'', i.e. the incremental insulin release observed after oral versus intravenous glucose administration [2]. GLP-1 exerts its effects both by stimulating insulin release by beta-cells and by inhibiting glucagon release by alpha-cells. In addition, GLP-1 was shown to protect beta-cells from apoptosis and to induce beta-cell proliferation, or rather differentiation of intrapancreatic precursor cells into insulin-secreting beta-cells, mostly by upregulation of PDX-1 expression [2]. One of the most important recent advances in the treatment of type 2 diabetes has been the development of the synthetic GLP-1 analogues, exenatide and liraglutide. In clinical trials, both agents, used either in combination or as monotherapy, have been efficient at lowering HbA1c [3].

Their remarkable pattern of effects conceptually makes GLP-1 analogues an ideal adjunct therapy for islet of Langerhans transplantation. Indeed, treatment with GLP-1 analogues could impact positively on engraftment, function and survival of islet grafts, all of which have been identified as key targets for the improvement of the results of clinical islet transplantation [4]. In particular, it seems now obvious that the next wave of improvement in

clinical islet transplantation will come from strategies that will successfully prevent immediate islet cell damage, rather than from novel immunosuppressive regimens.

Exenatide (Byetta, Eli-Lilly, Indianapolis, IN, USA) was approved by the US FDA for the treatment of type 2 diabetes in 2005. A few groups in North America took advantage of its commercial availability to add exenatide to their clinical islet transplant protocols, either for the enhancement of engraftment or for the rescue of failing grafts [5–8]. Overall, in these pilot trials, exenatide was more successful when administered at the time of transplantation than later as a rescue strategy. These results must be analysed with caution because of the small numbers of patients studied, the non-randomized nature of the trials and the difficulty to tolerate target doses of the drug for a significant proportion of patients because of side effects (nausea, vomiting).

Liraglutide (Victoza, Novo-Nordisk, Bagsvaerd, Denmark) has received marketing authorization in Europe in the third quarter of 2009. Liraglutide has a longer half-life than exenatide, which offers the advantage of once daily administration. It is also better tolerated, thanks to less pronounced side effects [3]. Liraglutide was tested on rodent and large animal islets *in vitro* and in experimental models of islet transplantation. These studies essentially confirmed the cytoprotective potential of this particular GLP-1 receptor agonist [9–11].

Interestingly, in spite of the considerable interest generated by GLP-1 analogues in the treatment of diabetes in general, and for islet transplantation in particular, it is the first time that one of these compounds is tested on a scientific and systematic basis on human islets. Confronting the experimental data reported in the paper by Toso *et al.* [1] and the clinical observations obtained with exenatide [5–8], one gets a clearer idea on what to expect from liraglutide treatment in a clinical protocol of islet transplantation and on how to administer it. First, liraglutide should be started in the pre-transplant period, probably with a dose escalation trial, to ensure that patients will tolerate the drug at its most efficient dosage and have a sufficient impregnation at the time of transplant. Second, islets should be cultured short-term [12] in the presence of liraglutide. Combination of liraglutide pre-treatment of the recipient as well as of the islets at the time of transplant should confer optimal cytoprotection precisely when islet cells are at their most vulnerable and the inflammatory phenomena they have to face at their most intense. Third, liraglutide treatment of the recipients should be continued for an as-yet-undetermined period of time to maintain the beneficial GLP-1 effects on islet cell survival, function and possibly, proliferation.

The time is right for a prospective randomized placebo-controlled study that will evaluate liraglutide treatment of islet grafts and their recipients. The most relevant endpoints would be the achievement of insulin-independence with single donor islet transplantation to assess engraftment and duration of insulin independence/graft function to assess graft survival. A multicenter trial is expected to be launched shortly with these aims and design, under the leadership of the University of Alberta. This collaborative effort, it is hoped, will prove to be a good example of bench-to-bedside research application and may provide a landmark in the sequence of small steps and quantum leaps that have characterized the timeline of progress in clinical islet transplantation.

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