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The Path for Tolerance Permissive Immunomodulation in Islet Transplantation

Camillo Ricordi

Diabetes Research Institute and Cell Transplant Program, University of Miami, Miami, Florida

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Clinical islet transplantation has progressed significantly over the past three decades (1, 2). Major collaborative efforts have contributed to a progressive improvement of both immunosuppressive strategies and the complex sequential procedural steps required for manufacturing of human islet cell products (2, 3, Figure 1). Islet allotransplantation has been approved in selected countries for treatment of the most severe forms of type 1 diabetes mellitus (T1DM), such as those associated with hypoglycemia unawareness and an increased risk for severe hypoglycemic episodes. A multicenter FDA Phase III trial, which included centers in North America and Europe, has been completed and may lead to approval and eventual reimbursement of the procedure also in the USA. However, for islet transplantation to become applicable to most patients with T1DM and possibly also to other forms of insulin-requiring diabetes it is now critically important to re-focus collective efforts on the development of successful strategies for transplantation of insulin producing cells in the absence of continuous recipient immunosuppression, towards what has been for decades the Holy Grail of transplantation: immune tolerance. Unfortunately, traditional immunosuppressive protocols, while successful at controlling the effector phase of the immune response and early autoimmune recurrence, may not be highly conducive to tolerance induction. To achieve this goal, it is important to develop novel approaches of immunosuppression/immunomodulation that are compatible with the survival, function, and post-transplant expansion of regulatory cell subsets. The recent paper by Maffi and collaborators (4) represents an excellent step in this direction. The protocol was in fact designed to avoid immunosuppressive agents with mechanism of action that can affect TCR signaling and/or calcineurin pathways, that could be detrimental to the survival, expansion and/or function of regulatory cells (4). In contrast, rapamycin has been associated with both expansion of human regulatory cells in vitro and promotion of their immunomodulatory function in vivo, without affecting IL-10 mediated regulatory pathways (4). However, some of the challenges associated with the requirement of balancing an adequate T cell directed induction immunosuppression with a regulatory permissive overall immunomodulatory strategy have also been highlighted. In fact, it was of interest that all early graft losses

(median graft survival of 37 days) were observed in recipients treated with lower doses of Antithymocyte Globulin (ATG) in the induction phase of immunosuppression. In these subjects, a less efficient depletion of CD3/CD8 T lymphocytes (in particular memory subset) was also observed (4) and none of them reached the primary endpoint of insulin independence at 3 years. In addition, a de novo, post islet infusion expression of auto- and/or allo-antibodies was more often observed in these patients. In striking contrast, the total median islet graft survival in islet transplant recipients treated with higher dose ATG induction was > 1,616 days and 4 out of 5 of them did reach the 3 year primary endpoint of insulin independence. Other variables that may have contributed to the success of this protocol in subjects receiving higher dose ATG induction treatment could include the selected peri-transplant anti-inflammatory strategy and recipient treatment with Granulocyte Colony Stimulating Factor (GCSF), whose administration has been associated with tolerance-permissive, regulatory cell promoting effects. Interestingly, the association of low dose ATG (2.5 mg/kg, IV) followed by pegylated GCSF (Neulasta; 6 mg SQ q2 weeks x 6 doses) was recently reported to have a significant effect on preservation of AUC C-Peptide in subject with T1DM compared to placebo treated subjects (Haller MJ et al. ADA 2014, 173-OR) and this effect was associated with preservation of regulatory T cells and increased T regulatory: T memory ratios. However, GCSF variable has not been discussed in the context of the observed outcomes of the reported pilot clinical trial (4). The encouraging results reported using the “regulatory cell accommodating” protocol (4) are timely also in the context of the recently increased clinical interest in tolerance induction protocols that could have a profound impact on the future of islet transplantation and the large-scale expansion of its indications. In fact, trials using expanded regulatory T cells are already in progress in T1DM and exciting results have been recently reported using bioengineered mobilized cellular products enriched for hematopoietic stem cells and tolerogenic cells (5) in combination with a nonmyeloablative conditioning that has resulted in stable high level chimerism and tolerance induction in recipients of highly mismatched kidney allografts (5). These very encouraging results using different strategies with tolerance accommodating and tolerance inducing protocols warrant additional efforts and re-focusing of our collective attention on the path for tolerance induction.

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Figure 1.