COMMENT ON HARLAN

Islet Transplantation for Hypoglycemia Unawareness/Severe Hypoglycemia: Caveat Emptor. Diabetes Care 2016;39:1072–1074

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Harlan (1) states that the benefits of islet transplantation in type 1 diabetes (T1D) are limited to patients already taking immunosuppressive agents because of having received a kidney transplant. We strongly disagree. The Clinical Islet Transplantation Consortium phase 3 trial (CIT-07) demonstrated the effectiveness of islet transplantation in restoring near normoglycemia, hypoglycemia awareness, and protection from severe hypoglycemic events in T1D patients with persistent severe hypoglycemic episodes (SHE) who are immunosuppressed only for the purpose of protecting the islet graft from rejection and autoimmune recurrence (2). The position of Harlan (1) seems to be that the morbidity and mortality of T1D complicated by persistent and unpredictable SHE are not sufficiently high to justify the immunosuppressive risks associated with an islet transplant–based approach. We disagree, and we feel that consideration of the risks and benefits of islet transplantation will result in a net benefit for some carefully selected patients. That evaluation and decision must be made on an individual basis, by a patient and his/her physician.

Harlan (1) expresses concern about the decline in islet graft function over time. We share that concern. However, at 2 years after the first islet transplant, the primary end point of the study continued to be met by 71% of participants; >90% of recipients remained protected from SHE and the median HbA_{1c} was 5.6% (2). Prolonged protection from SHE is not dependent upon freedom from use of exogenous insulin. As reported by the Collaborative Islet Transplant Registry in 2012, regardless of sustained graft survival, >90% of all T1D islet allograft recipients in its database remained free of SHE through 5 years of posttransplant follow-up (3). For comparison, follow-up of participants with T1D and impaired awareness of hypoglycemia in studies evaluating medical interventions rarely exceeds 1 year (4). We continue to follow patients from the CIT-07 study to evaluate the persistence of graft function and freedom from SHE.

Harlan (1) expresses concern about the decrease in renal function seen in the patients in the CIT-07 trial. We share that concern; although the measured glomerular filtration rate remained in the normal range, the decrease from 102 at baseline to 82 mL/min/1.73 m^2 at 2 years after the first islet transplant is concerning. This decrease may in part be attributable to correction of hyperfiltration in a normoglycemic environment (5), but it is most likely attributable to the use of calcineurin inhibitors. This observation is the reason that we believe, as stated in our article (2), that widespread application of islet transplantation for T1D will be inappropriate until there are less toxic immunosuppressive regimens or reliable approaches for inducing immunological tolerance to the transplanted islets.

Finally, Harlan (1) discourages islet transplantation for the treatment of T1D and recurrent SHE even in people who failed expert medical therapy without offering these high-risk patients a tested, viable, and available alternative intervention. As emphasized in our article (2), certainly all available technologies/treatments for T1D, including the use of less stringent HbA_{1c} goals and educational/behavioral interventions, should be used before consideration of islet transplantation. Although patients with intractable SHE were explicitly excluded from the trials that were the basis for licensure of advanced open and closed loop devices, those trials demonstrate a reduction of the number of hypoglycemic events and the time spent in the hypoglycemic range. Thus, it would be reasonable to try these technologies to reduce SHE before concluding that a patient is a good candidate for islet transplantation. Currently, the best tested and most viable intervention for those who continue to have SHE despite educational and

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behavioral programs and use of the most sophisticated diabetes technologies is pancreatic islet transplantation.

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