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COMMENTARY

Pancreatic islet transplantation in type 1 diabetes: Current state and future perspectives

Recently, Braulio Marfil-Garza *et al.*[1] reported long-term outcomes after islet transplantation in individuals with type 1 diabetes. In the report, 255 patients with type 1 diabetes receiving allogenic islet transplantation were included and followed for up to 20 years at the University of Alberta Hospital, Edmonton, Canada. As shown in Table 1, graft survival decreases by time and becomes stabilized at nearly 50% 15 years after islet transplantation. The median time of graft survival was 5.9 years. Glycemic control was significantly improved after islet transplantation. Near half of the patients maintained good glycemic control (defined by hemoglobin A1c <7%) 20 years after islet transplantation. In addition, the risk and severity of hypoglycemia was significantly reduced throughout the follow-up period. However, although insulin independence ever occurred in 79% of patients at a median of 95 days after islet transplantation, most patients still require insulin for glycemic control in the long term. The median duration of insulin independence was 2.3 years. At 5 years, only 32% of patients were insulin independent and the numbers decreased by time, as shown in Table 1. Meanwhile, insulin requirement decreased markedly and rapidly to 20% of baseline 1 year after islet transplantation. The mean insulin requirement during the whole follow-up period was between 20 and 30% of baseline, and was slowly increased by time. During follow up, 49.8% of the patients had ever used non-insulin glucose-lowering agents. Life-threatening infections occurred in 13% of patients, and cancers developed in 13% of patients.

Findings from the report[1] give us a great picture of long-term outcomes after islet transplantation in type 1 diabetes, which is in agreement with the reports in the literature,[2–4] and suggests that islet transplantation in type 1 diabetes can improve glycemic control, reduce severe hypoglycemia and decrease insulin requirement. However, the rate of insulin independence was low, 9.3% at the 5th year in the report from Switzerland,[2] and just 4.8% in the report from France,[4] which is similar to the Canadian report.[1] In addition, the average number of islet infusion in these reports were between two to three times per participant, and the graft survival decreased by time in all these studies, although the numbers varied in different cohorts that used different definitions of graft failure. In 2018, the International Pancreas & Islet Transplant Association and European Pancreas & Islet Transplantation Association held a workshop in Igls, Austria, to develop a consensus on defining outcomes for β-cell replacement therapy.[5] The Igls criteria evaluate graft functional status by hemoglobin A1c, severe hypoglycemic events per year, insulin requirements and fasting or stimulated C-peptide levels. Optimal or good graft functional status is defined by hemoglobin A1c ≤6.5% or <7%, the absence of severe hypoglycemic event, insulin independence or insulin requirement <50% compared with that before transplantation and an increase in C-peptide levels after transplantation, and both optimal and good graft functional status are regarded as treatment success. Based on these criteria, the current long-term status of islet transplantation succeeds in avoidance of severe hypoglycemia and marked reduction in insulin requirement, but fails partly in glycemic control and graft survival. After 15–20 years, only approximately half of the patients could maintain hemoglobin A1c <7% and a fasting C-peptide level >0.1 nmol/L (>0.3 ng/mL).[1] Furthermore, as the cut-off value for C-peptide level is higher in the Igls criteria (0.17 nmol/L or 0.5 ng/mL), the percentage of participants with graft survival in the Canadian report should be even lower by the Igls criteria.

In the report, combined use of anakinra plus etanercept and a high BETA-2 score within 1 year after the first islet infusion were predictors of sustained graft survival. In this cohort, the use of anti-inflammatory drugs included anakinra alone, etanercept alone, anakinra plus etanercept, infliximab and none. Only the use of anakinra plus etanercept was significantly higher in patients with sustained graft survival, compared with patients with non-sustained graft survival. In contrast, use of infliximab or without the use of anti-inflammatories were lower in patients with sustained graft survival. These findings suggest that dual anti-inflammatories, anakinra plus etanercept, might be a better choice over other anti-inflammatory drugs for graft survival. In contrast, BETA-2 score represents a combined evaluation of graft survival, glycemic control and insulin requirement, which is derived from a formula using data of fasting C-peptide, insulin dose, fasting plasma glucose and hemoglobin A1c. Findings from the Canadian report extend its usefulness to the prediction of long-term graft survival.

During the 20-year follow-up period, mortality and the percentage of participants with end-stage renal disease (ESRD), dialysis or kidney transplantation were not reduced in patients with sustained graft survival, compared with patients with non-sustained graft survival in the report.[1] These findings show that

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Table 1 | Long-term outcomes after islet transplantation in participants with type 1 diabetes in the Canadian cohort[1]

Time after first islet transplantation	1 year	5 years	10 years	15 years	20 years
Graft survival[†]	94%	75%	58%	50%	48%
Hemoglobin A1c <7%	73.7%	53.2%	47.5%	48.9%	55.5%
Risk of hypoglycemia	Significantly reduced during the whole follow-up period				
Insulin independence	61%	32%	20%	11%	8%
Insulin requirement	Between 20–30% of baseline during the whole follow-up period				

[†]Graft survival was defined as persistent fasting plasma C-peptide concentration ≤0.1 nmol/L (≤0.3 ng/mL).

although patients with sustained graft survival had a better glycemic control, percentage and duration of insulin independence, and lower insulin requirement, the differences were not large and long enough to result in a reduction in the risk of ESRD and mortality. In addition, as the report only compared the risk of ESRD or mortality in patients with sustained and non-sustained graft survival, it remains unknown if islet transplantation would decrease the risk of ESRD and mortality or not, when compared with patients who did not receive islet transplantation.

To cure type 1 diabetes is one of the goals of β-cell replacement therapy. However, there are currently two major hurdles for islet transplantation, including shortage of β-cell source and the method to overcome the recipient's immune response. Several strategies have been investigated for these hurdles.[6] For the shortage of β-cell source, new technologies are developing to produce β-like cells from embryonic stem cells or induced pluripotent stem cells. However, there are still some problems to be solved before their clinical application, especially the improvement in differentiation efficiency, interpatient variability of β-like cells' function, and long-term graft survival and safety data. In addition to stem cell-derived β-like cells, xenogeneic islets, especially pig islets, are another potential source of β-cells. Although safety regarding zoonosis is a concern, some successful reports have shown its feasibility by using islets from pigs raised in pathogen-free facilities. In contrast, to overcome the recipient's immune response, development of new technologies to induce immune tolerance, use of physical barriers and development of genetically engineered immune-evasive insulin-producing cells have been continuously investigated. Although some promising results have been reported, there are still more to be explored and solved.

Table 2 | Successes and drawbacks of the current state of islet transplantation

Successes	Drawback
Reduce severe hypoglycemia	Two or more islet infusion required
Reduce insulin requirement	Varied graft survival
	Low rate of insulin independence
	Long-term glycemic control still unsatisfactory
	Benefits on end-stage renal disease and mortality not shown

In conclusion, the successes and drawbacks of the current state of islet transplantation are summarized in Table 2. Based on current data, islet transplantation successfully reduces severe hypoglycemia and insulin requirement. However, graft survival is still not good enough, which leads to a low rate of insulin independence and an unsatisfactory long-term glycemic control. These drawbacks might be important causes for the lack of benefit in the risk of ESRD and mortality in patients receiving islet transplantation. In addition, the need for two or more islet infusions makes the source of β-cells a big problem to be solved. Currently, several strategies to overcome the shortage of β-cells and the recipient's immune response are being developed. In the future, with the success of these new technologies, it is believed that islet transplantation or β-cell replacement therapy will be an important clinical treatment option for patients with type 1 diabetes.

DISCLOSURE

The authors declare no conflict of interest.

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