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Mini Review

Islet Transplantation from Allogenic toward Xenogeneic

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Abstract

Islet transplantation is a minimum invasive therapy for the treatment of unstable type 1 diabetes. In 2000, the University of Alberta group demonstrated that 7 out of 7 type 1 diabetic patients became insulin independent after islet transplantation. This protocol (the Edmonton protocol) has led the islet transplantation into clinical reality. However, several issues including necessity of multi organ donors, low efficacy of islet isolation, poor long-term islet function, and poor reproducibility among institutes became apparent. The issues have been solved with the progresses of science but the shortage of donor is still major issue. To solve the donor-shortage issue, clinical islet xenotransplantation using porcine islets has been initiated.

Keywords: Type 1 diabetes; Islet transplantation; The Edmonton protocol; Islet xenotransplantation

Abbreviations

CD: Cluster Of Differentiation; HbA1c: Hemoglobin A1c; PHPI: Purified Human Pancreatic Islets

Introduction

Pancreatic transplantation and islet transplantation are considered as beta cell replacement therapies [1]. Simultaneous pancreas and kidney transplantation was established in 20th century for the treatment of diabetic nephropathy [2]. The major drawback of simultaneous pancreas and kidney transplantation is the risk of major surgery. In fact, due to invasiveness of pancreas transplantation, the benefit against the risk of pancreas transplantation alone for the treatment brittle type 1 diabetes is controversial [3].

Islet transplantation can solve the issue of invasiveness of pancreas transplantation; however, low efficacy had been one of the issues [4].

The edmonton protocol

In 2000, the University of Alberta group demonstrated that 7 out of 7 type 1 diabetic patients became insulin independent at one year after islet transplantation [5]. This method of islet transplantation has been called the Edmonton protocol. The Edmonton protocol is the major breakthrough of islet transplantation. The main features of the Edmonton protocol are as described below.

1. Multiple islet transplantation to provide enough islet mass
2. Steroid free immunosuppression protocol
3. Advanced islet isolation technology based on the Ricordi method [6].
4. Immediate islet transplantation without culture

Issues of islet transplantation with the edmonton protocol

Several issues were pointed out in the Edmonton protocol. At first, necessity of multiple donors for islet transplantation aggravated the donor shortage. Furthermore, success rates of clinical islet isolation have been low and even recent multicenter study demonstrated that success rates of islet isolation was only 27% (286/1056) [7].

In 2005, the University of Alberta group demonstrated that the insulin independence rate was less than 10% after 5 years of islet transplantation [8]. This poor long-term outcome was disappointed; on the other hand, islet function proved by positive C-peptide was maintained for more than 80% after 5 years of islet transplantation [8]. Interestingly, even patients could not maintain insulin independence; the patients with functional islets were able to maintain excellent glycemic control. Since then, the main goal of islet transplantation was switched from becoming insulin independence to maintaining excellent HbA1c and reducing hypoglycemic events.

In 2006, it was published that the success rates of islet transplantation varied among islet isolation centers [9]. Therefore, poor efficiency of islet isolation, poor long term insulin independence rate, and unstable islet isolation outcomes among institutes were major issues.

Resolution of the issues of islet transplantation

Improving the efficacy of islet transplantation became the major research target. In 2004 and 2005, the University of Minnesota group demonstrated that it was possible to achieve insulin independence with single donor islet transplantation [10,11]. Their first strategy included two-layer pancreas preservation before islet isolation, two day culture of islets before transplantation and anti-CD3 antibody for immune suppression induction. Their second strategy was using anti-thymocyte globulin and daclizumab for induction immunosuppression and etanercept for anti-inflammation at the time of islet transplantation.

In 2005, the Kyoto University group demonstrated that it was possible to achieve insulin independence by the living donor islet transplantation from half of pancreas [12].

After these early studies, several groups published successful single donor islet transplantation. Interestingly, the single donor islet transplantation protocol could prolong insulin independent period. The University of Minnesota [11], the University of Illinois Chicago [13], and the University of California San Francisco [14] groups demonstrated successful single donor islet transplantation resulted in long-term insulin independence. The University of Alberta group

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used Baylor single donor islet transplantation like protocol which also resulted in excellent long-term insulin independence [15].

Considering the donor-shortage, a low success rate of islet isolation has been a critical issue. The Baylor Research Institute group demonstrated that seven consecutive successful clinical islet isolation with the technique of pancreatic ducal injection [16]. Pancreatic ductal injection immediate after pancreas procurement improved collagenase delivery which resulted in successful islet isolation [17]. In fact, the success rate of clinical islet isolation was 90% (27/30) with the Baylor islet isolation method [18].

Recent multicenter, phase 3 study of the investigational product Purified Human Pancreatic Islets (PHPI) could solve the issue of the variability of outcomes among the institutes [19,20]. In this study, 8 manufacturing facilities participated and jointly developed a harmonized process of manufacture of PHPI. Manufacturing for 75 PHPI clinical lots demonstrated that it was achieved to implement harmonized process at multiple facilities for manufacture of a complex cellular product. In fact, 87.5% of subjects at 1 year met their primary end point which was HbA1c<7% at day 365 and freedom from severe hypoglycemic episodes from day 28 to day 365 after the first transplant.

Opinion leaders report and patient expectation on the islet transplantation

In 2014, to review the current status and needed research agenda of beta cell replacement therapies, a scientific workshop was held in Oxford, England [1]. At the meeting, it was declared that at present, the primary goal of islet transplantation should be optimal glycemic control without severe hypoglycemia rather than insulin independence. Because of the overall limited availability of human organ donors, islet allotransplantation is unable to provide a cure for all those affected with type 1 diabetes.

On the other hand, 85 % of patients and their family member wished to be insulin free as a result of questionnaire investigation in 2009 [21]. Furthermore, 95.3% of patients and their family members wished to be insulin free as a result of questionnaire investigation in 2014 [22]. These results suggested patients and their family member shopped that the advanced medicine would bring insulin free status. Therefore, allogeneic islet transplantation could not be the solution for the majority of patients at present.

Overcome the donor shortage

If the issue of donor shortage can be solved, islet transplantation should be able to bring patients insulin free status. Xenogeneic islet, stem cell-derived beta cells and endogenous beta cell regeneration are considered as candidates to overcome donor shortage [1]. Among them, xenogeneic islets have been entered in clinical stages [23-25].

Wide scale application of islet xenotransplantation requires specifically and tightly regulated environment [26]. In fact many countries have embraced the encouragement of the WHO to harmonize the procedures in more global scale. Important regulatory changes have taken place or are in progress in several areas including Europe, Korea, Japan and China [26]. Recently, the international xenotransplantation association updated the consensus statement on conditions for undertaking clinical trials of porcine islet products in type 1 diabetes [27]. The new statements updated i) national regulatory frameworks addressing xenotransplantation, ii) generation of suitable source pigs including genetically modified pigs, iii) manufacturing and release testing for porcine islet, iv) pre-clinical safety and efficacy data which justified clinical trial, v) recipient monitoring and iv) patient selection. This updates statements will assist the islet xenotransplant scientific community, sponsors, regulators, and other stakeholders in the clinical islet xenotransplantation.

Recently, encapsulated neonatal porcine islets were transplanted into type 1 diabetic patients without immune suppressive drugs [28,29]. Clinical outcomes demonstrated that prolonged excellent HbA1c without increasing hypoglycemic events [28], without major complications including infection [29]. On the other hand, patients did not become insulin independence.

It was demonstrated that long-term insulin free was achievable by porcine islet transplantation with immunosuppressive drugs using non-human primate model [30]. Islet xenotransplantation research towards insulin free is underway.

At this time point, islet xenotransplantation seems the leading option to solve the donor shortage issue.

Conclusion

Allogeneic islet transplantation has steady improved the outcomes and become an option for the treatment of unstable type 1 diabetes. To apply the treatment widely and improve patients' satisfaction, the donor shortage issue needs to be solved. The islet xenotransplantation seems the leading option for solving the issue.

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