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SECOND ANNUAL ANALYSIS OF THE COLLABORATIVE ISLET TRANSPLANT REGISTRY

N. Close, R. Alejandro, B. Hering, and M Appel for the CITR Investigators

Abstract

In September 2001, the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK) founded the Collaborative Islet Transplant Registry (CITR). Each year, CITR produces a complete set of analyses available to the public. In its second year, CITR represents the efforts of nineteen North American islet transplant programs reporting on 138 islet transplant recipient's information (1999–2004), 256 processed pancreata that led to infusion, and 266 infusion procedures. This analysis focuses on recipients of islet alone procedures. Median age of the recipient is 41.6 years (range 23.1 to 64.4), duration of diabetes is 29 years (range 4 to 50) and over 66% are female. Median weight of the recipient is 65 kg (range 47 to 97) and median body mass index (BMI) is 23.1 kg/m² (range 18.8 to 31.6). Examining outcomes at six months following the recipient's last infusion, 67.0% are insulin independent and at twelve months this percentage decreases to 58.0%. There is a striking decrease in the occurrence of severe hypoglycemic events subsequent to the first infusion. Over 82% of all recipients experience one or more severe hypoglycemic events in the year prior to their first infusion. However, only two recipients (2%) experience one or more severe hypoglycemic events between 30 days and 12 months post infusion, but both of these recipients were on insulin replacement therapy and one had experienced a complete islet graft failure. The information provided in this analysis and subsequent analyses of CITR provides current and comprehensive information on outcome measures in islet transplantation.

The number of transplant centers performing clinical islet transplantation continues to increase, as well as the number of centers participating and reporting to the Collaborative Islet Transplant Registry (CITR). The data compilation and analysis providing the basis of this second CITR Annual Report was made to facilitate the identification of both critical risk factors and key determinants for successful clinical islet/beta cell transplantation. These insights may then provide guidance to transplant centers in developing and refining protocols as islet/beta cell transplantation continues to evolve as a therapy option for the treatment of labile type 1 diabetes. This report represents a larger collaboration between islet transplant programs in North America with CITR using a more comprehensive database.

METHODS

The charter of CITR, as well as results from the inaugural year of the Registry, are reported elsewhere in detail.^{1,2} This analysis represents a 60% increase in the number of islet recipients, 48% increase in the number of pancreas donors, and a 68% increase in the number of infusion procedures over the number reported in the first report of the Registry. With increased cumulative data, greater precision in understanding comparative outcomes may be achieved across time.

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CITR adheres to strict quality control and assurance procedures. All data submitted are reviewed through several quality review processes. Islet transplant recipient data for this analysis reflect data entered by the islet transplant centers on recipients from January 1, 1999 to December 31, 2004. The cumulative data were subject to analyses.

These data were reviewed by the Coordinating Center for quality assurance, errors and data outliers. Any missing follow-up information on these recipients were identified and conveyed back to the site for verification and correction. Any questions concerning specific data elements were also sent to the islet transplant centers for review and correction, if necessary. All islet transplant centers were provided ample time for resolving issues of discrepant data. The database was then updated and closed for analysis on April 1, 2005. At this time 138 recipients had been registered for CITR and were eligible for analysis.

CITR also collects basic information from all islet transplant centers in North America each year, regardless of their participation with CITR (number of pancreata processed and used for islet transplant and number of patients infused). Thirty-eight islet transplant programs were sent a questionnaire asking for this information. All 38 programs responded and 27 of the 38 programs had been active during 1999–2004, transplanting at least one patient. The remaining programs had not transplanted yet, or were in the process of setting up their islet transplant program. This information provides the basis for determining the completeness of CITR and to summarize current activity of islet transplantation in North America.

Table 1 displays the data collected from the 27 active islet transplant programs in North America for 1999–2004 which is inclusive of all active islet transplant programs in North America. The analyses reported herein represent 53.7% of all islet transplant recipients in North America and 56.0% of all islet infusion procedures conducted.

RESULTS

Nineteen North American islet transplant programs have contributed to this annual analysis. Programs submitted information on 118 islet transplant alone recipients, 19 islet after kidney recipients and one autograft transplant recipient (N=138). The median age of islet transplant alone recipients (ITA) was 41.6 years (range 23.1 to 64.4) and the median duration of diabetes was 29 years (range 4 to 50). More than 66% of the recipients were female. The median recipient weight was 65 kg (range 47 to 97) and median body mass index (BMI) was 23.1 kg/m² (range 18.8 to 31.6). All recipients were diagnosed with type 1 diabetes. Table 2 shows the recipient's insulin requirement status prior to their first infusion, their fasting plasma glucose and their hemoglobin A_{1c}. On average, recipients required 36.6 units (SD 12.9) of insulin per day prior to their first infusion, their fasting plasma glucose was 169.8 mg/dL (SD 105.3), and their hemoglobin A_{1c} was 7.6% (SD 1.3).

The median age of the deceased donor for ITA recipients was 44 years (range 8 to 65) and body mass index was 28.3 kg/m² (range 13.3 to 59.8). Fifty-three percent of the donors were male and approximately 66% were white. The median serum creatinine of the donors was 1.1 mg/dL, total bilirubin 0.7 mg/dL, AST 39.0 IU/L, ALT 31.0 IU/L, serum lipase 28.0 IU/L and serum amylase 68.5 IU/L. Median time from cross clamp to pancreas recovery was 28 minutes (range 0 to 127) while duration of cold ischemia was 7 hours (range 1.5 to 27.0). UW, Two Layer, and UW Followed by Two Layer preservation were used for pancreas cold storage, and Liberase HI was used for collagenase digestion in 199/200 of the reported islet isolation procedures. All of the processing facilities used a density gradient for islet purification and 45.5% of the islet products incorporated islet cell culture incubation.

The majority of the islet alone recipients received Daclizumab for induction and Sirolimus combined with Tacrolimus for maintenance immunosuppression. Table 3 includes a listing of all reported immunosuppression regimens used at the time of the recipient's first infusion.

One hundred and twelve islet alone recipients have completed at least one follow-up evaluation after their last infusion (6 months, 12 months or 2 year evaluation). Of these 112, 55 (49.1%) are insulin independent, while 39 (34.8%) are insulin dependent at this evaluation following their last infusion. A total of 15 (13.4%) participants have experienced complete graft failure (loss of c-peptide function), while three participants have an unknown insulin status at the time of the analysis.

Table 4 describes the clinical outcomes at each evaluation time point. At six months following the participant's last infusion, 67.0% were insulin independent and at twelve months this percentage decreased to 58.0%. This table also shows comparisons of the insulin independence percentages by the total number of infusions the recipient has received.

For participants still requiring insulin at six months post their last infusion, there was a 56.5% mean reduction in their required daily insulin units compared to baseline. This ranged from a minimum reduction of 4.8% to an 83.3% reduction in their insulin requirements. At year 1 post last infusion, recipients remaining on insulin experienced a mean reduction of 69.0% in their required daily insulin requirements with a range of 16.7% to 92.4%.

A striking decrease in the occurrence of severe hypoglycemic events subsequent to the first infusion was observed during this analysis (Table 5). Over 82% of all islet alone participants experienced one or more severe hypoglycemic events in the year prior to their first infusion. However, severe hypoglycemia was observed in only 2.5% of the study participants at 30 days post infusion and was not encountered (0%) in the subsequent 5 months. Only two recipients (2%) experienced one or more severe hypoglycemic events between months 6 and 12 post last infusion, but both of these recipients were on insulin replacement therapy and one had experienced a complete islet graft failure.

Adverse events were reported from 18 of the 19 centers and this information comprises the analysis set for adverse events and serious adverse events. Almost 74% (61/83) of the islet alone transplant recipients experienced at least one adverse event in year 1 after their first infusion, while 36% (30/83) experienced one or more serious adverse events in this same period. Of the 235 reported adverse events during this time frame, 34.0% were related to the immunosuppression therapy (probably or definitely related), and 14.5% were related (probably or definitely) to the infusion procedure. Of the 52 reported serious adverse events reported up to year 1 post first infusion, 28.8% were related (probably or definitely) to the immunosuppression therapy and 23.1% were related (probably or definitely) to the islet infusion procedure.

Overall, a total of 77 serious adverse events have been reported to the Registry, with 22% (N=17) of them classified as life threatening and 58% (N=45) requiring an inpatient hospitalization. Almost 69% of the serious adverse events were classified by the reporting CITR investigator as unrelated to the islet infusion procedure, 5.2% unlikely related, 9.1% possibly related, 5.2% probably related and 11.7% as definitely related. Regarding the relationship of these 77 serious adverse events to the immunosuppression therapy, almost 38% were classified as unrelated, 15.6% unlikely related, 16.9% possibly related, 19.5% probably related and 7.8% definitely related. Ninety-five percent (N=73) of the serious adverse events were resolved without residual effects. Most of the reported serious adverse events were related to gastrointestinal disorders, blood and lymphatic system disorders, and infections or infestations as classified by the MedDRA classifications system. MedDRA® the Medical Dictionary for Regulatory Activities terminology is the international medical terminology

developed under the auspices of the International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH).³

DISCUSSION

This second annual report provides expanded analyses of the current cumulative islet transplantation experience in North America. However, some caution must be exercised in its interpretation. Despite the data submission efforts of the 19 participating centers, the total number of islet transplantation recipients in North America are still small. In addition, as with any registry, a number of potential biases may exist. First, not all islet transplant centers in North America participate in CITR. However, 19 of the 27 (70.4%) active islet transplant programs contributed to these analyses. Second, those Centers reporting information to CITR have not reported on all of the islet transplant recipients at their center yet or have not reported on all of the infusion procedures of their recipients. Those reported early from the Centers may constitute only the successful cases. Third, there is always the potential of hidden selection bias in a registry database. Since a registry is non randomized and reflects the real world choices of islet transplant centers and physicians, some information may be selective based on the center's protocol (e.g. protocols limiting donor age <60 years). As the Registry progresses these biases may lessen. However, this second analysis includes additional reported cases and a larger set of data to provide a more comprehensive review of the current status of islet transplantation in North America and hypothesis generation for future analyses.

References

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3. MedDRA® is a registered trademark of the International Federation of Pharmaceutical Manufacturers and Associations (IFPMA). [accessed on May 30, 2006]. Website <http://www.meddrasso.com/MSSOWeb/index.htm>

Table 1

Summary of North American Islet Transplant Activity 1999–2004

All Islet Transplant Programs in North America	Number of Human Islet Infusion Procedures Conducted	Number of Patients Receiving Their First Infusion
Total	475	257
1999	18	10
2000	33	22
2001	65	45
2002	142	82
2003	106	45
2004	111	53

Table 2
Recipient Summary Measures at Prior to First Infusion

	Overall		
	N	Mean	SD
Daily insulin requirement prior to infusion (units)	116	36.6	12.9
Duration of intensive therapy (yrs)	77	15.1	11.1
Fasting plasma glucose (mg/dL)	109	169.8	105.3
HbA _{1c} (%)	112	7.6	1.3

Table 3
Immunosuppression Regimen at Time of First Infusion

	Overall	
	N	%
Total	118	100.0
Sirolimus + Tacrolimus + Daclizumab	73	61.9
Sirolimus + Tacrolimus + Daclizumab + Infliximab	12	10.2
Sirolimus + Tacrolimus + Basiliximab + Etanercept	5	4.2
Sirolimus + Tacrolimus + MMF + Methylprednisolone + Anti-thymocyte Globulin + Daclizumab + Infliximab + Etanercept	5	4.2
Sirolimus + Tacrolimus + 15-deoxyspergualin + Daclizumab	5	4.2
Sirolimus + Tacrolimus + hOKT3 _γ -1(Ala-Ala)	3	2.5
Sirolimus + Tacrolimus + MMF + Daclizumab	2	1.7
Sirolimus + Tacrolimus + MMF + Methylprednisolone + Anti-thymocyte Globulin + Daclizumab + Etanercept	2	1.7
Neoral Cyclosporine + Methylprednisolone + Everolimus + Anti-thymocyte Globulin + Infliximab + Etanercept	2	1.7
Sirolimus + MMF + Anti-thymocyte Globulin + Daclizumab	1	0.8
Neoral Cyclosporine + Methylprednisolone + Anti-thymocyte Globulin + Etanercept	1	0.8
Missing Information on Immunosuppression	7	5.9

Table 4

Percent of Recipients Insulin Independent at Evaluation Time Points Following Their Last Infusion and by Total Number of Infusions Received

	Insulin Independent			
	Month 6		Year 1	
	N	%	N	%
Total	71	67.0	51	58.0
Total Infusions				
1	19	63.3	16	57.1
2	39	75.0	26	63.4
3	13	54.2	9	47.4

Table 5
Summary of Severe Hypoglycemic Events Prior to Recipient's First Infusion and Follow-Up Post Their Last Infusion

		Follow-Up							
		Pre First Infusion		Days 0–30 Post First Infusion		Months 1–6 Post Last Infusion		Months 6–12 Post Last Infusion	
		N	%	N	%	N	%	N	%
Total		118	100.0	118	100.0	112	100.0	102	100.0
Any Severe Hypoglycemic Episodes									
Yes		97	82.2	3	2.5	-	0.0	2*	2.0
No		16	13.6	106	89.8	103	92.0	84	82.4
Missing		5	4.2	9	7.6	9	8.0	16	15.7

* One recipient with insulin use and reported islet graft failure and one recipient with continued insulin use since infusion.