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Cost and clinical outcome of islet transplantation in Norway 2010-2015.

Simen W. Schive,[1,2,5] Aksel Foss,[1,2,5] Afaf Sahraoui,[1,2,5] Kristine Kloster-Jensen,[1,2,5] Geir Hafsahl,[3] Gunnar Kvalheim,[4] Torbjørn Lundgren,[6] Bengt von Zur-Mühlen,[7] Marie Felldin,[8] Ehab Rafael,[9] Marko Lempinen,[10] Olle Korsgren,[11] Trond G. Jenssen,[1,12] Vinod Mishra*[13] and Hanne Scholz*[1,2,5]

[1]Department of Transplant Medicine, [2]Institute for Surgical Research, [3]Department of Radiology, [4]Department of Cell Therapy, Cancer Institute, Oslo University Hospital, Oslo, [5]Institute of Clinical Medicine, University of Oslo, Oslo, Norway, [6]Division of Transplantation Surgery, CLINTEC, Karolinska Institutet, Stockholm, Department of Transplantation Surgery, University Hospital, Uppsala, [8]Department of Transplantation, Sahlgrenska University Hospital, Gothenburg, [9]Department of Nephrology and Transplantation, University Hospital, Malmo, Sweden, [10], Department of Surgery, Helsinki University Hospital, Helsinki, Finland, [11]Department of Immunology, Genetics and Pathology, Science for Life Laboratory, Uppsala University, Sweden, [12]Metabolic and Renal Research Group, UiT The Arctic University of Norway, Tromsø, [13]Department of Finance and Resource Management Unit, Oslo University Hospital, Oslo, Norway.

* These authors contributed equally to this work

Authorship: SWS analyzed the outcome data and wrote the manuscript; AF, AS, KKJ, GH, TGJ treated and followed up the patients, T.L, B.M, M.F, E.R, M.L supplied pancreata for islet isolation and research data; OK supplied islets, research data and contributed to the scientific discussion, GK heads the GMP facility for islet isolation at OUS; HS, VM design the study, analyzed the cost data, contributed to the scientific discussion and wrote/edited the manuscript; All authors have reviewed the manuscript and agree on its content.

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Corresponding author: Simen W. Schive, MD

Institute for Surgical Research, Oslo University Hospital Rikshospitalet

P. O. Box 4950 Nydalen, N-0424 Oslo, Norway

Telephone: +47 23 07 37 98

Fax: +47 23 07 35 30

E-mail: simen.walberg.schive@rr-research.no

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Abbreviations: ITA; islet transplantation alone, OUS; Oslo University Hospital, UCSF;

University of California San Francisco, GMP; Good Manufacturing Practices, ATG; anti-thymocyte globulin, LMWS-DS; low molecular weight dextrane sulphate, BMI; body mass index, CIT; cold ischemia time, PRA; panel reactive antibody, HLA; human leukocyte antigen, IAK; islets after kidney.

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Abstract

Islet transplantation is a minimally invasive β-cell replacement strategy. Islet transplantation is a reimbursed treatment in Norway. Here we summarize the cost and clinical outcome of 31 islet transplantations performed at Oslo University Hospital (OUS) from Januray 2010 – June 2015. Patients were retrospectively divided into 3 groups. 13 patients received either one or two islet transplantation alone (ITA), while 5 patients received islet transplantation after previous solid organ transplantation. For the group receiving 2 ITA, Kaplan-Meier estimates show an insulin independence of 20% more than 4 years after their last transplantation. An estimated 70% maintain at least partial graft function, defined as fasting C-peptide >0.1 nmol/L, and 47% maintain a HbA1c below 6.5% or 2 percent points lower than before ITA. For all groups combined we estimate that 44% of the patients have a 50% reduction in insulin requirement 4 years after the initial islet transplantation. The average cost for an islet transplantation procedure was 347 297 ± 60 588 NOK, or 35 424 ± 6182 EUR, of which isolation expenses represent 34%. We hereby add to the common pool of growing experience with islet transplantation, and also describe the cost of the treatment at our center.

Introduction

Islet transplantation is a minimally invasive β-cell replacement strategy for type 1 diabetic patients, improving glycemic control and decreasing hypoglycemic episodes [1]. Compared to solid organ transplantation, islet transplantation offers a less invasive alternative with shorter hospitalization, lowered risk of infections, and fewer re-operations [2]. Outcome after allogenic islets transplantation for patients with type 1 diabetes has continually improved since the introduction of the Edmonton Protocol in 2000 [3][4]. While only 10% of the original Edmonton cohort remained insulin independent after 5 years, Bellin et al recently reported insulin independence rates as high as 50% 5 years after transplantation [5][6]. Although multiple transplantations often are required to reach insulin independence, single donor islet transplantations with long-term insulin independence can be achieved [7]. Even though not all patients reach and maintain insulin independence, partial graft function can still affect the disease burden by reducing hypoglycemic episodes and the frequency of blood glucose measurements, thereby improving health related quality of life [8].

In addition to efficacy, cost is an important aspect of any new treatment modality. The Swiss-French Consortium GRAGIL has estimated the cost of an islet transplantation treatment to 77 745 EUR in 2004 [9]. This estimate includes one year follow-up, and covers multiple transplantations when needed, as well as the price for failed isolation attempts. Moassesfar et al. recently published a comparison between islet and pancreas transplantation at the University of California San Francisco (UCSF), and found the price of a single islet transplantation to be 99 194 USD. The final mean cost per patient was reported to 138 872 USD, comparable to the 134 748 USD for a whole organ pancreas transplantation [10]. Gerber et al. compared kidney transplanted patients receiving islet transplantations

with matched patients receiving intensified insulin therapy, and found islet transplantation to be cost neutral after 15 years [11]. Beckwith et al. estimated that islet transplantation becomes cost saving after 9-10 years in the setting of islet transplantation alone (ITA) [12]. Islet transplantation is a reimbursed treatment in Norway.

In this report we describe the cost of 31 islet transplantations, and outcome in 18 patients transplanted at OUS in the period January 2010 - June 2015. The aim of this study is to provide the cost and outcome of the complete islet transplantation program in Norway during the study period.

Patients and methods

Islet recipients

A total of 19 patients received 31 islet transplantations between January 2010 and June 2015 at OUS. As part of the Nordic Network for Clinical Islet Transplantation, our center at Oslo University Hospital (OUS) receives islet preparations from Rudbeck laboratory, Uppsala University Hospital in Sweden. OUS established a Good Manufacturing Practice (GMP) facility for islet isolation in 2013. Islets preparations were prepared at either the Uppsala facility in Sweden (n=26) or the OUS facility in Norway (n=5). Mean IEQ for transplanted preparations were comparable; 374 229±131 557 IEQ from Uppsala, 367 487±77 135 IEQ from Oslo. Data was retrospectively analyzed from patient medical records, adhering to OUS guidelines for consent and privacy. All patients were transplanted on the indication of "brittle" type 1 diabetes, i.e., difficulty in controlling blood glucose and frequent hypoglycemic episodes despite optimal conventional therapy. The recipients were

retrospectively divided into 3 groups. Group I – patients receiving a single ITA (n=3), group II – patients receiving 2 separate ITA (n=10), and group III – patients receiving one (n=4) or two (n=1) islet transplantations after previous organ transplantation (n=5). All patients in group I were offered whole organ pancreas transplantation after a single ITA. Patients in group II who did not reach insulin independence within 3 months after their first ITA were offered a second transplantation. Group III consists of a heterogeneous population where patients have previously received kidney, pancreas, or kidney and pancreas transplants 10.0±7.1 years prior to islet transplantation. All recipients were confirmed C-peptide negative prior to islet transplantation. Characteristically, the patients in group III were all immunosuppressed prior to their first islet transplantation. A single patient receiving 2 ITA in the study period was excluded from the outcome part of this paper as the patient had received 3 ITA prior to the study period, and thus did not fit in group I-III. The procedures were however included in the cost analysis. The patient had partial graft function with C-peptide positivity throughout the study period. Mean follow-up time for the patients included in the outcome part of this study was 32.2 ±17.4 months.

Islet isolation and transplantation

Human pancreata were obtained from brain-dead donors through organ allocation in the Nordic Network for Clinical Islet Transplantation. The organs were either transported to the Rudbeck laboratory at Uppsala University Hospital in Sweden, or to the Department for Cellular Therapies at OUS in Norway for processing. The islets were isolated and stored prior to transplantation using a previously described method of enzymatic and mechanical digestion before COBE separation [13]. Isolated islets were transported to OUS in a transfusion bag and transplanted by portal vein infusion after ultrasound guided portal vein

catheterization [14]. Islet transfusions were accompanied with 5000 IU heparin, except in 4 patients where heparin was replaced with low molecular weight dextrane sulphate (LMW-DS) as part of a study (ClinicalTrials.gov Identifier: NCT00789308). After transplantation all patients received low molecular weight heparin for 7 days. The patients following the Clinical Islet Consortium protocol (n=9) were administered 3000 IU enoxaparin sodium twice daily while patients not on this protocol (n=9) were administered 7500 IU dalteparin sodium twice daily. All transplantations were followed by i.v. insulin infusion for 2 to 5 days as needed, with frequent capillary blood glucose measurements to ensure blood glucose between 4-8 mmol/L. After discharge from the hospital, clinicians followed up the patients at OUS weekly the first month, then after 2.5 months, 6 months, and then yearly.

For Kaplan-Meier analysis of graft function, patients were censored by time at the end of the study period, if they received a solid organ pancreas transplantation with a functioning islet graft, if they left follow-up at our hospital with a functioning islet graft, or if they decided to stop taking the prescribed immunosuppressive treatment with a functioning islet graft. Graft failure was determined by repeated C-peptide measurements < 0.1nmol/L. For analysis of HbA1c, 2 repeated measurements above pre transplantation levels or above 6.5% or 2 percentage points drop were noted as events. For graphs of mean HbA1c and insulin use, mean values from the first islet transplantation until leaving the islet program or end of the study period were plotted.

Hospitalization and isolation costs

Cost was estimated based on clinical pathways identified through the hospital patient administrative systems for the 31 islet transplantation procedures performed in the study period. Cost estimates represent the hospital's total cost based on account numbers of Dec.

31st 2013. Costs were calculated by a two-step procedure. First, unit costs for healthcare personnel (i.e. a nursing hour), procedures and items were calculated along each clinical pathway. Unit costs included overhead costs. Second, the unit cost was multiplied by the patient's length of hospital stay at different stages of the clinical pathway, or by the number of items used, then summarized to obtain the total patient cost. For a detailed description of methods, see Mishra et al. 2010 [15].

Hospitalization costs were calculated for the following periods: i) Pre-transplantation was defined as the time from the patients were admitted to hospital to procedure. ii) Procedure period was from time of transplantation procedure to admission to the transplantation ward, and include intraportal catheterization by the intervention radiologist and the islet infusion procedure. iii) The post procedural period was from admission to the transplantation ward to discharge date. iv) The follow-up period was defined as the date of discharge to the end of June 2015 and included any cost associated with complications of transplantation as well as scheduled and unscheduled follow up. In addition to hospitalization, the cost of pancreas organ procurement and islet preparation was estimated. Mean cost for organ procurement was calculated based on the total cost of transport, procurement teams, transplantation coordinators, and supplies, divided by number of procured organs.

The cost evaluation was undertaken from the islet transplantation centre's perspective, so that costs from outside the hospital (admission to other hospitals, primary care consultations, maintenance immunosuppression while not in the hospital etc.) were not included. All costs were inflated to 2015 prices by the consumer price index.

Statistical analysis

Summarized data are expressed as mean ± SD, unless stated otherwise. GraphPad Prism 6.1 (GraphPad Software, San Diego, CA, USA) was used for statistical analysis, Kaplan-Meier survival estimates and survival curves, as well as data presentation. Comparisons were performed using Student's *t*-test. A *p* value <0.05 was considered statistically significant.

Results:

Donor and recipient characteristics

Donor characteristics for the isolated islets, divided into their respective groups, are represented in table 1. The differences in age, body mass index (BMI), cold ischemia time (CIT), purity, and time between transplantations did not reach significance. The total islet mass transplanted in group II was significantly higher compared to group I and III (p=0.007 and p=0.005). Recipient characteristics are shown in table 2. The differences in age (at first islet transplantation) and diabetes duration were significantly different in group III compared to group II (p=0.02 and p=0.002). Differences in BMI, HbA1c, and pre-transplantation insulin use did not reach significance. Of the transplantation recipients, 76% had documented various degrees of retinopathy prior to the first islet transplantation. In addition, 40% of patients in group II had documented neuropathy, and 80% of patients in group III had documented nephropathy or renal failure.

Recipient antibodies

We found no increase in panel reactive antibody (PRA) screening in any of our patients in any of the groups, measured 11.6±8.8 months after their first islet transplantation. Two patients (one in group I and one in group III) had a PRA >20% prior to their first islet

transplantation, and remained on the same level after the procedure. In group I, one patient showed persistent human leukocyte antigen (HLA) antibodies measured by Luminex 1 month after ITA. In group II, one patient had a transient appearance of HLA antibodies 7 months after ITA, while two patients with already present low levels of HLA antibodies displayed an increase of antibodies 4-6 months after ITA. In group III, two patients were positive for HLA antibodies prior to islet transplantation, and one of these patients had an increase 1 month after the procedure.

Medication

Induction therapy for the first ITA in group I and II was achieved by anti-thymocyte globulin (ATG) in combination with etanercept in 11/13 patients. A single patient in group I received intravenous immunoglobulin (IVIg) in addition to ATG and etanercept, and a single patient in group II received basiliximab alone. For their second ITA, 9/10 of group II patients received basiliximab in combination with etanercept. Group III received a heterogeneous combination based on their previous immunosuppression regimen, either basiliximab or ATG in different combinations with etanercept and prednisolone (Fig. 1A). For maintenance therapy, most of the patients in group I and II received a combination of a calceneurin inhibitor and sirolimus, while the preferred regimen in group III was a calceneurin inhibitor and mycophenolate mofetil (Fig. 1B). Patients following the Clinical Islet Consortium protocol (n=9) receiving ATG were given a total of 6mg/kg, administered as 0.5 mg/kg on day -2, 1.0 mg/kg on day -1, then 1.5mg/kg on day 0, 1, and 2, and Tacrolimus with target of 10-12 ng/ml day 1-90, 8-10 ng/ml month 3-6, and 6-8 ng/ml after 6 months. Patients not on this protocol (n=9) receiving ATG were given 2.5 mg/kg on day -1 with further doses dependant on T-cell levels with a target of $<0.050 \times 10^9$ cells/liter until day 10, and Tacrolimus

with at target of 10-12 ng/ml day 1-90, then 7-10 ng/ml after 3 months. All patients receiving Sirolimus had a target of 10-15 ng/ml day 7-90, and 7-10 ng/ml after this, Etanercept was given as 50 mg day 0, then 25 mg day 3, 7, and 10, Simulect as 20mg day 0 and 4, and MMF as 1g twice daily.

Graft function

Insulin independence was defined as C-peptide positivity and HbA1c <7% without use of exogenous insulin. None of the patients in group I reached insulin independence. Insulin independence was achieved by 40% of the patients in group II and III. One patient in group III achieved insulin independence after a single islet transplantation. Kaplan-Meier estimates show 20% insulin independence 4 years after the initial ITA in group II (Fig. 2A).

Defining partial function as fasting or stimulated C-peptide >0.1 nmol/L, we find that all patients in all groups reached at least partial graft function immediately after transplantation. While we observe complete graft failure in group I by month 20, we estimate a partial graft function or better in 70% of patients in group II at 4 years after first ITA. In group III we estimated 75% partial function at 32 months after the first islet transplantation (Fig. 2B). Mean recorded HbA1c and insulin use is shown in fig. 2 C-D. Of the patients with recorded Clarke score in group II, mean score prior to transplantation was 5.3±1.1 (n=7), while 3 and 6 months after first ITA the score was 4.0±1.3 (n=7) and 2.3±1.5 (n=4) subsequently.

Hyperglycemia and insulin use

Although insulin independence was not reached by all patients, partial graft function still alters the daily excursions in plasma glucose as well as the average glycemic control. All patients, except 1 patient in each of the 3 groups, had HbA1c above 6.5 % prior to their first islet transplantation. All patients in all groups obtained reduction in HbA1c after their first islet transplantation. In group II we estimate 59% of the patients achieve lower HbA1c compared to pre-transplantation levels more than 4 years after their first ITA (Fig. 3A). Despite a mean HbA1c of 7.6% prior to transplantation, 90% of patients in group II and 100% of patients in group III achieved a HbA1c < 6.5% or a drop of more than 2 percent points 1 year after their first islet transplantation. At 4 years we estimate 47% of the patients in group II retain HbA1c <6.5% or 2 percent points below their pre IAT levels (Fig. 3B). Moreover, insulin requirements were reduced in all patients after islet transplantation. We stratified insulin reduction into i) any reduction in insulin dosage compared to before transplantation, ii) more than 50% reduction, and iii) 100% reduction. In group II we estimate 75% reduced insulin requirement after 4 years, with 64% of patients achieving a 50% reduction (Fig. 3C). When we combine all 3 groups together, we find that all patients experienced reduced insulin requirement after the first islet transplantation, and estimate 66% of all patients in the three groups required less insulin more than 4 years after their first procedure. Finally, we estimate 46% of all patients reduce their insulin use by more than 50% 4 years after their first islet transplantation (Fig. 3D).

Adverse events

Prior to the islet transplantation procedure, we observed a single case of ATG anaphylaxis requiring admission to the intensive care unit. This was resolved, and the patient received the ITA as planned. Although we observed no periprocedural bleedings in our 31 procedures, we observed 1 case of periprocedural nausea, 2 cases of temporary headache, and 2 cases of ATG related rash. After the procedure we observed 1 case of rejection where solumedrol treatment recovered graft function. Related to the immunosuppressive medication we observed 1 case of neutropenia, 1 infection related to toxic levels of tacrolimus, and 1 patient decided to stop following the immunosuppressive regimen of sirolimus and tacrolimus due to headache, diarrhea, stomach pain and nausea, leading to graft failure. During follow-up, 8/19 of the patients had to alter their immunosuppressant regimen due to drug related adverse effects such as headache, hair loss, periorbital edema, leucopenia, abdominal pain and GI symptoms, all of which were resolved by change in medication. All of the 19 patients who received islet transplantations in the study period are alive at the time of writing.

Cost of transplantation and isolation

Cost was estimated based on patient events recorded in the OUS patient administrative system and included organ procurement, islet isolation, hospitalization and procedure, as well as follow up for the 31 islet transplantation procedures performed in the study period. The mean total transplantation cost was 347 297 ± 60 588 NOK or 35 424 ± 6 182 EUR. The organ procurement represents 23% (80 000 NOK or 8 163 EUR) of the total cost and the islet isolation process 34% (118 236 NOK or 12 065 EUR). The hospitalization cost account for 43% (149 061 NOK or 15 210 EUR) of the total cost. Analyzing the components of the

hospitalization, we find pre-procedural hospitalization to represent 4% (14 878 NOK or 1 518 EUR), the procedure 7% (25 097 NOK or 2 560 EUR), post procedural hospitalization 17% (57 379 NOK or 5 855 EUR), and the follow up 15% (51 707 NOK or 5 276 EUR) of the total islet transplantation cost (table 3).

Discussion

In this paper we report the cost and outcome of 31 islet transplantations in 19 patients performed at OUS in the period January 2010 to June 2015. Due to a heterogeneous patient population we retrospectively divided the recipients into 3 groups, with one patient not fitting into any of these groups. The procedures of this patient was however included in the cost analysis. Thus we here describe the entire islet transplantation activity at our center for the study period.

Our rate of insulin independence is lower than the 50% at 5 years reported by Bellin et al [6] or 29% recently reported in by the GRAGIL network, yet it seems in line with the 2013 UK published 2 year insulin independence of 15% [16][17]. Comparing this to registry data of 677 islet transplantations, our rate of insulin independence in group II and III is more in line with the results in the era 1999-2002, with 5 year insulin independence at 20% [4]. We have mainly been using what has been described as “state of the art” immunosuppression of the most recent era (2006-2010) with T cell depleting antibody (ATG) or IL-2 receptor antibody (basiliximab) in combination with a TNF-a inhibitor (etanercept) for induction, and for maintenance an mTOR inhibitor (sirolimus) or inosine monophosphate dehydrogenase inhibitor (mycophenolate mofetil) in combination with a calcineurin inhibitor (tacrolimus)

[18][19]. Several factors may explain the different outcome in our study compared to others. In patient selection 4/10 of the patients in group II had an insulin requirement above 0.7 U/kg/day, which has been associated with poorer outcome, and these patients are excluded from receiving ITA in several of the cited centers [4][7]. Donor age has been shown to influence outcome [20], and in groups II and III 14/28 donors were 50 years or older, with 6 of these 60 years or older, the oldest donor being 68 years old. Finally, in group II, 1/10 patients stopped taking the required immunosuppressant drugs leading to graft failure before reaching insulin independence, 1/10 patients received a solid organ pancreas transplantation as an option to a third ITA with a partially functioning islet graft, and 4/10 patients currently await their third ITA. Reaching optimal graft function in the short term is a predictor for favorable long-term outcome, and the number of patients awaiting their third transplantation could affect our long-term outcome in our study [21].

Insulin independence as a measurement of success is debated in islet transplantation. The indication for islet transplantation is a state of brittle diabetes with severe difficulty in controlling blood glucose, which results in frequent and severe hypoglycemic episodes. Elimination of these hypoglycemic episodes with normalization of average glycemia should be regarded as a positive outcome [16] [17][22]. Unfortunately, we do not have complete follow-up data on hypoglycemic episodes in our patient population.

In our patients, partial graft function with C-peptide positivity was more frequent than insulin independence. In order to describe the disease impact of our treatment, we evaluated HbA1c and insulin use. We estimated HbA1c <6.5% or 2 percent points drop to be 46% at 4 years in group II, similar to the CITR results of 50-60% in year 2-5 [4]. Islet transplantation can be considered a low risk procedure, and adverse events in our study

were mainly due to side-effects of immunosuppressants. Procedural complications have been shown to impair long-term outcome, but we observed no such complications in our patients [23].

When comparing our groups, group II and III appear to perform similarly, while group I, with only 1 ITA, performed worse. This is noteworthy, because group III received significantly fewer islets than group II (6035 IEQ/kg vs. 11431 IEQ/kg). Mean insulin use prior to transplantation in group III was 0.49 U/kg/day, compared to 0.63 U/kg/day in group II, and mean recipient age was 57 years in group III, compared to 44 years in group II. Both lower initial insulin requirement and higher recipient age have been associated with improved outcome [4]. Additionally, group III received immunosuppressive therapy prior to islet transplantation because of previous solid organ transplantation. Deng et al. reported possible favorable outcome in patients receiving islets after kidney (IAK) compared to ITA, and Lablanche et al. recently reported on 24 IAT and 20 IAK and described 31.5% insulin independence 60 months after the last islet transplantation in the IAK group, while the number was 14% in the IAT group [24][16]. These factors combined may explain similarity in results between group II and III despite lower IEQ transplanted in patients who received solid organ transplantation prior to islet transplantation.

We found the mean cost of a single islet transplantation at our center to be 347 297 ± 60 588 NOK or 35 424 ± 6182 EUR. Cost analysis shows that the islet isolation process represents 34% of the cost. Moassesfar et al. recently reported the cost estimate for a single IAT at UCSF to be 99 194 USD, or 851 272 NOK [10]. Interestingly, they estimated isolation cost in their GMP facility to be 37% (37 621 USD or 322 859 NOK) of the total cost, similar to our 34% for the isolation. A previous cost analysis by the GRAGIL group estimated the cost

for a single islet preparation to be 4 242 EUR or 39 926 NOK in 2004. However, our isolation procedure is more similar to the UCSF isolation which is done in a GMP facility [9]. The cost for islet isolation and infusion during simultaneous islet and kidney transplantation in Zurich has been described 23 098 USD in 2015, or 198 224 NOK [11]. However, when considering the isolation cost it is important to emphasize that we have only calculated the cost of a single successful isolation. As the patients usually require a repeated islet infusion, and not all islet isolations lead to clinical transplantation [9], the real cost for islet transplantation is higher. The islet isolation process does therefore represent a significant potential for cost reduction, and investigations into increasing the success rate and developing more efficient, low-cost isolation techniques are ongoing [25][26]. It is also important to note that isolations that fail to yield transplantation level amount of islets often result in human islets available to research [27][28]. This is a favorable part of an islet program that should not be ignored.

To summarize, we describe the cost and outcome of islet transplantation procedures performed at OUS January 2010 to June 2015. We find insulin independence to be lower than what should be expected, but partial graft function and disease impact seems to be in line with achievements at other centers. Finally, we describe the cost of a single islet transplantation at our center, and find the fraction spent on the isolation process to be one third of the total cost. Further research into patient medication an islet isolation process can improve outcome and reduce the cost of islet transplantation.

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References:

1. Ahearn AJ, Parekh JR, Posselt AM: Islet transplantation for Type 1 diabetes: where are we now? Expert Rev Clin Immunol 2015;11:59–68.

2. Maffi P, Scavini M, Socci C, et al.: Risks and benefits of transplantation in the cure of type 1 diabetes: Whole pancreas versus islet transplantation. A single center study. Rev Diabet Stud 2011;8:44–50.

3. Shapiro AM, Lakey JR, Ryan EA, et al.: Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med 2000;343:230–238.

4. Barton FB, Rickels MR, Alejandro R, et al.: Improvement in outcomes of clinical islet transplantation: 1999-2010. Diabetes Care 2012;35:1436–1445.

5. Ryan EA, Paty BW, Senior PA, et al.: Five-Year Follow-Up After Clinical Islet Transplantation. Diabetes 2005;54:2060–2069.

6. Bellin MD, Barton FB, Heitman A, et al.: Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes. Am J

Transplant 2012;12:1576–1583.

7. Al-Adra DP, Gill RS, Imes S, et al.: Single-Donor Islet Transplantation and Long-term Insulin Independence in Select Patients With Type 1 Diabetes Mellitus. Transplantation 2014;98:1007–12.

8. Tharavanij T, Betancourt A, Messinger S, et al.: Improved long-term health-related quality of life after islet transplantation. Transplantation 2008;86:1161–7.

9. Guignard AP, Oberholzer J, Benhamou P-Y, et al.: Cost analysis of human islet transplantation for the treatment of type 1 diabetes in the Swiss-French Consortium GRAGIL. Diabetes Care 2004;27:895–900.

10. Moassesfar S, Masharani U, Frassetto LA, et al.: A Comparative Analysis of the Safety, Efficacy, and Cost of Islet Versus Pancreas Transplantation in Nonuremic Patients With Type 1 Diabetes. Am J Transplant 2016;16:518–526.

11. Gerber PA, Locher R, Zuellig RA, et al.: Glycemia, Hypoglycemia, and Costs of Simultaneous Islet-Kidney or Islet After Kidney Transplantation Versus Intensive Insulin Therapy and Waiting List for Islet Transplantation. Transplantation 2015;99:2174–2180.

12. Beckwith J, Nyman JA, Flanagan B, Schrover R, Schuurman HJ: A health economic analysis of clinical islet transplantation. Clin Transplant 2012;26:23–33.

13. Friberg AS, Ståhle M, Brandhorst H, Korsgren O, Brandhorst D: Human islet separation utilizing a closed automated purification system. Cell Transplant 2008;17:1305–1313.

14. Baidal DA, Froud T, Ferreira J V, Khan A, Alejandro R: The Bag Method for Islet Cell

Infusion 2003;12:809–813.

15. Mishra V, Geiran O, Fiane AE, et al.: Costs and reimbursement gaps after implementation of third-generation left ventricular assist devices. J Hear Lung Transplant 2010;29:72–78.

16. Lablanche S, Borot S, Wojtusciszyn A, et al.: Five-Year Metabolic, Functional, and Safety Results of Patients With Type 1 Diabetes Transplanted With Allogenic Islets Within the Swiss-French GRAGIL Network. Diabetes Care 2015;38:1714–22.

17. Brooks AM, Walker N, Aldibbiat A, et al.: Attainment of metabolic goals in the integrated UK islet transplant program with locally isolated and transported preparations. Am J Transplant 2013;13:3236–3243.

18. Pellegrini S, Cantarelli E, Sordi V, Nano R, Piemonti L: The state of the art of islet transplantation and cell therapy in type 1 diabetes. Acta Diabetol 2016 Feb; DOI: 10.1007/s00592-016-0847-z

19. Rickels MR, Liu C, Shlansky-Goldberg RD, et al.: Improvement in b-Cell secretory capacity after human islet transplantation according to the CIT07 protocol. Diabetes 2013;62:2890–2897.

20. Niclauss N, Bosco D, Morel P, et al.: Influence of donor age on islet isolation and transplantation outcome. Transplantation 2011;91:360–366.

21. Vantyghem M-C, Kerr-Conte J, Arnalsteen L, et al.: Primary graft function, metabolic control, and graft survival after islet transplantation. Diabetes Care 2009;32:1473–1478.

22. Hering BJ, Clarke WR, Bridges ND, et al.: Phase 3 Trial of Transplantation of Human Islets in Type 1 Diabetes Complicated by Severe Hypoglycemia. Diabetes Care 2016; DOI: 10.2337/dc15-1988

23. Caiazzo R, Vantyghem MC, Raverdi V, et al.: Impact of Procedure-Related Complications on Long-term Islet Transplantation Outcome. Transplantation 2015;99:979–984.

24. Deng S, Markmann JF, Rickels M, et al.: Islet Alone vs. Islet After Kidney Transplantation: Metabolic Outcomes and Islet Graft Survival. Transplantation 2009;88:820–825.

25. Ståhle M, Friberg AS: Human Islet Isolation Processing Times Shortened By One Hour: Minimized Incubation Time Between Tissue Harvest and Islet Purification. Transplantation 2013;96:e89–91.

26. Ståhle M, Foss A, Gustafsson B, et al.: Clostripain, the Missing Link in the Enzyme Blend for Efficient Human Islet Isolation. Transplant Direct 2015;1:1–6.

27. Kaddis JS: Human Pancreatic Islets and Diabetes Research. Jama 2009;301:1580–1587.

28. Nano R, Bosco D, Kerr-Conte JA, et al.: Human islet distribution programme for basic research: activity over the last 5 years. Diabetologia 2015;1138–1140.

Tables

Table 1: Donor characteristics.

Group	Age (years)	BMI (kg/m2)	CIT (min)	Total islet mass (IEQ/kg/patient)	Purity (%)	Months btw ITA
I – 1 ITA	50.7 ±5.5	28.7 ±3.4	538 ±213	4850 ±359**	54.0 ±9.0	NA
II – 2 ITA	48.9 ±12.6	29.1 ±5.2	506 ±229	11431 ±2864	56.1 ±17.5	8.1 ±9.6
III – Previous Tx	45.8 ±14.1	28.2 ±4.2	351 ±157	5531 ±1487**	44.5 ±8.1	4.0

ITA, islet transplantation alone; Tx, transplantation. Student *t*-test **p<0.01 compared to group II.

Table 2: Recipient characteristics.

Group	n	Age (years)	Diabetes duration (Years)	Sex (M/F)	BMI (kg/m2)	HbA1c Pre-Tx (%)	Insulin pre-ITA (units/kg/day)
I – 1 ITA	3	45.0 ±5.6	38.0±5.7	2M/1F	22.2 ±3.3	7.4 ±2.2	0.74 ±0.12
II – 2 ITA	10	44.2 ±10.5	26.6±7.1	3M/7F	24.5 ±4.1	7.9 ±1.2	0.63 ±0.21
III – Previous Tx	5	57.0 ±7.6*	47.0±10.4**	1M/4F	24.0 ±1.3	7.8 ±1.3	0.49 ±0.24

ITA; islet transplantation alone, Tx; transplantation. Student *t*-test *p<0.05, **p<0.01 compared to group II.

Table 3: Average cost for a single islet transplantation procedure.

	NOK	EUR	*% of total*
Total cost	347 297 ± 60 588	35 424 ± 6 182	-
Organ procurement	80 000	8 163	*23%*
Islet isolation	118 236	12 065	*34%*
Sum hospitalization cost	149 061	15 210	*43%*
- Pre procedure hospitalization	14 878	1 518	*4%*
- Procedure	25 097	2 561	*7%*
- Post procedure hospitalization	57 379	5 855	*17%*
- Follow up	51 707	5 267	*15%*

NOK; Norwegian kroner, EUR; Euro

Figure legend

Figure 1: Immunosuppression administered to islet recipients during their first and second islet transplantation (Tx). Presented as parts of whole, each column represents the total number of patients in each group (I - 1 ITA, II – 2 ITA, III – previous solid organ). For induction (A) gray represents patients receiving basiliximab based therapy, black represents anti-thymocyte globulin (ATG). For maintenance therapy (B) gray represents patients receiving calcineurin inhibitor in combination with mycophenolate mofetil (MMF), black represents calcineruin inhibitor with sirolimus.

Figure 2: Graft survival. Kaplan-Meier estimates for insulin independence (A) and partial graft function (C-peptide >0.1 nmol/L) (B). Mean HbA1c % (C) and insulin use U/kg/day (D) plotted against time. Dotted line group I (1 ITA), solid line group II (2 ITA), dashed line group III (previous solid organ transplantation).

Figure 3: Diabetes impact. Kaplan-Meier estimates for HbA1c reduction compared to pre-

transplantation levels (A), and HbA1c <6.5% or 2 percentage points lower than pre-transplantation (B). Dotted line group I (1 ITA), solid line group II (2 ITA), dashed line group III (previous solid organ transplantation). Estimates for insulin use for group II (C) and in all groups combined (D). Solid line indicates any reduction in insulin use compared to pre-transplantation levels, dashed line a 50% or more reduction in insulin requirement, dotted line a 100% reduction in insulin use.