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Technology Assessment Unit of the McGill University Health Centre (MUHC)

Islet transplantation in patients with Type 1 Diabetes Mellitus

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ABSTRACT

Islet transplantation (IT) is used to treat type 1 diabetic patients who suffer from unstable metabolic control and frequent hypoglycaemic episodes despite receiving intensive insulin treatment (IIT). It is less invasive than whole organ pancreas transplantation (PT), the standard treatment for these patients. So far it has primarily been used in research settings.

This report reviews the most recent evidence on the effectiveness and safety of IT to determine whether it can be considered an alternative to PT in routine practice and to assess the economic implications of this from the point of view of the McGill University Health Centre (MUHC). IT for patients who have undergone a kidney transplant is considered because they are already on immunosuppression therapy and present with stable renal function.

Effectiveness of IT is reported in terms of full graft function and partial graft function. Patients with full graft function are insulin independent, while patients with partial graft function require insulin but exhibit a substantially reduced risk of severe hypoglycaemia and other diabetes-related complications. While the percentage of patients achieving either full or partial graft function following IT therapy was initially low, it has steadily increased over the last decade. The risk of adverse events due to the procedure and/or immunosuppression therapy has also decreased significantly during this time. No studies have compared patient outcomes (insulin independence or survival) between IT and PT or IT and IIT. Being a more expensive procedure, the initial budget impact of treating 10 patients with IT instead of PT is estimated at $45,079. IT may also be considered for patients who are not considered candidates for PT, e.g. due to high surgical risk, in which case the initial budget impact will be higher, but will decrease over time due to the higher risk of diabetes related complications with IIT.

A cost-effectiveness analysis was performed using a simulation model. Contrary to PT, the risk of procedure related mortality due to IT is thought to be negligible. This difference resulted in an average 0.092 life-years gained per patient over 5 years in the model when comparing IT to PT. This was achieved at an incremental cost of $6,120, or $66,552 per life-year gained, which is attributable to the higher procedural cost as well as the cost due to increased incidence of diabetes related complications among patients who receive IT.

There is as yet insufficient evidence that IT is equal or superior to PT to justify its routine use when PT is the contemplated procedure. However, given its potential benefit, there is sufficient evidence of effectiveness and safety to justify its use in a limited number of patients.

RÉSUMÉ

La transplantation d'îlots (TI) est utilisée pour traiter les patients diabétiques de Type I qui souffrent d'un contrôle métabolique instable et d'épisodes d'hypoglycémie fréquents, malgré un traitement intensif à l'insuline (TII). Cette approche est moins invasive que la transplantation totale du pancréas (TP), le traitement standard pour ces patients. Jusqu'à aujourd'hui, la transplantation d'îlots a surtout été utilisée dans les milieux de la recherche.

Ce rapport examine les données les plus récentes sur l'efficacité et l'innocuité des TI afin de déterminer si cette technique peut être considérée comme une alternative à la TP dans la pratique courante et d'évaluer les implications économiques de cette approche du point de vue du Centre universitaire de santé McGill (CUSM). La TI est considéré pour les patients qui ont déjà subi une greffe rénale car ceux-ci sont déjà sur une thérapie d'immunosuppression et présentent une fonction rénale stable.

L'efficacité des TI est rapportée en termes de fonction complète du greffon et de fonction partielle du greffon. Les patients présentant une fonction complète du greffon sont indépendants de l'insuline tandis que les patients avec une fonction partielle du greffon ont besoin d'insuline mais présentent un risque considérablement réduit d'hypoglycémie sévère et d'autres complications liées au diabète. Bien que le pourcentage de patients démontrant une fonction complète ou partielle du greffon suite à une TI était initialement faible au départ, celui-ci a régulièrement augmenté au cours de la dernière décennie. Le risque d'effets indésirables en raison de cette procédure et/ou du traitement immunosuppresseur a également diminué de façon significative au cours de la même période. Aucune étude n'a comparé les résultats des patients (dépendant de l'insuline ou non) entre la TI et la TP, ou entre la TI et le TII. Étant une procédure plus dispendieuse, l'impact budgétaire initial pour traiter 10 patients avec la TI plutôt qu'avec la TP est estimé à 45 079 $. Cette procédure peut également être envisagée chez les patients qui ne peuvent être candidats pour la TP, par exemple dû à un risque chirurgical important; l'impact budgétaire initial sera alors plus élevé mais diminuera au fil du temps en raison du risque plus important de complications liées au TII.

Une analyse coût-efficacité a été réalisée à partir d'un modèle de simulation. Contrairement à la TP, le risque de décès relié à la procédure de TI semble négligeable. Cette différence se traduit par un gain moyen de 0.092 année de vie par patient sur 5 ans, en comparant la TI et la TP dans le modèle. Le coût de ce gain est de 6 120 $ (coût incrémentiel) ou de 66 552 $ par année de vie gagnée résultant d'un coût procédural plus élevé ainsi qu'aux coûts des complications liées au diabète dont l'incidence est accrue pour les patients ayant reçu une TI.

Il n'y a pas encore assez de preuves démontrant que la TI est comparable ou supérieure à la TP pour justifier son utilisation sur une base routinière lorsque la TP est envisagée. Toutefois, compte tenu de ses avantages potentiels, il y suffisamment de preuves en regard de son efficacité et de son innocuité pour justifier son utilisation chez un nombre limité de patients.

List of abbreviations

$CAD	Canadian Dollar
AE	Adverse Event
BMI	Body Mass Index
CITR	Collaborative Islet Transplant Registry
CMV	Cytomegalovirus
CRD	Centre for Research and Dissemination
DARE	Database of Abstracts of Reviews of Effects
DCCT	Diabetes Control and Complications Trial
HbA1c	Glycated hemoglobin
HTA	Health Technology Assessment
IAK	Islet After Kidney Transplantation
ICER	Incremental Cost Effectiveness Ratio
ICU	Intensive Care Unit
IHE	Institute of Health Economics
IPTR	International Pancreas Transplant Registry
IT	Islet transplantation
IIT	Intensive Insulin Therapy
ITA	Islet Transplantation Alone
LOS	Length Of Stay
MUHC	McGill University Health Centre
ODEM	Ontario Diabetes Economic Model
OR	Operating Room
PAK	Pancreas After Kidney Transplantation
PRBC	Packed Red Blood Cells
PT	Whole Organ Pancreas Transplantation
QALY	Quality Adjusted Life Year
QoL	Quality Of Life
RR	Risk Ratio
SD	Standard Deviation
SICU	Surgical Intensive Care Unit
SIK	Simultaneous Islet and Kidney Transplantation
TAU	MUHC Technology Assessment Unit
TCDAb	T cell depleting antibodies
TNF	Tumor necrosis factor
UAITR	University of Alberta Islet Transplantation Review
UKPDS	United Kingdom Prospective Diabetes Study

EXECUTIVE SUMMARY

Background

Whole organ pancreas transplantation (PT) is the classical approach to treat diabetic patients who suffer from unstable metabolic control and frequent hypoglycaemic episodes despite receiving intensive insulin treatment (IIT). Islet transplantation (IT) is a newer, less invasive treatment that has not been used in routine practice in most centres. The Technology Assessment Unit was requested to review the most recent evidence on the effectiveness and safety of IT to determine whether it can be considered an alternative to PT in routine practice and to assess the economic implications of this from the point of view of the McGill University Health Centre (MUHC). IT procedures can be classified with respect to the patient's kidney transplant status as islet after kidney transplant (IAK), simultaneously islet and kidney transplant (SIK), and islet transplant alone (ITA). IAK will be the first considered at the MUHC, because patients are already on immunosuppression therapy and present with stable renal function, and it will be the focus of this report.

Objectives

This report has two objectives: i) to carry out a literature review of the effectiveness of IT (in terms of achieving insulin independence) and of its safety, ii) to carry out an economic evaluation of IT, by estimating its cost, budget impact and cost-effectiveness relative to PT and IIT, among patients who have previously undergone a kidney transplant.

Methods

Review of effectiveness and safety of IT

A literature search was carried out to identify systematic reviews and Health Technology Assessment (HTA) reports of IT published in 2008 or later. The collaborative islet transplant registry (CITR) website was searched to obtain the latest clinical data from the largest registry of IT worldwide. We also searched online medical literature databases for reports published in the last 5 years from centres performing IT. Effectiveness of IT was reported in terms of full graft function and partial graft function. Patients with full graft function are typically insulin independent, while patients with partial graft function are protected from severe hypoglycaemia and are less dependent on insulin than prior to transplant.

Economic evaluation

We carried out a literature search to identify previous economic evaluations.

Procedure cost and budget impact

We estimated the procedure costs of IT and PT from the perspective of the MUHC. In addition to procedure costs, we considered cost of procedure-related complications. We ignored immunosuppression related costs and overhead costs which are assumed to be the same for patients receiving IT or PT. We also estimated the budget impact based on the expected number of IT and PT procedures that will be carried out at the MUHC annually.

Cost-effectiveness analysis

A Markov decision-analytic model was constructed to compare the long-term health-economic consequences of IT vs. PT therapy for the subgroup of patients who previously underwent a kidney transplant. In addition to the cost of the procedure and procedure-related complications, we also considered the cost of diabetes-related complications during follow-up. All costs were expressed in 2013 Canadian dollars. Risk of diabetes-related complications were allowed to vary with graft function status. The most recent publications based on the International Pancreas Transplant Registry (IPTR) were identified to obtain estimates of the probabilities of full graft function or graft loss states following PT. The same model was also used to compare IT to intensive insulin treatment (IIT) under the assumption that patients on IIT are similar to those who experience graft loss. In order to account for both the lower procedural mortality and morbidity associated with IT in the short term and the greater percentage of insulin independence in the long-term following PT, effectiveness was defined in terms of life-years. We carried out scenario analyses to study the impact of: i) higher insulin independence following IT, ii) linking graft function to mortality and iii) increasing the risk of procedural mortality following PT.

Results

Review of effectiveness and safety of IT

We identified one systematic review of patient-reported outcomes following IT published in 2010 and one HTA of IT published in 2013, respectively. There were no comparative studies of the effectiveness of IT vs. PT.

Effectiveness of IT based on international registry data

Based on CITR data, we estimated that at 3 years after the last IT infusion the full and partial graft function rates were 44% and 21%, respectively. At 5 years after the last infusion, they were 24% and 19%, respectively.

Effectiveness of IT based on single-centre research studies

Recent studies (though with relatively small sample sizes) have reported that 5-year insulin independence rates can be as high as 50% under new immunotherapy protocols in some IT centres. The severity level of hypoglycaemia episodes was reduced among insulin dependent patients. Some studies showed that IT was

associated with reduced progression of diabetic microvascular complications and improved cardiovascular function. One large case series of 138 patients at the University Alberta reported that patient survival was 96% at 12 years using a Kaplan Meier analysis.

Safety of IT

Based on CITR data, the risk of adverse events (AEs) and severe AEs due to IT infusions and/or immunosuppression therapy reported in recent years was significantly lower than those in earlier years (e.g. the risk of severe adverse events decreased to 26% in 2007-2009 compared to 47% in 2004-2006 and 69% in 1999-2003). Our review of individual research studies found that besides an accidental unrelated death reported in one study, other studies did not report any procedure-related mortality. The most common procedure-related complications included intra-peritoneal bleeding (2%), partial branch-vein occlusion (8%) and liver abnormality (40%). Most severe adverse events were related to immunosuppression.

Quality of life following IT

Following recovery from the procedure, IT improved the diabetes-specific quality of life (QoL) compared with before IT therapy, and some studies reported that the benefits were maintained over 3 years. Some studies found that IT therapy improved psychological well-being and reduction of the fear of hypoglycaemia.

Economic evaluation

Review of previous economic evaluations

We identified 2 economic evaluations of IT published in 2012 and 2013. In the first study, from the United States, the one-time cost of an IT procedure (one infusion) was about US$93,500, and the cost of follow up was US$19,000 annually. The second study, an HTA by the Institute of Health Economics (IHE) in Edmonton, estimated the IT procedure cost was about CAD$ 131,000 per infusion.

Procedure cost of IT

The average procedure cost of IT per patient at the MUHC (excluding complications) is projected to be about $29,575, with an IT procedure requiring on average 1.8 infusions (range1-3). The much lower cost estimate compared to earlier publications is largely attributable to the fact that there is no cost to the MUHC for organ retrieval and because the estimated laboratory costs of islet cell extraction ($10,536 per infusion), are substantially lower at the MUHC than in other centres.

Effectiveness, safety and quality of life following PT

According to the most recent data from the International Pancreas Transplant Registry (IPTR), the 1-year and 5-year insulin independence rates are 86% and 65%, respectively, for pancreas after kidney transplant. The overall unadjusted 1 year survival rates were ≥96%. Common complications following PT include pancreas graft thrombosis (10%), deep wound infections (15-20%), duodenal leaks

(5%) and rejection (50%). Graft loss has a negative impact on the patient's survival and quality of life.

Procedure cost of PT and incremental cost of IT vs PT at the MUHC

The estimated procedure cost (excluding complications) for PT is $18,293. Thus, the incremental cost of the initial IT procedure versus PT is $11,282 per patient on average. PT therapy was associated with significantly higher risk and costs of procedure-related complications ($6,832 per patient for PT versus $57.6 per patient for IT). After including costs for treatment of procedure-related complications, the incremental cost of IT versus PT was reduced to $4,508 per patient.

Budget impact of IT vs PT

If IT is used as a replacement for PT the net annual budget increase in procedure costs due to using IT rather than PT would be $27,048, $45,079 and $90,159 for 6, 10 and 20 recipients per year, respectively. It is possible, though it is difficult to estimate precisely, that IT may be offered to patients who are not typically considered candidates for PT (e.g. those at high surgical risk). If 20% of IT procedures were performed in such patients, then the initial budget impact due to the procedure costs of 6, 10 or 20 IT procedures would increase to $57,129, $95,214 and $190,428, respectively.

Cost-effectiveness analysis

Procedural mortality was estimated to be 2% following PT and negligible following IT. We estimated that, relative to PT, the IT strategy would result in 0.092 life-years gained at a higher incremental cost of $6,120 in 5 years per procedure. It should be noted that the gain in life-years is entirely due to the mortality related to PT at the time of the procedure, while the increase in cost is due to the higher cost of the procedure as well as costs associated with the management of diabetes-related complications, the risk of such complications being higher following IT than PT. The corresponding incremental costs per life-year gained are $66,552 at 5 years follow up. The average total graft survival time (either full graft or partial graft) for IT is slightly shorter than that for PT (At 5 years: 42.5 months versus 44.3 months). Sensitivity and scenario analyses show that the incremental cost per life year gained ranges from $50,000 to $80,000 in most situations. Under a scenario analysis allowing for the procedure-related mortality following PT to be as high as 10%, we found that incremental cost per life year gained decreased to $19,965 at 5 years follow up. If the alternative to IT were intensive insulin therapy (IIT), the incremental cost of IT would be $28,383 (IT: $34,860; IIT: $6,476) at one year and $23,023 (IT: $59,917; IIT: $36,894) at 5 years post IT, due to the much higher risk of diabetes-related complications in the IIT arm.

Limitations

We have attempted to evaluate the effectiveness, safety, cost, budget impact and cost effectiveness of IT, primarily in comparison with PT. It should be noted that there are as yet no direct comparisons of these two procedures. All the following conclusions are based on indirect comparisons of different case series and should

be considered with appropriate caution. Furthermore, these comparisons are limited to situations when IT or PT are carried out post-kidney transplant.

CONCLUSIONS

Effectiveness For type 1 diabetes patients with unstable metabolic control who have previously undergone a kidney transplant, islet transplantation (IT) therapy can improve glycemic control and reduce the risk of hypoglycaemia. The rate of insulin independence following IT appears to be lower than that achievable with the standard procedure of whole pancreas transplant (PT). However, the rate of graft survival (i.e. when the patient has either full or partial graft function) following the two procedures is similar.

Safety PT is associated with a risk of procedural mortality and of serious post procedural complications. By contrast IT is associated with a negligible risk of procedural mortality or complications. Both procedures carry a high risk of severe adverse events that are associated primarily with the immunosuppression therapy.

Cost Compared to PT, IT is a more expensive procedure. It costs an estimated $29,575 per procedure. Using a six-month time horizon, our cost analysis shows that after adjusting for the cost of treating procedure-related adverse events, the IT procedure has a higher net cost of $4,508 per patient compared to PT.

Budget impact The budget impact of a single IT procedure will depend on whether it replaces PT or is offered to a patient who is not a candidate for PT. For example, the budget impact of using IT *instead of* PT for 10 patients per year, would be approximately $45,079. If IT were to be used instead of PT for 8 patients, and for 2 patients who were *not candidates* for PT, the budget impact would be approximately $95,212.

Cost-effectiveness Compared with PT, IT leads 0.092 life-years or approximately one month gained in 5 years follow up. This translates into a relatively high incremental cost-effectiveness ratio of IT vs PT of $66,552 per life-year gained at 5-years post-transplant. Compared with IIT, IT is associated with a significantly higher cost, but, also with a significantly reduced risk of diabetes-related complications. After adjusting for the cost of diabetes-related complications but not considering costs of maintenance of immunosuppression therapy, we estimated the incremental cost to be $23,023 at 5 years follow up.

RECOMMENDATIONS

- **There is as yet insufficient evidence that IT is equal or superior to PT to justify its *routine use* when PT is the contemplated procedure. This decision should be reviewed in approximately 2 years.**

- **The evidence of effectiveness and safety is adequate to justify IT being offered as an alternative to carefully selected patients. The interdisciplinary pancreas and kidney transplant groups (within the MUHC multi-organ transplant program and Transplant Quebec) should develop a list of inclusion and exclusion criteria for IT and define a protocol for its appropriate use.**
- **Because confident evidence of effectiveness is lacking, and the somewhat higher costs, the use of IT should be limited to not more than seven patients per year.**
- **As an innovative and not yet routine procedure, detailed, regularly updated patient records, including details of patient selection, should be kept available for review by the Director of Professional Services or her nominee at any time.**
- **A proposal for provincial funding of this technology should be submitted to the Ministry.**

SOMMAIRE

Contexte

La transplantation complète du pancréas (TP) est l'approche classique pour traiter les patients diabétiques souffrant d'un contrôle métabolique instable et d'épisodes d'hypoglycémie fréquents, malgré des traitements intensifs d'insuline (TII). La transplantation d'îlots (TI) est un traitement récent, moins invasif, qui n'a pas été utilisée comme pratique courante dans la majorité des centres. L'Unité d'évaluation des technologies ("Technology Assessment Unit") a été sollicitée pour revoir les données les plus récentes sur l'efficacité et l'innocuité de la TI afin de déterminer si celle-ci peut être considérée comme une alternative à la TP dans la pratique courante et pour évaluer les implications économiques de cette approche du point de vue du Centre universitaire de santé McGill (CUSM). Les procédures de TI peuvent être classées par rapport au type de transplantation rénale, soit îlots après transplantation rénale (IAR), îlots et reins transplantés simultanément (IRS) et îlots transplantés seuls (ITS). L'IAR sera la première approche considérée au CUSM car les patients sont déjà sur une thérapie d'immunosuppression et présentent une fonction rénale stable; cette approche fera l'objet de ce rapport.

Objectifs

Ce rapport vise deux objectifs: i) de procéder à une revue de la littérature sur l'efficacité de la TI (en termes d'atteinte à une indépendance à l'insuline) et son innocuité, ii) de procéder à une évaluation économique de la TI en évaluant son coût, son impact budétaire et son coût-efficacité par rapport à la TP et au TII chez les patients ayant déjà subi une greffe rénale.

Méthodologie

Revue de l'efficacité et de l'innocuité de la TI

Une recherche documentaire a été effectuée afin d'identifier les revues systématiques et les rapports d'évaluation des technologies (ETS) sur la TI publiés de 2008 à ce jour. Le registre du site collaboratif web sur la transplantation des îlots ("Collaborative Islet Transplant Registry" (CITR)) fut consulté pour obtenir les dernières données cliniques du plus important registre mondial de TI. Nous avons également recherché dans les bases de données médicales en ligne, les rapports publiés depuis les 5 dernières années par les centres réalisant la TI. L'efficacité de la TI était rapportée en termes de fonction complète du greffon et de fonction partielle du greffon. Les patients présentant une fonction complète du greffon sont généralement indépendants de l'insuline tandis que les patients avec une fonction partielle du greffon sont protégés des hypoglycémies sévères et sont moins dépendants de l'insuline qu'avant la transplantation.

Évaluation économique

Nous avons effectué une recherche documentaire pour identifier les évaluations économiques antérieures.

Coût des procédures et impact budgétaire

Nous avons estimé les coûts des procédures pour la TI et la TP du point de vue du CUSM. En plus des coûts des procédures, nous avons aussi considéré le coût des complications liées à ces procédures. Nous avons ignoré les coûts liés à l'immunosuppression et les frais généraux qui devraient être les mêmes pour les patients faisant l'objet d'une procédure TI ou d'une procédure TP. Nous avons également estimé l'impact budgétaire sur la base du nombre attendu de procédures TI et TP qui seront effectuées au CUSM, annuellement.

Analyse coût-efficacité

Un modèle de décision analytique Markov fut construit pour comparer les conséquences économiques à long terme relatives à la santé pour les procédures TI et TP, pour le sous-groupe de patients ayant déjà fait l'objet d'une transplantation rénale. En plus du coût des procédures et des coûts liés à leurs complications, nous avons également considéré le coût lié aux complications dues au diabète pendant le suivi. Tous les coûts ont été exprimés en dollars canadiens selon l'année 2013. Les risques liés aux complications du diabète pouvaient variés selon la fonctionnalité du greffon. Les publications les plus récentes, basées sur le registre de l'organisme "International Pancreas Transplant Registry" (IPTR), furent identifiées pour estimer les probabilités d'obtenir une fonction complète ou partielle du greffon suite à la TP. Le même modèle fut également utilisé pour comparer la TI au TII selon l'hypothèse que les patients sous TII ont une condition semblable à ceux qui font l'expérience de la perte d'un greffon. Afin de tenir compte à la fois du plus faible taux de mortalité et de morbidité lié à la TI à court terme ainsi que du plus fort pourcentage d'indépendance à l'insuline à long terme suite à une TP, l'efficacité fut définie en termes d'années de vie. Nous avons analysé différents scénarios pour étudier l'impact: i) d'une plus grande indépendance à l'insuline suivant la TI, ii) du lien entre la fonctionnalité du greffon et la mortalité et iii) de l'accroissement du risque de mortalité suivant une procédure TP.

Résultats

Revue de l'efficacité et de l'innocuité de la TI

Nous avons identifié une revue systématique publiée en 2010 portant sur les résultats de patients ayant subi une TI, et une ETS sur la TI publiée en 2013,

respectivement. Il n'y avait aucune étude comparative sur l'efficacité de la TI vs la TP.

Efficacité de la TI basée sur les données du registre international

En se basant sur les données du registre international CITR, nous avons estimé que 3 ans après la dernière infusion de la TI, les taux de fonction complète et partielle des greffons étaient de 44% et de 21%, respectivement. Cinq ans après la dernière infusion, ces taux étaient de 24% et 19%, respectivement.

Efficacité de la TI basée sur les recherches de centres indépendants

Des études récentes (faites à partir d'échantillons relativements faibles) ont rapporté que des taux d'indépendance à l'insuline peuvent être aussi élevés que 50% après 5 ans de traitement sous de nouveaux protocoles d'immunothérapie, dans certains centres spécialisés en TI. Le niveau de sévérité des épisodes d'hypoglycémie était réduit parmi les patients insulino-dépendants. Certaines études ont montré que la TI était associée à une progression plus faible des complications microvasculaires diabétiques et à une amélioration de la fonction cardiovasculaire. Une importante série de cas de 138 patients à l'Université de l'Alberta a rapporté que la survie des patients était de 96% à 12 ans, en utilisant une analyse de Kaplan-Meier.

Innocuité de la TI

Basé sur les données du registre CITR, le risque d'évènements indésirables et graves signalé ces dernières années, suite à des infusions TI et/ou à une thérapie d'immunosuppression, était nettement plus faible que ceux des années précédentes (par exemple, le risque d'évènements indésirables sévères est diminué à 26% en 2007-2009, comparativement à 47% en 2004-2006 et 69% en 1999-2003). Notre revue des recherches individuelles a révélé que, à l'exception d'une mort accidentelle non-reliée à l'étude en question, les autres études n'ont signalé aucun décès lié à cette intervention. Les complications les plus courantes liées à cette procédure comprenaient le saignement intra-péritonéal (2%), l'occlusion partielle d'une branche veineuse (8%) et une anomalie du foie (40%). Les effets indésirables les plus graves étaient liés à l'immunosuppression.

La qualité de vie suite à la TI

Après la période de récupération suivant cette procédure, la TI améliorait la qualité de vie relative au diabète par rapport à la situation avant thérapie, et certaines études soulignèrent que ces bénéfices étaient maintenus pour plus de 3 ans. Certaines études montrèrent que la thérapie TI améliorait le bien-être psychologique ainsi que la diminution de la crainte de l'hypoglycémie.

Évaluation économique

Revue des évaluations économiques antérieures

Nous avons identifié 2 évaluations économiques de la TI publiées en 2012 et 2013. La première étude, réalisée aux États-Unis, mentionnait que le coût de la première infusion TI était d'environ 93 500 $US et que le coût du suivi était de 19 000 $US, annuellement. La seconde étude, un rapport ETS réalisé par l'"Institute of Health Economics" d'Edmonton, a estimé qu'une procédure TI coûtait environ 131 000 $CAN par infusion.

Coût d'une procédure TI

Le coût moyen d'une procédure TI au CUSM (en excluant les complications) devrait être d'environ 29 575 $ par patient, où une procédure TI requiert en moyenne 1.8 infusions (entre 1-3). L'estimation beaucoup plus faible des coûts, comparée aux publications antérieures, est attribuable en grande partie au fait qu'il n'y a aucun coût pour le CUSM quant au prélèvement d'organes et que l'estimation des coûts de laboratoire pour l'extraction des cellules d'îlots (10 536 $ par infusion) sont considérablement plus faibles que ceux d'autres centres.

Efficacité, innocuité et qualité de vie suite à une procédure TP

Selon les plus récentes données de l'organisme "International Pancreas Transplant Registry" (IPTR), les taux d'indépendance à l'insuline à 1 an et 5 ans sont de 86% et 65%, respectivement, pour le pancréas suite à une greffe rénale. Le taux global de survie non-ajusté après 1 an était plus grand ou égal à 96%. Les complications habituelles suite à une procédure TI incluent les tromboses de la greffe du pancréas (10%), les infections de plaies profondes (15-20%), les fuites duodénales (5%) et le rejet (50%). La perte d'un greffon a un impact négatif sur la survie d'un patient ainsi que sur sa qualité de vie.

Coût d'une procédure TP et coût supplémentaire de la procédure TI vs TP au CUSM

Le coût estimé d'une procédure TP (excluant les complications) est de 18 293 $. Ainsi, le coût supplémentaire moyen d'une procédure TI initiale vs une procédure TP est de 11 282 $ par patient. La thérapie TP comportait des risques et des coûts de complications plus élevés (6 832 $ par patient pour une procédure PT versus 57.6 $ par patient pour une procédure TI). Si l'on tient compte des coûts liés aux complications, le coût supplémentaire des procédures TI vs PT est réduit à 4 508 $ par patient.

Impact budgétaire des procédures TI vs TP

Si la procédure TI est utilisée pour remplacer une procédure TP, l'augmentation nette du budget annuel due à l'utilisation de la procédure TI plutôt que TP serait de 27 048 $, 45 079 $ et 90 159 $ pour 6, 10 et 20 bénéficiaires par année, respectivement. Il serait possible d'offrir la procédure TI aux patients qui ne sont pas généralement considérés comme candidats à la procédure TP (par exemple, les patients à haut risque chirurgical), mais ceci est difficile à évaluer avec précision. Si 20% des procédures TI étaient réalisées chez ces patients, l'impact budgétaire initial dû au coût de 6, 10 ou 20 procédures augmenterait alors à 57 129 $, 95 214 $ et 190 428 $, respectivement.

Analyse coût-efficacité

Le taux de mortalité fut estimé à 2% suite à une procédure TP et négligeable, suite à une procédure TI. Nous avons estimé que, comparativement à la TP, la stratégie TI se traduirait par un gain de 0.092 année de vie à un coût supplémentaire plus élevé de 6 120 $ par procédure, pour 5 ans. Il convient de noter que le gain en années de vie est dû entièrement au taux de mortalité relatif au TP au moment de la procédure, tandis que l'augmentation des coûts résulte du coût plus élevé de la procédure ainsi qu'aux coûts rattachés à la gestion des complications diabétiques, le risque de telles complications étant plus grand suivant une TI qu'une TP. Le coût supplémentaire correspondant par année de vie additionnelle est de 66 552 $ après un suivi de 5 ans. La durée moyenne totale de la survie d'une greffe (que ce soit une greffe totale ou partielle) pour une TI est sensiblement plus courte que celle pour une TP (après 5 ans: 42.5 mois versus 44.3 mois). Les analyses de sensibilité et des divers scénarios montrent que le coût supplémentaire par année de vie ajoutée varie entre 50 000 $ et 80 000 $ pour la plupart des situations. Dans une analyse de scénarios où le taux de mortalité lié à la TP était fixé à une valeur aussi élevée que 10%, nous avons constaté que le coût supplémentaire par année de vie ajoutée diminuait à 19 965 $ après un suivi de 5 ans. Si l'alternative à la TI était le traitement intensive à l'insuline (TII), le coût supplémentaire à la TI serait de 28 383 $ (TI: 34 860 $; TII: 6 476 $) après une année et 23 023 $ (TI: 59 917 $; TII: 36 894 $) après 5 ans suivant cette approche, dû au risque beaucoup plus élevé de complications diabétiques dans la branche TII.

Limites de l'étude

Nous avons tenté d'évaluer l'efficacité, l'innocuité, les coûts, l'impact budgétaire et le coût-efficacité de la TI, essentiellement en la comparant à la TP. Il convient de noter qu'il n'y a encore aucune comparaison directe entre ces deux procédures. Toutes les conclusions suivantes se fondent sur des comparaisons indirectes de différentes séries de cas et doivent être considérées avec prudence. En outre, ces comparaisons se limitent aux situations où la TI ou la TP sont effectuées après une greffe rénale.

CONCLUSIONS

Efficacité

Pour les patients diabétiques de type 1 avec un contrôle métabolique instable qui ont déjà eu une transplantation rénale, la thérapie par transplantation d'îlots (TI) peut améliorer le contrôle glycémique et réduire le risque d'hypoglycémie. Le taux d'indépendance à l'insuline suivant la TI semble plus faible que celui découlant de la procédure standard qui est la greffe totale du pancréas (TP). Cependant, le taux de survie de la greffe (c'est-à-dire, lorsque le patient a une fonction complète ou partielle du greffon) est identique suite à ces deux procédures.

Innocuité

La procédure TP comporte un risque de mortalité et un risque de graves complications post-procédurales. Par comparaison, la TI comporte un risque négligeable de mortalité ou de complications. Ces deux procédures montrent un risque élevé d'évènements indésirables graves, liés principalement à la thérapie d'immunosuppression.

Coûts

Par comparaison à la TP, la TI est une procédure plus dispendieuse. Le coût d'une procédure est estimé à 29 575$. Sur un horizon de six mois, notre analyse de coûts montre qu'après avoir fait un ajustement pour le traitement des évènements indésirables liés à cette procédure, la procédure TI a un coût net plus élevé de 4 508 $ par patient, par comparaison à la TP.

Impact budgétaire

L'impact budgétaire d'une seule procédure TI dépendra du fait qu'elle remplace la TP ou qu'elle est offerte à un patient qui n'est pas candidat à une TP. Par exemple, l'impact budgétaire d'utiliser la TI plutôt que la TP chez 10 patients par année serait d'environ 45 079 $. Par contre, si la TI était utilisée plutôt que la TP chez 8 patients et que l'on ajoute 2 patients qui n'étaient pas candidats pour la TP, l'impact budgétaire serait d'environ 95 212 $.

Coût-efficacité

Par rapport à la TP, la TI ajoute 0.092 année de vie additionnelle ou un gain d'environ un mois sur un suivi de 5 ans. Ceci se traduit par un ratio coût-efficacité supplémentaire sensiblement élevé de la TI vs la TP de 66 552 $ par année de vie ajoutée, 5 ans après la transplantation. Par rapport à la TII, le coût de la TI est significativement plus élevé mais celle-ci offre un risque réduit de façon significative quant aux complications liées au diabète. Après réajustement pour le coût des

complications liées au diabète mais sans considérer les coûts de la thérapie d'immunosuppression, nous avons estimé que le coût supplémentaire est de 23 023 $ après un suivi de 5 ans.

RECOMMANDATIONS

- **Il n'existe pas encore de preuves suffisantes démontrant que la TI est égale ou supérieure à la TP pour justifier son utilisation courante lorsque la TP est la procédure envisagée. Cette décision devrait être reconsidérée dans environ 2 ans.**

- **Les preuves de l'efficacité et de l'innocuité de la TI sont suffisantes pour la proposer comme alternative à des patients soigneusement sélectionnés. Les groupes de transplantation interdisciplinaires du pancréas et des reins (à l'intérieur du programme de transplantation multi-organes du CUSM et de Québec Transplant) devraient élaborer une liste de critères d'inclusion et d'exclusion pour la TI et définir un protocole pour une utilisation appropriée.**

- **Comme les preuves solides de son efficacité sont absentes et que ses coûts sont quelque peu élevés, l'utilisation de la TI devrait être restreinte à un maximum de sept patients par année.**

- **En tant que procédure innovante mais pas encore d'utilisation courante, des registres patients détaillés, mis à jour régulièrement et incluant les détails de la sélection des patients, devraient être disponibles pour consultation par le directeur des services professionnels ou son représentant, en tout temps.**

- **Une proposition pour le financement provincial de cette technologie devrait être soumise au Ministère.**

Islet transplantation in Patients with Type 1 Diabetes Mellitus

1. BACKGROUND

Intensive insulin therapy is an effective and safe treatment for most type 1 diabetes mellitus patients to control blood glucose level, as well as to reduce the risks of long term diabetic complications. However, intensive insulin therapy can increase the risk of severe hypoglycaemic episodes, especially for brittle diabetes patients - a small subgroup of patients with unstable metabolic control and frequent hypoglycaemic episodes[1]. It has been estimated that 5% of patients account for 54% of severe hypoglycaemic episodes[2]. The classical approach to treat these patients is by means of beta cell replacement which is achieved by whole organ pancreas transplantation (PT). PT has been shown to achieve normoglycaemia and prevent hypoglycaemia[3] as long as graft survival can be sustained. The 5-year graft survival (or insulin independence rate) following PT is estimated to be about 65-70% at the McGill University Health Centre (MUHC)[4]. However, PT is associated with a high risk of surgical complications, and a non-negligible risk of perioperative mortality.

Islet transplantation (IT) an alternative treatment to PT, has been used in patients since 1974[5]. The technical details of islet preparation and transplantation have been described elsewhere[6]. Briefly, the human cadaveric pancreas is enzymatically and mechanically dissociated to isolate islet cells. The patient is admitted and administered immunosuppressive medication prior to receiving IT. Normally, the IT procedure is conducted with radiological control under local anaesthesia. The islet cells are transferred to the patient's liver via infusion through the portal vein[7]. The liver can tolerate the infusion of islet cells without permanent injury. Thus, compared with PT, IT is less invasive and results in fewer and less severe procedure-related complications with a negligible risk of procedural mortality. Another advantage of IT is that the pool of donors whose pancreas can be used is much broader, including older donors and overweight donors. Both IT and PT procedures are differentiated on the basis of whether or not the patient also receives a kidney transplant. The three categories for IT are: i) simultaneously islet and kidney transplant (SIK), islet after kidney transplant (IAK) and islet transplant alone (ITA). The analogous categories for PT are simultaneous pancreas and kidney transplant (SPK), pancreas after kidney transplant (PAK) and pancreas transplant alone (PTA).

IT appears to have advantages over PT in terms of being a less invasive and risky procedure. However, due to the low success rate in terms of achieving insulin independence in the early cases (insulin independence lasted over 1 week in just 12.4% out of 267 cases performed during the 1990's[6]), IT remained a relatively rare procedure until a case series of 7 consecutive patients treated with an innovative

technique (known as the “Edmonton protocol”) was reported in 2000[6]. This study demonstrated that the quantity of islets required to achieve insulin independence was about 2 times that which had been assumed previously. Two to three infusions of islet cells resulted in a higher chance of insulin independence. Since then, the IT procedure has been used increasingly, though it is still limited to a few clinical centres worldwide. The collaborative islet transplant registry (CITR) was established to collect data on IT patient outcomes. From 1999 to 2010, it comprised data from 677 IT recipients , which represents approximately 81% of patients who received this treatment in North America, Europe and Austrialia[8]. Over the last decade there have been further improvements to the immunosuppression therapy used in the ‘Edmonton protocol’ resulting in better outcomes[1;8].(discussed below)

Another factor contributing to the reported success of the IT procedure is the change in definition of success from insulin independence (full graft function) to positive c-peptide level (either full or partial graft function, partial graft function being defined as positive c-peptide level in the absence of insulin independence), since patients with partial function maintain glycemic control with a significantly lower insulin requirement, and are protected from hypoglycaemia compared to those having experienced graft loss[9].

However, the IT procedure remains very expensive and its effectiveness in terms of achieving insulin independence is still evolving. It is considered experimental by the FDA (Food and Drug Administration) in the United States and is only carried out as part of Phase 3 trials at sanctioned institutes in that country. According to a recent health technology assessment report from the Institute of Health Economics in Alberta, IT is not reimbursed by insurance plans in most countries, and physicians in Alberta are currently not reimbursed for carrying out islet infusions[1]. In the United Kingdom, on the other hand, IT is a recognized treatment option for patients in need of a pancreas transplant[10].

The McGill University Health Centre (MUHC) has been supporting research related to IT for a number of years. The Technology Assessment Unit (TAU) received a request to review IT from Dr. Ewa Sidorowicz, Associate Director of Professional Services, (MUHC) to determine whether it can be routinely considered as an alternative to whole organ transplantation in the subgroup patients who have previously had a kidney transplant. The rationale for focusing on this subgroup of patients is that they are already undergoing immunosuppression therapy and present with stable renal function; extending IT to a broader group of patients could potentially be considered at a future time, but such indications will not be considered in this report.

OBJECTIVES

This report has two main objectives:

1. to carry out a literature review of the effectiveness of IT in achieving insulin independence and of its safety,

2. to carry out an economic evaluation of IT, estimating its cost, budget impact and its cost-effectiveness relative to PT and IIT, among patients who have previously undergone a kidney transplant

METHODS FOR LITERATURE REVIEW OF EFFECTIVENESS AND SAFETY OF IT

A systematic literature search was carried out using Pubmed, as well as the Health Technology Assessment (HTA) database and the Database of Abstracts of Reviews of Effects (DARE) maintained by the Centre for Reviews and Dissemination (CRD)[11] of the University of York, UK. The goal of the search was to identify systematic reviews, HTA reports and economic evaluations concerning islet transplantation in type 1 diabetes patients. The CRD's HTA database includes completed and ongoing health technology assessments from around the world[11].

To identify systematic reviews, we used the following key words in Pubmed: ((islet transplantation) or (Islet transplantation) or (islet transplant) or (Islet cell transplant)) and ((Diabetes mellitus type 1) or (type 1 diabetes) or T1DM)). We limited the search to meta-analyses or systematic reviews on human subjects published in the last 5 years. We used additional terms (economics or economic or cost or expenditure) to identify economic evaluations. We searched the CRD database using the keyword (Islet). To identify individual studies, a further search was conducted by using the same key words without any limits in Pubmed and by tracking references in retrieved publications. We also searched the medical literature databases for recent reports from major centres performing IT (i.e. University of Minnesota, University of Alberta and Medical Centre of Giessen, Germany). We excluded studies for indications other than severe type 1 diabetes, such as chronic pancreatitis. We only included studies reporting clinical outcomes and excluded those that exclusively reported non-clinical results. The last literature search was conducted on November 25th 2013.

We also searched the collaborative islet transplant registry (CITR) website (http://www.citregistry.org/) to obtain reports and peer-reviewed publications based on the latest clinical data from the largest registry of IT worldwide. This voluntary

participation registry database established in 2001 includes the majority of IT recipients in North America, Europe and Australia since 1999[12].

METHODS FOR ECONOMIC EVALUATION

Procedure costs and budget impact

We estimated the procedure costs of IT and PT from the perspective of the MUHC, including costs for Operating Room (OR), radiology, laboratory, pharmacy (induction of immunosuppression therapy), Intensive Care Unit (ICU) and inpatient costs. We excluded the physician fee, the costs for organ retrieval (which are not charged to hospitals in Quebec), and the maintenance of immunosuppression therapy (which is necessary for both types of transplantation). Hospital overhead costs were also excluded. Estimates of usage of various components within the two treatment approaches were provided by Dr. Paraskevas (See Table 1). It was estimated that 34%, 52% and 14% patients would receive 1, 2 and 3 Islet infusions, respectively, within a short period (1-3 months)[4]. We estimated the average cost per patient as a weighted average of the cost for patients receiving 1, 2 or 3 infusions of IT.

Since the risks of procedure-related complications for the PT procedure are much higher than those for IT, we adjusted the procedure cost to include the cost of treatment of complications. Although numerous possible adverse events (AEs) post IT and PT procedures have been reported[12;13], we included only those complications that met the following criteria. Firstly, the complications had to be related to the interventions directly, not the immunosuppression therapy which is assumed to be constant across the treatments being compared; secondly, the complication was not too rare, having a risk 1% or more; thirdly, we included severe complications only (as listed in Table 2). We included the cost of rejection management for PT therapy, but ignored it for IT, since it is difficult to verify and offer therapy for IT patients experiencing rejection. Dr. Paraskevas provided estimates of the risks of complications for both therapies, as well as the treatment and resource use following each complication (See Table 2). These estimates were comparable to those reported in the literature [3;12-16].

We also estimated the budget impact based on the expected number of IT and PT procedures that will be carried out at the MUHC annually. All costs were expressed in 2013 Canadian dollars ($CAD)[17].

Cost-effectiveness analysis

Whereas there is an advantage of lower procedure-related mortality and procedure-related complications following IT, the percentage of patients achieving insulin independence over the long term has to date been higher following PT. In order to compare the two interventions using the same metric, we carried out a cost-

effectiveness analysis. As explained below, we considered procedure costs as well as cost of diabetes related complications whose risk increases from loss of graft function. We chose to use life-years as the measure of effectiveness in order to account for both the lower procedural mortality and morbidity associated with IT in the short term and the greater percentage of insulin independence in the long-term following PT.

Model

A Markov decision-analytic model was constructed to estimate the long-term health-economic consequences of IT or PT therapy (See Figure 1). One IT treatment session is composed of 1-3 (average 1.8) IT infusions within 1 year. Our model starts after the last infusion. Immediately after treatment with either IT or PT, survivors enter the full graft function state. From here they can move to one of 4 health states that are determined by the patient's graft function - full graft, partial graft, graft loss and death. At each cycle in the Markov chain (which corresponds to a fixed time interval of one month), patients can either stay in their current state or transition to a worse state (e.g. from full graft state to partial graft or graft loss states), but cannot return to a better health state (e.g. patients in partial graft or graft loss states cannot return to full graft function)In order to obtain estimates of long term insulin independence rates and mortality following the comparator PT, we searched for the most recent publications based on the International Pancreas Transplant Registry (IPTR). Due to the absence of published data, we do not define the partial graft function state in the PT arm; i.e. we only consider the three health states full graft, graft loss and death. We also modelled the occurrence of diabetes-related complications, i.e. severe hypoglycaemia, retinopathy, nephropathy, neuropathy, cardiac events and peripheral vascular events.

We used a first-order simulation ("individual random walks") to capture the heterogeneity and track patients' disease history. Briefly, we simulate numerous "patients" with baseline demographics and disease history (See Table 3). The simulated patients were then assigned to one of the possible treatment arms, either IT or PT. The health-care resource use of each patient is associated with their baseline characteristics, as well as outcomes and complications following treatment.

Principal assumptions

The goal of this analysis is to estimate the differences in costs and effectiveness (in terms of life-years) between IT and PT and also to estimate the resulting incremental cost-effectiveness ratio (ICER). For simplicity, we ignored certain clinical events and corresponding health care resource use that are likely to be similar in both arms. The following assumptions are proposed to simplify the model, but do not alter our primary goal. We assumed that:

- Besides differences in procedure-related mortality of PT and IT (2% vs. 0%, Table 2), patients in either arm have identical risks of mortality conditional on covariates.
- The age and sex-specific relative risk of mortality of our target patients is 7 times that in the general Canadian population in 2009[18] (We made this assumption to match the 1-year and 5-year survival rates in the IPTR registry of PT cases reported by Gruessner et al 2012[19]).
- In our principal analysis we assumed that graft function loss does not result in higher risk of mortality, but we relax this assumption in a scenario analysis.
- Patients' baseline characteristics are not associated with the risk of graft loss.
- All patients who survive the procedure have full graft function at time zero post IT or PT procedure.
- Patients in either arm would receive identical maintenance of immunosuppression therapy, and would hence have identical risks of immunosuppression-related adverse events (AEs). Thus, we do not consider the AEs and costs related to the maintenance of immunosuppression therapy.
- The risks of diabetes related complications are related to graft function. Full graft function is associated with lower risk of long-term diabetes-related complications relative to graft loss. The risk ratio is allowed to vary uniformly from 0.25 to 0.75 for each such complication (Table 6). For partial graft function, the risk ratio relative to full function is uniformly distributed in the range 1 to 1.4, corresponding to the assumption that partial function confers 70% to 100% of the benefit of full graft function.
- Diabetes-related complications do not accelerate graft function loss and are not associated with increased risk of mortality.
- Patients do not receive additional IT infusions or a repeat PT during follow up.

Model inputs

A comprehensive literature search was conducted to identify the most reliable model inputs for our economic evaluation model. We also searched for reports based on CITR or IPTR data and online medical literature databases. When it was impossible to obtain the desired estimates, available data were supplemented and/or adapted following discussion with the clinical expert.

Baseline characteristics: Based on a large case series from Alberta[9] (UAITR for University of Alberta Islet Transplantation Review) and the CITR data[12], we outlined the baseline characteristics, both demographic characteristics and diabetes-related complications, of target patients (See Table 3). We assumed that different baseline characteristics are independent of each other.

Procedure related complications: See section 4.1 and 6.2. We assumed that different procedure-related complications are independent of each other.

Mortality rate: See section 4.2.3, Principal assumptions.

Transition probabilities between graft states in IT arm: Based on the CITR data[12;20], we estimated the time-dependent transition probabilities between full graft, partial graft and graft loss states following IT (See Table 4). In brief, we calculated the proportion of patients in the 3 graft states at 6 months, 1 year, 2 years, 3 years, 4 years and 5 years post the last infusion, and the changes in the proportions in the 3 states at each time interval. We assumed that all patients have full graft function at time zero, and that patients in the full graft function state are not allowed to transition to the graft loss state, but must pass through the partial graft function state to reach the graft loss state. Also, assuming that the transition rate is constant in each interval, we estimated the transition probabilities between graft states up to 5 years.

We obtained estimates of insulin independence rates from a recently published article based on the CITR data that provides up to 3-year follow-up on patients who received IT in 2007-2010[20]. However, for the positive C-peptide rate (i.e. the percentage of patients with full or partial graft function) we chose to use estimates for the 2004-2007 era from an earlier annual report published by the CITR[12] because the report appeared more complete, providing actual numbers of patients used in the estimation. The article, though more recent, was less detailed and provided different estimates from the earlier annual report. For example, the estimate of insulin independence at 3 years (37%) was identical in both documents among patients who received IT during roughly the same era 2003-2006 in the article vs. 2004-2007 in the earlier report. However, the estimates of positive c-peptide level (which is an indicator of full or partial graft function) in this same period were much higher in the article[20] compared to the earlier report[12]. The estimates of 1-, 2-, 3-, and 4- year graft survival rate were approximately 87%, 78%, 76% and 74%, based on the article compared to 78% (148/189), 66%(108/163), 58%(78/135) and 49%(49/100) based on the earlier report. No explanation was received from the authors of the article[16] when contacted.

Furthermore, we re-created individual level data on the basis of the aggregated data reported in the CITR report, and used multi-state models (“msm” package in R 2.15) to estimate transition probabilities between year 2 and year 5[21].

Transition probabilities between graft states in PT arm: We used a report based on the International Pancreas Transplant Registry (IPTR) data[15;22] of more than 42,000 patients to estimate the transition probabilities following PT[22]. We only included 2 graft states for PT, full graft and graft loss, since no data were available that allowed us to quantify the partial graft function state. This is because PT patients probably do not remain in a partial function stage for a sustained period of time (Dr. Paraskevas, personal communication). According to the recent data, the 2-month, 1-year and 3-year insulin independence rates are 90%, 82.3% and 70.5%,

respectively, for pancreas after kidney transplant[19]. Based on those data, we divided the hazard of graft loss into three phases, the first 2 months, the subsequent 10 months (the 3rd to 12th month) and 2nd-3rd year. We calculated the transition probability in each interval by assuming that the hazard of graft loss is constant in each interval (See Table 5). According to an earlier publication based on IPTR data, transition probability post the first year is relatively stable over time. We assumed that the transition probability post 3 years is the same as that in year 2 to year 3. The detailed description of estimates of transition probabilities in the PT arm can be found in Appendix 2.

Risks of diabetes related complications: We assumed that the risks of diabetes-related complications are not directly affected by the treatment strategy per se, but by graft function. Thus, any estimates of the risks of diabetes-related complications were applied to both IT and PT arms. The 7th CITR Annual Report provided the risk of severe hypoglycaemia events by C-peptide levels. We assumed that the C-peptide levels < 0.3, 0.5-0.9 and >1 ng/mL were equivalent to graft loss, partial graft function and full graft function, respectively. Then, we calculated the risk of hypoglycaemia within these three categories (Table 6)[12].

We did not find any studies using severe microvascular or macrovascular events as endpoints to assess the risks of long-term diabetes-related complications post IT or PT therapy[1;3;23;24]. But, some studies showed that IT or PT therapy was associated with reduced progression of diabetic microvascular complications[3;7;25-27], and improved cardiovascular function[3;28;29]. These benefits are very likely due to improved glycemic control, i.e. HbA1c level. Thus, we assumed that these benefits are sustained in patients with full or partial graft, but not in those with graft loss. A large case series of 138 patients in Alberta showed that the mean values of “current” HbA1c level were 6.1%, 7.0% and 8.3% for patients with full graft, partial graft and graft loss, respectively[9]. The Diabetes Control and Complications Trial (DCCT) showed that the median HbA1c levels were about 7% and 9% for intensive insulin therapy and conventional therapy, respectively[30]. Due to relatively close HbA1c levels, we used the risk in the conventional treatment arm in the group of patients with limited retinopathy (secondary intervention group) in DCCT as the reference for patients without graft function[30-32]. Due to the very low risk of stroke in DCCT, we did not include this outcome in our model. It should be noted that our target patients probably have more severe diabetes than those in the secondary intervention group in DCCT[30], leading us to underestimate the reference (baseline) risk of diabetes-related complications. We assumed that patients with full function would have 25% to 75% lower risks of diabetic complications, and that patients with partial graft function retained 70% to 100% effects of full graft function. See Table 6 for details.

Procedure cost: See sections 4.1 and 6.2. Instead of using the fixed values of procedure cost in Table 1, we used Gamma distributions for OR time and LOS, assuming that the standard deviation is 10% of the mean.

Costs of procedure-related complication: See section 4.1 and 6.2.

Costs of diabetes management and diabetes related complications: The estimates of costs of diabetes management and diabetes-related complications were mainly based on an Ontario Diabetes Economic Model (ODEM)[33]. This model adapted the United Kingdom Prospective Diabetes Study (UKPDS) model for diabetes patients in Ontario, considering variables including local incidence of diabetes, diabetes risk factors, mortality rate and complication rates. This study used a two-part model (first part: logistic regression for the probability of incurring cost within a single patient-year; second part: ordinary least square regression for the cost data, conditional on incurring any costs) to estimate the cost in the year the event occurred and the cost in each subsequent year. To adapt these data to our Markov model, we assumed that the difference in costs between the year the event occurred and the subsequent year was the "event cost", and the cost in the subsequent year was the annual "state cost" for chronic disease management, due to the existing diabetes-related complication. We considered both event cost and state cost for peripheral vascular disease and coronary artery disease, the state cost only for neuropathy, retinopathy and nephropathy diseases, and only the event cost for severe hypoglycaemia.

The ODEM focused on severe complications, but our model allowed for complications with different severity levels. Thus, we adapted the available data in consultation with Dr. Paraskevas. For instance, we used one quarter (25%) cost of amputation in ODEM for the average event cost of a peripheral vascular event. See Table 7 for details. Again, all costs were expressed in 2013 Canadian dollars[17].

An example of the calculation of costs for diabetes management and related complications is as follows: Assume a patient has peripheral vascular disease history at baseline, loses graft function at the 5th cycle (month), experiences retinopathy at the 10th cycle, and suffers a cardiac event in the present cycle (the 15th cycle). Then, the undiscounted cost at the 15th cycle = \$170.46 (diabetes management) + \$67.77 (Insulin use for graft loss) + \$226.94 (peripheral vascular event management) + \$186.99 (retinopathy disease management) +\$ 2,489.68 (cardiac event cost) = \$3,142.84. The total diabetes related discounted cost for this patient is the cost in each cycle accrued over time with a defined discounting rate.

Data Analysis and Software

Using a decision-analytic Markov model, we carried out a health economic analysis of IT versus PT. We used a first-order simulation to create 10,000 hypothetical patients, and repeated the analysis 100 times to estimate the results reported in our primary analysis. For the scenario analyses and sensitivity analyses, we reported results based on a single simulated trial with 10,000 hypothetical paired patients in the two arms. The sum of procedure cost, procedure-related complication cost and discounted diabetes-related cost is the total cost for a patient. As the evidence of quality of life (QoL) post IT or PT was poor, we used life-years as the measure of effectiveness in our analysis. Our main outcome measure was the ICER, the

incremental cost per life-year gained. Since the CITR[12] data followed patients up to 5 years, a time horizon of 5 years was chosen in the primary analysis. The annual discount rate of 3% was applied for both life-years and cost in the base case. We also conducted sensitivity analyses assuming 20 years follow up, discounting rate of 0 and 5% annually, and different risk of mortality.

We used our model to compare the average durations spent by patients in each of the graft function states following IT versus PT in 5-year. We also calculated the risk of diabetes-related complications for both strategies. In addition, we conducted analyses of 3 scenarios separately, by assuming that 1) an optimistic estimate of IT efficacy, namely 50% insulin independence at 5 years, 2) the loss of graft function increases the risk of mortality, 3) a greater risk of procedure-related mortality in PT patients, namely 10%, intended to reflect a group of patients at high surgical risk, and 4) more optimistic graft function estimates in the IT arm based on Barton et al. 2012[20]. In scenario 1 where we assumed 50% insulin independence following IT, we continued to assume that the same immunosuppression treatment was used in both arms.

We also compared the cost of IT versus intensive insulin therapy (IIT) for another subgroup of patients, assuming that both treatments have the same survival rate and the age and sex-specific relative risk of mortality of this subgroup of patients is 3 times that in the general Canadian population in 2009[18]. Thus, there are no life-years gained due to IT and we limit the comparison to cost only. It should be noted that the population eligible for either IT or IIT is different from the subgroup eligible for either IT or PT. We used the same model structure as that for IT versus PT, and assumed that patients in the IIT arm have two health states, survival without graft function (i.e. equivalent to graft loss) and death. Except for the mortality rate, the IT arm had the same model inputs as those used in the IT versus PT model. We estimated the incremental cost of IT versus IIT at 1 year, 5 years and 20 years follow up.

Analyses were conducted using Treeage pro 2013 (TreeAge Software, Williamstown, USA), Excel 2007 (Microsoft, Redmond, USA), R 2.15 (R Development Core Team, Vienna, Austria.) and SAS 9.3 (SAS, Cary, USA).

RESULTS OF LITERATURE REVIEW OF EFFECTIVENESS AND SAFETY OF IT

Results of literature search

We selected one systematic review of patient-reported outcomes following IT or PT in type 1 diabetes for detailed review[34]. The review by Speight et al. in 2010[34] identified twelve studies, 10 of IT and 2 of PT, using various outcome measures to assess the overall and diabetes-specific quality of life (QoL), and other patient-reported outcomes.

We also identified a recently updated HTA report of IT from the Institute of Health Economics (IHE), Edmonton[1]. Before the IHE published this updated HTA report in 2013[1], they had published two earlier versions in 2003[35] and 2008[36]. This recent HTA included 6 non-randomized comparative studies appearing in 8 publications and 13 case series appearing in 20 publications. We based our observations in the following sections on the evidence from this HTA[1], the systematic review mentioned above[34] and selected observational studies that summarize the effectiveness, safety and QoL associated with the IT procedure.

We also identified two economic evaluation of IT[1;37]. See section 6.1 for details.

Summary of review of effectiveness and safety of IT

There are 3 types of IT procedures, islet transplantation alone (ITA), islet after kidney transplantation (IAK) and simultaneous islet and kidney transplantation (SIK) for non-uremic or uremic adult patients with type 1 diabetes. The sample sizes in most studies of IT were relatively small, and some studies reported results for mixed types of IT procedures or patients. Although there were 6 comparative studies of IT vs PT none used a sufficiently rigorous study design to allow an unbiased comparison. For instance, the quality of donor pancreas used for IT was often worse than that for PT[1;38;39]. In Frank et al, all cadaveric donor pancreas used for IT were rejected for the use of pancreas transplantation[38]. Furthermore, the baseline characteristics were often imbalanced in the two groups. In Gerber et al, compared with the PT group, patients in the IT group were older (53 versus 40), with longer diabetes duration (42 versus 30 years) and higher body mass index (BMI) (25 versus 22)[39]. Also, it is not completely appropriate to compare patients treated by IT therapy with those on waiting lists receiving intensive insulin therapy[25]. Thus, we must interpret the reported relative effects of IT with other therapies with caution. Due to the considerable heterogeneity of types of IT and patients' characteristics, both the review by Speight et al and IHE's HTA did not pool results using meta-analysis, but described individual studies' results separately. Thus, there were no pooled estimates of effects and complication rates available. More details can be found in IHE's HTA in 2013[1] and Speight et al 2010[34].

Summary of effectiveness results from international registry data

As mentioned in 3.3.4, we identified two sources reporting recent IT registry data, the 7th CITR Annual Report of 2011[12] and Barton et al 2012[20].We summarize first the number of IT transplants, IT recipient characteristics, rates of graft function and adverse events from the 7th CITR Annual Report of 2011 [12]. Following this, we present some important updates based on the CITR data that appear in the recent article by Barton et al 2012.

During 1999-2009 a total of 656 patients (North American: 453; European and Australian: 203) received IT therapy[12]. Of these patients, 571(87%) patients (North American: 376; European and Australian: 195) from 32 IT centres (North American:

27; European and Australian: 5) registered at CITR. ITA accounted for 84 percent of all IT procedures (ITA: 897 infusions; IAK or SIK: 175 infusions). Overall, 31%, 47% and 22% patients received one, two and three or more infusions, respectively. Besides 4 cases with indications of cystic fibrosis or pancreatectomy, the indication was of severe type 1 diabetes for almost all recipients (551 out of 555). (Note: CITR does not cover the Asian countries, i.e. Japan[40].)

After the Edmonton protocol was published in 2000, the number of IT centres in North America increased quickly to reach the peak of 23 in 2005, and then dropped down to 11 in 2009. Also, the number of annual IT recipients decreased from a peak of 107 in 2002 to the 61 in 2009 worldwide. The drop in the number of centres offering IT can partially be explained by the decision of the FDA in the United States to support only selected centres.

IT recipient characteristics have changed over time. According to recent data, the mean age of IT recipients was 49 (standard deviation (SD) 9), with a mean diabetes duration of 32 (SD 13) years. About 60% of the recipients were women.

The major clinical outcomes (graft function, adverse events etc.) are summarized in the Table 8, and more details (patients' survival, neoplasms etc.) can be found in Appendix 3. Basically, graft survival declined over long-term follow up, though this tendency improved over the last decade. The registry data showed that in 215 recipients in 2004-2007 the rate of insulin independence and the rate of positive C peptide were 24% and 43%, respectively, at 5 years post the last infusion.

Additionally, the "accumulated experience" suggests that the ideal candidates for IT are those who are 35 or older, with relatively better glycemic control. Results from the multivariable regression model indicated that the induction and maintenance immunosuppression are significantly associated with graft survival. Although some subgroups (such as those who received induction immunosuppression therapy of TCDAb plus TNF-α inhibitors) of patients in the CITR registry were reported to have very high 5-year insulin independence rates (60-70%), these estimates are not very reliable being based on less than 10 patients who were followed till the 5th year in those subgroups (See the Page 78-79 in CITR Appendix: A4 Insulin independence prevalence).

Update from Barton et al 2012:

In the years 2007-2010, the 3-year insulin independence rate was 44%. Authors also reported that the graft survival rate was as high as 83% at 3 years. This study reported that those with TCDAb plus TNF-α inhibitors have higher insulin independence rates, 50%-62% in 3-5 years post last infusions. However, they did not report how many patients these estimates were based on. Interestingly, the 3-year insulin independence rate is 50% while the 5-year insulin independence rate is 62%, suggesting that these estimates are not very precise, presuming that once graft

function is lost patients cannot re-gain it without further intervention. One possible explanation for the apparent increase is that patients who lost graft function were more likely to be lost to follow up, compared with those with graft function. The safety statistics in this article were similar to those in the CITR 7th annual report.

Summary of effectiveness results from single-centre studies

Graft survival, glycemic control and hypoglycaemia: Although the insulin independence rates were relatively low in case series published prior to 2008, most recent studies have reported that 5-year insulin independence rates can be as high as 50%. Bellin et al 2012 reported that the insulin independence rates were 74% at 1 year, 50% at 3 years and 50% at 5 years in 29 patients at the IT centre at the University of Minnesota[41], but they did not report how many patients were followed at year 3 and year 5. In the same study, authors also reported that recipients in CITR given TCDAb + TNF-α inhibitors (n = 20) had the same 5-year insulin independence rate (50%) as that in the Minnesota centre. In comparison, CITR recipients given TCDAb without TNF-α inhibitors (n = 43) and recipients given IL-2RAb alone (n = 177), had insulin independence rates of 0% and 17% respectively. Based on data from the Alberta IT centre[9], using more modern immunotherapy protocols, the insulin independence rate reached 60% at 4 year follow up (more details about the protocol and number of recipients treated by the new protocol were not available).

Furthermore, the HbA1c level and insulin requirement were significantly reduced in most patients, indicating an improvement in glycemic control with IT therapy[1]. A multicentre study showed that the HbA1c levels were under 6.0% and 7.0% in patients with full graft function and partial graft function, respectively[1]. Also, case series suggested that IT patients achieving insulin independence were free from hypoglycaemia episodes, and the severity level of hypoglycaemia episodes was reduced for the insulin dependent patients[1].

Recent data from the largest international registry, the International Pancreas Transplant Registry (IPTR), showed that the 1-year and 5-year insulin independence rates following various types of PT were 82-89% and 58-71%, respectively[22]. Though patients with IT therapy experienced a lower insulin independence rate, it should be noted that there were considerable differences between the IT and PT treatment cohorts in terms of the indications, patients' baseline co-morbidity and donors' characteristics[1]. However, compared with results observed in patients receiving intensive insulin therapy, IT therapy increased C-peptide secretion and reduced HbA1c level and insulin use[1].

Long term diabetic complications: No studies used severe microvascular or macrovascular events as endpoints to assess the risk reduction of IT therapy for long term diabetes-related complications. But some studies showed that IT was

associated with reduced progression of diabetic microvascular complications[7;25-27], and improved cardiovascular function[28;29].

Patient's survival: Patient's survival was not the primary focus of IT cohort studies. Most studies did not report long-term survival after IT therapy. A large case series of 138 patients at the University Alberta reported patient survival was 96% at 12 years using Kaplan Meier analysis[9]. Six patients died during follow up, but no deaths were related to the transplantation or immunosuppression.

Summary of safety results

The risks of adverse events (AEs) and severe AEs in recent IT patients were significantly lower than those in earlier years (e.g. severe adverse event: 26% in 2007-2009 versus 47% in 2004-2006 and 69% in 1999-2003). Besides the improvement in IT techniques and in immunosuppression therapy, another possible explanation for apparently lower risk of AEs in the recent series (2007-2009) is the shorter follow up duration.

The common AEs following IT procedures included portal vein thrombosis, haemorrhage, infection, liver function test abnormal, emergency exploratory laparotomy, chronic liver steatosis, hypoglycaemia, anaemia, and diarrhoea. Usually, AEs are categorized as IT procedure-related AEs and immunosuppression-related AEs. The risks of immunosuppression-related AEs were higher than that of IT procedure-related AEs, 50% versus 37%. It should be noted that some AEs were possibly not related to either the IT procedure or immunosuppression, but to one of the patient's own co-morbidities. According to the CITR data, in 2007-2009 islet transplant recipients had a high prevalence of comorbidities, with an average diabetes duration of 32 years: unaware hypoglycaemia (68%); peripheral neuropathy (29%); autonomic neuropathy (20%); coronary artery disease history (21%); peripheral vascular disease history (9%); retinopathy (59%).

Besides an accidental death reported in one study, other studies did not report any procedure-related mortality[1]. The most common procedure-related complications included intra-peritoneal bleeding, partial branch-vein occlusion and liver abnormality[1]. Most procedure-related adverse events were manageable. Also, there were quite a few immunosuppression-related adverse events following IT therapy, such as decline of renal function, leucopenia, diarrhea, neutropenia, presence of ovarian cysts, cytomegalovirus (CMV) infection. According to the limited available evidence, compared with PT, IT is associated with lower risks of severe procedure-related complications, but higher risks of immunosuppression-related complications[1].

Summary of results on quality of life following IT

The articles we identified reported that IT improved the diabetes-specific QoL, and that the benefits were maintained over 3 years[1;34]. For studies using generic QoL instruments, the evidence was inconsistent. Some reported that IT therapy improved

QoL significantly whereas others did not find important changes[34]. Also, some studies found that IT therapy improved psychological well-being, i.e. reduction in fear of hypoglycaemia[34]. But, not surprisingly, IT was associated with short-term pain due to the procedure and adverse events, and the potential of being in a depressed mood due to graft loss[34].

RESULTS OF ECONOMIC EVALUATION

Review of published economic studies

We identified 2 economic evaluations of IT published in 2008 or later[1;37]. Both studies used a Markov model to assess the cost-effectiveness of IT versus intensive insulin therapy, not IT versus PT. In Beckwith et al 2012 in the United States[37], the one-time cost of an IT procedure was about US$ 93,500 (organ retrieval: $25,000; islet isolation: $40,000; and screening and medical procedure: $28,500), and the follow up cost was US$ 19,000 annually (immunosuppression and follow-up consultations). The cumulative cost and quality-adjusted life years (QALY) of IT versus intensive insulin therapy over 20 years were US$519,000 and 10.9 QALYs, and US$663,000 and 9.3 QALYs, respectively. The IT strategy was more effective and less costly. However, these results are questionable for a couple of reasons. First, the authors overestimated the effectiveness of IT, in terms of maintaining full or partial graft function. Based on the authors' assumptions, the proportion of patients with full and partial function at 1-year, 5-years and 10-years were 93% and 7%, 47% and 37%, and 27% and 49%, respectively. These estimates suggest a much higher success rate of IT than has been reported so far based on the CITR registry. Second, the above cost estimate was based on the assumption that IT treatment consists of only one IT infusion, while the evidence accrued so far suggests that most patients need 2 or 3 infusions to reach insulin independence. Thus, these assumptions resulted in underestimating the costs and overestimating effectiveness of IT. Furthermore, the authors assumed that patients with full or partial graft function did not have any risk of diabetes-related complications, such as amputation or end-stage renal disease. Yet they assumed high risks and costs for diabetes-related complications at baseline (for the entire intensive insulin therapy group and for patients in the graft loss state in the IT group), such as end-stage renal disease (5% annually and $106,000 per year). Clearly, this approach favoured the IT arm significantly.

A Health Technology Assessment (HTA) by the Institute of Health Economics (IHE) estimated the cost of IT was about CAD$131,000 per infusion (including costs of organ retrieval $22,409, isolation laboratory $56,394, clinical program $24,692 and post-transplantation assessment $17,743)[1]. The authors assumed that one patient can receive up to 4 infusions. The cumulative costs in 20 years were $410,373 and $35,769 in the IT arm and the intensive insulin therapy arm, respectively. The IT arm

was also superior in terms of effectiveness with 2.06 QALYs gained and the incremental cost per QALY gained was $181,847. The authors concluded that IT was not cost-effective compared to intensive insulin treatment due to the very high incremental cost-effectiveness ratio.

Procedure cost and budget impact to MUHC

Procedure costs: Including the costs for induction of immunosuppression therapy, we calculated a cost of $16,744 for the first IT infusion and $16,040 for subsequent IT infusions (See Table 1), and the weighted average cost was about $29,575 per patient for IT therapy of 1-3 infusions. The procedure cost for PT was about $18,293, after including the cost of induction of immunosuppression (See Table 1). Thus, the incremental cost of IT versus PT was $11,282 per patient on average. The islet laboratory cost ($10,536 per infusion) accounts for more than 60% of the procedure cost of IT, while the OR time, ICU stay and the hospital stay were the main components of PT cost. Although the costs are ignored in this estimate, it should be noted that use of IT instead of PT will reduce demand on the OR and recovery room, a valuable asset when these facilities are rate limiting for patient flow.

The costs for procedure-related complications of both therapies are summarized in Table 2. Briefly, PT therapy was associated with significantly higher risk and costs than IT for procedure-related complications ($6,832 versus $57.6 per patient). With inclusion of costs for treatment of procedure-related complications, the incremental cost of IT versus PT was reduced to $4,508 per patient.

Budget impact: Dr. Paraskevas proposes to start the IT program with 6-7 IAK (islet after kidney) transplantations per year, and expanding to 10 to 20 patients with other indications in the coming years. Including the costs of the procedure related complications, and excluding immunotherapy related costs, the net annual budget increase due to use of IT rather than PT would be $4,508 per patient or $27,048, $45,079 and $90,159 for 6, 10 and 20 recipients per year, respectively. IT could also be considered for a group of patients considered inoperable, and hence not candidates for PT. If 20% of IT procedures were performed in such patients, then the annual budget impact of 6, 10 or 20 IT procedures would increase to $57,129, $95,214 and $190,428.

Results of cost-effectiveness analysis

Validation of economic model: The plots of the health state probabilities (i.e. the probabilities of full and partial graft function, graft loss and mortality over time) following IT and PT based on our Markov model are shown in Figures 2A and 2B. These plots reflect our model inputs and assumptions, and assume that the model captures the different health state probabilities appropriately.

- **Duration of graft survival:** The average duration of time (in months) spent by the average patient in different graft function states following the two treatments is summarized in Table 10. The total graft survival time (either full graft or partial graft) for IT is shorter than that for PT (5 years: average of 42.5 versus 44.3 months). Thus, under the assumptions of our model, PT offers a small benefit of graft survival.
- **Diabetes-related complications:** Since the risk of diabetes-related complications is associated with patients' graft function, PT results in better outcomes than IT. For example, on average, the number of severe hypoglycaemia episodes per patient during 5-year follow up are 0.358 following PT and 0.433 following IT. See Table 11 for more details of the other diabetes-related complications.

Figure 2A: Health state probabilities following Islet transplantation

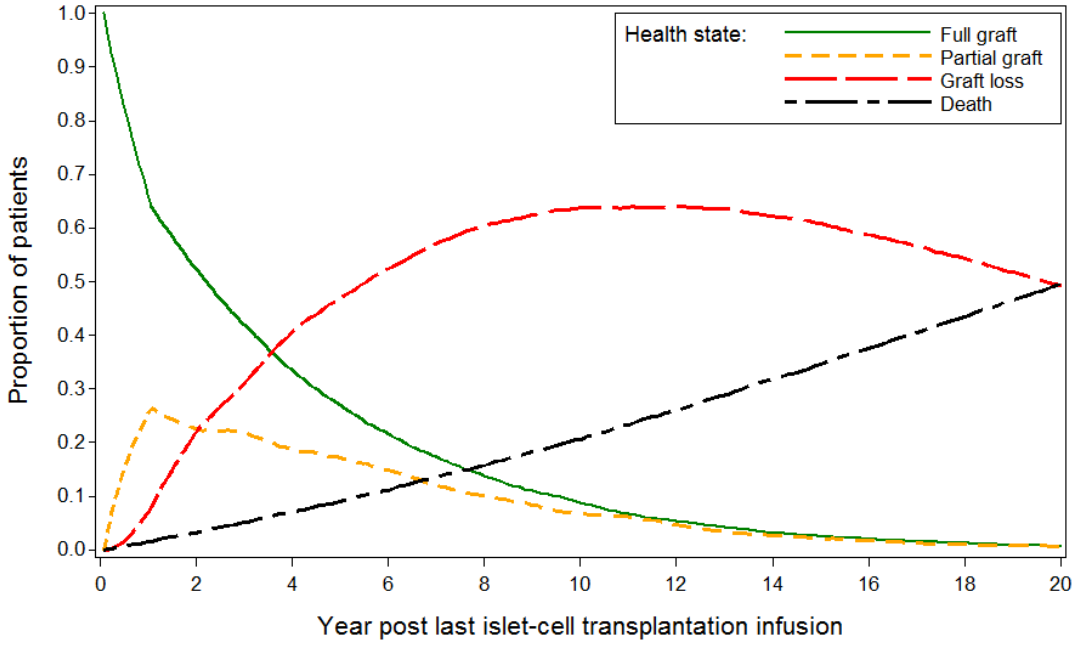
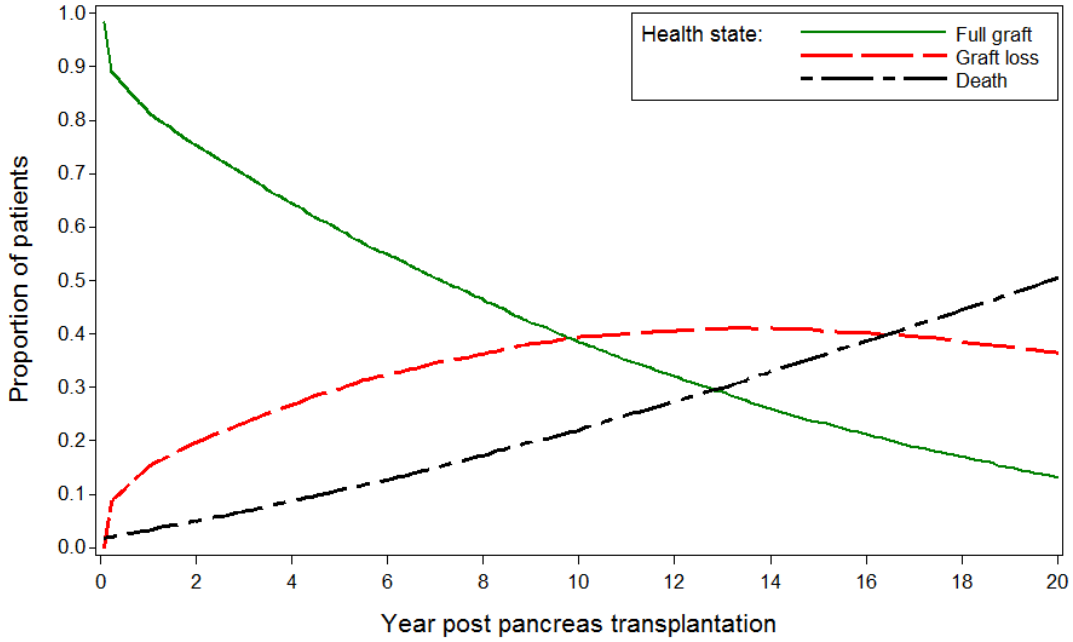


Figure 2B: Health state probabilities following whole organ pancreas transplantation



Incremental cost per life-year gained (Primary analysis or base case): The accrued costs and life-years at 5 years of follow up for both treatment strategies are summarized in Table 9. The IT strategy results in a marginal number of life-years gained (0.092) with substantial incremental costs ($6,120), and the corresponding incremental costs per life-year gained are $66,552. It should be noted that the incremental cost arises primarily from the greater procedure cost of IT together with a smaller proportion attributable to increased cost of treatment of diabetes-related complications resulting from the shorter duration of graft survival following IT. The incremental increase in life-years is due to the reduction in procedure-related mortality associated with IT.

Sensitivity analysis: When the discounting rate is 0 or 0.05 annually, the incremental cost per life-year gained (ICER) are $65,367 and $69,419, respectively. If the age and sex-specific relative risk of mortality of our target patients is 3 and 10 times that in the general Canadian population, the ICERs are $76,024 and $74,146, respectively. Considering a longer follow up time, ICER is $66,264 for 10 years follow up and $73,216 for 20 years.

Scenario analyses: We conducted a scenario analysis to study the impact of an optimistic estimate of graft function following IT similar to that reported in some recent studies of small case series[41]. We assumed that 50% of patients have full graft function at 5 years, but other parameters do not change. This assumption results in a marginal reduction of cost of the IT strategy at 5 years (Table 12). Since graft function is not associated with mortality, the mean number of life-years does not change. Thus, the ICER at 5 year decreases moderately to $55,834 per life-year gained. We considered a second scenario where we allowed graft function to be related to mortality. We assumed that the risk ratio of mortality in those with graft loss versus full graft function is 4.16 as in Gruessner 2011[19], and that the risk of

mortality for those with full graft function is 4 times that in the corresponding age and sex group in the general population. The main results are summarized in Table 12. The ICER of IT increases to $68,003 per life year gained at 5 years follow up. This ICER value is also quite similar to the base case analysis, as the duration of graft survival in this scenario in 5 years is similar to that in the base case. IT is dominated by PT in longer follow up (≥ 10 years) in this scenario, since PT has the better long term graft function. We conducted a third scenario analysis by assuming a very high procedure-related mortality of 10% in the PT arm, with other parameters remaining the same as those in the preceding scenario 2. It results in an ICER of $19,964 per life year gained at 5 years follow-up. Finally, we used the transition probabilities between graft functions based on Barton et al[20] for IT arm, while other parameters are same as those in base case model. These figures were more optimistic than those in the CITR annual report in terms of the percentage of patients with a positive C-peptide level (i.e. patients with either partial or full graft function). This assumption results in significant increase of the average duration of partial graft in the IT arm (16.7 months versus 11.7 month in base case). But the ICER changes only marginally to $64,423 per life-year gained. See Table 12.

Comparison of IT with IIT: Compared with IIT, IT is associated with a significantly higher cost. We estimated the incremental cost to be $23,023 (IT: $59,917 vs IIT: $36,894) at 5 years follow up. But, the IT arm has a significantly reduced risk of diabetes-related complications, such as severe hypoglycaemia (mean episodes per patient: 0.45 in IT and 1.15 in IIT in 5 years follow up). When adjusting for the increased cost of diabetes-related complications, the incremental cost of IT over IIT reduces over time. It decreases from $28,383 (IT: $34,860; IIT: $6,476) at one year follow-up to $13,881 (IT: $157,172; IIT: $143,191) at 20 years follow-up. It should be noted that we did not consider costs of maintenance of immunosuppression therapy and the related complications of immunosuppression therapy in these analyses, assuming all patients receiving IIT were also receiving immunosuppression as they also underwent a previous kidney transplant.

We also estimated the cost-effectiveness (in terms of difference in cost per life-year gained) of IT vs IIT. As mentioned above we assumed the risk ratio of mortality in those with graft loss versus full graft is 4.16[19], and risk of mortality for those with full function is 3 times that in the age and sex specified general population. In this scenario, IT treatment results in an incremental gain of 0.19 life-year, and the incremental cost is $24,779 compared to IIT at 5 years follow up. The associated ICER is thus $128,179 per life-year gained. At 10 and 20 years, the ICERs reduce to $42,442 (incremental cost: $23,610; incremental life-year: 0.56) and $24,865 (incremental cost: $26,183; incremental life-year: 1.05), respectively.

DISCUSSION

Although IT has been used for treatment of severe hypoglycaemia in type 1 diabetes patients for more than 3 decades[5], it is only for slightly over a decade that it has been considered as a possible alternative for PT at a few centres worldwide. The body of evidence on IT therapy is thus relatively small, with roughly 700 patients having received the procedure since 1999 in North America, Europe and Australia. The evidence suggests that IT will improve glycemic control and reduce the risk of hypoglycaemia among those maintaining full or partial graft function, thus slowing the progression of long-term diabetes related complications. Based on data from the CITR registry, it appears that full and partial graft function are maintained in 44% and 20% of patients, respectively, at 3 years. In comparison, the most recent results from a registry of PT procedures, estimate that full graft function is maintained in 65% of patients at 5 years. Recent series from IT centres using an immunosuppression protocol involving TCDAb plus TNF-α inhibitors have reported more promising results suggesting that full graft function is maintained in up to 50% of patients at 5 years. Though the procedure-related mortality has been reported to be almost zero and most complications are "manageable", the overall (IT infusion related and/or immunosuppression related) severe AE rate was still high at about 26% based on the CITR data for patients who received IT in 2007-2009 [12].

We estimated that the procedure cost of IT therapy (1-3 infusions, average 1.8) to be about $29,575 per patient, or $4,508 higher than that for PT therapy, even when taking into account the potential additional costs for surgical complications. The islet laboratory cost accounts for the majority of the IT procedure cost. In a recent abstract, Moassesfar et al. reported on a review of hospital costs for 10 IT and 11 PT cases[42]. They concluded that IT can result in cost savings in those patients who achieve insulin independence following a single infusion, while IT is much more expensive than PT if requiring 2+ infusions.

We found the estimated IT procedure costs at the MUHC to be substantially lower compared to other centres[1;37]. For example, it has been reported that the cost of IT in Alberta is about $131,000 per infusion[1]. implying that the IT procedure cost per patient (not including costs for the follow up) would be more than one quarter of a million dollars for most patients (≥2 infusions). The difference in the two cost estimates may be explained in large part by the fact that there is no additional cost to the MUHC for organ retrieval and the estimated islet laboratory costs are substantially lower at the MUHC compared to those in Alberta.

A challenge in comparing IT to PT is that there have been no controlled trials comparing these two treatments. We compared the data obtained from two separate registries of IT and PT patients and concluded that PT therapy appears to be associated with a higher probability of maintaining insulin independence in the long term. A limitation of this comparison is that it ignores possible differences between patients in the two registries in terms of patients' baseline characteristics and donors'

characteristics. Similar concerns, related to selection bias and uncontrolled confounding, would hold for other studies comparing IT with other therapies.

Another challenge in comparing IT to PT is the difference in the definition of a 'successful outcome' for the two procedures. Partial function has typically not been measured for PT patients. A recent article by Dong et al 2013 provided clear definitions of full graft function, partial graft loss (i.e. partial function) and complete graft loss following PT. According to this study, a non-negligible proportion of PT patients had partial graft function in their cohort, 8% at 1 year, 15.5% at 5 years and 24.5% at 10 years (we estimated these figures as the difference in % between patients with at least partial graft loss and patients with complete loss). However, very few such patients have been encountered in the transplant program at the MUHC (Dr. Paraskevas, personal communication). According to the current protocol at the MUHC, if PT patients are no longer insulin independent, they will be weaned off immunosuppression therapy. In such a situation it is unlikely that, partial graft function will be sustained for long. Therefore, we felt it was reasonable to ignore the partial function state among patients who underwent PT therapy in our economic model.

Another difference between reporting in IT and PT studies is that the first point of observation of graft function was 1 year in the IT registry. This does not allow us to model the impact of loss of graft function during the first year post-transplant. As a result, under our assumption of a constant transition rate during the 1st year, the duration of graft survival of the IT arm is probably slightly overestimated.

Our cost-effectiveness analysis suggests that the incremental cost-effectiveness ratio (ICER) is $66,552 per life-year gained. The ICERs ranged between $50,000 and $80,000 in the scenarios we considered. When interpreting these figures it should be emphasized that the gain in life-years due to IT is very small (in the order of two months over a 5 year period), resulting in the ICERs being very high. As such, the goal of the IT or PT procedures is to achieve insulin independence and decrease risk of hypoglycaemia rather and not to prolong life. However, we chose life-years as our measure of effectiveness because it allowed us to combine the procedural mortality as well as the impact of graft function on survival into a single metric. Another limitation of our analysis is that we did not use quality-adjusted life-years, which may have been more appropriate as a measure effectiveness that also captured the improvement in quality of life due to better graft function. But, the duration of graft survival following both procedures reported in present study can be regarded as a measurement of quality of life.

Our economic evaluation in this report focused on the patients who receive either IT or PT post-kidney transplantation. Such transplants account for a small percentage of the total IT or PT transplants. Simultaneous (i.e. islet with kidney or pancreas with kidney) transplants are far more common, and there are also patients who receive pancreas (or islets) alone without the kidney transplant. Since the insulin independence rate for simultaneous whole organ pancreas and kidney transplants is

very good (1 year: 89%; 5 years: 71%)[22], IT is unlikely to be cost-effective in patients who are candidates for this procedure. But, the insulin independence rate is lower for pancreas transplant alone (1 year: 82%; 5 years: 58%)[22]. Thus, we would expect the ICER to be more favourable for IT alone versus PT alone, as IT alone would be associated with a longer graft survival than PT alone at 5 years.

Compared with IIT, clearly IT is more costly. The incremental cost is about $23,000 at 5 years follow up. If considering the cost of maintenance of immunosuppression therapy (about $10,000 per year[1]) for IT therapy but not for IIT assuming patients being considered are those with good kidney function, the incremental cost would be even higher. Although the benefit of IT vs IIT in terms of life-years is not clear, some studies have shown that IT substantially improves patient's diabetes-specific QoL[34]. A majority of patients achieve full graft function for at least some period of time during the first 5 years post IT therapy, and this reduces the risk of diabetes related complications, particularly episodes of severe hypoglycaemia.

While we have attempted to compare PT and IT procedures in this report, it should be pointed out that the indications for the two therapies are not identical. Pre-existing co-morbidities are an important consideration for selecting the treatment strategy[43]. For instance, if a patient has cardiac disease and/or high risk of peri-operative mortality, then this patient may be a better candidate for IT therapy.

Also, the requirements for donor characteristics are not the same for IT or PT. For instance, obese donors are not good candidates for PT, but are excellent donors for IT in terms of islet yield[5]. A study of the Swiss donor population showed that about 45% of donors were suitable for IT and 28% were suitable for PT with 14% overlapping[44]. The United Kingdom (UK) has adopted the 2010 National Pancreas Allocation Scheme for all deceased donor pancreases[10]. In the past 2 years, under this new scheme, the number of IT transplants has increased significantly, while the number of PT transplants has remained stable at about 200 cases per year[45]. Importantly, the waiting time for PT has also decreased. Thus, without consideration for the scarcity of health care resources, the availability of both treatments allows doctors to choose the most appropriate treatment strategy for individual patients and optimally utilize the donated pancreases. However, the availability of IT as an alternative to PT is likely to increase the budget impact due to the increase in the number of patients who will undergo a transplantation procedure.

It should be noted that the effectiveness of IT has consistently improved over the last decade. Recent studies, suggest that the insulin independence rate following IT is approaching parity with PT in some centres owing to the use of TNF-α inhibitors in the immunosuppression protocol. However, these optimistic results are based on small case series with a short follow-up of typically 3-5 years.

It has been suggested that PT therapy and IT therapy could be considered complementary rather than competitive to maximally utilize donated organs for

patients with different risk profiles. This will likely lead to an increase in the total number of transplants carried out, and therefore result in a net budget increase.

CONCLUSIONS

Effectiveness For type 1 diabetes patients with unstable metabolic control who have previously undergone a kidney transplant, islet transplantation (IT) therapy can improve glycemic control and reduce the risk of hypoglycaemia. The rate of insulin independence following IT appears to be lower than that achievable with the standard procedure of whole pancreas transplant (PT). However, the rate of graft survival (i.e. when the patient has either full or partial graft function) following the two procedures is similar.

Safety PT is associated with a risk of procedural mortality and of serious post procedural complications. By contrast IT is associated with a negligible risk of procedural mortality or complications. Both procedures carry a high risk of severe adverse events that are associated primarily with the immunosuppression therapy.

Cost Compared to PT, IT is a more expensive procedure. It costs an estimated $29,575 per procedure. Using a six-month time horizon, our cost analysis shows that after adjusting for the cost of treating procedure-related adverse events, the IT procedure has a higher net cost of $4,508 per patient compared to PT.

Budget impact The budget impact of a single IT procedure will depend on whether it replaces PT or is offered to a patient who is not a candidate for PT. For example, the budget impact of using IT *instead of* PT for 10 patients per year, would be approximately $45,079. If IT were to be used instead of PT for 8 patients, and for 2 patients who were *not candidates* for PT, the budget impact would be approximately $95,212.

Cost-effectiveness Compared with PT, IT leads 0.092 life-years or approximately one month gained in 5 years follow up. This translates into a relatively high incremental cost-effectiveness ratio of IT vs PT of $66,552 per life-year gained at 5-years post-transplant. Compared with IIT, IT is associated with a significantly higher cost, but, also with a significantly reduced risk of diabetes-related complications. After adjusting for the cost of diabetes-related complications but not considering costs of maintenance of immunosuppression therapy, we estimated the incremental cost to be $23,023 at 5 years follow up.

RECOMMENDATIONS

- **There is as yet insufficient evidence that IT is equal or superior to PT to justify its *routine use* when PT is the contemplated procedure. This decision should be reviewed in approximately 2 years.**
- **The evidence of effectiveness and safety is adequate to justify IT being offered as an alternative to carefully selected patients. The interdisciplinary pancreas and kidney transplant groups (within the MUHC multi-organ transplant program and Transplant Quebec) should**

develop a list of inclusion and exclusion criteria for IT and define a protocol for its appropriate use.

- **Because confident evidence of effectiveness is lacking, and the somewhat higher costs, the use of IT should be limited to not more than seven patients per year.**
- **As an innovative and not yet routine procedure, detailed, regularly updated patient records, including details of patient selection, should be kept available for review by the Director of Professional Services or her nominee at any time.**
- **A proposal for provincial funding of this technology should be submitted to the Ministry.**

TABLES

Table 1 MUHC Resource use and procedure costs ($CAD 2013) for PT and IT treatment

	Unit cost	PT	First IT	Subsequent IT
LOS (days)		21	5	3
Operating room (OR)				
OR hourly cost	$884	--	--	--
OR hours	--	3.80	--	--
OR – Total cost	--	$3,359	--	--
Radiology	$255	--	$255	$255
Laboratory				
Labs – daily cost	$75	--	--	--
Labs – Total cost	--	$1,575	$375	$225
Pharmacy- Cost of induction of immunosuppression *	--	$2,849	$3,578	$3,824
Inpatient/Nursing				
Cost per day – SICU	$1,455	--	--	--
Inpatient SICU – days	--	2	--	--
SICU costs – Total	--	$2,910	--	--
Inpatient –days	--	19	5	3
Cost per day – inpatient (ward)	$400	--	--	--
Inpatient nursing – Total cost	--	$7,600	$2,000	$1,200
Summary				
Total hospital costs	--	$18,293	$6,208	$5,504
Total Islet Lab costs	--	--	$10,536	$10,536
TOTAL	--	**$18,293**	**$16,744**	**$16,040**

PT: whole organ pancreas transplantation; IT: Islet transplantation; LOS: length of stay; OR: operating room; SICU: surgical intensive care unit.

*: Cost of Induction of immunosuppression: PT (ATG: $2,849); first IT (ATG: $2,849 plus Etanercept: 364.28 per day for 5 days and 2 days' cost paid by MUHC); and subsequent IT (Simulect: $3,095 plus Etanercept: 364.28 per day for 5 days and 2 days' cost paid by MUHC).

Table 2 Complication rates and corresponding costs for PT and IT therapies at MUHC

Complication	Estimated rate at MUHC*	Rate in literature	Treatment and resource use*	Cost ($CAD 2013)
Islet transplant				
Haemorrhage	4%	4%[12]	Transfusion of 2 units of PRBC	$800 ($400 *2)
Portal vein thrombosis	0%**	1%[12]	--	--
Procedure-related mortality	0%	< 1% [12]	--	--
Expected cost per patient (for 1.8 infusions on average)			--	**$57.6** ($800* 0.04*(0.34+0.52*2+0.14*3)
Pancreas transplant				
Pancreas graft thrombosis	10%	3-10%[13]	2 hours of OR plus LOS of 7 days	$4,568 ($884*2 + $400*7)
Deep wound infections	15-20%	Up to 50%[14]#	LOS for 4-6 weeks	$14,000 ($400*35)
Duodenal leaks	5%	2-10%[14]	LOS for 3months	$36,400 ($400*91)
Major bleeding	5%	Overall impact is marginal[13]	4/5: Transfusion of 2 units of PRBC; 1/5: Re-operation: 2 hours of OR	$800 ($400 *2); $1,768 ($884*2)
Procedure related mortality	2%	< 5% [15]	--	--
Rejection	50%	15%[3], and about 65%[16]	LOS for 3 days, ATG, and Biopsy and pathology test	$4,110.4 ($400*3 + $2,849 + $61.4)
Expected cost per patient (for a single procedure)			--	**$6,832** ($4,568*0.1 + $14,000*0.175 + $36,400 * 0.05 + $800*0.04 + $1,768 *0.01 + $4,110.4*0.5)

PT: whole organ pancreas transplantation; IT: Islet transplantation; LOS: length of stay; OR: operating room; PRBC: packed red blood cells.

Unit cost: PRBC: (minimal) $400 per unit; LOS (inpatient): $400 per day; OR: 884 per hour; ATG: $2,849; Biopsy and pathology test: $61.4.

*: Dr. Paraskevas provided estimates for the risks of complications for both therapies, as well as the treatment and resource use following each complication

**: It was a concern previously, the use of a coagulant has removed this risk.#: Both superficial and deep infection.

Table 3 Model inputs: Baseline characteristics of simulated patients

	Value	Distribution	Reference
Baseline characteristics			
Age (years)	30 - 60	Uniform	UAITR [9]
Male	45%	Bernoulli	UAITR [9]
Number of infusions per patient*	(1: 34%; 2: 52%; 3: 14%)	Categorical	HTA Request Form[4]
Diabetes related complications*			
Unaware hypoglycaemia#	68%	Bernoulli	CITR [12]
Peripheral neuropathy	29%	Bernoulli	CITR [12]
Autonomic neuropathy	20%	Bernoulli	CITR [12]
Coronary artery disease	21%	Bernoulli	CITR [12]
Peripheral vascular disease	9%	Bernoulli	CITR [12]
Retinopathy	59%	Bernoulli	CITR [12]

UAITR: University of Alberta Islet Transplantation Review; CITR: collaborative islet transplant registry.
*: The number of infusions and the diabetes related complications at baseline are not related with risks of further events, but they are linked with health care cost.
#: Patient has a lack of autonomic warning symptoms at a glucose level of < 54 mg/dL(page 28, CITR[12]).

Table 4 Model inputs: Transition probabilities between graft function states in the Islet transplantation arm

Time since last islet infusion (months)	Probability per cycle/month	Reference
Full graft TO partial graft		
1-12	0.0340	CITR[20]
13-36	0.0168	CITR[20]
≥36	0.0168	Estimated
Partial functioning graft TO Graft loss		
1-6	0.0483	Assumption
7-12	0.0483	CITR [12]
13-24	0.0517	CITR [12]
25-36	0.0360	CITR [12]
37-48	0.0440	CITR [12]
49-60	0.0333	CITR [12]
≥61	0.0347	Estimated [12;21]

CITR: collaborative islet transplant registry.

Note: See Appendix 1 for details of estimating transition probabilities in Islet transplantation (IT) arm, and the transition probabilities of full graft to partial graft was updated using the data in 2007-2010.

Table 5 Model inputs: Transition probabilities to graft loss in whole organ pancreas transplantation arm

Time (months)	probability per cycle/month	Reference
1-2	0.0437	IPTR[19]
3-12	0.0076	IPTR[19]
13-36	0.0050	IPTR
≥37	0.0050	Estimated

IPTR: international pancreas transplant registry.

Note: See Appendix 2 for details of estimating transition probabilities in whole organ pancreas transplantation (PT) arm.

Table 6 Model inputs: Risk of diabetes-related complications during follow up

	Risk per cycle/month *	Reference
Risk of severe hypoglycaemia		
Full graft	0.0028	CITR [12]
Partial graft	0.0042	CITR [12]
Graft loss	0.0195	CITR [12]
Risk of long term complications for patients without graft function (the reference)		
Retinopathy	0.0020	DCCT[30]
Nephropathy	0.0059	DCCT[30]
Neuropathy	0.0133	DCCT[30]
Cardiac events	0.0004	DCCT[31;32]
Peripheral vascular events	0.0012	DCCT[31;32]
Risk reduction among patients with full graft function versus those with graft loss	Uniform distribution (0.25, 0.75)	Assumption
Effect maintained in patients with partial graft function, relative to patients with full graft	Uniform distribution (0.70, 1)	Assumption

CITR: collaborative islet transplant registry.

*We converted the event rates reported in literature into transition probabilities using the formula[46].

Transition probability = 1- exp(- rate * t) [46]

Table 7 Model inputs: The estimated costs for diabetes management and diabetes related complications

	Cost ($CAD 2013)	Explanation	Reference
Diabetes management without complications (per month)	170.46	Cost for diabetes without complications	ODEM[33]
Insulin use for graft loss (per month)	67.77	--	Alberta HTA [9]
Insulin use for partial graft (% of graft loss)	22.4 (11.5, 33.9)	--	CITR[12] and Alberta HTA [9]
Diabetes related complications			
Severe hypoglycaemia (per episode)	2,039.94	--	CADTH [47]
Retinopathy Management (per month)	186.99	ODEM: Blindness	ODEM[33]
Nephropathy Management (per month)	482.53	ODEM: Renal Failure * 50%	ODEM[33]
Neuropathy Management (per month)	179.10	--	Alberta HTA [9]
Cardiac diseases			
Event cost	2,489.68	ODEM: Ischaemic Heart Disease	ODEM[33]
State cost (per month)	283.42	ODEM: Ischaemic Heart Disease	ODEM[33]
Peripheral vascular diseases			
Event cost	8,580.33	ODEM: Amputation * 25%	ODEM[33]
State cost (per month)	226.94	ODEM: Amputation * 50%	ODEM[33]

Note: For the Ontario Diabetes Economic Model (ODEM)[33], authors cannot separate patients with type 1 and type 2 diabetes, so the costs would reflect type 2 diabetes. But, since the data for type 1 diabetes are relatively rare, researchers often use the estimated diabetes-related complication costs from type 2 diabetes in the economic modelling of type 1 diabetes, by assuming that types of diabetes do not impact the complication costs significantly. Also, the cost estimates in ODEM were based on 63 years old male, the typical diabetes in Ontario. Also, we used Gamma distribution for the diabetes related cost, assuming that the standard deviation of cost is 10% of the mean (Gamma distribution: alpha=100; beta=mean/100)[46].

Table 8 Main clinical outcomes following IT reported in the 7th CITR Annual Report

Full graft function: insulin independence rate post last IT infusion	
2004-2007	1-year: 53%; 5-year: 24%
1999-2003	1-year: 52%; 5-year: 20%
ITA	1-year: 54%; 5-year: 24%
IAK or SIK	1-year: 46%; 5-year: 9%
Full or partial graft function: positive C peptide (fasting C peptide ≥ 0.3 ng/mL) rate post last IT infusion	
2004-2007	1-year: 78%; 5-year: 43%
1999-2003	1-year: 74%; 5-year: 35%
ITA	1-year: 76%; 5-year: 36%
IAK or SIK	1-year: 76%; 5-year: 44%
Severe hypoglycaemia episode post last IT infusion	
2004-2007	1-year: 13%; 5-year: 61%
1999-2003	1-year: 12%; 5-year: 57%
ITA	1-year: 13%; 5-year: 61%
IAK or SIK	1-year: 9%; 5-year: 47%
Adverse Event (AE): recipients with AE and severe AE (SAE) at any time post IT infusion	
Any AE and SAE	AE: 67% (383/571); SAE: 51% (294/571)
2007-2009	AE: 38% (51/135); SAE: 26% (35/135)
2004-2006	AE: 61% (115/190); SAE: 47% (90/190)
1999-2003	AE: 88% (217/246); SAE: 69% (169/246)

ITA	AE: 67% (324/481); SAE: 51% (244/481)
IAK or SIK	AE: 66% (59/90); SAE: 56% (50/90)
Any AE and SAE ever related to IT infusion	AE: 37% (212/571); SAE: 24% (139/571)
Any AE and SAE ever related to immunosuppression	AE: 50% (287/571); SAE: 35% (198/571)

CITR: collaborative islet transplant registry; IT: Islet transplantation; ITA: islet transplantation alone; IAK: islet after kidney transplantation; SIK: simultaneous islet and kidney transplantation.

Note: See Appendix 3 for more details.

Table 9 Main results of cost-effectiveness analysis of IT versus PT

	Costs ($CAD)	Incremental cost ($CAD)	Life-years	Incremental Life-years	Incremental cost ($CAD) per life-year gained
Follow up of 5 years					
PT	53,215(164)	--	4.431 (0.009)	--	--
IT	59,335(157)	6,120 (166)	4.523 (0.008)	0.092 (0.007)	66,552 (4,361)

PT: whole organ pancreas transplantation; IT: Islet transplantation.

Results are expressed as mean (standard deviation) of 100 simulated trials. Each trial has 10,000 hypothetical paired identical patients for two arms.. Annual discount rate of 3% was applied for both cost and life-year.

Table 10 Results: Duration (in months) spent by the average patient in different graft function states following PT or IT treatment

	Full graft	Partial graft	Graft loss	Incremental duration of graft survival*
Follow up of 5 years				
PT	44.3 (0.21)	--	12.0 (0.19)	--
IT	30.8 (0.22)	11.7(0.16)	15.0 (0.19)	-1.8 (0.18)

PT: whole organ pancreas transplantation; IT: Islet transplantation.

Results are expressed in mean (standard deviation) in month, without discounting.

*: Graft survival: patients with full or partial graft function.

Table 11 Results: Diabetes-related complications

	Baseline	Follow up of 5 years	
		PT	IT
Severe hypoglycaemia			
At least one episode (%)*	68	76.3	78.0
Mean episodes per patient	--	0.358	0.433
Retinopathy (%)*, any	59	62.3	62.4
Nephropathy (%) *#, any	--	17.7	19.3
Neuropathy (%)*, any	43	56.9	65.1
Cardiac diseases			
Any (%)*	21	22.4	22.4
Events per patient (mean)	--	0.016	0.017
Peripheral vascular diseases			
Any (%)*	9	12.6	12.9
Events per patient (mean)	--	0.042	0.047

PT: whole organ pancreas transplantation; IT: Islet transplantation; N: number.

*: Either patient with the diabetes-related complication at baseline or experiencing it in the follow up is defined as the “any” with this disease.

#: Our target patients have stable renal function at baseline.

Table 12 Results of scenario analyses

	Costs ($CAD)	Life-years	Incremental cost per life-year gained (IT versus PT) ($CAD)	Duration of full graft (month)	Duration of partial graft (month)	Duration of graft loss (month)	Incremental duration of graft survival (IT versus PT) (month)
Scenario 1: Insulin independence at 5-years following IT is 50%							
Follow up of 5 years							
PT	53,452	4.44	--	44.2	--	12.1	--
IT	58,268	4.52	55,834	41.8	7.8	8.0	5.3
Scenario 2: Graft function affects mortality							
Follow up of 5 years							
PT	53,446	4.45	--	44.8	--	11.7	--
IT	59,096	4.53	68,003	30.8	12.1	14.6	-1.9
Scenario 3: Procedure-related mortality in whole organ pancreas transplant arm is 10%							
Follow up of 5 years							
PT	50,436	4.08	--	41.3	--	10.5	--
IT	59,248	4.52	19,965	30.8	12.2	14.4	1.7

Scenario 4: Graft function in IT arm based on Barton et al. 2012							
Follow up of 5 years							
PT	53,215	4.44	--	44.3	--	12.1	--
IT	58,765	4.53	64,423	31.3	16.7	9.5	3.7

PT: whole organ pancreas transplantation; IT: Islet transplantation.

Scenario 1: 50% of patients transfer from full graft to partial graft in 5 years, and there is no transition from full graft to graft loss state.

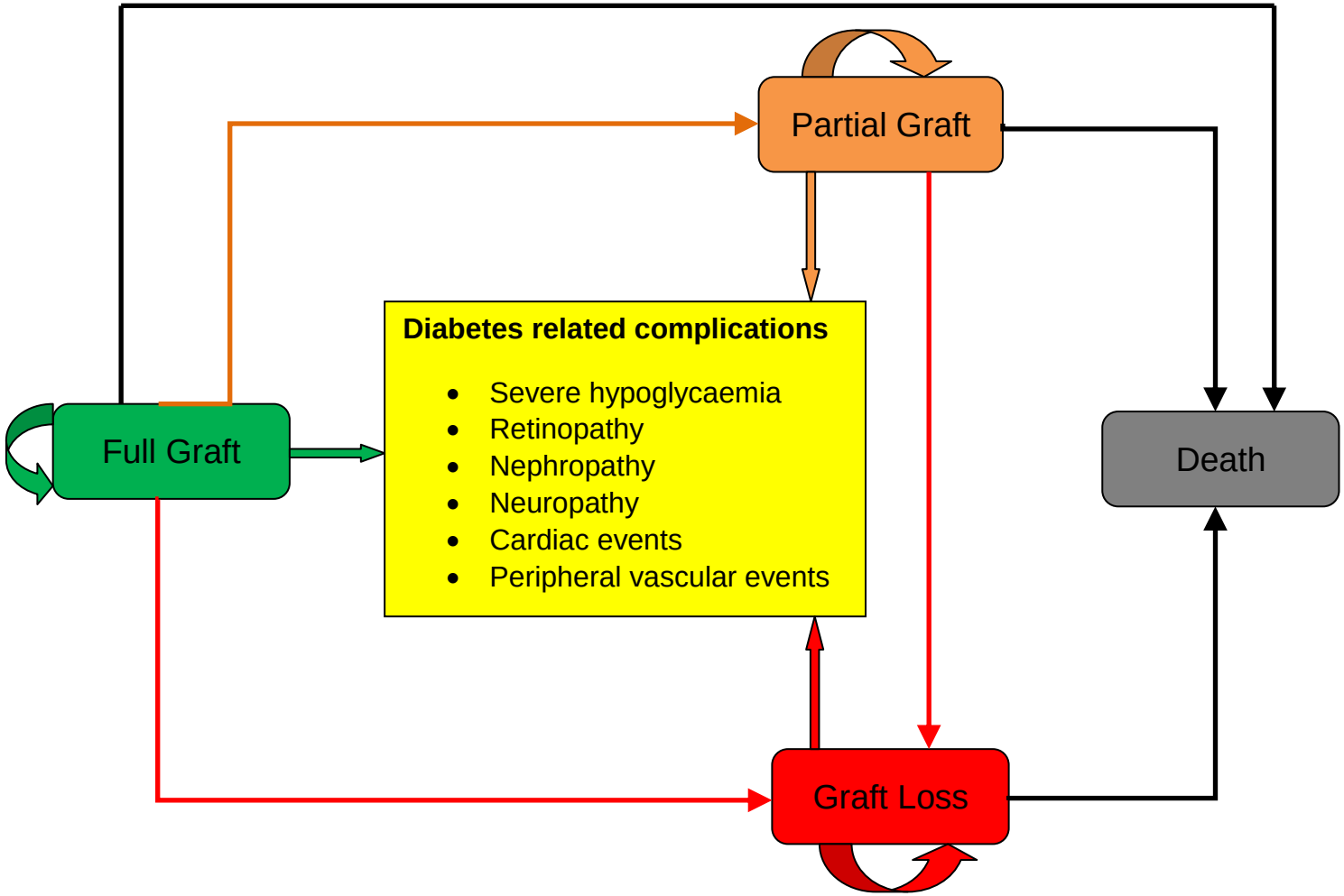
Scenario 2: The risk ratio of mortality in those with graft loss versus full graft is 4.16, and risk of mortality for those with full function is 4 times as that in the age and sex specified general population.

Scenario 3: The procedure related mortality is 10% in PT arm. Other parameter estimates are same as those in scenario 2.

Scenario 4: There were some discrepancies of estimates of positive C peptide between the 7th CITR Annual Report of 2011[12] and Barton et al 2012[20]. We used the transition probabilities between graft functions based on Barton et al in this sensitivity analysis, while other parameters are same as those in base case model.

FIGURES

Figure 1: Markov model illustrating how patients move between 4 different health states (full graft function, partial graft function, graft loss and death) following Islet Transplantation



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APPENDICES

Appendix 1: The calculation of transition probabilities between graft states in the IT arm

1. Transition probability estimates up to 5 years

We estimated the transition probabilities between graft states based on CITR data for 2004-2007[12]. Appendix 4 of the CITR document provided the numbers of patients with insulin independence and dependence at different follow up times; and Appendix 6 provides the numbers of patients with positive or negative C peptide levels. This information is summarized in Tables A1-1 and A1-2 below.

Table A1-1: Number of insulin independent patients post the last infusion of islet transplantation (from CITR Appendix 4)

	Time 0	6 month	1 year	2 year	3 year	4 year	5 year
Number of patients who are insulin independent	15	123	106	81	61	41	21
Number of patients who are insulin dependent	200	81	95	110	105	93	67

Table A1-2: Number of patients with positive C peptide levels post the last infusion of islet transplantation (from CITR Appendix 6)

	Time 0	6 month	1 year	2 year	3 year	4 year	5 year
Number of patients with a positive C peptide level (≥0.3 ng/mL)	127	164	148	108	78	49	27
Number of patients with a negative C peptide level (<0.3 ng/mL)	79	30	41	55	57	51	36

Ignoring the difference in the sample size of the two tables above, and assuming random censoring, we calculated the proportion of patients in each of the 3 graft function states at each observed time point using the expressions below. Final estimates are summarized in Table A1-3. We assumed that all patients had full function at time zero. Note: We did not take into account the risk of mortality in this analysis.

> % of patients with full graft function = N of patients with insulin independence / (N of patients with insulin independence + N of patients with of insulin dependence)
>
> % of patients with graft loss = N of patients of negative C peptide / (N of patients of positive C peptide + N of patients of negative C peptide)
>
> % of patients with partial graft function = 1- % of full graft - % of graft loss

Table A1-3: The proportion of patients in each of the 3 graft function states (derived from Tables A1-1 and A1-2)

	Time 0	6 month	1 year	2 year	3 year	4 year	5 year
Full graft	1	0.6029	0.5274	0.4241	0.3675	0.3060	0.2386
Partial graft	0	0.2424	0.2557	0.2385	0.2103	0.1840	0.1899
Graft loss	0	0.1546	0.2169	0.3374	0.4222	0.5100	0.5714

The changes in the proportion of patients in the 3 states at each time interval can be estimated based on the estimates in Table A1-3. We assumed that patients in the full graft function state have to pass through the partial graft function state to reach the graft loss state after first 6 cycles (or 6 months). Assuming that the transition rate is constant in each time interval, the event rate over t months can be obtained from the changes in the proportions using the formula below[46].

Event rate = - [ln(1-p)]/t, [46]

p= (change in the proportion of patients in a state)/(the proportion of patients at risk).

t= time interval in months

For example: From time zero to 6 months, 24% patients from full graft function state transfer to partial graft function state. The transition rate per month = -[ln(1-0.2424)]/6 = 0.0463.

Using this formula, and considering the proportion of patients at risk, we can get the event rate of each transition. See Table A1-4.

Table A1-4: Monthly transition rates

Time since Islet transplant (months)	**Rate per month**
Full graft TO partial graft	
1-6	0.04627
7-12	0.02232
13-24	0.01816
25-36	0.01194
37-48	0.01526
49-60	0.02071
Full graft TO Graft loss	
1-6	0.02800
Partial functioning graft TO Graft loss	
1-6	0.00000
7-12	0.04950
13-24	0.05310

25-36	0.03661
37-48	0.04502
49-60	0.03385

Finally, we converted the event rates into transition probabilities using the following formula[46]

Transition probability = 1- exp(- rate * t) [46]

For example: Transition probability from full graft to partial graft per month (first 6 month) = 1- exp(-0.0463 *1)= 0.0452.

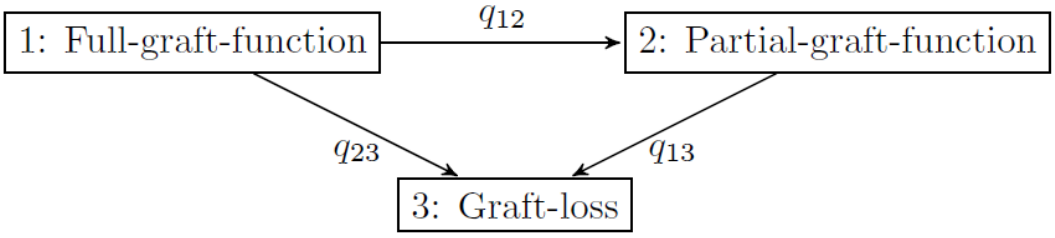
The final transition probabilities used in our decision-analytic Markov model can be found in Table 4 in the main text.

2. Extrapolation of transition probability estimates to long term

We are interested in estimating the long-term probability of graft function following IT therapy, so we have to project the transition probabilities to the long term. We created individual level data on the basis of aggregated data, and used multi-state models ("msm" package in R) to analyze those data to obtain transition probability estimates between year 2 and year 5[21]. These estimates were used to extrapolate results to the long-term, assuming that transition probabilities after year 5 are the same as those in year 2 to year 5. See below for more detailed explanations of our assumptions, data preparation and fitting the model.

It was assumed that 215 patients had undergone Islet transplantation in this study (Table A1-1) but that due to right censoring, the numbers of patients tested for insulin independence and for C-Peptide prevalence (i.e. proportion of patients above 0.3ng/mL) post last infusion diminished over time. It was assumed that missingness was monotone (i.e. due to right-censoring), and that the patients tested for C-Peptide prevalence post last infusion (where the number tested is smaller) formed a subset of those tested for insulin independence.

The model that was assumed to correctly describe these data was a multi-state illness-death-type time-homogeneous Markov model with transition occurring in continuous time but observation made at fixed time points resulting in interval-censored panel data.



To fit this model, individual trajectories are required which were, however, not available. We reconstructed individual trajectories to match the marginal totals in the observed data according to the following rules. First, it was assumed that the censoring mechanism could be ignored. Under this assumption, inverse probability weighting was used to impute the marginal totals under the full data without censoring prior to the end-of-study. For instance if K patients out of D tested were found to be insulin independent at a particular time point, the imputed number had all 215 been tested is w*K, rounded to the nearest integer, where the weight is given by $w = (D/215)^{-1}$. Second, it was assumed that patients could not transition directly from the full-graft-function state to the graft loss state without having first been observed in the partial-graft-function state (except in the first time interval). Finally, even without censoring the aggregate data do not determine the individual trajectories without further assumptions; the number of transitions is known, but not the individual patients undergoing the transitions. This was resolved somewhat arbitrarily as it turns out to be without consequence for the current model because all choices lead to the same likelihood (See the formula 1 in Jackson 2011[21]).

With the individual trajectories constructed, the model is fit by maximum likelihood using the R package "msm"[21]. This produces an estimate of the intensity matrix Q. Under the assumptions made, the point estimates are valid while the standard error estimates and confidence intervals derived from them are not as the imputation of missing data has nowhere been accounted for. From the Q matrix, the probability of transitioning between any states in an interval of length t can be obtained from the matrix exponential $P(t) = \exp(tQ)$. Since it is believed that the transition intensities in the first year would differ substantially from the intensities in subsequent years (i.e. time-homogeneity does not hold), we fitted the model by excluding the data from the first year. The results are summarized below.

The monthly probability of full graft to partial graft = 0.0158.

The monthly probability of partial graft to graft loss = 0.0347.

These transition probability estimates from the "msm" package were similar to the average crude values for year 2 to year 5. In summary, we used the observed or crude transition probabilities for the first 5 years, and used the results from the multi-state model for 6th year or later for the purpose of extrapolation.

Appendix 2: The calculation of transition probabilities between graft states in the PT arm

The mortality rate was rather high, about 10% at 5 years, for pancreas after kidney transplantation (PAK) in the large International Pancreas Transplant Registry (IPTR)[22]. Following our assumption that both treatments have identical risks of

mortality besides the procedure-related mortality, we estimated transition probabilities between graft states post PT ignoring mortality to match the estimates for IT. The partial graft function state probably also exists for patients of PT therapy, but there were rare data that we could use to quantify it. Thus, there are only 2 graft states for PT, full graft function and graft loss.

To approximate the transition probabilities without mortality, firstly we estimated the proportions of patients at the 3 states (full graft, graft loss and death) using the IPTR data. Next, we divided the patients who died into 2 categories, death with full graft function and death without graft function. The proportion of patients who survived with graft loss plus the proportion who died with graft loss at death would approximately equal the total proportion of patients without graft function if there were no mortalities. See below for details.

According to the recent data, the 2-month, 1-year and 3-year insulin independence rates are 90%, 82.3% and 70.5%, respectively, for pancreas after kidney transplant[19]. Based on those data, we divided the hazard of graft loss into three phases, the first 2 months, the subsequent 10 months (the 3rd to 12th month) and 2nd-3rd year. We calculated the transition probability in each interval by assuming that the hazard of graft loss is constant in each interval.

Table A2-1: survival with full graft and mortality (IPTR data[19])

	Time 0	2 months	1 year	3 years
Survival with full graft	1	0.90	0.823	0.704
Mortality (with or without graft function)	0	0.02*	0.033	0.064

*: The estimated value.

From these data, we can derive the proportions of survival with graft loss as follows:
L (proportion of survival with graft loss) = 1- G (proportion of survival with graft function) - D(proportion of death, with or without graft)

According to IPTR[15], failed pancreas graft increased the risks of mortality 4.16 fold for PAK. Thus, we can approximate the proportion of patient who died with graft loss as (L*4.16/(L*4.16+G) * D). The sum of survival with graft loss and death with graft loss (L + L*4.16/(L*4.16+G) * D) was the total graft loss at each time point. Using the same methods introduced in Appendix 1, we obtained transition probabilities from full graft to graft loss in the 3 time intervals. See results in Table 5 in main text.

Appendix 3:Additional clinical outcomes post-IT in the 7th CITR Annual Report

Patients' survival	
Overall	18 (3%) deaths during a mean of 6 years of follow-up - 1 death possibly related to IT infusions and immunosuppression therapy, 3 related to or possibly related to immunosuppression therapy, another 13 deaths not related or unlikely to be related to IT infusion or immunosuppression therapy.
2007-2009	0.7% (1/135)
2004-2006	1.1% (2/190)
1999-2003	6.1% (15/246)
ITA	2.5% (12/481)
IAK or SIK	6.7% (6/90)
Adverse Event: recipients with AE and severe AE (SAE) at any time post IT infusion.	
Life threatening SAE	23% (132/571)
2007-2009	10% (14/135)
2004-2006	28% (54/190)
1999-2003	26% (64/246)
ITA	23% (109/481)
IAK or SIK	26% (23/90)
SAE with sequelae	15% (86/571)
2007-2009	12% (16/135)
2004-2006	21% (40/190)
1999-2003	12% (30/246)
ITA	15% (72/481)
IAK or SIK	16% (14/90)
SAE of Long term disability	3% (18/571)
2007-2009	4% (6/135)
2004-2006	2% (3/190)
1999-2003	4% (9/246)
ITA	3% (16/481)
IAK or SIK	2% (2/90)
Neoplasms	29 instances in 27 patients during an average 3.2 years of follow up - 21(72%) possibly related to immunosuppression. All 21 (72%) instances were classified as benign. Basal or squamous cell carcinoma of skin: 16 instances in 13 patients; malignant ovarian cyst: 6 instances; breast cancer: 3 instances in 2 patients; lung cancer: 2 instances; thyroid cancer: 2 instances.