

Cost Analysis of Human Islet Transplantation for the Treatment of Type 1 Diabetes in the Swiss-French Consortium GRAGIL

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OBJECTIVE — To evaluate the cost of islet transplantation in type 1 diabetic patients with a functional renal graft in a multicenter network.

RESEARCH DESIGN AND METHODS — The study involved nine diabetic patients transplanted in the Swiss-French Groupe Rhône-Alpes, Rhin et Geneve pour la transplantation d'îlots Langerhans (GRAGIL) consortium between March 1999 and June 2000. The direct medical costs were estimated from Social Security's perspective from the inclusion of the patient to 1 year after transplantation. All cost components were computed separately and included evaluation, screening and candidacy, organ retrieval, islet processing, pancreas and islet transportation, hospitalization for transplantation, follow-up, medications (immunosuppressive, antidiabetic, and adjuvant drugs), and adverse events requiring hospitalization.

RESULTS — During the study period, 56 pancreata were processed and 14 islet preparations were transplanted. The average cost of an islet transplantation (procedure and 1-year follow-up) was €77,745 (French rate, year 2000). The four main cost components were islet preparation (30% of the total cost), adverse events (24%), drugs (14%), and hospitalization (13%).

CONCLUSIONS — Overall costs of islet transplantation are slightly higher than those of pancreas transplantation. The cell isolation process is a critical point; a reduction in overall cost will require more efficient ways of isolating high yields of viable islets. Costs generated by shipments within the GRAGIL network did not represent an economic burden. It can be expected that the costs will decrease with growing experience and improving technology.

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Abbreviations: CMV, cytomegalovirus; DRG, disease-related group; GRAGIL, Groupe Rhône-Alpes, Rhin et Geneve pour la transplantation d'îlots Langerhans; IEQ, islet equivalent.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

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Islet transplantation is a promising experimental treatment for type 1 diabetes (1–3). It is widely recognized that tight control of blood glucose levels reduces diabetes-related morbidity and mortality (4,5) and can prohibit or delay the development of costly complications (6–12). Islet replacement, by either islet or whole-pancreas transplantation, is the sole therapy to achieve independence from exogenous insulin and a constant normoglycemic state, avoiding hypoglycemic episodes (13). By June 2001, the 1-year insulin independence rate in 237 adult islet allograft recipients performed worldwide between 1990 and 1999 and reported by the Giessen Islet International Registry was 11% (14). Recently, significant improvements in the outcome of islet transplantation have been recorded, in particular, those achieved by the Edmonton protocol (15,16). In contrast, pancreas-alone transplantation and simultaneous kidney-pancreas transplantation achieve, according to the 2000 United Network for Organ Sharing—Organ Procurement and Transplantation Network (UNOS OPTN) report, 76 and 84% insulin independence rates at 1 year, respectively (17). However, whole- or segmental-pancreas transplants are complex surgical procedures and are associated with significant mortality and morbidity (18). Thus, islet transplantation is an alternative for many individuals who have the medical need for a pancreas transplant but are not surgical candidates for this operation (19).

An early appraisal of the cost of islet transplantation is required as well as the evaluation of the procedure's clinical efficacy. The identification of the main sources of costs will be helpful for targeting the data collection on resource use. As the viability of islet transplantation approaches that of conventional insulin therapy or pancreas transplantation, the cost will represent an important criterion in medical decision making as well as the

assessment of the procedure's efficacy. The objective of this study was to evaluate the cost of islet transplantation in a two-stage phase I–II trial conducted by the Swiss-French consortium Groupe Rhône-Alpes, Rhin et Geneve pour la transplantation d'îlots Langerhans (GRAGIL) in a multicenter network.

RESEARCH DESIGN AND METHODS

GRAGIL network

GRAGIL is a multicenter research group involving the following teaching hospitals at the time of the study: the University of Geneva in Switzerland and the Universities of Grenoble, Lyon, Strasbourg, and Besançon in France (20). The GRAGIL network has been approved by the French Transplantation Agency (Etablissement Français des Greffes) and the National Health Department (Direction Générale de la Santé) in 1998.

Patients

This study involved the nine patients transplanted in the GRAGIL network between 1 March 1999 and 1 June 2000. All patients presented with type 1 diabetes (basal and glucagon-stimulated serum C-peptide <0.2 ng/ml). During this period, nine islet-after-kidney transplantations were performed after a minimal period of 6 months after the kidney transplantation (glomerular filtration rate >40 ml/min) (20). All patients received immunosuppressive therapy (various combinations of some of the following drugs: cyclosporine or tacrolimus, steroids, mycophenolate mofetil, and azathioprine). Their main characteristics on the days of transplantation are described in Table 1.

Islet preparation and transplantation

Potential recipient selection, transplantation, and patient follow-up were possible in each center of the network, but the islet preparation was performed exclusively in the University of Geneva laboratory.

Pancreata were procured from cadaveric heart-beating donors, and islet isolation was performed as previously described in detail (21). Islet transplantation was performed according to the criteria of a defined threshold of 6,000 islet equivalents (IEQs)/kg (islet equivalents per kilogram of recipient's body weight). The islets were transplanted as soon as

Table 1—Characteristics of recipients

	City	Sex	Age (years)	Diabetes duration (years)	Type of transplantation
Patient ID					
1	Geneva	M	47	33	IAK
2	Geneva	F	50	41	IAK
3	Lyon	F	41	31	IAK
4	Strasbourg	M	52	24	IAK
5	Grenoble	M	38	28	IAK
6	Grenoble	M	38	27	IAK
7	Grenoble	F	48	39	IAK
8	Grenoble	F	28	15	IAK
9	Grenoble	F	32	27	IAK
Median			41	29	

IAK, islet-after-kidney transplantation.

possible (if possible, the following day); otherwise, they were cultured for a maximum of 14 days, until a second islet preparation yielded a sufficient total number of islets to reach the threshold. Functional islets with a purity of >50% were collected in syringes and shipped by ambulance to the transplant center and were transplanted as described previously (21).

Islet transplantation was done by a percutaneous transhepatic approach. The portal vein was catheterized under ultrasound guidance, and the islets were slowly infused over an average period of 30 min, with portal venous pressure monitored throughout the procedure.

The methods of patient inclusion, pancreas procurement, islet preparation, transplantation, and treatment have been further described elsewhere (20).

Treatment and follow-up

Induction immunosuppression consisted of basiliximab (Simulect; Novartis), and maintenance immunosuppression included mycophenolate mofetil (Cellcept; Roche), cyclosporine (Neoral; Novartis), or tacrolimus (Prograf; Fujisawa) and steroids. Adjuvant therapy consisted of nicotinamide, vitamin E, verapamil, pentoxifylline, cotrimoxazole, and omeprazole. For patients having a negative cytomegalovirus (CMV) serology and receiving islets from a donor with a positive CMV serology, CMV prophylaxis was performed with ganciclovir intravenously (Roche) for 14 days, followed by oral administration for 2.5 months. Insulin therapy was maintained unless the patients experienced hypoglycemia.

Follow-up was planned on a monthly basis, with scheduled outpatient consultation and laboratory tests.

Cost analysis

The direct medical costs were estimated from the French Social Security's (French third-party payer system) perspective, including ambulatory care costs and hospital expenses. Indirect costs and direct nonmedical costs were not considered in this analysis. The data on medical resource use were studied retrospectively and were extracted from the patients' medical files and from the follow-up records.

The selected time frame covered the period from the inclusion for islet transplantation to 1 year after the procedure. The low rate of insulin-free recipients at 1 year (11% according to the Giessen Registry) led us to assume that the majority of the costs would be generated by the procedure itself and on the first year of follow-up. There was no actualization performed. The following cost components were considered:

- Organ and islet transportation costs were calculated applying the invoicing system of the provider during the study period.
- Pancreas procurement costs and islet preparation costs were computed according to the bills issued by the hospital and the laboratory during the study period (including equipment and personnel fees).
- The hospitalization costs were estimated for patients receiving an islet-after-kidney transplantation by

researching an appropriate disease-related group (DRG) in the French classification and its monetary value in the 2000 National Costs Study. By definition, a DRG groups together several hospital stays that deal with the same anatomic region and consume similar resources, therefore having connected costs. The National Costs Study is performed each year and is based on a sample of hospitals with detailed analytical accounting and provides the national cost reference for each DRG, with the following items and cost elements: number of observations, physician wages, nursing staff wages, other wages, medical supplies and drugs, maintenance and replacement of medical equipment, laboratory tests, operating room costs, imaging procedures, dialysis, anesthesiology, other interventions, functional exploration, radiotherapy, interventions performed in other structures, catering, laundry, overhead hospital costs (administration, management, heating, etc.), building depreciation reserve, and total costs. Some of these items are also expressed using a standard resource unit (laboratory test, surgery, imaging procedures, etc.). The mean hospital stay length for each DRG is also provided. Moreover, data on network patients' resource use during hospitalization have been extracted from the medical file and compared with the corresponding elements in the National Costs Study to assess the validity of the estimation.

- The costs of the follow-up for the pre- and posttransplantation period were valued on the basis of the standard number of consultations and laboratory and diagnostic tests performed according to the protocol for patients receiving an islet-after-kidney transplant.
- The costs of drugs related to islet-after-kidney transplantation and diabetes (immunosuppressive, antidiabetic, adjuvant, and anti-CMV drugs) were taken into account, but the cost of other possible medications was not.
- The costs of adverse events leading to hospitalizations of patients receiving an islet-after-kidney transplant during the follow-up year were considered and valued according to the corre-

sponding DRG in the National Costs Study.

Statistical mean and median value and range (minimal and maximal values) were calculated for each element, except for hospitalization and follow-up costs (the estimation method did not allow it). The total cost for islet transplantation was computed by summing the values of each cost component.

The estimates were initially calculated in French francs and converted to euros using the currency conversion rate of 1€ = 6.559 French francs.

RESULTS — The patients received islet transplantation with a mean (\pm SD) number of $9,200 \pm 3,600$ IEQs/kg of the recipient's body weight. These islet preparations were obtained from 14 pancreata; four patients received islets from one donor pancreas, whereas the remaining five patients received islets from two donor pancreata. During the study period, a total of 56 pancreata were shipped to Geneva (20). Of the available 56 islet preparations, 6 were used for four simultaneous islet-kidney transplantations performed at the Geneva center. These transplants have been excluded from our analysis. Of the islet preparations, 36 of 56 were not used for transplantation, but were taken into account for the current cost analysis. Twelve of the nontransplanted preparations contained $>200,000$ IEQs, but could not be transplanted because of logistical reasons, the lack of a suitable recipient, or insufficient quality. A total of 25 islet preparations had too low of a yield and did not reach 6,000 IEQs/kg for patients on the waiting list. Therefore, the following results concern the average case of a transplantation of islets stemming from 1.6 pancreata and requiring a total of 5.6 isolation procedures.

- The mean cost for the procurement of one pancreas was €1,086 (median 1,073, range 749–1,421). Thus, a transplantation using an average of 5.6 pancreata represents a €6,082 procurement cost. The cost for organ acquisition can vary widely according to the billing procedure applied by the particular hospital and the number of other organs recovered simultaneously.
- The mean cost to ship one pancreas

from the retrieval center to the Geneva laboratory was €574 (median 485, range 0–1,602). The mean cost to ship the islets to the transplantation center was €312 (median 490, range 0–1,163). Therefore, the total transportation cost for a transplantation requiring an average of 5.6 pancreata was €5,526.

- The procedure for one islet preparation costs €4,242. Thus, one transplantation necessitating 5.6 pancreata costs €23,755 for islet processing.
- The inclusion and pretransplantation (evaluation, screening, and candidacy) expenses were €582 for each patient. Posttransplantation follow-up visits were made on a monthly basis. The posttransplantation follow-up costs were €3,596 for each patient with a full-year follow-up; the majority (85%) of costs were represented by laboratory tests.
- The hospitalization costs after islet-after-kidney transplantation were estimated to be €10,423. The DRG applied here has an average hospital stay length of 14.2 days in the 2000 National Costs Study, whereas the mean hospitalization length observed in the patients transplanted in GRAGIL was 15.6 days.
- The immunosuppressive and adjuvant medications used in recipients of islet-after-kidney transplantations were the following: seven patients out of nine received cyclosporine (Neoral), and two patients on tacrolimus (Prograf) after kidney transplantation were maintained under this regimen. Two patients received a CMV prophylaxis with ganciclovir, and one patient was treated for a CMV infection. For two patients, insulin therapy was discontinued at 6 and 7 months after transplantation, respectively; they remained insulin-independent with a follow-up of 12 months. Six patients used an external insulin pump. The other patients continued to practice traditional injection therapy (syringe or pen). The drug costs (excluding the hospitalization period) are estimated at €10,674 (median 10,614, range 8,390–13,395), with 66% for immunosuppressive drugs, 17% for insulin treatment, 6% for adjuvant therapy, and 11% for CMV infection prophylaxis or treatment.
- The costs of adverse event hospitaliza-

Table 2—Value of the different cost components (€2,000) for an islet transplantation requiring the procurement of 5.7 pancreata

Cost component	Average cost (€2,000)
Evaluation, screening, and candidacy*	582
Organ recovery	6,082
Transportation	
Pancreata	3,214
Islet	312
Total	3,526
Islet preparation	23,755
Hospitalization (for the transplantation)†	10,423
Drugs (ambulatory care)‡	10,674
1-year follow-up*	3,596
Complications	19,107
Total	77,745

*Costs of pre- and posttransplantation follow-up have been estimated from the standard number of consultations and laboratory tests scheduled in the protocol. †Complete hospitalization costs extracted from the 2000 French National Cost Study. ‡The costs of drugs used during the hospitalization are included in the costs of hospitalization.

tion during the follow-up year averaged €2,123 per patient (total of €19,107). These hospitalizations affected five patients out of nine. For one patient, it represented €7,620. All the costs have been considered here for treatment of conditions as diverse as CMV infection, pneumonia, intraventricular hemorrhage, vitrectomy, herpes zoster, retrosternal pain, or a fall at home.

In the average case, an islet transplantation represents a cost of €77,745 (calculated by summing up the average value of each cost component [Table 2]). The repartition of the different cost components is shown in Fig. 1. The four main sources of expense are islet preparation (30% of the total cost), adverse events during the year following the procedure (24%), drugs (14%), and hospitalization (13%). These four main expenses represent 81% of the costs for a single transplantation.

CONCLUSIONS— Islet transplantation can be considered as a possible alternative to exogenous insulin for diabetic patients with a functional renal graft. Al-

though the number of procedures on which our estimations are based is limited, it is significant in such an innovative therapy. It underlines the need for more multicenter studies, thus permitting the enrollment of more patients and the increase of experience. To aggregate the economic data, we have chosen to apply a single price list, because mixing the French and Swiss costs would have been difficult to analyze. We have estimated the use of medical resources in both countries involved in the network and expressed it in a single monetary value to make the analysis feasible. Hospitalization costs, for instance, are not applicable to a hospital in particular but are a global approach for this type of expense. Because the average length of hospitalization of GRAGIL patients is very similar to the hospitalization length of the applied DRG (15.6 and 14.2 days, respectively), we can assume that the DRG value gives a correct appraisal of the costs charged to the length of the hospital stay (wages, overhead hospital charges, etc.), which account for 48% of the total. Some disparities are noted in other items: the drug and laboratory test costs for the transplanted patients are higher than the reported costs of the corresponding DRG; however, they prove to be lower concerning the surgical

intervention, radiology, and anesthesia costs. These differences compensate partially, which makes the DRG's value a plausible estimate of the hospitalization costs. There were no outliers for the length of hospitalization (it ranged from 11 to 19 days), and, consequently, the costs of hospitalization for islet transplantation were comparable among all patients.

The cost of the immunosuppressive drugs has been entirely ascribed to the islet transplant, although the patients were already receiving an immunosuppressive regimen before receiving the islets. In the GRAGIL protocol, there was a substantial modification of the immunosuppressive regimen, with an increase in the doses of mycophenolate mofetil (Cellcept), cyclosporine (Neoral), or tacrolimus (Prograf) and the addition of basiliximab (Simulect), steroids, and adjuvant drugs during the first months after the procedure. We cannot know what the immunosuppressive drug cost would have been had the patients not undergone islet transplantation. It is not possible to determine to what extent islet transplantation alone contributes to these costs, but very likely it is by >50%.

The costs evaluated are specific to the GRAGIL Group and depend on its orga-

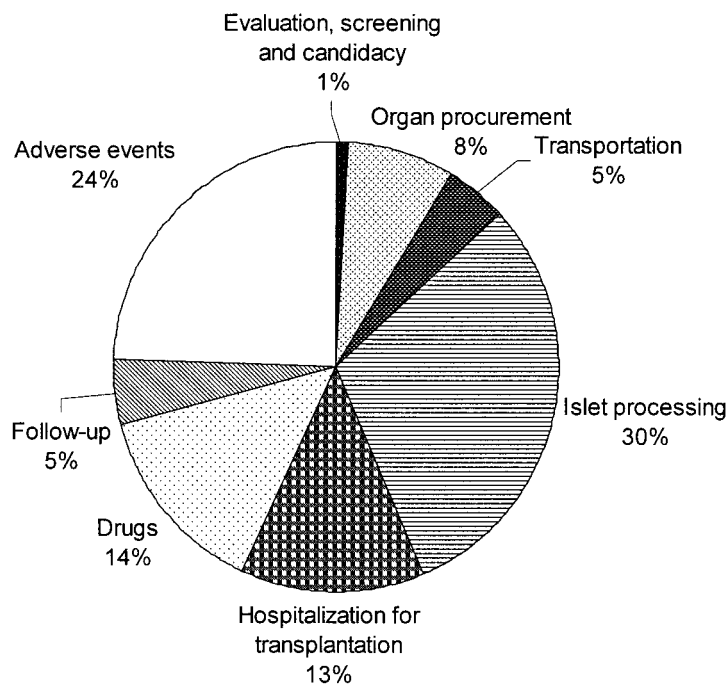


Figure 1—Mean relative contribution of each cost component to the total cost for an islet transplantation requiring 5.6 pancreata (the islets that are actually transplanted stem from 1.6 pancreata; the other preparations are not suitable for transplantation).

nization. The costs of follow-up, calculated from the standard number of procedures performed (as defined in the protocol), may have been undervalued. On the other hand, it is foreseeable that the hospitalization length will become shorter as islet transplantation enters into an increasingly routine phase. In a Canadian trial of islet transplantation involving diabetic patients without a renal graft, the median hospital stay was 2.3 days and 24 h for 40% of the patients (15). Such an evolution would have an important impact on the costs of the procedure. It must be underlined that this evaluation has been made only after the first nine transplantations performed in the network. At such an early stage, the need for close monitoring may explain the long hospitalization time, which will probably be shorter with the gain of experience of the teams involved.

Costs generated by shipments within the GRAGIL network did not represent an economic burden of islet transplantation. This multicentric organization might in fact have optimized the cost-effectiveness of the procedure by increasing the availability of good quality organs and appropriate recipients.

The costs generated by adverse events during the year after the procedure are high. However, all adverse events have been considered. Because a link of causality between these events and islet transplantation could not be assessed, the cost of the procedure has probably been overvalued. If the financial consequences of adverse events were not incorporated, a single islet transplantation would cost €58,638.

This study indicates that the cell isolation process is a critical point in terms of costs, especially if one takes into account the organ loss (more than two pancreata out of three). The actual data on islet transplantation efficacy indicate that the number of transplanted cells must reach a certain level, requiring sometimes two or three pancreata, to achieve good results (16). This might represent a strong limitation. Theoretically, a transplantation of islets stemming from two pancreata with a similar rate of organ loss during the isolation process (72%) would cost €53,812 (considering organ procurement, transportation, islet processing, patient evaluation, and hospitalization for transplantation). Ideally, a transplantation requiring only one pancreas without loss

during the preparation would cost €32,565 (i.e., €21,247 less). The extent of the expenses for islet preparation could hinder the diffusion of this therapy (13). A better reproducibility of islet processing will be essential for the diffusion of this technology. Presently, the major limiting factor for successful islet isolation is the inconsistency in the quality of the enzymes necessary for islet isolation and the quality of the donor pancreas (22,23).

A 1995 Italian study performed in a single hospital setting (24) compared the cost of simultaneous kidney-islet transplantation and the cost of simultaneous kidney-pancreas transplantation (from transplantation to discharge, including the 1-week admission for pretransplant evaluation); the resulting totals were very close, at \$47,791 and \$46,087, respectively (1995 U.S. dollars). The hospitalization costs were the most significant for the latter (67% of the total cost for kidney-pancreas transplantation vs. 44% for kidney-islet transplantation), but the islet preparation expenses were so high (32% of the cost for kidney-islet transplantation) that they compensated for the difference between the procedures. According to the 2000 French National Cost Study (25), the costs of hospitalization for pancreas transplantation (DRG 279) were €25,674. The processing of the 5.6 pancreata used for a single islet transplantation costs €23,755; with the hospitalization, the total costs are about €34,178. It is higher than the costs of pancreas transplantation, all the more because such an islet transplantation requires almost five more organs than a pancreas transplantation and induces additional costs in organ retrieval and transportation. Nevertheless, the comparison should not be restricted on the short period after the transplantation. Whole-organ transplantations are likely to be more costly in the long term because they have significant morbidity and mortality rates and surgical re-interventions might be necessary.

Diabetes is known for being a costly disease, due particularly to the number and the severity of the complications it entails. In 1998, French Social Security spent a total of €4.1 billion for diabetic patients (i.e., €3,680 per patient, type 1 and type 2 mixed) (26). The costs for a single islet transplantation (€50,966 when including the processing of islets that are not suitable for transplantation)

represent 13.8-fold the average expense per year and per diabetic patient. It must be noted that some costs presented here are not entirely ascribable to the islet transplantation. All of the diabetic patients involved in the study already had a functional renal graft and therefore received immunosuppressive drugs. They also had a regular follow-up for their renal transplant and the diabetic disease. After the islet transplantation, the immunosuppressive treatment was intensified and the consultation frequency increased. The patients also received adjuvant drugs, and some of them received an insulin pump, which is more costly than traditional injections.

Some interventions for diabetes have been classified as clearly cost-effective or even cost-saving, such as diabetic nephropathy screening and treatment programs to prevent end-stage renal disease (12). A simulation on a hypothetical cohort of 10,000 type 1 diabetic patients (5) showed that, compared with conventional therapy patients, intensive insulin therapy patients will, on average, gain 15.3 years of life free from any significant microvascular or neurological complications. With a discount rate of 3% per year, intensive therapy costs \$28,661 (1994 U.S. dollars) per year of life gained. At the moment, it is too early to predict the long-term outcomes and the impact on diabetic complications of islet transplantation, but it would be of great interest to compare it with other interventions for diabetes. It has been shown that an improved glycemic control (resulting in a sustained reduction in HbA_{1c} level) among adult diabetic patients was associated with significant cost-savings within 1 or 2 years of improvement (27,28). Therefore, in the future, the costs of islet transplantation will have to be submitted to the comparison with a conventional management of diabetes and pancreas transplantation.

Overall, because of all the limitations mentioned above, our data must be analyzed cautiously before any extrapolation can be made toward other islet transplantation programs. Despite these limitations, we can conclude that the overall costs of islet transplantation are slightly higher than the costs of pancreas transplantation. However, islet transplantation is still an experimental procedure entering clinical reality, whereas pancreas transplantation is a well-established therapy. It can be expected that elevated costs

for islet isolation will decrease with increasing experience and improving technology. Moreover, it is very likely that the duration of hospitalization for islet transplantation can be reduced significantly. With this promising outlook, islet transplantation may become a cost-effective treatment for type 1 diabetes.

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