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Islet Transplantation in Type 1 Diabetic Patients Using Calcineurin Inhibitor-Free Immunosuppressive Protocols Based on T-Cell Adhesion or Costimulation Blockade

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Abstract

Background—The applicability of islet transplantation as treatment for type 1 diabetes is limited by long-term graft dysfunction, immunosuppressive drug toxicity, need for multiple donors, and increased risk of allosensitization. We describe two immunosuppressive regimens based on the costimulation blocker belatacept (BELA) or the antileukocyte functional antigen-1 antibody efalizumab (EFA), which permit long-term islet allograft survival and address some of these concerns.

Methods—Ten patients with type 1 diabetes with hypoglycemic unawareness received intraportal allogeneic islet transplants. Immunosuppression consisted of antithymocyte globulin induction and maintenance with sirolimus or mycophenolate and BELA (n=5) or EFA (n=5).

Results—All five BELA-treated patients achieved independence after single transplants; one resumed partial insulin use 305 days after transplant but is now independent after a second transplant. All five patients treated with EFA achieved independence after one (3/5) or two (2/5) islet transplants and remained independent while on EFA (392–804 days). After EFA was discontinued because of withdrawal of the drug from the market, two patients resumed

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intermittent insulin use; the others remain independent. No patient in either group developed significant side effects related to the study drugs, and none have been sensitized to alloantigens. All have stable renal function.

Conclusions—These two novel immunosuppressive regimens are effective, well tolerated, and the first calcineurin inhibitor/steroid-sparing islet protocols resulting in long-term insulin independence. Although EFA is no longer available for clinical use, these early results demonstrate that a regimen using BELA may be an effective alternative to improve graft function and longevity while minimizing renal and β -cell toxicity.

Keywords

Islet transplantation; Belatacept; Efalizumab; Type 1 diabetes

Pancreatic islet transplantation offers a minimally invasive approach to restore normoglycemia in patients with type 1 diabetes while avoiding the hypoglycemic episodes observed with intensive insulin therapy and the surgical complications associated with pancreas transplantation (1–6). Beginning with the development of the Edmonton protocol, significant progress has been made in clinical islet transplantation; however, overall outcomes remain suboptimal in that most patients lose insulin independence several years after transplantation, multiple donors are needed to achieve independence, currently used immunosuppressive drugs are toxic, and patients are at risk for allosensitization (5, 7–12).

To address some of these concerns, we evaluated the outcomes of islet transplantation in patients treated with maintenance immunosuppressive regimens based on the costimulation blocker belatacept (BELA, LEA29Y, BristolMyers Squibb, New York, NY) or the antileukocyte functional antigen-1 antibody efalizumab (EFA, Raptiva, Genentech, Inc., S. San Francisco, CA). These biologic agents were selected for their potent immunosuppressive properties, absence of β -cell and renal toxicity, and lack of many of the side effects observed with other currently used drugs.

EFA inhibits T-cell activation and trafficking by blocking attachment of the CD11a subunit of leukocyte functional antigen-1 to the intercellular adhesion molecule-1 (13–15). This drug has been used successfully in kidney transplantation, and we have previously reported similarly encouraging early results in islet transplantation (16, 17). Unfortunately, EFA was linked to the development of progressive multifocal leukoencephalopathy (PML) in several patients receiving the drug as a treatment for psoriasis and was withdrawn from the market in May 2009, leading us to discontinue the drug in our patients (18). As a result, we are now focusing our attention on BELA to provide effective immunosuppression in a calcineurin inhibitor (CNI) and steroid sparing regimen.

BELA is a costimulatory signal-blocking fusion protein that binds the ligands CD80 and CD86 on antigen-presenting cells. The costimulatory signal is required for full T-cell activation once antigen-specific T-cell receptor binding has occurred. Blocking this signal prevents T-cell activation and promotes anergy and apoptosis. In a recent clinical kidney transplant trial, BELA was effective in preventing graft rejection and allowed reduction of conventional immunosuppressive drugs such as cyclosporine and tacrolimus (19, 20).

Moreover, BELA is not nephrotoxic and has no reported β -cell toxicity, making it an ideal agent for islet transplantation.

This study describes our early experience with BELA in a pilot trial of islet transplantation in preuremic type I diabetic patients who uses a CNI and steroid-free immunosuppressive protocol. In addition, we provide additional long-term safety and efficacy outcomes in our previously reported EFA-treated islet recipients and describe the consequences of EFA withdrawal on long-term graft function (17).

Results

Donor and Islet Characteristics

Donor and islet graft characteristics are listed in Table 1. A total of 14 organs were processed to yield 13 preparations suitable for transplantation into 10 recipients. All islet preparations had greater than 90% viability and glucose-stimulated insulin release indices more than or equal to 1.0 before transplant. The mean $\pm$ standard deviation (SD) islet yield/pancreas was 559, 462 ± 94 , and 724 islet equivalent (IEQ).

Recipient Characteristics and Posttransplant Islet Function

The clinical characteristics and posttransplant courses of the 10 islet recipients are shown in Table 2. All 10 patients became insulin independent after their last islet transplant and had complete resolution of their hypoglycemic episodes. Five of five BELA patients became independent after the first transplant; patient BELA-5 resumed intermittent insulin use approximately 300 days after transplant, received a second transplant, and is now independent. Three of five EFA patients achieved insulin independence after their first islet transplant, and two became independent after two transplants. After discontinuation of the EFA, two patients have resumed insulin use but continue to make C-peptide. The length of follow-up, timing of islet transplants, duration of independence, and time of EFA discontinuation are depicted in Figure 1.

Glycemic Control After Transplantation

Glycemic control improved, and hypoglycemic episodes resolved in all subjects after transplantation. Mean pretransplant hemoglobin A1c (HbA1c) levels in both the BELA and EFA groups were increased ($7.7\% \pm 0.9\%$ and $7.4\% \pm 0.7\%$, respectively) but had decreased to normal when measured at the most recent posttransplant evaluation ($5.5\% \pm 0.8\%$ and $6.2\% \pm 0.6\%$, respectively). All patients in the BELA-treated group and the three insulin-independent patients in the EFA-treated group had HbA1c levels below the upper limit of normal for our laboratory. HbA1c levels in the two insulin-dependent patients were 6.7% and 7.0%, respectively. Mixed meal tolerance tests (MMTTs) in BELA-treated patients preformed at least 180 days after final islet transplant showed appropriate C-peptide responses, with mean fasting and stimulated C-peptide levels of 1.2 ± 0.3 and 7.3 ± 5.6 ng/mL, respectively. The most recent MMTT results in the insulin-independent EFA-treated patients also showed appropriate fasting and stimulated C-peptide responses (1.2 ± 0.3 and 6.1 ± 2.0 ng/mL, respectively). In contrast, MMTT results in the two EFA-treated patients who resumed insulin use showed significantly reduced fasting and stimulated C-peptide

responses (patient EFA-3: 0.4 and 2.1 ng/mL, respectively; patient EFA-5: 0.4 and 0.8 ng/mL, respectively).

Renal Function

Renal function as determined by iohexol clearance remained stable in both groups when measured at their most recent evaluation (Fig. 2). The mean glomerular filtration rates (GFRs) in the BELA group were 65 ± 19 mL/min/1.73 m² before transplant and 77 ± 30 mL/min/1.73 m² at the most recent evaluation between 180 and 365 days after transplant ($P=ns$). Similarly, mean GFRs in the EFA group before transplant and 1 year after final transplant were 93 ± 21 mL/min/1.73 m² and 102 ± 24 mL/min/1.73 m², respectively ($P=ns$). Pretransplant 24-hour urinary protein and albumin excretion rates were normal in the majority of patients and remained normal during the most recent evaluation. Two patients in the BELA group had moderate proteinuria and albuminuria (excretion rates of 200–350 and 60–100 mg/24 hr, respectively) before transplant, and these also remained stable when assessed at the most recent evaluation between 180 and 365 days after transplantation.

Immunologic Studies

Peripheral blood mononuclear cell samples from patients in the EFA-treated groups showed significant increases in the percentage of circulating CD4⁺ FoxP3⁺ T cells in the first year after transplant and also showed decreased in vitro responses to donor stimulators and preserved third-party responses. These results have been described previously (19). When mean CD4⁺ FoxP3⁺ T-cell percentages were determined in EFA-treated patients just before discontinuation of EFA (392–804 days after initial transplant), they were found to be significantly lower than at 1 year after transplant ($6.8\% \pm 3.2\%$ and $22.6\% \pm 10.4\%$, respectively). CD4⁺ FoxP3⁺ T-cell percentages continued to decrease slightly after EFA was stopped, reaching mean levels of $4.0\% \pm 1.1\%$ between 10 and 36 weeks after EFA discontinuation. The two patients who lost graft function did not show significant differences in CD4⁺ FoxP3⁺ T-cell percentages compared with the other EFA-treated patients.

In contrast to the EFA-treated patients, the percentage of CD4⁺ FoxP3⁺ T cells in the BELA-treated patients did not change significantly at any time after transplantation. Mean $\pm$ SD percentages of CD4⁺ FoxP3⁺ T cells before and 3, 6, 9, and 12 months after transplant were 3.2 ± 1.8 , 3.2 ± 2.0 , 3.1 ± 1.7 , 3.4 ± 1.6 , and 3.1 ± 0.3 , respectively.

None of the patients in either group were found to have de novo anticlass I or II human leukocyte antigen antibodies when tested at varying times after their transplants. The results of the most recent assays performed on sera obtained 6 months to 3 years after the final islet transplant are shown (Table 2).

Adverse Events

All patients complained of mild abdominal discomfort and nausea after the islet cell infusion, which resolved over 24 to 36 hr. One subject experienced self-limited bleeding from the liver puncture site but this resolved without the need for transfusion. One subject (patient EFA-5) developed a partial portal vein thrombosis that was detected on routine

ultrasound performed 1 day after her second islet transplant. She was treated with oral anticoagulation with complete resolution of the thrombus.

BELA therapy was well tolerated, and no significant side effects were noted with its use. EFA therapy was also well tolerated by all study patients, with documented side effects being limited to the development of a rash or erythema at the injection site in two subjects. Serial neurologic examinations and serum screens for the John Cunningham virus were normal in all patients. One EFA-treated patient developed transient detectable Epstein-Barr virus levels that resolved without intervention. Symptomatic oral ulcers developed in many of our patients and were the main reason for sirolimus dosing reduction and addition of mycophenolate mofetil (MMF). Additional side effects of the protocol drugs included nausea (n=3), diarrhea (n=4), neutropenia (n=3), and thrombocytopenia (n= 1).

Discussion

Our results provide preliminary evidence that an immunosuppressive protocol based on thymoglobulin induction followed by maintenance immunosuppression with the biologic agents BELA or EFA can be used effectively in clinical islet transplantation and provides significant advantages over currently used regimens. Specifically, these protocols allow CNIs and corticosteroid avoidance, are well tolerated, reduce the risk of sensitization to alloantigens, and seem to improve islet engraftment and function.

Avoiding CNIs was an important goal of the study, particularly because these agents have renal toxicity that should be minimized or eliminated in a patient population, which is already at risk for renal insufficiency because of their diabetes (2). We were able to avoid CNI use in all our patients while they were receiving the study drugs, and only one patient in the EFA group started low-dose tacrolimus therapy after EFA discontinuation because they could not tolerate sirolimus or appropriate doses of MMF. Although the long-term benefits of CNI avoidance on renal and islet function are difficult to evaluate in this study because follow-up is relatively short, we did observe stable or improved renal function in all patients during the study period. This is in contrast to other studies reporting significant reductions in GFR in islet recipients treated with conventional immunosuppressive protocols that include CNI (21, 22).

In contrast to most previously reported studies, we were able to achieve durable insulin independence in the majority of our patients after single islet transplants, an important consideration given the concerns for sensitization from multiple donors, the shortage of donor organs, and the efficacy of whole organ transplantation (5, 23). Several factors may be responsible for our results. First, we made important modifications in our organ selection and islet isolation protocols to optimize islet yields and quality (24). Second, the avoidance of CNIs and use of potent T-cell-depleting induction agents may improve islet engraftment and minimize long-term graft dysfunction. Third, it is possible that the use of biologic agents that inhibit T-cell signaling or migration may provide more durable protection against T-cell-mediated alloimmune and autoimmune responses. One potential mechanism that was identified in our previously published study is the induction of regulatory T cells, which were significantly increased in the peripheral lymphocyte populations of EFA-treated

patients (17, 25–27). Although the levels of regulatory T cells declined with time, the initial induction of this cell population may play a role in promoting long-term graft function in the EFA-treated patients who continue to have good islet function despite remaining on relatively low doses of immunosuppression. This expansion of regulatory T cells was not observed in our BELA-treated patients, who maintained baseline regulatory T-cell percentages after transplantation. This finding has been reported in other clinical trials using BELA and raises the possibility that chronic therapy with the drug may be needed to preserve long-term graft function (28).

The absence of significant sensitization to alloantigens was another important finding that differed from previously reported studies (12). None of the patients who maintained insulin independence showed any significant evidence of allosensitization to class I or II alloantigen at varying times after transplantation. In addition, the two patients who lost graft function in the EFA group and the other patients who received two transplants showed no evidence of allosensitization or developed only transient low level increases in antibody that resolved with repeated testing. These results persisted even after discontinuation of EFA in the EFA group. Because all of our patients continue to take some immunosuppressive drugs, the effect of complete immunosuppressive drug withdrawal on allosensitization in this cohort is not known; nonetheless, these findings provide preliminary evidence that the risk of allosensitization after islet transplantation can be reduced with this immunosuppressive regimen.

A central aspect of this study was to determine the safety and tolerability of the immunosuppressive regimens used in these patients. Previous trials with these drugs in transplant and nontransplant settings showed an increased incidence of PML and posttransplant lymphoproliferative disorder (PTLD), particularly when higher doses and longer duration of treatment were used (20, 29, 30). To minimize the risk of these events, we used a BELA dose that corresponded to the “less intensive” regimen reported in the phase II/III kidney transplant trials and in the follow-up study of the phase II trial where it was well tolerated for over 5 years after transplantation without any additional cases of PTLD or PML (20, 31). Similarly, we used the lowest dose of EFA that provided effective coating the CD11a ligand and which had not been associated with the development of PML or PTLD in previous trials (19, 32). By using these dosing regimens, we did not observe any cases of PTLD or PML throughout the follow-up period, and none of our patients developed serologic or radiographic evidence of infection on serial examinations. Interestingly, the risks of PML and PTLD are well established with several other currently used immunosuppressive drugs such as MMF, rituximab, prednisone, and antithymocyte globulin (33–36).

In summary, this study describes two novel immunosuppressive strategies for achieving insulin independence after islet transplantation that do not rely on CNIs or other nephrotoxic and β -cell toxic immunosuppressive agents. Both of these protocols are well tolerated, allow establishment of independence after single islet transplantation, and minimize allosensitization. In particular, our early results suggest that BELA may be an attractive immunosuppressive agent for future protocols involving islet transplantation. On the basis of our findings and those of other investigators demonstrating the potential benefits of these

drugs, we believe that judicious use of these agents in closely controlled trials of organ transplantation continues to be warranted.

Materials and Methods

Patients

Patients were considered eligible for transplantation if they met the following criteria: (1) more than or equal to 5 years of insulin-dependent type 1 diabetes mellitus; (2) stimulated C-peptide levels less than 0.5 ng/mL; (3) severe hypoglycemic episodes requiring assistance by another person for treatment or hospitalization despite management by an experienced diabetologist; (4) body mass index less than 28 kg/m² or weight less than 80 kg; (5) insulin requirements less than 55 units/day; (6) creatinine clearance more than or equal to 60 mL/min/m²; and (7) no history of malignancy within 10 years (except treated basal or squamous cell carcinoma of the skin). All study procedures were reviewed and approved by the institutional review board at the University of California, San Francisco, and all subjects signed informed consent after extensive discussions with the transplant staff. Both studies are registered at clinicaltrials.gov.

Islet Preparation and Transplantation

Pancreatic islets were purified from pancreata procured from deceased donors as described previously (17, 24, 37). Criteria for suitability for clinical islet transplantation included: more than or equal to 4000 IEQ/kg recipient body weight, viability more than or equal to 70%, purity more than or equal to 20,000 IEQ/mL settled tissue volume, settled tissue volume more than or equal to 15 cm³, glucose stimulated insulin release index more than or equal to 1.0, endotoxin levels less than or equal to 5.0 EU/kg recipient body weight, and negative gram stain of the islet culture fluid (24).

Islets were infused by percutaneous transhepatic portal vein catheterization as described previously (38). Patients who were not insulin independent 2 to 3 months after transplantation but who had detectable C-peptide were listed for second islet transplants.

Immunosuppressive Protocol

Induction immunosuppression in all patients consisted of antithymocyte globulin (thymoglobulin) and was initiated 2 days before islet transplant. A total of 4 mg/kg thymoglobulin was given intravenously (IV) in two divided doses on days 2 and 1 relative to transplant. A single dose of methylprednisolone was used as a premedication before the first dose of thymoglobulin. BELA-treated patients (n=5) received BELA at a dose of 10 mg/kg IV on days 0, 4, 14, 28, 56, and 75 after transplant, followed by 5 mg/kg IV every 4 weeks until 18 months after final transplant, at which time the dosing frequency was further reduced to 5 mg/kg every 8 weeks. This regimen corresponds to the "less intensive" regimen used in previously published kidney transplant studies (19). EFA-treated patients (n=5) received EFA at a dose of 1 mg/kg per week subcutaneously starting 1 day before transplant and continuing for 3 months after transplant, after which the dose was reduced to 0.5 mg/kg per week (17). Sirolimus was initiated on day 2 in both groups, and target serum trough levels were more than or equal to 8 ng/mL. Most patients were unable to tolerate these levels

and required dose reduction and addition of MMF (360–720 mg orally bid) to maintain adequate levels of immunosuppression. Patients who required second islet transplants received induction immunotherapy with basiliximab (20 mg IV on days 0 and 4 relative to transplant), continued maintenance dosing of sirolimus or MMF, and recycled EFA or BELA according to the dosing guidelines for the first islet transplant.

EFA was discontinued in all patients in May 2009 because of safety concerns as described previously. Since then, three EFA-treated patients have been maintained on sirolimus and MMF, one patient has been maintained on MMF monotherapy, and one patient has been maintained on tacrolimus and MMF. Our previously published report was a multicenter trial that also included three patients transplanted elsewhere (17). Because protocols after termination of EFA were center specific, this report only describes the University of California, San Francisco experience.

Assessment of Islet Function

Patients measured blood glucose levels three to five times per day throughout the study period and kept diaries of carbohydrate intake and insulin requirements. Graft function was assessed at each visit by reviewing blood glucose data and measuring fasting plasma glucose, C-peptide, and HbA1c. HbA1c levels greater than 6.4% are considered abnormal in our laboratory. Before transplant and at 3- to 6-month intervals after each transplant, subjects underwent MMTT and continuous glucose monitoring using a 24-hr glucometer (39, 40).

Assessment of Renal Function

GFRs were determined using iohexol infusion before islet transplantation and biannually after transplantation (41). Twenty-four hour urine collections were performed before transplant and biannually after transplant and analyzed for urine protein and albumin excretion and creatinine clearance. Protein and albumin excretion rates were considered abnormal if they exceeded 150 and 30 mg/24 hr, respectively (42, 43).

Immunologic Evaluation of Islet Recipients

Peripheral blood mononuclear cells were prepared from recipient blood samples obtained before and at various times after transplant and analyzed by flow cytometry for expression of CD3, CD4, CD25, CD127, FoxP3, and interferon- γ as described previously (17, 44).

Alloantibody Screening

Sera were obtained from all study participants before the first transplant and at regular intervals after transplantation and were screened for the presence of anti-human leukocyte antigen antibodies using the LABScreen protocol according to manufacturer's instructions (One Lambda Inc., Canoga Park, CA) (45).

Statistical Analysis

Data are expressed as a mean $\pm$ SD unless otherwise stated. Differences within groups were examined using analysis of variance. *P* values less than or equal to 0.05 were considered significant.

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Figure 1.
Duration of follow-up and insulin independence after islet transplantation in patients receiving a belatacept (BELA)-based or efalizumab (EFA)-based immunosuppressive regimen. *Time at which efalizumab was discontinued.

Figure 2.

Mean glomerular filtration rates (GFRs) in islet transplant recipients before (time 0) and at varying times after initial transplantation. *Vertical bars* depict standard deviations. Values within each group were not significantly different when compared by analysis of variance.

*This value represents the mean of the two patients who have reached the 365-day time point.

Table 1

Donor and islet characteristics

Donor	1	2	3	4	5	6	7	8	9	10	11	12	13
Recipient	BELA-1	BELA-2	BELA-3	BELA-4	BELA-5		EFA-1		EFA-2	EFA-3	EFA-4	EFA-5	
Age (yr)	18	31	46	44	46	37	37	33	17	38	17	48	29
Gender (M/F)	F	M	M	M	M	M	M	M	M	M	M	M	F
Weight (kg)	114	94	89	117	88	134	112	97	91	94	114	139	101
BMI (kg/m ²)	37.1	28.1	29.1	34.6	30.0	34.7	35.8	27.2	26.9	24.5	37.2	42.9	31.5
Cause of death	CVA	Trauma	Trauma	CVA	CVA	CVA	CVA	Trauma	Trauma	CVA	Trauma	Trauma	CVA
Cold ischemic time (hr)	6.0	8.0	6.0	7.0	3.3	7.2	5.0	7.0	7.5	7.0	7.0	7.5	7.5
Total purified IEQ	507,660	645,500	691,500	608,400	557,500	419,000	542,777	600,900	661,409	482,050	630,165	574,950	351,195
IEQ/kg body weight	7577	10,940	12,805	8112	17,665		17,226		11,023	8034	11,670	13,620	
Viability (%)	99.4	100	99.5	99.5	98	99.7	94	100	100	97	100	100	100
GSIR index pretransplant	2.3	2.7	10	2.1	1.1	1.3	6.9	5.2	1.2	1.3	1.9	2.6	2.3

BMI, body mass index; CVA, cerebrovascular accident; IEQ, islet equivalent; GSIR, glucose-stimulated insulin release; M, male; F, female; BELA, belatacept; EFA, efalizumab.

Recipient characteristics and posttransplant course

Table 2

Recipient characteristics										
Age (yr)	56	53	60	43	62	47	58	48	58	40
Gender (M/F)	F	F	F	M	F	F	F	F	F	F
Weight (kg)	67	59	54	75	55	68	60	60	54	68
BMI (kg/m ²)	24.7	23.6	19.1	29.3	21.2	25.4	21.3	25.6	19.2	24.9
Duration of diabetes (yr)	33	49	52	30	49	40	50	45	30	19
Pretransplant HbA1c (%)	8.7	6.5	7.6	8.4	7.6	6.7	8.2	7.3	8.0	6.7
Insulin use (U/d)	25	30	25	50	25	40	30	30	22	40
Pretransplant hypoglycemia (episodes/yr)	6	12	6	3	6	3	12	5	5	12
Complications of diabetes	Retinopathy	Autonomic neuropathy	Retinopathy, autonomic neuropathy	Retinopathy	Autonomic neuropathy	HTN	HTN Autonomic neuropathy, retinopathy	Autonomic neuropathy	HTN, autonomic neuropathy, retinopathy	Autonomic neuropathy
Posttransplant course										
Posttransplant hypoglycemic episodes	0	0	0	0	0	0	0	0	0	0
Insulin independent?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No
Duration of insulin independence after last islet transplant (d)	222	237	311	515	305/167	491	1019	850	1087	826
Duration of efalizumab therapy (d)	—	—	—	—	—	504	568	583	392	804
Duration off efalizumab (d)	—	—	—	—	—	450	467	462	720	450
Current immunosuppressive regimen	BELA, sirolimus, MMF	BELA, sirolimus, MMF	BELA, sirolimus, MMF	BELA, sirolimus, MMF	BELA, sirolimus, MMF	Tacrolimus, MMF	Sirolimus, MMF	Sirolimus, MMF	MMF	Sirolimus, MMF
Most recent class I / class II PRA (%)	0/0	0/0	0/0	0/0	0/0	0/0	0/0	2/0	0/0	2/0

BMI, body mass index; HTN, hypertension; PRA, panel reactive antibody; M, male; F, female; BELA, belatacept; EFA, efalizumab.