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Potent induction immunotherapy promotes long-term insulin independence after islet transplantation in type 1 diabetes

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Abstract

The seemingly inexorable decline in insulin independence after islet transplant alone (ITA) has raised concern about its clinical utility. We hypothesized that induction immunosuppression therapy determines durability of insulin independence. We analyzed the proportion of insulin independent patients following final islet infusion in four groups of ITA recipients according to induction immunotherapy: University of Minnesota recipients given FcR nonbinding anti-CD3 antibody alone or T cell depleting antibodies (TCDAb) and TNF- α inhibition (TNF- α -i) (Group 1; n=29); recipients reported to the Collaborative Islet Transplant Registry (CITR) given TCDAb +TNF- α -i (Group 2; n=20); CITR recipients given TCDAb without TNF- α -i (Group 3; n=43); and CITR recipients given IL-2 receptor antibodies (IL-2RAb) alone (Group 4; n=177). Results were compared with outcomes in pancreas transplant alone (PTA) recipients reported to the Scientific Registry of Transplant Recipients (Group 5; n=677). 5-yr insulin independence rates in Group 1 (50%) and Group 2 (50%) were comparable to outcomes in PTA (Group 5: 52%; $p >> 0.05$) but significantly higher than in Group 3 (0%; $p = 0.001$) and Group 4 (20%; $p = 0.02$). Induction immunosuppression was significantly associated with 5-year insulin independence ($p = 0.03$), regardless of maintenance immunosuppression or other factors. These findings support potential for long-term insulin independence after ITA using potent induction therapy, with anti-CD3 Ab or TCDAb+TNF- α -i.

Keywords

Islet transplant; Anti-thymocyte globulin; CD3; T-cell; Alemtuzumab; OKT3

INTRODUCTION

Type 1 diabetes mellitus (T1D) continues to present therapeutic challenges. Intensive insulin therapy reduces the risk of microvascular complications but is limited by an increased risk of life-impacting hypoglycemia (1). Some patients with long-standing T1D will develop unawareness of hypoglycemia, preventing achievement of goal glycemic control. Successful intraportal allogeneic islet transplantation can substantially reduce glycemic variability,

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eliminate severe hypoglycemia, re-establish hypoglycemia awareness, and permit insulin independence by restoring endogenous insulin secretion (2–5).

A majority of islet transplant recipients at experienced centers achieve insulin independence within the first year after transplant (2–4). Recipients are protected from severe hypoglycemia, the most common indication for islet transplant. However, early studies suggest a rapid loss of insulin independence beyond 1 year in many patients (2,3). Identifying transplant strategies which minimize the decline in insulin independence is critical to developing islet transplant as an effective therapeutic intervention for T1D.

Proposed factors contributing to islet graft decline include alloimmune rejection, autoimmune recurrence (6), immunosuppressive drug toxicity (7), and non-immunologic factors including exhaustion of a marginal beta cell mass (8). It is unclear whether manipulation of immune modulating therapies can prolong insulin independence. Most islet transplant recipients in the recent era received IL-2 receptor antibodies (IL-2RAB; daclizumab or basiliximab) for induction (2). Within this population, insulin independence declines significantly after one year (2,3). Another approach to induction therapy involves the administration of potent induction immunosuppression (PII) regimens, with either FcR-nonbinding anti-CD3 monoclonal antibody or the novel combination of anti-thymocyte globulin (ATG) or alemtuzumab combined with tumor necrosis factor-alpha inhibition (TNF- α -i) (9,10). These PII protocols target T-cells, while preserving or expanding regulatory T cells and their function, and minimizing cytokine toxicity on transplanted islets.

The mechanism by which these induction immunosuppression regimens may exert benefit is two-fold. First, PII may provide better early posttransplant protection of islets from innate and alloimmunity, thereby increasing the *engrafted* beta cell mass (11). Second, we speculate that these regimens may mitigate recurrent autoimmunity directed at transplant islets. This is supported by preclinical observations that T-cell depletion therapy reverses diabetes in NOD mice (12,13), and clinical studies documenting prolonged C-peptide production in type 1 diabetics receiving short-term monotherapy with anti-CD3 (14,15).

In the present study, we investigate the impact of induction immunosuppression on long-term insulin independence in islet transplant recipients at the University of Minnesota (UMN) and in the Collaborative Islet Transplant Registry (CITR), which represents the largest collection of islet transplant data available in the world to date. Those patients receiving anti-CD3 monoclonal antibody alone, or ATG or alemtuzumab plus TNF- α -i exhibited greater long-term insulin independence compared to patients treated with IL-2RAB. Outcomes are comparable to that seen with pancreas transplant alone (based on UNOS/SRTR data).

MATERIALS AND METHODS

Transplant cohorts

Islet allograft recipients meeting the following criteria were included in the analysis: 1) last islet infusion between 2002 to 2008, 2) at least one year of follow-up, and 3) at least 50% of primary endpoint data reported (based on November 2010 data lock). We analyzed outcomes in four groups of islet transplant alone ITA recipients according to induction immunotherapy: University of Minnesota recipients enrolled in single-center clinical trials (9,10,16) given FcR nonbinding anti-CD3 antibody teplizumab alone or the T cell depleting antibody (TCDAb) ATG and TNF- α -i with etanercept, with or without daclizumab (Group 1; n=29); recipients reported to the Collaborative Islet Transplant Registry (CITR) given TCDAb + TNF- α -i (Group 2; n=20); CITR recipients given TCDAb without TNF- α -i (Group 3; n=43); and CITR recipients given IL-2RAB alone (Group 4, n=177). Each

individual allograft recipient was analyzed in only one of the four groups. The patients from the University of Minnesota included in group 1 were excluded from groups 2 or 3 (CITR groups).

Results were compared with outcomes in pancreas transplant alone (PTA) recipients reported to the Scientific Registry of Transplant Recipients (Group 5; n=677), obtained for the UNOS/SRTR 2002–2007 5-year cohort from the 2009 SRTR Annual Report (http://optn.transplant.hrsa.gov/ar2009/data_tables_section6.htm).

ITA recipients received 1 to 6 donor infusions (1–3 in 98%). Selection of immunosuppression was at the discretion of the transplant center. Immunosuppression agents were coded as ever or never given and grouped in categories according to mode of action, over all infusions for a recipient. Maintenance immunosuppression, unless stated otherwise, consisted of a low-dose calcineurin inhibitor (tacrolimus, cyclosporine) with either mTOR inhibitor therapy (everolimus, sirolimus) or mycophenolate acid/mycophenolate mofetil.

Outcome Measures

The proportion of insulin independent patients (defined by no exogenous insulin use for 14 consecutive days) was determined at 1, 3, and 5 years following the final islet infusion in groups 1–4. Rates of insulin independence following PTA were obtained from UNOS/SRTR for pancreas graft survival, equivalent to euglycemia without the need for exogenous insulin therapy (UNOS/SRTR 2009 Annual Report Table 11) (17). Fasting C-peptide to glucose ratios (calculated as C-peptide (ng/ml) × 100 divided by glucose (mg/dl)) were evaluated at 28 days posttransplant, to reflect functional beta cell mass in the early post-transplant period. Autoantibody status at pretransplant baseline was defined by the following antibodies: glutamic acid decarboxylase antibody, insulin autoantibody, and islet cell antibody. Other outcome measures included complete graft failure (C-peptide < 0.3 ng/mL) and absence of severe hypoglycemic episodes (SHE) defined as requiring assistance by another person to restore euglycemia.

Statistical Analysis

Baseline characteristics were compared across the four groups. Continuous measures were compared by the Wilcoxon test and discrete measures by the chi-square test.

Insulin independence and severe hypoglycemia at follow up were analyzed as the percent of patients meeting the endpoint annually post last infusion; missing data was considered missing at random (i.e., deducted from both numerator and denominator). The data was analyzed by generalized estimating equation (GEE) models with repeated measures within subject to determine which factors were associated with insulin independence over time. Recipient, donor, and islet characteristics, plus transplant center and immunosuppression categories (cumulative for all infusions) were first analyzed univariately. Factors significant at p < 0.10 were included in multivariate models, and then stepped down at p < 0.05. Hazard ratios are reported for significant factors in final models.

RESULTS

Comparison of long-term insulin independence in ITA recipients treated with differing induction immunosuppression

Patient, donor, and islet graft characteristics are outlined in Table 1. The islet transplant groups did not differ in terms of baseline insulin use, weight, or BMI. Total IEQ transplanted was slightly lower and islet autoantibodies were more often positive in group 1.

Observed rates of insulin independence in UMN patients receiving PII were 74% at 1 year, 50% at 3 years, and 50% at 5 years. Forty percent were insulin independent at 10 years, although the number of cases that have yet reached this time point is small (n=2/5). Mean hemoglobin A1c levels were normal or near-normal in insulin independent recipients ($5.5\pm 0.4\%$ at 3 years, $5.6\pm 0.5\%$ at 5 years).

Insulin independence rates at 3 and 5 years post-last infusion (figure 1) are superior for the groups 1 and 2 (UMN and TCDAb+TNF- α -i) compared to group 3 (TCDAb without TNF- α -i) (p 0.01 at 3 yrs and 0.001 at 5 yrs) and group 4 (IL2R-Ab recipients) (p=0.05 at 3 yrs and 0.002 at 5 yrs), a difference which was sustained within the subset of autoantibody positive patients. Observed rates of insulin independence in groups 1 and 2 were 50% and 45% respectively at 3 years and 50% in both groups at 5 years. The proportion of insulin independence at 3 and 5 years in these two groups was comparable to that of PTA (group 5), based on registry data from SRTR (p>>0.05).

Insulin independence rates were significantly higher when TNF- α -i was given in the peritransplant period. TNF- α -i conferred substantial benefit with ATG or alemtuzumab induction (group 2), and marginal benefit with daclizumab (group 4) (Figure 2). TNF- α -i with anti-CD3 monoclonal antibody was never used.

Virtually everyone in group 2 (TCDAb+TNF- α -i) received calcineurin inhibition (CNI), while only about half of group 3 (TCDAb without TNF- α -i) received CNI. However, when subdividing group 3 by presence or absence of CNI, both CNI +/- groups experience substantial graft function losses over 5 years relative to group 2. Outcomes were poor in group 3, regardless of CNI use-- no patient in the CNI +subgroup and fewer than 10% of patients in the CNI- subgroup were insulin independent at 3 years, and none were insulin independent at 5 years. Hence, there is no evidence that the superior outcome in group 2 is due to the confounding effect of CNI.

Comparison of early post-transplant islet graft function, measured by fasting C-peptide to glucose ratios

The fasting C-peptide to glucose ratio at day 28 post-transplant was higher in group 1 (1.2 ± 0.1) as compared to group 3 (0.6 ± 0.1) and group 4 (0.8 ± 0.1 ; p 0.001). There was a trend toward higher C-peptide to glucose ratios in group 2 (0.9 ± 0.1) compared to group 3 (p=0.12) and group 4 (p=0.23). Long term retention of any graft function (C-peptide production 0.3 ng/mL) was greater when TNF- α -i was administered with TCDAbs (data not shown).

Reduction in severe hypoglycemia post-transplant

Severe hypoglycemic episodes were uncommon in all ITA recipients, regardless of induction therapy. Over 62% of ITA recipients suffered from severe hypoglycemic episodes pre-first transplant. In contrast, over 80% of ITA recipients in all groups at 1– 3 years posttransplant reported absence of severe hypoglycemia.

Adjusted analysis of effect of TCDAb and TNF- α -i on insulin independence

An adjusted analysis was performed to determine the relative impact of induction immunosuppression when accounting for potential confounding variables, including other immunosuppression and baseline characteristics (Table 1). Insulin independence decreased over time in all groups. TCDAb or anti-CD3 (p=0.03), TNF- α -i (p=0.03), and length of follow up (p<0.0001) emerged as significant variables associated with insulin independence regardless of other recipient, donor, graft, or immunosuppression variables. None of the

donor, islet or recipient pre-infusion characteristics included in the model blunted or explained the effects of T-cell depletion or TNF- α -i on insulin independence.

DISCUSSION

The decline in insulin independence rates beyond 1 year after alloislet transplant for T1D has raised concern about the therapeutic value of islet allografts. Proposed factors contributing to islet loss include non-immunologic injury such as amyloid-mediated islet apoptosis (18) and immunologic factors such as recurrent beta cell autoimmunity (6,19). We demonstrate here that patients receiving potent induction immunosuppression, with FcR non-binding anti-CD3 or either ATG or alemtuzumab with TNF- α inhibitors, are more than twice as likely to maintain long-term insulin independence for 5 years post-transplant compared to those receiving IL-2 receptor antagonists, despite the fact that only a single donor pancreas was utilized in over 70% of group 1 recipients. Such regimens may benefit long-term outcomes through improved engrafted islet mass and minimization of recurrent autoimmunity. Insulin independence rates in these recipients approach those seen in PTA. These data demonstrate the potential for sustained insulin independence after alloislet transplantation for T1D and highlight the importance in selection of induction immunosuppression.

Initial reports evaluating long-term insulin independence in islet allotransplant recipients receiving IL-2RAb suggested frequent return to insulin dependence after one year post-transplant, with ~10% of recipients insulin independent at 5 years (2). The present analysis shows half of patients treated with PII maintained insulin independence through 5 years, a proportion comparable to that seen in PTA recipients.

Although much research has focused on the immunologic factors contributing to islet loss, non-immunologic factors, in particular the exhaustion and decline of a marginal mass likely play a role (20). Constant overstimulation of an inadequately low islet mass causes endoplasmic reticulum stress-mediated islet apoptosis (21,22), a potential mediator of gradual islet loss. This is supported by recent observations of wide spread amyloid deposition in transplanted human islets (18), as well as observations of gradual loss of insulin independence in islet autotransplants (which are not subject to immune destruction) in canines (23) and in humans with a marginal islet mass (<2500 IEQ/kg) (24). Under this reasoning, the transplanted and engrafted islet mass in IL-2RAb-treated patients was borderline adequate to facilitate short-term insulin independence but insufficient to sustain long-term graft survival. In contrast, we hypothesize that sustained islet graft survival is achievable in patients receiving PII, through engraftment of a higher proportion of transplanted islets.

Early studies in alloislet transplant documented sustained insulin independence primarily in the context of multiple donor infusions to increase transplanted beta cell mass (3,5,25). Induction immunosuppression regimens that inhibit innate and adaptive immunity protect islets from immune-mediated destruction early posttransplant and thereby increase engrafted beta cell mass, insulin secretory capacity, and islet reserve. Single center trials have documented achievement of insulin independence with fewer islets and sustained insulin independence with a single islet donor when induction was comprised of anti-CD3 or TCDAb and TNF- α -I (9,10,26). Insulin secretory capacity in response to glucose-potentiated arginine (a surrogate marker of beta cell mass) is superior in patients receiving TCDAb + TNF- α -i compared to IL-2RAb induction immunosuppression (11).

We postulate that these PII regimens may have further benefit through their effect on the autoimmune process of T1D. Autoimmunity has been identified as one cause of pancreas

transplant failure, as evidenced by autoreactive T cells and insulinitis in pancreas allografts (27). In animal models, islets are even more susceptible to recurrent autoimmunity (28,29). In clinical islet transplant recipients, the presence of T-cell autoreactivity to β -cell antigens is associated with failure to achieve or delayed achievement of insulin independence (19). Whole organ are much less prone to recurrent autoimmune destruction than islet grafts in immunosuppressed recipients, presumably due to immunomodulatory effects of donor T cells co-transplanted with peripancreatic lymph nodes (29). Thus, islet transplant protocols must adequately protect from recurrent autoimmunity for optimal success.

Anti-CD3, ATG, and alemtuzumab may manifest a long-term benefit through restored self-tolerance. In clinical trials for new onset T1D, short-term monotherapy with anti-CD3 monoclonal antibody has resulted in sustained superior C-peptide production and lower insulin requirements (14,15). In contrast, no such benefit was observed in recent onset T1D patients receiving the IL-2RAb daclizumab plus mycophenolate mofetil (30). In pancreas transplant recipients, although daclizumab suppressed β -cell autoimmunity while sparing T cell memory responses to bacterial and viral antigens, the effect was short-lived, limited to the duration of drug action; in contrast, ATG resulted in prolonged alteration of the cellular autoreactivity, for >1 year after drug administration (31).

The mechanism for prolonged abrogation of autoimmunity likely relates to the potential of these agents to enhance T regulatory cells (Tregs) and shift the balance of Tregs and memory T-effector cells towards a more tolerant phenotype (13,32–36). Treatment with anti-CD3 mAb or anti-lymphocyte serum in NOD mice restores self-tolerance to beta-cell antigens and results in prolonged reversal of diabetes (12,13). Both agents can induce expansion of foxp3+ CD4+CD25+ and, in the case of anti-CD3, also CD8+CD25+ T-regs (13,32–34). This effect of ATG is preserved or even enhanced in the presence of tacrolimus (35). Islet transplant recipients treated with alemtuzumab had an increase in CD4+foxp3+Tregs that was not seen with daclizumab (36).

Co-administration of TNF- α -i at induction resulted in a greater likelihood of insulin independence in the multivariate model, particularly when ATG or alemtuzumab were used for induction. TNF- α -i may mediate this benefit by two proposed mechanisms. First, TNF- α -i may prevent the detrimental effects of cytokine exposure at the time of islet infusion. TNF- α exposure is known to be cytotoxic to human islets in culture (37), and innate immunity—including cytokine toxicity—in the peritransplant period is one proposed contributor to islet loss (38). In heart allograft models, TNF- α -i substantially reduces early leukocyte infiltration of the allograft and prolongs graft survival (39). The protective effect of TNF- α -i may be more important with an agent such as ATG, which is well known to induce a cytokine release syndrome in the recipient (40). Second, TNF- α -i may have a sustained impact on autoimmunity. The timing of TNF- α -I exposure is likely critical. TNF- α -i increases Tregs and completely prevents onset of autoimmune diabetes in NOD mice only if given in the neonatal period but not when administered later (41,42). Similarly, TNF- α -i may be particularly effective when given peritransplant (i.e. during the initial period of antigen exposure).

This is the largest study to date reporting such a sustained benefit of induction therapy in islet transplantation. One limitation is that results derive from a voluntary, although audited, registry rather than a controlled trial. In order to account for this limitation, we controlled for potential confounders in a multivariate analysis that included patient and islet graft characteristics, concurrent maintenance immunosuppression, and transplant center. We acknowledge that there are some limitations inherent in the registry despite the controlled analysis. Patients were categorized as ever treated with a particular immunosuppression agent over time, and were not able to account for changes in maintenance

immunosuppression and/or adequacy of immunosuppression (trough levels). The number of patients, although large for the islet transplant field, is small within the subgroups and diminishes over time. In addition, mechanistic data, including cellular autoimmunity assays are not available for these recipients. Although autoantibody data is contained within the registry, autoantibodies are poor markers for the presence of active autoimmunity (19).

The comparison between the CITR islet transplant and the UNOS/SRTR whole pancreas alone data is limited by the use of two separate data registries, and results must be carefully interpreted within this context. While not randomized, this comparison is concurrent and based on the most complete data available. Both CITR and UNOS/SRTR collect similar data in transplanted type 1 diabetic recipients, particularly with regards to insulin independence, and provide the best opportunity for comparison of these two groups outside a clinical trial. Notably, this analysis was restricted to islet transplant alone versus solitary pancreas transplant (without kidney transplant) for this analysis, in order to maintain comparability.

In conclusion, these results highlight the potential for prolonged insulin independence after alloislet transplant when potent induction immunosuppression is used, and emphasize the critical impact of induction immunosuppression on long-term islet graft function. Prolonged insulin independence was superior in alloislet transplant recipients receiving PII, with either FcR non-binding anti-CD3 monoclonal antibody alone, or ATG or alemtuzumab plus TNF- α -i for induction immunosuppression compared to IL-2RAb induction. This benefit may in part be mediated by improved islet engraftment and mitigation of autoreactive T cell responses. These results show that with potent induction strategies, intraportal alloislet grafts can provide prolonged glycemic benefits in selected recipients, approaching those seen with solitary vascularized pancreas grafts, with a far less invasive impact.

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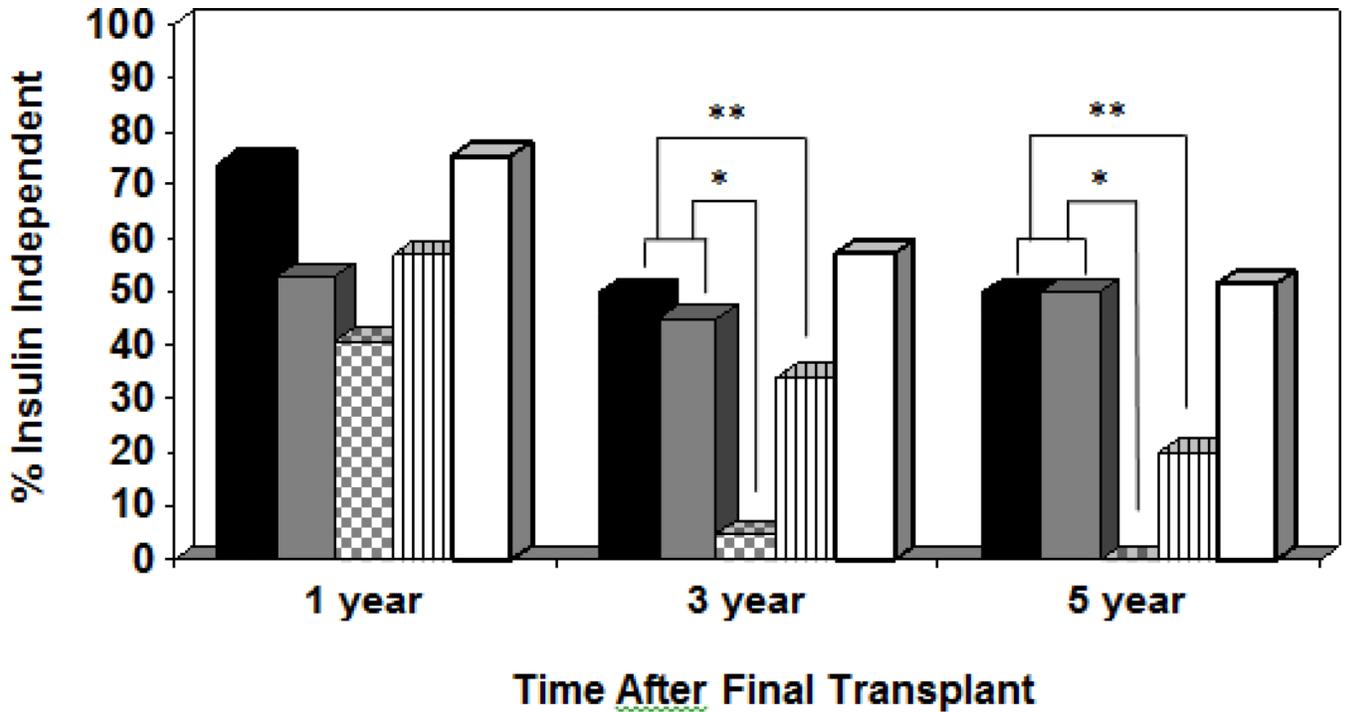
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| Ns | 1 year | 3 year | 5 year |
|-----------------------------------|--------|--------|--------|
| Group 1 (UMN) | 27 | 22 | 20 |
| Group 2 (TCDAb+TNF- α -i) | 17 | 11 | 4 |
| Group 3 (TCDAb- TNF- α -i) | 34 | 17 | 7 |
| Group 4 (IL2RAb) | 171 | 146 | 105 |

Figure 1.

Observed insulin independence in pancreas transplant alone and in islet transplant alone recipients based on induction immunosuppression administered. Islet transplant groups are indicated as follows: group 1 (UMN recipients, solid black), group 2 (CITR recipients receiving TCDAb +TNF- α -i, solid grey), group 3 (CITR recipients receiving TCDAb without TNF- α -i, grey checkered), group 4 (CITR recipients receiving IL-2RAb, vertical lines), group 5 (pancreas transplant alone recipients, white). Insulin independence was superior in groups 1 and 2 compared to groups 3 and 4 at 3 and 5 years posttransplant; groups 1 and 2 did not differ statistically from pancreas transplant alone (group 5).

* p<0.01; ** p 0.05

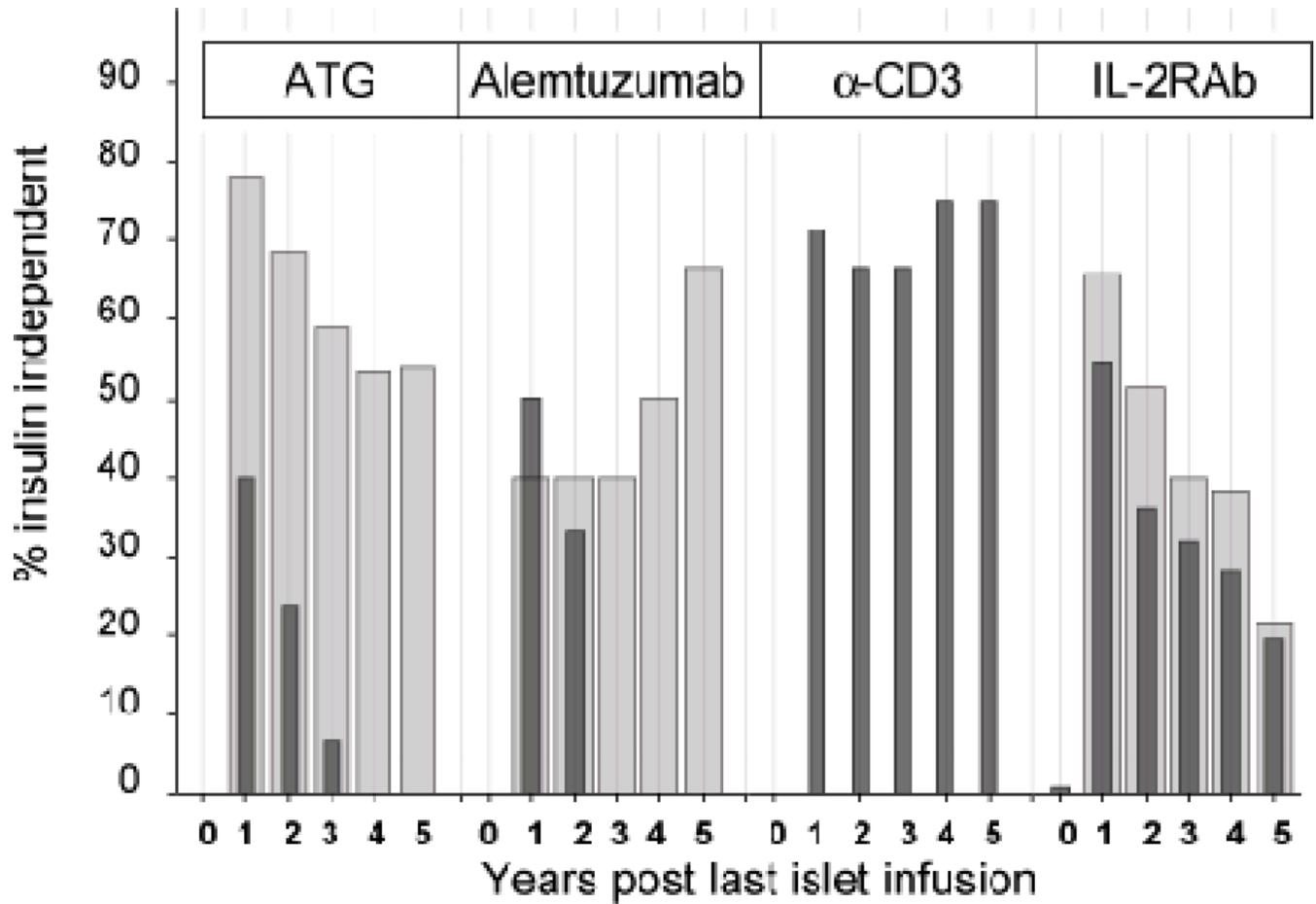


Figure 2. Insulin independence by induction agent, in the presence of TNF-alpha inhibitor therapy (wide bars) or absence of TNF-alpha inhibitor (narrow bars). Insulin independence was significantly lower at every time point in the ATG group in the absence of TNF-alpha inhibitor as compared to ATG with TNF-alpha inhibitor.

Table 1
Baseline recipient characteristics, concomitant immunosuppression, and transplant characteristics

| Era | Group 1 UMIN | | Group 2 CITR:TCO+TNF- α -i | | Group 3 CITR:TCO+TNF- α -i | | Group 4 CITR:IL2RAB | | PTA N (%) or Mean \pm SE | p ^{\$} |
|---|---------------------------|---------------------------|--------------------------------------|---------------------------|--------------------------------------|---------------------------|---------------------------|--|----------------------------------|-----------------|
| | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | | | |
| 1999–2003 | 29 16 (55%) | 22 3 (14%) | 41 3 (7%) | 177 86 (46%) | 1104 341# | <0.01 | | | | |
| 2004–2006 | 4 (14%) | 11 (50%) | 10 (24%) | 78 (44%) | 555 | | | | | |
| 2007–2009 | 9 (31%) | 8 (36%) | 28 (68%) | 18 (10%) | 208 | | | | | |
| Patient characteristics | | | | | | | | | | |
| Age at transplant (yrs) | 40.6 \pm 1.4 | 45.2 \pm 1.5 | 44.3 \pm 1.6 | 44.1 \pm 0.8 | 33.3 \pm 7.1 | NS | | | | |
| BMI (kg/m ²) | 23.6 \pm 0.5 | 23.6 \pm 0.5 | 23.2 \pm 0.5 | 23.0 \pm 0.2 | - | NS | | | | |
| Weight (kg) | 64.2 \pm 1.7 | 63.6 \pm 1.6 | 65.0 \pm 1.6 | 64.9 \pm 0.8 | - | NS | | | | |
| Insulin Use (u/day) | 0.5 \pm 0.01 | 0.6 \pm 0.01 | 0.5 \pm 0.01 | 0.5 \pm 0.01 | - | NS | | | | |
| Female | 23 (79%) | 14 (64%) | 28 (68%) | 104 (59%) | 670 (60.7%) | NS | | | | |
| Presence of SHE | 29 (100%) | 17 (77%) | 31 (76%) | 137 (77%) | - | NS | | | | |
| Immunosuppression, induction | | | | | | | | | | |
| Anti-thymocyte globulin | 18 (62%) | 14 (64%) | 36 (88%) | .. | 537 (48.6%) | ** | | | | |
| Alemtuzumab | - | 6 (27%) | 5 (12%) | | 267 (24.2%) | | | | | |
| Anti-CD3 mAb | 11 (38%) | 2 (9%) | | | 36 (0.3%) | | | | | |
| IL-2 receptor antagonists | 14 (48%) | 10 (46%) | 7 (17%) | 177 (100%) | 164 (14.9%) | | | | | |
| TNF alpha inhibitors | 15 (51%) | 22 (100%) | .. | 29 (16%) | - | | | | | |
| Other immunosuppression in first month post-transplant | | | | | | | | | | |
| IMDPH (mycophenolic acid) | 3 (10%) | 14 (64%) | 34 (83%) | 28 (16%) | (58.6%) | <0.01 | | | | |
| m-TOR inhibitors | 28 (97%) | 17 (77%) | 26 (63%) | 173 (98%) | (16.5%) | 0.03 | | | | |
| Calcineurin inhibitors | 25 (86%) | 22 (100%) | 21 (51%) | 176 (99%) | (91.6%) | 0.04 | | | | |
| Efalizumab | 3 (10%) | | 5 (12%) | 12 (7%) | | NS | | | | |
| Infusions | | | | | | | | | | |
| 1 | 21 (72%) | 8 (36%) | 14 (34%) | 36 (20%) | - | <0.01 | | | | |
| 2 | 7 (24%) | 8 (36%) | 18 (44%) | 81 (46%) | - | | | | | |
| 3 | 1 (3%) | 4 (18%) | 8 (20%) | 59 (33%) | - | | | | | |

| | Group 1 UMN | | Group 2 CTTR:TCD+TNF- α -i | | Group 3 CTTR:TCD-TNF- α -i | | Group 4 CTTR:IL2Rab | | PTA N (%) or Mean \pm SE | p [§] |
|------------------------------------|---------------------------|---------------------------|--------------------------------------|---------------------------|--------------------------------------|---------------------------|---------------------------|---|----------------------------------|----------------|
| | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | N (%) or Mean \pm SE | | | |
| 4 | .. | 2 (9%) | 1 (2%) | 1 (0.6%) | - | - | - | - | 0.01 | |
| Cumulative IEQs (*100,000) | 614 \pm 46 | 889 \pm 88 | 908 \pm 87 | 906 \pm 32 | - | - | - | - | 0.01 | |
| Donor/Graft Characteristics | | | | | | | | | | |
| <i>Donor BMI</i> | 34 \pm 1.5 | 31.1 \pm 1.1 | 29.7 \pm 0.9 | 29.0 \pm 0.4 | - | - | - | - | 0.003 | |
| <i>Donor age</i> | 32 \pm 3 | 45.1 \pm 2.1 | 45 \pm 3 | 43 \pm 1 | - | - | - | - | <0.001 | |
| <i>Cold Ischemia Time</i> | 6.0 \pm 0.5 | 6.8 \pm 0.4 | 6.8 \pm 0.4 | 7.5 \pm 0.2 | 12.2 \pm 3.5 | NS | - | - | NS | |
| <i>Packed cell volume</i> | 5.0 \pm 0.8 | 7.7 \pm 0.9 | 7.7 \pm 0.9 | 8.4 \pm 0.4 | - | - | - | - | 0.02 | |

*The 2009 UNOS/SRTR Report did not include any transplants done in 2009.

Abbreviations: SHE= severe hypoglycemic episodes; IMDPH= ionosine monophosphate dehydrogenase, including mycophenolic acid and mycophenolate mofetil; m-TOR= mammalian target of rapamycin and includes sirolimus and everolimus. TNF- α = tumor necrosis factor- α ; TNF- α inhibitors include etanercept and infliximab. Calcineurin inhibitors include tacrolimus and cyclosporine. T-cell depleting agents include anti-CD3 monoclonal antibodies, anti-thymocyte globulin, alemtuzumab.

**These define the study categories, hence testing is not necessary.

§ p-values relate to differences among the islet transplant groups (do not include the PTA)

#Results are shown here and in Figure 1 for TPAs done in 2002–2007, comprising the 5-year cohort of US Scientific Registry of Transplant Recipients, thus, TPAs transplanted in 1999–2001 are not included.