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Islet cell transplant: Update on current clinical trials

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Abstract

In the last 15 years clinical islet transplantation has made the leap from experimental procedure to standard of care for a highly selective group of patients. Due to a risk-benefit calculation involving the required systemic immunosuppression the procedure is only considered in patients with type 1 diabetes, complicated by severe hypoglycemia or end stage renal disease. In this review we summarize current outcomes of the procedure and take a look at ongoing and future improvements and refinements of beta cell therapy.

Keywords

Clinical trials; Pancreatic Islet transplantation; Type 1 Diabetes mellitus; Immunosuppression; clinical outcomes; Registry

Introduction

Evolution of clinical Islet transplantation

Type 1 Diabetes has evolved from being a fatal diagnosis to becoming a manageable chronic condition. The discovery and immediate commercialization of insulin in 1920 was seen as a cure at the time[1]. As a result, experimental attempts to replace pancreatic tissue[2] were abandoned. A few decades later it became apparent that exogenous insulin therapy, while averting death from dehydration, could not prevent hitherto unknown secondary complications such as diabetic nephropathy, retinopathy and neuropathy. Furthermore, exogenous insulin bears the inherent risk of inducing severe hypoglycemia. These findings rekindled interest into β -cell replacement therapy, leading to the development of protocols for islet isolation[3-5] and the successful restoration of euglycemia by islet transplantation in mice[6].

Clinical islet transplantation dates back as far as 1977[7], but the first two decades of clinical transplants were met with rather unsatisfactory results. A total of 355 patients had been transplanted before the year 2000 but only 11 % of 237 documented recipients were insulin

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independent > 1 year and the longest insulin independence of nearly 6 years was achieved after simultaneous islet and kidney transplant[8]. The group at the University of Alberta reported a consecutive series of 7 recipients that were insulin independent after a median follow up of 11.9 months[9]. This unprecedented success was attributed mainly to the avoidance of steroids for immunosuppression (IS) and minimization of Calcineurin inhibitors to prevent diabetogenicity of these drugs. The grafts were ABO compatible but not HLA matched, and recipients were not sensitized pre-transplant (negative panel reactive antibody (PRA)). The Edmonton IS regimen consists of Daclizumab for induction, Sirolimus and a low dose of Tacrolimus for maintenance. In addition to this new IS regimen, all recipients received at least two infusions of different donors to achieve a mean total islet mass of 13,000 IEQ/kg body weight. Henceforth it became known as the Edmonton protocol which was put to a broader test in the international, multicenter Edmonton trial[10].

The results after 5 years of this Phase 1/2 trial dampened expectations and hopes that were raised by the initial series of 7 patients as only 44% of recipients achieved insulin independence at 1 year[10]. The trial results further highlighted that despite considerable rates of insulin independence at 1 year follow up, the islet grafts exhibited a near linear and inexorable loss of potency over time with only 31% of the initially insulin independent recipients remaining off insulin after 2 years, corresponding to 14% of all transplanted patients[10]. Nevertheless, partial graft function was retained in 67% of the recipients. The benefits of partial islet function are not to be underestimated as it has been shown to prevent the acute complications ketoacidosis, severe hypoglycemia as well as reducing long term secondary complications and reducing glycemic variability, facilitating diabetes management[11-13]. It was further noted that outcomes varied greatly between centers which was attributed to different level of experience with islet isolation, - transplantation and Sirolimus maintenance IS. Subsequently, the newly founded Clinical Islet Transplantation Consortium (CIT) collaborated to write a set of consensus Standard Operation Procedures (SOP) to be used by all north American islet transplant centers for forthcoming clinical trials. The detailed protocols can be found online at www.isletstudy.org.

The reasons for the observed slow but intractable attrition of islet function remain elusive and is likely multifactorial[14]. Non-invasive Imaging studies of the transplanted islet mass are not yet routinely available clinically[15, 16] but have provided valuable insight into islet survival and engraftment early following infusion[15-21]. The observed early loss of transplanted islet mass has been estimated to be up to 70%[21]. This considerable early graft loss, can be explained by experimental evidence of Instant Blood Mediated Inflammatory Reaction (IBMIR) after portal vein infusion. Mechanistically, this reaction has been ascribed to the action of activated platelets, Complement and cytokines [22, 23]. Following the engraftment period, islet graft loss appears to be a much more gradual process that is thought to be caused by a combination of factors including allogeneic rejection, recurrent autoimmunity, toxicity of immunosuppressive drugs, cellular hypoxia, insufficient revascularization and reinnervation[14]. In this review we will discuss several clinical trials which aim to overcome some of these factors.

Current outcomes of clinical islet transplantation

Clinical islet transplantation has continuously advanced over the last 15 years, with clear improvements in islet manufacturing and clinical outcomes[24]. Nevertheless, the ultimate objective of a durable, curative therapy for all patients with Type 1 Diabetes remains elusive for allogeneic islet transplantation. Currently the procedure is primarily indicated for patients with a history of life threatening, severe hypoglycemia and hypoglycemia unawareness for which Islet transplantation has been highly effective both in the short and long term[24-26]. Importantly, this effect is independent of insulin independence but does correlate with existing graft function[26]. Kidney transplantation, either simultaneously or preceding an islet transplant is an ideal setting for either pancreas or islet transplantation as it does not incur the added risk of immunosuppression since kidney patients are already obligated to lifelong treatment with these drugs. Importantly, β -cell replacement therapy has been shown to ameliorate a decline in kidney function[27, 28].

Outcome improvement over the last decade is attributed to both refinement of the production of islets from allogeneic donors and evolution in the management of the recipient during and after the transplantation procedure. In North America, the collaborative approach of the CIT has led to incremental improvements and standardization of the islet isolation procedure resulting in less failed isolations and higher Islet yields[24]. The success of the Edmonton protocol demonstrated the central importance of IS and further trials using T-cell depleting induction therapy, TNF- α and various maintenance IS drugs further improved islet transplant survival[29-32]. While it has been widely presumed that the Liver is a suboptimal transplantation site, an alternative site with better engraftment and function has yet to be identified in preclinical and clinical studies. However, recent reports using the omentum[33], bone marrow[34] and an extracorporeal, oxygenated device[35] in patients are promising.

According to the most recent public presentation from the Collaborative Islet transplant registry (CITR), 1,055 allogeneic islet transplantations have been reported by 50 islet transplantation centers in North America, Europe, Australia and South Korea(IPITA,IXA,CTS Joint conference in Melbourne 2015)[26]. Of these cases, islet transplant alone (ITA) was the most frequent procedure (n=858) followed by islet after kidney (IAK) and simultaneous islet and kidney transplantation (SIK) (n=197). The number of allogeneic islet transplants has fluctuated since the year 2000, with peaks in the 2000-2005 period and 2009-2012. In the most recent years, the numbers have waned with only about 35 reported cases in 2014 compared i.e. to approximately 110 transplants in 2011. In contrast, the number of reported autologous Islet transplants has continuously increased between 2007 and 2013 to a current total of 707 cases. Interestingly, this recent decline is evident both in the North American and European/Australian cohorts. While Canada has established reimbursement of the procedure by health insurance providers[36], it continues to be considered an experimental treatment in the United states. Since the NIH funding for experimental clinical islet transplantation has lapsed, there currently is no funding for allogeneic islet transplants available which may explain the reduced activity in North America. In Europe and Australia, the procedure is generally reimbursed for the indication of hypoglycemia unawareness.

Multivariate analysis of the CITR data has identified factors that predict the achievement and maintenance of insulin independence as recipient age over 35 years, more than half a million infused IEQ, islet stimulation index >1.5, induction therapy with T-cell depletion and TNF α Inhibitor and maintenance with calcineurin inhibitor and mTOR inhibition. The combination of these factors in 60 recipients resulted in stable insulin independence after 5 years in 60% of the patients. Recipient age, IEQ and CNi maintenance were also predictive of positive c-peptide levels (>0.3 ng/ml; N=308) and HbA1c (<6.5% or drop >2%; n=530) and age and IEQ predicted absence of SHE (>90% of patients at 5 years). As another indicator of improvements in the procedure, the number of adverse events has dropped significantly in the past 5 years, with 80% free of any AE[26].

A recently completed multicenter prospective phase III trial by the CIT, designed to provide evidence for efficacy of a standardized islet product suitable to gain FDA licensure, demonstrated that islets can be manufactured reproducibly using a common manufacturing process and insulin independence at 1 year can be achieved with 1-2 infusions in about half of the patients. Although gaining only 50% insulin independence may seem low, it is critical to understand that insulin independence was not the trial objective, rather absence of hypoglycemia with normalization of glycemic control (i.e. HbA1c) defined success even if patients required ongoing low dose insulin therapy. To this point, even when insulin independence is not achieved, glycemic control is improved and hypoglycemia unawareness is treated effectively [37•, 38]. The results of this trial will hopefully help to establish islet transplantation as standard of clinical care in the US, enabling reimbursement through private health insurances. Further validating these results, an Australian multicenter trial using the same endpoints, found similar results in 17 islet recipients[39]. The primary endpoint of HbA1c <7% and cessation of severe hypoglycemia was reached by 82% of recipients, 53% achieved insulin independence for a median of 26 months and 35% were still insulin independent at the end of follow up[39]. In both trials a considerable total islet mass was transplanted (11,972 IEQ/kg and 15,366 IEQ/kg BW respectively) and IS was induced with rabbit-ATG and with Basiliximab for subsequent infusions. The US trial used Etanercept in addition to ATG and maintenance was achieved with Sirolimus and low-dose Tacrolimus, whereas recipients in the Australian trial received Tacrolimus and MMF for the first six months and were switched to Sirolimus and MMF after that. However, only half of the recipients tolerated the Sirolimus/MMF treatment[39].

Furthermore, the islet isolation procedure was standardized between institutions in both trials, and in the Australian trial the transplant was performed at a site remote from the islet isolation facility. As a result, and contrary to the Edmonton trial, the outcome between the different sites was comparable[37•, 39, 40]. The concept of a centralized isolation facility with several satellite institutions that perform the transplant procedure has successfully been realized in several countries, including Switzerland/France (GRAGIL network)[41], the United Kingdom and Scandinavia (NORDIC network)[42]. Despite concerns regarding cold ischemia times and prolonged operative times, the remote processing and transplantation of donor pancreata for autologous and allogeneic has had no significant negative effects on outcome[43-48]. The comparable results between centers, with or without remote distribution, confirms the value of standardized protocols, such as the CIT SOP (www.isletstudy.org), and solved the variability between centers observed in the Edmonton

trial[10]. The development of a closed, nearly automated method with minimized user interaction may help to reduce variability in the manufacturing process even further and reduces the cost for islet manufacturing[49].

Immunosuppression protocols

As mentioned above, the choice of IS regimen has a significant influence on the outcome of islet transplantation. Firstly, the Edmonton protocol by virtue of using steroid free immunosuppression enabled the surge in islet transplantation in the last decade. Since then it has been recognized that the more potent induction therapy with T-cell depleting antibodies not only allows for successful single donor islet transplants but also improved long term outcomes[29]. Maintenance immunosuppression has also been shown to have a significant impact. The main drugs used for Islet transplantation are Tacrolimus and Sirolimus as in the Edmonton trial and more recently MMF (Mycophenolate mofetil), Belatacept and Efalizumab have been used. Of these, Efalizumab has shown the most remarkable impact on graft survival and insulin independence[30, 31, 50], while MMF was often used to replace Sirolimus to avoid adverse events and to protect the kidney from nephrotoxic effects. Efalizumab has enabled 90% insulin independence at 1 year and 70 % at 3 years with a mean duration of insulin independence of 35 months[30, 50]. The other trial using Efalizumab and MMF IS, achieved Insulin independence in all recipients with just one islet donor [31]. Unfortunately, Efalizumab was withdrawn from the market because of a rare incidence of progressive multifocal leukoencephalopathy (PML) after long term exposure to the drug when use in a non transplant setting. However, conversion of the Efalizumab treated islet recipients to Belatacept IS maintained the high rates of insulin independence, suggesting that the main effect of maintenance IS drugs may fall into the early post-transplant phase[50].

Transplant Site

The intraportal route for islet transplantation has been used almost exclusively in clinical procedures. It has been identified as a suitable site for islet transplantation after much trial and error in experimental models[51]. In the modern era of clinical islet transplantation, it has widely been recognized that the liver may not represent the ideal site for islet transplantation[14]. It is inaccessible for safe graft biopsy[52] and removal of the graft is impossible. Furthermore, it does not seem to allow for optimal engraftment, due to high levels of IS in the portal circulation and the effect of IBMIR[53, 54]. However, thus far no alternative site has conclusively shown to be superior to the liver for islet transplantation. Most recently, a minimally invasive approach to implant islets laparoscopically into an omental pouch and immobilizing them with coagulated serum has been successfully performed in a single patient[33]. Another group used the Bone marrow as an immunoprivileged site for islet transplantation[34]. An external, oxygenated and perfused device has also shown promising result in a single patient leading to an ongoing trial with an implantable form of this device(Table 1)[35, 55]. Finally, the intramuscular site has always been considered highly desirable due to its easy accessibility and well oxygenated environment. While it has been used very successfully to transplant parathyroid glands, results with islet cells have been very disappointing. The intramuscular site has recently been revisited and following promising experimental results and in a single patient[56] this

is now being tested in broader clinical trials in Europe (Table 1). Finally, the gastric submucosa has been used to transplant islets endoscopically in pigs and is now being tested in a clinical trial at UCSF (Table 1) [56-58]. This site is attractive also due to its easy accessibility and for its desirable portal drainage but it remains to be shown whether the space is large enough to accommodate islet grafts in humans.

While these preliminary results of alternative clinical transplant sites are encouraging, larger clinical trials will be needed to show their safety and efficacy. Lastly, encapsulation in various forms has been investigated intensively over the past 30 years. Despite promising results in rodents with normoglycemia reported mainly for fasting blood glucose but not convincingly showing improvement of overall glycemic control, no effective reversal of diabetes has been demonstrated in large animal models or man. It is conceivable that the diffusion barrier for nutrients, glucose and secreted insulin is counterproductive and even detrimental to the function and viability of the encapsulated cells. Despite these considerable shortcomings, macroencapsulation is currently being used to test the safety and efficacy of embryonic stem cell derived pancreatic progenitors as it allows containment and potential retrieval of the graft in case of malignant transformation [59, 60].

Prevention of severe hypoglycemic events (SHE)

Recent clinical trial results have shown that islet transplantation is highly effective in preventing severe hypoglycemic events (SHE) and restoring hypoglycemia awareness [25, 28, 37•]. It has been recognized that 4-14.5% of type 1 diabetes related mortality is attributed to severe hypoglycemic events [61-63] and the risk of death is increased 3.4 fold 5 years after a single episode [61, 64]. Therefore, a history of SHE justifies the use of IS when other treatment modalities have been exhausted [25]. It is unclear what causes hypoglycemia unawareness and how islet transplantation may restore the physiological reaction. Behavioral changes, such as early intervention aided by continuous glucose monitoring also have the potential to restore hypoglycemia awareness in a majority of patients [25, 65-68]. However, in between 20 and 50% of patients such interventions fail to prevent SHE [25, 66] and nearly 30% required beta-cell replacement therapy [66]. Behavioral and technology aided therapy to prevent SHE may come at the expense of deteriorating HbA1c levels, as levels of up to 8% are tolerated [25, 69]. Nonetheless, recent trials have shown that a reduction of severe hypoglycemia can be achieved with a concomitant improvement in HbA1c levels [66, 68, 70]. Though, the median HbA1c levels were above the primary endpoint of islet transplantation trials (~7.6%) [70]. Large cohort analyses found the lowest incidence of SHE in a HbA1c range between 7-7.5% [71] with an unexpected increase of SHE with HbA1c >7.5% [71, 72]. This illustrates the barrier of hypoglycemia to safely achieving normal glycemic control with exogenous insulin therapy [73]. In addition, treatment failures in preventing SHE are more common in these patients [66, 70, 72] than with islet transplantation. On the contrary, the fine-tuned insulin secretion achieved with islet transplantation is able to both prevent SHE in nearly all patients while achieving optimal glucose control with HbA1c <7% [24, 26, 37•, 74].

Finally, the restoration of hypoglycemia awareness may be due to a behavioral training effect based on early hypoglycemia intervention through conventional therapy or

transplantation rather than a direct effect of the islet graft. That would explain why some islet recipients continue to be protected from severe hypoglycemia even after the islet graft has failed, as determined by negative c-peptide levels[26].

With improved glycemic control and reduction of SHE, islet transplantation resulting in persistent graft function with or without insulin independence significantly improves the recipient's quality of life[75, 76]. The burden of daily diabetes management has been shown to be a significant cause of distress and depression in patients with Type 1 Diabetes[77-79]. This is probably most pronounced in patients that repeatedly experienced SHE and developed anxiety surrounding diabetes management[80].

Closing the gap with pancreas transplantation

The history of clinical pancreas transplantation reaches back to the 70s with a much more rapid adaptation in the clinical realm[3, 81]. The last 40 years have seen a constant improvement in pancreatic transplantation with outcomes superior to the early era of clinical islet transplantation[82]. Insulin independence rates after simultaneous Pancreas Kidney transplant (SPK) have increased from 77% in the time between 1987 and 1993 to 91.3% in 2010 to 2014[83, 84]. The improvements in islet transplantation over the last decade, mentioned above, have narrowed but not closed this gap[28, 50, 85]. On the one hand, pancreas transplantation continues to have a higher postoperative morbidity and requires more intensive IS with the known side effects while providing more robust insulin independence rates. However, when a pancreas graft fails it usually does so as a result of acute surgical or graft complications, necessitating surgical graft removal and resulting in immediate and complete loss of graft function. In Islet transplantation on the other hand, the loss of graft function tends to be progressing slowly and when patients return to exogenous insulin therapy patients continue to benefit from partial graft function by avoiding SHE and improving glycemic control. Unfortunately, islet transplant still requires multiple islet infusions which potentially increase the chance of immunologic sensitization and procedural costs. In comparison to pancreas transplants which usually requires a single donor per recipient, an average of 2 islet infusions is compounded by an isolation failure rate of approximately 50%[24, 86] equating to roughly four donors per islet recipient. A recent analysis has shown that the cost of multiple infusions is offset in the pancreas transplant cohort by the cost for re-hospitalizations and procedures for postoperative complications. Therefore, the cost for Islet transplantation and pancreas transplantation is similar[50, 87, 88].

An unresolved question is whether differences in outcome are a result of pancreas organ utilization and allocation policies. The utilization rates appear more favorable to islet transplantation where 40% of pancreata offered for islet transplantation were accepted[86], whereas only 17.6 % of pancreata from all organ donors are transplanted[89]. In addition, the allocation of donor organs is biased towards pancreas transplantation as donors with a BMI of $<30 \text{ kg/m}^2$ and aged <50 years are preferentially allocated towards whole organ transplant[90]; conferring organs of lesser quality to islet transplantation. In the UK, a more complex allocation scheme has been implemented which takes several factors into account, including wait times, sensitization, dialysis requirements as well as procedure relevant

factors such as donor age and BMI[91, 92]. This algorithm allocates pancreata more fairly by offering high quality pancreata for recipients of either procedure on a single waiting list. Interestingly, the scheme resulted in improved access to good quality organs for islet transplantation and an increase in islet transplant activity and at the same time increased the number of whole organ transplantation[91]. It remains to be seen whether equal access to donor organs will improve functional results of islet transplantation and help to bridge the gap.

Perhaps the focus on insulin independence rates for the outcome of both procedures is too restrictive as the differences between pancreas and islet transplantation are more nuanced[50, 85]. Unfortunately, there is still no prospective, randomized controlled trial available to compare the two treatment modalities; the studies mentioned above are of retrospective nature, thus, their evidential value is limited.

Outlook

The isolation procedure continues to evolve, with a notable recent approach to automate the procedure in a nearly closed system that cut processing time in half and thereby has the potential to further increase the quality of isolated human islets[49]. More experience with alternative transplantation sites that are more accommodating for islet graft engraftment, function and survival may be able to further improve long-term outcomes of clinical islet transplantation[34, 35, 93, 94]. The encouraging results of trials using modern IS drugs in avoiding nephrotoxicity and other adverse events while allowing single donor islet transplantation and higher rates of long-term insulin independence suggest that with evolving IS, current outcomes can still be improved while shifting the risk/benefit ratio between IS and Insulin independence[95]. Recent research in diverse transplantation tolerance protocols may allow the transplantation of islet without IS[96-99].

Finally, alternative sources of pancreatic beta cells promise to make β -cell replacement therapy available to a much broader number of patients[60, 100-102]. The differentiation of pluripotent cells to β -cell progenitor cells[60] and, more recently, to cells more closely resembling mature human β -cells *in-vitro*[100, 102] is an ongoing scientific endeavor[103]. Nevertheless, the first clinical trial using allogeneic human embryonic stem cell derived pancreatic progenitor cells, contained in a macroencapsulation device, is underway[104, 105]. This trial will provide invaluable information about the feasibility of this approach and hopefully enable further clinical trials. However, whether metabolic function and graft survival can be achieved in the long-term using encased, allogeneic cells remains to be shown. A more attractive approach would be the use of freely transplanted, autologous iPS derived β -cell like cells[106, 107]. Another potentially replenishable source, porcine xenogeneic islets, have been at the forefront of a clinical translation of xenotransplantation[108, 109]. However, the immune barrier towards xenogeneic cells and tissues remain a formidable challenge. The first clinical trial using encapsulated porcine islets was met with no significant adverse events and limited efficacy[110]. The recent genetic revolution, facilitating genetic modification of donor animals, may reduce the immunogenicity and infectious risk and therefore renew interest in porcine islet transplantation[111-116].

Conclusion

In conclusion, summarizing the most recent available trial data, a realistic expectation from an allogeneic islet transplant is that >80 % will reach the combined endpoint of improved glycemic control as expressed by HbA1c <7% and a restoration of hypoglycemia awareness at 1 year. Whereas hypoglycemia awareness alone is restored and maintained long-term in nearly all patients[26]. Insulin independence can be maintained by about half of the recipients for up to 5 years in some cohorts [24, 26, 37•, 39]. Under ideal conditions, stable insulin independence can be maintained for 5 years in 60% of all patients[26]. C-peptide can be detected in 60-80% at 1 year and is maintained in about 30-60% at 5 years under non-favorable and favorable conditions respectively[26]. The present trial results strongly confirm the procedure's value in preventing SHE and restoring hypoglycemia unawareness while improving and stabilizing management of glycemia in a majority of recipients, irrespective of insulin independence. While insulin independence can be maintained in some cases to over 10 years[74, 117-119], only about a third of recipients are insulin independent after 5 years. It is likely that future refinements in the islet manufacture and transplantation procedure will lead to further improved outcomes. Lastly, the experience gained with isolated islet transplantation will be instructive for the clinical translation of alternative cell sources for β -cell replacement.

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Table 1
Overview of selected ongoing and recently completed clinical trials in islet transplantation

Trial ID	Study aim	Investigators	Phase / n=	Completion / Publications
Transplantation Site / Encapsulation				
NCT01722682	Bone marrow versus liver as site for islet transplantation (Phase 1 NCT01345227)	Ospedale San Raffaele	2 (RCT) 12	11/2016 [34, 99-101]
NCT02213003	Minimally invasive omental transplantation using autologous plasma	University of Miami / Diabetes Research institute	1/2 6	5/2018 [33]
NCT01571817 NCT02402439	Islet transplantation into gastric submucosa (after kidney transplant)	University of California, San Francisco	1 4/6	12/2014 [102] 1/2021
NCT00790257	Encapsulated islet allotransplantation in Monolayer Device (subcutaneous space)	Cliniques universitaires Saint Luc Université Catholique de Louvain	1/2 15	4/2019
NCT02064309	Implantable βAir device (peri-umbilical, subcutaneous)	Uppsala University Hospital	1/2 8	3/2016 [35]
NCT01379729	Alginate encapsulated islet transplantation in the peritoneal cavity	Ziekenhuis Brussel/Ziekenhuizen LeuvenBelgium	1/2 10	5/2018 [103]
NCT01967186	Intramuscular vs. intraportal islets in SIK (half of i.m. recipients receive islets + autologous MSC)	Nordic Network for clinical islet transplantation	1/2 36	7/2016 [56, 104]
NCT01652911	Safety and efficacy of Cell Pouch™ (Sernova) for therapeutic, subcutaneous islet transplantation	University of Alberta	1/2 20	6/2016 [86]
Metabolic efficacy / Complications				
NCT02627690	Renal outcome with IAK/SIK 10 years post-transplantation	University Hospital Lille	Observational 50	12/2019
NCT01148680	Comparing efficiency between IAK/ITA with intensive insulin therapy	University of Grenoble	2 40	12/2015
NCT01974674	Efficacy to restore normal glycemic control 6 months post-transplant	Saint Louis hospital, Paris	2 19	1/2022
NCT01909245	T cell depletion and Treg expansion in IAK and ITA	City of Hope	2 30	7/2021
N/A ACTRN083020	Multicenter, single arm trial using islet culture and ATG, CNI, Sirolimus, MMF	University of Sidney, Melbourne University	3 17	2013 [39]

Trial ID	Study aim	Investigators	Phase / n=	Completion / Publications
NCT01309022	EXIIST – Extended IS in Islet Transplant	US Islet transplant centers,	1/2	4/2014
NCT00014911	Follow up of “Edmonton trial”	University of Alberta	7(36)	[10, 74]
NCT00434811	Efficacy of islet transplantation alone	NIAID/NIDDK CIT-07	3 48	5/2014 [37••, 105]
NCT00468117	Efficacy of islet after Kidney transplantation	NIAID/NIDDK CIT-06	2 24	7/2017
NCT00315627	IAK with and without Etanercept	Massachusetts General Hospital, Boston, MA	1/2 4	8/16
Alternative immunosuppression				
NCT00315627	Steroid/CNI free IS with Campath/Sirolimus/MMF	University of Miami	2 12	12/2016
NCT00672204	Efalizumab and Sirolimus Immunosuppression	UCSF, University of Minnesota	2 8	12/2012 [30, 50]
N/A	Efalizumab and MMF compared to Edmonton protocol	Emory University	2 12	[31]
Alternative β-Cell Sources				
NCT02239354	hESC derived pancreatic beta cells in s.c. macroencapsulation device	Viacyte, UCSD, University of Alberta, UCSF	1/2 40	8/2017 [59, 60, 106]
NCT00940173 NCT01736228 NCT01739829	Encapsulated, isolated porcine islet transplantation	Living Cell Technologies, New Zealand/ Hospital Agudos Eva Peron, Argentina	1/2 16/14/8	10/2013 N/A

ITA = Islet transplant alone, IAK = Islet after kidney, SIK = Simultaneous Islet Kidney, PTA = Pancreas transplant alone, hESC = human Embryonic stem cells, MSC = Mesenchymal stem cells