

Review of experimental attempts of islet allotransplantation in rodents: Parameters involved and viability of the procedure

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donors and advance the treatment options for type 1 diabetes.

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Key words: Islet transplantation; Allograft; Immunosuppression; Type 1 diabetes; Islet grafts; Diabetes mellitus; Islet; Hyperglycemia

Core tip: This is an important systematic review for readers to analyze the different existing methodologies of islet allotransplantation. This article reviews all aspects of donors and recipients, the types and dosages of immunosuppressive therapy, graft survival time and evolution of the recipient's blood glucose. Therefore, the present article permits reproduction and improvement of the experiments involving islet allotransplantation in rodents to develop alternative therapies for type 1 diabetes.

Abstract

The purpose of the present study was to organize the parameters involved in experimental allotransplantation in rodents to elaborate the most suitable model to supply the scarcity of islet donors. We used the PubMed database to systematically search for published articles containing the keywords "rodent islet transplantation" to review. We included studies that involved allotransplantation experiments with rodents' islets, and we reviewed the reference lists from the eligible publications that were retrieved. We excluded articles related to isotransplantation, autotransplantation and xenotransplantation, *i.e.*, transplantation in other species. A total of 25 studies related to allotransplantation were selected for systematic review based on their relevance and updated data. Allotransplantation in rodents is promising and continues to develop. Survival rates of allografts have increased with the discovery of new immunosuppressive drugs and the use of different graft sites. These successes suggest that islet transplantation is a promising method to overcome the scarcity of islet

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INTRODUCTION

It is estimated that 4% of the world population is affected by diabetes mellitus, of which 10% have type 1 diabetes^[1]. Furthermore, the incidence of diabetes cases in Europe has increased, especially in children and teenagers, in whom the incidence of type 1 diabetes increased by 4% last year. One trend is the occurrence of type 1 diabetes mellitus at younger ages, between 10 and 14 years. Today, the disease is already at 0-5 years^[2]. According to the IBGE-CENSUS-2010, there are currently 12054827

diabetics patients in Brazil^[3]. Thus, approximately 1.2 million diabetics in Brazil may benefit from research aimed at improving treatment of type 1 diabetes.

Currently, insulin is the primary treatment method for diabetes. However, approximately 5%-10% of patients have severe and unexpected fluctuations in their blood glucose levels, resulting in multiple episodes of hypoglycemia, which has serious clinical consequences. In such cases, pancreas transplantation is an alternative treatment option that is already in clinical use. Another alternative option is islet transplantation, which is a less invasive therapeutic method but is still in development^[3]. Regarding the effectiveness of treatment, some results showed 80% insulin independence within the first year in postoperative patients treated with islet transplantation^[4]; however, the survival rate of islets remains low.

The scarcity of islets is a significant obstacle hindering the widespread use of islet allograft therapy. According to the Network of Organ Procurement and Transplantation, in 2011, only 1562 pancreases were recovered from 8000 donor organs available in the United States. Furthermore, many donated pancreases are not suitable for islet extraction or do not fit the selection criteria. It is also common for islets to be handled incorrectly. For these reasons, only a small number of islet transplantations can be carried out^[5].

Some restrictions were found in the technical development of islet transplantation: the number of donor pancreases available for islet transplantation, below that required for healing the millions of people with type 1 diabetes; technical difficulties and the cost of islet isolation; poor durability of insulin independence; and autoimmunity and rejection after transplantation, which must still be overcome. It is therefore essential to develop an unlimited source of cells capable of secreting insulin in response to glucose and that can be transplanted with little or no need for systemic immunosuppression^[6,7].

The purpose of the present study is to review experimental allotransplantation procedures that have been attempted in rodents to analyze the parameters involved and the viability of the procedure.

SEARCH PROCESS

Search process

The study was performed using the PubMed database to search for published articles containing the keywords "rodent islet transplantation". However, to filter the results, we searched PubMed records for the period January 2000-December 2013 using the following search terms for islet allotransplantation in rodents: "{rodent islet transplantation AND ["2000"(Date-Completion): "3000"(Date-Completion) AND (allotransplantation) NOT porcine] NOT tilapia} NOT nonhuman primate".

This ensured that articles discussing transplantation in porcine, tilapia and nonhuman primates (more common species used for transplantation) were excluded from the review to focus on those articles related to allotransplantation in rodents. Following the PubMed search, we re-

viewed the references from the publications retrieved and obtained the entire text of publications that could potentially be included in the systematic review. Unpublished studies and letters were ignored. Studies that did not have a full text available in English were purchased for review.

Eligible studies were selected for analysis based on the following inclusion criteria: (1) studies must be related to allotransplantation; (2) the species studied must be rodent species; and (3) articles must be relevant and the information up to date.

The review was written in English, and the relevant information, such as donor/recipient, immunosuppression, allotransplantation site, graft survival time, glucose variations and diabetes induction method, was organized into tables.

DATA ABSTRACTION

The authors abstracted the characteristics of the study, such as the source(s) for experimental (*e.g.*, medical records and clinical databases) and relevant data, into the tables-donor/recipient; immunosuppression; allotransplantation site; graft survival time; glucose variations; and diabetes induction method.

SEARCH RESULTS

A total of 2650 articles from 2000 to 2013 were found. Only 25 articles were related to allotransplantation. These articles were selected based on their relevance and updated information (Tables 1-6; Figure 1A and B).

DISCUSSION

Islet transplantation has the potential to provide an adequate supply of insulin to the transplanted patient and provide a solution to the problem of islet donor shortage^[6].

The first successful islet transplantation for the surgical treatment of diabetes occurred in 1990 by Shapiro *et al.*^[7]. Insulin independence was achieved in a patient with type 1 diabetes at one month post-transplant. However, many technical difficulties were found that needed to be overcome to continue the development of this technique and reproduce this experiment. In the decade between 1991 and 2000, 450 islet transplantation attempts were made in type 1 diabetic patients, with a success rate of only 8%. Fifty percent of successful cases were reported when patients had become diabetic because they were undergoing a pancreatectomy.

Then, in 1999/2000, Shapiro *et al.*^[7] successfully achieved insulin independence in 7 diabetic patients by performing experiments based on the modified Edmonton protocol^[2,7].

Islet transplantation has increasingly been shown to reduce morbidity 20-fold compared to pancreas transplantation because it is surgically less invasive^[8].

In the present study, we reviewed studies consisting of rodents similar in age and weight undergoing allograft transplantation. Strains of mice aged 6-12 wk and weighing 200 g to 350 g were used. According to these studies

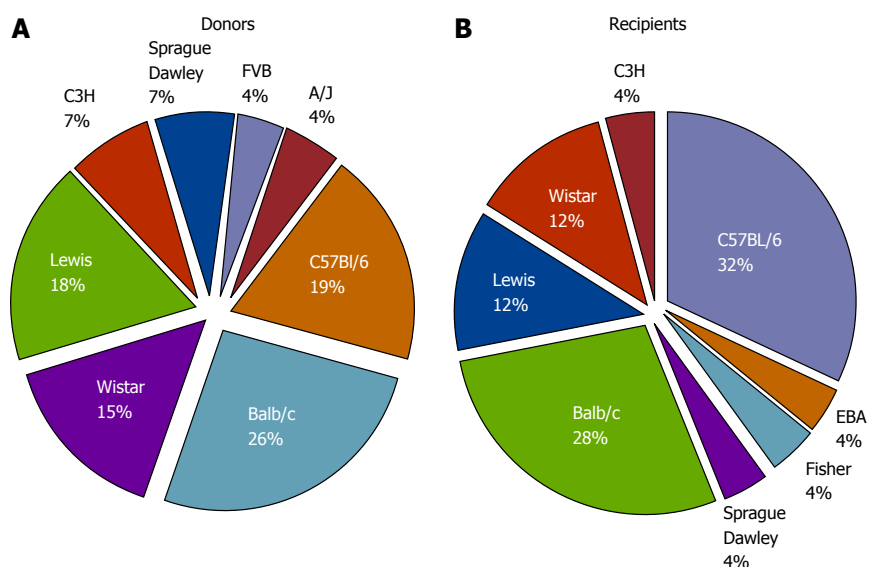


Figure 1 Quantitative and comparative analysis of the different donor strains (A) and recipient strains (B).

Table 1 Description of the experimental studies on allografts in rodents

Ref.	Donor/recipient	Immunosuppression	Allotransplantation site	Graft survival time
Fotiadis <i>et al</i> ^[9]	Lewis→Wistar	Mycophenolate mofetil (MMF) and Cyclosporine A (CsA)	Spleen	N/A
Merani <i>et al</i> ^[10]	Lewis →Wistar	AEB-071 (Protein kinase C inhibitor) + CsA, CTLA4-Ig, MMF	Kidney capsule	100 d
Nishimura <i>et al</i> ^[11]	C57BL/6 → Balb/c	Tacrolimus	Nonmetallic dorsal skinfold chamber	N/A
Makhlouf <i>et al</i> ^[12]	C57BL/6/Balb/c	Blockade of CD28:B7 and anti-CD40L; CTLA-4	Kidney capsule	1 wk
Salazar-Bañuelos <i>et al</i> ^[13]	Wistar →Sprague Dawley	No immunosuppression	Medullary channel	21 d
Wee <i>et al</i> ^[14]	Lewis → Fisher	CsA + Tautomycin (synergist)	Liver (portal vein)	Control group - 5.2 ± 0.5 d TMC - 5.1 ± 0.9 d TMC (0.03 mg/kg) + CsA (5 mg/kg) - > 41 d TMC (0.1 mg/kg) + CsA (5 mg/kg) - 103.8 ± 56.8 d
Plesner <i>et al</i> ^[15]	Balb/c →EBA	No immunosuppression	Kidney capsule	60 d
Watanabe <i>et al</i> ^[16]	Balb/c → C57BL/6	Tacrolimus and DHMEQ (NF-κB inhibitor)	Kidney capsule	100 d
Gysemans <i>et al</i> ^[17]	Balb/c→C57BL/6	No immunosuppression	Kidney capsule	9.2 ± 4.9 d (Autoimmune diabetes) 15 ± 3 d (Not chemically diabetic autoimmune)
Xekouki <i>et al</i> ^[18]	Wistar→Lewis	CsA and MMF	Spleen (parenchyma)	8 d (CsA) 10.92 d (MMF 1) 11 d (MMF 2) 19.7 ± 2.3 d (C57Bl/6) 20.2 ± 2.7 d (CXCR3-/-C57Bl/6)
Baker <i>et al</i> ^[19]	A/J→C57Bl/6J	Monoclonal antibody antiBIP-10	Kidney capsule	N/A
Li <i>et al</i> ^[20]	FVB→Balb/c	No immunosuppression	Kidney capsule	N/A
Vieiro <i>et al</i> ^[21]	C57Bl/6→C3H	Tritiated thymidine (preoperative) and CsA	Subcutaneous	N/A
Neuzillet <i>et al</i> ^[22]	C3H → Balb/c	No immunosuppression	Kidney capsule	13.8-27.5 d
Melzi <i>et al</i> ^[23]	C57Bl/6 → Balb/c	Rapamycin+ FK506+ anti-IL-2Ra chain mAbs and rapamycin+IL-10	Kidney capsule	> 100 d
Fiorina <i>et al</i> ^[24]	Balb/c→C57Bl/6	No immunosuppression	Kidney capsule	14 d
Fan <i>et al</i> ^[25]	C57Bl/6 → Balb/c	LTβ R-Ig, CTLA4-Ig or LTR mAb anti mouse	Kidney capsule	LTβ R-Ig- 27 d CTLA4-Ig- 55 d LTβ R-Ig+CTLA4-Ig - > 100 d LTR mAb anti mouse - 11 d

Jung <i>et al</i> ^[26]	Balb/c → C57Bl/6	CD154 mAb (MR1) anti mouse and ROS-A (Reactive Oxygen Specie - A)	Kidney capsule	ROS-A - 53 d MR1 - 82 d ROS-A+MR1 - > 160 d
Pählman <i>et al</i> ^[27]	Balb/c → C57Bl/6J	AR-C117977 (10 or 30 mg/kg) or CsA 20 mg/kg	Kidney capsule	CsA - 16 d AR-C117977, 10 mg/kg - >100 d AR-C117977, 30 mg/kg -29,33 d
Wang <i>et al</i> ^[28]	Balb/c → C57Bl/6	B7-H4 and Ad-LacZ	Kidney capsule	B7-H4 - approximately 60 d Ad-LacZ - approximately > 20 d
Chen <i>et al</i> ^[29]	Sprague Dawley → Lewis	No immunosuppression	Intra-abdominal	8 wk
Giraud <i>et al</i> ^[30]	C3H → Balb/c	No immunosuppression	Kidney capsule	SCOT + PEG 20 kDa *10 g/L - 20 d, CMRL-1066 + 1% BSA - 17.5 ± 1 d, Solution UW - 17.2 ± 0.4 d, SCOT without PEG - 14 ± 0.9 d Solution HBSS + 0.5% BSA - 14 ± 0.7 d
Qi <i>et al</i> ^[31]	Wistar/Lewis → Lewis	No immunosuppression	Intraperitoneal (Macroencapsulated) Kidney capsule (not macroencapsulated)	24 wk (Macroencapsulated) 48 h (not macroencapsulated)
Potiron <i>et al</i> ^[32]	Wistar → C57Bl/6	CTLA4 Ig or CD40 Ig	Kidney capsule	24.3 ± 9.7 d
Jahr <i>et al</i> ^[33]	Lewis → Wistar	Anti-rat antilymphocyte serum	Liver (portal vein)	

N/A: Not available.

Table 2 Sites of islet infusion based on the literature from the PubMed database

Sites of islet infusion	Literature from the PubMed database
Kidney capsule	70%
Liver	23%
Other sites ¹	7%

¹Subcutaneous, bone marrow, sub-retinal space, sub-conjunctival space, spleen, intraperitoneal cavity and sub-mucosal space of the duodenum.

(Table 3), C57BL/6 (B6) and Balb/c were the most commonly used strains in allograft experiments as both islet donors (23.8% and 16.67%) and as islet recipients (28.57% and 16.67%). However, no significant difference was observed in the results obtained using other strains.

The efficacy of combined immunosuppressive drug therapy on islet transplantation in rodents has been widely studied. Among these studies, Fotiadis *et al*^[9] tested the effects of cyclosporine A (CsA) given in combination with mycophenolate mofetil (MMF) and found that the survival rate increased significantly compared to the isolated use of CsA and MMF; this observation was presumably due to its lower toxicity in the combined regimen.

Nishimura *et al*^[11] conducted studies with tacrolimus and demonstrated a suppression in vascular endothelial growth factors, protein kinase 14 activated by mythogen, tissue factor F, specific cyclin D1 for G1/S cell division and protein kinase 4. Thus, they concluded that the drug inhibits pancreatic islet revascularization. However, hypoxia-inducible factor 1 alpha (HIF1A) was not observed. Thus, there was a minor engraftment of islets and subsequent degeneration. Furthermore, no differences were observed in gene expression between the control group and the group receiving tacrolimus.

Wee *et al*^[14] studied the effects of tautomycin and concluded that it does not affect the viability of the islets and spleen, but it is capable of inhibiting the proliferation of T cells. When tautomycin was combined with subtherapeutic doses of CsA, it led to increased survival of islets. A dose of CsA of 15 mg/kg prolonged the survival of islets the longest. Thus, the mixture of tautomycin with CsA or other calcineurin inhibitors increased islet survival.

Merani *et al*^[10] demonstrated that inhibition of PKC using the new drug AEB -071 slowed the rejection of islet allografts in rodents. Furthermore, addition of CsA therapy with 5 mg/kg AEB prevented graft rejection in 80% of the rats transplanted by immunosuppressive action of the complement system and had no toxic effects.

Watanabe *et al*^[16] conducted studies with DHMEQ, an inhibitor of NF-κB, and concluded that the proinflammatory responses activated by HMGB1 were reduced. Moreover, the immunosuppression allows allograft acceptance even in cases where only a few islets were transplanted.

Xekouki *et al*^[18] analyzed the effects of CsA and MMF. Their results suggest a beneficial effect of MMF in maintaining the architecture of the islets without prominent side effects in other organs, such as the kidneys or liver.

Baker *et al*^[19] studied CXCR3 gene deletion and αIP-10 antibody therapy and concluded that they modulate post-transplant lymphocytic infiltration into the graft and contribute to prolonging allograft survival.

Fan *et al*^[23] concluded that the simultaneous blockade of LIGHT and CD28 prolongs graft survival because of a synergistic effect; the presence of T-regulatory cell activity develops donor-specific immunological tolerance. Moreover, prevention of allograft rejection and induction of donor-specific tolerance in lymphocyte-sufficient recipients can be achieved by local cotransplantation of the

Table 3 Comparative analysis of the different types of rodents used and their basic characteristics-Age and Weight

Ref.	Donor/recipient	Age	Weight
Fotiadis <i>et al</i> ^[9]	Lewis→Wistar	N/A	220 g-300 g
Merani <i>et al</i> ^[10]	Lewis→Wistar	N/A	200 g (male)/150 g (female)
Nishimura <i>et al</i> ^[11]	C57BL/6 → Balb/c	9-12 wk /8-12 wk	N/A
Makhlouf <i>et al</i> ^[12]	C57BL/6→ Balb/c	6-8 wk (male)/ N/A	N/A
Salazar-Bañuelos <i>et al</i> ^[13]	Wistar→ Sprague Dawley	N/A	260-326 g
Wee <i>et al</i> ^[14]	Lewis→ Fisher	10-12 wk	N/A
Plesner <i>et al</i> ^[15]	Balb/c→ EBA	8-10 wk /N/A	N/A
Watanabe <i>et al</i> ^[16]	Balb/c→ C57BL/6	10-14 wk /male	N/A
Gysemans <i>et al</i> ^[17]	Balb/c→ C57BL/6	(8-21 d) → (> 180 d)	N/A
Xekouki <i>et al</i> ^[18]	Wistar→Lewis	N/A/male	220-300 g
Baker <i>et al</i> ^[19]	A/J→ C57BL/6J	8-12 d/male	N/A
Li <i>et al</i> ^[20]	FVB→ Balb/c	8-12 wk	N/A
Vieiro <i>et al</i> ^[21]	C57BL/6→ C3H	N/A	N/A
Neuzillet <i>et al</i> ^[22]	C3H → Balb/c	N/A	N/A
Melzi <i>et al</i> ^[23]	C57BL/6 → Balb/c	9 wk (female) → 9 wk (female)	20-22 g
Fiorina <i>et al</i> ^[24]	Balb/c→ C57BL/6	N/A	N/A
Fan <i>et al</i> ^[25]	C57BL/6 → Balb/c	N/A - adults (female)	N/A
Jung <i>et al</i> ^[26]	Balb/c → C57BL/6	12 wk (male) → 12 wk (male)	25-30 g
Pählman <i>et al</i> ^[27]	Balb/c → C57BL/6J	N/A - (female)	N/A
Wang <i>et al</i> ^[28]	Balb/c → C57BL/6	8-10 wk (female) → 8-10 wk	N/A
Chen <i>et al</i> ^[29]	Sprague Dawley → Lewis	N/A (male)	250-350 g → 196 ± 15 g
Giraud <i>et al</i> ^[30]	C3H → Balb/c	6 wk	N/A
Qi <i>et al</i> ^[31]	Wistar/Lewis → Lewis	9-10 wk (male)	250-300 g
Potiron <i>et al</i> ^[32]	Wistar → C57BL/6	N/A (male)	200-300 g
Jahr <i>et al</i> ^[33]	Lewis → Wistar	N/A (male) → N/A (male)	310-330 g→ 215-245 g

N/A: Not available.

Table 4 Analysis of the immunosuppressant drugs used at international islet transplantation research centers

Immunosuppressant	Number of centers using the immunosuppressant (based on data from the literature)
CsA	6
MMF	3
CTLA4 Ig	4
CD40 Ig	2
NF-κB Inhibitor (DHMEQ)	1
Anti-CD154 mAb (MR1)	2
Tritiated thymidine	1
Tacrolimus	1
Blockade of CD28:B7	1
Tautomycetin	1
Protein Kinase C Inhibitor (AEB-071)	1
Monoclonal antibody anti-BIP-10	1
Rapamycin+FK506+anti-IL-2Ra chain mAbs, n31 and rapamycin+IL-10; n29	1
LTβ R-Ig	1
LTR mAb	1
ROS-A	1
AR-C117977	1
B7-H4 and Ad-LacZ	1
Anti-rat antilymphocyte serum	1
No immunosuppression	9

allografts with regulatory T cells.

Jung *et al*^[26] concluded that the combination of Ros A and MR1 in a murine allogeneic islet transplantation model prolonged graft survival compared to the MR1-alone treatment group.

Pählman *et al*^[27] evaluated the immunosuppressive limitations of AR-C117977, an immunosuppressant drug that maintains long-term graft survival and induces operational tolerance, and concluded that AR-C117977 combined with CsA resulted in significant prolongation of graft survival compared with AR-C117977 or CsA therapy alone. Furthermore, CsA therapy alone did not prevent acute rejection.

Wang *et al*^[28] studied local expression of B7-H4 and concluded that it prolongs islet allograft survival *in vivo*.

Studies investigating immunosuppressant drugs and their toxic effects on islets *in vivo* are still in development. The most utilized immunosuppressants were CsA, MMF and CTLA4 Ig, as shown in Table 4. The concomitant use of glucocorticoids was associated with high rejection rates and is not recommended. Their immunosuppressive and toxic effects have not been rigorously tested, and studies are still underway.

In relation to the different locations for transplantation studied according to the table, the kidney capsule was the most frequently used site for transplantation. Second was the portal vein in the liver^[14]. The spleen^[9,19], intraperitoneal site^[32], bone marrow (tibia)^[13], dorsal skin fold-intra-abdominal^[30] nonmetallic chamber^[11] or subcutaneous^[22] was used in a small percentage of studies.

In our review of the studies, it was found that the highest survival rate was obtained by Wee *et al*^[14], who used the portal vein (liver) as the site of allograft transplantation and sacrificed the mice at 100 d postoperative. Melzi *et al*^[23], Watanabe *et al*^[16] and Merani *et al*^[10] obtained a survival rate of 100 d, where the site of engraftment

Table 5 Quantitative analysis of immunosuppressant drugs use

Ref.	Immunosuppression	Dose	Administration frequency
Fotiadis <i>et al</i> ^[9]	MMF and CsA	12 mg/kg and 23 mg/kg (MMF) 5 mg/kg (CsA)	-
Merani <i>et al</i> ^[10]	AEB-071 (Protein Kinase C Inhibitory) + CsA, CTLA4-Ig, MMF	30 mg/kg (AEB-071) 2.5 mg/kg and 5 mg/kg (CsA) 0.25 mg (CTLA4-Ig Intraperitoneal)	2 times a day, oral (AEB-071) 2 times a day, oral (CsA) 0, 2, 4 and 6 PO, Intraperitoneal (CTLA4-Ig)
Nishimura <i>et al</i> ^[11]	Tacrolimus	10 mg/kg (MMF)	Once a day, oral (MMF)
Makhlouf <i>et al</i> ^[12]	Blockade of CD28:B7 and anti-CD40 L; CTLA-4	0.5 mg/kg 250µg	Infused subcutaneously - Daily - for 14 d Intraperitoneal - 0, 2, 4 and 6 PO
Wee <i>et al</i> ^[14]	CsA+Tautomycetin (Synergist)	5 mg/g and 15 mg/kg (CsA)	Once a day for 7 d
Watanabe <i>et al</i> ^[16]	Tacrolimus and DHMEQ	1.5 mg/kg (Tacrolimus) 20 mg/kg (DHMEQ)	Once a day 0 to 3 PO and 2 times a day 0 to 14 PO (DHMEQ); 0 to 14 PO (Tacrolimus); Once a day 0 to 3 PO (DHMEQ)+0 to 14 PO (Tacrolimus)
Xekouki <i>et al</i> ^[18]	CsA and MMF1	5 mg/kg (CsA) 12 mg/kg (MMF) 23 mg/kg (MMF)	Oral - Daily - 12 consecutive days
Baker <i>et al</i> ^[19]	Monoclonal antibody antiBIP-10	300 µg intraperitoneal	Daily - 14 d ¹
Vieiro <i>et al</i> ^[21]	Tritiated thymidine (preoperative) and CsA	20 mg/kg (CsA)	N/A
Melzi <i>et al</i> ^[23]	Rapamycin + FK506 + anti-IL-2Ra chain mAbs and rapamycin+IL-10	1 mg/kg (Rapamycin) 0.05 µg/kg (IL-10) 0.3 mg/kg (FK506) 1 mg/kg (mAbs)	Intraperitoneal: Once a day - 30 PO (Rapamycin) 2 times a day - 30 d (IL-10) Once a day - 30 d (FK506) 0.4 PO (mAbs)
Fan <i>et al</i> ^[25]	LTβ R-Ig, CTLA4-Ig or LTR mAb anti mouse	200 µg	Intraperitoneal- days -1, 1, 3, 5, 7 and 9
Jung <i>et al</i> ^[26]	CD154 mAb (MR1) anti mouse + ROS-A	250 µg (CD154 mAb (MR1) anti mouse) 200 mg/kg of Ros A	Intraperitoneal injection 0, 2, 4, 6 and 8 PO (CD154 mAb (MR1) anti mouse) 8 consecutive days (ROS-A)
Pählman <i>et al</i> ^[27]	AR-C117977 or CsA	0.2 mL - 3, 10, 30, or 100 mg/kg (AR-C117977)	Subcutaneous - once a day 0 to 9 PO (AR-C117977)
Wang <i>et al</i> ^[28]	B7-H4	0.5 mL - 20 mg/kg (CsA) 5 plaque-forming units (pfu) of Ad-B7-H4 or Ad-LacZ	Once a day 0-9 PO or 0-39 PO (CsA) N/A
Potiron <i>et al</i> ^[32]	CTLA4 Ig or CD40 Ig	5 10 ⁹ IP of AdCTLA4 IM and/or 5 10 ⁹ IM or 2 10 ⁹ IV of AdCD40Ig; IM administration: 10 µL per point (3 points) IV administration: 150 µL with 0.9% sodium chloride	IM administration - anterior tibialis muscle; IV administration - venile vein
Jahr <i>et al</i> ^[33]	Anti-rat antilymphocyte serum	Intraperitoneal administration 0.5 mL	1 d after islet transplantation

¹First dose administered 4 h preoperatively. N/A: Not available; MMF: Mycophenolate mofetil; CsA: Cyclosporine A.

Table 6 Analysis of induction and treatment of diabetic process with islet transplantation

Ref.	Number of transplanted islets	Diabetes induction method	Hyperglycemia induction (preoperative)	Normalization of hyperglycemia (postoperative)	Graft rejection	Criteria for primary graft dysfunction (PGD)
Fotiadis <i>et al</i> ^[9]	1812 ± 145	Streptozotocin (60 mg/kg) + PBS-Solution (Phosphate Buffer Solution) - 10 mg/mL (pH 4.5);	7 d	3 d	12 d (MMF) 10 d (CsA)	Glucose above 200 mg/dL; after 2 nd PO 2 consecutive times
Merani <i>et al</i> ^[10]	1500	Streptozotocin (75 mg/kg) intraperitoneal	5 d	3 d	22 d	Glucose above 324 mg/dL after 2 consecutive days
Nishimura <i>et al</i> ^[11]	2-10/dorsal skinfold chamber	-	-	-	N/A	-
Makhlouf <i>et al</i> ^[12]	350 (Balb/c) 700 (NOD)	Streptozotocin and spontaneously (225 mg/kg in peritoneal cavity)	2 wk	3 d	10 d (Balb/c) 5 d (NOD) and 7 d complete rejection (NOD)	200 mg/dL - 2 to 3 consecutive days
Salazar-Bañuelos <i>et al</i> ^[13]	840 (of Wistar)	-	-	-	N/A ¹	N/A

Wee <i>et al</i> ^[14]	4000	Streptozotocin (35 mg/kg)	N/A	N/A	Untreated - 5.2 d (± 0.5) TMC - 5, 1 d ($\pm 0, 9$) TMC (0.03 mg/kg) + CsA (5 mg/kg) - > 41 d TMC (0.1 mg/kg) + CsA (5 mg/kg) - 103.8 \pm 56.8 d	200 mg/dL after 2 consecutive days
Plesner <i>et al</i> ^[15]	550	Streptozotocin (375 mg/dL) intraperitoneal	3-5 d	5 d ¹	60 d	≥ 198 mg/dL after 2 consecutive days
Watanabe <i>et al</i> ^[16]	600 or 300	Streptozotocin (180 mg/kg) intraperitoneal	5-7 d	N/A	69 d (Tacrolimus) 100 d (DHMEQ 3 d and Tacrolimus 14 d)	> 350 mg/dL for 2 consecutive days
Gysemans <i>et al</i> ^[17]	300	Alloxan (90 mg/kg)	24 h	N/A	N/A - 23%	Glucose level > 200 mg/dL more than 3 consecutive days
Xekouki <i>et al</i> ^[18]	2000	Streptozotocin (60 mg/kg) diluted in phosphated solution 10 mg/mL	1 wk	N/A	7 d (MMF '1)	-
Baker <i>et al</i> ^[19]	300	Streptozotocin (220 mg/kg)	N/A	N/A	7 d	-
Li <i>et al</i> ^[20]	400 (200/Kidney capsule)	Streptozotocin (220 mg/kg)	N/A	N/A	8.36 \pm 1.67 (islets of FVB) 16.2 \pm 2.52 (islets of MT)	Glucose levels > 250 mg/dL - 2 consecutive measurements
Vieiro <i>et al</i> ^[21]	200	Streptozotocin (270 mg/kg) intraperitoneal	N/A	N/A	3-7 d	≥ 250 mg/dL - 3 consecutive measurements
Neuzillet <i>et al</i> ^[22]	550	N/A	N/A	4 h	PEG-Solution 8 kDa 27.50 \pm 3.70 d; PEG PEG-Solution 20 kDa 23.13 \pm 4.39 d; PEG-Solution 35 kDa 13.80 \pm 3.49 d	> 199.8 mmol/L - 2 consecutive measurements
Melzi <i>et al</i> ^[23]	400	175 a 200 mg/kg intravenous	1-2 wk	5 d	29 d (mouse with Glucose levels < 450 mg/dL) and 16 d (mouse with Glucose levels > 450 mg/dL)	> 250 mg/dL - 2 consecutive measurements on postoperative
Fiorina <i>et al</i> ^[24]	NA	Streptozotocin	N/A	N/A	14 d	N/A
Fan <i>et al</i> ^[25]	500	Streptozotocin (200 mg/kg)	N/A	N/A	27 d (LT[α]R-Ig) 55 d (CTLA4-Ig) After 100 d or more (LT[β]R-Ig and CTLA4-Ig)	> 300 mg/dL- after 2 consecutive days
Jung <i>et al</i> ^[26]	300 IEQ	Streptozotocin (180 mg/kg)	N/A	1 d	ROS-A - 53 d MR1 - 82 d ROS-A+MR1 - > 160 d	> 200 mg/dL - 2 consecutive measurements on the same week
Påhlman <i>et al</i> ^[27]	500-600	Alloxan Intravenous	N/A	N/A	CsA - 16 d AR-C117977, 10 mg/kg - > 100 d AR-C117977, 30 mg/kg - 29, 33 d	N/A
Wang <i>et al</i> ^[28]	400	Streptozotocin (200 mg/kg)	3-4 d	3 d	B7-H4 - approximately 60 d Ad-LacZ - approximately > 20 d	> 250 mg/dL after primary graft success
Chen <i>et al</i> ^[29]	3000 IEQ	Streptozotocin dissolved in saline (50 mg/kg)	N/A	1 wk	13 wk (SGA - microencapsulated) 7 wk (ABa- microencapsulated) 5 wk (APA- microencapsulated)	N/A

Giraud <i>et al</i> ^[30]	1400 IEQ	Streptozotocin (250 mg/kg), intraperitoneal	N/A	N/A	SCOT + PEG - Solution 20 kDa ³ 10 g/L - 20 d, CMRL-1066 + 1% BSA - Solution 17.5 ± 1 d, UW-Solution - 17.2 ± 0.4 d, SCOT without PEG -14 ± 0.9 d HBSS + 0.5% BSA - Solution - 14 ± 0.7 d	> 200 mg/dL - 2 consecutive measurements
Qi <i>et al</i> ^[31]	1940 (± 39)	Streptozotocin (55 mg/kg)	7 d	N/A	N/A	N/A
Potiron <i>et al</i> ^[32]	800-1000	Streptozotocin (180 mg/kg)	1 wk	4 d	24.3 ± 9.7 d	250 mg/dL on 2 successive measurements
Jahr <i>et al</i> ^[33]	700-900	Streptozotocin (55 mg/kg)	7-10 d	Right after transplantation	1 wk	> 300 mg/dL after 8.9 ± 0.7 d

¹Rodents that had normalized blood glucose in 5 d were included in the study. N/A: Not available; IEQ: Islet equivalents.

Table 7 Analysis of the parameters of hyperglycemia

Ref.	Blood Glucose Levels: hyperglycemia (mg/dL)
Fotiadis <i>et al</i> ^[9]	180 on 2 consecutive measurements
Merani <i>et al</i> ^[10]	180 on 3 consecutive days
Makhlouf <i>et al</i> ^[12]	Moderate diabetes: between 240 and 350 Severe diabetes: between 351 and 550 Very severe diabetes: more than 550
Wee <i>et al</i> ^[14]	200
Plesner <i>et al</i> ^[15]	≥ 360
Watanabe <i>et al</i> ^[16]	200 on 2 consecutive days
Gysemans <i>et al</i> ^[17]	200 on 2 consecutive days
Xekouki <i>et al</i> ^[18]	300
Baker <i>et al</i> ^[19]	300 on 3 consecutive days
Li <i>et al</i> ^[20]	350 to 500 after 2 consecutive measurements
Melzi <i>et al</i> ^[23]	250 on 2 consecutive measurements
Fan <i>et al</i> ^[25]	300 on 2 consecutive measurements
Jung <i>et al</i> ^[26]	300 on 2 consecutive days
Pählman <i>et al</i> ^[27]	288 on 2 consecutive measurements
Wang <i>et al</i> ^[28]	300 after 2 consecutive days
Chen <i>et al</i> ^[29]	302.4 on more than 3 consecutive days
Giraud <i>et al</i> ^[30]	350 after 2 consecutive days
Qi <i>et al</i> ^[31]	450
Potiron <i>et al</i> ^[32]	> 200

was the kidney capsule.

It is important to note that there was no standard level of hyperglycemia that the mice must present to be recipients of islet transplantation. A range of blood glucose levels from 180 mg/dL to 500 mg/dL was observed, as shown in Table 7.

The articles have many independent variables that influence the study results, such as species of rodent, immunosuppressant drugs and dosages, criteria for diabetes and allograft site. Thus, more research is needed to develop the ideal allograft model of islet transplantation.

CONCLUSION

Based on the analyzed studies, we can infer that islet allotransplantation in rodents is promising and continues to develop. The survival rates of allografts have increased with the discovery of new immunosuppressive drugs and

the use of different graft sites. These advancements have the potential to overcome the scarcity of islet donors and improve the treatment of type 1 diabetes.

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