MedicalExpress

REVIEW

Parameters involved and viability of immunosuppression on islet allotransplantation procedure in rodents

Immunosupression and islet transplantation

Leandro R. Iuamoto, Alberto Meyer, Eleazar Chaib, Luiz AC D'Albuquerque

Liver and Pancreas Transplantation Surgery Unit, Department of Gastroenterology, University of São Paulo School of Medicine, Sao Paulo, Brazil

INTRODUCTION: Autoimmunity and rejection after transplantation must still be overcome in the technical development of islet transplantation for the treatment of type 1 diabetes. It is therefore necessary to inhibit rejection of islet grafts while maintaining the graft's ability to secrete insulin. Although the use of immunosuppressants reduces the acute rejection rate in transplant patients, long-term side effects must be prevented.

OBJECTIVES: The aim of the present study is to organize and analyze the parameters of immunosuppression involved in experimental attempts of allotransplantation in rodents.

METHODOLOGY: This review was performed using the Pubmed database to search for published articles containing the keywords "rodent islet transplantation". The inclusion criteria involved allotransplantation with rodents' islets and the reference lists of the publications retrieved that were eligible. The exclusion criteria involved isotransplantation, autotransplantation, and xenotransplantation such as transplantation in other species.

RESULTS: Twenty studies related to allotransplantation were selected for this systematic review based on immunosuppression.

CONCLUSION: New immunosuppressive drugs increased the survival rates of allotransplantation in rodents by reducing the side effects. The advances in immunosuppression raise the possibility of overcoming autoimmunity and rejection after allotransplantation.

KEYWORDS: islet transplantation; allograft; immunosuppressive therapy.

Iuamoto LR, Meyer A, Chaib E, D'Albuquerque LAC. Parameters involved and viability of immunosuppression on islet allotransplantation procedure in rodents. MEDICALEXPRESS. 2014 Aug;1(4):190-194.

Received for publication on April 9 2014; **First review completed on** May 27 2014; **Accepted for publication on** June 6 2014

E-mail: leandro.iuamoto@gmail.com

INTRODUCTION

According to the Instituto Brasileiro de Geografia e Estatística (IBGE) – CENSUS – 2010, there are currently 12.054.827 diabetics in Brazil[1]. Furthermore, the incidence of cases of diabetes in Europe has increased, especially in children and teenagers, where the incidence of type 1 diabetes increased by 4% last year. There is a trend for the occurrence of type 1 diabetes mellitus at even lower ages, namely between 10 and 14. Today the disease already occurs between 0 and 5 years of age[2]. It is estimated that 4% of the world population is affected by diabetes mellitus, of which 10% have type 1 diabetes[3]. Thus, approximately 29 million diabetics in the world may benefit from research lines related to treatment of type 1 diabetes.

Currently, insulin is the primary treatment for the disease. However, about 5% to 10% of patients have severe and unexpected fluctuations in their blood glucose levels, resulting in multiple episodes of hypoglycemia with serious clinical consequences. In some cases, pancreas transplantation is the alternative that is already in clinical use. Another alternative is islet transplantation, which is a less invasive therapeutic method currently in development. Regarding the effectiveness of treatment, some results showed 70% insulin independence in the first postoperative year of patients treated with islet transplantation[4]. However, the survival rate of transplanted islets remains low.

The scarcity of islets is a significant obstacle to the widespread use of islet allografts. According to the Network of Organ Procurement and Transplantation in 2011, only

DOI: 10.5935/MedicalExpress.2014.04.06

1,562 pancreata were recovered from 8,000 donor organs available in the United States. In fact, many pancreas donors are not suitable for islets extraction and do not fit the selection criteria. Additionally, incorrect handling of islets is common, so that only a small number of islet transplantations can be performed[5].

One of the most important restrictions hampering the technical development of islet transplantation consists of the autoimmune response and rejection after transplantation which must still be overcome. It is essential, therefore, to develop an unlimited source of cells capable of secreting insulin in response to glucose and able to be transplanted with little or no need for systemic immunosuppression[6,7].

The aim of the present study is to conduct a review of experimental attempts at allotransplantation in rodents, in order to analyze the parameters involved and viability of the immunosuppression.

METHODOLOGY

Search process

The study was performed searching for published articles in the Pubmed database containing the keywords: "rodent islet transplantation". Nevertheless, in order to filter the results, we searched PubMed records for the period January 2000–December 2013 using the following search terms for the involved parameters and the viability of immunosuppression on islet allotransplantation in rodents: ((((((rodent islet transplantation) AND ("2000"[Date – Completion]: "3000"[Date – Completion])) AND allotransplantation)) NOT porcine) NOT tilapia) NOT nonhuman primate.

Articles related to transplantation involving porcine, tilapia, and nonhuman primate (more common species used for transplantation) were excluded from our review in order to select articles related to allotransplantation in rodents with or without immunosuppression. Afterwards, we reviewed the reference lists of the publications retrieved, and obtained the entire text of publications that potentially could be included in this systematic review. Unpublished studies and letters were ignored. Studies that did not have full text freely available were bought for review.

Studies that were considered potentially eligible were selected for analysis following the inclusion criteria:

- –studies must be related to allotransplantation;
- –the species studied must be a rodent species;
- –relevance and information update of the articles.

RESULTS

A total of 2,650 articles published from 2000 to 2013 were found, but only 25 articles were related to allotransplantation. These articles were selected based on their relevance and updated information.

The analysis of the number of research centers which used different immunosuppressive drugs in islet transplantation is shown in Table 1.

In Table 2, we display data referenced by the various reports, experimental dosage, and frequency of immunosuppressant regiment.

To solve the problem of the shortage of pancreas donors, the technique of islet transplantation has been developed to acquire an adequate supply of insulin in the transplanted patient [6].

Table 1 - 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
CTLA4Ig	3
CD40Ig	2
NF-kB Inhibitor (DHMEQ)	1
Anti-CD154 mAb (MR1)	2
Tritiated thymidine	1
Tacrolimus	1
Blockade of CD28:B7	1
Tautomycetin	1
Protein Kinase C Inhibitory (AEB-071)	1
Monoclonal antibody antiBIP-10	1
Rapamycin + FK506 + anti–IL-2Ra chain mAbs, n31 e rapamycin + IL-10; n29	1
LTß R-Ig	1
LTRmAb	1
ROS-A	1
AR-C117977	1
B7-H4 and Ad-LacZ	1
Anti-rat antilymphocyte serum	1
No immunosuppression	8

In 1990, Scharp et al. obtained the first success in islet allografts in the surgical treatment of diabetes achieving insulin independence for one month in a patient with type 1 diabetes. Nevertheless, there were some technical difficulties in the reproduction of this experiment. In the nineties, 450 of islet transplantation attempts were made in type 1 diabetic patients, with a success rate of only 8%; 50% of the successful cases were performed in patients who had become diabetic because they had undergone pancreatectomy.

Afterwards in 1999/2000, Shapiro et al. obtained insulin independence in 7 diabetic patients, performing procedures based on the modified Edmonton protocol[7].

Islet transplantation is less invasive than pancreas transplants, from the surgical point of view. It has increasingly been shown as an intervention that presents morbidity 20 times smaller than that of pancreas transplant[8].

In the present study, the combination of immunosuppressive drugs related to efficacy of islet transplantation in rodents have been reviewed. Fotiadis et al.[9] tested the effects of cyclosporine A (CsA) along with mycophenolate mofetil (MMF), and found that the survival rate increased significantly compared to the use of drugs CsA and MMF alone, due to a lower level of toxicity with the combined use.

Nishimura et al.[11] conducted studies with tacrolimus. Results were suppression of (i) vascular endothelial growth factors, (ii) protein kinase-14 activated by mythogen; (iii) tissue factor F; (iv) specific cyclin D1 for G1/S, and (v) cell division protein kinase 4. Thus, the conclusion was that the drug inhibits pancreatic islet revascularization. However, factor 1 alpha inducing hypoxia (HIF1A) was not observed. Thus, there was a low level of irrigation of islets and its consequent degeneration. Furthermore, no differences were observed in gene expression compared to the control group and the group receiving tacrolimus.

Table 2 - Quantitative analysis of immunosuppressant drugs use

Authors	Immunosuppression	Dose	Administration frequency
Fotiadis et al. [9]	MMF and CsA	12 mg/kg and 23 mg/kg (MMF) 5 mg/kg (CsA)	–
Merani et al. [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) 10 mg/kg (MMF)	2 times a day, oral (AEB-071) 2 times a day, oral (CsA) 0, 2, 4 and 6 PO, Intraperitoneal (CTLA4-Ig) Once a day, oral (MMF)
Nishimura et al. [11]	Tacrolimus	0.5 mg/kg	Infused subcutaneously – Daily – for 14 days
Makhlouf et al. [12]	Blockade of CD28:B7 and anti-CD40 L; CTLA-4	250 μg	Intraperitoneal – 0, 2, 4 and 6 PO
Wee et al. [13]	CsA + Tautomycetin (Synergist)	5 mg/g and 15 mg/kg (CsA)	Once a day for 7 days
Watanabe et al. [14]	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 et al. [15]	CsA and MMF*	5 mg/kg (CsA) 12 mg/kg (MMF) 23 mg/kg (MMF)	Oral – Daily – 12 consecutive days
Baker et al. [16]	Monoclonal antibody antiBIP-10	300 μg intraperitoneal	Daily – 14 days*
Vieiro et al. [17]	Tritiated thymidine (preoperative) and CsA	20 mg/kg (CsA)	N/A
Melzi et al. [18]	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 days (IL-10) Once a day – 30 days (FK506) 0.4 PO (mAbs)
Fan et al. [19]	LTß R-Ig, CTLA4-Ig or LTR mAb anti mouse	200 μg	Intraperitoneal – days −1, 1, 3, 5, 7 and 9
Jung et al. [20]	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)
Påhlman et al. [21]	AR-C117977 or CsA	0.2 mL – 3, 10, 30, or 100 mg/kg (AR-C117977) 0.5 ml – 20 mg/kg (CsA)	Subcutaneous – once a day 0 to 9 PO (AR-C117977) Once a day 0-9 PO or 0-39 PO (CsA)
Wang et al.[22]	B7-H4	5 plaque-forming units (pfu) of Ad-B7-H4 or Ad-LacZ	N/A
Potiron et al.[23]	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 et al. [24]	Anti-rat antilymphocyte serum	Intraperitoneal administration 0.5 ml	1 day after islet transplantation

*First dose administered 4 hours preoperatively; N/A = not available.

Makhlouf et al.[12] concluded that the islets could adapt to the environment and function because reversal of diabetes in severely diabetic BALB/c mice 15 days after transplantation was observed when mice were treated with costimulation blockade. Nevertheless, islet transplantation into NOD mice with very severe diabetes treated with costimulation blockade did not reverse diabetes, demonstrating that the islets could not function in the absence of alloimmune responses nor during the adaptation period.

Wee et al.[13] studied Tautomycetin, and concluded that it does not affect the viability of the islets and spleen, but is capable of inhibiting the proliferation of T cells. When tautomycetin was combined with subtherapeutic doses of CsA, it led to increased survival of islets. The dose of CsA that most prolonged survival of islets was 15mg/kg. Thus, the mixture of tautomycetin CsA or calcineurin inhibitors increased the survival of the islets.

Merani et al.[10] demonstrated that inhibition of PKC using the new drug AEB−071 slowed the rejection of islet allografts in rodents.

Watanabe et al.[14] conducted studies with DHMEQ (an inhibitor of NF-kß) and concluded that the proinflammatory responses activated by HMGB1 are reduced. Moreover, the immunosuppression allows allograft acceptance even in cases of few islets.

Xekouki et al.[15] analyzed the effects of CsA and MMF and obtained results that apparently suggest a beneficial effect of MMF in maintaining the architecture of the islets while not having prominent side effects (in organs such as kidneys and liver).

Baker et al.[16] studied CXCR3 gene deletion and αIP-10 antibody therapy and concluded that they modulate posttransplantation lymphocytic graft infiltration and prolong allograft survival.

Vieiro et al.[17] conducted a study in which treated and control islets were transplanted to diabetic mice treated daily with cyclosporine. The allogeneic proliferative response was maximal when allogeneic mononuclear cells were mixed with control islets. It was significantly decreased with treated islets. Mean proliferative inhibition rate of treated vs. control was 62%. IA-d expression on monocytes was maximal in control islets. Reversion was significantly different for treated versus control islets with its duration varing from 3 to 7 days.

Melzi et al.[18] observed that the use of Rapamycin + FK506 + anti−IL-2Ra chain mAbs and rapamycin + IL-10 removed the influence of pretransplant hyperglycemia, but after treatment was withdrawn, the timing and the probability of graft loss correlate with the pretransplant hyperglycemia.

Fan et al.[19] concluded that the simultaneous blockade LIGHT and CD28 prolongs graft survival because of the synergistic effect. The presence of T-regulatory cell activity develops donor-specific immunological tolerance. The prevention of allograft rejection and donor-specific tolerance in lymphocyte-sufficient recipients can be achieved by local cotransplantation of the allografts with the regulatory T cells.

Jung et al.[20] concluded that the combination between Ros A and MR1 in a murine allogeneic islet transplantation model prolonged graft survival when compared to the MR1-alone treatment group.

Påhlman et al.[21] evaluated the immunosuppressive limitations of AR-C117977, a 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 when compared with AR-C117977 or CsA monotherapy. Furthermore, CsA monotherapy did not avoid acute rejection.

Wang et al.[22] studied local expression of B7-H4 and concluded that it prolongs islet allograft survival in vivo.

Potiron et al.[23] used adenoviruses coding for CTLA4Ig or CD40Ig and compared the efficacy of genetic modification of islets to systemic production through either intramuscular (IM) or intravenous (IV) injection of these vectors in a rat-to-mouse islet transplantation model. When gene transfer was performed into islets, a high level of primary nonfunction was induced. Furthermore, transduced functional grafts were rejected with the same kinetics as nontransduced islets. In contrast, IM AdCTLA4Ig and IV AdCD40Ig significantly delayed rejection (mean survival time of 54 ± 26.9 and 67.6 ± 44.9 days, respectively, vs. 24.3 ± 9.7 days for unmodified islets, $p < 0.05$).

Jahr et al.[24] studied the effects of anti-rat antilymphocyte serum in single-donor-to-single-recipient transplantation of allogeneic rat pancreatic islets and concluded that complete normoglycemia was restored within 1 day after transplantation in seven out of seven rats, and persisted up to immunological rejection about 1 week later.

DISCUSSION

Immunosuppressants for islet transplantation are still in development and some have toxic effects on islets in vivo. The most used immunosuppressants were CsA, MMF and CTLA4Ig,as listed in Table 1. The concomitant use of glucocorticoids is not recommended, due to the high associated rejection rates. Their immunosuppressive and toxic effects have not been rigorously tested, and studies are still underway.

According to Fotiadis et al.[9], low doses of MMF provided effective immunosuppression in an experimental allograft islet transplantation model and compared favorably to CsA in terms of islet morphology and side effects. Given the fact that the complications of immunosuppressive therapy continue to be one of the major hurdles to successful islet transplantation, management of immunosuppression requires careful risk vs benefit assessment. Favorable benefit/side effects ratio for the biochemical and histological parameters with the low dose monotherapy of MMF was observed in this study, compared to data presented in other reports. This drug might represent a standard suitable immunosuppressive agent for improving the outcome of pancreatic islet allotransplantation.

Xekouki et al.[15] showed that CsA and MMF are equally effective in maintaining graft function. No severe side effects were seen with the use of MMF, and animal weight remained steady or even increased. Laboratory assessment confirmed these findings. Values for creatinine, sGOT/sGPT, and GT were within normal limits.

It seems that treatment with MMF as single immunosuppressive agent in experimental islet allotransplantation facilitates islet allograft acceptance and prolongs recipient survival without severe adverse effects.

Fan et al.[19] found that the blockade of CD28 signaling with CTLA4-Ig inhibits T cell response and prolongs allograft survival in several rodent models; in some organ transplantation models, it leads to tolerance. The cotransplantation of islet allografts might be essential for amplification and

maintenance of the grafted regulatory T cell locally, which contributes to induction of tolerance. The results indicate that combined treatment with LTβ R-Ig and CTLA4-Ig can facilitate long-term islet graft survival by induction of allospecific tolerance in a mouse model. This novel strategy may have potential for clinical application because of its effectiveness and simplicity.

Påhlman et al.[21] demonstrated that CsA treatment alone had no effect at all; they claim that not even 40 days of treatment in the low responder combination achieved more than a couple of days of prolongation of graft survival compared to controls. Interestingly, the combination of the two drugs (CsA and AR-C117977) achieved substantial graft protection, but donor specific operational tolerance was not induced.

The reviewed articles have many independent variables that may affect the results, such as: species of rodent, immunosuppressive drugs and dosages, criteria for diabetes and allograft site. Thus, more research is needed to determine the ideal model of allograft.

CONCLUSION

New immunosuppressive drugs increased the survival rates of islet allotransplantation in rodents by reducing the side effects. The advances in immunosuppression can possibly overcome autoimmunity and rejection after transplantation.

RESUMO

INTRODUÇÃO: A autoimunidade e a rejeição após o transplante ainda precisam ser superadas no desenvolvimento técnico de transplante de ilhotas para o tratamento de diabetes tipo 1. Inibir a rejeição de enxertos de ilhotas, mantendo a capacidade do enxerto para segregar insulina é uma estratégia essencial. O uso de agentes imunossupressores reduz a taxa de rejeição aguda em transplantados, mas os efeitos colaterais a longo prazo deve ser evitados.

OBJETIVOS: O objetivo do presente estudo é o de organizar e analisar os parâmetros de imunossupressão envolvidos em tentativas experimentais de alotransplante em roedores.

METODOLOGIA: Esta avaliação foi realizada utilizando o banco de dados PUBMED para pesquisar artigos publicados que contenham a palavra-chave "o transplante de ilhotas de roedores". Os critérios de inclusão envolveram alotransplante com ilhotas de roedores e as listas de referências das publicações recuperadas que eram elegíveis. Os critérios de exclusão incluíram isotransplante, autotransplante, e xenotransplante definido como o transplante para outras espécies.

RESULTADOS: Vinte estudos relacionados ao alotransplante foram selecionados para esta revisão sistemática baseada em imunossupressão.

CONCLUSÃO: Novas drogas imunossupressoras aumentaram as taxas de sobrevivência de alotransplante em roedores, reduzindo os efeitos colaterais. Os avanços na imunossupressão levantam a possibilidade de superar a autoimunidade e rejeição após alotransplante.

REFERENCES

1. Sociedade Brasileira de Diabetes [Internet]. São Paulo: Sociedade Brasileira de Diabetes; 2012 [cited 2012 April 18]. Available at: http://www.diabetes.org.br/sala-de-noticias/2116-sao-12-milhoes-de-diabeticos-no-brasil.
2. Chaves G. Incidência de diabetes tipo 1 aumenta 3% ao ano [Internet]. Minas Gerais: Saúde Plena; 2013 [updated 2013 July 21; cited 2013 July 22]. Available at: http://sites.uai.com.br/app/noticia/saudeplena/noticias/2013/07/22/noticia_saudeplena,144088/incidencia-de-diabetes-tipo-1-aumenta-3-ao-ano.shtml.
3. King H, Aubert RE, Ronald E, Herman W. Global burden of diabetes, 1995-2025: prevalence, numerical estimates, and projections. Diabetes Care. 1998;21(9):1414-31.
4. Merani S, Shapiro AM. Current status of pancreatic islet transplantation. Clin Sci (Lond). 2006;110(6):611-25.
5. United States of America. 2007. National Institute of Diabetes and Digestive and Kidney Diseases. Pancreatic Islet Transplantation. NIH Publication 07−4693.
6. Eliaschewitz DG, Franco DR, Mares-Guia TR, Noronha IL, Labriola L, Sogayar MC. Transplante de ilhotas na prática clínica: estado atual e perspectivas. Arq Bras Endocrinol Metab. 2009;53(1):15-23.
7. Shapiro AM, Lakey JR, Ryan EA, Korbutt GS, Toth E, Warnock GL, et al. Islet transplantation in seven patients with type 1 diabetes mellitus using a glucocorticoid-free immunosuppressive regimen. N Engl J Med. 2000;343(4):230-8.
8. Ryan EA, Paty BW, Senior PA, Bigam D, Alfadhli E, Kneteman NM, et al. Five-year follow-up after clinical islet transplantation. Diabetes. 2005;54 (7):2060-9.
9. Fotiadis C, Xekouki P, Papalois AE, Antonakis PT, Sfiniadakis I, Flogeras D, et al. Effects of mycophenolate mofetil vs cyclosporine administration on graft survival and function after islet allotransplantation in diabetic rats. World J Gastroenterol. 2005;11(18):2733-8.
10. Merani S, Pawlick RL, Edgar RL, Toso C, Emamaullee J, Anderson CC, et al. Protein kinase C inhibitor, AEB-071, acts complementarily with cyclosporine to prevent islet rejection in rats. Transplantation. 2009;87 (1):59-65.
11. Nishimura R, Nishioka S, Fujisawa I, Shiku H, Shimada M, Sekiguchi S, et al. Tacrolimus inhibits the revascularization of isolated pancreatic islets. PLoS One. 2013;8(4):e56799.
12. Makhlouf L, Duvivier-Kali VF, Bonner-Weir S, Dieperink H, Weir GC, Sayegh MH. Importance of hyperglycemia on the primary function of allogeneic islet transplants. Transplantation. 2003;76(4):657-64.
13. Wee YM, Choi MY, Kang CH, Kim YH, Kim JH, Lee SK, et al. The synergistic effect of Tautomycetin on Cyclosporine A-mediated immunosuppression in a rodent islet allograft model. Mol Med. 2010;16(7-8): 298-306.
14. Watanabe M, Yamashita K, Kamachi H, Kuraya D, Koshizuka Y, Shibasaki S, et al. Efficacy of DHMEQ, a NF-κB inhibitor, in islet transplantation: II. Induction DHMEQ treatment ameliorates subsequent alloimmune responses and permits long-term islet allograft acceptance. Transplantation. 2013;96(5):454-62.
15. Xekouki P, Papalois A, Fotiadis C, Sfiniadakis J, Karampela E, Papadopoulou A, et al. In vivo test of two low doses of mycophenolate mofetil in an experimental model of islet allotransplantation. Transplant Proc. 2002;34(5):1446-8.
16. Baker MS, Chen X, Rotramel AR, Nelson JJ, Lu B, Gerard C, et al. Genetic deletion of chemokine receptor CXCR3 or antibody blockade of its ligand IP-10 modulates posttransplantation graft-site lymphocytic infiltrates and prolongs functional graft survival in pancreatic islet allograft recipients. Surgery. 2003;134(2):126-33.
17. Vieiro M, Ceballos C, Barrionuevo P, Hyon SH, Isturiz M, Argibay P. Inhibition of allospecific response in pancreatic islet transplantation: the glycan approach. Transplant Proc. 2005;37(1):242-4.
18. Melzi R, Battaglia M, Draghici E, Bonifacio E, Piemonti L. Relevance of hyperglycemia on the timing of functional loss of allogeneic islet transplants: implication for mouse model. Transplantation. 2007;83 (2):167-73.
19. Fan K, Wang H, Wei H, Zhou Q, Kou G, Hou S, et al. Blockade of LIGHT/HVEM and B7/CD28 signaling facilitates long-term islet graft survival with development of allospecific tolerance. Transplantation. 2007;84 (6):746-54.
20. Jung da Y, Kim EY, Joo SY, Park JB, Moon C, Kim SH, et al. Prolonged survival of islet allografts in mice treated with rosmarinic acid and anti-CD154 antibody. Exp Mol Med. 2008;40(1):1-10.
21. Påhlman C, Malm H, Qi Z, Veress B, Ferguson D, Bundick R, et al. Operational tolerance in nonvascularized transplant models induced by AR-C117977, a monocarboxylate transporter inhibitor. Transplantation. 2008;86(8):1135-8.
22. Wang X, Hao J, Metzger DL, Mui A, Ao Z, Verchere CB, et al. Local expression of B7-H4 by recombinant adenovirus transduction in mouse islets prolongs allograft survival. Transplantation. 2009;87(4):482-90.
23. Potiron N, Chagneau C, Boeffard F, Soulillou JP, Anegon I, Le Mauff B. Adenovirus-mediated CTLA4Ig or CD40Ig gene transfer delays pancreatic islet rejection in a rat-to-mouse xenotransplantation model after systemic but not local expression. Cell Transplant. 2005;14(5):263-75.
24. Jahr H, Hussmann B, Eckhardt T, Bretzel RG. Successful single donor islet allotransplantation in the streptozotocin diabetes rat model. Cell Transplant. 2002;11(6):513-8.