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REVIEW

Induction therapy in pancreas transplantation

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Summary

Induction therapy, the initial high-dose bolus of immunosuppression given perioperatively to transplant patients, is almost ubiquitous in pancreas transplantation. Despite the frequent use, scientific data on the risks and benefits of induction therapy are scarce, especially as it concerns use specifically for pancreas transplantation. Indeed, none of the currently used induction agents are approved as induction therapy for pancreas transplantation, yet potential benefit is largely extrapolated from trials in kidney transplant recipients. This review summarizes which induction therapy agents are available both now and historically, their mechanisms of action, and provides an overview of the published literature describing the use of these agents in simultaneous pancreas–kidney transplant and solitary pancreas transplant recipients. In summary, there are two multicenter randomized trials, several single-center randomized trials, and many other single-center descriptive reports. Overall, the main benefit of induction therapy is the ability to wean steroids earlier, and the main downside is a higher risk of opportunistic infections. Despite a lack of solid evidence, over 90% of pancreas transplants performed annually in the United States receive some type of induction immunosuppression.

Definition

Induction therapy refers to the initial bolus of high-dose immunosuppressive medications, usually given intravenously in the inpatient setting to prevent early acute rejection and possibly induce tolerance to the transplanted organ. When and where this term originated is somewhat unclear, but it may have its origins in oncology, where induction chemotherapy is the initial treatment bolus of chemotherapeutic agents given in the inpatient setting.

Induction therapy became commonplace in solid organ transplantation in the 1970s when the first formal induction agents became available, and was designed foremost to prevent early acute rejection. As pancreas transplant recipients have experienced higher rates of rejection than either kidney or liver recipients, most pancreas transplants have been and are currently being performed using some form of induction immunosuppression [1,2]. In particular, patients thought to be at very high risk of rejection, such as sensitized patients, patients receiving solitary pancreas transplants, repeat transplants, African American patients, or patients receiving positive crossmatch organs, are thought to benefit from induction therapy [3] for the prevention of early acute rejection. A second purpose of induction therapy is to reduce the overall amount of maintenance immunosuppression given early after transplantation, thus avoiding potential negative side effects of corticosteroids or calcineurin inhibitors [3]. Lastly, when they first became available for clinical use, it was hoped that induction agents would be able to promote immune hyporesponsiveness or tolerance to the transplanted organ, thus minimizing or avoiding the need for maintenance immunosuppression altogether [3].

As newer maintenance immunosuppressive medications were developed and used clinically, the question whether induction therapy, which is often quite costly, is always necessary, has generated renewed controversy. Because pancreas transplant recipients experience a higher rate of acute

rejection than recipients of other solid organs including kidney transplants [2] and because pancreas rejection has historically been difficult to diagnose, induction therapy continues to be routinely used in the pancreas transplant setting at most centers across the world [1]. And so, the question is not *if*, but *which* induction agent to use. Unfortunately, data on the use of induction therapy specifically for pancreas transplantation are scant. Only six prospective randomized studies that focus on simultaneous pancreas–kidney transplantation have been performed. Most suffer from low numbers of patients, use older induction agents that are no longer available, or comparison of different maintenance regimens in addition to different induction agents. Therefore, this review will focus mostly on common outcomes, such as graft survival and rejection, as definitive conclusions on less frequent events (such as infection rates, malignancy rates, or frequencies of the use of hypoglycemic agents) are difficult to support, given the scarcity of available data and the low power of the available studies. Parenthetically, none of the currently clinically available induction agents are labeled for use in pancreas transplantation [3].

Historic agents [4]

Minnesota ALG

In 1968, Najarian *et al.* isolated and purified anti-lymphoblast globulin (ALG) from horses for intravenous injection. After application for an investigational new drug status in 1970, Minnesota ALG was then manufactured for prevention and treatment of acute rejection in organ transplantation. Both Sollinger [4] and Sutherland [5] reported excellent outcomes using Minnesota ALG in simultaneous pancreas–kidney transplant recipients in the late 1980s, with corticosteroid, azathioprine, and cyclosporine maintenance therapy. After these reports, the improvement in patient and graft survival was so impressive that the discussion of whether to use induction immunosuppression became moot, and the remaining debate was only which induction agent to use. The FDA withdrew Minnesota ALG from the market in 1992.

OKT3

Muromonab-CD3 (Orthoclone OKT3; Ortho Biotech, Raritan, NJ, USA) was introduced in 1986 for the treatment of acute allograft rejection after kidney, heart, or liver transplantation and was the first monoclonal antibody licensed by the FDA. It was a murine monoclonal IgG2a antibody, and because of its purity and monoclonality had very predictable response rates. OKT3 bound to the T-cell receptor complex at the CD3 region and thus inhibited T-cell activation and proliferation, consequently resulting in T-cell depletion, which occurred via opsonization. OKT3 was given intravenously over 1 min at a dose of 5 mg/day with a half-life of about 18 h. Close monitoring for cytokine release syndrome was required during and after administration of the first several doses, and premedication with steroids, antihistamines, and acetaminophen was routine. Cytokine release syndrome manifested as fever, chills, malaise, nausea, headache, arthralgia, myalgia, vomiting, and/or diarrhea as a result of TNF release. Other common, and more concerning, side effects included pulmonary edema, aseptic meningitis, and seizures. Human anti-mouse antibodies (HAMA) developed in some instances; thus requiring patients who were re-dosed for OKT3 to be tested for these antibodies. OKT3 was voluntarily withdrawn from the US market because of decreased demand with supplies exhausted by 2010.

Daclizumab

Daclizumab (Zenapax; Roche Pharmaceuticals, Nutley, NJ, USA) is a recombinant mouse-human IL-2 receptor antagonist that binds to the alpha subunit, thus preventing IL-2 binding to the receptor and inhibiting T-cell activation. Daclizumab was given intravenously at 1 mg/kg every 2 weeks for 5 weeks. Daclizumab was stopped being produced by Roche in 2009 because of diminishing market demand. There were no safety concerns and most transplant studies suggested equal efficacy to basiliximab.

Currently available agents [3]

Equine ATG

Equine antithymocyte globulin (ATG) (eATG, ATGAM, Pharmacia&Upjohn Co, Kalamazoo, MI), is a polyclonal antilymphocyte globulin generated by immunizing horses to human T lymphocytes and harvesting the antibodies recovered from the horse serum. It has been approved by the FDA since 1981 for use in kidney transplants. Equine ATG reduces the serum lymphocyte count rapidly via complement-dependent cell-mediated cytotoxicity and resulting lysis of lymphocytes. Because of cross-reactivity of the antibodies to endothelial components, equine ATG is given as a slow IV infusion over at least 4 h via a central line to prevent thrombophlebitis. It is packaged as 50 mg of horse gammaglobulin/ml in 5 ml ampules. Dosing runs at 15 mg/kg daily for 14 days; however, shorter treatment courses are more commonly prescribed as the half-life is estimated at more than 5 days [6]. Common adverse reactions include fever, chills, thrombocytopenia, leucopenia, rashes, and systemic infection. Rare (5–10%) but serious side effects include serum-sickness, dyspnea or apnea, arthralgia, chest pain, flank pain, back pain, diarrhea, nausea, and vomiting. Equine ATG should be sterile filtered with a 0.2 micron filter before administration to minimize

acute side effects. CMV infections have been reported to be common after induction or treatment with equine ATG [7].

Rabbit ATG

Rabbit ATG (rATG is marketed as Thymoglobulin in the US by Genzyme Corp., Cambridge, MA, a subsidiary of Sanofi SA, Bridgewater, NJ, or as ATG-Fresenius by Fresenius SE &Co, KGaA, Bad Homburg, Germany in Europe) is a polyclonal anti-human thymocyte globulin of the IgG class which has been FDA approved since 1998 for *reversal* of acute rejection in kidney transplants. Similar to equine ATG, rATG is produced by immunizing rabbits with human thymocytes and recovering the antibodies from rabbit serum. Cross-reactive antibodies to human red blood cells are removed by adsorption to human blood cells obtained from US-registered or FDA-licensed blood banks. Thereafter, the drug is pasteurized to eliminate viruses. Because of the similarity of thymocyte epitopes to those on mature T lymphocytes, the binding of antibodies to T lymphocytes results in complement-dependent and/or antibody-dependent cell-mediated cytotoxicity, opsonization and cell phagocytosis by macrophages, and interaction with T-cell surface antigens, possibly resulting in apoptosis or anergy. T-cell depletion is the result. Rabbit ATG is given intravenously over 6 h or more at 1.0–1.5 mg/kg daily for 7–14 days. As a result of cell lysis, a cytokine release syndrome may occur, resulting in fever, chills, rashes, nausea, vomiting, diarrhea, hypotension, and dyspnea. This can occur especially with the first infusion. Thus, premedication (corticosteroids, antihistamines, acetaminophen) is commonly given. Thrombocytopenia and leucopenia are common and reversible. Although there are no direct comparisons of ATG therapy given intraoperatively versus postoperatively in pancreas transplant recipients, a study in kidney recipients suggests better early graft function and lower delayed graft function rates if ATG is administered intraoperatively [8] possibly related to reduced ischemia reperfusion injury.

Alemtuzumab

Alemtuzumab (Campath, Genzyme and Sanofi SA) is a humanized monoclonal IgG antibody engineered using a human Fc-gamma segment and murine antibody-binding regions against human CD52. It was initially developed to treat lymphoid malignancies. Administration results in prolonged and profound lymphocyte depletion [9]. It was FDA approved in 2001, but currently is available only off-label for transplantation. CD52 is a cell surface antigen found on T and B lymphocytes, macrophages, monocytes, and NK cells, as well as on some granulocytes. Precisely how binding to CD52 results in lymphocyte depletion remains unknown, but it is likely that induction of apoptosis or complement activation plays a role. Very mild cytokine release may occur after the initial dose of Campath. Campath is given as an IV infusion over 2 h, typically as a single dose of 30 mg, or as 20 mg given in two doses several days apart. Possible side effects include hypotension, fevers, rigors, chills, rash, bronchospasm, and shortness of breath; thus, premedication with antihistamines and acetaminophen is recommended. Because of profound lymphopenia, opportunistic infections are common, and monitoring is recommended.

Basiliximab

Basiliximab (Simulect; Novartis, East Hanover, NJ, USA) is a IL-2 receptor antagonist similar to daclizumab. It inhibits T-cell activation by binding to, and blocking, the IL-2 receptor alpha subunit, and is thus a non-T-cell depleting antibody. Basiliximab is given at 20 mg intravenously over 30 min; usually two doses are given 3–4 days apart. Basiliximab is usually very well tolerated. Even though it is potentially antigenic, anaphylactic reactions are rare.

Clinical trials and evidence of benefit for induction therapy

As induction therapy is commonly used in pancreas transplantation, and as there are several agents available, there have been a number of reports on the benefits (or lack thereof) of induction immunosuppression. Because pancreas transplantation is significantly less common than kidney, or even liver, transplantation, most of these reports are small, single-center studies, often with a focus on simultaneous pancreas–kidney transplantation, and including only small numbers of solitary pancreas transplants, either as pancreas-alone transplants, or pancreas-after-kidney transplants. In the sections below, we will highlight the conclusions of a few existing multicenter reports and those of some larger single-center studies as well. Table 1 summarizes existing multi- and single-center randomized trials as well as other comparative studies of pancreas transplantation induction therapies. Different dosing strategies for various induction methods used in the available studies are also delineated in Table 1.

Evidence for or against induction therapy in SPK transplants

Multicenter randomized trials

The largest multicenter randomized trial evaluating induction therapy in pancreas transplantation was performed right around the turn of the century. Known as the PIVOT

Table 1. Studies of Induction Therapies used in Pancreas Transplantation.

Authors	Participants		Induction therapy group	Maintenance immunosuppression	Graft survival	Acute rejection	Strengths	Weaknesses
Multicenter randomized trials of induction regimens								
Stratta [9,10]	SPK (n = 303)	Study	Daclizumab 1 mg/kg every other week ×5	CS, TAC, MMF	92% and 85% 6 month and 3 year kidney	21% and 25% 6 month and 3 year kidney	Large study	Daclizumab is no longer available
					86% and 77% 6 month and 3 year pancreas	4% and 10% 6 month and 3 year pancreas	3 year follow-up	
		Study	Daclizumab 2 mg/kg every other week ×2	CS, TAC, MMF	98% and 84% 6 month and 3 year kidney (P = NS)	12% and 27% 6 month and 3 year kidney (P = NS)		
					88% and 74% 6 month and 3 year pancreas (P = NS)	4% and 9% 6 month and 3 year pancreas (P = NS)		
		Control	None	CS, TAC, MMF	96% and 86% 6 month and 3 year kidney (P = NS)	36% and 30% 6 month and 3 year kidney (P = NS)		
					84% and 79% 6 month and 3 year pancreas (P = NS)	9% and 18% 6 month and 3 year pancreas (P = NS)		
Kaufman [11]	SPK	Study	Basiliximab, daclizumab, OKT-3, thymoglobulin, or ATG (n = 87)	CS, TAC, MMF	96.6% kidney, 83.9% pancreas 1 year	25% 1 year, BPAR 13% 1 year	Good-sized study	Variable induction
		Control	None (n = 87)	CS, TAC, MMF	92% kidney, 85.1% pancreas 1 year	31% 1 year (P = NS), BPAR 21% 1 year (P = NS)		
Single-center randomized trials of induction regimens								
Farney [12]	222 Kidney, SPK, PAK	Study	Alemtuzumab 30 mg once (n = 113)	CNI, MMF, CS (dosed based on risk)	1 year 94%, 3 year 88% kidney	14%	3 year follow-up	Variable ATG dose
			SPK (n = 24)	CNI, MMF, CS (dosed based on risk)	1 year 90% pancreas	12%		Few pancreas recipients
		Control	Rabbit ATG 3–7 doses every other day (n = 109)	CNI, MMF, CS (dosed based on risk)		26% (P = 0.02)		Variable steroid dose
			SPK, PAK (n = 18, including 4 PAK)	CNI, MMF, CS (dosed based on risk)		27% at 3 years (P = 0.03)		
Farney [13]	77 Kidney	Study	Alemtuzumab (n = 48)	CNI, MMF	6 month 96% kidney, 95% pancreas	Similar pancreas; kidney alone 0%	Steroid-free/ sparing	Variable ATG dose
	17 SPK and 4 PTA	Control	Rabbit ATG 3–7 doses every other day (n = 50)	CNI, MMF	6 month 96% kidney, 95% pancreas	Similar pancreas; kidney alone 20% (P < 0.05)		Few pancreas recipients

Table 1. continued

Authors	Participants		Induction therapy group	Maintenance immunosuppression	Graft survival	Acute rejection	Strengths	Weaknesses
Lo [14]	SPK	Study	Daclizumab or basiliximab (n = 17)	TAC, CS, MMF	76% pancreas, 88% kidney at > 6 months	>6 month, 12% kidney >6 month, 35% pancreas	Uniform groups	Small study
		Control	None (n = 17)	TAC, CS, MMF	88% pancreas, 100% kidney at >6 months (P = NS)	>6 month, 12% kidney (P = NS) >6 month, 24% pancreas (P = NS)		
Desai [15]	SPK	Study	OKT-3 2.5 mg/d for 10–14 days (n = 30, 16 increased)	CS/MMF or AZA/CNI starting 3–4 days pre-OKT3 finish				OKT-3 no longer available variable maintenance
		Control	OKT-3 5 mg/d for 10–14 days (n = 25, 11 increased)	CS/MMF or AZA/CNI starting 3–4 days pre-OKT3 finish				
Cantarovich [16]	SPK	Study	None (n = 25)	CSA starting day 0/ AZA/CS	90% kidney, 86% pancreas at mean 36 months	76% BPAR, mean 36 month follow-up	Defined groups	Long ATG course
		Control	ATG 10 days 1.5 mg/kg/d (n = 25)	CSA starting day 9/ AZA/CS	96% kidney, 86% pancreas at mean 36 months	36% (P < 0.01) BPAR, mean 36 month follow-up		Delayed CNI
Boesmueller [17]	SPK (n = 30)	Study	Alemtuzumab 30 mg once (n = 14)	TAC monotherapy	93% kidney and pancreas at 1 year	3 episodes of BPAR (kidney)	Steroid-free/ sparing	Small study
		Control	ATG (8 mg/kg total) (n = 16)	CS (3 months), MMF, TAC	100% kidney and 87% pancreas at 1 year	0 episodes of BPAR (kidney)		Different maintenance therapy
Nonrandomized comparisons of induction regimens using contemporary or historical controls								
Sundberg [18]	30 Kidney, 1 SPK, 1 PAK	Study	30 mg alemtuzumab (n = 16)	Single-dose CS/TAC/ MMF	94% kidney	12.5%	Steroid avoidance	Variable maintenance
		Control	Rabbit ATG 1.5 mg/kg/d 3–7 doses every other day (n = 16)	CS/TAC/MMF	100% kidney	12.5% (P = NS)		Variable ATG dose
Pascual [19]	SPK	Study	C1H 30 mg day 0 and day 1 (n = 91)	TAC/CS/MMF	94.8% and 86.2% 1 and 3 year kidney	3.1% kidney ACR, 18% kidney AMR	Same maintenance	2-dose alemtuzumab not commonly used
					91.7% and 88.9% 1 and 3 year pancreas		Defined induction	Very uniform recipient pool
		Control	Basiliximab 20 mg day 0 and day 4 (n = 39)	TAC/CS/MMF	97.4% and 91.8% 1 and 3 year kidney (P = NS) 87.2% and 81.8% 1 and 3 year pancreas (P = NS)	15.4% kidney ACR, 14.4% kidney AMR		

Table 1. continued

Authors	Participants		Induction therapy group	Maintenance immunosuppression	Graft survival	Acute rejection	Strengths	Weaknesses
Reddy [20]	SPK	Study	Alemtuzumab 30 mg (n = 41)	5 days CS, TAC/MMF	93% 1 year kidney 88% 1 year pancreas	15% clinical, 5% BPAR	Steroid-free/ sparing Defined induction	Not randomized
		Control	Rabbit ATG 1.5 mg/ kg/d × 4 (n = 33)	5 days CS, TAC/MMF	97% 1 year kidney (P = NS) 94% 1 year pancreas (P = NS)	12% clinical (P = NS), 6% BPAR (P = NS)		
Magliocca [21]	SPK	Study	C1H 30 mg day 0 and day 1 (n = 105)	TAC/CS/MMF	93.4% 2 year kidney 91.6% 2 year pancreas	20% kidney at 2 years 26.6% pancreas at 2 years	Same maintenance Defined induction	2-dose alemtuzumab not commonly used Very uniform recipient pool
		Control	Basiliximab 20 mg day 0 and day 4 (n = 226)	TAC/CS/MMF	89.7% 2 year kidney (P = NS) 85.3% 2 year pancreas (P = NS)	31.2% kidney at 2 years (P = 0.09) 17.9% pancreas at 2 years (P = NS)		
Kaufman [22]	SPK	Study	Alemtuzumab 30 mg (n = 50)	3 days CS/TAC/SIR	92% 1 year kidney (P = NS) 88% 1 year pancreas (P = NS)	6.1% 1 year, 8.2% 2 year	Steroid-free/ sparing Defined induction	Same maintenance
		Control	Rabbit ATG 1 mg/kg/d for 6 mg/kg total (n = 38)	3 days CS/TAC/SIR	97.4% 1 year kidney (P = NS) 100% 1 year pancreas (P = NS)	2.6% 1 year, 5.3% 2 year (P = NS)		
Burke [23]	SPK	Study	OKT-3 5 mg/d for 5–7 days (n = 14, including 5 donor BMTs)	TAC/CS/MMF		5 episodes within 1 month (30%)	Same maintenance	Variable induction
		Control	No induction (n = 9)	TAC/CS/MMF		0 episodes within 1 month		
Bazerbachi [24]	SPK	Study	ATG 1 mg/kg/d for 5 doses (n = 79)	TAC/CS/MMF	90%, 87%, and 78% 1, 3, and 5 year pancreas 98%, 95%, and 95% 1, 3, and 5 year kidney	6% and 14% at 3 and 12 months	Defined induction Same maintenance	Not randomized
		Control	Basiliximab 20 mg day 0 and day 4 (n = 49)	TAC/CS/MMF	93%, 89%, and 83% 1, 3, and 5 year pancreas (P = NS) 98%, 98%, and 95% 1, 3, and 5 year kidney (P = NS)	21% and 27% at 3 and 12 months (P < 0.05)		

study, it compared two dosing strategies of daclizumab induction with no induction in SPK recipients [10,11]. Daclizumab was given either as 1 mg/kg in five doses every other week, or as 2 mg/kg in two doses 2 weeks apart, or not at all. All participants received corticosteroids, tacrolimus, and mycophenolate as maintenance immunosuppression. Twenty-four transplant centers participated, and enrolled 303 participants. A preliminary report of 182 participants at 6 months showed similar patient and graft survival among the three induction therapy groups [10]. Biopsy-proven acute kidney rejection occurred in 21% (1 mg/kg × 5 doses daclizumab group), 12% (2 mg/kg × 2 doses daclizumab group), and 36% (no-induction group) of SPK recipients, whereas acute pancreas rejection occurred in four patients in each daclizumab arm and nine patients in the no-induction arm. The 3-year follow-up data included the outcomes of 298 SPK transplants and showed similar patient and graft survival between the induction and no-induction groups. Moreover, similar rates of acute rejection were also observed, although rejection occurred later in subjects who underwent daclizumab induction compared with those treated without induction therapy [11]. Kidney graft survival at 3 years was reported between 84 and 86%, and pancreas graft survival was slightly lower at 74–79%. Comparisons of kidney function by creatinine measurements showed no differences between groups; however, participants who had experienced acute rejection had marginally higher creatinine levels at 3 years compared with those who had never experienced rejection (1.7 vs. 1.5 mg/dl, $P = 0.056$) [11].

In 2001, a second multicenter induction trial was performed, which demonstrated no clear benefit to induction therapy with respect to patient and graft survival rates. However, use of induction therapy was associated with a lower rate of early rejection episodes [12]. Participants were primary SPK recipients from brain dead donors who did not experience DGF. Maintenance immunosuppression was with corticosteroids, tacrolimus, and mycophenolate. Enrollment resulted in 87 participants each in the induction and noninduction groups. In the induction group, 59% of participants received one of the two IL-2 receptor antagonists (basiliximab or daclizumab), and 41% received a depleting induction regimen (either muromonab-OKT3, thymoglobulin, or antithymocyte globulin). Patient and graft survival at 1 year were similar between the induction and no-induction groups, as were the number of overall acute rejection episodes in the first year (25 vs. 31%, $P = 0.28$). Biopsy-proven acute rejection rates were 13 vs. 21% in the first year, respectively, with a P-value of 0.08. CMV viremia occurred most frequently in the depleting-agents induction group at 46 vs. 7% in the nondepleting induction group, but tissue-invasive CMV did not differ between induction and noninduction arms at 3.5%.

International pancreas transplant registry data

Despite these randomized multicenter reports, Gruessner *et al.* reported as part of the International pancreas transplant registry (IPTR), that most pancreas transplant recipients continue to receive some form of induction therapy [1]. This includes roughly over 90% of pancreas-alone transplants, about 90% of simultaneous pancreas–kidney recipients, and 85% of pancreas-after-kidney recipients. Baseline immunosuppression consisted mostly of tacrolimus and mycophenolate, and one of every three pancreas recipients was discharged from the hospital steroid-free. In this report, the risk of pancreatic graft failure was lower when depleting antibody induction was used and when tacrolimus was part of the maintenance therapy.

While two of these large reports suggest that pancreas transplantation can be successfully performed without induction therapy, the study populations were very homogeneous and at low risk for rejection. Both large multicenter trials excluded repeat transplant recipients, DCD pancreas transplants, or high-risk pancreas transplants (e.g. with a positive crossmatch or highly sensitized patients). These important exclusions reinforce that despite existing evidence showing that induction therapy is not absolutely necessary for successful pancreas transplantation, over 85–90% of transplant programs continue to prescribe induction therapy for pancreas allograft recipients [1]. Of those receiving induction therapy, over 90% receive T-cell depleting agents and 10% or less receive nondepleting antibody therapies [1].

Single-center randomized trials

Since the late 1990s, five single-center randomized trials of induction therapy in pancreas transplantation have been published. The two most recent studies compared alemtuzumab induction with thymoglobulin [13,14]. While both studies mostly targeted kidney recipients, several SPK, PTA, and PAK recipients were also included. Patient survival was 96% at 3 years, and pancreas graft survival was 95% at 6 months [14], and 90% at 1 year [13]. Among kidney-only recipients, biopsy-proven acute rejection occurred in fewer patients in the alemtuzumab group over the first 3 years (12 vs. 27%, $P = 0.03$), and a similar observation was noted when SPK recipients only were analyzed (13 vs. 36%, $P = 0.07$), although the P-value here is not significant which is probably because of the relatively low numbers of SPK transplants included in the analysis [13,14].

Before these two most recent randomized trials of induction therapy, three single-center induction trials were performed in the 1990s. The most recent one compared interleukin-2 receptor blockade with no-induction therapy in 34 SPK recipients on steroid, tacrolimus, and mycophenolate

maintenance therapy, and found that patient and graft survival were similar, as were biopsy-proven rejection episodes at 6 months of the kidney (12% each group) and pancreas (35 vs. 24%, $P = 0.45$) [15]. Desai *et al.* compared two different dosing strategies of muromonab-OKT3 in 55 SPK recipients with either corticosteroids and mycophenolate, or azathioprine and calcineurin inhibitor maintenance therapy, with the calcineurin inhibitor starting 3–4 days prior to completion of OKT3 [16]. OKT3 was given at low dose (2.5 mg/day) or at high dose (5 mg/day) for 10–14 days. No differences in outcomes were observed, and both dosing strategies were equally effective in reducing CD3 counts. Lastly, Cantarovich *et al.* compared no induction with a 10-day course of ATG given at 1.5 mg/kg/day in SPK recipients maintained on steroids, azathioprine, and cyclosporine starting on day 0 in the no-induction group versus on day 9 in the ATG induction group [17]. Patient and graft survival were similar for both organs, but biopsy-proven kidney acute rejection was much higher in the no-induction group (76 vs. 36%, $P < 0.01$).

Most recently, Boesmueller *et al.* [18] reported a small randomized trial of alemtuzumab induction versus antithymocyte globulin induction in SPK recipients with the intent of steroid sparing tacrolimus monotherapy in the alemtuzumab group. Graft survival and rejection rates were similar between groups, and most patients receiving alemtuzumab and tacrolimus monotherapy remained steroid-free at 1 year post-transplant.

Thus, it appears that the benefit of induction lies chiefly in its ability to significantly reduce the incidence of acute rejection, which would be expected to lead to a decrease in early repeat hospitalizations and lower cumulative corticosteroid utilization. Short-term patient and graft survival are excellent, regardless of the type of induction therapy used.

Controlled but nonrandomized comparisons of induction regimens

Most recent nonrandomized studies of induction therapy in pancreas transplantation have focused on alemtuzumab induction and steroid elimination. In all cases, patient survival exceeds 95% at 1 year, and 1-year allograft survival of the pancreas is greater than 85% in all reports [19–25]. Given these overall excellent outcomes, it is difficult to prove a clear benefit of one type of induction therapy over another without evaluating acute rejection rates and allograft function.

Alemtuzumab versus antithymocyte globulin

Sundberg *et al.* reported on rapid steroid elimination in a small group of mostly kidney-only recipients the setting of alemtuzumab or thymoglobulin induction, in which two patients included SPK and PAK recipients [19]. Outcomes of patient and kidney allograft survival were 94% in the alemtuzumab group vs. 100% in the thymoglobulin group, with a total of 32 recipients enrolled, and no statistical differences seen.

Kaufman *et al.* compared alemtuzumab induction with rabbit ATG induction in 88 SPK recipients on tacrolimus and sirolimus maintenance therapy after a 3-day steroid taper (i.e. early withdrawal) [23]. Patient survival at 1 year was similar in both groups and better than 96%, and at 3 years remained excellent above 91% in both groups. Kidney and pancreas allograft survival at 1 and 3 years was not significantly different between the alemtuzumab and ATG induction groups. Serum creatinine over the first 2 years postoperatively was identical between groups. Rejection rates were very low at 1 and 2 years (6.1 vs. 2.6% and 8.2 vs. 5.3%), and again, no difference between groups was seen. The authors, however, did observe slightly more CMV infections in the thymoglobulin-treated group.

A comparison between alemtuzumab and ATG induction was also reported by Reddy *et al.* in 2008, with identical 1-year patient survival, and no differences between the groups in kidney (93 vs. 97%, P = NS) or pancreas (88 vs. 94%, P = NS) 1-year allograft survival [21]. Furthermore, renal function (as measured by serum creatinine) and fasting blood glucose levels were similar; however, glycated hemoglobin levels were lower in the alemtuzumab group compared with the thymoglobulin group (5.3 vs. 5.6%, $P = 0.0021$). All patients were maintained on tacrolimus and mycophenolate after a rapid 5-day corticosteroid taper, and 80% in both groups remained steroid-free at 1 year. There was no difference in rejection rates (15 vs. 12%, P = NS).

Alemtuzumab versus basiliximab

Alemtuzumab induction was compared with basiliximab induction by Pascual *et al.* and Magliocca *et al.* [20,21]. All patients were maintained on steroids, mycophenolate, and tacrolimus, and received two doses of alemtuzumab induction or basiliximab induction. Pascual *et al.* reported outstanding 1- and 3-year patient survivals (above 97 and 94%, respectively) [20]. Allograft survival of the kidney and pancreas were similar in both groups at 1 and 3 years, with 3-year kidney graft survival being 86 vs. 92%, and pancreas graft survival being 89 vs. 82% in alemtuzumab and basiliximab induction groups, respectively. Glycated hemoglobin was slightly higher 3 months post-transplant in the basiliximab-treated group (at 5.6 vs. 5.1%, $P = 0.019$), which may relate to more frequent steroid boluses given for a slightly higher rate of acute rejection that was seen in the basiliximab group. Magliocca compared a larger cohort from the same center, and found no statistically significant differences in 2-year patient survival (99 vs. 95%), kidney allograft survival (93 vs. 90%), and pancreas allograft

survival (92 vs. 85%), between alemtuzumab and basiliximab induction groups, respectively [21]. Acute rejection rates were statistically the same, as were rates of delayed graft function. However, similar to several other T-cell depleting agent induction studies [20], more CMV was seen in the alemtuzumab group (29.3 vs. 16.4%, $P = 0.002$) [21].

Antithymocyte globulin versus basiliximab

Bazerbachi *et al.* compared thymoglobulin induction (1 mg/kg/d for 5 days) with basiliximab induction (20 mg on day 0 and day 4), in combination with triple maintenance immunosuppression [25]. Patient survival at 1, 3, and 5 years was above 95%. The 1-, 3-, and 5-year pancreas allograft survival was similar between thymoglobulin and basiliximab groups, but declined steadily over time from 90 vs. 93% to 87 vs. 89%, and to 78 vs. 83%, respectively at 1,3, and 5 years. Kidney allograft survival remained above 95% at all time-points. Serum creatinine was no different at any time between groups. There was a difference in early acute rejection rates at 3 months of 6 vs. 21% ($P = 0.01$) in the thymoglobulin vs. basiliximab groups, respectively, but this difference was not as remarkable at 1 year (14 vs. 27%, respectively, $P = 0.049$).

Based on these relatively recent comparisons of induction therapy in SPK transplantation, one can conclude that alemtuzumab and thymoglobulin are associated with the lowest rates of acute rejection, probably at the cost of a higher rate of viral complications, mainly in the form of CMV viremia [7,12,22,23]. CMV infection rates in the form of viremia in these studies range from 16 to 46% with depleting antibody induction, and around 7% with nondepleting induction. One study, however, demonstrated similar rates of tissue-invasive CMV disease at around 4% [12]. Therefore, some surgeons try to avoid a CMV-mismatch (donor positive, recipient negative) when depleting induction is considered otherwise necessary. CMV prophylaxis with oral valganciclovir for 6 months may be advisable if the decision to proceed with transplantation is made in these situations, as it has been shown in kidney transplantation to decrease the early incidence of CMV infection [26]. In addition, early post-transplant neutropenia and lymphopenia are more common after T-cell depletion. Long-term outcomes of allograft function or survival do not appear to be affected by the choice of induction therapy in primary, relatively low immunological risk SPK recipients.

Currently, there are no randomized trials in pancreas transplantation designed to examine the value of calcineurin inhibitor avoidance or minimization. However, several trials summarized in this review employ a steroid sparing regimen [14,18,20]. Overall, these protocols have similar rates of pancreas rejection and graft survival compared with non-steroid-sparing regimens (Table 1).

Uncontrolled descriptive reports on outcomes of induction therapy in pancreas transplantation

There is a wealth of small- and medium-sized descriptive studies of induction therapy for pancreas transplantation. Back in the mid-1990s, Corry *et al.* described a regimen without induction therapy, instead utilizing immediate IV tacrolimus with steroids and azathioprine or mycophenolate in 123 recipients of pancreatic allografts [27]. Most were SPK recipients. Kidney allograft survival was 94%, and pancreas survival 83% with a median follow-up of 18 months.

Descriptive studies using different dosing strategies of thymoglobulin include the following: Knight *et al.* described the use of rabbit ATG at 1.5 mg/kg/d for 5 days with sirolimus/cyclosporine and a selective steroid taper maintenance for 6 months and were switched to mycophenolate/sirolimus and selective corticosteroid maintenance [28]. Among 25 SPKs, kidney graft survival was 100% at 1 year, and two pancreatic allografts were lost during that time. Creatinine clearance at 1 year was 63 ± 19 ml/min/1.73 m^2, and fasting blood glucose was 90 ± 9 mg/dl. Similarly, Tan *et al.* reported using ATG induction for 3–7 doses with 1.5 mg/kg/day and triple maintenance immunosuppression with steroids, tacrolimus, and mycophenolate in PAK and PTA recipients [29]. Graft survival was 96% at 1 year, with a 27% acute rejection rate and 9% rate of opportunistic infection. Bonatti *et al.* described the outcomes of 112 pancreas transplant recipients with different dosing strategies of thymoglobulin induction, and triple maintenance immunosuppression with steroids, tacrolimus, and mycophenolate [30]. Patient survival was 96% at 1 year and 93% at 2 years. Kidney graft survival was 95% at 1 year and 89% at 3 years, and pancreas graft survival was slightly lower at 87% at 1 year and 79% at 3 years. More recently, Dawson *et al.* described effects of rabbit ATG induction on sensitization for future transplants, based a review of UNOS/OPTN data, and found that using no-induction therapy or using IL-2 receptor blockade induction may be risk factors for sensitization to future transplants [31].

Zhang *et al.* described 91 SPK transplants performed with 2-dose basiliximab induction and triple maintenance immunosuppression with steroids, tacrolimus, and mycophenolate without a control group [32]. Again, patient survival was very good at 91% at 1 year, and declined to 88% at 7 years. Kidney graft survival was 90% at 1 year, 85% at 3 years, 79% at 5 years, and 71% at 7 years. Pancreas graft survival was slightly lower at 87% at 1 year, 81% at 3 years, 71% at 5 years, and 59% at 7 years. Biopsy-proven acute rejection rates for the renal allograft were 14% at 1 year, 21% at 3 years, 25% at 5 years, and 29% at 7 years.

Several descriptive studies have reported on the use of alemtuzumab induction in a mixed group of pancreas

transplant recipients. Muthusamy *et al.* reported in 2007 on 102 pancreas recipients with 2-dose alemtuzumab induction and tacrolimus/mycophenolate maintenance therapy [33]. One-year patient survival was above 95%. One-year pancreas allograft survival was 90% for SPKs ($n = 83$), 80% for PAKs ($n = 15$), and 100% for PTAs ($n = 4$). Acute rejection rates were 22% in SPKs, 27% in PAKs, and 0% in PTAs. Glycated hemoglobin levels at 3 months were 5.2 ± 0.6 mg/dl. Uemura *et al.* described outcomes of single-dose alemtuzumab induction with tacrolimus/mycophenolate maintenance without long-term corticosteroids in a small group of mixed pancreas transplant recipients [34]. They noted acute cellular rejection occurred in 42% of recipients, antibody-mediated rejection in 7%, and CMV viremia or infection in 28%. Despite the relatively high rate of rejection and CMV, the outcomes were reported to be excellent. One-year patient and pancreas allograft survival was 100%; 3-year graft survival remained at 100% in the SPK ($n = 17$) and PAK ($n = 5$) groups, and was 83% in the PTA group ($n = 6$). Allograft function at 1 and 3 years was excellent (HbA1c < 6 mg/dl) in all groups.

Conclusions

Induction therapies used in pancreas transplantation continue to evolve, and safer, less toxic agents such as basiliximab, ATG, and alemtuzumab continue to be used. Despite the absence of pancreas transplant labeling for existing induction agents, and the absence of convincing evidence of better efficacy, induction therapy is firmly entrenched in pancreas transplantation immunosuppressive regimens. The relatively low volume of pancreas transplants performed at individual centers combined with the lack of interest from pharmaceutical companies to sponsor trials of induction therapies in pancreas transplantation results in limited solid evidence in the existing literature. The nonrandomized, retrospective nature of many reports involving small and mixed groups of subjects further complicates interpretation of the literature. While the interpretable literature is scant, certain conclusions from existing reports can be tentatively made.

First, T-cell depleting induction therapy probably allows for more successful minimization or early withdrawal of corticosteroids while maintaining low early rejection rates. Most studies comparing depleting and nondepleting antibody induction therapy indicate depleting antibody therapy is associated with a lower rate of acute rejection. Second, most transplant surgeons and physicians believe certain groups of patients are at higher risk of rejection than primary SPK recipients and these include solitary pancreas transplants, repeat pancreas transplants, highly sensitized recipients, and African American and Hispanic recipients. It is precisely these patients that stand to benefit most from induction therapy. Third, T-cell depletion is probably associated with higher rates of early leucopenia and CMV infection than non-T-cell depleting induction therapy and consideration should be given to closer monitoring and/or prophylaxis in this setting. Based on numerous preclinical studies supporting a potential benefit of antithymocyte globulin in reducing ischemia reperfusion injury (IRI), the possible role of this agent in reducing IRI in clinical pancreas transplantation should be explored further. As newer induction agents become available and show initial efficacy in kidney transplantation, it is likely they will be tested in the setting of pancreas transplantation. This will hopefully lead to improved efficacy and safety, and especially lower rates of rejection in immunologically at-risk populations.

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