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REVIEW

Induction therapy in heart transplantation: where are we now?

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Summary

Although induction therapy has been used in heart transplantation for many years, its role has not been fully elucidated. Early safety concerns relating to OKT3 or intensive lymphocyte-depleting regimens have largely been addressed by modern induction protocols using rabbit antithymocyte globulin (rATG [Thymoglobuline® or ATG-Fresenius]) and interleukin-2 receptor antagonist (IL-2RA) agents, but although the number of randomized controlled studies has expanded there are still gaps in the evidence base. Rejection prophylaxis may be somewhat more effective with rATG than IL-2RA agents, but this has not been proven conclusively. Administration of induction therapy to support delayed introduction of calcineurin inhibitors in patients at risk of renal dysfunction is relatively well documented and widely used. Increasingly, it is recognized that sensitized patients and individuals with primary graft function are suitable candidates for induction therapy, and the possibility that rATG may inhibit cardiac allograft vasculopathy is also of considerable interest. Until the question of whether rATG is associated with increased risk of infection, routine prophylaxis is advisable. IL-2RA induction has an excellent safety profile. Dosing rATG according to lymphocyte count reduces cumulative dose without compromising efficacy. Further controlled trials are required to determine when and how to deploy induction most effectively following heart transplantation.

Introduction

Almost all immunosuppressive regimens for solid organ transplant recipients are designed to provide additional potency during the first few days and weeks after transplantation, when the risk of allograft rejection is greatest. Typically, specialized antibody induction preparations or high-dose intravenous corticosteroids – or a combination of both – are administered to achieve adequate immunosuppressive efficacy in this period. Approximately, half of all heart transplant centers use some form of antibody induction therapy, but the evidence for its benefit is not yet clear-cut [1].

Induction therapy can take the form of a polyclonal agent, with a broad spectrum of specificity and multiple immunological targets, or monoclonal agents that target a specific receptor (Table 1). Over the last decade, the newer polyclonal agents rabbit antithymocyte globulin [rATG (Thymoglobuline®, Genzyme Coporation, Cambridge, MA, USA)] and, to a lesser extent, Fresenius-ATG, have superseded the earlier ATGAM (Minnesota-ATG) preparation. Concurrently, use of the murine monoclonal antibody OKT3 declined and it has now been withdrawn from the market. OKT3 has largely been replaced by the monoclonal antibody basiliximab (Simulect®, Novartis Pharma AG, Basel, Switzerland), which following the withdrawal of daclizumab is now the only interleukin-2 receptor antagonist (IL-2RA) available. Alemtuzumab (Campath, Genzyme Coporation, Cambridge, MA, USA), another monoclonal antibody, showed promise as a potent lymphocyte-deplet-

Table 1. Characteristics of available induction agents.

	Polyclonal	IL-2 receptor antibodies
Type of agent	A mixture of antibodies which are active against different targets	Recombinant DNA-derived chimeric (human-murine) monoclonal antibody
Preparations	Rabbit-derived antithymocyte globulin (rATG) (Thymoglobuline®, Genzyme) Rabbit-derived antithymocyte globulin (Fresenius-ATG, Fresenius) Horse-derived antithymocyte globulin (ATGAM, Upjohn)	Basiliximab (Simulect®, Novartis)
Immunomodulatory effect	Dose-dependent T-cell depletion in blood and peripheral lymphoid tissues Possibly also co-stimulation blockade, adhesion molecule modulation and B-cell depletion [2–6]	Selective inhibition of IL-2 driven T-cell proliferation
Proposed mode of action	Complement-dependent lysis and activation-associated apoptosis	Inhibition of the CD25 IL-2 receptor on the surface of antigen-activated T-cells
Spectrum of specificity	Broad	Narrow
Licensed indication/s	Thymoglobuline®: Immunosuppression in solid organ transplantation, including the prevention of graft rejection in renal transplantation, treatment of steroid resistant graft rejection in renal transplantation and prevention of graft rejection in heart transplantation. ATG-Fresenius: Prophylaxis and therapy of rejection crisis in organ and tissue transplantation	Prophylaxis of acute organ rejection in patients receiving renal transplantation as part of an immunosuppressive regimen that includes cyclosporine and corticosteroids

ing agent following kidney transplantation, [7–9] but has been withdrawn from the market. Indeed, at present rATG (Thymoglobuline®) and ATG-Fresenius are the only induction agents licensed in heart transplantation.

Analysis of the impact of induction therapy on allograft rejection and other efficacy or safety outcomes in heart transplantation is handicapped by the relative scarcity of randomized trials. Most prospective studies of induction regimens have been single-center studies involving fewer than 100 patients, although larger retrospective studies with long-term follow-up have compared efficacy and long-term safety between different induction agents. This review considers the available clinical data relating to the different categories of induction therapy in heart transplant recipients and discusses particular types of patients in whom induction may be a useful immunosuppressive option.

Induction therapy with standard maintenance immunosuppression

Several prospective and retrospective studies have evaluated addition of induction therapy to a standard triple regimen of calcineurin inhibitor (CNI), an antimetabolite and corticosteroids in heart transplant patients (Table 2). For rATG, data are limited to one large retrospective trial [10] and one smaller prospective study [11] using Thymoglobuline®, each of which compared the two preparations with no control arm. The retrospective analysis in 484 recipients showed a significantly lower rate of biopsy-proven acute rejection (BPAR) in favor of rATG (Thymoglobuline®) after multivariate analysis was used to adjust for confounding factors [10], but no difference in immunosuppressive efficacy was observed in a smaller prospective single-center trial by Schnetzler *et al.* For the IL-2RA agents basiliximab and daclizumab, prospective, randomized trials have assessed their effect versus control groups receiving no induction therapy and have shown mixed results (Table 2). Of these, the most robust study design was that of Mehra *et al.* [12]. In a double-blind, placebo-controlled, randomized, multicenter trial in 56 patients, the time to first BPAR was numerically longer with basiliximab (73.7 days versus 40.6 with placebo, n.s.), but the rate of BPAR grade $\geq$3A did not differ between the basiliximab and control groups at month 6 ($P = 0.552$) or month 12 ($P = 0.307$) [12] (Table 2). A previous randomized trial by Beniaminovitz *et al.*, in contrast, showed a significant reduction in BPAR grade $\geq$2 by month 12 in patients receiving daclizumab (18%) versus no induction (63%, $P = 0.04$) [13]. This difference between the two trials may have been because of more selective criteria for the trial by Mehra, which is likely to have reduced the overall risk of rejection in the study population, and by inclusion of BPAR grade 2 in the results from Beniaminovitz. Two prospective [14,15] and three retrospective [16–18] trials have compared IL-2RA induc-

Table 2. Biopsy-proven acute rejection (BPAR) in studies of induction therapy with standard triple immunosuppression regimens in heart transplant recipients.

						BPAR			
Study	Design	*N*	Investigational drug	Comparator	Duration of follow-up	Endpoint	Investigational drug	Comparator	*P* value
rATG									
Zuckermann 2000 [10]	Retrospective Single center	484	rATG (Thymoglobuline®)	ATG-Fresenius	5 years	BPAR grade ≥ 2 or grade 2 with hemodynamic compromise	28%	58%	<0.01
Schnetzler 2002 [11]	Prospective Randomized Open- label Single center	50	rATG (Thymoglobuline®)	ATG-Fresenius	12 months	Mean (SD) number of BPAR episodes Mean time to first BPAR	2.9 (1.2) 41.5	2.9 (1.9) 48.0	n.s. n.s.
IL-2RA									
Mehra 2005 [12]	Prospective Randomized Double-blind Multicenter	56	Basiliximab	Placebo	12 months	Time to BPAR grade $\geq$ 3A to month 6 (days) Incidence of BPAR to grade $\geq$ 3A month 12	73.7 (59.7) 48.0%	40.6 (53.3) 35.5%	n.s. 0.307
Beniaminovitz 2000 [13]	Prospective Randomized Open- label Single center	55	Daclizumab	No induction	12 months	Incidence of BPAR grade ≥ 2	18%	63%	0.04
Hershberger 2005 [45]	Prospective Randomized Open- label Multicenter	434	Daclizumab	No induction	12 months	Incidence of any BPAR	25.5%	41.3%	Not provided*
IL-2RA versus rATG									
Mattei 2007 [14]	Prospective Randomized Multicenter Open-label	80	Basiliximab	rATG (Thymoglobuline®)	6 months	BPAR grade $\geq$ 1B	50.0%	45.2%	0.37
Carrier 2007 [15]	Prospective Randomized Multicenter Non-inferiority Open-label	35	Basiliximab	rATG†	6 months	BPAR grade 3 or 4	35%	17%	Non-inferiority for basiliximab was not shown‡
Flaman 2006 [16]	Retrospective Single center	48	Basiliximab	rATG (Thymoglobuline®)	12 months	Mean (SD) biopsy score¶	0.85 (0.40)	0.63 (0.15)	0.12

Table 2. continued

Study	Design	*N*	Investigational drug	Comparator	Duration of follow-up	BPAR			
						Endpoint	Investigational drug	Comparator	*P* value
Carlsen 2005 [17]	Retrospective Single center	40	Daclizumab	rATG (Thymoglobuline®)	3 months	Treated BPAR grade ≥ 2	45%	60%	n.s.
Chou 2008 [18]	Retrospective Single center	43	Basiliximab¶	rATG§	12 months	BPAR grade ≥ 2	0%	0%	–

*Primary endpoint (composite of moderate or severe cellular rejection, hemodynamically significant graft dysfunction, a second transplantation, or death or loss to follow-up within 6 months) was 35.6% with daclizumab versus 47.7% with placebo ($P = 0.007$).
†rATG preparation not specified.
‡Upper limit of the 1-sided 90% CI for the difference was 37.2%, exceeding the 22.5% noninferiority margin.
¶Sum of rejection scores according to International Society for Heart and Lung Transplantation (ISHLT) classification (Grade 0, 0; Grade 1A, 1; Grade 1B, 2; Grade 2, 3; Grade 3A, 4; Grade 3B, 5; Grade 4, 6) divided by the number of biopsies performed.
§Maintenance immunosuppression was cyclosporine with everolimus in basiliximab group, and cyclosporine or tacrolimus in the rATG group (all with corticosteroids).

tion versus rATG (Table 2). Of the two prospective studies of basiliximab versus rATG, one showed no difference in rejection [14] while the other reported a higher rate of rejection with basiliximab [15]; survival rates were similar in each trial [14,15]. Overall, it appears that the efficacy in preventing rejection may be somewhat higher with rATG, but the data are not conclusive.

Induction therapy and delayed CNI therapy

Patients who have severe renal dysfunction either pre- or peri-operatively, or who are at high risk of renal insufficiency, may benefit from delayed introduction of CNI therapy to minimize CNI-related nephrotoxicity during the period of highest CNI exposure in the immediate post-transplant period. Antibody induction can provide rejection prophylaxis while kidney function normalizes, or at least improves, before CNI initiation. This strategy is used frequently in heart transplant recipients, although the evidence base is currently restricted to retrospective studies (Table 3). The time to introduction of CNI therapy has varied between studies, from as soon as day 4 [19] or 5 [20] after transplant, up to a mean of day 12 [21] or even as long as 18 or 29 days in some patients [21,22].

Three of these analyses, using rATG (Thymoglobuline®) [21] or IL-2RA agents [19,20], have compared delayed CNI introduction versus a standard CNI regimen (Table 3). Rejection prophylaxis was highly effective in the delayed CNI patients, with two analyses reporting a lower rate of BPAR than with a standard CNI regimen [20,21]. Encouragingly, the cohorts with renal dysfunction at the time of transplant demonstrated similar serum creatinine levels to their counterparts with normal renal function at subsequent time points (Table 3). It is difficult, however, to determine the benefit of such an approach reliably in the absence of more data. Only one of these retrospective studies compared induction (basiliximab) with delayed CNI versus no induction and standard CNI, in 57 patients at risk of poor post-operative renal function [19]. In that small study, the difference in mean (SD) serum creatinine at hospital discharge did not differ significantly between groups (1.5 [0.6] mg/dl with basiliximab versus 1.7 [0.8] mg/dl with no induction).

Use of induction therapy with CNI-free regimens

Although complete avoidance of CNI therapy has been investigated extensively in renal transplantation [23–27], with conflicting results, only two publications have described CNI avoidance in cardiac transplantation [28,29]. In a pilot trial, Meiser *et al.* examined CNI avoidance in eight patients using a regimen of sirolimus, mycophenolate mofetil (MMF), and corticosteroids [28]. All

Table 3. Induction therapy and delayed introduction of calcineurin inhibitors in heart transplant recipients.

Study	Design & baseline renal status	*N*	Investigational drug	Comparator	Duration of follow-up	Biopsy-proven acute rejection				Renal function			
						Endpoint	Investigational drug	Comparator	*P* value	Endpoint	Investigational drug	Comparator	*P* value
rATG													
Cantarovich 2004 [21]	Retrospective Single center SCr $\geq$ 150 μM in investigational group	32	rATG (Thymoglobuline®) with CNI only when SCr <150 μM	rATG (Thymoglobuline®) Standard CsA	12 months	BPAR grade $\geq$ 3A	27%	59%	<0.001	Mean (SD) SCr, μmol/l	118 (30)	101 (35)	n.s.
IL-2RA													
Rosenberg 2005 [19]	Retrospective Single center High risk of post-operative renal dysfunction in all patients*	57	Basiliximab CsA from day 4 post-tx	No induction Standard CsA	-	BPAR grade $\geq$ 2A	0%	13%	0.13	Mean (SD) SCr at hospital discharge, mg/dl	1.5 (0.6)	1.7 (0.8)	n.s.
Delgado 2005 [20]	Retrospective Single center Baseline SCr $\geq$ 200 μmol/l in all patients	14	Basiliximab CsA $\geq$ 5 days post-tx	rATG† CsA <5 days post-tx	6 months	Mean (SD) biopsy score†	0.25 (0.22)	0.65 (0.34)	0.026	Mean SCr, μmol/l	179 (45)	154 (30)	0.24
Sanchez-Lazaro 2011 [22]	Case reports Single center Acute renal failure immediately post-tx in all patients Single center	6	Daclizumab with CNI only when renal function recovered (days 7–18 post-tx)	None	Not stated	BPAR	Grade 1 (n = 2) or grade 2 (n = 6) BPAR in all 6 cases			Recovery of renal function (not defined)	Achieved in all 6 cases		

SCr, serum creatinine; CsA, cyclosporine; tx, transplantation.

*Defined as poor baseline renal function (creatinine clearance 35–50 ml/min or serum creatinine >2.5 mg/dl), a markedly reduced cardiac index despite inotropic therapy, had an intraaortic balloon pump, or had received a left ventricular assist device.

†rATG preparation not specified.

patients received rATG (rATG-Fresenius) for 4 days after transplantation. Over a follow-up period of 3–12 months, patient survival was 100% and the incidence of BPAR grade ≥ 2 was 25%. Mean serum creatinine initially decreased and remained stable thereafter. The most frequent adverse events were effusions (38%), peripheral edema (50%), and wound healing complications (50%). Gonzalez-Vilchez treated 20 patients who had significant pretransplant renal insufficiency with an mTOR inhibitor (sirolimus or everolimus), MMF, and corticosteroids [29]. In the nine patients who were also given IL-2RA induction, the incidence of treated acute rejection was lower (3/9, 33%) than in induction-free patients (8/11, 73%). Ten of the patients (50%), however, were eventually converted to a standard CNI-based regimen because of mTOR inhibitor-related adverse events. These scanty data suggest that CNI-free protocols are associated with higher rejection rates following heart transplantation, although rATG induction appears to be more effective than IL-2RA agents and might be favored in this setting.

rATG administration and cardiac allograft vasculopathy

The impact of cardiac allograft vasculopathy (CAV) on long-term survival following heart transplantation is well documented [30]. The etiology of endothelial injury in CAV is both immunologic (e.g., activation of alloreactive T-cells) and nonimmunologic (e.g., pre-transplant coronary artery disease, viral infections, metabolic disorders, and ischemia-reperfusion injury) [30]. Several experimental studies have shown that ATG preparations may have a beneficial effect against ischemia-reperfusion injury in non-transplant models [31–33], an effect that has been confirmed in kidney transplant recipients [34]. This raises the intriguing possibility that ATG induction might inhibit the development of CAV after heart transplantation. Clinical examination of this question, however, requires long-term follow-up if any effect is to be identified since CAV develops progressively over time [35]. At present, data are limited to three single-center retrospective analyses [36–38]. The largest of these, by Zuckermann *et al.*, analyzed risk factors for CAV in 662 patients who survived for at least 1 year after heart transplantation [36]. During up to 5 years' follow-up, 111 patients (16.9%) exhibited signs of CAV. Multivariate analysis revealed that induction therapy with rATG (Thymoglobuline®) compared with any other induction therapy showed a significant independent protective effect against development of CAV (risk ratio 0.634, $P < 0.001$) or severe CAV (risk ratio 0.277, $P < 0.001$). In another single-center series, 10-year follow-up of 163 patients given rATG (Thymoglobuline®) induction demonstrated a numerically lower rate of CAV over time: 7%, 32%, and 50% at 1, 5, and 10 years compared with 7%, 42%, and 70%, respectively, in 48 controls who did not receive any induction [37]. Lastly, Zhang *et al.* have described a statistically significant reduction in the incidence and severity of CAV, and a longer time to first diagnosis, among 25 heart transplant patients given ATG-Fresenius versus 25 induction-free controls over a mean follow-up of 13.4 years [38]. The cumulative dose of rATG may also be relevant: one study involving 30 heart transplant recipients showed a trend to less CAV in patients given rATG (ATG-Fresenius) for 7 days vs. 3 days (28% vs. 50%, $P = 0.05$) [39].

The question of whether the benefits of rATG in experimental models translate to a meaningful reduction in the risk of CAV following heart transplantation merits further examination.

Safety concerns

Infection

Concerns about a higher rate of viral, fungal or bacterial infection in heart transplant patients who receive induction therapy stem initially from early data with OKT3 [40,41]. The advent of routine antiinfective prophylaxis and the switch to other induction agents, and successively lower doses over time, may have helped to overcome this issue although robust evidence in heart transplantation is lacking.

In kidney transplants, trials have suggested that rATG is associated with a higher rate of infection, particularly CMV infection, although doses may now be lower than those employed in these studies [34]. In liver transplantation, recent prospective and retrospective data have not shown a higher rate of infections overall, or CMV infection specifically, using rATG as an adjunct to CNI-based regimens [42]. No trial has compared rATG versus no induction in this setting. In heart transplant recipients, two large observational studies have compared infection rates with rATG versus no induction in adult [43] and pediatric [44] patients. One of these, an analysis of 2086 patients in the United Kingdom national registry during 1995–2008 showed a higher incidence of infection with rATG induction compared with no induction during the first year post-transplant [43], while a multicenter registry of 2374 children found that rATG conferred a lower risk of infections [44]. In the absence of conclusive evidence, it would seem reasonable to ensure that rATG-treated patients receive prophylactic therapy for viral and bacterial infection and lymphocyte count should be monitored closely.

Prospective, randomized trials of IL-2RA induction versus controls have not shown any increase in infection rates following heart transplantation [12,13,45] (Table 4). In the double-blind trial of basiliximab versus placebo by Mehra

Table 4. Infection and infection-related deaths with induction therapy and standard triple therapy immunosuppression in heart transplant recipients.

						Infection				Infection-related death		
Study	Design	*N*	Investigational drug	Comparator	Duration of follow-up	Endpoint	Investigational drug	Comparator	*P* value	Investigational drug	Comparator	*P* value
rATG												
Zuckermann 2000 [10]	Retrospective Single center	484	rATG (Thymoglobuline®)	ATG-Fresenius	5 years	Any infection Viral infection CMV infection	80% 53% 17%	62% 39% 13%	– <0.05 –	36%	29%	n.s.
Schnetzler 2002 [11]	Prospective Randomized Open- label Single center	50	rATG (Thymoglobuline®)	ATG-Fresenius	12 months	Any infection	57.7%	75.0%	n.s.	2 pneumonia-related deaths	0	–
IL-2RA												
Mehra 2005 [12]	Prospective Randomized Double-blind Multicenter	56	Basiliximab	Placebo	12 months	Any infection as Any adverse event Serious adverse event	84.0% 48.0%	74.2% 35.5%	n.s. 0.417	–	–	–
Beniaminovitz 2000 [13]	Prospective Randomized Open- label Single center	55	Daclizumab	No induction	12 months	Readmission because of Infection CMV infection	39.3% 25.0%	25.0% 18.5%	n.s. n.s.	1 pneumonia-related	1 infection 1 CMV-related	–
Hershberger 2005 [45]	Prospective Randomized Open- label Multicenter	434	Daclizumab	No induction	12 months	Any infection	38.6%	32.9%	n.s.	Death from infection in patients receiving cytolytic therapy: daclizumab 15.0%, controls 0%		
IL2RA versus rATG												
Mattei 2007 [14]	Prospective Randomized Multicenter Openlabel	80	Basiliximab	rATG (Thymoglobuline®)	6 months	Any infection CMV infection	50.0% 15.8%	61.9% 23.8%	0.366 –	0%	14.3%	0.027
Carrier 2007 [15]	Prospective Randomized Multicenter Non-inferiority Open-label	35	Basiliximab	rATG*	6 months	Any infection CMV infection at 3 months	71% 5.9%	78% 38.5%	0.514 0.051	0	0	–

Table 4. continued

Study	Design	*N*	Investigational drug	Comparator	Duration of follow-up	Infection				Infection-related death		
						Endpoint	Investigational drug	Comparator	*P* value	Investigational drug	Comparator	*P* value
Flaman 2006 [16]	Retrospective Single center	48	Basiliximab	rATG (Thymoglobuline®)	12 months	Number of infections Mean (SD) infections per patient	19 0.79 (0.8)	26 1.13 (0.8)	0.16 –	–	–	–
Carlsen 2005 [17]	Retrospective Single center	40	Daclizumab	rATG (Thymoglobuline®)	12 months	CMV infection Bacterial infection	10.0% 15.0%	5.0% 50.0%	n.s. 0.05	1 (septicemia)	0	–
Chou 2008 [18]	Retrospective Single center	43	Basiliximab	rATG*†	12 months	Any infection	42.9%	37.9%	0.757	1 (sepsis)	0	–

CMV, cytomegalovirus.
*rATG preparation not specified.
†Maintenance immunosuppression was cyclosporine with everolimus in basiliximab group, and cyclosporine or tacrolimus in the rATG group (all with corticosteroids).

et al., the rate of infections reported as adverse events or serious adverse events was similar in both treatment arms [12], consistent with data in kidney [46] and liver [42] transplantation. Similarly, the largest randomized trial of IL-2RA induction, which compared daclizumab to induction-free controls, showed no increased infection among patients receiving daclizumab [45]. Of note, there were more infectious deaths in the daclizumab arm (6/40) versus controls (0/37) within the subpopulation who received cytolytic therapy (OKT3, ATGAM or rATG) to treat severe rejection. Rejection therapy with lymphocyte-depleting agents in patients receiving IL-2RA induction appears to result in over-immunosuppression and should be avoided. Overall, however, the rate of infection or CMV infection does not appear to be affected by use of IL-2RA induction following heart transplantation, as confirmed by a recent meta-analysis [47].

The available comparisons of IL-2RA induction versus rATG in heart transplant populations have tended to show numerically fewer infectious episodes in patients receiving IL-2RA agents (Table 4), although there were no differences in survival. In the largest of these trials ($n = 80$), Mattei *et al.* observed a higher rate of infectious death in the rATG (Thymoglobuline®) group (14.3% vs. 0%, $P = 0.027$), but the absolute numbers were low (six cases versus 0) [14]. CMV infection rates were generally similar between treatment groups [14,17], other than one trial which showed a trend to more cases of CMV infection detected by polymerase chain reaction (PCR) during the first 3 months after transplantation with rATG compared with basiliximab [15].

Malignancy

Any intervention that could increase the risk of malignancy in heart transplant recipients is of particular concern since rates of cancer are higher in thoracic transplant recipients than in kidney or liver transplant patients [48]. The question of whether antibody induction is associated with a higher risk of malignancy in heart transplant patients has persisted for the last 20 years. Generally, evaluation of malignancy risk requires interrogation of registry or large-scale retrospective data to obtain adequate patient numbers and duration of follow-up. However, since malignancies usually develop only several years after transplantation, it is difficult to determine whether an induction agent given immediately postoperatively is causally related to the subsequent onset of cancer. Moreover, since it is now widely believed that any excessive immunosuppression is associated with an increased risk of malignancy, determining the relative contributions of specific components within an immunosuppressive regimen is extremely difficult.

Early reports of the use of OKT3 suggested that it markedly elevates the risk of post-transplant lymphoma [49], confirmed by subsequent long-term retrospective analyses in OKT3-treated patients [49–51]. These findings have not been borne out in patients receiving ATG preparations. In an analysis of data from over 22 000 heart transplant patients registered with the international Collaborative Transplant Study, Opelz *et al.* reported that ATG induction did not confer an added risk for lymphoma versus no induction during the periods 1985–1989, 1990–1994 or 1995–2001 [48]. More recently, Emin *et al.* did not find any evidence of increased mortality from lymphoma in ATG-treated adult heart transplant recipients in the UK [43]. Single-center reports have suggested that the risk of malignancy in patients receiving rATG (Thymoglobuline®) is low, but the data are not conclusive [10,11,37]. El-Hamamsy *et al.* assessed the role of rATG (Thymoglobuline®) in the development of neoplasms in 207 patients at a single center [52]. Multivariate analysis did not indicate that rATG increased the risk of cancer, but rATG-treated patients who did develop malignancy had early diagnoses and died more rapidly postdiagnosis. However, the analysis spanned the period from 1982 to 2002 so its relevance to modern rATG dosing regimens may be limited. In children, Dayton *et al.* reported that the use of induction therapy was not associated with development of post-transplant lymphoproliferative disease (PTLD) during long-term follow-up of 324 heart transplant recipients, but no distinction was drawn between different types of induction therapy [53].

IL-2RA induction does not confer any increase in malignancy risk [48,54]. In their analysis of data from the Collaborative Transplant Society, Opelz and colleagues observed no increase in risk of malignancy using IL-2RA induction, based on a cohort of over 3000 heart transplant patients [48].

Clinical considerations

Patient selection

Certain categories of heart transplant recipients may gain a particular benefit from induction therapy. First, in patients who develop primary acute graft failure where there is suspicion of an immunological cause such as hyperacute or antibody-mediated rejection, lymphocyte-depleting induction therapy may be helpful to suppress the antibody response [55]. Moreover, graft dysfunction is often associated with acute renal failure, a setting in which the use of rATG or IL-2RA induction to delay the introduction of CNI might be beneficial.

Second, induction is likely to be an appropriate option in patients at high risk of acute rejection. The presence of circulating preformed antibodies is a growing problem in heart transplantation, with sensitization occurring in post-transfusion patients, multiparous women, and reoperative sternotomy in patients with or without a left ventricular assist device (VAD). Such patients face longer waiting times, a higher risk of death on the waiting list and a higher incidence of rejection [56]. Despite various strategies to reduce circulating antibodies, analyses have shown that patients with raised pre-transplantation panel reactive antibody (PRA) levels ($\geq 11\%$) tend to have earlier and more severe rejections with significantly lower post-transplant survival [57,58]. A consensus conference on sensitized patients in 2008 concluded that induction therapy with rATG should be considered for patients with a high risk for antibody-mediated rejection [59].

Third, patients at risk of post-transplant renal dysfunction are candidates for induction therapy to facilitate delayed CNI introduction without loss of efficacy. In addition to patients with severe renal dysfunction pre- or perioperatively, patients with an intraaortic balloon pump or VAD may benefit from delayed CNI therapy to maximize early renal function. In cases of severe pretransplant renal insufficiency, rATG induction with CNI-free immunosuppression could be attempted, with careful monitoring, but caution is advised.

Dosing and safety issues

When using rATG induction, it should be borne in mind that dosing regimens have evolved over the last decade, both in kidney [34] and heart transplantation [39,60–62]. Faggian *et al.* assessed a shorter course of rATG (ATG-Fresenius), with a single high intraoperative dose followed by 1.5 mg/kg for 5 days ($n = 14$), and observed similar efficacy to a standard 7-day course ($n = 16$) [39]. It appears that the early high dose is necessary to maintain efficacy, however, since a fixed dose of 1.5 mg/kg for 5 days alone may offer less effective rejection prophylaxis than 7 days [60]. A more promising strategy may be to individualize rATG dosing with the aim of maintaining lymphocyte count at 100/μl or higher [61,62]. In 2002, Krasinskas *et al.* demonstrated that dosing ATG preparations (Thymoglobuline® or ATGAM) based on peripheral CD3 lymphocyte count in heart transplant recipients led to a reduction in the cumulative ATG dose from 10–15 mg/kg to 1–5 mg/kg without an increase in acute rejection [62]. Koch and colleagues have since confirmed that this lymphocyte-adapted dosing can preserve efficacy with a significant reduction in cumulative rATG (Thymoglobuline®) dose compared with a conventional fixed-dose regimen [61].

To minimize the risk of infection, prophylactic therapy should be given routinely in patients given rATG. These agents should be used only with extreme caution to treat rejection in patients given basiliximab within the previous

6 months to avoid overimmunosuppression. Lymphocyte monitoring during rATG administration is a promising approach to minimize dosing while preserving efficacy, and a more robust examination of this strategy would be valuable.

Conclusions

Induction therapy has been part of the immunosuppressive armamentarium for more than 40 years, but there is still uncertainty about when and how it should be used in heart transplantation. Early safety concerns arising from the administration of OKT3 or high-dose lymphocyte-depleting regimens, particularly regarding infectious complications, have largely been overcome. Nevertheless, although there is a growing pool of data demonstrating its efficacy and tolerability, the case for induction therapy in all heart transplant recipients remains unproven. Deployment of induction to delay the start of CNI therapy in patients at risk of poor renal function after heart transplantation is effective without a safety penalty, and is currently one of the most frequent uses for induction therapy in heart transplant recipients. Other groups, such as sensitized patients or those with primary graft dysfunction, are also well-placed to benefit from induction therapy. Notably, the potential for inhibiting progression to CAV with rATG induction is of considerable interest and future studies are awaited with interest.

Rejection prophylaxis may be somewhat more effective with rATG than IL-2RA agents, but confirmatory data are required. Although perhaps less potent than rATG, IL-2RA induction has an excellent safety profile. Modern protocols in which rATG dosing is adjusted based on lymphocyte count have helped to reduce dosing with a potential benefit for safety and cost without compromising efficacy. Further controlled trials are required to identify the most suitable candidates for induction therapy and to define the optimal combination of induction and maintenance regimens in specific types of heart transplant recipients.

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