Use of Thymoglobulin® (antithymocyte immunoglobulin) in renal transplantation: practical guide

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Abstract

The combination of immunosuppressive drugs is part of the treatment regimen of patients undergoing kidney transplantation (RT). Thymoglobulin®, a rabbit immunoglobulin directed against human thymocytes, is the most commonly agent used for induction therapy in RT in the US. In Brazil, Thymoglobulin® is approved by ANVISA for the use in patients who underwent kidney transplantation and despite being widely used, there are controversies regarding the drug administration. We prepared a systematic review of the literature, evaluating studies that used Thymoglobulin® for induction and for acute rejection treatment in patients undergoing RT. The review used the computadorized databases of EMBASE, LILACS and MedLine. Data were extracted from the studies concerning general features, methodological characteristics and variables analyzed in each study. From the results, a practical guide was prepared analyzing various aspects on the use of Thymoglobulin® in patients submitted to RT.

Keywords: antilymphocyte serum; immunoglobulins, intravenous; kidney transplantation.

Introduction

Combined immunosuppressant therapy is commonly used in the protocols developed for kidney transplant patients.[1] The term induction therapy refers to immunosuppressive treatment prescribed specifically in the perioperative period, with effects extending until after the transplant procedure. Current international recommendations on induction therapy for renal transplantation suggest the use of biological agents such as monoclonal and polyclonal antibodies against T cells.[1] Thymoglobuline®, a rabbit anti-thymocyte globulin, is the most commonly used drug in induction therapy regimens offered to kidney transplant patients in the United States.[2] Interleukin-2 receptor antagonists (IL2-Ra) such as Basiliximab are also recommended.[1]

In Brazil, Thymoglobuline® was approved by the National Health Surveillance Agency (ANVISA) for use in the prevention and treatment of organ (kidney, liver, pancreas etc.) transplant patients facing acute rejection. Thymoglobuline® is also used in the treatment of aplastic anemia and in cases of graft-*versus*-host disease.[3]

Although Thymoglobuline® is broadly prescribed to kidney transplant patients, there is no clear favorite among treatment schemes or choice of route of infusion, dosage, duration, and ideal therapy start time.

This study aimed to assess the scientific evidence on the prescription of Thymoglobuline® to kidney transplant patients in terms of route of administration, dosage, duration of treatment, and ideal therapy start time.

Objective

This systematic review included studies in which Thymoglobuline® was prescribed to kidney transplant patients on induction therapy or individuals treated for rejection, with the purpose of listing the recommended uses of Thymoglobuline® in kidney transplantation scenarios.

Methods

An extensive search for papers using keywords "Thymoglobuline," "randomized," and "renal" was carried out in the EMBASE (Excerpta Medica Database), LILACS (Latin American and Caribbean Health Sciences), and MedLine (Medlars On Line) databases. The resulting references were considered for analysis and included in a literature review.

The review included randomized trials comparing anti-thymocyte globulin (ATG) to other drugs used in induction therapy and analyzing the efficacy of ATG administered at different times.

The search included every study published in English and enrolling adult patients carried out within a thirty-year period (1982-2012), in which the use of Thymoglobuline® was assessed for its two indications: induction therapy and treatment of rejection. The following variables were analyzed: route of infusion, number of days of administration, time of first infusion, total dose infused, adverse events (leucopenia, delayed graft function, cytomegalovirus infection, and tumors), graft rejection rate, graft survival, and reversal rate of cases of rejection treated with Thymoglobuline®. Papers in which Thymoglobuline® was not analyzed, non-randomized trials, and studies enrolling liver/pancreas transplant patients were excluded, as described in Table 1. Two reviewers read the titles and abstracts of the references retrieved from the search. The papers were then independently assessed based on the inclusion criteria and data sets were extracted from the included studies. Two reviewers extracted the data from each included study independently. The first author's name and the year of publication were used to identify the studies. General data, methodological characteristics, and the variables considered in each study were collected. Only randomized trials were included in this review; some were open-label and others were blind studies. All were intention-to-treat studies and groups were compared for at least one primary outcome.

Eight questions concerning the use of Thymoglobuline® by kidney transplant patients were prepared, as seen below. The main aspects considered were:

- Time of infusion;
- Total dose infused;
- Route of infusion;
- Prevention and treatment of acute rejection; the cases of acute rejection included in this study were confirmed by biopsy;
- Delayed graft function (DGF), defined as need for dialysis within the first week of transplantation;
- Graft and patient survival;
- Management of leucopenia;
- Prevalence and prevention of cytomegalovirus (CMV) infection; the authors defined CMV infection as positive viremia detected by increased titers of IgG, and/or IgM-positive tests, and/or CMV-positive PCR tests;

Results

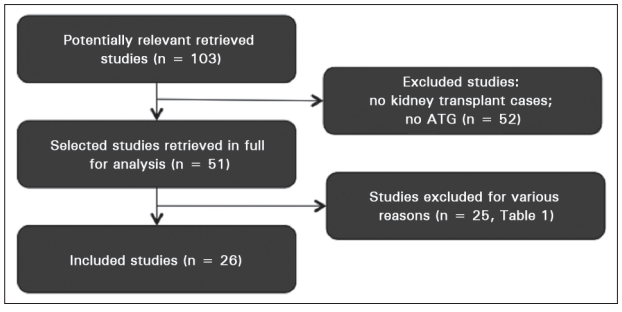
The flowchart used to identify the included studies, as recommended by PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses),[4] is shown in Figure 1.

The first search yielded 103 studies, of which 26 met the inclusion criteria (randomized studies on the use of Thymoglobuline®). Nineteen discussed the use of the medication in induction therapy

Table 1 Characteristics od reviewed and excluded studies

Study	Reasons for exclusion
Chaparro *et al.* 2009[39]	Not randomized
Díaz *et al.* 2008[40]	Not randomized
Kuypers *et al.*2005[41]	Kidney/pancreas transplants
Mehrabi *et al.* 2007[42]	Not randomized
Agha *et al.* 2002[43]	Not randomized
Moura *et al.* 2006[44]	Not randomized
Nicoluzzi *et al.* 2010[45]	Pancreas transplants
Sampaio *et al.* 2010[46]	Not randomized
Sancho *et al.* 2006[47]	Not randomized
Laftavi *et al.* 2011[48]	Not randomized
Anil Kumar *et al.* 2008[49]	Did not assess anti-thymocyte globulin
Ciancio *et al.* 2008[50]	Did not assess anti-thymocyte globulin
Buchler *et al.* 2007[51]	Did not assess anti-thymocyte globulin
Aoun *et al.* 2007[52]	Kidney/pancreas transplants
Bogetti *et al.* 2005[53]	Liver transplants
Hardinger *et al.* 2005[54]	Did not assess anti-thymocyte globulin
Lo *et al.* 2004[55]	Did not assess anti-thymocyte globulin
Stegall *et al.* 2003[56]	Did not assess anti-thymocyte globulin
Kim *et al.* 2012[57]	Not randomized
LaMattina *et al.* 2012[58]	Not randomized
Ciancio *et al.* 2011[59]	Did not assess anti-thymocyte globulin
Hourmant *et al.* 1994[60]	Not randomized
Martin *et al.* 2011[61]	Not randomized
Thielke *et al.* 2005[62]	Not randomized
Ulrich *et al.* 2011[63]	Not randomized

Figure 1. Flowchart used in the identification of studies.



regimens (Table 2) and seven in the treatment of cases of severe rejection (Tables 3 and 4).

Table 2 is a summary chart of the included studies and contains data on sample sizes, comparisons between groups, transplant types (live or deceased donor), and clinical outcomes.

The recommendations over the use of Thymoglobuline® in kidney transplant patients are outlined below in the form of the most frequently asked questions in clinical practice, according to experts.

Question 1a

What is the preferred route of infusion of Thymoglobuline® for kidney transplant patients?

Answer:

Route of infusion: there is no direct comparison between different routes of infusion in the literature. Only five of the randomized trials[5-9] on the use of Thymoglobuline® in induction therapy included in this review - adding up to 562 patients - described the route of infusion. Peripheral catheters were used in only one study[6] with 58 patients. Central catheters or arteriovenous fistulae were the devices of choice in the other studies. In the study in which patients were given peripheral devices, Thymoglobuline® was administered intraoperatively or postoperatively; no adverse effects were reported.

Question 1b

What are the adverse events reported for kidney transplant patients given peripheral infusions of Thymoglobuline®?

Answer

A retrospective[10] study reported data from 244 peripheral infusions of ATG or basiliximab, with Thymoglobuline® accounting for 152 infusions. None of the patients were given concurrent courses of heparin or hydrocortisone. Adverse events were mild and rare. Local pain was observed in four patients (2.6%), erythema in two (1.3%), and edema in one patient (0.7%). No cases of thrombosis or thrombophlebitis were described. Patients with adverse events were maintained on peripheral drug infusion. The authors of the study concluded this was a safe infusion route.

Table 2 Randomized studies on the use of anti-thymocyte globulin in the induction therapy of kidney transplant patients

	Type of study	Comparison	N	Acute rejection rate	Chronic injury rate	Delayed graft function	Survival (+ 6-12 months)	Graft survival (+ 6-12 months)	Graft loss rate
Ciancio *et al.* 2010[64]	RCT, live donors	ATG *vs.* Alemtuzumab *vs.* Daclizumab	13	0 (0%)	0 (0%)	2 (15.3%)	NR	NR	0 (0%)
			13	1 (7.69%)	3 (23.%)	0 (0%)			0 (0%)
			12	1 (8.33%)	0 (0%)	0 (0%)			0 (0%)
					p = 0.01				
Brennan *et al.* 1999[21]	RCT, deceased donors	ATG *vs.* Atgam	48	2 (4.2%)	NR	1/72 (1%)	47 (98%)	47 (98%)	0 (0%)
							23 (96%)	20 (83%)	3 (13%)
			24	6 (25%)			*p* = 0.606	*p* = 0.020	
				p = 0.014					
Brennan *et al.* 2006[13]	RCT, deceased donors	ATG *vs.* Basiliximab	141	22 (15.6%)	NR	57 (40.4%)	135 (95.7%)	128 (90.8%)	13 (9.2%)
							131 (95.6%)	123 (89.8%)	14 (10.2%)
			137	35 (25.5%)	NR	61 (45.5%)	*p* = 0.90		*p* = 0.68
				p = 0.02		*p* = 0.54			
Noël *et al.* 2009[8]	RCT, deceased donors	ATG *vs.* Daclizumab	113	17 (15%)	NR	35 (31.5%)	108 (95.6%)	93 (82.3%)	20 (17.7%)
							110 (96.5%)	98 (86.0%)	16 (14%)
			114	31 (27.2%)		50 (44.6%)	*p* = 0.75	*p* = 0.47	*p* = 0.47
				p = 0.016		*p* = 0.044			
Mourad *et al.* 2004[23]	RCT, deceased or live donors	ATG *vs.* Basiliximab	53	5 (9.4%)	NR	16 (30%)	51 (98.1%)	50 (96.2%)	2 (3.8%)
							52 (98.1%)	50 (94.2%)	2 (3.9%)
			52	5 (9.6%)		15 (28%)			
Abou-Ayache *et al.* 2008[26]	RCT, deceased donors	ATG *vs.* Daclizumab	55	8 (14.5%)	NR	20 (36%)	54 (98%)	52 (95%)	NR
							53 (98%)	51 (94%)	
			54	9 (16.7%)		17 (32%)			
				p = NS					
Ciancio *et al.* 2005/2008[27,65]	RCT, deceased donors	ATG *vs.* Alemtuzumab *vs.* Daclizumab	30	6 (17%)	5 (14%)	4 (13.3%)	25 (85%)	24 (81%)	1 (3.33%)
							26 (88%)	22 (74%)	6 (20%)
			30	7 (24%)	11 (37%)	2 (6.7%)	25 (85%)	24 (82%)	1 (3.33%)
							p = 0.89	*p* = 0.66	
			30	7 (25%)	3 (11%)	2 (6.7%)			
					p = 0.02	*p* = 0.58			
Khosroshahi *et al.* 2008[11]	RCT, live donors	Immunosuppression # *vs.* Immunosuppression # + ATG	37	12 (32.4%)	NR	NR	NR	NR	0 (0%)
									1 (3.22%)
			31	4 (12.9%)					
				p = 0.05					
Farney *et al.* 2008[5]	RCT, deceased or live donors	ATG *vs.* Alemtuzumab	45	9 (20%)	NR	8 (18%)	NR	43 (96%)	NR
								30 (94%)	
			32	0 (0%)		5 (16%)		*p* = NS	
				p = 0.007		*p* = NS			
Hernandez *et al.* 2007[18]	RCT, deceased donors	ATG + Cyclosporine + Azathioprine *vs.* Basiliximab + Cyclosporine + MMF *vs.* Basiliximab + Tacrolimus + MMFBasiliximabe + Tacrolimus + MMF	80	12 (15%)	NR	22 (27.5%)	80 (100%)	73 (91%)	NR
							79 (98.7%)	72 (90%)	
			80	11 (13.8%)		26 (32.5%)	78 (97.5%)	65 (82%)	
			80	13 (16.3%)		32 (40%)			
				p = NS					

Continued Table 2.

Thomas *et al.* 2007[16]	RCT, deceased donors	Alemtuzumab + Tacrolimus Tacrolimus *vs.* ATG + Tacrolimus + MMF + steroids	11 10	2 (18.2%) 3 (37.5%)	NR	NR	11 (100%) 7 (87.5%)	9 (85.7%) 7 (87.5%) *p* = NS	1 (9%) 2 (25%)
Goggins *et al.* 2003[6]	RCT, Deceased donors	ATG IO *vs.* ATG PO	27 31	1 (3.6%) 5 (16%) *p* = 0.11	NR	4 (14.8%) 11 (35.5%) *p* < 0.05	27 (100%) 31 (100%)	27 (100%) 31 (100%)	NR
Lebranchu *et al.* 2002[7]	RCT, deceased donors	Basiliximab + Cyclosporine *vs.* ATG + Cyclosporine	50 50	4 (8%) 4 (8%)	NR	9 (18%) 11 (22%)	49 (98%) 50 (100%)	47 (94%) 48 (96%)	2 (4%) 0
Charpentier *et al.* 2003[14]	RCT deceased donors	Tacrolimus *vs.* ATG + Tacrolimus *vs.* ATG + Cyclosporine	185 186 184	47 (25.4%) 28 (15.1%) 39 (21.2%) *p* = 0.004	NR	NR	180 (97%) 183 (98.4%) 179 (97%)	172 (93.2%) 177 (95.2%) 167 (90.8%)	10 (5.4%) 7 (3.76%) 16 (8.69%) *p* = 0.23
Thibaudin *et al.* 1998[15]	RCT, deceased and live donors	RCT, deceased and live donors	42 47	27 (64%) 18 (38%) *p* = 0.02	NR	14 (33%) 13 (28%) *p* = NS	NR	32 (76%) 42 (89%) *p* = 0.04	12 (28.5%) 5 (10.63%)
Kyllonen *et al.* 2007[12]	RCT, deceased donors	ATG *vs.* Basiliximab *vs.* Immunosuppression *	53 58 44	6 (11.3%) 0 (0%) NR	NR 7 (15.9%) *p* < 0.025	3 (5.7%) 14 (24.1%)	53 (100%) 58 (100%) 42 (95.4%)	52 (98.1%) 56 (96.6%) 41 (93.2%)	1 (1.88%) 1 (1.72%) 4 (9.09%)
Soulillou *et al.* 1990[9]	RCT, deceased donors	ATG *vs.* 33B3.1	50 50	5 (10%) 7 (14.5%) *p* = NS	15 (30%) 16 (32%)	NR	48 (96%) 48 (96%)	42 (85%) 42 (85%)	8 (16%) 7 (14%)
Shidban *et al.* 2003[17]	RCT, Deceased donors	ATG *vs.* Basiliximab	50 25	4 (8%) 3 (12%) *p* = NS	NR	22 (44%) 19 (76%) *p* = 0.01	NR	NR	NR
Tullius *et al.* 2003[66]	RCT, deceased donors	ATG *vs.* Basiliximab	62 62	22 (35%) 20 (32%) *p* = NS	NR	NR	62 (100%) 58 (93.5%)	NR	2 (3.22%) 6 (9.6%)

ATG: antithymocyte globulin; Atgam (equine anti-thymocyte globulin); MMF: mycophenolate mofetil; IO: intraoperative; PO: postoperative. # Cyclosporine + mycophenolate mofetil or azathioprine and prednisone; * Cyclosporine + azathioprine and steroids. Farney *et al.* 2008[5] looked into renal transplant data only.

Recommendation

Although some studies suggest peripheral infusions are safe, central catheters are preferred. When a central line cannot be used, infusions can be made through a large peripheral vein.

Question 2a

What dosage of Thymoglobuline® should be given to patients on induction therapy?

Answer

The search yielded no randomized trials directly comparing different dosages of ATG. In the included studies, the dosage of Thymoglobuline® ranged from 1-1.5 mg/kg/day (maximum of 2.5 mg/kg/day). Induction therapy was generally started on D0 (i.e., on the day of transplantation) and as long as on D10. Drug infusion took no less than four hours in most studies. The

Table 3 Randomized studies on the use of anti-thymocyte globulin in the treatment of kidney transplant patients with acute rejection

	Comparison	N	Rejection reversal rate
Hoitsma *et al.* 1982[31]	ATG (4 mg/kg per day and additional doses of 2-7 mg/kg)** *vs.* steroids	20	18 (90%)
		20	15 (75%)
Hilbrands *et al.*1996[33]	ATG (200 mg in alternate days for ten days) *vs.* methylprednisolone	19	16 (84%)
		17	9 (53%)
Theodorakis *et al.* 1998[32]	ATG (4 mg/kg per day for seven days) *vs.* methylprednisolone	25	NR*
		25	
Baldi *et al.* 2000[22]	ATG (4 mg/kg per day for ten days) *vs.* OKT3	28	21 (75%)
		28	14 (50%)
			$p = 0.05$

ATG: anti-thymocyte globulin; NR: Not reported. * No difference in severity of acute renal failure between groups on first episode of acute rejection. Reduced occurrence seen in second and third episodes of rejection favoring ATG. ** Dose adjusted based on T cell counts (50-150/mm^3).

Table 4 Randomized studies on the use of anti-thymocyte globulin in the treatment of kidney transplant patients with steroid resistant rejection

	Comparison	N	Rejection reversal rate	Graft survival rate (30-90 days)	Recurrent rejection rate (90 days)
Gaber *et al.* 1998/ Tesi *et al.* 1997/ Schroeder *et al.* 1999[34-36]	ATG 7-14 days (1.5 mg/kg/day) *vs.* Atgam	82	72 (88%)	77 (94%)	14 (17%)
		81	61 (76%)	73 (90%)	29 (36%)
			$p = 0.027$	$p = 0.17$	$p = 0.011$
Mariat *et al.* 1998[37]	ATG < 40 kg = 25 mg/day 40 - 75Kg = 50 mg/day > 75 kg = 75 mg/day *vs.* OKT3	31	97%	1 (3%)	28%
		29	87%	3 (10%)	38%
			p = NS	p = NS	p = NS
Midtvedt *et al.* 2003[38]	ATG D1 (2 mg/kg) administered again 1 mg/kg if needed *vs.* OKT3	27	20 (74%)	26 (96.2%)	12 (44%)
		28	22 (78.5%)	26 (92.8%)	14 (50%)
			p = NS	p = NS	p = NS

ATG: anti-thymocyte globulin; NR: not reported; NS: not significant; Atgam (equine anti-thymocyte globulin - eATG).

search yielded no randomized trials comparing different treatment lengths or different times of drug infusion. Two randomized studies reported the use of single-dose ATG.[11,12] In one study[11] Thymoglobuline® was infused preoperatively at a dosage of 4-5 mg/kg; in another study[12] a single dose of 9 mg/kg was infused intraoperatively. The main adverse events reported in these studies are listed in Table 5.

Recommendation

The authors recommend the use of 1 mg to 1.5 mg of Thymoglobuline® for four to six days, with the total cumulative dose ranging from 4 to 8 mg/kg based on the patient's immune risk.

Question 2b

When should induction therapy be started?

Answer

The time at which patients were started on Thymoglobuline® varied significantly between studies (Table 6). Only one randomized trial[6] compared intraoperative (prior to graft reperfusion) *versus* postoperative infusion. Patients given ATG during surgery had better outcomes in terms of DGF (Table 2).

Recommendation

The authors believe the first infusion should be started before graft reperfusion.

Table 5 Rates of occurrence of the main adverse effects observed in the included studies

	N	Treatment	Leucopenia (approx.1 month)	Cytomegalovirus (infection)	Tumor
Ciancio *et al.* 2010[64]	13	ATG	0 (0%)	0 (0%)	0 (0%)
	13	Alemtuzumab	6 (46.2%)	0 (0%)	1 (7.69%)
	12	Daclizumab	0 (0%)	0 (0%)	0 (0%)
			(p = 0.0002)		
Brennan *et al.* 1999[21]	48	ATG	27 (56%)	6 (12.5%)	0 (0%)
	24	Atgam	1 (4%)	8 (33%)	1 (4%)
			p = NS	p = 0.056	
Brennan *et al.* 2006[13]	141	ATG	47 (33.3%)	11 (7.8%)	5 (3.5%)
	137	Basiliximab	20 (14.6%)	24 (17.5%)	1 (0.7%)
			p < 0.001	p = 0.02	p = 0.21
Noël *et al.* 2009[8]	113	ATG	9 (7.96%)	21 (18.6%)	1 (0.9%)
	114	Daclizumab	5 (4.38%)	12 (10.5%)	0 (0%)
			p = 0.36	p = 0.093	p = NS
Mourad *et al.* 2004[23]	53	ATG	27 (51%)	22 (41.5%)	NR
	52	Basiliximab	10 (19.2%)	11 (21.2%)	
			p = 0.0007	p = 0.025	
Abou-Ayache *et al.* 2008[26]	55	ATG	NR	19 (68%)	0 (0%)
	54	Daclizumab		18 (83%)	0 (0%)
Ciancio *et al.* 2005/2008[27,65]	30	ATG	NR	1 (3.33%)	0 (0%)
	30	Alemtuzumab		2 (6.66%)	0 (0%)
	30	Daclizumabe		0 (0%)	1 (3.33%)
Khosroshahi *et al.* 2008[11]	37	Immunosuppression #	NS	NR	NR
	31	Immunosuppression # + ATG			
Farney *et al.* 2008[5]	45	ATG	NR	2 (4.44%)	NR
	32	Alemtuzumab		1 (3.12%)	
				p = NS	
Hernandez *et al.* 2007[18]	80	ATG + Cyclosporine + Azathioprine	NR	33 (41%)	3 (3.75%)
	80	Basiliximab + Cyclosporine + MMF		16 (20%)	2 (2.5%)
	80	Basiliximab + Tacrolimus + MMF		20 (25%)	2 (2.5%)
				p = 0.008	
Thomas *et al.* 2007[16]	11	Alemtuzumab + Tacrolimus	p < 0.05 in favor of Alemtuzumab	NR	0 (0%)
	10	ATG + Tacrolimus + MMF + steroids			0 (0%)
Goggins *et al.* 2003[6]	27	ATG IO	NR	1 (3.7%)	NR
	31	ATG PO		2 (6.5%)	
				p = NS	
Lebranchu *et al.* 2002[7]	50	Basiliximab + cyclosporine	0 (0%)	6 (12%)	0 (0%)
	50	ATG + cyclosporine	5 (10%)	19 (38%)	0 (0%)
			p < 0.03	p = 0.005	

Continued Table 5.

	185	Tacrolimus	16 (8.6%)	29 (15.7%)	1 (0.54%)
Charpentier *et al.* 2003[14]	186	ATG +	72 (38.7%)	45 (24.2%)	2 (1.07%)
	184	Tacrolimus	64 (34.8%)	52 (28.3%)	4 (2.17%)
		ATG + cyclosporine	$p < 0.001$	$p = 0.012$	
	42	Immunosuppression *	7 (17%)	17 (40%)	NR
Thibaudin *et al.* 1998[15]	47	Immunosuppression *+ ATG	20 (43%)	28 (59%)	
			$p = 0.007$	p = NS	
	53	ATG *vs.* Basiliximab *vs.* Immunosuppression*	NR	9 (17%)	2 (3.77%)
Kyllonen *et al.* 2007[12]	58			9 (16%)	0 (0%)
	44			5 (11%)	1 (2.27%)
				p = NS	p = NS
	50	ATG *vs.* 33B3.1	> in the ATG arm	9 (18%)	NR
Soulillou *et al.* 1990[9]	50			10 (20%)	
			$p < 0.005$		
Theodorakis *et al.* 1998[32]	25	ATG *vs.* methylprednisolone	NR	NS	NR
	25				
	28	ATG *vs.* OKT3	4 (14.2%)	2 (7.1%)	2 (7.14%)
Baldi *et al.* 2000[22]	28		3 (10.7%)	3 (10.7%)	0 (0%)
			p = NS	p = NS	
Mariat *et al.* 1998[37]	31	ATG *vs.* OKT3	NR	12 (39%)	0 (0%)
	29			13 (45%)	2 (7%)
	27	ATG *vs.* OKT3	NR	14 (51.8%)	NR
Midtvedt *et al.* 2003[38]	28			11 (39.2%)	
				p = NS	
Hoitsma *et al.* 1982[31]	20	ATG *vs.* steroids	NR	NS	NR
	20				
	62	ATG *vs.* Basiliximab	NR	7 (11.3%)	NR
Tullius *et al.* 2003[66]	62			2 (3.22%)	
				p = NS	

NR: not reported; NS: not significant; Atgam (equine anti-thymocyte globulin (eATG); MMF: mycophenolate mofetil; IO: Intraoperative; PO: Postoperative; # Cyclosporine + mycophenolate mofetil or azathioprine and prednisone; * Cyclosporine + azathioprine and steroids.

Question 3a

Does Thymoglobuline® decrease the rates of acute rejection and delayed graft function of kidney transplant patients?

Answer

The use of ATG was associated with low acute rejection rates in most of the included studies (Table 2).[6,8,13,14] Thymoglobuline® was statistically superior to IL-2R antagonists in two studies.[8,13] In three studies,[11,14,15] patients given a regimen of ATG combined with other immunosuppressants (including calcineurin inhibitors) had significantly lower acute rejection rates than controls not given Thymoglobuline®. The efficacy of Thymoglobuline® in terms of immune risk deserves careful analysis, once the definition of high immune risk was inconsistent among the included studies. Some studies attributed high immune risk to patients with peak panel reactive antibody (PRA) levels ≥ 30%,[8,13] whereas others considered levels ≥ 20% or > 25%.[7,16] Brennan *et al.*[13] reported that Thymoglobuline® was more effective than

Table 6 Details pertaining to the route of infusion of anti-thymocyte globulin in induction therapy described in the included studies

	Route of infusion	Days of infusion	Time of first anti-thymocyte globulin infusion	Dose mg/kg/day (total ATG dose)
Ciancio *et al.* 2010[64]	NR	D0 to D7	After surgery	1 mg/kg/day (7 doses)
Brennan *et al.* 1999[21]	NR	D0 to D6	During surgery (before graft reperfusion)	1.5 mg/kg/day (6 doses)
Brennan *et al.* 2006[13]	NR	D0 to D4	During surgery (before graft reperfusion)	1.5 mg/kg/day (7.5mg/kg)
Noël *et al.* 2009[8]	Central catheter	D0 to D7	During surgery (before graft reperfusion)	1.25 mg/kg/day
Mourad *et al.* 2004[23]	NR	NR	NR	1 mg/kg/day D0 and D1 and adjusted based on CD3 + (mean of 5.4 infusions)
Abou-Ayache *et al.* 2008[26]	NR	D0 to D9	After surgery	1-1.5mg/kg/day (< 9 doses, mean of 6.5 days)
Ciancio *et al.* 2005/2008[27,65]	NR	7 days	After surgery	1 mg/kg/day (x 7 doses)
Khosroshahi *et al.* 2008[11]	NR	D0	Before surgery (12h hours before the procedure)	4-5 mg/kg
Farney *et al.* 2008[5]	Central catheter	D0, D2, D4, D6, etc.	During surgery	1.5 mg/kg/day (< 7 doses + 5 mg/kg)
Hernandez *et al.* 2007[18]	NR	7 days	NR	1-1.5 mg/kg/day (7 days)
Thomas *et al.* 2007[16]	NR	D0 to D4	Before surgery	1.5 mg/kg/day (x4)
Goggins *et al.* 2003[6]	Mostly peripheral catheters	D0 to D6	During or after surgery	1 mg/kg (≤ 6 doses)
Lebranchu *et al.* 2002[7]	AV fistula or central catheter	D1 to D10	After surgery (24 hours after transplantation)	1-1.5 mg/kg/day (6-10 days; no more than 10 days)
Charpentier *et al.* 2003[14]	NR	D1 to D10	After surgery (< 12 hours after transplantation)	1.25 mg/kg and adjusted based on clinical status
Thibaudin *et al.* 1998[15]	NR	D0 to D10	During surgery (before graft reperfusion)	1.25 mg/kg/day D0 and adjusted based on CD 2+ and CD3+
Kyllonen *et al.* 2007[12]	NR	D0	During surgery (before graft reperfusion)	9 mg/kg single dose
Soulillou *et al.* 1990[9]	AV fistula or central catheter	D0 to D14	After surgery	1.5 mg/kg/day (maximum of 2.5 mg/kg)
Shidban *et al.* 2003[17]	NR	D0 to D5	NR	1.5 mg/kg/day for 5 days under 100 mg/day);
Tullius *et al.* 2003[66]	Tullius	NR	NR	9 mg/kg perioperatório

NR: Not reported.

IL-2R antagonists in decreasing the rates of acute rejection in high-risk patients; high risk was assigned to patients at increased risk of rejection and DGF. In general, most of the studies included mildly sensitized or unsensitized patients. DGF rates were similar in most of the studies on the use of Thymoglobuline® (Table 2). In three studies, Thymoglobuline® was statistically superior to IL-2R antagonists in this indication.[8,12,17]

Question 4a

Does ATG improve graft and patient survival after renal transplantation?

Answer

Thymoglobuline® has not changed patient survival within the first or second year of renal transplantation[8,13,18] (Table 2) regardless of patient immune risk level. One study[15] described improved graft survival when Thymoglobuline® was added to the immunosuppressive regimen. Low and high-risk patients (anti-HLA sensitization of any level was deemed as high immune risk) were included; the outcome was not assessed separately for each level of immune risk.

Question 5

How should other immunosuppressants be managed when ATG is used in induction therapy?

Answer

Triple-therapy immunosuppression (cyclosporine, mycophenolate mofetil/sodium, steroids) was prescribed in most of the studies assessing Thymoglobuline®. A meta-analysis showed that reducing the use of steroids or discontinuing them altogether was not associated with increased mortality or graft loss when Thymoglobuline® was used.[19]

The ideal dosage of other immunosuppressants used concomitantly with ATG has not been published the literature. ATG may delay the introduction of calcineurin inhibitors without negatively affecting rejection rates.[20] The induction therapy in most immunosuppression minimization studies (calcineurin inhibitors and steroids) included Thymoglobuline®, and none reported inferior outcomes.

Recommendation

Modified immunosuppression protocols with induction therapy vary significantly. There is no standard recommendation.

Question 6

How should patients treated with ATG be monitored? How should dosage be adjusted?

Answer

In most early studies, Thymoglobuline® dosage was adjusted to maintain CD3+ counts below 20 cells/mm^3. Another method used to monitor patients dictated that peripheral lymphocyte counts should be kept between 50-150 cells/mm^3. Thymoglobuline® was tapered down or temporarily suspended in cases of leucopenia or thrombocytopenia.[21,22]

Recommendation

Monitor lymphocyte counts and consider the discontinuation/reduction of the drug when counts are below 100 cells/mm^3.

Question 7

Is there a recommendation to monitor or offer prophylactic or preemptive therapy against cytomegalovirus infection?

Answer

Increased rates of CMV infection were observed in four studies[7,14,18,23] with Thymoglobuline® (Table 5). In most studies, prophylactic therapy was prescribed to patients at increased risk of CMV infection (individuals with serologic evidence of exposure to CMV before renal transplantation;[21] or CMV-positive donors matched with CMV-negative recipients[13]). The authors defined CMV infection as positive viremia detected by increased titers of IgG, and/or IgM-positive tests, and/or CMV-positive PCR tests.

The guidelines published by The Transplantation Society[24] consider the prescription of CMV prophylactic therapy for patients on ATG, and further recommends courses of ganciclovir or valganciclovir for a period of three months after renal transplantation in individuals at high risk of infection.

Among the medications used in prophylactic therapy against CMV, ganciclovir was superior to acyclovir[1]. Oral and intravenous ganciclovir were equally efficacious.[25]

Most studies included prescriptions of three grams per day (three doses of one gram) of oral ganciclovir or 450-900 mg/day of valganciclovir for up to 90 days after transplantation.[1,13,26,27] Randomized trials[28,29] and a meta-analysis of a systematic review of the literature[25] revealed that the incidence of CMV infection decreased when antiviral drugs were prescribed in courses of prophylactic or preemptive therapy. This decrease was associated with better graft survival.[1]

Recommendation

Patients on Thymoglobuline® should be assessed for CMV prophylactic or preemptive therapy.

Question 8

What is the role of ATG in the treatment of acute graft rejection? What is the recommended dosage and length of treatment? What about more severe cases of rejection (vascular and antibody-mediated rejection)?

Answer

A systematic review[30] comparing Thymoglobuline® *versus* steroids in the treatment of first episodes of acute rejection reported a trend toward reduced graft loss favoring Thymoglobuline®. Since 2009, lymphocyte-depleting agents such as Thymoglobuline® have been recommended for patients not responding to initial steroid therapy.[1] The mean dose of ATG prescribed in early studies for the treatment of acute rejection was 4 mg/kg/day for seven to ten days.[22,31,32] In one study,[33] the patients prescribed a fixed dose of 200 mg/day on alternate days for ten days of Thymoglobuline® had better outcomes than the group given methylprednisolone. The dosage most commonly prescribed to patients with steroid-resistant acute rejection was 1.5 to 2 mg/kg/day.[34-38]

Recommendation

There are no randomized studies on the use of Thymoglobuline® in the treatment of individuals with severe rejection. However, consensus stipulates that more severe cases (vascular and antibody-mediated rejection) should be treated with lymphocyte-depleting agents.[30] Dosages and routes of administration are the same used in induction therapy, but treatment time ranges between seven and ten days.

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Erratum

The paper "Use of Thymoglobulin® (antithymocyte immunoglobulin) in renal transplantation: practical guide", published on the April of 2015 issue of the Brazilian Journal of Nephrology [J Bras Nefrol. 2015; 37: 228-240], has been changed, where the author's affiliation, Luciane Deboni, was misquoted, and the her correct affiliation is: São José Municipal Hospital.