Different induction therapies for kidney transplantation with living donor

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Submitted on: 10/22/2014.
Approved on: 12/19/2014.

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DOI: 10.5935/0101-2800.20150033

Abstract

Introduction: Indications for induction therapy is not consensual in living donors. **Objective:** The objective of this study was compare no induction with thymoglobulin and basiliximab induction in the incidence of acute rejection in kidney transplantation with living donor. **Methods:** We select all cases of renal transplantation with living donor performed in Hospital das Clínicas de Botucatu da UNESP during the period of January 2010 to December 2013. The group was divided by the type of medication used for induction. **Results:** A total of 90 patients were evaluated. There were no differences in baseline characteristics of age and underlying disease. The rate of biopsy-proven acute rejection was higher in the group without induction (42.9%) compared to basiliximab group (20%) and Thymoglobulin (16.7%), p = 0.04. The rejection by compatibility shows that the identical had the lower rejection rate (10%). The haploidentical group without induction had the highest rejection rates (53.3%). In all distinct group the rejection rates were similar with basiliximab or Thymoglobulin, p = NS. The use of induction therapy was associated independently with a lower risk of rejection (OR = 0.32 CI: 0.11 to 0.93, p = 0.036). There were no differences in renal function at 6 months and patient survival and graft in the three groups. **Discussion:** The haploidentical patients without induction were those with higher rates of acute rejection. The group of patients induced with Thymoglobulin had a higher immunological risk, however showed low rates of rejection. **Conclusion:** The use of induction therapy resulted in lower rates of rejection in transplantation with living donor.

Keywords: graft rejection; immunosuppression; living donors.

Introduction

Induction therapy with biological agents such as interleukin-2 (IL-2) receptor antagonists has been indicated as part of the initial immunosuppressant therapy offered to kidney transplant patients. According to the KDIGO,[1] patients at high immunological risk should be prescribed lymphocyte-depleting agents (LDA). LDAs can also be safely used in living-donor transplant patients.[2] The purpose of induction therapy is to modulate the response of effector T-cells to the presence of antigens, and thus reduce the incidence of acute rejection. IL-2 receptor antagonists such as basiliximab and T-cell depleting agents such as thymoglobulin are used as induction agents.[3] A recent systematic review reported a 38% reduction in the number of cases of acute rejection in patients prescribed IL-2 receptor antagonists *versus* subjects given placebo, without increasing the incidence of side effects of infection.[4] IL-2 receptor antagonists yielded higher one-year biopsy-confirmed rejection rates than thymoglobulin, but fewer side effects from CMV infection and malignant disease.[4]

Although the literature recommends induction therapy even to moderate risk patients such as haploidentical living donors transplant recipients,[1] there is no consensus over this issue

in Brazil[5] or in the world.[6] Therefore, this study aims to report the progress of low to moderate immunological risk recipients of living-donor transplants treated with and without induction therapy.

Primary objective

This study aims to compare the effects of the administration to the non-administration of induction therapy with basiliximab or thymoglobulin on recipients of living-donor transplants in terms of incidence of acute rejection, renal function six months after the transplant, and graft/patient survival.

Materials and methods

This study included all recipients of living-donor transplants seen at the Kidney Transplantation Service of the University Hospital at Botucatu (HC UNESP) from January 2010 to December 2013. The patients were divided into groups based on induction therapy regimen (no induction, induction with basiliximab, or induction with thymoglobulin). The following demographic and clinical data were collected: age, gender, underlying disease, panel reactive antibodies, HLA compatibility, immunosuppressants, creatinine level at discharge, creatinine level after six months, length of hospitalization, follow-up time, occurrence of acute rejection, graft loss, and death.

The data were collected from the hospital records and did not include patients lost during follow-up. Normal course after transplantation was considered for patients with 50% decrease in creatinine levels within 24 hours rebounding to normal levels in four to five days. Patients failing to achieve normal creatinine levels (> 1.4 mg/dl) five days after transplantation or with deteriorating renal function on Doppler ultrasound tests underwent kidney biopsies. Cases of rejection were confirmed by biopsy and assessed up to six months after transplantation. Three biopsy specimens were collected and analyzed for C4d by immunohistochemistry and immunofluorescence. A pathologist with experience in kidney transplantation processed all collected specimens.

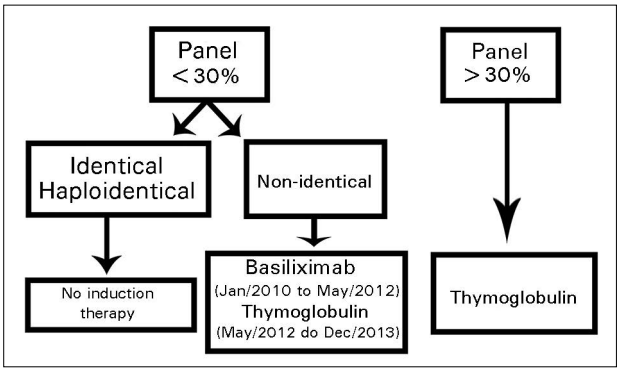
The prescribed immunosuppression regimen included a combination of calcineurin inhibitors, mycophenolate sodium or azathioprine, and prednisone for haploidentical and non-identical patients. More than 90% of the patients were on tacrolimus combined with mycophenolate sodium. Target tacrolimus serum levels were set at 8-12 ng/dl in the first month after transplantation and 4-8 ng/dl afterwards. Cyclosporine trough levels (C0) were set at 200-300 ng/dL in the first month and 100-200 ng/dl afterwards. Haploidentical patients with no panel reactive antibodies were prescribed a combination of mycophenolate sodium and prednisone, and were kept off calcineurin inhibitors. All patients were given 30 mg of prednisone in the first month, followed by tapering doses until a threshold of 5 mg at the end of the third month.

Cases of T cell-mediated rejection were treated with pulse methylprednisolone therapy (500 mg) for three days. Patients not responding to methylprednisolone pulse therapy, individuals with Banff type IIB rejection or higher, and individuals with mixed rejection (C4d+) were treated with a total dose of 6 mg/kg of thymoglobulin.

Induction therapy included thymoglobulin for patients with panel reactive antibody levels greater than 30% irrespective of HLA compatibility. Identical and haploidentical recipients with panel reactive antibody levels lower than 30% were not given induction therapy. The non-identical recipients in this group were given induction therapy with basiliximab until May 2012 and thymoglobulin thereafter due to changes in the induction protocol in effect at the service (Figure 1). Patients were given 20 mg of basiliximab at the day of transplantation and 20 mg four days after the procedure. Thymoglobulin was administered at a dose of 1 mg/kg/day for five days. Patients on thymoglobulin were offered prophylactic therapy with 5 mg/kg of intravenous ganciclovir three times a week and monitored weekly for pp65 antigenemia.

In statistical analysis, the chi-square test or Fisher's exact test were used for categorical variables. Directional association measures

Figure 1. Induction therapy for living-donor transplant recipients in use at HC UNESP based on panel reactive antibody levels and HLA compatibility.



were used in the chi-square test to compare between subgroups (Lambda and Goodman and Kruskal's tau). ANOVA was used in the analysis of parametric continuous variables and the Kruskal-Wallis test in non-parametric variables. The Bonferroni post-hoc test was used in subgroup comparisons. Survival was analyzed through Kaplan-Meier plots and the log-rank test. In multivariate analysis, binary logistic regression was performed with forward stepwise selection with inclusion and exclusion probabilities of 0.05 and 0.10, respectively. The model considered the risk of rejection as a dependent variable and prescription of induction therapy as a covariate (present or absent) adjusted for age, gender, and panel reactive antibody levels. Statistical significance was attributed to events with a $p < 0.05$.

Results

Ninety living-donor transplants were carried out over the time period considered in the study. A higher percentage of male patients was seen in the group not given induction therapy (61.9%) and in the group prescribed basiliximab (76.7%) than in the group administered thymoglobulin (38.9%), $p = 0.033$. Group mean ages were not statistically different (Table 1). Chronic glomerulonephritis and undetermined disease were the most frequent underlying conditions, observed in 66.7% of the subjects not given induction therapy, in 40% of the individuals on basiliximab, and in 72.2% of the patients on thymoglobulin, p = NS (Table 1). Panel reactive antibodies were seen in 2,97 ± 6,4% of the patients in the group not given induction therapy, in 5,74 ± 18,1% of the individuals on basiliximab, and in 23,64 ± 34,9% of the subjects on thymoglobulin, with a tendency toward increased levels in the latter group, $p = 0.06$. Seventy percent of the individuals in the group not given induction therapy and 100% of the subjects in the basiliximab and thymoglobulin groups were on tacrolimus ($p = 0.0001$). The use of mycophenolate, prednisone, azathioprine, and sirolimus was similar between groups (Table 1).

Patients were discharged after 13.5 ± 18.4 days in the group not given induction therapy, 11.3 ± 6.5 days in the group prescribed basiliximab, and 11.28 ± 5 days in the thymoglobulin group, p = NS. Creatinine levels at discharge and six months after discharge were 1.59 ± 0.7 and 1.36 ± 0.5 mg/dl in the group not given induction therapy; 1.28 ± 0.5 and 1.34 ± 0.7 mg/dl in the patients prescribed basiliximab; and 1.22 ± 0.4 and 1.33 ± 0.5 mg/dl in the thymoglobulin group, p = NS. The group kept off induction therapy had the highest percentage of identical (24.4%) and haploidentical (73.2%) living-donor transplant recipients when compared to the basiliximab and thymoglobulin groups, $p = 0.0001$. Non-identical recipients were predominantly found in the basiliximab (70%) and thymoglobulin (61.1%) groups when compared to the group not given induction therapy, $p = 0.0001$ (Table 1). The occurrence of acute rejection confirmed by biopsy was greater in the group not given induction therapy (42.9%) *versus* the basiliximab (20%) and thymoglobulin (16.7%) groups, $p = 0.04$. The group given thymoglobulin (16.7%) had lower rejection rates than the individuals prescribed basiliximab (20%), $p = 0.044$.

Rejection was observed in 10% of the HLA-identical patients in the group not given induction and in none of the subjects in the thymoglobulin group, p = NS. Identical patients were not prescribed induction therapy with basiliximab and only two took thymoglobulin for having panel reactive antibody levels greater than 30%.

Table 1 Clinical and demographic characteristics of living-donor transplant recipients not given induction therapy or prescribed basiliximab or thymoglobulin

		Induction Therapy			
		None N = 42 (A)	Basiliximab N = 30 (B)	Thymoglobulin N = 18 (C)	*p*
Males		61.9%	76.7%	38.9%	0.033*
Age (years)		36.50 ± 10.4	35.30 ± 18.9	34.83 ± 11.3	NS
	Hypertension	4.8%	16.7%	11.1%	
	DM	9.5%	10.0%	5.6%	NS
Baseline disease	CGN	31.0%	20.0%	44.4%	
	Undetermined	35.7%	20.0%	27.8%	
	Other	19.0%	33.3%	11.1%	
Time on follow-up (months)		23.83 ± 14.3	28.67 ± 12.0	10.56 ± 7 (A/B)	0.0001+
Panel reactive antibodies (%)		2.97 ± 6.4	5.74 ± 18.1	23.64 ± 34.9	0.06#
On tacrolimus		71.4%	100.0%	100.0%	0.0001*
On mycophenolate		97.6%	93.3%	100.0%	NS
On prednisone		100.0%	100.0%	100.0%	NS
On sirolimus		0%	0%	0%	NS
On azathioprine		2.4%	6.7%	0%	NS
On cyclosporine		2.4%	0%	0%	NS
PO de Alta (dias)		13.57 ± 18.4	11.33 ± 6.5	11.28 ± 5	NS
Creatinine at discharge (mg/dl)		1.59 ± 0.7	1.28 ± 0.5	1.22 ± 0.4	NS
Creatinine at six months (mg/dl)		1.36 ± 0.5	1.34 ± 0.7	1.33 ± 0.5	NS
	Identical	24.4%	0%	11.1%	
HLA	Haploidentical	73.2%	30.0%	27.8%	0.0001*
	Non-identical	2.4%	70.0%	61.1%	
Acute Rejection		42.9%	20.0%	16.7%	0.044*
	Banff I A+B	38.9%	80%	33.3%	
	Banff II A	44.4%	20%	0	0.059*
Categorization	Banff III	0	0	33.3%	
	Antibody-mediated	5.6%	0	33.3%	
	Mixed	11.1%	0	0	
C4d		29.4%	0	66.7%	NS
Death		4.8%	0%	0%	NS
Graft Loss		2.4%	3.3%	0%	NS

DM: Diabetes; CGN: chronic glomerulonephritis; * Chi-square; + ANOVA; # Kruskal-Wallis.

In the haploidentical group, rejection rates were higher in the group not given induction therapy (53.3%) *versus* the subjects given basiliximab (11.1%) and thymoglobulin (0%), $p = 0.013$. Non-identical subjects had rejection rates of 23.8% with basiliximab and 27.3% when given thymoglobulin, p = NS (Table 2). In terms of severity, most subjects in the three groups had T cell-mediated rejection (Banff IA and IB), with a tendency toward more severe cases in the thymoglobulin group (33% of the subjects had antibody-mediated rejection, $p = 0.059$; Table 1).

Multivariate analysis by logistic regression showed that induction therapy (basiliximab or thymoglobulin) was independently associated with protection against rejection, OR = 0.32 (CI: 0.11 to 0.93, $p = 0.036$).

Table 2 Acute rejection cases by HLA compatibility (haploidentical, non-identical, identical) in subjects not given induction therapy and patients prescribed basiliximab or thymoglobulin

Rejection cases per type of HLA compatibility	Induction Therapy			
	None (A)	Basiliximab (B)	Thymoglobulin (C)	*p*
Identical	10%	0%	0%	NS
Haploidentical	53.3%	11.1%	0%	0.013*
Non-identical	0%	23.8%	27.3%	NS

*Chi-square.

Death and graft loss rates were similar between groups (Table 1).

After 24 months, 92.8% of the patients in the group not given induction therapy were alive, *versus* 100% in the basiliximab and thymoglobulin groups ($p = 0.35$). Graft survival at 24 months was 90.2% in the group not given induction therapy, 85.7% in the basiliximab group, and 100% in the thymoglobulin group, $p = 0.59$.

Discussion

The results have shown that the group of living-donor transplant recipients not given induction therapy contained mostly haploidentical subjects with low levels of panel reactive antibodies. The vast majority of the haploidentical recipients (> 90%) were on a combined therapy with tacrolimus, mycophenolate, and prednisone. This group was made up of moderate-risk recipients, for whom induction therapy is not deemed mandatory according to the Brazilian guidelines.[5] Conversely, the KDIGO recommends induction therapy with IL-2 receptor antagonists for this population.[1] The evidence for this recommendation, however, is not strong, once it is based on small trials and retrospective studies.[6] A high rate of rejection was found among individuals in this population enrolled in our study (53.3% in haploidentical recipients), although most patients had mild cases of rejection (T cell-mediated mediated by T cells - Banff IA and IB). This may be partly explained by the more aggressive biopsies carried out four or five months after surgery in patients with compromised kidney function, thus increasing the sensitivity of rejection detection. No impact on kidney function was observed at six months or in patient and graft survival one year after transplantation in comparison to individuals prescribed induction therapy.

Identical living-donor transplant recipients were on a regimen of prednisone and mycophenolate without calcineurin inhibitors, and most of them did not receive induction therapy. There is no consensus over the use of this scheme. Some studies reported superior outcomes when calcineurin inhibitors were added,[7,8] while others indicated it might not be needed.[9-11] The subjects in this group had lower rates of acute rejection (10%), although few were on induction therapy and none took calcineurin inhibitors due to service protocol restrictions.

Most of the patients (70%) in the group on induction therapy with basiliximab were non-identical recipients on a combination of tacrolimus, mycophenolate, and prednisone. Twenty percent had acute rejection, a finding consistent with the global literature.[12] All cases were T cell-mediated rejections (Banff IA and IB); no antibody-mediated rejections were observed.

Most of the individuals (61%) in the group given thymoglobulin were non-identical recipients and had panel reactive antibody (PRA) levels above 30% (mean PRA level of 23%). The patients in this group were on a combination of tacrolimus, mycophenolate, and prednisone. Despite the higher immunological risk, this group had the lowest rejection rates (16.7%) of the three groups analyzed. These acute rejection rates are in agreement with the TAILOR trial on induction therapy with thymoglobulin for living-donor transplant recipients.[2] However, a tendency toward more severe manifestations was seen in this group, as 33% of the patients developed antibody-mediated rejection ($p = 0.06$), indicating these subjects were at higher immunological risk.

The limitations of the present study include the fact that it enrolled a retrospective cohort, in which groups were not distributed homogeneously for their baseline characteristics. This may result in imbalances in areas such as immunological risk and other unanalyzed risk factors for rejection, such as the incidence of cytomegalovirus.[13,14] Multivariate analysis may partially correct these imbalances.[13] Logistic regression yielded lower risk of rejection for patients on induction therapy *versus* subjects not given induction therapy. The small number of cases was another limitation, particularly in the group given thymoglobulin, which may also explain the absence of differences in patient and graft survival. Despite these limitations, worse outcomes were clearly associated with non-prescription of induction therapy to living-donor transplant recipients.

Conclusion

The prescription of induction therapy, either in the form of an interleukin-2 receptor antagonist or thymoglobulin, resulted in lower rejection rates in living-donor transplant recipients *versus* individuals not given induction therapy. Haploidentical patients not given induction therapy had the highest rates of acute rejection.

Although they were not prescribed calcineurin inhibitors or induction therapy, identical living-donor transplant recipients had the lowest rejection rates.

Patients on induction therapy with thymoglobulin were at higher immunological risk (panel reactive antibodies and non-identical donors) and had lower rejection rates, although their cases of rejection were more severe.

Induction therapy (basiliximab or thymoglobulin) was independently associated with lower risk of rejection in living donor transplant recipients.

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