

CLINICAL EXPERIENCE WITH INDUCTION THERAPY IN RENAL TRANSPLANTATION

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Abstract

Introduction. Acute rejection (AR) is a major determinant of renal allograft survival. The incorporation of new immunosuppressive agents explains the improvement seen in the results of transplantation in recent years.

Objective. To assess the optimal immunosuppression regimen according to the immunological risk of renal transplant patients.

Method. We performed a retrospective study of 977 consecutive patients transplanted in our institution between January 2000 and December 2011. Recipients were classified according to the immunological risk (high, intermediate and low) and the type of induction therapy received. We evaluated the incidence of early acute rejection (eAR) and late acute rejection (LAR) and their influence on graft and patients survival in relation to the immunological risk and induction regimen used.

Results. The incidence of eAR was 5.4%, 6.4% and 1.4% in relation with the immunological risk, high, intermediate and low respectively. The most commonly used induction immunosuppression was rabbit antithymocyte globulin (ATG), followed by methylprednisolone and basiliximab. No statistical difference was found between the incidence of eAR according to the type of induction therapy and immunological risk. The graft survival was significantly better for the cases without eAR at 1 year (98.6% versus 94.4%, $p=0.019$), and 3 years (94.9% versus 88.9%, $p=0.056$). The patients survival was significantly better for those without eAR at 1 year after transplant (95.7% vs. 88.9%, $p=0.051$), 3 years (93.1% vs. 83.3%, $p=0.008$) and 5 years (92.2% vs. 79.6%, $p=0.001$). The incidence of LAR was between 0 and 7.1% according to the induction therapy, lacking any statistical significance ($p=0.450$).

Conclusion. Tailoring the induction immunosuppression according to the immunological risk reduces the incidence of early acute rejection.

Keywords: induction therapy, acute rejection, renal transplantation

Introduction

A number of trials involving renal transplant recipients have demonstrated significant reductions in the frequency of acute rejection and improved one-year graft survival when certain biological agents were used for induction therapy. By using these highly potent immunosuppressive agents, the body loses much of its innate ability to mount an immune response, thereby increasing the risk of infectious complications and malignancy [1,2]. Many risk factors are known to influence graft survival such as age, gender, body

weight, type of donor, transplant function immediately after surgery, HLA mismatches and the degree of immunological risk before transplantation. Acute rejection episodes have consistently been reported to be the most important risk factor leading to allograft failure [3].

Objective

To assess the optimal immunosuppression regimen according to the immunological risk of renal transplant patients.

Material and Method

We evaluated the efficacy and safety of immunosuppressive agents as induction therapy in transplantation in

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reducing the incidence of acute rejection and preventing allograft failure. We retrospectively analyzed data of 977 consecutive kidney transplants performed between January 2000 and December 2011. The recipients mean age was 38 years (range: 2 to 69). The patients were divided into three groups according to the immunological risk.

High immunological risk patients were considered patients with: high PRA>50%, history of immunization (retransplanted patients, prior positive cross-match, simultaneous pancreas/liver/heart and kidney transplant), all the patients with deceased donor graft. Intermediate immunologic risk patients criteria included: PRA 10-50%, without a history of immunization, age under 18 years, 4-6 HLA mismatches, living donor. Low immunological risk was represented by adult patients at the first transplant from living donor, PRA<10%, 0-2 HLA mismatches or age >60 years.

For induction therapy we used Methylprednisolone (M) 1gr/day for 3 days and oral premedication 3 days before transplant (calcineurin inhibitor) or Methylprednisolone in combination with antilymphocyte polyclonal antibodies (ALG- globulin obtained by immunization of horses or ATG- globulin obtained by immunization of rabbits) for 3 to 10 days. Starting with 2002 we used monoclonal antibodies Daclizumab and Basiliximab in standard doses. The selection of the induction therapy was decided for the most cases by the immunological risk of each patient at the moment of transplant, more aggressive immunosuppression for patients with high risk of rejection or Methylprednisolone only for those who had low risk of rejection. Since 2008, for several cases of highly sensitized patients (N=20) we used a combination of antilymphocyte polyclonal antibodies and basiliximab.

Acute rejection episodes were classified in early acute rejection (eAR), which occurs in the first 3 months from transplantation and late acute rejection episodes (LAR) after 3 months from transplantation disregarding previous eAR. AR was defined as an acute deterioration of the allograft function without obvious other causes, excluded by paraclinical examinations and confirmed histologically.

The patients were followed until death, return to dialysis or until 31 December 2012. We compared the graft and patient survival rates with and without eAR and LAR. The statistical analysis was done by SPSS, using χ^2 test for uni and multivariate analysis.

Results

Early acute rejection episodes according to the immunological risk group and type of induction therapy are presented in Table I.

The incidence of eAR in the group with high immunological risk (N=480) was 5.4% (N=26). According to the induction therapy, the patients treated with Methylprednisolone

(N=20), ALG (N=6) and Daclizumab (N=1), had no episodes of early acute rejection, but for the last medication the incidence is not relevant because of the small number of patients. The highest incidence of eAR was recorded in the patients treated with ATG (6.6%), followed by the combination ATG + Basiliximab (5.0%) and Basiliximab (1.4%). Statistically there was no significant difference between the type of induction therapy used for this category of patients regarding the incidence of eAR (p=0.428).

The incidence of eAR in the group with intermediate immunological risk (N=425) was 6.4% (N=27). According to the induction therapy, the highest incidence of eAR was recorded for the patients treated with ATG (7.1%), followed by ALG (6.2%) and Methylprednisolone (5.3%). The small number of patients treated by Basiliximab (N=8) and Daclizumab (N=1) does not allow a relevant interpretation of the incidence of eAR for this category of patients. Statistically there was no significant difference between the type of induction therapy used for patients with intermediate immunological risk (p=0.911).

The incidence of eAR in the group with low immunological risk (N=72) was 1.4% (N=1). One single episode of acute rejection occurred in this category of patients, this patient was treated only with Methylprednisolone in the period of induction therapy; no rejection was recorded in the patients treated with ATG. Again, a small number of patients treated by Basiliximab (N=4) and ALG (N=6) does not allow a relevant interpretation of the incidence of eAR for this category of patients. Statistically there was no significant difference between the type of induction therapy used for patients with low immunological risk (p=0.857).

The graft survival was significantly better for the cases without eAR at 1 year (98.6% versus 94.4%, p=0.019), and 3 years (94.9% versus 88.9%, p=0.056). The rate of graft survival for the patients without eAR continued to be better at 5 years (94.9% versus 88.9%), even though there was no significant statistical difference (p=0.334). Same results for the analysis of the patients' survival, a significantly better survival for patients without eAR at 1 year after transplant (95.7% vs. 88.9%, p=0.051), 3 years (93.1% vs. 83.3%, p=0.008) and 5 years (92.2% vs. 79.6%, p=0.001).

The relation between late acute rejection and induction therapy is presented in Table II.

The incidence of late acute rejection was between 0 and 7,1% according to the induction therapy, without any statistically significance related to the type of induction treatment (p=0.450).

Discussion

Antithymocytes globulins exert their action through the depletion of lymphocytes. Reconstitution of the immune system can take up to a year, and full recovery is questionable, especially in elderly patients. These drugs are

Table I. Distribution of episodes of early acute rejection in regard to immunosuppression induction and the immunological risk.

eAR	High risk group				Intermediate risk group				Low risk group			
	yes		no		yes		no		yes		no	
No. of patients	26		454		27		398		1		71	
	N	%	N	%	N	%	N	%	N	%	N	%
Induction therapy												
M	0	0.0%	20	100.0%	10	5.3%	179	94.7%	1	2.4%	40	97.6%
ALG	0	0.0%	6	100.0%	1	6.2%	15	93.8%	0	0.0%	6	100.0%
ATG	24	6.6%	337	93.4%	15	7.1%	195	92.9%	0	0.0%	21	100.0%
Daclizumab	0	0.0%	1	100.0%	0	0.0%	1	0.0%				
Basiliximab	1	1.4%	71	98.6%	1	11.1%	8	88.9%	0	0.0%	4	100.0%
ATG+Basiliximab	1	5.0%	19	95.0%								

Table II. Incidence of late acute rejection in relation to induction therapy

Induction	M		ALG		ATG		Daclizumab		Basiliximab		ATG+Basiliximab		TOTAL
	N	%	N	%	N	%	N	%	N	%	N	%	
Early AR	11	4.4%	1	3.6%	39	6.6%	0	0.0%	2	2.4%	1	5.0%	54
Late AR	8	3.2%	2	7.1%	9	1.5%	0	0.0%	2	2.4%	1	5.0%	22
No AR	231	92.4%	25	89.3%	544	91.9%	2	100.0%	81	95.3%	18	92.2%	901
TOTAL	250	100.0%	28	100.0%	592	100.0%	2	100.0%	85	100.0%	20	100.0%	907

generally associated with an increased risk of infectious complications and malignancy beyond that of standard immunosuppression [1]. Brennan et al. conducted an analysis of patients receiving antithymocyte globulin (rabbit) versus antithymocyte globulin (equine) as induction therapy. Ten-year follow-up results from this study revealed that the composite endpoint of event-free survival, including acute rejection episodes, remained higher for the antithymocyte globulin (rabbit) group compared with the antithymocyte globulin (equine) group [4,5].

Lebranchu et al. conducted the first comparison of basiliximab and antithymocyte globulin (rabbit) for induction therapy. Efficacy endpoints, including patient survival, graft survival, episodes of biopsy-documented acute rejection and treatment failure were similar between groups [6]. Basiliximab is not as potent but has a much more favorable adverse-effect profile compared with antithymocyte globulin (rabbit) and is most commonly used in low-risk patients. Safety is one of the most evident benefits of induction therapy with a monoclonal antibody, especially the absence of any increased risk of CMV infection or malignancy [7].

Daclizumab is comparable to basiliximab, with an

adverse-effect profile comparable to that seen with placebo. The major difference between daclizumab and basiliximab is that daclizumab has a more complicated, lengthy, and potentially more costly dosing regimen [8].

In our experience, over a 10 years period, the great majority of transplanted patients were patients with high immunological risk (N=480), patients transplanted from deceased donors or immunologically sensitized patients. We treated the great majority of this patients with antithymocyte globulin (N=337) and we recorded a low incidence of eAR (6.6%). Basiliximab appears to be efficient, 71 patients treated and 1.4% incidence of eAR. Using combination antithymocyte globulin + Basiliximab for highly sensitized patients was safe regarding eAR (5%). The next numerous category was the intermediate immunological risk category (N=425) which included the most patients transplanted from living donor with a high number of HLA mismatches, or children. We used antithymocyte globulin and Methylprednisolone almost in the same proportion for these cases (N=195 vs. N=179), without any statistically difference. Less aggressive immunosuppression such as Methylprednisolone or monoclonal antibodies is suitable and safe for these patients according to the risk of acute

rejection, but also for infections and malignancy.

The low immunological risk category was small (N=72), here were patients transplanted from living donors, elderly or very well HLA-matched. Using mild immunosuppressive induction therapy such as Methylprednisolone was safe regarding acute rejection.

The presence of an episode of early acute rejection reduces significantly graft survival and patient survival at 1 and 3 years. The incidence of late acute rejection is not related to induction therapy, the maintenance therapy plays a major role for long-term survival graft [9].

Conclusions

Tailoring the induction immunosuppression according to the immunological risk reduces the incidence of early acute rejection.

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