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Impact of basiliximab use on renal function after liver transplantation

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Abstract

Background: The development of Acute renal failure (ARF) in the postoperative period of liver transplantation (LT) is very frequent. ARF can condition the evolution of the transplanted patient in an important way. One of the main causes is the use of immunosuppressants at doses with nephrotoxic effects. The objective of this study was to evaluate ARF after LT, analyzing the causes and related risk factors and measuring the impact that the use of basiliximab could have had on this.

Methods: A total of 231 recipients were included in the retrospective, longitudinal, and nonrandomized study.

Results: The overall incidence of acute renal failure, was 59.8%, being significantly lower in the group that received basiliximab (Group B 49.2% *vs* Group A 70.8%). Like renal replacement therapy was required by 5.1% in Group B compared to 30.1% of the patients in group A. Multiple variables were associated with an increased risk of ARF, and two others were protective: portocaval shunt and basiliximab use. The results of the multivariate analysis identified the main risk factors for ARF: increased by an average of 11% for each point increase in the MELD score, use of vasoactive drugs in the operating room and red blood cell transfusion in the first 24 hours. In contrast, the Basiliximab use proved to be a protective factor against ARF, capable of reducing its appearance by up to 78%.

Conclusions: Knowing and acting on the risk factors for the development of ARF can improve outcomes after LT, having a positive impact. The use of basiliximab was found to be a protective factor against the development of ARF after LT, without increasing postoperative infection or rejection rates.

Keywords: acute renal failure; liver transplantation; basiliximab.

Introduction

Acute renal failure (ARF) is a frequent postoperative complication after liver transplantation (LT), present in up to 94% of patients [1-3], most of whom will have subsequent normalization of renal function. However, in some cases, kidney failure persists, significantly conditioning the evolution and quality of life of the transplant patient [4-6]. Among the main causes of ARF, the following stand out: hepatorenal syndrome, hemodynamic instability during the perioperative period and nephrotoxicity due to some drugs [7]. In drug toxicity, the use of calcineurin inhibitors (CI), cyclosporine or tacrolimus, which are the cornerstone of induction and maintenance immunosuppression in organ transplants, deserves special mention. The pathogenesis of ARF associated with cyclosporine and tacrolimus seems to be related to its powerful acute renal vasoconstrictor effect, especially in the afferent arteriole, which causes an increase in renal vascular resistance and, consequently, a decrease in renal perfusion accompanied by a decrease in glomerular filtration rate. This renal toxicity of ACNs has a number of characteristics. It depends on the dose, so the reduction in the dose of ACNs is usually accompanied by an improvement in renal function. Due to the above, it is usually reversible, although, if it is not corrected early, it can evolve into Chronic Kidney Disease (CKD) [8]. These circumstances have determined the search for different patterns of induction of immunosuppression, called "renal protection", aimed at reducing the dose of these drugs, delaying their introduction and even their abolition [9]. The objective of this study was to evaluate the rate of acute renal failure after liver transplantation, according to two immunosuppressive treatment regimens, analyzing the related risk factors and measuring the impact of immunosuppressive therapy on renal function.

Patients and methods

A total of 265 consecutive adult LT were performed at the Ramón y Cajal Hospital, from August 2007 to December 2014, and 231 recipients were included in the retrospective, longitudinal, and nonrandomized study. We excluded patients with chronic kidney disease with baseline serum creatinine level >3 mg/dL, those who required renal replacement therapy (RRT), those who underwent a simultaneous liver and kidney transplant, re-transplanted patients (during the first 10 days following the LT), and deceased patients the first 10 days after LT. The patients were distributed into two groups, consecutive in time, non-randomized, based on the immunosuppressive regimen received in the immediate post-transplant period.

Group A: methylprednisolone (5 mg/kg IV) was administered intraoperatively followed by 20 mg/day IV administration post transplantation for 3 weeks and gradually tapered to oral prednisone. Oral tacrolimus (.15 mg/kg/day) was started within 24 hours postoperatively.

Group B: methylprednisolone (same doses as in group A), basiliximab 20 mg was administered 6 hours after portal vein reperfusion. Tacrolimus administration was delayed until the third day after surgery (.10 mg/kg/day), and mycophenolate mofetil (CellCept, Roche, Humacoa, Puerto Rico) was administered postoperatively with a starting dose of 1000 mg every 12 hours.

Diagnosis of preoperative renal dysfunction

Previous renal dysfunction was considered to exist when the glomerular filtration rate was less than 60 mL/min/1.73 m^2 in the baseline analysis, prior to transplantation. Both patients with acute and chronic renal failure were included here, and according to the the Kidney Disease Improving Global Outcomes system definitions (KDIGO) [10]. Therefore, all those with pre-transplant creatinine greater than 1.5mg/dL were included in this consideration. However, those who, having had hepatorenal syndrome, had corrected their glomerular filtration rate and creatinine at the time of LT were not included in this group.

Diagnosis of acute renal failure in the postoperative period

Acute renal failure (ARF) was considered to exist when, according to the KDIGO classification, based on the assessment of serum creatinine (SCr) with respect to baseline, an increase in creatinine was observed during the first 10 days after transplantation. SCr was determined by protocol before surgery and 24 hours after surgery, at least once a day during the following 10 postoperative days, at discharge and one year after liver transplantation. When there was more than one SCr value per day, the determination with the highest value was collected. To define ARF, the highest value of SCr presented in those 10 days post-transplantation was taken into account. The need for postoperative RRT was also assessed. Likewise, renal function was monitored at hospital discharge and one year after the transplant, based on the SCr value. At the same time, the patients who required RRT during the study period and at home discharge were recorded. In the analysis of the possible factors that could be related to the existence of ARF, clinical and analytical variables of the period studied were considered. These were framed in different phases: preoperative, intraoperative and postoperative. A total of 77 variables were evaluated in each patient.

Statistical analyses

Statistical comparisons were made between the patients who developed acute renal failure with those who did not according to the two treatment groups A and B. A statistical sub-analysis was carried out excluding patients with pre-transplantation renal failure to determine their possible bias in the results. Pearson, c2 test, or the Fisher exact test was used for categorical data. The Student t test or Mann-Whitney U test was used for quantitative data. Normality was assessed with the Kolmogorov-Smirnov test. A multivariate analysis of estimated logistic regression was carried out. Differences were considered to be statistically significant when P was <0.05. Analyses were undertaken using the statistical package SPSS 18 (SPSS Inc, Chicago, Ill, United States).

Results

The overall incidence of acute renal failure, in the first 10 postoperative days, was 59.8% (138 patients), present in 70.8% of patients in group A (n: 80) and in 49.2% % of group B (n: 58); this difference showed statistical significance. Half of the patients in group A who showed ARF did so in a severe stage (KDIGO 3), unlike what happened in group B, where it happened in 20.7% (n: 40 *vs* n: 12; *p: 0.002*). The differences in serum creatinine during the first 10 days after transplantation, at

discharge and at one year, were also significant, between both groups, all being higher in group A. Only one patient, belonging to group A, required RRT at discharge. The different aspects related to renal complications in the postoperative period are shown in (Table 1).

Table 1: Kidney complications in the early postoperative period, during the first 10 days and other data on hospital stay and kidney function at discharge and after one year.

	Group A N (%) / X ± SD	*Group B N (%) / X ± SD*	*p*
Acute kidney failure after LTs	80 (70.8)	58 (49.2)	.001
Need for RRT after LTs	34 (30.1)	6 (5.1)	<.001
RRT time (days)	4.8 ± 5.9	3.0 ± 3.9	ns
At discharge, per year			
Serum creatinine at discharge (mg/dL)	1.34 ± 0.77	0.92 ± 0.46	<.001
Serum urea at discharge (mg/dL)	74.9 ± 52.4	49.9 ± 33.4	<.001
Serum creatinine per year (mg/dL)	1.14 ± 0.36	1.03 ± 0.56	<.001

Results expressed as mean *± SD.*
Abbreviation: LT, liver transplantation; ns: nonsignificant; RRT, renal replacement therapy; SD, standard deviation.

Risk factors for the development of ARF

In the initial evaluation of the risk factors for the development of ARF, all the patients were included. Their results are shown in (Tables 2 and 3). Multiple variables were associated with an increased risk of AKI, and two others were protective: portocaval shunt and basiliximab use. Postoperative stay was significantly longer in patients with ARF than in patients who did not present this complication (32 ± 24.7 days vs 23.4 ± 32 days).

Table 2: Factors related to the development of ARF. Univariate analysis of qualitative variables.

Factors	*Present n (ARF/ total)*	*Absent n (ARF/ total)*	*p*	*OR*	*CI95%*
Preoperative variables					
Hepatorenal syndrome	21/28	117/203	ns	2.2	0.9-5.4
Ascites	93/132	45/99	<.001	2.9	1.7-4.9
Hepatic encephalopathy	73/96	65/135	<.001	3.4	1.9-6.1
Previous renal dysfunction	34/49	104/182	ns	1.7	0.9-3.3
Intraoperative variables					
Vasoactive drugs use	124/184	13/42	.001	4.6	2.2-9.5
Reperfusion syndrome	52/68	86/163	.001	2.9	1.5-5.5
Portocaval shunt	40/79	93/140	<.05	0.5	0.3-0.9
Postoperative variables					
Basiliximab	58/118	80/113	.001	0.4	0.2-0.7
Orotracheal reintubacion	26/28	109/200	<.001	10.9	2.5-47.0
Readmission to ICU	18/23	115/203	<.05	2.8	1.0-7.7
Hemorrhage (yes / no)	26/28	112/203	<.001	10.6	2.4-45.7
Reoperation	20/23	117/206	.005	5.1	1.5-17.6
Infection	56/79	82/152	.013	2.1	1.2-3.7
Central nervous system complications	27/33	111/198	.005	3.5	1.4-8.9

Abbreviations: ARF: Acute Renal Failure; CI: Confidence Interval; ICU: Intensive Care Unit; OR: Odds Ratio; Ns: Nonsignificant.

Table 3: Factors related to the development of ARF. Univariate analysis of continuous quantitative variables.

Factors	*Present X ± SD*	*Absent X ± SD*	*p*
Preoperative variables			
MELD score	18.2 ± 6.3	13.7 ± 7.0	<.001
Serum creatinine (mg/dL)	1.0 ± 0.4	1.0 ± 0.4	ns
Intraoperative variables			
Red blood cell transfusión (N)	7.5 ± 7.6	3.4 ± 4.2	<.001
Duration of the surgical intervention (minutes)	407 ± 95.7	379.3 ± 83.7	<.05
Postoperative variables			
Days of stay in ICU	8.6 ± 10.4	3.5 ± 3.2	<.001
Duration of mechanical ventilation (hours)	32.4 ± 117.5	7.4 ± 4.2	.007

Results expressed as mean *± SD.*
Abbreviation: ICU: Intensive Care Unit; MELD: Model For End-Stage Liver Disease; Ns: Nonsignificant; RRT: Renal Replacement Therapy; SD: Standard Deviation.

The result of the multivariate analysis carried out is shown in (Table 4), which shows the factors that were significant and independent. It should be noted that Basiliximab proved to be a protective factor against ARF, capable of reducing its appearance by up to 78%. On the other hand, the risk of ARF increased by an average of 11% for each point increase in the MELD score.

Table 4: Factors related to the development of postoperative ARF. Multivariate analysis.

Factors	*p*	*OR*	*CI95%*
Basiliximab	.001	.22	.09 -.55
MELD score	.002	1.11	1.04-1.18
Use of vasoactive drugs in the operating room	.015	3.94	1.30-11.88
Red blood cell transfusion in the first 24 hours	.039	1.34	1.02-1.78

Abbreviation: CI: confidence interval; MELD: model for end-stage liver disease.

In order to reduce the bias that could derive from the higher incidence of pre-transplant renal dysfunction among patients in group A, and despite the fact that pre-transplant serum creatinine, hepatorenal syndrome and preoperative renal dysfunction were not significant for the development of AKI in the univariate and multivariate analysis, a second comparative evaluation between both groups was performed, omitting all patients with preoperative renal dysfunction (n: 42) (Table 5).

Coinciding with the previous ones, even when excluding those who already had preoperative renal dysfunction, it was found that the incidence of ARF was also significantly lower when induction therapy with basiliximab was carried out (46% group B *vs* 70.7% % group A, *p: .001*). In addition, basiliximab turned out to be a protective factor against the need for RRT, reducing the need for RRT by an average of 90%.

Table 5 show the data related to said analysis. A multivariate analysis was also carried out (Table 6), where the variable Basiliximab also maintained a protective effect against ARF, even after excluding patients with preoperative renal dysfunction. Basiliximab reduced the risk of ARF by an average of 62%

Table 5: Univariate analysis of ARF and RRT in relation to the use of basiliximab after exclusion of patients with preoperative renal dysfunction.

Factors	*Present n / N*	*Absent n / N*	*p*	*OR*	*CI95%*
Basiliximab – ARF	46/100 (46%)	58/82 (70.7%)	.001	0.4	0.2 – 0.7
Basiliximab – RRT postoperative	4/100 (4%)	23/82 (28%)	<.001	0.1	0.0 – 0.3

Abbreviation: ARF: Acute Renal Failure; CI: Confidence Interval; RRT: Renal Replacement Therapy.

Table 6: Estimated multivariate analysis of ARF after excluding patients with preoperative renal dysfunction.

Factors	*p*	*OR*	*CI95%*
Basiliximab	.020	0.38	0.17- 0.86
MELD score	<.001	1.15	1.07-1.22
Use of vasoactive drugs in the operating room	.024	3.06	1.16-8.05
Number of blood products transfused	.036	1.03	1.00-1.06

Abbreviation: CI: confidence interval; MELD: model for end-stage liver disease.

Discussion

Acute renal failure (ARF) is a frequent complication in seriously ill and critically ill patients [11]; consequently, it is more common in the postoperative period of LT than in that of other types of surgical interventions. In the literature, the incidence of post-liver transplant ARF varies between 12% and 94.2% [1, 4-6,8,9,12-15]. This wide variability is due to the criteria used for its definition, as well as the different cut-off points, the different immunosuppressive therapy regimens used (nephroprotective or not) and the various inclusion criteria of the studies. Among patients who develop ARF, 5-35% require RRT, this being an independent risk factor associated with mortality [5,6,13,15,16].

ARF increases postoperative mortality and healthcare costs related to LT. In fact, it has been considered one of the factors most related to the death of patients [17,18]. Among other reasons, this could be linked to alterations in the immune system induced by uremia, such as the accumulation of proinflammatory cytokines as a consequence of the decrease in its removal; or by increased production, oxidative stress, volume overload, etc [19,20]. These alterations, present in ARF, contribute to a higher risk of infection, which is the main cause of death in patients undergoing LT. A better understanding of the determinants of ARF could contribute to its prevention and the consequent benefit in terms of survival, quality of life and healthcare costs.

In our experience, the incidence of ARF was significantly lower among patients who received the induction immunosuppressive regimen with Basilixiamb (49.2% *vs* 70.8%). Different authors report similar facts when nephroprotective immunosuppressive therapies are applied based on delaying the administration of CI and reducing their dose, based on induction immunosuppression with this drug [9,12,21,22-28]. In our study, Basiliximab turned out to be a protective factor against ARF, reducing the average of its appearance by 78%. This result was significant on multivariate analysis, even when groups were analyzed excluding patients with preoperative renal dysfunction. Similarly, this immunosuppressive regimen was significantly associated with a decrease in RRT requirements (5.1% *vs* 30.1%).

Several factors may intervene, with different degrees of importance, in the development of ARF after LT. Some depend on the patient's condition before the transplant; others may be caused by intraoperative hemodynamic changes, postoperative complications, or immunosuppressive therapy [6,29].

CI are drugs that produce nephrotoxicity, depending on their dose and the time of use [30]. The renal dysfunction induced by CI is usually reversible, but occasionally it can be progressive [31]. The immunosuppressive strategy to minimize postoperative renal damage, with the delayed use of CI, through immunosuppressive induction with anti-CD25 drugs, such as Basiliximab, provides an improvement in glomerular filtration rate and a reduction in postoperative renal dysfunction (26% *vs* 67% % of the control group) in controlled clinical trials [32]. We have corroborated this fact. The incidence of ARF in group B was significantly lower than in group A (49.2% *vs* 70.8%). These results were maintained even when patients with preoperative renal dysfunction were excluded (46% group B *vs* 70.7% group A, *p: .001*). On the other hand, Basiliximab was a protective factor against postoperative ARF in the multivariate analysis, preventing the development of ARF in an average of 78%. The need for RRT was also significantly lower in group B than in group A (5.1% *vs* 30.1%).

In our study we found nonsignificant differences in the incidence of infections between the different immunosuppressive treatment groups (30.1% group A, *vs* 33% group B), but regarding the appearance of acute rejection, higher in the group A (37.2% *vs* 17.9%), findings described by other authors [25, 33, 34]. It could be due to an additive immunosuppressive effect between Basiliximab and CI [25, 33], or due to triple therapy maintained by patients receiving basiliximab (corticosteroids, mycophenolate mofetil and tacrolimus) [34]. In our series, this occurred in 100% of patients in group B, compared to only 26.5% in group A. No However, other authors have not found significant differences in the incidence of acute rejection [12].

Conclusion

Early post-transplant acute renal failure is a very common complication in patients undergoing liver transplantation, reaching an overall incidence of 59.8%. This incidence was significantly lower in the group treated with Basiliximab (49.2% vs 70.8%; p: 0.001), whose use managed to reduce this complication by an average of 78%. The need for renal replacement therapy was also significantly lower in this treatment group (5.1% vs 30.1%; p<0.001).

Knowing and acting on the risk factors for the development of ARF can improve outcomes after LT, having a positive impact. The use of Basiliximab was found to be a protective factor against the development of acute renal failure after liver transplantation, without increasing postoperative infection or rejection rates.

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