Role of basiliximab in the prevention of acute cellular rejection in adult to adult living-related liver transplantation: a single center experience

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Abstract: We report our single center experience with the use of basiliximab, a chimeric monoclonal antibody directed against the alpha chain of the interleukin-2 (IL-2) receptor (CD25), in combination with a steroid- and tacrolimus-based regimen in adult to adult living-related liver transplantation (ALRLT). Sixty consecutive ALRLTs were analyzed. All patients received two 20-mg doses of basiliximab (days 0 and 4 after transplantation) followed by tacrolimus (0.15 mg/kg/day; 10–15 ng/mL target trough levels) and a dose regimen of steroids (starting with 20 mg iv, switched to po as soon as the patient was able to eat, and weaned off within 1–2 months). Follow-up ranged from 6 to 1699.4 days after transplantation (mean 517.5 days, SD ± 413.4; median 424 days). Of the recipients, 95% remained rejection-free during follow-up, with an actuarial rejection-free probability of 96.61% within 3 months. Three patients had episodes of biopsy-proven acute cellular rejection (ACR). Actuarial patient and graft survival rates at 3 years were 82.09% and 75.61%. Six patients (10%) experienced sepsis. There was no evidence of cytomegalovirus infections or side-effects related to the basiliximab. We found zero de novo malignancy, although we observed 5 patients with metastatic spread of their primary malignancy during the follow-up. Basiliximab in association with tacrolimus and steroids is effective in reducing episodes of ACR and increasing ACR-free survival after ALRLT.

Keywords: living-related liver transplantation, acute cellular rejection, basiliximab

Introduction

Living-related liver transplantation (LRLT) was initially performed successfully in the pediatric population (Otte 2002), and then proposed as one of the most effective measures to counteract organ-donor shortage for adults. LRLT evolved naturally from other surgical procedures, namely reduced-size liver transplantation and split-liver transplantation (Heffron et al 1998), based on the segmental anatomy of the liver and on its peculiar capacity to regenerate. However, there has been ongoing debate over the ethics of posing a potential risk to the donor (Marcos 2000), and some uncertainty as to recipient outcomes (Gruttadauria et al 2005a). Since adult to adult living-related liver transplantation (ALRLT) first became as a valuable therapeutic option for end-stage liver diseases, the immunosuppressive protocols available to reduce the risk of acute cellular rejection (ACR) have been continually changing. The transplanted liver is generally considered immunologically privileged, regardless of the source of donation (from living or deceased donor), with low incidences of graft loss due to acute or chronic rejection. However, despite advances in immunosuppression, ACR remains an important risk factor. Immunosuppressive therapy in ALRLT is usually aimed at achieving early corticosteroid weaning and maintenance with low-dose calcineurin inhibitor, at minimizing potential deleterious pharmaceutical side-effects, and at trying to induce a potential mechanism of tolerance (Ringe et al 2005). With the advent of newer immunosuppressive agents, including interleukin-2 receptor antibody

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(IL-2Rab) (Brennan et al 2006), and sirolimus, early steroid reduction or withdrawal in liver transplant recipients appears to be practical. Monoclonal antibodies (MAb) specifically targeting the interleukin-2 (IL-2) receptor were developed to reduce these adverse effects (Moser 2003). IL-2 receptor antibodies include the chimeric IL-2 receptor antibody basiliximab (Simulect) (Nashan et al 1997; Kahan et al 1999; Adu et al 2003; Ponticelli et al 2001) and the humanized IL-2 receptor antibody daclizumab (Zenapax®). Both are directed against the α-chain (CD25), which is expressed on activated T cells. As inhibitors of IL-2 binding, they prevent ACR by inhibiting IL-2-driven T-cell proliferation.

Herein we report our single center experience with the use of basiliximab as part of the immunosuppressive regimen in our group of ALRLT recipients.

Materials and methods

From January 2002 to December 2006 we performed 60 ALRLTs. The number of cases per year has been progressively increasing, with a peak reached in 2006, when 24 liver transplants out of a total of 102 were ALRLT. All recipient and donor demographics are presented in Table 1, and primary indications to transplantation are listed in Table 2. Donors always had genetic or emotional relationships with the recipients; 33 couples were ABO identical, and 27 compatible. Donor liver resections resulted in 58 right hepatectomies and two left hepatectomies; graft implantation was performed with the preservation of the recipient inferior vena cava, and in 50 cases with the use of veno-venous bypass.

The immunosuppressive protocol included 20 mg basiliximab (Simulect®) in association with 500 mg methylprednisolone at the time of liver reperfusion; both were given by iv bolus. An additional 20 mg dose of basiliximab was administered by iv bolus on day 4 after transplantation. Tacrolimus (Prograf®) was administered at 0.15 mg/kg/day by mouth or through the nasogastric tube within 24 hours after the transplant, and adjusted to achieve trough levels in the range of 8–10 ng/mL. At 30 days post-transplantation, the target trough level was reduced to 5–7 ng/mL. Corticosteroids were administered in a standard rapid taper regimen for the first month: methylprednisolone at 50 mg iv every 6 hours on day 1; 40 mg iv every 6 hours on day 2; 30 mg iv every 6 hours on day 3; 20 mg iv every 6 hours on day 4; and 20 mg iv every 12 hours on day 5; and 20 mg prednisone by mouth or through the nasogastric tube on days 6–15; then 10 mg/day for 1 week; and 5 mg/day for 1 additional week. After the first year, we prescribed only methylprednisone 20 mg iv for the first 2–3 days and then 20 mg prednisone by mouth, slowly decreasing and weaning from corticosteroids within 1–2 months. In the case of ACR, depending

Table 1 Demographic characteristics of 60 living donors and recipients

	Donor		Recipient	
Characteristics	**n**	**Mean ± SD or percent**	**n**	**Mean ± SD or percent**
Age		32.26 ± 9.44		52.65 ± 12.23
Range		[18;53]		[18;67]
Classes				
0–20	5	8.33%	2	3.33%
21–40	43	71.67%	6	10.00%
41–60	12	20.00%	37	61.67%
61–80	0	0.00%	15	25.00%
Sex				
Male	28	46.67%	20	33.33
Female	32	53.33%	40	66.67
Height (cm)		169.10 ± 8.94		167.55 ± 9.41
Weight (kg)		68.53 ± 11.12		69.98 ± 12.74
Donor to recipient relationship				
Biologically related	52	86.67%		
Sibling	7	11.67%		
Child	41	68.33%		
Parent	4	6.67%		
Not biologically related	8	13.33%		
Spouse	3	5.00%		
Other nonbiological	5	8.33%		

Table 2 Primary indication to transplantation

Characteristics	n	Percent
Diagnosis		
HCC+HCV	22	36.67
HCV	17	28.33
HBV	3	5.00
PBC	2	3.33
Cystic fibrosis	2	3.33
HCC+alcohol	2	3.33
HBV-HCV	1	1.67
HCC+HBV	1	1.67
Calcinoid mets	1	1.67
HCC+HCV+HBV	1	1.67
Alcohol	1	1.67
HBV-HDV	1	1.67
HCC+NASH	1	1.67
HBV-HCC	1	1.67
PSC	1	1.67
Cryptogenic	1	1.67
OTC deficiency	1	1.67
Biliary atresia	1	1.67
MELD Score		
8–10	6	10.00
11–20	25	41.67
21–30	27	45.00
31–40	1	1.67
Missing	1	1.67

Abbreviations: HBC, hepatitis B core ; HBV, hepatitis B virus; HCC, hepato cellular carcinoma; PBC, primary biliary cirrhosis; NASH, non-alcoholic steatohepatitis; OTC, ornithine transcarbamylase; PSC, primary sclerosing cholangitis; MELD, Model End-Stage Liver Disease.

on the gravity of the rejection, the protocol comprised a bolus administration of 500 mg methylprednisolone to be repeated 3 times. Simultaneously, the tacrolimus target level was increased to 8–10 ng/mL. Cytomegalovirus (CMV) pp65 antigenemia-guided pre-emptive therapy was used for CMV prophylaxis; surveillance for CMV antigenemia was performed at weeks 2, 4, 6, 8, 12, and 16 post-transplantation. If positive, oral ganciclovir was used for 6 weeks (Singh et al 2000). Follow-up ranged from 6 to 1699.4 days after transplantation (mean 517.5 days, SD ± 413.4, median 424 days). Parameters evaluated included graft failure, need and indication for retransplantation, and number of retransplants. The diagnosis of ACR was always biopsy proven.

Statistical analysis

Continuous variables are presented as the mean values ± SD, and categorical variables as rates. For survival, the Kaplan-Meier method was used. Patient survival/death, ACR-free time, and infection rate also were measured. The analyses were performed using SPSS (SPSS Inc., Chicago, Ill, United States).

Results

The majority of patients experienced a successful outcome. Actuarial patient survival rate at 3 years was 82.09%, while graft survival rate was 75.61% (Figure 1). Of all patients, 95% were free of ACR episodes during the follow-up period, with a rejection-free probability of 96.61% within 3 months; OKT3 or other antibody therapy was never required to treat rejection. Table 3 synthesizes morbidity and mortality in the recipient population. There were 10 deaths: 6 due to sepsis (60%) and 4 due to recurrence of neoplastic disease (40%). Three patients had ACR episodes: 2 within 3 months; 1 within 6 months. Retransplantation was necessary in 6 patients (10%): 5 due to hepatic artery thrombosis and 1 due to graft malfunction.

Four patients developed a CMV infection: 3 within 3 months, 1 within 6 months. We found zero de novo malignancy, but we observed 5 patients (8.33%) with progression of their neoplastic disease at different stages after transplantation.

Basiliximab was well tolerated by all patients. No acute side-effects were noted, including acute infusion reactions. No patients or grafts were lost due to acute or chronic rejection.

Discussion

This single center experience here reported shows that basiliximab in a tacrolimus-based immunosuppression regimen is well tolerated and effective in both reducing episodes of ACR and increasing ACR-free survival after LRLT.

We believe that there are two important advantages of this protocol; the first is achieving early steroid reduction. Previous reports have shown that early reduction or elimination of corticosteroids can significantly reduce the incidence of many complications in liver transplant recipients. Moreover, corticosteroids are frequently implicated in the acceleration of viral replication and recurrence after liver transplantation (Marino et al 2004).

In our series, although more than 50% of the patients transplanted had primary diagnosis end stage liver disease secondary to hepatitis C virus infection, only 9 patients had recurrence of their primary disease and are all undergoing antiviral treatment.

Corticosteroids are associated with a number of hemodynamic and metabolic effects which may generate risk factors that favor cardiovascular diseases. Among these risk factors are hypertension, diabetes mellitus, and hyperlipidemia. Corticosteroids are also associated with cataract

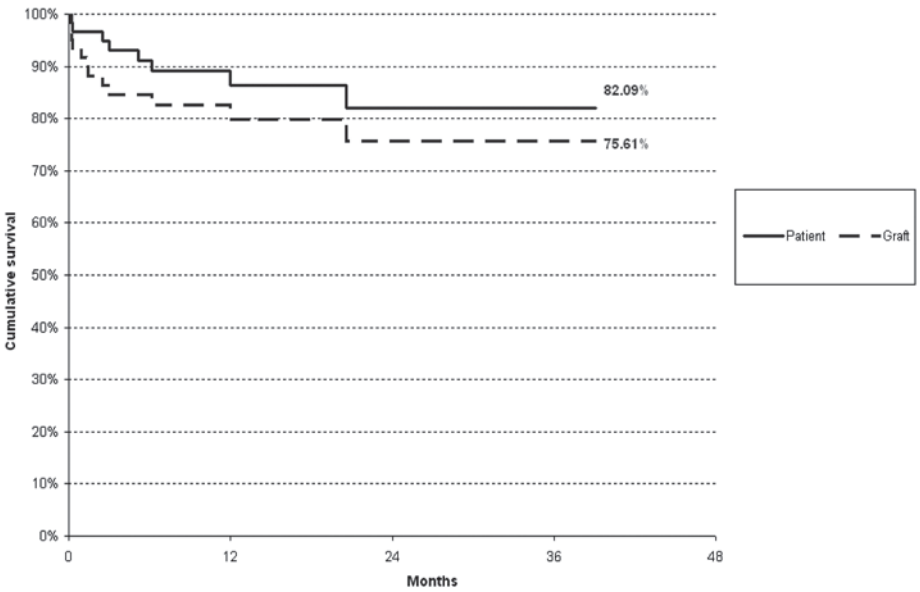

Figure 1 Actuarial survival curve of the patients and grafts in the 60 living-related liver transplants performed (3 years).

formation, aseptic necrosis of bone, osteoporosis, and cosmetic alterations such as acne vulgaris and obesity.

The second advantage lies in trying to create a tolerogenic protocol by using a chimeric monoclonal antibody. In this report the use of basiliximab in ALRLT treated with tacrolimus-based immunosuppression decreased ACR while avoiding the serious adverse effects associated with broad T-cell depletion.

However, MAb also may be beneficial to patients when used in calcineurin inhibitor-sparing regimens. The improved rates of ACR and patient survival without significant adverse events seen in our group of recipients support the further investigation of basiliximab as an agent that facilitates the withdrawal of cyclosporine or tacrolimus over time.

We previously reported that this drug does not increase the incidence of opportunistic infections or malignancies above baseline in patients treated with conventional calcineurin inhibitor-based immunosuppression, with a reasonable cost-benefit ratio (Gruttadauria et al 2005b, 2006).

Antibody induction is a means of reducing the risk of ACR in the early post-transplantation period, while simultaneously attempting to avoid the long-term use of corticosteroids. The immunosuppressive protocol here reported was based on our previous experience with patients who received cadaveric liver donations; thus this series represents a learning curve reflecting surgical and clinical management improvements.

Table 3 Morbidity and mortality in the ALRLT recipients

	90 days 0–90	**1 year 91–365**	**After 1 year**	**Total**
All deaths	4	3	3	10
Cause of death				
Recurrence of neoplastic disease	0	1	3	4
Sepsis	4	2	0	6
Retransplants (10.00%)	6	0	0	6
Cause of retransplant				
Hepatic artery thrombosis	5	0	0	5
Multifactorial	1	0	0	1
ACR	2	1	0	3
CMV infection	3	1	0	4

Abbreviations: ACR, albumin-to-creatinine ratio; ALRT, adult living-related liver transplantation; CMV, cytomegalovirus.

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