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The Role of Basiliximab Induction Therapy in Adult-to-Adult Living-Related Transplantation and Deceased Donor Liver Transplantation: A Comparative Retrospective Analysis of a Single-Center Series

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ABSTRACT

Aim. The aim of this study was to report our single-center experience with the use of basiliximab, in combination with a steroid and tacrolimus–based regimen in adult to adult living-related liver transplantation (ALRLT) and in deceased donor liver transplantation (DDLT).

Materials and Methods. Seventy-seven consecutive ALRLT recipients (group 1) and 244 DDLT recipients (group 2) were analyzed. All patients received 2 20-mg doses of basiliximab (days 0 and 4 after transplantation) followed by tacrolimus (0.15 mg/kg/d; 10–15 ng/mL target trough levels) and a dose regimen of steroids. Follow-up ranged from 4–1972 days after transplantation in group 1 and from 1–2741 days in group.

Results. In group 1, 89.32% of the patients remained rejection-free during follow-up, with an actuarial rejection-free probability of 93.51% within 3 months. Actuarial patient survival rate at 3 years was 84.49%. In group 2, 86.07% of the patients remained rejection-free during follow-up, with an actuarial rejection-free probability of 93.04% within 3 months. Actuarial patient survival rate at 3 years was 87.69%. We observed 14 cases of hepatitis C virus (HCV) recurrence in group 1 (prevalence of 26.92%) and 80 cases in group 2 (prevalence of 54.05%).

Conclusion. Basiliximab in association with tacrolimus and steroids is effective in reducing episodes of acute cellular rejection (ACR) and increasing ACR-free survival after ALRLT and DDLT. No difference in patient and graft survival was found between group 1 and 2, nor was there any difference in the incidence of ACR between the 2 groups. However, less risk of HCV recurrence was present in the LRLT group.

LIVER transplantation has become the standard treatment for both chronic and acute end-stage liver disease. Because of a progressive increase in the of number of patients on waiting lists for liver transplants, a number of strategies have been developed in the last few years to increase the donor pool.

One of these strategies is adult living-related liver transplantation (ALRLT).[1] Since 2001, our institute has performed 77 ALRLT, with overall survival similar to deceased donor liver transplantation (DDLT).

In both DDLT and ALRLT, acute cellular rejection (ACR) remains an important risk factor for a patient's outcome. Immunosuppressive therapy is usually aimed at achieving early corticosteroid weaning and maintenance with low-dose calcineurin inhibitor, minimizing potential deleterious pharmaceutical side effects, and trying to induce a potential mechanism of tolerance.[2] Antibody induction is

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a means of reducing the risk of ACR in the early posttransplantation period, while simultaneously attempting to avoid adverse effects such as nephrotoxicity.[3]

Experience with basiliximab in liver transplantation has been extensively reported in the recent literature.[4] In this study we aimed to compare profiles of basilixmab in combination with tacrolimus and early steroid weaning in adult recipients of living and deceased donor liver transplantations performed at our center.

MATERIALS AND METHODS

From January 2002 to October 2007 we performed 349 liver transplantations in 321 patients. The number of cases has been progressively increasing per year because of extensive use of living donor liver transplantation, split liver transplantation, and extended criteria donor whole liver transplantation, with a peak reached in 2006 when we performed 102 liver transplantations (24 ALRLT, 78 DDLT).

In this study we divided the liver transplant recipients into 2 groups: group 1, 77 ALRLT patients, and group 2, 244 DDLT patients.

In both groups, the most common indications for transplantation were hepatocellular carcinoma on C viral cirrhosis (31.17% and 30.88% in groups 1 and 2, respectively), and liver cirrhosis secondary to viral etiology (42.86% and 27.93%, respectively). In the ALRLT population, the donors (mean age, 32.25 years +/− SD 9.17 years) always had genetic or emotional relationships with the recipients; 43 couples were ABO identical, and 34 were compatible. Donor liver resections resulted in 75 right hepatectomies and 2 left hepatectomies; graft implantation was performed with the preservation of the recipient inferior vena cava, and, in 67 cases, with the use of veno-venous bypass. Donor evaluation and surgical technique have been previously described.[1,5]

In the DDLT population (donor mean age, 45.27 years +/− SD 19.63 years) we performed 119 whole liver transplantations, 118 extended criteria donor whole liver transplantations, and 35 split liver transplantations.

The immunosuppressive protocol was identical in both groups and included 20 mg basiliximab (Simulect) in association with 500 mg methylprednisolone at the time of liver reperfusion; both were given as intravenous (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/d by mouth or through a nasogastric tube within 24 hours after the transplantation, and was adjusted to achieve trough levels in the range of 8–10 ng/mL. At 30 days posttransplantation, 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 to 15; then 10 mg/d for 1 week; and 5 mg/d for 1 additional week. After the first year of activity, we prescribed only methylprednisone 20 mg IV for the first 2 to 3 days and then 20 mg prednisone by mouth, slowly decreasing and weaning from corticosteroids within 1 to 2 months. In the case of ACR, a bolus of 500 mg methylprednisolone, to be repeated 3 times, was administered, as per institutional protocol; simultaneously, the tacrolimus target level was increased to 8–10 ng/mL. The diagnosis of ACR was always biopsy-proven. Follow-up ranged from 4 to 1972 days after transplantation in group 1 (mean, 558.17 days, SD ± 465.45; median, 470 days) and from 1 to 2741 days in group 2 (mean, 887.16 days, SD ± 722.12; median, 794 days).

Primary outcomes of this study were as follows: patient and graft survival, incidence of ACR, cytomegalovirus (CMV) infection, de novo malignancy hepatitis C virus (HCV) recurrence, and chronic rejection.

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 overall patient survival rates at 3 years in group 1 and group 2 were 84.49% and 89.96%, respectively ($P = .95$), whereas graft survival rates were 79.04% and 79.37%, respectively ($P = .58$). In the general transplanted population (ALRLT + DDLT), 86.92% were ACR-free during the follow-up period, with a rejection-free probability of 93.15% within 3 months; 89.32% in group 1 and 86.07% in group 2 were rejection-free with an actuarial rejection-free probability within 3 months of 93.04% (group 1) and 93.51% (group 2). Forty-two patients had episodes of biopsy-proven ACR: 8 cases in group 1, and 34 cases in group 2. OKT3 or other antibody therapy was never required to treat rejection. No patients or grafts were lost due to acute or chronic rejection.

We observed 14 cases of HCV recurrence in group 1 (prevalence, 26.92%) and 80 cases in group 2 (prevalence, 54.05%) ($P = .05$), with an incidence of HCV recurrence in the first 3 months after transplantation of 3.84% and 14.86%, respectively.

Incidences of HCV recurrence in the first 12 months were 19.23% in group 1 and 41.89% in group 2.

Eighteen patients developed a CMV infection: 4 in group 1, and 14 in group 2, with CMV infection incidence in the first 3 months after transplantation of 3.89% and 4.5%, respectively.

We found 6 de novo malignancies: 1 in group 1, and 5 in group 2.

Table 1 summarizes primary outcome in both recipient populations.

Basiliximab was well tolerated by all patients. No acute side effects were noted, including acute infusion reactions.

DISCUSSION

Interleukin (IL) 2 receptor antibodies include the chimeric IL-2R antibody basiliximab (Simulect) and the humanized IL-2R antibody daclizumab (Zenapax). Both are directed against the alpha 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.

Among the different induction agents, basilixmab is the most commonly used (7% of all liver transplant recipients)

Table 1. Morbidity in ALRLT and DDLT Recipients

	0–90 d		91–365 d		After 1 year		Total		
	ALRLT	DDLT	ALRLT	DDLT	ALRLT	DDLT	ALRLT	DDLT	*P*
ACR	5	17	2	11	1	6	8 (10.38%)	34 (13.93%)	.74 NS
CMV infection	3	11	1	2	0	1	4 (5.19%)	14 (5.73%)	.65 NS
HCV recurrence	2	22	8	40	4	18	14/52 (26.92%)	80/148 (54.05%)	.05 S
De novo neoplasias	1	0	0	1	0	4	1 (1.30%)	5 (2.04%)	.75 NS
Chronic rejection	0	0	0	0	0	5	0	5 (2.04%)	.23 NS

Abbreviation: NS, not significant.

because of such advantages as the following: (1) evidence of reduced overall cost demonstrated by pharmacoeconomic analysis; (2) ease of administration; (3) short-term use; (4) no need for blood level monitoring; and (5) lack of major toxicity.[6]

Several trials have investigated basiliximab in the induction therapy of liver transplantation, in combination with calcineurin inhibitor and steroids, or in a triple regimen with the addition of azathioprine. These trials noted lower mean ACR rates in the basiliximab group compared with the standard therapy (23% vs 41%).[7,8]

A large multicenter randomized study investigating basiliximab versus placebo in liver transplant recipients showed a lower incidence of ACR (35% vs 44%) in the basiliximab group.[9]

Basiliximab induction exhibited no difference in its action in both recipient populations reported in this retrospective comparative analysis.

On the other hand, the data concerning the rate of HCV recurrence in the 2 different groups of recipients are particularly interesting. In fact, our series shows a lower rate of HCV after living related liver transplantation.

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REFERENCES

1. Marcos A: Right lobe living donor liver transplantation: a review. Liver Transpl 6:3, 2000

2. Ringe B, Moritz M, Zeldin G, et al: What is the best immunosuppression in living donor liver transplantation. Transplant Proc 37:2169, 2005

3. Moser MAJ: Options for induction immunosuppression in liver transplant recipients. Drugs 62:995, 2002

4. Kahan BD, Rajagopalan PR, Hall M: Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. Transplantation 67:276, 1999

5. Gruttadauria S, Marsh JW, Cintorino D, et al: Adult to adult living-related liver transplantation: report on an initial experience in Italy. Dig Liver Dis 39:342, 2007

6. Ramirez CB, Marino IR: The role of basiliximab induction therapy in organ transplantation. Expert Opin Biol Ther 7:137, 2007

7. Marino IR, Doria C, Scott VL, et al: Efficacy and safety of basiliximab with a tacrolimus-based regimen in liver transplant recipients. Transplantation 78:886, 2004

8. Calmus Y, Scheele JR, Gonzalez-Pinto I, et al: Immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor-monoclonal antibody, in combination with azathioprine-containing triple therapy in liver transplant recipients. Liver Transpl 8:123, 2002

9. Neuhaus P, Clavien PA, Kittur D, et al: CHIC 304 International Liver Study Group. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. Liver Transpl 8:132, 2002