Brief Report

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Basiliximab as therapy for acute rejection after liver transplantation for hepatitis C virus cirrhosis

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Summary **Steroid bolus therapy for acute rejection after liver transplantation for hepatitis C virus (HCV) cirrhosis often results in graft loss due to adverse effects. The efficacy and safety of basiliximab for the treatment of acute cellular rejection (ACR) in adult liver transplantation has not been adequately evaluated. Three patients received basiliximab as rescue therapy for acute rejection. The outcome and biochemical parameters were recorded before and after treatment with basiliximab. These results were compared to 11 patients who received steroid therapy for ACR. The median time from transplantation to the development of ACR was 19 days (range, 9-49 days). The degree of ACR was mild or moderate. Resolution of rejection was obtained in all patients and the median time from the onset to resolution of ACR was 16 days (range, 6-41 days). A steroid resistant reaction occurred in 2 of 11 patients and OKT3 was used, and the rejection eventually resolved in all patients. Five patients died within 2 to 22 months after transplantation and four of them died from graft failure. In the basiliximab group, there were no significant immediate adverse effects. One patient died from pneumonia 8 months after transplantation. In conclusion: Basiliximab can be safely used as rescue therapy for ACR without significant adverse effects in patients who underwent liver transplantation for HCV cirrhosis.**

Keywords: Hepatitis C, donor, living donor liver transplantation

1. Introduction

Liver transplantation is an effective treatment for end-stage liver disease due to hepatitis C virus (HCV). Despite major advances in immunosuppression, acute cellular rejection (ACR) remains a significant postoperative issue. This can be a major risk factor for the development of chronic allograft rejection and graft loss. Despite the use of calcineurin inhibitors, ACR occurs in 36% to 57% of transplant recipients (*1*). Typical management involves optimization of baseline immunosuppression and methylprednisolone boluses. In addition, 28% to 35% (*2*) of patients do not respond to high-dose steroid therapy and require further intervention, including antithymocyte globulin or OKT3. Repeated high-dose steroids and OKT3, however, reduce graft survival as a consequence of severe HCV recurrence (*3*).

Basiliximab is a chimeric (human/mouse) monoclonal antibody that selectively binds to the α subunit (CD25) of the interleukin-2 (IL-2) receptor (*4*), preventing normal T-cell proliferation and thereby the progression of ACR (*5*). IL-2 promotes the proliferation of activated T cells by engaging the IL-2 receptor, and this has a crucial role in the mediation of ACR. The efficacy of basiliximab has been evaluated and has been shown to rescue the graft from ACR (*6*). In the present study, we examined the efficacy and safety of basiliximab as a therapeutic agent for rescue of ACR in liver recipients for HCV-related cirrhosis, in comparison with conventional high-dose steroid therapy.

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2. Patients and Methods

We performed 213 adult liver transplantations from 2004 to September 2010. Of these, 89 were transplanted due to HCV cirrhosis (4 patients co-infected with HIV were excluded). Of the 89 patients, 16 (18%) were complicated with ACR within 60 days after transplantation at the University of Tokyo Hospital. The ACR rate in the patients other than HCV during the same period was 29% (n = 294) which was higher than that of HCV patients without significant difference. After transplantation, all of the patients received the same immunosuppressive treatment with tacrolimus and methylprednisolone, as described previously (*7*). Briefly, target tacrolimus trough levels were 15 to 20 ng/mL during the first 2 weeks and 10 to 15 ng/mL thereafter. Intravenous methylprednisolone was started during the operation (20 mg/kg/day), and gradually tapered thereafter (7 days after transplantation, 0.75 mg/kg; two weeks, 0.35 mg/kg; one month, 0.3 mg/kg; two months, 0.25 mg/kg; three months, 0.2 mg/kg; 4 months, 0.2 mg/kg). The subjects comprised 12 men and 4 women who underwent liver transplantation with subsequent development of ACR. ACR was defined as a biopsy-proven episode and graded according to the Banff schema (*8*). The indication for liver biopsy was a significant increase in total bilirubin, aspartate, and alanine aminotransferase levels.

Until the end of 2007, the patients were treated with bolus intravenous methylprednisolone, regardless of ACR severity, at a starting dose of 20 mg/kg/day, as previously described (*9*). The dose was reduced by half each day and the therapy was continued for 5 days. When acute rejection was refractory to high-dose methylprednisolone therapy, a second bolus was then given with mycofenolate mofitile (CellCept, Roche Pharmaceuticals, Basel, Switzerland; 3 g/day). If the rejection was not cured by two rounds of steroid therapy the episode was diagnosed as steroid-resistant rejection and OKT3 was administered (Figure 1). After 2008, the regimen was changed. Basiliximab (two 20-mg doses with a 2-day inter-dose interval; Simulect, Novartis Pharmaceuticals, Basel, Switzerland) was added to the immunosuppressive treatment with tacrolimus and methylprednisolone. No bolus intravenous methylprednisolone was administered. The primary outcome measures were treatment success with resolution of ACR, as indicated by normalization of alanine aminotransferase or resolution of liver biopsy changes, or treatment failure due to ongoing rejection. No infectious prophylaxis was done. Immediate treatment of adverse effects and infectious complications within 1 month of treatment were recorded.

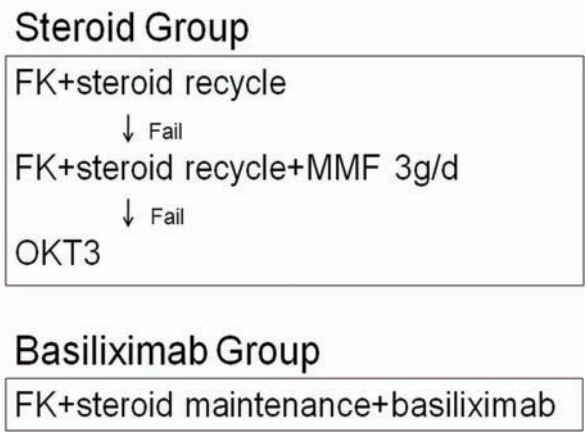

Figure 1. Regimens in the steroid and basiliximab groups. Abbreviations: FK, tacrolimus; MMF, mycophenolate mofetil.

3. Results and Discussion

The median time from transplantation to the development of ACR was 19 days (range, 9-49 days). The degree of ACR was mild or moderate. Median follow-up from transplantation was 25 months (range, 2-81 months).

Treatment outcomes are summarized in Table 1. Of the 11 patients in the steroid group, 2 had a steroid-resistant reaction and OKT3 was used. The overall rejection grade in the two patients was moderate. In a semi quantitative assessment, venous endothelial inflammation was scored as 2 (moderate). Rejection eventually resolved in all patients, which was confirmed by the subsequent biopsy in 7. Five patients died within 2 to 22 months after transplantation and four of them died from graft failure. In all three patients in the basiliximab group, rejection resolved without significant immediate adverse effects. In one patient the resolution was histologically confirmed (Banff rejection activity index changed from 4 to 2 after the therapy). One patient died of pneumonia 8 months after transplantation.

Aspartate aminotransferase levels normalized in all patients. The median time from the onset to resolution of ACR was 16 days (range, 6-41 days).

The present report confirms that basiliximab can be effective in reversing ACR in HCV patients. All patients with histologic evidence of ACR before treatment with basiliximab had resolution of ACR. Three patients with ACR were managed effectively with basiliximab without the addition of other immunosuppressive agents. Furthermore, none of these patients had recurrent episodes of ACR. In contrast, of the 11 patients complicated with ACR that received steroid pulse therapy, 4 died of graft failure, probably due to HCV recurrence, although ACR was successfully resolved in all cases.

The safety of basiliximab was previously reported, with no evidence of significant acute toxicity (*2,10*) or increased risk of infection (*11*). There have been

Table 1. Patients and treatment outcomes

Age, sex	ACR onset (d)	On the day ACR diagnosis		Number of steroid boluses	MMF	OKT	Interval for ACR resolution (d)	After the therapy		Outcome	Cause of death
		Banff score	Blood test (ALT/ALP/TB)					Banff score	Blood test (ALT/ALP/TB)		
Steroid group											
44, M	42	3	314/546/0.7	1	No	No	23	–	36/471/1.2	81A	–
57, M	11	4	86/521/1.3	3	Yes	No	39	2	28/338/0.8	81A	–
57, M	39	3	58/752/0.7	1	No	No	26	–	30/461/0.5	80A	–
48, F	34	5	315/180/1.1	3	Yes	Yes	8	2	30/121/2.6	3D	Graft failure
63, M	18	4	89/318/0.8	1	No	No	10	–	33/218/0.6	73A	–
45, M	30	5	192/143/2.9	2	Yes	Yes	12	1	44/180/3.6	22D	Graft failure
49, M	16	3	185/269/1.9	2	Yes	No	40	1	30/258/3.1	3D	Graft failure
47, M	9	3	44/134/1.4	1	No	No	12	–	14/118/0.7	58A	–
47, M	9	3	45/229/14.5	2	Yes	No	41	1	34/470/9.2	2D	Graft failure
49, M	12	4	127/288/0.9	1	No	No	17	1	35/225/0.5	50A	–
58, F	19	3	45/469/4.5	1	No	No	38	1	35/431/3.1	9D	TMA
Basiliximab group											
55, M	44	3	125/888/0.5	0	No	No	7	–	14/432/0.5	27A	–
61, F	49	4	112/1077/2.1	0	Yes	No	15	2	48/653/1.6	8D	Pneumonia
60, F	19	3	100/448/3.5	0	No	No	6	–	36/265/2.2	3A	–

Abbreviations: ACR, acute cellular rejection; A, alive; D, dead; TMA, thrombomicroangiopathy; MMF, mycophenolate mofetil; ALT/ALP/TB, alanine aminotransferase (IU/L)/alkaline phosphatase (IU/L)/total bilirubin (md/dL).

several reports of cytomegalovirus viremia after induction with anti-IL-2 receptor antibodies, but to date there is no evidence of a significant increased risk of cytomegalovirus infection (*12*). In this series, one patient died of pneumonia 8 months after liver transplantation, which may not be directly attributable to basiliximab therapy.

HCV recurrence developed in most HCV-positive recipients. The intensity of immunosuppression correlates with recurrent HCV hepatitis after transplantation (*13*). Importantly, Kato *et al*. (*14*) reported that tacrolimus along with daclizumab and a steroid-free regimen resulted in fewer HCV infection recurrences after transplantation. The use of basiliximab therefore seems to be advantageous over steroid therapy in HCV-positive patients.

Our results are comparable to those of other case series in which basiliximab was used as rescue therapy. Orr *et al*. (*15*) used basiliximab in 16 patients with steroid-resistant ACR, and resolution was achieved in 12 (75%) cases. Similarly, in another study (*16*), 5 (71.4%) of 7 liver transplant recipients with steroid-resistant ACR were successfully treated with basiliximab. Another series (*6*) showed resolution of ACR in adult renal and liver recipients, 72% of whom were successfully treated with basiliximab. The findings of that study (*6*) suggest that the efficacy of anti-IL-2 receptor antibody in ACR is similar to that of high-dose steroids, although there are no prospective randomized trials that have tested this hypothesis.

Anti-IL-2 receptor antibodies are now widely used in liver transplantation as induction agents targeted at reducing the incidence of ACR (*2,17,18*) or as a calcineurin-inhibitor (*19*) or steroid-sparing strategy (*20,21*) to protect renal function in the immediate postoperative period. Comparison of induction therapy (*12*) between antithymocyte globulin + cyclosporine + steroid + azathioprine and anti-IL-2 receptor antibody + tacrolimus + steroid + azathioprine demonstrated a reduced ACR incidence in the anti-IL-2 receptor antibody group (43% *versus* 29%; $p < 0.01$). Patients treated with anti-IL-2 receptor antibodies also had fewer infective complications. The results of a meta-analysis of treatment with anti-IL-2 receptor antibodies in renal transplantation (*22*) confirmed that the risk for ACR was reduced by 49% at 6 months. Importantly, however, their use did not significantly reduce graft loss or mortality at 1 year. Prospective randomized studies comparing calcineurin inhibitors + steroid + basiliximab and calcineurin inhibitors + steroid showed a lower (*23*) or similar (*24,25*) ACR rate and no difference in graft survival.

A limitation of this study is that it was a retrospective and nonrandomized case series. The small number of patients enrolled in the study was insufficient to yield statistically meaningful results. These preliminary data, however, indicate that the use of anti-IL-2 receptor antibodies is safe for the treatment of ACR in HCV-positive patients. Prospective studies are now needed to evaluate the use of anti-IL-2 receptor antibodies as a first-line therapy for ACR for HCV-positive patients.

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