Study of Immune Tolerance Cases in Adult Living Donor Liver Transplantation

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ABSTRACT

Background. Complete immune tolerance is the chief goal in organ transplantation. This study aimed to evaluate patients who successfully withdrew from immunosuppressive (IS) agents after living donor liver transplantation (LDLT).

Materials and Methods. A retrospective review of all adult LDLT from July 1999 to March 2012 was conducted. In patients who acquired immune tolerance after LDLT, their background and the course of surgical procedures were evaluated.

Results. Of a total of 101 adult LDLT patients, 8 patients were completely free of IS agents. Six of these patients (75%) were female, and the median age at the time of transplantation was 56 years (range, 31–66 years). The primary disease causing liver failure was type C liver cirrhosis (50%), fulminant hepatitis (25%), type B liver cirrhosis (12%), and alcoholic liver cirrhosis (12%). The median Child-Pugh score and MELD score were 13 points (range, 8–15 points) and 19 points (range, 10–18 points), respectively. The living related donor was the recipient's child (75%), sibling (12%), or parent (12%). ABO compatibility was identical in 62%, compatible in 25%, and incompatible in 12%.

Conclusions. In this study, we evaluated the adult patients who successfully withdrew from IS agents after LDLT. In most cases, it took more than 5 years to reduce IS agents. Because monitoring of the serum transaminase level is not adequate to detect chronic liver fibrosis in immune tolerance cases, further study is required to find appropriate protocols for reducing IS agent use after LDLT.

IMMUNOLOGIC tolerance, defined as the absence of graft rejection without immunosuppression, is a chief goal of organ transplantation. Recent clinical and experimental reports suggest that the induction of tolerance is now an achievable goal in clinical transplantation. Even though some recipients who acquired spontaneous tolerance for their grafts without any immunosuppression have been reported, especially in liver transplantation [1], there are no ideal biological markers to identify patients in whom immunosuppressive (IS) agents can be safely withdrawn. In renal transplantation, the combination of pre-transplantation myeloconditioning and hematopoietic cell infusion from human leukocyte antigen (HLA)–identical siblings has induced long-term graft acceptance without immunosuppression in patients with hematological malignancies and end-stage renal failure [2].

Although there might be some discussion of trials to reduce IS agents or to stop them altogether [3], we have to investigate the possibility of IS-free states after liver transplantation to improve the quality of life of patients after surgery.

As one of the institutions attempting immunosuppression withdrawal, we evaluated the cases in which IS agents were successfully stopped after living donor liver transplantation (LDLT) in adults.

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MATERIALS AND METHODS

Patients

A retrospective review of 101 adult LDLT patients who underwent transplantation from July 1999 to March 2012 was conducted. In the cases of acquired immune tolerance after LDLT, the background of patients, the course of the surgical procedures, and the period until the patients stopped use of immunosuppressants were evaluated. The state of immune tolerance was defined based on complete withdrawal of any IS agents.

Baseline Immunosuppression

Tacrolimus and steroids were initially administered as baseline IS agents. Target tacrolimus trough levels were 10 to 15 ng/mL for the first month, followed by 5 to 10 ng/mL for the next 2 months after LDLT, and thereafter approximately 5 ng/mL. Intravenous administration of methylprednisolone was used for induction, which was switched to oral prednisolone 1 week after LDLT. Prednisolone was gradually weaned and discontinued 6 months after LDLT, as long as graft function was maintained. In patients with adverse effects such as renal failure, mycophenolate mofetil or azathioprine were added to the first drugs. In ABO-incompatible patients, in order to lower their serum anti-A and anti-B antibodies, exchange transfusion and rituximab administration (375 mg/m^2) were performed before transplantation (7 days and 1 day before surgery). In exchange transfusion, the mixture of red blood cells with the recipient's blood type and type AB fresh frozen plasma were used to perform apheresis transfusion. These procedures were repeated according to the preoperative values of anti-A and anti-B antibodies. Postoperatively, serum antibody levels were regularly measured. To maintain antibody titers less than 32 times that of normal, blood apheresis or addition of another IS agent was used as necessary.

Withdrawal of Immunosuppression

The frequency of tacrolimus administration was gradually reduced in patients who survived more than 2 years after transplantation, maintained a good graft function, and had no rejection episodes. The frequency of administration was reduced from 4 times a week to 3 times a week, twice a week, once a week, twice a month, once a month, and finally the patients were completely weaned off. The dosage was returned to the previous dosage immediately if progression of liver dysfunction was seen after reduction of the IS agents.

RESULTS

Characteristics of LDLT Recipients in Whom IS Agents Were Successfully Withdrawn

Eight patients were completely free of IS agents. Six of the patients were female, and the median age at the time of transplantation was 56 years (range, 31–66 years). The primary disease leading to liver failure was type C liver cirrhosis (50%), fulminant hepatitis (25%), type B liver cirrhosis (12%), and alcoholic liver cirrhosis (12%). The median Child-Pugh score and MELD score were 13 (range 8–15) and 19 (range 10–28), respectively (Table 1).

Table 1. Characteristics of LDLT Recipients Who Successfully Stopped IS Agents

No.	Age	Sex	Primary Disease	Child-Pugh Classification	Child-Pugh Score	MELD Score
1	61	F	Liver cirrhosis C	B	8	10
2	46	M	Liver cirrhosis C	C	13	15
3	58	M	Liver cirrhosis B	C	13	17
4	58	F	Liver cirrhosis C	C	12	21
5	54	F	Fulminant hepatitis	C	15	22
6	31	F	Alcoholic cirrhosis	C	13	28
7	46	F	Fulminant hepatitis	C	12	28
8	66	F	Liver cirrhosis C	C	12	16

Characteristics of Donor and Liver Graft

The living related donor was a child (75%), sibling (12%), or parent (12%) of the recipient. ABO compatibility was identical in 62% of cases, compatible in 25%, and incompatible in 12%. The liver graft was the left lobe in 62% and the right lobe in 37% of cases, and the median graft-to-recipient weight ratio (GRWR) was 0.86% (Table 2).

Perioperative Course

The median operative time, cold ischemic time, and warm ischemic time were 678, 44, and 48 minutes, respectively. The mean amount of bleeding was 9575 mL (range, 5490–19,218 mL). The postoperative hospital length of stay was 81 days (range, 23–141 days), and the period until complete cessation of immunosuppressant use after LDLT was 69 months (range, 21–138 months). The observation period after immune tolerance was 117 months (range, 75–148 months) (Tables 3 and 4).

DISCUSSION

Immune tolerance to solid organ allografts has been achieved in a variety of experimental animal models, especially rodents, but it has been more difficult to attain in large animals [4]. There are a few cases of clinical transplant recipients who electively tried to reduce IS agent use [5]. Some experimental supports for transplant tolerance were demonstrated in 1950s, when Billingham and Medawar induced tolerance to skin allografts in mice by injection of allogeneic cells in the neonatal period [6–8]. The liver is the most immunoregulatory solid organ that can be transplanted, and contains a high number of extramedullary hematopoietic cells and a large mass of nonhematopoietic cells. The liver also secretes a variety of proteins and cytokines with immunoregulatory effects. Consistent with some

Table 2. Characteristics of Donor and Liver Graft

No.	Donor	Age	Blood Type	Liver Graft	GRWR (Graft/Recipient Weight Ratio)
1	Son	35	Identical	Right lobe	1.13
2	Brother	52	Identical	Left lobe	0.69
3	Son	31	Compatible	Right lobe	1.22
4	Son	31	Identical	Left lobe	0.86
5	Son	28	Identical	Left lobe	0.74
6	Mother	56	Incompatible	Right lobe	1.09
7	Son	44	Compatible	Left lobe	0.77
8	Daughter	38	Identical	Left lobe	0.68