Research Article

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ABO-incompatible living donor liver transplantation is suitable in patients without ABO-matched donor

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Background & Aims: ABO-incompatible liver transplantation is usually contraindicated because of the risk of antibody-mediated humoral rejection of the graft. We describe 22 successful cases of patients who had living donor liver transplantation (LDLT) from ABO-incompatible donors.

Methods: The immunosuppressive protocol consisted of rituximab and plasmapheresis prior to LDLT. Plasmapheresis was planned for up to 2 weeks after LDLT aiming at maintaining levels of anti-ABO titers below 1:32.

Results: The median age of recipients was 54 years and the median MELD score was 13. The initial range of isoagglutinin IgM and IgG titers were 1:8–1:1024 and 1:2–1:1024, respectively. Preoperative isoagglutinin IgM and IgG titers were achieved less than or equal to 1:8 by performing therapeutic plasma exchange (TPE). While the median number of TPE was 4 (range, 2–18) in all patients, it was 4 (range, 2–8) in the initial low titer group (<1:256) and 8 (range, 6–18) in the high titer group (⩾1:256). There were no statistically significant differences for liver function tests in the first 2 weeks after transplantation between the groups having high MELD score (⩾20) *vs.* low MELD score (<20), local graft infusion *vs.* systemic infusion, or high initial isoagglutinin titer (⩾1:256) *vs.* low initial isoagglutinin titer (<1:256). Patient and graft survival was 100% and there was no acute humoral rejection in recipients at a mean follow-up of 10 months (range, 3–21).

Conclusions: ABO-incompatible LDLT can be safely performed when rituximab and TPE are used, and may be proposed when ABO-compatible donors are not available.

Keywords: Living donor liver transplantation; ABO-incompatible; Therapeutic plasma exchange; Plasmapheresis; Rituximab; Systemic infusion; MELD score; Isoagglutinin titer.

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Introduction

In western countries where liver grafts from deceased donors are the main tissue source, recipients are selected based on their ABO-compatible group. In Korea, sociocultural reasons limit the supply of deceased donor organs, resulting in the number of patients in the waiting list being always multiple times of the number of liver donors. Although living donor liver transplantation (LDLT) has been established as a treatment for patients with end-stage liver disease, donor selection is limited primarily to relatives and spouses. However, the growth of waiting lists and the urgency of liver transplantation have increased the drive to expand the donor pool by considering more unconventional or higher-risk techniques. This strategy includes transplantation from ABO-incompatible donors, which would normally be considered a barrier to transplantation.

The first ABO-incompatible LDLT was reported in the year 2000 [1]. ABO-incompatible liver transplantation is performed only in an emergency, and the results are not usually satisfactory with respect to patient and graft survival [2,3]. Indeed, the current literature indicates that the overall Japanese experience using ABO-incompatible LDLT for adult recipients is only slightly greater than 20% patient survival after 2 years. The main reason for this poor result is severe hyperacute rejection due to the presence of anti-donor ABO antibodies during the early postoperative period. Nonetheless, ABO-incompatible LDLT in East Asia has not been abandoned, and several different protocols have been proposed with the aim of avoiding acute graft necrosis and chronic biliary damage, both of which are recognized as major causes of poor outcome. Plasmapheresis to decrease anti-ABO titers, splenectomy, aggressive immunosuppressive protocols, and intrahepatic portal and arterial infusions have all been utilized to improve the outcome of ABO-incompatible LDLT [4]. The lack of alternatives to LDLT is a strong ongoing justification for performing ABO-incompatible LDLT in East Asia.

The purpose of this study was to review our ABO-incompatible life donor transplant program and assess the efficacy of our antibody removal regimen in achieving a sufficient titer for transplantation as well as to determine how much plasma exchange is required to achieve a successful transplantation.

Patients and methods

Patients

A total of 157 LDLTs were performed at the Samsung Medical Center, Seoul, Republic of Korea between September 2010 and March 2012, with consecutive 22 patients entering the protocol described in this study. Those patients did not have suitable ABO-compatible living donors and had to go through ABO-incompatible living donor liver transplantation. The medical records of all patients were reviewed for epidemiologic and clinical characteristics. We collected demographic data, model for end-stage liver disease (MELD) scores, blood group information for recipients, operative records including duration of surgery and graft-recipient weight ratio, and postoperative histopathological data including antibody-mediated rejection (AMR) and acute cellular rejection (ACR). All patients were followed from the end of the study until July 2012. All patients were assessed in our life donor clinic, with selection criteria consisting of the presence of hepatocellular carcinoma or end-stage liver disease and the absence of a suitable ABO-compatible life donor.

Preoperative preparation and immunosuppression

All patients received a single intravenous dose of rituximab (375 mg/m^2 body surface area) 2 weeks prior to undergoing LDLT. Immunoglobulin M (IgM) and G (IgG) isoagglutinin titers against donor erythrocyte antigens in recipients were measured at admission as well as before and after each apheresis by standard direct-agglutination techniques. Recipient blood samples were sent to the department of laboratory medicine in our medical center for assessment of anti-ABO isoagglutinin titers. Basiliximab is used in all recipients as an induction agent during LDLT. Most patients were infused with prostaglandin E1 (PGE1), gabexate mesilate, and methylprednisolone (MPD). Tacrolimus, steroids, and mycophenolate mofetil (MMF) were the primary agents used for immunosuppression after LDLT. All transplant recipients were given 500 mg of intravenous methylprednisolone during the anhepatic phase until postoperative day two, followed by a tapered dose of 60 mg per day for a period of five days and 8 mg, twice per day, for one month thereafter starting on postoperative day eight. Since then, recipients received 4 mg of MPD twice a day for 2 months, and it was discontinued after 3 months in the post-transplant period. Tacrolimus treatment was initiated on postoperative day three, and the optimal blood level was adjusted to maintain a trough plasma concentration of 10 ng/ml during the first month, which was reduced to 5–8 ng/ml thereafter. MMF was used in combination with tacrolimus and steroids. Starting on postoperative day one, 750 mg of MMF was administered twice per day. In the event of tacrolimus toxicity or tacrolimus refractory rejection, cyclosporin (plasma concentration adjusted to 100–200 ng/ml) was given orally twice a day. A liver biopsy was performed if acute rejection was suspected. Methylprednisolone (500 mg) was administered intravenously every day for three days if acute rejection was confirmed by biopsy, and tapered to 60 mg per day for four days thereafter [5].

Therapeutic plasma exchange (TPE) protocol

All patients received plasma exchange before transplantation. Dual needle plasmapheresis procedures (1.0–1.5 calculated plasma volumes with 100% fluid balance) were performed using a Cobe Spectra Apheresis System, consisting of a single stage channel filler and a disposable TPE set (Gambro BCT, Lakewood, CO). Uniformly, vascular access was a double lumen, dialysis-type catheter (internal jugular). The flow rate was adjusted based on the patient's tolerance, and was approximately 50 ml/min. ACD was added as an anticoagulant at a ratio of 18:1 to the whole blood volume. Concurrently, 10% calcium gluconate was administered intravenously at a rate of 20–40 ml/h, if the patient complained of hypocalcemic symptoms such as oral, perioral and acral paresthesias during TPE procedures. Pre-procedure laboratory tests included complete blood cell count, complete metabolic panel, isoagglutinin titers, and coagulation studies consisting of prothrombin time, partial thromboplastin time, and fibrinogen. Patients were transfused with red blood cells if their hematocrit was below 23%. The volume set for exchange (range, 1.0–1.5 plasma volume) was determined by apheresis prior to the procedure. The replacement fluid was blood group AB fresh frozen plasma (FFP) that presumably did not contain anti-A and anti-B antibodies. Plasmapheresis was performed every other day before transplantation. TPE continued before transplantation until IgM and IgG isoagglutinin titers corresponding to the donor ABO blood group were less than or equal to 1:8. If this target was not met then the surgery was postponed and TPE was continued until the desired titer was achieved. Patient anti-ABO isoagglutinin (IgG/IgM) titers were checked daily until the second week after transplantation. At first, the target titer at transplantation and during the first 2 weeks after transplantation was 1:32. TPE was performed only if a patient's ABO-antibody titer increased over 1:32 during the first 2 weeks after transplantation.

Surgical procedure

The recipient operation was performed using standardized techniques. All recipients received a right graft from the donor liver and a continuous infusion of liposomal PGE1 (Alprostadil, Eglandin, Mitsubishi Tanabe Pharma, Seoul, Korea) immediately after reperfusion of the allograft, provided that their blood pressure was stable. PGE1 was administered as a continuous infusion at a dose of 0.73 μg/kg/h for the first 10 postoperative days using a syringe pump. Nine of the recipients received PGE1 via the internal jugular vein, and the remaining 13 recipients received PGE1 through a catheter placed in the inferior mesenteric vein. Intraportal PGE1 infusions were performed as follows. A 16-gauge double-lumen antithrombotic catheter was inserted via the inferior mesenteric vein before the recipient's liver was removed. The tip of the catheter was then positioned 1 cm above the porto-splenic confluence and fixed in place by ligation with a rubber band. The other end was drawn outside the body via the surgical wound. The study drug was administered continuously through the catheter during the operation and while patients were in the intensive care unit. We removed the catheter seven days after liver transplantation.

Monitoring and prophylaxis

Isoagglutinin titers were measured after transplantation to monitor antibody-mediated rejection. During the second week after transplantation, the isoagglutinin titer was checked daily. Isoagglutinin was measured once per week while in the hospital and every three months after discharge. If a patient's isoagglutinin titer was increased over 1:32, we performed TPE, along with an augmented immunosuppressive regimen. No additional doses of rituximab were administered. Protocol liver biopsy was performed in all recipients. Follow-up triphasic dynamic computed tomography (CT) after transplantation was routinely performed at the first 14 days, and every three months for the first year, and annually thereafter. For prophylaxis of opportunistic infections, all patients received itraconazole for the first month and bactrim for the first year after transplantation. Cytomegalovirus (CMV) infection was monitored weekly by CMV antigenemia test. If the patient had an unexplained fever or if a CMV infection was clinically suspected, a CMV antigenemia assay was conducted. CMV infection was defined as a CMV pp65 antigen-positive cell number greater than one positive cell per 400,000 white blood cells. CMV disease presented either as CMV syndrome or as tissue-invasive CMV disease. CMV syndrome was defined as a positive antigenemia assay with more than one of the following symptoms or signs: unexplained fever (>38.3 °C), constitutional symptoms such as fatigue or general myalgia, leukopenia (white blood cell count <3000/mm^3), or thrombocytopenia (platelet count <100,000/mm^3). Tissue-invasive CMV disease was defined as the presence of hepatitis, pneumonitis, retinitis, or gastroenteritis, confirmed by biopsy [6]. When a patient's viral count rose above 10/400,000 white blood cell counts, we used intravenous ganciclovir as a preemptive therapy. AMR was diagnosed histologically by periportal edema and endothelial C4d staining clinically correlating with increased anti-ABO antibody titers. ACR was diagnosed by Banff criteria [7]. Biliary complications suspected clinically and histologically were confirmed by cholangiogram.

HBV prophylaxis

All patients with hepatitis B virus infection or recipients without hepatitis B surface antigen (HBs Ag), who received liver allografts from hepatitis B core antibody (HBc Ab) positive donors, were given 10,000 units of hepatitis B immunoglobulin (HBIG) (Green Cross Corp., Yongin, South Korea) intravenously during the anhepatic phase, which was followed by a seven-day intravenous course of 10,000 units HBIG per day. Patients received 10,000 units intravenously every month to maintain anti-hepatitis B surface antibody titers at ⩾200 IU/ml. Patients received a combination of entecavir (0.5 mg/d) and HBIG for hepatitis B virus prophylaxis.