

Characteristics of Recipients Who Achieved Spontaneous Operational Tolerance in Adult Liver Transplantation

M. Shin, S. Song, H.H. Moon, S. Lee, T.S. Kim, J.M. Kim, J.B. Park, C.H.D. Kwon, S.-J. Kim, S.-K. Lee, and J.-W. Joh

ABSTRACT

Background. Chronic immunosuppression is associated with unwanted adverse effects and increased morbidities. Long-term acceptance of transplanted organs without the requirement for immunosuppression, or operational tolerance, remains an important goal in clinical transplantation.

Methods. We reviewed the characteristics of recipients who achieved spontaneous operational tolerance after liver transplantation (OLT) among a consecutive series of 1014 adult recipients in a single center.

Results. We observed 5 cases (0.5%) of operational tolerance. All cases were men who underwent transplantations for hepatitis B virus-related liver cirrhosis. The mean time from OLT to achievement of spontaneous operational tolerance was 83.1 ± 62.9 months (range, 21.3–156.2). Characteristics common to all tolerant recipients were superior graft quality and good pretransplant recipient condition: specifically, high graft–recipient weight ratio (median, 1.18; range, 1.15–2.69), low hepatic macrosteatosis (median, 3; range, 0–15), low score of model for end-stage liver disease (median, 13; range, 7–21), and no history of preoperative intensive care.

LIVER TRANSPLANTATION (OLT) is the treatment of choice for end-stage liver disease. Advances in surgical techniques and immunologic understanding have noticeably improved outcomes. However, administration of lifelong immunosuppressive therapy is required to maximize graft function and survival, and is associated with unwanted adverse effects such as hypertension, renal failure, diabetes mellitus, cardiovascular disease, malignancy, infection, and neurotoxicity.¹ These complications may contribute to posttransplant mortality and morbidity in OLT recipients.² For these reasons, long-term acceptance of transplanted organs without the requirement for immunosuppression remains an important goal in clinical transplantation.³

Operational tolerance is defined as the state of sustained specific nonresponsiveness of the recipient immune system to donor alloantigen, allowing a well-functioning graft lacking histologic signs of rejection in the absence of any immunosuppressive drugs.^{4,5} Experimental animal models⁶ and clinical data⁷ support the concept that operational tolerance could be achieved in selected patients⁴ and is attained more frequently after OLT than after other solid organ transplantations.⁸ The aim of this study was to describe the characteristics of recipients who achieved

spontaneous operational tolerance after transplant among a consecutive series of 1014 adult OLT recipients in a single center.

PATIENTS AND METHODS

We included all adult recipients (aged >18 years) who underwent OLT between May 1996 and December 2011. We retrospectively analyzed the medical records of 1014 consecutive adult recipients. We investigated the characteristics of recipients among this population who achieved spontaneous operational tolerance after OLT. Operational tolerant recipients are defined as those with normally preserved graft function in the absence of immunosuppression for ≥ 1 year. After 1 year posttransplantation, clinical and biochemical follow-ups were performed every 2 months. Post-transplant observation was continued until October 2012.

From the Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, Seoul, Korea.

Address reprint requests to Jae-Won Joh, MD, PhD, Professor, Department of Surgery, Samsung Medical Center, Sungkyunkwan University School of Medicine, 50 Irwon-dong, Gangnam-gu, Seoul 135-710, Korea. E-mail: jw.joh@samsung.com

Case 1

A 43-year-old man who was repeatedly admitted for hepatic encephalopathy developed a single hepatocellular carcinoma. He underwent deceased-donor OLT and maintained all normal liver function tests without any posttransplant events. Approximately 12 years later, we found that he did not take immunosuppressive drugs.

Case 2

A 34-year-old man who suffered intractable ascites received a liver graft from a deceased-donor with the same ABO blood group. He remained asymptomatic and his liver tests were normal. His noncompliance for immunosuppressive drugs was detected by the end of the 11th year after OLT.

Case 3

A 35-year-old man developed multiple hepatocellular carcinomas, that were estimated to be beyond the Milan criteria: Four nodules ($1.8 \times 1.7 \times 1.0$, $1.6 \times 0.8 \times 0.6$, $2.5 \times 2.0 \times 1.7$, and $3.8 \times 3.2 \times 2.4$ cm) with definite microvascular tumor emboli. He underwent living-donor OLT. At 1 year posttransplant, multiple pulmonary metastases were found. Concerned about patient survival, we recommended a gradual reduction of the dose of immunosuppression, which was ultimately discontinued. Although the recurrent malignancy was not resolved and actually slightly progressed, his graft function was normal.

Case 4

A 65-year-old man had ascites controlled by diuretics secondary to liver cirrhosis and was diagnosed with hepatocellular carcinoma. Living-donor OLT was performed. At 2 years posttransplant, we became aware of the absence of immunosuppressive drugs, and since then we have contacted him every 2 months.

Case 5

A 38-year-old man with intractable ascites had hepatic encephalopathy. We decided to conduct living-donor OLT. The initial immunosuppressive regimen included tacrolimus, mycophenolate mofetil, and steroids. Two years after OLT, mycophenolate mofetil was discontinued because of recurrent intestinal obstruction and gastrointestinal discomfort. After another 18 months, he was diagnosed with bacterial pneumonia. Although adequate antibiotics were administered, he did not respond. We therefore decided to remove the immunosuppressive medication from his current therapy. He returned asymptomatic and his liver tests were normal after this period.

RESULTS

Five (0.5%) tolerant recipients were identified among the study population. All were men who underwent OLT for chronic hepatitis B virus-related liver cirrhosis. Among these 5, 3 had hepatocellular carcinoma. Two cases underwent deceased-donor OLT. The mean time from OLT to achievement of spontaneous operational tolerance was 83.1 ± 62.9 months (range, 21.3–156.2). In 3 patients, the use of immunosuppressive drugs was gradually reduced owing to noncompliance. The other 2 patients abandoned immunosuppressive medication because of severe bacterial pneumonia and recurrent hepatocellular carcinoma. There was

no case of physician-directed elective or intentional withdrawal. After spontaneous operational tolerance was attained, all recipients maintained hepatic parameters within normal limits during a mean period of 47.9 ± 31.6 months (range, 23.7–102.4). Recipient characteristics, including baseline demographics, donor information, allograft figures, immunologic data, and time from transplant to absence of immunosuppression, are described in Table 1.

The characteristics common to all tolerant recipients are superior quality of graft and a good pretransplant condition of the recipient specifically, high graft-recipient weight ratio (median, 1.18; range, 1.15–2.69), low hepatic macrosteatosis (median, 3; range, 0–15), low Model for End-Stage Liver Disease Score (median, 13; range, 7–21), and no history of preoperative intensive care. However, the recipients had no common characteristics from an immunologic perspective, such as lymphocytotoxic crossmatch, human lymphocyte antigen compatibility, or diagnosis of graft rejection before tolerance was achieved. There was 1 case of positive pretransplant lymphocytotoxic crossmatch and 3 cases of human lymphocyte antigen mismatch >4 . Two recipients experienced graft rejection before achievement of operational tolerance, and one even had a moderate degree of acute cellular rejection requiring treatment with pulsed steroid.

DISCUSSION

The achievement of an immunosuppression-free state after transplantation represents the ultimate goal of any immunosuppressive regimen.⁹ The phenomenon of operational tolerance is defined as long-term graft acceptance without features of graft rejection and without the need for immunosuppressive drugs.² The landmark report of operational tolerance after OLT was published by the Pittsburg group, which described 23 OLT patients¹⁰ and showed that a moderate proportion of patients with good liver function could be weaned off all immunosuppression. Since then, there have been sporadic reports of immunosuppression discontinuation after OLT over the past 2 decades. Published studies of operational tolerance indicate that approximately 20% of selected adult recipients,^{11,12} and $\leq 60\%$ of highly selected pediatric recipients of parental living donor liver transplants¹³ could be successfully weaned off immunosuppression completely. Recently, Tryphonopoulos et al.¹⁴ demonstrated that the long-term outcome of operationally tolerant OLT recipients was at least as good as that of control patients who continued immunosuppression. However, this clinical state has remained an elusive goal in current routine practice,³ and immunosuppressive regimens are still required to control the alloreactive T-cell response after OLT.¹⁵

Many studies, including various animal models, have been performed to identify the factors associated with achieving operational tolerance.^{12,16–23} Some studies have focused on the role of donor-derived passenger leukocytes that are thought to induce antigen-specific tolerance by migrating

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