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ORIGINAL ARTICLE

Steroid-resistant acute rejection after cadaveric liver transplantation: Experience from one single center

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Summary
Background and objectives: Steroid-resistant acute rejection (SRAR) is an infrequent event under current immunosuppressant but still a risk factor leading to graft loss and patients' death after liver transplantation. There are several strategies for managing this complication according to current literatures, but none of the treatment seems convincing and widely accepted. Here we retrospectively analyzed the clinical data of a cohort of patients to gain an insight into this complication.
Materials and methods: A total of 962 adult patients receiving whole liver grafts at a single center between January 2004 and December 2012 were studied. One hundred and forty-two recipients experienced 158 episodes of acute rejection after the operation, 14 recipients had no response to steroid bolus treatment. The clinical data was analyzed retrospectively.
Results: Incidence rate of acute rejection after liver transplant in our single center was 14.7% (142/962), among them 8.8% (14/158) were steroid-resistant. These episodes occurred on 19 days (6—72 days) after the operation, 3 were controlled by anti-T3-receptor antibody (OKT3) treatment, 4 were reversed by IL-2 receptor inhibitors combining with MMF treatment, 2 were reversed by antithymocyte globulin (ATG) treatment. Five did not recover and 2 received retransplantation. Mortality associated with SRAR was 28.6% (4/14, 1 died from acute liver failure, 1 from chronic liver failure, 1 from renal failure after retransplantation and 1 from pulmonary infection after OKT3 treatment).

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Conclusion: SRAR is a severe complication with high mortality after liver transplantation; ATG might serve as a potential treatment.

Introduction

Over 90% of acute rejection after liver transplantation can be reversed by steroid bolus treatment. However, SRAR remains a challenge even if the incidence rate is low [1—3]. Although most articles indicate that the current immunosuppressive strategy can ensure a relatively low rate of acute rejection, including SRAR, the latter will lead to liver graft failure and retransplantation remains the only option to rescue the patient if rejection episodes cannot be reversed in a timely manner. Most of the current literatures about this rare complication are with small samples. To gain a better understanding about this complication, we retrospectively analyzed the clinical data of 14 patients suffering from SRAR in our single center.

Patients and methods

General information

The clinical data were collected from the center's database and the medical documents. Form January 2004 to December 2012, 962 cases of adult liver transplantation were performed in the Organ Transplantation Center, the First Affiliated Hospital of Sun Yat-Sen University, including 783 males and 179 females (mean age, 49.7 years; age range, 18—75 years). The immunosuppressive regimens after transplant included double regimen (steroid and tacrolimus) and triple regimen (steroid, tacrolimus and mycophenolate mofetil). IL-2 receptor monoclonal antibody induction was adopted in patients with high risk factors before surgery, such as older patients (over 65 years old), with hepatorenal syndrome, with a history of upper abdominal operation, and with a model for end-stage liver disease score over 30. Liver function and blood concentration of immunosuppressants were monitored routinely after surgery.

Fourteen patients, including 13 males and 1 female, had SRAR after the operation (mean age, 46.6 years; age range, 33—61 years). Of the 14 patients, 7 had hepatitis B-related cirrhosis, 6 had primary hepatocellular carcinoma with liver cirrhosis secondary to hepatitis B infection and 1 had acute liver failure. The model for end-stage liver disease score before transplant was 22.6 ± 7.3. Cold ischemia time was 6.2 ± 4.3 hours. Immunosuppressive strategy included IL-2 induction in 3 cases, bigeminy strategy in 6 cases and trigeminy strategy in 5 cases. The baseline characteristics are shown in Table 1. Prior to the study, the protocol was approved by our local institutional ethics committee. Each organ donation and transplant in our center was performed strictly according to the guidelines of the 1975 Helsinki Declaration and the principles of the Declaration of Istanbul; written, informed consent was obtained from all subjects.

Diagnosis and treatment protocol for patients with acute rejection

Rejection was suspected on patients with clinical manifestation and elevated biochemical examinations, after exclusion of vascular complications by Doppler ultrasound, the diagnosis of acute rejection was made on the basis of pathologic evidence of graft biopsy. Each specimen was scored by 2 pathologists blinded to the immunosuppressant regimens according to the Banff scoring system. SRAR was defined as acute rejection episodes with persistent elevation of bilirubin or transaminase levels, a repeat biopsy showing acute rejection after being treated with one or two courses of methylprednisone (MP) bolus, each course of MP bolus treatment was defined as at least 7 days of intravenous injection with or without subsequent oral medication.

Patients with acute rejection were treated according to the following strategies. In those with mildly impaired liver function, immunosuppressants were strengthened by augmentation with basic immunosuppressive agents, MMF or sirolimus was also added in patients who received primary immunosuppressive regimen without these agents. A high dose bolus of steroid was administered in patients who either had moderate or severe elevation of biochemical parameters or those who had mild impairment of liver function but no response to strengthened immunosuppressants. One thousand milligrams intravenous MP were used at the first day, the dosage was diminished continuously until the intravenous dosage was transferred to oral tablet on 8th day. Intravenous steroids could be repeatedly used if needed.

Treatment protocol for patients with SRAR

OKT3 was applied in 3 such patients in 2004 and 2005, 50 mg per day with the course of treatment lasting 7 to 10 days. We began to use IL-2 receptor inhibitors (Daclizumab or Basiliximab) combining with MMF treatment since the year of 2006, 2 doses of simulect were adopted with an interval of 4 days, MMF was given with a daily dose of 1.5 g (0.75 g, twice a day). Inspired by the encouraging result reported by Cem Aydogan et al. [4] and Schmitt et al. [5], we used ATG in two patients after the year 2010.

During the treatment course mentioned above, concentration of FK506 was maintained at the low limit of normal range. Intravenous antibiotics and ganciclovir were applied. For patients with improved hepatic parameters, a third biopsy was not necessary.