Transpl Int (1994) 7 [Suppl 1]: S88–S90

Prospective randomized trial of steroid withdrawal in liver transplant patients: preliminary report

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Abstract Although steroid withdrawal has been successfully performed in heart and kidney transplant recipients, no controlled studies of SW have been carried out in liver transplant patients. To evaluate this possibility a prospective controlled study was carried out in 46 liver transplant recipients operated on after may 1991. They all received a sequential quadruple immunosuppression consisting of 3 mg/kg antithymocyte globulins (RATG) for the first 5 postoperative days, cyclosporin A (starting from day 3–5 and maintaining parenteral whole-blood trough levels at 200–300 ng/ml during the first month and at 150–250 thereafter), azathioprine (1 mg/kg per day for the first month) and steroids. Prednisone was started at a dose of 200 mg per day 1 and then tapered to 20 mg/day over the first posteroperative week; this dose was maintained until day 90 when the patients were randomly allocated either to long-term steroid therapy (0.1 mg/kg per day) or to steroid withdrawal. Minimum follow-up after randomization was 6 months (6–27 months). Liver biochemistry was checked at regular intervals throughout the follow-up period. Liver biopsies were performed whenever clinically indicated and also in the first 19 patients during readmission for annual review. The incidence ot acute and chronic rejection 90 days from liver transplantation was 2.5% in patients maintained on long-term therapy. No patient in the steroid-withdrawal group had experienced either an acute or a chronic rejection episode so far. Steroid-related complications did not differ significantly between the two groups. The most recent interim analysis showed that steroid withdrawal is a safe undertaking in liver transplant recipients and may be successfully accomplished in almost all patients.

Key words Liver transplantation
Steroid withdrawal

Introduction

Steroids appear to be a useful complement to the immunodepressive activity of cyclosporin A (CyA) and since the introduction of CyA, maintenance immunosuppression protocols in solid organ transplants have generally included steroids. Only in recent years has long-term immunosuppression without steroids been shown to be

possible in almost 50% of kidney and heart recipients, and this observation has been confirmed in prospective studies [1, 3, 6]. Surprisingly, despite the presumed lower immunological potential of the grafted liver when compared to heart and kidney, long-term immunosuppression without steroids is not widely practised in liver transplantation [4, 5] and to our knowledge no prospective randomized studies have ever been performed. Concern exists that late weaning from steroids may be associated with more severe rejection episodes. We report here our preliminary experience in 46 liver transplant patients who were randomly allocated 3 months after transplantation either to long-term steroids therapy or to steroid withdrawal.

Patients and methods

The study group comprised 51 first orthotopic liver transplants patients operated on between May 1991 and February 1993. The primary indications for liver transplantation were posthepatitis B and/or C cirrhosis (40 cases), ethanol cirrhosis (2 cases), primary biliary cirrhosis (2 cases), Caroli disease (1 case), Budd-Chiari syndrome (1 case), cholangiocarcinoma (1 case) and cryptogenic cirrhosis (4 cases). Immunosuppression was as follows. All patients received rabbit antithymocyte globulins (RATG, Fresenius) for the first 5 postoperative days. CyA was given endovenously until the patients were able to eat and then orally at a dose which was adjusted to maintain therapeutic levels (Ria Monokit Whole Blood Trough Levels) of 200–300 ng/ml for the first month and 150–250 ng/ml thereafter. Azathioprine was given at a dose of 1.5–2 mg/kg for the first 30 days. Steroid therapy was initiated with methylprednisolone 500 mg intraoperatively and continued postoperatively with methylprednisolone 200 mg on day 1, 160 mg on day 2, 120 mg on day 3, 80 mg on day 4, 40 mg on day 5 and 20 mg on day 6. Patients were then continued on this dose until day 90 when they were randomly allocated either to long-term therapy after a progressive reduction to a maintenance dose of 0,1 mg/kg per day (27 patients) or to steroid withdrawal (24 patients). The two groups of patients were comparable wit respect to age (46 ± 14 and 41 ± 18), gender (male/female ratio 22:5 vs 17:7), preoperative diagnosis (HBV and/or HCV cirrhosis 83.3% vs 75%), previous acute rejection episodes (29% vs 27.7%) and length of follow-up (511 ± 198 days vs 460 ± 173 days). Patients were reviewed monthly from 3 to 6 months postoperatively, 3 monthly until 1 year and 3–6 monthly thereafter by the same two physicians. Percutaneous liver biopsies were performed whenever clinically indicated and during patient readmission for annual review. The definition of graft rejection was based on a combination of clinical, histological and biochemical changes. The histological features of acute rejection were mixed inflammatory cell portal infiltrate, and bile duct epithelial and venous endothelial inflammation. Acute rejection was also graded histologically as mild, moderate or severe [6]. The histological features of chronic rejection were ductopenia (> 50% bile duct loss) and cholestasis. Mean follow-up was 490 ± 185 days (270–840 days). Two patients who died in the short-term group with a follow-up after randomization of less than 6 months were excluded from the analysis of results. Shifted patients (three in the long-term therapy group) were not-considered in the analysis of immunological complications. Data were analysed using two tailed *t*-tests on means and Chi-squared test on absolute values where appropriate.

Results

Patient survival

Two patients in the long-term therapy group died 12 and 14 months after randomization, respectively, from HBV and HCC recurrence ($2/27 = 7.4\%$). Three patients in the steroid-withdrawal group died 2, 3 and 14 months after randomization, respectively, from biliary sepsis in the first case and recurrent HCV infection in the other two ($3/24 = 13.5\%$).

Immunological complications

No patient in the steroid-withdrawal group had to be converted to steroid maintenance due to acute rejection episodes. Only one patient on long-term therapy experienced a single episode of acute rejection 3 months after randomization ($1/22 = 4.5\%$) which responded to steroid pulses. A second patient in the long-term therapy group had clinical and histological signs of chronic rejection 6 months after transplantation which gradually reverted after increasing CyA blood levels. No patient in the steroid-withdrawal group had to be treated either for acute or chronic rejection.

Other major complications after randomization

As reported before, three patients on long-term therapy had steroids withdrawn 5, 7 and 8 months, respectively, after randomization. Reasons for withdrawal were obesity, diabetes and bone complications. Eight patients in the long-term therapy group ($8/24 = 33.3\%$) and six patients in the steroid-withdrawal group ($6/22 = 27.2\%$) required antihypertensive medication. Three patients in both groups required antidiabetic medication ($3/24 = 12.5\%$ and $3/22 = 13.6\%$), but they all were diabetic before transplantation. Significant septic complications requiring hospitalization occurred in only two patients (one cholangitis and one bacterial pneumonia). Both patients were in the long-term therapy group.

Discussion

From this preliminary prospective randomized study it appears that steroid-free maintenance immunosuppression after transplantation is feasible in the vast

majority of liver transplant recipients. The incidence of acute and chronic rejection developing in patients maintained on long-term steroid therapy was identical to that observed in patients in whom corticosteroids were discontinued. Furthermore, the incidence of acute and chronic rejection in our patients favourably compares with an incidence of 7.7% and 3.8% reported by Klintmalm et al. [2] in patients maintained on 10–20 ng/day prednisone. These findings are in sharp contrast to the experience with kidney and heart transplants where only about 50% of these patients could be safely kept off steroids [1, 3, 6]. By way of explanation we can hypothesize that the liver is less immunogenic that the heart and kidney and this concept has often been claimed in the past but never demonstrated. It could also be that the immune system of our cirrhotic recipients was less reactive to alloantigen than that of other patient populations. In effect a peculiar aspect of our series is that almost 80% of the patients were transplanted because of a chronic viral hepatitis and an underlying defect in T-cell immunity might be present in patients whose liver disease is caused by a chronic viral infection. Finally, it is possible that our quadruple drug induction therapy during the early post-transplant period may have facilitated the achievement of subsequent steroid-free maintenance immunotherapy.

Late benefits of steroid withdrawal have been reported to include reduced infectious complications requiring intravenous antibiotics, less obesity, less antihypertensive and antidiabetic drugs and lower cholesterol levels than a steroid-maintained group. Although three patients in our series had to have their corticosteroids withdrawn for medical reasons, no substantial short-term benefits in infection rate, diabetes or blood pressure control were found. From this experience we conclude that steroid withdrawal from maintenance immunosuppression is a safe undertaking in liver transplant patients and is associated with a desirable outcome. Nevertheless, studies with a longer follow-up and a larger sample size are necessary to obtain conclusive results.

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