Transpl Int (1998) 11 [Suppl 1]: S267–S269

G. Tisone
M. Angelico
G. Palmieri
F. Pisani
L. Baiocchi
G. Vennarecci
A. Anselmo
G. Orlando
S. Negrini
C. U. Casciani

Immunosuppression without prednisone after liver transplantion is safe and associated with normal early graft function: preliminary results of a randomized study

G. Tisone (✉) · M. Angelico · G. Palmieri · F. Pisani · L. Baiocchi · G. Vennarecci · A. Anselmo · G. Orlando · S. Negrini · C.U. Casciani
Centro Trapianti d'Organo, Clinica Chirurgica e Cattedre di Gastroenterologia e di Anatomia Patologica, Università di Roma Tor Vergata, Ospedale S. Eugenio, Piazzale dell'Umanesimo 10, I-00144 Rome, Italy
Tel. + 39-6-590422681; Fax + 39-6-5922681
e-mail VENNARECCI@utovrm.it

Abstract Prednisone has been commonly considered the mainstay of immunosuppressive therapy after liver transplantation. Recent data suggest that prednisone withdrawal late after transplant reduces complications without affecting graft function. We report here the preliminary results of an open-label, randomized study aimed at investigating whether prednisone therapy can be completely avoided during the first 3 months after transplantation. Twenty-seven consecutive patients were randomized to receive double (group A: cyclosporine and azathioprine) or triple (group B: prednisone, cyclosporine, and azathioprine) immunosuppressive therapy after liver transplantation. Six patients died within the first 3 weeks in each group and were excluded from the calculations. The present results refer to 10 patients in group A and 11 in group B. The actuarial 1-year survival did not differ between the two groups (90.9% vs 88.8%). There were no differences with respect to infectious complications or episodes of histological acute graft rejections. Only one severe acute rejection occurred in group A and two in group B. During the first month after transplant, liver and kidney functions tended to be better in the group of patients treated without prednisone, although there were no differences in the mean cyclosporine blood levels. These data, though preliminary, indicate that early immunosuppression without the use of prednisone is safe and tends to be associated with improved liver and renal functions compared to conventional triple therapy.

Key words Liver transplantation · Immunosuppression · Prednisone

Introduction

Prednisone has been commonly considered a keystone in immunosuppression therapy after liver transplantation. In practice, all standard immunosuppressive regimens always include the administration of steroids, although with reduced doses in comparison with the past. The introduction of new potent drugs such as tacrolimus and micophenolate has not changed this appoach. However, the benefits of prednisone therapy are not well established. Recent data suggest that prednisone withdrawal late after orthotopic liver transplantation (OLTx) reduces complications without affecting graft function [1]. Since liver transplant recipients are much less prone to develop clinically significant acute rejection [2] than recipients of kidney [3] and heart allografts [4], we investigated whether prednisone therapy can be completely avoided during the initial 3 months after surgery. To test this hypothesis within a prospective open-label pilot study, a consecutive series of patients undergoing OLTx at our Institution were randomized to receive a conventional immunosupression therapy with or without prednisone. We report here the preliminary results of this ongoing study.

Materials and methods

Patients

Twenty-seven adult patients undergoing OLTx at our Institution entered the study. Patients included 18 males and 9 females, with an age of between 20 and 63 years (mean 49 ± 9 years). None had evidence of active cytomegalovirus (CMV) infection. In the majority of patients the cause of liver transplantation was cirrhosis due to viral infections (in 11 patients due to HCV and in 6 to HBV). Four patients had alcoholic cirrhosis, two cryptogenic cirrhosis, two fulminant hepatic failure due to HBV infection, and one had Wilson disease.

Randomization and treatment

Patients were randomized to receive: (group A) a double immunosuppressive therapy including cyclosporine and azathioprine (1–1.5 mg/kg per day); or (group B) a conventional triple therapy including cyclosporine, azathioprine, and prednisone. The latter was initially given at a dose of 20 mg/day, gradually tapered from day 30, and then discontinued at the end of the third month. Cyclosporine doses were modified to maintain blood levels between 300 and 400 ng/ml by monoclonal radioimmunoassay (Abbot) in the first 2 months and around 200 ng/ml in the third month. Azathioprine doses were adjusted on the basis of white blood cells (WBC) count.

All patients gave their informed consent prior to their inclusion in the study and the protocol had been approved by the local ethics committee. Six patients died within the first week and were therefore excluded from the study. The preliminary results thus refer to 21 patients (10 in group A and 11 in group B), who were followed up for at least 3 months after transplant. Graft function after OLTx was evaluated by conventional liver tests daily during the first month and at weekly intervals until day 90.

The occurrence of infectious complications was evaluated according to international recommendations [5]. Liver biopsies were obtained at the time of surgery and at days 7, 30, and 90 after transplantation. Biopsy specimens were formalin fixed and paraffin embedded. Sections, 5-um-thick, were stained with hematoxylin–eosin and Masson's trichrome. Individual histological features were scored according to a semiquantitative scoring system. Acute graft rejection was diagnosed according to international criteria [6]. The decision to treat severe episodes of acute rejection with supplemental immunosuppressive therapy was based on a combination of clinical, histological, and biochemical findings.

Statistical analysis of data was performed using the SOLO package (BMDP). Group differences were assessed by Student's *t*-test for unpaired data and by the Fisher exact test.

Table 1 Baseline characteristics of liver transplant recipients treated with or without prednisone during the first 3 post-operative months. Data are given as actual numbers or means ± SD

	Without prednisone (n = 13)	With prednisone (n = 14)
Recipient age (years)	51.0 ± 46.5	47.4 ± 11.5
Donor age (years)	39.0 ± 17.9	40.1 ± 13.7
Recipient gender (M/F)	9/5	10/3
Donor gender (M/F)	10/4	4/9*
Cause for transplantation		
HCV cirrhosis	4	7
HBV cirrhosis	3	3
Alcoholic cirrhosis	3	1
Cryptogenic and others	2	3
Cold ischemia time (h)	6.9 ± 2.1	6.5 ± 3.4
Warm ischemia time (h)	0.9 ± 0.2	0.8 ± 0.1
Days before discharge	24 ± 9	28 ± 19

* Significantly different ($P < 0.01$) from patients treated without prednisone

Table 2 Liver and kidney function during the first 3 months after transplantation in patients treated with and without prednisone (*AST* aspartate transaminase, *γ-GT* γ-glutamyltransferase)

Parameter	Without prednisone (n = 10)	With prednisone (n = 11)
AST (mg/dl)[a]	136 ± 463	195 ± 522
AST, day 90 (mg/dl)	19 ± 12	25 ± 11
γ-GT (mg/dl)[a]	89 ± 96	141 ± 166*
γ-GT, day 90 (mg/dl)	38 ± 24	83 ± 26
Bilirubin (mg/dl)[a]	1.7 ± 0.3	1.6 ± 0.3
Bilirubin, day 90 (mg/dl)	1.6 ± 1.2	1.6 ± 0.9
Creatinine (mg/dl)[a]	1.9 ± 1.3	2.1 ± 1.7
Creatinine, day 90 (mg/dl)	1.7 ± 0.4	1.8 ± 0.5

[a] Data recorded in the first month after transplant (mean ± SD)
* Significantly different ($P < 0.001$) from patients treated without prednisone

Results

As summarized in Table 1, the two groups did not differ in demographic or clinical features at baseline, nor for the technical parameters related to organ preservation and surgical procedures.

The actuarial 12-month graft survival did not differ between patients treated with (88.8%) or without (90.9%) prednisone. Similarly, there were no differences with respect to infectious complications. These included ten patients (four in group A) with a a body temperature above 38° C and a WBC count of ≥ 12000 cell/mm for several days after the transplant; six patients (four in group A) with a body temperature above 38° C and a WBC count of < 4000 cell/mm, without anti-CMV IgM antibodies; and one patient with active CMV infection group B.

At the liver biopsy obtained at day 7, mild to moderate acute graft rejection was observed in 72% of patients in both groups, while severe rejection only occurred in three patients, two of whom in the group were receiving prednisone. Only two episodes of severe rejection were treated with additional immunosuppressive therapy. No late episodes of acute rejection occurred in either group.

Liver function tests (Table 2) showed a better profile in the first month in group A than in group B, although the differences did not reach statistical significance. However, during the first postoperative month, the mean values of γ-glutamyltransferase were significantly lower ($P < 0.001$) in the group treated without prednisone, although there were no differences in bilirubin levels. Kidney function did not differ significantly between the two groups, however, the mean levels of creatinine during the first postoperative month tended to be lower in group A than in in group B (2.1 ± 1.7 mg/dl), despite there being no differences in mean cyclosporine levels (349 ± 8 vs 343 + 9 ng/ml, respectively).

Discussion

The preliminary results of this study indicate that, after liver transplantation, an early immunosuppressive treatment which does not include the use of prednisone is safe and does not modify the risk of potential postoperative complications. In particular, we found that early immunosuppression without prednisone is not associated with an increased risk of acute graft rejection, is unrelated to the emergence of infectious complications, and tends to be associated with better liver and kidney functions, particularly in the first months after transplant. These data, although preliminary, suggest that there is no need to use prednisone as a routine treatment after liver grafting.

The rationale for using steroid therapy after liver transplantation is not well established. Its routine use has been justified by the fear of acute rejection, by analogy to the incidence after kidney transplantation. However, the incidence and severity of graft rejection after liver transplantation are lower in liver than in kidney allograft recipients and there are no data available to support the notion that steroids can prevent acute rejection after liver transplantation. Mild or moderate acute rejection occurs frequently after liver grafting, as did occur in this study, but usually does not require additional immunosuppressive treatment. Further, 10–20% of recipients develop steroid-resistant rejections. Moreover, steroid therapy may increase the risk of infectious and metabolic complications, although these events were not observed in our series.

In this study, the mean levels of γ-glutamyltransferase were significantly lower during the first postoperative month in patients treated without prednisone, which may reflect a lower degree of cholestasis and ductular regeneration, although there were no differences in bilirubin levels. Similarly, the other liver function tests and the serum creatinine levels tended to be lower during the first month after transplant in patients treated without steroids, although no significant differences were observed, possibly due to the limited number of observations so far available. Further data are therefore needed to evaluate whether prednisone treatment is associated with worse liver and kidney function.

Recent data have shown that prednisone withdrawal is a safe procedure in the late course after liver transplantation [1]. To our knowledge, this study is the first formal evaluation of the usefulness of prednisone in the early course after transplant. Our preliminary findings are in agreement with and reinforce the above findings, showing that immunosuppression without prednisone can also be safe as an early procedure. While we are currently waiting for the completion of our trial, we believe that further independent studies are urgently needed to confirm our data and to investigate the potential emergence of infectious or metabolic complications, in order to address whether the routine use of prednisone after liver transplantation is still justified.

References

1. Stegall MD, Everson G, Schroter G, Bilir B, Karrer F, Bilir B, Sternberg T, Shrestha R, Wachs M, Kam I (1997) Prednisone withdrawal late after adult liver transplantation reduces diabetes, hypertension, and hypercholesterolemia without causing graft loss. Hepatology 25: 173–177
2. Klintmalm GB, Nery JR, Husberg BS, Gonwa TA, Tillery GW (1989) Rejection in liver transplantation. Hepatology 10: 978–985
3. Hricik DE, O'Toole MA, Schulak JA, Herson J (1993) Steroid-free immunosuppression in cyclosporine-treated renal recipients: a meta-analysis. J Am Soc Nephrol 4: 1300–1305
4. Kobashigawa JA, Stevenson LW, Brownfield ED, Morigucki JC, Kawata N, Randrich R, Drinkwater DC, et al (1992) Initial success of steroid weaning late after heart transplantation. J Heart Lung Transplant 11: 428–431
5. The American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference (1992) Definitions for sepsis and organ failure and guidelines for the use of innovative therapies in sepsis. Crit Care Med 20: 864–874
6. International Working Party (1995) Terminology of hepatic allograft rejection. Hepatology 22: 648–654