Online Submissions: wjg.wjgnet.com
www.wjgnet.com
wjg@wjgnet.com

World J Gastroenterol 2007 October 21; 13(39): 5273-5276
World Journal of Gastroenterology ISSN 1007-9327

RAPID COMMUNICATION

Early steroid withdrawal after liver transplantation for hepatocellular carcinoma

Zhi-Shui Chen, Fan He, Fan-Jun Zeng, Ji-Pin Jiang, Dun-Feng Du, Bin Liu

Zhi-Shui Chen, Fan He, Fan-Jun Zeng, Ji-Pin Jiang, Dun-Feng Du, Bin Liu, Institution of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China
Correspondence to: Zhi-Shui Chen, Institution of Organ Transplantation, Tongji Hospital, Tongji Medical College, Huazhong University of Science and Technology, Wuhan 430030, Hubei Province, China. zschen@tjh.tjmu.edu.cn
Telephone: +86-27-83663674 Fax: +86-27-83662892
Received: April 12, 2007 Revised: August 13, 2007

Abstract

AIM: To evaluate the impact of early steroid withdrawal on the incidence of rejection, tumor recurrence and complications after liver transplantation for advanced-stage hepatocellular carcinoma.

METHODS: Fifty-four patients underwent liver transplantation for advanced-stage hepatocellular carcinoma from April 2003 to June 2005. These cases were divided into a steroid-withdrawal group (group A, n = 28) and a steroid-maintenance group (group B, n = 26). In group A, steroid was withdrawn 3 mo after transplantation. In group B, steroid was continuously used postoperatively. The incidence of rejection, 6-mo and 1-year recurrence rate of carcinoma, 1-year survival rate, mean serum tacrolimus trough level, and liver and kidney function were compared between the two groups.

RESULTS: In the two groups, no statistical difference was observed in the incidence of rejection (14.3 *vs* 11.5%, $P > 0.05$), mean serum tacrolimus trough levels (6.9 ± 1.4 *vs* 7.1 ± 1.1 μg/L, $P > 0.05$), liver and kidney function after 6 mo [alanine aminotransferase (ALT): 533 ± 183 *vs* 617 ± 217 nka/L, $P > 0.05$; creatinine: 66 ± 18 *vs* 71 ± 19 μmol/L, $P > 0.05$], 6-mo recurrence rate of carcinoma (25.0 *vs* 42.3%, $P > 0.05$), and 1-year survival rate (64.2 *vs* 46.1%, $P > 0.05$). The 1-year tumor recurrence rate (39.2 *vs* 69.2%, $P < 0.05$), serum cholesterol level (3.9 ± 1.8 *vs* 5.9 ± 2.6 mmol/L, $P < 0.01$) and fasting blood sugar (5.1 ± 2.1 *vs* 8.9 ± 3.6 mmol/L, $P < 0.01$) were significantly different. These were lower in the steroid-withdrawal group than in the steroid-maintenance group.

CONCLUSION: Early steroid withdrawal was safe after liver transplantation in patients with advanced-stage hepatocellular carcinoma. When steroids were withdrawn 3 mo post-operation, the incidence of rejection did not increase, and there was no demand to maintain tacrolimus at a high level. In contrast, the tumor recurrence rate and the potential of adverse effects decreased significantly. This may have led to an increase in long-term survival rate.

Key words: Hepatocellular carcinoma; Liver transplantation; Steroids; Tumor recurrence

Chen ZS, He F, Zeng FJ, Jiang JP, Du DF, Liu B. Early steroid withdrawal after liver transplantation for hepatocellular carcinoma. *World J Gastroenterol* 2007; 13(39): 5273-5276

http://www.wjgnet.com/1007-9327/13/5273.asp

INTRODUCTION

Liver transplantation is well recognized as a treatment for prolonging survival in patients with advanced-stage hepatocellular carcinoma[1]. Obviously, tumor recurrence is the main reason for the poor long-term survival after transplantation in these patients. It has been shown that long-term immunosuppression can facilitate the growth and spread of malignant cells[2]. There is evidence that steroids play an important role in tumor recurrence after liver transplantation for hepatoma[3], but whether steroids can be safely withdrawn remains controversial. In this study, we contrasted patients with early steroid withdrawal with those using continuous steroids, in order to establish the validity of the steroid-withdrawal regimen.

MATERIALS AND METHODS

Patients

Fifty-four patients suffering from advanced-stage hepatoma (all exceeding the Milan criterion) underwent liver transplantation between April 2003 and June 2005. There were two immunosuppressive protocols: 28 patients (group A) were given an early steroid-withdrawal protocol and 26 patients (group B) were given a steroid-maintenance protocol. Factors such as age at transplantation, stage of carcinoma, Child-Pugh score, graft cold ischemic time, anhepatic phase, operation time, and mean level of liver function before operation were noted, and these parameters were well matched in both groups (Table 1).

Table 1 Preoperative and intraoperative data for patients in the 2 groups

Parameter	Group A (n = 28)	Group B (n = 26)	P value
Sex (F/M)	1/27	0/26	0.3370
Mean age at OLT	45.7 ± 3.5	47.4 ± 6.3	0.2310
TNM stage of carcinoma			0.9914
Ⅱ	1 (3.5%)	1 (3.8%)	
Ⅲ A	8 (28.6%)	7 (26.9%)	
Ⅲ B	5 (17.9%)	4 (15.4%)	
Ⅳ A	14 (50.0%)	14 (53.8%)	
Child-Pugh class			0.5259
A	20 (71.4%)	21 (80.8%)	
B	7 (25.0%)	5 (19.2%)	
C	1 (3.5%)	0 (0.0%)	
Liver and kidney function			
ALT (nka/L)	935.1 ± 383.3	1010.2 ± 536.8	0.5545
T-Bil (μmol/L)	23.1 ± 11.2	20.1 ± 10.8	0.3314
Creatinine (μmol/L)	67.8 ± 22.2	59.8 ± 24.3	0.2218
Graft cold ischemic time (min)	481.6 ± 97.0	462.1 ± 88.0	0.4464
Anhepatic phase (min)	51.5 ± 3.4	50.8 ± 3.1	0.4339
Operation time (min)	375.2 ± 98.1	391.5 ± 116.7	0.5799

OLT: Orthotopic liver transplantation.

Immunosuppressive regime

All the patients took tacrolimus, with a target serum trough level of 6-8 μg/L until 12 mo, and 4-6 μg/L thereafter. Mycophenolate mofetil was prescribed for 1 year at a dose of 0.5-1.0 g/d. Methylprednisolone was given at 500 mg/d intravenously for 3 d, during and after transplantation. Patients in group A received a rapid steroid reduction with the intention of withdrawing steroid by 3 mo. Patients in group B received a slow taper of steroid to prednisone 10 mg/d at 3 mo, and were maintained on this dose thereafter.

Postoperative treatment

ALT, creatinine, total cholesterol and fasting blood sugar were noted regularly after operation. Biopsies were used to establish the diagnosis of rejection on a histological basis when biochemical analysis suggested rejection. The following adjuvant chemotherapy regimen was adopted: E-ADM 40-60 mg/m^2 on d 1 and C-DDP 20-40 mg/m^2 on d 2-5, with 28 d as a cycle and 6 cycles in all. Tumor recurrence was confirmed by computed tomography or magnetic resonance imaging.

Statistical analysis

Statistical analysis was performed on preoperative and intraoperative data in the two groups, such as sex, age, stage of carcinoma, Child-Pugh score, liver and kidney function, Graft cold ischemic time, anhepatic phase and operation time. The rejection rate, tumor recurrence rate, patient survival rate and mean levels of biochemical parameters were compared between the two groups. Statistical analyses were conducted using the Statistical Package for the Social Sciences computer program (SPSS for Windows 11.5; SPSS, Chicago, IL, USA). The Student's t test and χ^2 test were used to determine statistical significance between the groups. $P < 0.05$ was considered significant.

Table 2 Rejection, tumor recurrence, and survival rate

Group n	Rejection rate	Tumor recurrence rate		1-yr survival rate (%)
		6-mo	1 yr	
A 28	14.3	25.0	39.2[a]	64.2
B 26	11.5	42.3	69.2	46.1

[a]$P < 0.05$ *vs* Group B.

RESULTS

There were no significant differences between the two groups for rejection rate and 6-mo tumor recurrence rate. One-year tumor recurrence rate (39.2 *vs* 69.2%, $P < 0.05$) was significantly higher in the steroid-maintenance group. One-year survival rate was higher in group A than in group B, but the difference was not statistically significant (64.2 *vs* 46.1%, Table 2).

At 6 mo, the mean serum tacrolimus trough level was (6.9 ± 1.4) μg/L in group A and (7.1 ± 1.1) μg/L in group B, although the difference was not significant. There was no difference in liver and kidney function (ALT and creatinine) between the two groups. However, at 6 mo post operation, the mean levels of total serum cholesterol and fasting blood sugar were significantly lower in group A (Table 3).

DISCUSSION

Corticosteroids, with their multifaceted immunosuppressive properties, have long been considered as a linchpin in the prevention and treatment of transplant rejection. In addition to inhibiting the release and function of cytokines, such as interleukin-2, steroids can also regulate T- and B-lymphocyte apoptosis[4]. However, there are well-known adverse effects that result in significant morbidity, including hypertension, diabetes, hyperlipidemia, obesity, and infectious complications. The adverse effects of long-term steroid use, even at a low dose, have stimulated interest in the feasibility of steroid-free maintenance immunosuppressive regimens.

This randomized clinical study was focused on a particular group of recipients who suffered from advanced-stage hepatocellular carcinoma before liver transplantation. In this group of patients, the high tumor-recurrence rate may cause the long-term survival rate to decrease sharply. Indisputably, the use of steroids has exacerbated this problem, either *via* a direct negative impact and/or by its adverse effects. One multicenter study has shown that when steroids were withdrawn 3-6 mo after liver transplantation, tumor recurrence was reduced to its lowest level[2]. A retrospective study of three centers in Italy has found that the risk of hepatoma recurrence in patients with permanent use of steroids was almost fourfold when compared with patients made steroid-free not later than 6 mo after liver transplantation[3]. Steroids may contribute to tumor recurrence. The potential

Table 3 Biochemical indicator after operation (mean ± SD)

Group *n*	FK506 trough levels (μg/L)	ALT (nka/L)		Creatinine (μmol/L)		Total cholesterol (mmol/L)	Blood-fasting sugar (mmol/L)
		3-mo	6-mo	3-mo	6-mo	6-mo	6-mo
A (*n* = 28)	6.9 ± 1.4	567 ± 233	533 ± 183	69 ± 18	66 ± 18	3.9 ± 1.8[b]	5.1 ± 2.1[b]
B (*n* = 26)	7.1 ± 1.1	500 ± 350	617 ± 217	75 ± 15	71 ± 19	5.9 ± 2.6	8.9 ± 3.6

[b]$P < 0.01$ *vs* Group B.

mechanism of this may be that steroids can inhibit malignant-cell apoptosis and promote migration of these cells. Yazawa *et al*[5] have reported that glucocorticoids can inhibit human neutrophil-mediated tumor cell cytostasis. Ho *et al*[6] have found that, in patients with hepatoma, the survival rate is higher when hepatoma cells are negative for corticosteroid receptors, compared with those that are positive. In our study, the 1-year tumor recurrence rate in the steroid-withdrawal group was lower than that in the steroid-maintenance group. This demonstrates that early steroid withdrawal can reduce tumor recurrence. The 1-year survival rate was higher in the steroid-withdrawal group. However, because of the small sample size and short time of follow-up, the difference was not statistically significant.

Early steroid-withdrawal regimens do not increase the rejection rate[7-11]. Padbury[12] has reported that, when steroids were withdrawn safely in 140/197 patients (71%), the acute and chronic rejection rate was 4.5 and 3.9%, respectively, and this was similar to the reported rates with steroid-containing regimens. In Jane's study[13], 499 liver transplant recipients accepted early steroid-withdrawal immunosuppression, and only 9.8% of patients had steroid reintroduction. Stegall's study has shown that early steroid withdrawal after liver transplantation does not increase the fatality rate and the rate of chronic graft dysfunction[14,15]. In our study, the incidence of acute rejection during the withdrawal phase did not increase, and each episode of rejection had only a modest effect and was steroid-responsive. No graft was lost to immunological causes. The tacrolimus trough levels were similar in the two groups. There was no demand to increase serum tacrolimus levels to prevent extra rejection. Thus, this early steroid-withdrawal protocol was safe in most patients.

The toxicity of steroids includes increased susceptibility to infection (particularly opportunistic organisms), hyperlipidemia, hypertension, diabetes mellitus, osteoporosis and aseptic necrosis, acne, Cushingoid facies, and growth retardation in children. The cumulative toxicity of immunosuppressive agents remains a major source of morbidity and mortality after liver transplantation, therefore, a protocol eliminating the steroid component has been a goal. Stegall's study has shown that steroid withdrawal after adult liver transplantation reduces diabetes, hypertension and hypercholesterolemia, without causing graft loss[15]. In our study, total serum cholesterol and fasting blood sugar were significant lower in the early steroid-withdrawal group. This effect suggests that corticosteroids are a major causative agent in new-onset diabetes and hypercholesteremia in liver transplantation recipients. Considering the adverse effects of steroid treatment, steroid should be withdrawn earlier, except in patients who use prednisone preoperatively, such as primary biliary cirrhosis and sclerosing cholangitis[13].

This study indicates that steroid withdrawal at 3 mo after liver transplantation is safe and necessary. Early steroid withdrawal does not lead to a high incidence of rejection or a high level of immunosuppressive drugs. In addition, steroid withdrawal may lead to a decreased incidence of tumor recurrence, new-onset diabetes and hypercholesteremia. The decrease in tumor recurrence and adverse effects may lead to a higher survival rate for liver transplantation recipients with hepatocellular carcinoma. However, the 1-year survival rate in the steroid-withdrawal and steroid-maintenance groups was not significantly different. This result may have been due to the small sample size and short follow-up. Therefore, large long-term follow-up (several years), prospective, randomized and multicenter trials will be necessary to confirm the potential benefit of this regimen for the incidence of tumor recurrence, adverse events, and graft and patient survival.

COMMENTS

Background

Steroids have been the pillars of immunosuppression in organ transplantation for over 50 years. However, the fact that immunological graft loss is rare after liver transplantation, combined with the severe adverse effects of long-term prednisone therapy, supports steroid withdrawal in liver transplantation patients. Especially for patients suffering from advanced-stage hepatoma before liver transplantation, the long-term use of steroids may exacerbated the problem of reduced graft survival and patient survival. However, few clinical studies have focused on this group of recipients.

Research frontiers

Many clinical trails have proven the necessity of steroid withdrawal. The main findings of this study were that early withdraw of steroids was confirmed as a positive posttransplant action with a significant influence in reducing hepatoma recurrence.

Related publications

The present study was a randomized clinical trial of steroid withdrawal after liver transplantation in patients with advanced-stage hepatocellular carcinoma. We have cited several articles from other investigators that report research on steroid withdrawal after liver transplantation.

Innovations and breakthroughs

In prior studies of liver transplantation, little attention has been paid to the immunosuppression of hepatoma transplant recipients. This present clinical trail studied a steroid-withdrawal protocol for this group of recipients. We reached the conclusion that tumor recurrence can be reduced when steroids are withdrawn at 3 mo postoperatively. This protocol can be used as the guide for hepatoma transplant recipients.

Applications

In patients suffering from advanced-stage hepatocellular carcinoma, immuno-

suppression with early steroid withdrawal can reduce tumor recurrence after liver transplantation. In addition, total serum cholesterol and fasting blood sugar decrease sharply in steroid-withdrawal patients. This means that the use of steroids is one of the major causes of new-onset diabetes and hypercholesteremia after liver transplantation. Therefore, this steroid-withdrawal protocol can also be used following liver transplantation for other indications.

Terminology

Advanced-stage hepatocellular carcinoma is the end stage of a primary malignant neoplasm of the liver. Liver transplantation is the treatment for this disease. However, because of the high incidence of tumor recurrence, the outcome is poor. Steroids are a group of hormones that affect carbohydrate, fat and protein metabolism. They also possess pronounced anti-inflammatory activity. They have been used for immunosuppression for over 50 years.

Peer review

This is a brief but well-executed study which underscores what Starzl and others have been writing about for some time: the need to reduce immunosuppression in liver transplant recipients. In the authors' study, steroids were withdrawn successfully 3 mo after operation. This protocol caused a reduction in tumor recurrence and incidence of diabetes and hypercholesteremia after liver transplantation.

REFERENCES

1 **Chen ZS,** Zeng FJ, Ming CS, Lin ZB, Zhang WJ, Wei L, Zhu XH, Jiang JP, Chen ZK. The survival and value of liver transplantation for liver carcinoma: a single-center experience. *Transplant Proc* 2004; **36**: 2284-2286

2 **Yokoyama I,** Carr B, Saitsu H, Iwatsuki S, Starzl TE. Accelerated growth rates of recurrent hepatocellular carcinoma after liver transplantation. *Cancer* 1991; **68**: 2095-2100

3 **Mazzaferro V,** Rondinara GF, Rossi G, Regalia E, De Carlis L, Caccamo L, Doci R, Sansalone CV, Belli LS, Armiraglio E. Milan multicenter experience in liver transplantation for hepatocellular carcinoma. *Transplant Proc* 1994; **26**: 3557-3560

4 **McDiarmid SV,** Farmer DA, Goldstein LI, Martin P, Vargas J, Tipton JR, Simmons F, Busuttil RW. A randomized prospective trial of steroid withdrawal after liver transplantation. *Transplantation* 1995; **60**: 1443-1450

5 **Yazawa H,** Kato T, Nakada T, Sendo F. Glucocorticoid hormone suppression of human neutrophil-mediated tumor cell cytostasis. *Int J Cancer* 1999; **81**: 74-80

6 **Ho WL,** Wu CC, Yeh DC, Chen JT, Huang CC, Lin YL, Liu TJ, P'eng FK. Roles of the glucocorticoid receptor in resectable hepatocellular carcinoma. *Surgery* 2002; **131**: 19-25

7 **Punch JD,** Shieck VL, Campbell DA, Bromberg JS, Turcotte JG, Merion RM. Corticosteroid withdrawal after liver transplantation. *Surgery* 1995; **118**: 783-786; discussion 786-788

8 **Pageaux GP,** Calmus Y, Boillot O, Ducerf C, Vanlemmens C, Boudjema K, Samuel D. Steroid withdrawal at day 14 after liver transplantation: a double-blind, placebo-controlled study. *Liver Transpl* 2004; **10**: 1454-1460

9 **Lerut JP,** Ciccarelli O, Mauel E, Gheerardhyn R, Talpe S, Sempoux C, Laterre PF, Roggen FM, Van Leeuw V, Otte JB, Gianello P. Adult liver transplantation and steroid-azathioprine withdrawal in cyclosporine (Sandimmun)-based immunosuppression - 5 year results of a prospective study. *Transpl Int* 2001; **14**: 420-428

10 **Pirenne J,** Aerts R, Koshiba T, Van Gelder F, Roskams T, Schetz M, Verhaegen M, Lauwers P, Fevery J, Nevens F. Steroid-free immunosuppression during and after liver transplantation--a 3-yr follow-up report. *Clin Transplant* 2003; **17**: 177-182

11 **Innocenti F,** Hepp J, Humeres R, Sanhueza E, Zapata R, Rios H, Suárez L, Sandoval R, Rius M, Zamboni M. Rapid steroid taper and neoral monotherapy in liver transplantation in Chile: a step in the right direction? *Transplant Proc* 2004; **36**: 1675-1676

12 **Padbury RT,** Gunson BK, Dousset B, Hubscher SG, Buckels JA, Neuberger JM, Elias E, McMaster P. Steroid withdrawal from long-term immunosuppression in liver allograft recipients. *Transplantation* 1993; **55**: 789-794

13 **Jain A**, Kashyap R, Marsh W, Rohal S, Khanna A, Fung JJ. Reasons for long-term use of steroid in primary adult liver transplantation under tacrolimus. *Transplantation* 2001; **71**: 1102-1106

14 **Stegall MD,** Everson GT, Schroter G, Karrer F, Bilir B, Sternberg T, Shrestha R, Wachs M, Kam I. Prednisone withdrawal late after adult liver transplantation reduces diabetes, hypertension, and hypercholesterolemia without causing graft loss. *Hepatology* 1997; **25**: 173-177

15 **Stegall MD,** Wachs ME, Everson G, Steinberg T, Bilir B, Shrestha R, Karrer F, Kam I. Prednisone withdrawal 14 days after liver transplantation with mycophenolate: a prospective trial of cyclosporine and tacrolimus. *Transplantation* 1997; **64**: 1755-1760

S- Editor Ma N **L- Editor** Kerr C **E- Editor** Li HY