

Original Article

Tacrolimus Related Hypertrophic Cardiomyopathy in Liver Transplant Recipients

Seyed Mohsen Dehghani MD^{*****}, Mahmood Haghghat MD^{*****},
 Mohammad Hadi Imanieh MD^{*****}, Mozghan Zahmatkeshan MD^{***},
 Mohammad Borzooei MD^{***}, Hamid Amoozegar MD^{***},
 Mahmood Zamirian MD^{*}, Siavash Gholami MD^{*},
 Ali Bahador MD^{*}, Saman Nikeghbalian MD^{*}, Heshmatollah Salahi MD^{*},
 Seyed Ali Malek-Hosseini MD^{*}

Background: Recently there are a number of reports on the cardiotoxicity of tacrolimus in post-transplant patients. There is no protocol for cardiovascular evaluation in these patients. This study was performed to evaluate the cardiotoxicity of tacrolimus in liver transplant recipients.

Patients and Methods: We evaluated 63 post-liver transplant patients who received tacrolimus. They were evaluated for cardiovascular complications by physical examination, electrocardiographic and echocardiographic examinations within three and six months following liver transplantation. Serum tacrolimus levels were checked by ELISA. For comparison, we selected 50 post-liver transplant patients who received no tacrolimus and evaluated them for cardiovascular function identically.

Results: Among 63 patients, 42 were male (66.7%) and 21 were female (33.3%); 70% of the patients were adults, and 19 (30%) were within the pediatric age group. The cardiovascular examinations, electrocardiogram and echocardiography of all patients three months post-transplantation were normal except for two children who developed tacrolimus related cardiac complications. Both had high serum tacrolimus levels. No adults developed cardiovascular complications. In the control group, the results of the cardiovascular evaluations were normal in all cases.

Conclusion: The cardiovascular toxicity of tacrolimus, such as hypertrophic cardiomyopathy, may be observed in pediatric patients. Therefore, we recommend routine regular cardiovascular evaluation of children after liver transplantation.

Archives of Iranian Medicine, Volume 13, Number 2, 2010: 116 – 119.

Keywords: Cardiotoxicity • liver transplantation • tacrolimus

Introduction

Tacrolimus, a calcineurin inhibitor, is the major immunosuppressive medication used in the treatment of patients after liver transplantation. It has been used with low doses or without steroids in children receiving liver

transplants.¹ Tacrolimus has a mode of action similar to that of cyclosporine, but is 10 – 100 times as potent and is associated with fewer rejection episodes.^{2,3}

The major side effects of tacrolimus in children include: anemia, renal toxicity, hyperkalemia, gastrointestinal symptoms, allergic reactions, and post-transplant lymphoproliferative disease.⁴ Compared with cyclosporine, however, gingival hyperplasia, hirsutism, coarsening of the facial features and hypertension solely due to tacrolimus are notably absent.⁴ In clinical trials, tacrolimus has been shown to be better tolerated and associated with fewer rejection episodes, in

Authors' affiliations: *Shiraz Transplant Research Center, **Gastroenterohepatology Research Center, ***Department of Pediatrics, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.

•**Corresponding author and reprints:** Seyed Mohsen Dehghani MD, Shiraz Transplant Research Center, Nemazee Hospital, Shiraz University of Medical Sciences, Shiraz, Iran.
 E-mail: dehghanism@sums.ac.ir

Accepted for publication: 9 November 2009

addition to better graft and patient survival compared with cyclosporine. Therefore, tacrolimus has been increasingly used by many transplant centers as the primary immunosuppressive agent immediately after transplantation.⁵ It has been reported that tacrolimus can cause cardiac toxicity.^{4,6,7} The potential cardiac toxicity of tacrolimus has been found in rabbits and baboons during animal studies.⁸ Cardiotoxicity has been described in a group of pediatric patients receiving tacrolimus as a part of immunosuppression for orthotopic liver transplantation.⁷

This study was performed to evaluate cardiac toxicity in post-liver transplant patients who received tacrolimus for more than six months.

Patients and Methods

This study approved by local institutional review board. Patients and for children parents or legal guardians signed approved informed consents to participate in study.

We prospectively studied 63 liver transplant recipients who underwent liver transplantation between September 2006 and September 2007, and received tacrolimus as the main immunosuppressive medication.

All patients had a normal cardiac examination, normal electrocardiogram (ECG), chest X-ray and echocardiography which were performed before transplantation by our cardiologists. All children were visited by pediatric cardiologists. Echocardiographic examination was performed using the GE VIVID 3 echocardiographic machines by probe 3 MHz.

Oral tacrolimus was started one day after the operation with a dose of 0.1 – 0.15 mg/kg/day. The whole blood trough levels of tacrolimus were monitored, with target levels of 10 – 20 ng/mL.

All patients received 20 – 25 mg/kg intravenous methyl prednisolone for three consecutive days and then a 1 mg/kg/day oral prednisolone taper during the three month post-transplant period.

All patients were visited by the same cardiologists three and six months after liver transplantation and underwent full cardiovascular evaluation including ECG and echocardiography.

Tacrolimus trough levels were checked during these visits.

In addition, 50 patients who underwent liver transplantation prior to September 2006 and received cyclosporine as the main

immunosuppressive medication were evaluated as the control group. These patients were also evaluated by the same cardiologists and underwent full cardiac evaluation and echocardiography.

Results

There were 63 tacrolimus treated recipients (42, 66.7% male and 21, 33.3% female) with a mean age of 27.8±16.1 years (range, 2 – 58 years).

We studied 19 (30%) pediatric patients (age under 18) and 44 (70%) adult patients.

The indications for liver transplantation included: HBV cirrhosis (n=12, 19%), Wilson disease (n=12, 19%), autoimmune cirrhosis (n=11, 17.5%), cryptogenic cirrhosis (n=10, 15.9%), primary sclerosing cholangitis (n=4, 6.3%), progressive familial intrahepatic cholestasis (n=4, 6.3%), Caroli disease (n=2, 3.2%), tyrosinemia (n=2, 3.2%), HCV cirrhosis, primary biliary cirrhosis, Budd-Chiari syndrome, biliary atresia, neonatal hepatitis and biliary hypoplasia, all of which had one case (n=1, 1.6%) each.

There were 52 (81.3%) patients who received a whole graft from deceased donors and 3 (4.7%) cases that underwent split liver transplantation.

The remaining 8 (12.5%) patients received a graft from living donors (their parents).

The mean tacrolimus levels of patients at three and six months after liver transplantation were 11.2±5.8 ng/mL (range 1 – 32.1) and 7.5±4.5 ng/mL (range 2.1 – 31.5), respectively.

Cardiac evaluation, ECG and echocardiography three months post-surgery were normal in all cases with the exception of two children. The first case was a two year old boy who underwent split liver transplantation due to tyrosinemia with multiple hypoechoic nodules in the liver. He received tacrolimus at a dose of 0.15 mg/kg/day and prednisolone (5 mg/day). Three months after the operation, he developed a fever and dyspnea. On physical examination, he had high blood pressure (150/80 mmHg) and a heart murmur. ECG showed tachycardia, left axis deviation and left ventricular hypertrophy. Echocardiography showed obstructive hypertrophic cardiomyopathy with asymmetric hypertrophy of the interventricular septum, left ventricular hypertrophy and aortic valve stenosis. The tacrolimus trough level of the patient at this time was 32.1 ng/mL. He also had cervical lymphadenopathy and a lymph node excision biopsy was performed which indicated

post-transplant lymphoproliferative disorder. Tacrolimus was discontinued and sirolimus was started but the patient did not respond and died one month later. The second case was a five year-old girl, a case of biliary atresia without any signs and symptoms of a cardiac problem, but echocardiography three months after liver transplantation showed aortic stenosis and mitral and tricuspid regurgitation. The tacrolimus trough level of this case was 30.3 ng/mL. We adjusted the dose of tacrolimus and her echocardiography became normal six months after the liver transplant.

Cardiac evaluations and echocardiography were normal in the remaining patients six months after liver transplantation.

In the control group which included 15 (30%) children and 35 (70%) adult patients who received cyclosporine, cardiac evaluations and echocardiography results were all normal.

Discussion

Tacrolimus is a potent immunosuppressive agent with a mechanism of action similar to that of cyclosporine.⁹ It is 10 to 100 times more potent than cyclosporine.³ This potency has contributed to its superiority in preventing allograft rejection and has allowed most patients to be weaned off corticosteroids.¹⁰ Tacrolimus has significant adverse effects; namely renal toxicity, neurotoxicity, anemia, gastrointestinal symptoms and post transplant diabetes mellitus.^{4,11}

In 1995, Atkinson et al.¹² reported the first series of five pediatric patients (two liver transplant recipients) who developed tacrolimus associated symmetric hypertrophy of the left ventricle or concentric hypertrophic cardiomyopathy. Later, other authors reported a few cases of cardiac toxicity related to tacrolimus.^{7,9,10,12-15} A number of mechanisms have been proposed to explain the cardiotoxicity of tacrolimus, including arteritis of cardiac arteries and extensive calcification of cardiac tissue,¹⁴ tacrolimus mediated hypertension,⁷ and a reduced serum selenium level.¹⁶ However, the true underlying mechanism of tacrolimus related cardiomyopathy is not completely understood.

It is likely that the cardiotoxicity due to tacrolimus is related to high blood levels of this medication, particularly at levels greater than 20 ng/mL.¹⁷

There are no prospective control studies on a large group of liver transplant recipients with tacrolimus cardiotoxicity with a six months follow-up.

Nakata et al.¹⁸ evaluated 32 patients who underwent living related liver transplantation for evidence of tacrolimus associated cardiotoxicity. None of their patients developed this complication despite some having the same blood level of tacrolimus as our patients (12.2 ng/mL vs. 11.2 ng/mL). This may be due to the shorter duration of follow-up in the Nakata et al.¹⁸ report in comparison to the present study (four weeks vs. six months).

Our study showed two cases of tacrolimus associated cardiac toxicity in pediatric patients. Therefore, long term follow-up is needed to determine whether or not tacrolimus induces cardiomyopathy.

Our first case is similar to a case that was reported by Pappas et al.¹⁹ who did not respond to sirolimus therapy.

Turska-Kmiec et al.²⁰ reported a case of tacrolimus associated hypertrophic cardiomyopathy who was responsive to sirolimus treatment.

The levels of tacrolimus in both cases in our study with cardiac problems were high (32.1 and 30.3 ng/mL), in comparison to previous studies.^{18,19}

Hypertrophic cardiomyopathy has also been reported to arise from the administration of steroids.²¹ One of our cases received a low dose of prednisolone and the other did not receive steroids. The cardiomyopathy of steroids was correlated to its immunomodulating effects in addition to some of its side effects such as fluid retention and hypertension. Pappas et al.¹⁹ have reported that concurrent use of steroids and tacrolimus may accelerate the development of hypertrophic cardiomyopathy. In our center, the adult patients received steroids for a longer period than the pediatric patients due to potential growth impairment, with no cases of cardiotoxicity in the adult patients despite the fact that 70% of our cases were adults and only 30% were children. This finding is consistent with a previous study.²² Considering previous studies and our findings, it seems that cardiotoxicity of tacrolimus is seen almost exclusively in pediatric patients, as four of our adult patients had tacrolimus levels above 20 ng/mL but none of them developed cardiac

problems. The differences between the adult and pediatric population need further investigation.

It is imperative to develop guidelines for clinical evaluation and follow-up to monitor the potential cardiac effects of tacrolimus, especially in children.

References

- 1 Tzakis AG, Reyes J, Todo S, Nour B, Shapiro R, Jordan M, et al. Two-year experience with FK 506 in pediatric patients. *Transplant Proc.* 1993; **25**: 619 – 621.
- 2 Textor SC, Wiesner R, Wilson DJ, Porayko M, Romero JC, Burnett JC Jr, et al. Systemic and renal hemodynamic differences between FK506 and cyclosporine in liver transplant recipients. *Transplantation.* 1993; **55**: 1332 – 1339.
- 3 The US Multicenter FK506 liver Study Group. A comparison of tacrolimus (FK 506) and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med.* 1994; **331**: 1110 – 1115.
- 4 Chang RK, Alzona M, Alejos J, Jue K, McDiarmid SV. Marked left ventricular hypertrophy in children on tacrolimus (FK506) after orthotopic liver transplantation. *Am J Cardiol.* 1998; **81**: 1277 – 1280.
- 5 Pham SM, Kormos RL, Kawai A, Murali S, Hattler BG, Demetris AJ, et al. Tacrolimus (FK506) in clinical cardiac transplantation: a five-year experience. *Transplant Proc.* 1996; **28**: 1002 – 1004.
- 6 Chang RK, McDiarmid SV, Alejos JC, Drant SE, Klitzner TS. Echocardiographic findings of hypertrophic cardiomyopathy in children after orthotopic liver transplantation. *Pediatr Transplant.* 2001; **5**: 187 – 191.
- 7 Roberts CA, Stern DL, Radio SJ. Asymmetric cardiac hypertrophy at autopsy in patients who received FK506 (tacrolimus) or cyclosporine A after liver transplant. *Transplantation.* 2002; **74**: 817 – 821.
- 8 Nomoto S, Fujiwara H, Ban T, Ohara K. Cardiotoxicity of long-term intravenous administration of FK506 in rabbits: dose relationship and recovery after discontinuance. *Transplant Proc.* 1994; **26**: 855 – 857.
- 9 Peters DH, Fitton A, Plosker GL, Faulds D. Tacrolimus. A review of its pharmacology, and therapeutic potential in hepatic and renal transplantation. *Drugs.* 1993; **46**: 746 – 794.
- 10 Cox KL, Freese DK. Tacrolimus (FK506): the pros and cons of its use as an immunosuppressant in pediatric liver transplantation. *Clin Invest Med.* 1996; **19**: 389 – 392.
- 11 Shapiro R. Tacrolimus in pediatric renal transplantation: a review. *Pediatr Transplant.* 1998; **2**: 270 – 276.
- 12 Atkison P, Joubert G, Barron A, Grant D, Paradis K, Seidman E, et al. Hypertrophic cardiomyopathy associated with tacrolimus in paediatric transplant patients. *Lancet.* 1995; **345**: 894 – 896.
- 13 Uchida N, Taniguchi S, Harada N, Shibuya T. Myocardial ischemia following allogeneic bone marrow transplantation: possible implication of tacrolimus overdose. *Blood.* 2000; **96**: 370 – 372.
- 14 Atkison PR, Joubert GI, Guiraudon C, Armstrong R, Wall W, Asfar S, et al. Arteritis and increased intracellular calcium as a possible mechanism for tacrolimus-related cardiac toxicity in a pediatric transplant recipient. *Transplantation.* 1997; **64**: 773 – 775.
- 15 Cox KL, Lawrence-Miyasaki LS, Garcia-Kennedy R, Lennette ET, Martinez OM, Krams SM, et al. An increased incidence of Epstein-Barr virus infection and lymphoproliferative disorder in young children on FK506 after liver transplantation. *Transplantation.* 1995; **59**: 524 – 529.
- 16 Dhawan A, Mack DR, Langnas AN. Immunosuppressive drugs and hypertrophic cardiomyopathy (letter). *Lancet.* 1995; **345**: 1644.
- 17 Uemoto S, Inomata Y, Egawa H. Effects of tacrolimus on cardiac function after living related liver transplantation in pediatric patients. Paper presented at 15th Annual Meeting of the American Society of Transplant Physicians; May 26 – 30, 1996; Dallas, TX. May 26 – 30, 1996: 196.
- 18 Nakata Y, Yoshibayashi M, Yonemura T, Uemoto S, Inomata Y, Tanaka K, et al. Tacrolimus and myocardial hypertrophy. *Transplantation.* 2000; **69**: 1960 – 1962.
- 19 Pappas PA, Wepler D, Pinna AD, Rusconi P, Thompson JF, Jaffe JS, et al. Sirolimus in pediatric gastrointestinal transplantation: the use of sirolimus for pediatric transplant patients with tacrolimus-related cardiomyopathy. *Pediatr Transplant.* 2000; **4**: 45 – 49.
- 20 Turska-Kmieć A, Jankowska I, Pawłowska J, Kaliciński P, Kawalec W, Tomyn M, et al. Reversal of tacrolimus-related hypertrophic cardiomyopathy after conversion to rapamycin in a pediatric liver transplant recipient. *Pediatr Transplant.* 2007; **11**: 319 – 323.
- 21 Brand PL, Brus F. Immunosuppressive drugs and hypertrophic cardiomyopathy. *Lancet.* 1995; **345**: 1644.
- 22 Coley KC, Verrico MM, McNamara DM, Park SC, Cressman MD, Branch RA. Lack of tacrolimus-induced cardiomyopathy. *Ann Pharmacother.* 2001; **35**: 985 – 989.