Alteration of Panel-Reactive Antibodies Following Treatment With Either Atorvastatin or Low-Dose Mycophenolate Mofetil in Sensitized Hemodialysis Patients

Ali Ghorbani,[1] Heshmatollah Shahbazian,[1] Ali Ehsanpour,[2] Asieh Aref[2]

[1]Division of Nephrology, Department of Internal Medicine, Ahvaz Jondi Shapour University of Medical Sciences, Ahvaz, Iran
[2]Department of Internal Medicine, Ahvaz Jondi Shapour University of Medical Sciences, Ahvaz, Iran

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Original Paper

Introduction. Both atorvastatin and mycophenolate mofetil (MMF) have been used for panel reactive antibodies (PRA) reduction in transplant candidates. The purpose of this study was to compare the effect of low-dose MMF and atorvastatin on PRA in sensitized hemodialysis patients waiting for kidney transplantation.
Materials and Methods. A total of 40 adult patients with end-stage renal disease who were highly sensitized to human leukocyte antigens (PRA > 40%) were enrolled and randomly assigned into atorvastatin or low-dose MMF groups. All of the patients received the treatments for 2 months. The PRA status was determined at the end of the 1st and 2nd month.
Results. Forty percent of the patients in the atorvastatin group compared with 5% in the low-dose MMF group showed complete response, defined as a minimum 50% reduction in PRA (P = .02). Reduction of PRA in the atorvastatin group was significantly higher than that in the low-dose MMF group (P = .01). No major infectious or other complications occurred in our patients.
Conclusions. Atorvastatin has a significant effect on lowering of PRA in sensitized hemodialysis patients waiting for kidney transplantation. In addition, a short course of low-dose MMF is safe in ESRD patients; however, it has no effect on reduction of PRA.

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INTRODUCTION

Kidney transplantation is the desired treatment of choice in patients with end-stage kidney disease.[1,2] However, the average waiting time to receive a deceased donor kidney transplant is 3 to 5 years. Currently, there are about 60 000 individuals on the national waiting list in the United States, and about 13 000 to 14 000 kidney transplants are performed each year. Approximately, 25% of patients on the waiting list are highly sensitized, meaning that they have natural proteins (antibodies) that aggressively protect their bodies from the invasion of foreign proteins.[3] Humoral sensitization is associated with poor allograft outcome.[4] Two main protocols have been suggested for reduction of human leukocyte antigen (HLA) antibodies in the presence of HLA allo-antibodies, high-dose intravenous immunoglobulin (IVIG), and low-dose IVIG in combination with plasmapheresis.[5-13] Peritransplant immunoadsorption, administration of the monoclonal anti-CD20 antibody rituximab, statins, and mycophenolate mofetil (MMF) are currently alternative approaches to increase the chance of a highly sensitized patient for a transplant.[14,15]

Over the past several years, the presence of

preformed anti-HLA antibodies in the recipient's serum (highly sensitized) has been recognized as a prominent risk factor for episodes of allograft rejection.[16,17] Screening to identify antibodies to HLA class I antigens has been performed with a panel of HLA-typed lymphocytes referred to as panel reactive antibodies (PRA) analysis. Inhibitors of 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase have been reported to decrease the incidence of rejection in heart transplant patients. Some studies showed that HMG-CoA reductase inhibitors might prevent acute and chronic allograft rejection.[18-20] Statins have been shown to have anti-inflammatory and immunosuppressive effects that decrease PRA content and lymphocyte cross-match positivity. Both inhibitors of HMG-CoA reductase and MMF have been shown to have anti-inflammatory and immunosuppressive effects.[21,22] Both drugs have been used for PRA reduction in transplant candidates.

The purpose of this investigation was to compare the effect of low-dose MMF and atorvastatin on PRA in sensitized hemodialysis patients waiting for kidney transplantation. Our objective was to determine whether a 2-month course of either low-dose MMF or atorvastatin adequately decreases the PRA. This research study was done because currently, there are very limited and cumbersome treatment options to decrease PRA, and patients who are highly sensitized with antibodies may unfortunately wait for a very long time or may never get transplanted.

MATERIALS AND METHODS

Study Population

From March 2007 to October 2007, a total of 40 patients with end-stage renal disease aged 18 years old or greater with a PRA greater than 40% were enrolled in this study. These patients were on hemodialysis (3 times per week) and were on kidney transplantation list at the Nephrology, Dialysis and Transplantation Center, Golestan Hospital, Ahvaz, Iran. Included patients were candidates for their first kidney transplant and were on hemodialysis for at least 3 months. The exclusion criteria were an active infection or a recent infectious event in the past month, liver dysfunction based on laboratory studies, active hepatic disease, hyperlipidemia requiring statin therapy, pregnancy, the need for ongoing blood products, failed organs having active rejection, and a life expectancy less than 6 months.

Informed consent was obtained after explaining possible adverse effects. The study was conducted according to the guidelines of the Declaration of Helsinki, as reflected in the approval given by the Ethics Committee of Ahvaz Jondi Shapour University of Medical Sciences.

Study Protocol

The patients were randomized (1:1) to receive atorvastatin or low-dose MMF. Patients allocated in the atorvastatin group were treated with a starting dose of 10 mg/d. After two weeks, atorvastatin was increased to 20 mg/d. At 4 weeks, the dose was increased again to a maximum of 30 mg/d. Patients assigned to the MMF group were treated with a starting dose of 500 mg/d. After 2 weeks, MMF was increased to 1000 mg/d, and at 4 weeks, the dose was increased again to a maximum of 1500 mg/d. All of the patients were treated for 2 months.

Laboratory Studies

Panel reactive antibodies were measured using the National Institute of Health lymphocytotoxicity method, which relies on the serological reaction of a panel of viable human lymphocytes with anti-HLA antibodies in the presence of rabbit complement. Panels of 20 different lymphocytes were used. A positive test was graded from 10% to 100% lysed lymphocytes. The PRA status determinations were performed at monthly intervals at the end of the 1st and 2nd month. In order to prevent test result variations due to changes in lymphocyte antigens, frozen serial sera of the patients were tested again against a single panel of lymphocytes to evaluate their reactivity against the same set of lymphocytes at the end of the 2nd month. The patients were assessed monthly to check for drug compliance and to search for clinical evidence of drug side effects. The complete response to the therapy was defined as a decrease in PRA by 50% or more at the end of trial compared to baseline values.

Statistical Analyses

Data are presented as mean ± standard deviation for continuous variables and as percentages for categorical variables. The Wilcoxon sum rank test and *t* test were used to compare groups in

continuous variables. The Fisher exact test was used comparison of categorical variables. Statistical significance was considered for *P* values less than .05 (two-sided). The statistical program utilized was the SPSS software (Statistical Package for the Social Sciences, version 13.0, SPSS Inc, Chicago, Ill, USA).

RESULTS

Between March 2007 and October 2007, a total of 40 patients (15 women and 15 men; mean age, 32.3 ± 9.3 years) met the study criteria for enrollment. There were no significant differences in terms of age, gender, dialysis duration, baseline PRA level, ESRD etiology, history of pregnancy, blood transfusion, and kidney transplantation between the two groups (Table 1). All of the patients completed the trial.

No significant differences were observed in the 1st month PRA between the two groups. However, PRA was significantly higher in the MMF group compared to the atorvastatin group after 2 months (*P* =.01; Table 2). Atorvastatin caused a significant reduction in PRA both at the 1st and 2nd month. The mean percentage of PRA changes from baseline in the atorvastatin group were 7.25 ± 1.75 (95% confidence interval [CI], 3.75 to 10.92; *P* = .001) and 15.25 ± 3.17 (95% CI, 8.61 to 21.88; *P* = .001) at 1 and 2 months, respectively. In comparison, PRA changes were not significant after 2 months in the MMF group (Table 2). The mean percentage of PRA changes from baseline in the MMF group were 4.00 ± 2.47 (95% CI, -1.18 to 9.18, *P* = .80) and 4.25 ± 2.27 (95% CI, -0.5 to 9.00, *P* = .08) at 1 and 2 months, respectively. Complete response to therapy, which was defined as a decrease in PRA by 50% or more compared to baseline values, was observed in 8 patients of the atorvastatin group (40.0%) and 1 patient of the MMF group (5.0%; *P* = .02).

Table 2. Panel Reactive Antibodies Levels*

PRA	Study Arms		*P*
	Atorvastatin	MMF	
Baseline, %	54.5 ± 1.3	53.5 ± 1.8	.37
First month, %	47.3 ± 1.3	49.5 ± 2.3	.37
Second month, %	39.3 ± 2.8	49.3 ± 2.1	.01

*Values are mean ± standard deviation. PRA indicates panel reactive antibodies and MMF, mycophenolate mofetil.

No death or serious event was recorded during the study period. Mild nausea occurred in 2 patients of the atorvastatin group at the 2nd and 3rd weeks, and mild to moderate dyspepsia occurred in 4 patients of the MMF group. Both complications were controlled with conservative management.

DISCUSSION

In the present study, we showed that 2 months of treatment with atorvastatin reduces PRA in highly sensitized hemodialysis patients. Low-dose MMF, however, was not effective in reducing PRA in our patients. Ferro and colleagues showed that HMG-CoA reductase had anti-inflammatory and immunosuppressive effects.[21] Ozdemir and colleagues showed that treatment with simvastatin resulted in the reduction of PRA from 44.8 ± 19.01 to 14.3 ± 16.3. They concluded that simvastatin had high efficiency, high tolerability, and low cost for treating sensitized patients.[23] Later, they suggested that continuous simvastatin therapy is effective for treating highly sensitized patients, and that it had a beneficial effect on 1-year graft survival in patients in a sensitized kidney transplantation group.[24] More recently, Yakupoglu and coworkers reported the effect of simvastatin in lymphocyte cross-mach–positive kidney transplantation candidates.[25] In this trial, PRA reduced to 25% or less in 40% of the treated patients. However, using lovastatin, Ossareh and colleagues reported that

Table 1. Patients Characteristics at Baseline*

Characteristic	All Patients	Study Arms		*P*
		Atorvastatin	MMF	
Age, y	34.5 ± 1.2	33.5 ± 2.1	35.5 ± 1.4	.32
Dialysis duration, y	4.2 ± 0.4	3.7 ± 0.7	4.7 ± 0.5	.07
Gender				
Male	18 (45.0)	9 (22.5)	9 (22.5)	
Female	22 (55.0)	11 (27.5)	11 (27.5)	> .99
Kidney transplant history	6 (15.0)	3 (7.5)	3 (7.5)	> .99

*Values are either mean ± standard deviation or frequency (percentage). PRA indicates panel reactive antibodies and MMF, mycophenolate mofetil.

they failed to replicate the results of Yakupoglu and colleagues' report about the possible effects of HMG-CoA reductase inhibitors on lowering of the percentage of PRA.[26] In our study, we showed that atorvastatin (another drug in the statin group) with a constant dose could significantly reduce PRA in sensitized hemodialysis patients after 2 months. In our study, 40% of patients treated with atorvastatin showed a reduction in PRA of more than 50%.

Mycophenolate mofetil has become the single most used immunosuppressant in solid organ transplantation. It inhibits proliferation of both T and B lymphocytes.[22] Mycophenolate mofetil has been shown to decrease response to neo-antigens in the transplant population.[27] In a study of cardiac transplant recipients, MMF treatment resulted in reduced antibody production in comparison with azathioprine treatment.[28] Schmid and associates studied a similar strategy to reduce PRA levels in a presensitized patient awaiting cardiac transplantation.[29] In this case report, PRA levels were reported to be as high as 70% before initiation of therapy and zero to 5% on average following treatment with MMF. In a study of Terasaki and Ozawa, HLA showed a lower antibody frequency in patients treated with cyclosporine and MMF compared with those who received cyclosporine and azathioprine (9.8% versus 18%).[30] Mycophenolate mofetil has also been shown to decrease PRA formation in a sensitized adult cardiac transplant recipient; Shaddy and colleagues also demonstrated the ability of MMF, at a dose of 1200 mg/m^2/d, to prevent elevation in PRA levels after cardiac valve allograft implantation in 8 children.[31] Wong and coworkers reported successful use of prophylactic MMF in preventing the formation of PRA in a pediatric kidney transplant recipient with multiple donor exposures.[32] Our study, however, failed to show any change in PRA in a group of sensitized hemodialysis patients treated with low-dose MMF. The discrepancies observed between our results and previous studies might either be due to the treatment protocol or the low number of allocated patients. We used MMF in a very low dose and gradually increased it to a maximum dose of 1500 mg/d within 1 month. In addition, we discontinued MMF after 2 months. The treatment protocol had low-dose MMF and prescribed for a short period of time. Our treatment protocol had been principally designed for documentation of the MMF safety in ESRD patients.

The major limitation of our study is the treatment protocol in the low-dose MMF arm. Mycophenolate mofetil was administered for a limited period of time and in a limited dosage. A small sample size may be another limitation that caused failure to show the possible effect. Our study showed the safety of low-dose MMF in ESRD patients. The duration of PRA reduction in hemodialysis patients and its impact on considering patients for transplantation were not assessed in our study.

CONCLUSIONS

We conclude that atorvastatin has a significant effect on lowering of PRA in sensitized hemodialysis patients waiting for kidney transplantation. In addition, a short course of low-dose MMF is safe in ESRD patients; however, it has no effect on reduction of PRA.

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CONFLICT OF INTEREST

None declared.

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Correspondence to:
Ali Ehsanpour, MD
Department of Nephrology, Dialysis, and Kidney Transplantation, Golestan Hospital, Ahvaz 61355-173, Iran
Tel: +98 611 338 6258
Fax: +98 611 334 3964
E-mail: ali990ehs@yahoo.com

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