

# Impaired Kidney Allograft Function Following Ezetimibe Therapy

Nader Nouri-Majalan, Sara Moghaddasi, Reza Majidi

Division of Nephrology,  
Department of Internal  
Medicine, Shahid Sadoughi  
University of Medical Sciences,  
Yazd, Iran

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Although ezetimibe therapy has been shown to be effective in lowering serum cholesterol level, it has not been reported to affect serum cyclosporine level in transplant recipients. Here, we describe a kidney transplant recipient who experienced acute kidney allograft dysfunction after ezetimibe prescription. Our patient showed an increase in serum creatinine level as well as a decrease in serum cyclosporine levels 1 month after taking ezetimibe. This suggests that ezetimibe may interact with cyclosporine and decrease its serum level resulting in allograft dysfunction. In this regard, careful monitoring of kidney function along with the serum cyclosporine level in kidney allograft recipients is recommended when cyclosporine is co-administered with ezetimibe.

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## INTRODUCTION

Hyperlipidemia is very common in kidney transplant recipients.<sup>1</sup> Ezetimibe, a novel inhibitor of intestinal cholesterol absorption,<sup>2</sup> has been shown to be effective in lowering serum cholesterol levels in renal transplant patients.<sup>3,4</sup> There is no report regarding significant adverse effects of ezetimibe on allograft function.<sup>5,6</sup> Ezetimibe impairs dietary and biliary absorption of cholesterol at the brush border level of the intestine without affecting the absorption of triglycerides or fat soluble vitamins.<sup>2</sup> Here, we describe a kidney transplant recipient who experienced acute kidney allograft dysfunction after ezetimibe administration.

## CASE REPORT

A 56-year-old man with end-stage renal disease secondary to diabetes mellitus had received a kidney allograft transplant from a living unrelated donor 7 year earlier. After transplantation, he did not experience any episode of acute rejection, and his serum creatinine level was maintained between 0.9 mg/dL and 1.1 mg/dL. He was on a maintenance immunosuppressive therapy with prednisolone, 5 mg/d, mycophenolate mofetile, 2 g/d, and cyclosporine, 150 mg/d. Moreover, because

of hyperlipidemia, he was taking gemfibrozil, 300 mg/d, and atorvastatin, 20 mg/d. During that time, serum trough levels of cyclosporine were obtained between 121 ng/mL and 125 ng/mL. Due to the lack of response, ezetimibe was added to his medications to lower serum cholesterol level. After 1 month, total serum cholesterol level decreased from 224 mg/dL to 172 mg/dL, serum low-density lipoprotein cholesterol decreased from 143 mg/dL to 78 mg/dL, and serum triglyceride level increased from 224 mg/dL to 305 mg/dL, while serum creatinine level increased from 1.1 mg/dL to 4.4 mg/dL and cyclosporine trough level decreased to 45 ng/mL (Table). Renal radionuclide scan showed evidence

Laboratory and Biochemical Variables Before and After Ezetimibe Therapy

Variable	Before Ezetimibe Therapy	After Ezetimibe Therapy
Serum creatinine, mg/dL	1.1	4.4
Cyclosporine dose, mg/d	150	150
Cyclosporine trough level, ng/mL	125	45
Total serum cholesterol, mg/dL	224	172
Serum LDLC, mg/dL	143	78
Serum triglyceride, mg/dL	224	305

\*LDLC indicates low-density lipoprotein cholesterol.

of acute kidney allograft rejection. Ezetimibe was discontinued and the patient was administered 4 pulses of prednisolone, 1000 mg, resulting in a decrease in serum creatinine level to 2 mg/dL. In addition, diltiazem, 120 mg/d, was added to increase the serum trough level of cyclosporine, which rose to 169 mg/dL.

## DISCUSSION

In our knowledge, this is a first report of acute kidney allograft dysfunction following to ezetimibe therapy seven years after renal transplantation. Unfortunately, we did not perform a kidney allograft biopsy. We need to have a renal biopsy to confirm the diagnosis of an acute rejection. However, sudden increase in serum creatinine level decreased cyclosporine trough level and dramatic response to anti-rejection therapy are indicating to the diagnosis of acute allograft rejection. As we had not made any changes in the previous treatment protocol and administered doses of cyclosporine and any other medications, it is likely that ezetimibe might be a probable cause of decreased serum cyclosporine level as well as the occurrence of acute allograft rejection. Nevertheless, the other differential diagnosis in the setting of the acute allograft dysfunction should be considered.

Few studies have assessed the effects of ezetimibe on allograft function and its interaction with cyclosporine. In two clinical trials, ezetimibe had not any adverse effect on kidney allograft function but exerts protective effects on creatinine clearance.<sup>5,7</sup> Furthermore, ezetimibe did not significantly alter the serum trough level of cyclosporine during one year follow up period. Although findings of these trials differ from those in our patient, most randomized clinical trials were performed including a few patients to identify any adverse effects.

In rats, ezetimibe inhibited the intestinal absorption of alpha-tocopherol (vitamin E) but had not any effect on the uptake of retinol (vitamin A) and cyclosporine A.<sup>8</sup> Although several studies showed ezetimibe had no effect on the serum level of cyclosporine in transplant recipients,<sup>5,7,9</sup> multiple 20 mg doses of ezetimibe were found to increase mean serum cyclosporine level by approximately 15% in healthy subjects.<sup>10</sup> Moreover, pharmacokinetic interactions between ezetimibe and cyclosporine in transplant recipients were found to result in a significant increase in the

serum level of ezetimibe.<sup>11,12</sup>

In addition to ezetimibe, our patient had received gemfibrozil and atorvastatin for management of hyperlipidemia. Although a combination of ezetimibe and fenofibrate has been safely used in patients with hyperlipidemia,<sup>13</sup> fenofibrate has been found to increase the serum level of ezetimibe in healthy subjects.<sup>14,15</sup> Ezetimibe does not have any significant effect on the plasma level of atorvastatin.<sup>16</sup> In this way, interactions of cyclosporine, ezetimibe, and gemfibrozil in transplant recipients is not clear. Because of the limited experience in the setting of cyclosporine therapy, physicians are recommended to be cautious when adding ezetimibe to the treatment protocol including cyclosporine and monitor carefully the serum level of cyclosporine.<sup>16</sup>

Findings in our patient suggest that, in renal transplant recipients, ezetimibe may decrease the serum cyclosporine level, resulting in acute kidney allograft dysfunction. Because the long-term safety of ezetimibe and its interaction with cyclosporine are not yet well understood, careful considerations and consistent monitoring of kidney allograft function as well as serum cyclosporine level in all transplant recipients is recommended.

## CONFLICT OF INTEREST

None declared.

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## Correspondence to:

Nader Nouri-Majelan, MD  
 Division of Nephrology, Department of Internal Medicine, Shahid  
 Sadoughi Medical University, Yazd, Iran  
 Tel: +98 913 152 6380  
 Fax: +98 351 822 4100  
 E-mail: dr\_nori\_majelan@yahoo.com

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