LIVER TRANSPLANTATION 15:504-508, 2009

ORIGINAL ARTICLE

Safety and Effectiveness of Ezetimibe in Liver Transplant Recipients with Hypercholesterolemia

Fawaz Almutairi,[1] Theresa C. Peterson,[1,2] Michele Molinari,[3,4] Mark J. Walsh,[3,4] Ian Alwayn,[3,4] and Kevork M. Peltekian[1,4]

Departments of [1]Medicine, [2]Pharmacology, and [3]Surgery, Dalhousie University, Halifax, Nova Scotia, Canada; and [4]Atlantic Multi-Organ Transplantation Program, Queen Elizabeth II Health Sciences Centre, Halifax, Nova Scotia, Canada

Hypercholesterolemia is a common problem among transplant recipients. Despite package-insert warnings about the potential side effects of the use of statins in patients with chronic liver disease, they are often prescribed for liver transplant recipients. Unlike statins, ezetimibe acts through inhibition of enterohepatic recirculation of lipids. We report the effectiveness and safety of ezetimibe among liver transplant recipients because this has been evaluated previously only in kidney and heart transplant patients. A consecutive cohort of 25 liver graft recipients with serum low-density lipoprotein (LDL) levels $>$ 100 mg/dL (2.5 mmol/L) after a mean ($\pm$standard deviation) of 55 $\pm$ 21 months following liver transplantation received ezetimibe (10 mg orally every day) for at least 6 months. Serum lipid profiles, liver and renal function tests, and dosages and blood levels of the immunosuppression drugs at baseline, 3 months, and 6 months were prospectively collected. The overall mean age was 58 $\pm$ 12 years, and 56% were males. Statin therapy and fibrates were already being used in 32% and 20% of recipients for elevated LDL and/or triglycerides, respectively. The immunosuppression regimen included cyclosporine in 48% of subjects, tacrolimus in 32%, sirolimus in 48%, and mycophenolate mofetil in 44%; only 12% were on oral prednisone with a maximum daily dose of 5 mg. After ezetimibe was started, an 18% reduction in LDL values was observed [at baseline, 147 $\pm$ 35 mg/dL (3.8 $\pm$ 0.9 mmol/L), and at 6 months, 120 $\pm$ 31 mg/dL (3.1 $\pm$ 0.8 mmol/L); $P = 0.010$]. After 6 months, an additional 32% achieved the target LDL level of $<$100 mg/dL. None of the remaining variables, including immunosuppression drug levels, varied significantly during ezetimibe therapy. None of the subjects required adjustments in their pharmacological dosages. One discontinued ezetimibe 3 months later because of cost, 2 subjects had minimal nausea, 1 subject had myalgias without a rise in creatine phosphokinase, and 1 subject had a transient elevation (3-5 times) in liver enzymes from baseline with increases in the total and indirect bilirubin levels. In conclusion, among liver transplant recipients, hypercholesterolemia can be effectively treated with ezetimibe with few side effects and no interaction with immunosuppressive regimens. ***Liver Transpl 15:504-508, 2009.*** © **2009 AASLD.**

Received August 5, 2008; accepted November 16, 2008.

After orthotopic liver transplantation (OLT) in the adult population, between 16% and 43% of recipients will develop hypercholesterolemia, and 40% will develop hypertriglyceridemia, with the majority suffering from mixed hyperlipidemia.[1,2] The cause of post-OLT hyperlipidemia is multifactorial,[2] but often immunosuppression drugs are the main offenders. Corticosteroids enhance appetite and caloric intake, contribute to obesity, and enhance hepatic secretion of very low-density lipoprotein and its conversion to low-density lipoprotein (LDL). Calcineurin inhibitors, especially cyclosporine, bind to the LDL receptors, thereby increasing circulating levels of LDL cholesterol.[2] Mammalian target of rapamycin inhibitors are also considered some of the offenders for hyperlipidemia, especially at a high dosage.

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; INR, international normalized ratio; LDL, low-density lipoprotein; OLT, orthotopic liver transplantation.

Address reprint requests to Kevork M. Peltekian, Atlantic Multi-Organ Transplantation Program (Liver Team), 1278 Tower Road, VG Site Room 6-302, Halifax, Nova Scotia, Canada B3H 2Y9. Telephone: 902-473-2898; FAX: 902-473-2783; E-mail: kevork.peltekian@dal.ca

DOI 10.1002/lt.21710
Published online in Wiley InterScience (www.interscience.wiley.com).

Survival rates after solid-organ transplantation have improved over the last 2 decades, with the majority of OLT recipients surviving beyond 5 years. Reducing cardiovascular risk is becoming increasingly important because many OLT recipients develop posttransplant metabolic syndrome with increasing cardiovascular events.[3] Pharmacotherapy is necessary when dietary modifications and lifestyle changes prove inadequate.[4] Agents used to treat hyperlipidemia include 3-hydroxy-3-methyl glutaryl-coenzyme A reductase inhibitors (statins), bile acid sequestrants, niacin, fibrates, and, more recently, an inhibitor of cholesterol absorption, ezetimibe. The efficacy of pravastatin and atorvastatin has been established in patients with hyperlipidemia after liver transplant.[1,5] Often, statins are considered first-line therapy, but most may impact calcineurin inhibitors serum levels through the cytochrome P-450 system. Bile acid sequestrants are also avoided because they affect the absorption of immunosuppression drugs. Although newer formulations of niacin are better tolerated, there is limited experience among liver transplantation recipients.

Ezetimibe is a novel drug that inhibits the absorption of dietary and biliary cholesterol without affecting the absorption of triglycerides or fat-soluble vitamins.[6] It has been used alone and in combination with statins for patients affected by hypercholesterolemia. Ezetimibe has been shown to be effective in patients after heart and kidney transplantation, but there is a lack of data for OLT recipients.[7] Following our previous study on the prevalence of metabolic syndrome and hyperlipidemia among OLT recipients[3] and the encouraging experience with ezetimibe in kidney transplant recipients,[8] ezetimibe was introduced for the treatment of hypercholesterolemia in our patients after OLT. The aim of this study was to assess the effectiveness and safety of ezetimibe as monotherapy or in combination with statins in adult OLT recipients with hyperlipidemia.

PATIENTS AND METHODS

Since our posttransplant metabolic syndrome study,[3] hyperlipidemia has been managed aggressively in our program. The first priority is to minimize prednisone and discontinue it if possible. All patients are advised on dietary changes and regular exercise according to the recommendations of the Working Group on Hypercholesterolemia and Other Dyslidemias.[9] During a patient's annual follow-up visit, lipid profiles are routinely reviewed; an attempt is made to reduce sirolimus and calcineurin inhibitors with consideration of conversion of cyclosporine to tacrolimus in nondiabetic subjects as per our previous study.[10] In subjects with LDL $>$ 100 mg/dL, statins are introduced. The 2 drugs of choice in our program are pravastatin (starting daily dose of 10 mg) and fluvastatin (starting dose of 20 mg every second day). Pravastatin is not significantly metabolized via the cytochrome P-450 system, whereas fluvastatin is water-soluble and has minimal interactions with calcineurin inhibitors. The dose of statins is titrated upward once every 3 to 6 months to achieve a target LDL level of $<$100 mg/dL or until subjects develop intolerance to statins. Since the publication of local experience with ezetimibe,[8] all liver transplant recipients in our program with elevated LDL $>$ 100 mg/dL for more than 12 months have been offered prescriptions for ezetimibe.

Among 207 patients followed at the Atlantic Multi-Organ Transplant Program in Halifax, Canada, 25 consecutive adult OLT recipients were identified during their routine annual clinic visit who had elevated hypercholesterolemia (fasting serum LDL $>$ 100 mg/dL) and who received at least 1 dose of ezetimibe either as monotherapy or in combination with a statin.

We conducted a retrospective analysis of all the data extracted from the Atlantic Multi-Organ Transplant Program database. These data included demographics, immunosuppression regimen (including respective dosages and blood immunosuppressive drug levels), liver enzyme and function tests, serum creatinine, fasting serum lipid profiles, lipid management regimens, and ezetimibe dosage. All these routine blood tests had been completed at baseline and then at 3 and 6 months after the start of ezetimibe. The study was approved by the Capital District Research Ethics Board (Halifax, Canada).

Statistical analysis was performed with Minitab software, version 14 (Minitab, State College, PA), with standard methodology, including the Student t test for continuous variables, χ^2 test for nonparametric data, and analysis of variance whenever means at baseline, 3 months, and 6 months were being compared. A P value < 0.05 was considered significant.

RESULTS

The baseline patient characteristics and their treatment modalities are described in Table 1. The overall mean age (±standard deviation) was 58 ± 12 years with 56% males. Subjects were already on statins (32%) and fibrates (20%) for high LDL and/or triglyceride levels. The immunosuppression drugs were cyclosporine (48%), tacrolimus (32%), sirolimus (48%), mycophenolate mofetil (44%), and prednisone (12%), but in the latter group, the maximum dose was only 5 mg. The ezetimibe dose was 10 mg/day in 92% of cases, with 2 subjects taking only 10 mg of ezetimibe every second day. The reduced dose was initiated temporarily when a study suggesting a possible interaction between cyclosporine and ezetimibe was published.[11]

After ezetimibe was started, we observed an 11% reduction in total cholesterol levels from 236 ± 46 mmol/L at baseline to 208 ± 46 mmol/L at 6 months (P = 0.022) and an 18% reduction in LDL cholesterol levels from 147 ± 35 mmol/L at baseline to 120 ± 31 mmol/L at 6 months (P = 0.010). The remaining variables for the lipid profile did not show significant differences (Fig. 1). Furthermore, after 3 and 6 months of therapy with ezetimibe, 28% and 32% achieved the target LDL level of ≤100 mg/dL, respectively. Of those who achieved the target LDL level of $<$100 mg/dL, 62% had

TABLE 1. Baseline Characteristics of the Patient Population

Age (mean ± standard deviation)	58 ± 12 years
Gender: male	14 (56%)
Duration post-OLT	55 ± 21 months
Primary indication for OLT	
Cryptogenic cirrhosis	9 (36%)
Hepatitis C virus	6 (24%)
Primary biliary cirrhosis	4 (16%)
Alcohol-related cirrhosis	2 (8%)
Miscellaneous	4 (16%)
Immunosuppression drugs (% subjects on therapy): daily dose	
Cyclosporine (20%)	150 ± 83 mg
Tacrolimus (68%)	2.5 ± 1.3 mg
Sirolimus (52%)	2.8 ± 1.6 mg
Mycophenolate mofetil (40%)	1050 ± 438 mg
Prednisone (12%)	4.2 ± 1.4 mg
Antilipid agents (daily dose range)*	
Atorvastatin (20-40 mg)	1 (4%)
Fluvastatin (10-20 mg)	4 (16%)
Pravastatin (10-40 mg)	2 (8%)
Rosuvastatin (10-20 mg)	1 (4%)
Fenofibrate (micronized; 200 mg)	5 (20%)
Lipid profile	
Total cholesterol	236 ± 46 mg/dL
Low-density lipoprotein	147 ± 35 mg/dL
High-density lipoprotein	54 ± 22 mg/dL
Triglycerides	195 ± 321 mg/dL
Other cardiovascular risk factors	
Diabetes mellitus	16 (64%)
Hypertension	18 (72%)
Obesity (BMI > 30 kg/m^2)	14 (56%)
Posttransplant metabolic syndrome	20 (80%)

Abbreviations: BMI, body mass index; OLT, orthotopic liver transplantation.
*All doses for antilipid agents were stable for at least 12 months before ezetimibe was started and throughout the study period.

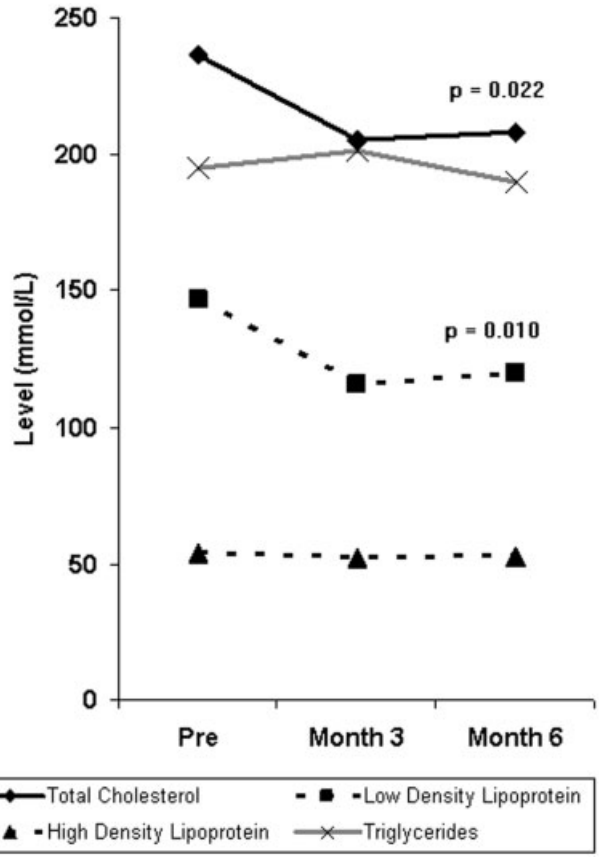

Figure 1. Lipid profile of liver transplant recipients treated with ezetimibe.

been on stable doses of statins for at least 12 months. During treatment with ezetimibe, no adjustments were required in medication dosages. We observed no significant variations in immunosuppression drug levels. There were no significant biochemical variations during the ezetimibe therapy (Table 2).

One subject discontinued the drug 3 months later because of cost, 2 subjects had grade 1 nausea,[12] and 1 subject had myalgias without a rise in creatine phosphokinase. In 1 subject, 6 months after ezetimibe was started, there was a transient 3-fold elevation in alanine aminotransferase and aspartate aminotransferase and a 5-fold elevation in alkaline phosphatase from baseline that resolved spontaneously 2 weeks later without adjustments in medications. This was associated with a rise in total and indirect bilirubin. The hepatic imaging studies were nondiagnostic. Despite these biochemical changes, this subject remained asymptomatic throughout the event without long-term consequences.

DISCUSSION

Hyperlipidemia occurs in all solid-organ transplants, but prevalence rates vary, being greatest for heart transplant recipients and least for OLT recipients.[13] As in the general population, control of hyperlipidemia is one of the cornerstones for management of cardiovascular risk factors for recipients of solid-organ transplants. In addition, in transplantation, hypercholesterolemia may be associated with transplant vasculopathy, an unusually accelerated form of atherosclerotic disease.[14] In cardiac transplant recipients, graft vasculopathy takes the form of de novo coronary artery disease; in renal transplant recipients, vasculopathy manifests as chronic rejection. Some authors consider vanishing bile duct syndrome a manifestation of endothelial pathology in liver grafts similar to what has been observed in cardiac and renal transplants at the vascular level.[14]

Potential causes of hyperlipidemia in transplant recipients include diet, genetic predisposition, and the effects of immunosuppression drugs. Patients with

TABLE 2. Biochemical Profile and Immunosuppression Drug Levels During Ezetimibe Therapy

	Baseline	3 Months	6 Months	*P* Value
ALT (IU/L)	52 ± 43	50 ± 37	69 ± 124	0.669
AST (IU/L)	39 ± 30	38 ± 29	45 ± 60	0.814
ALP (IU/L)	137 ± 84	148 ± 84	178 ± 163	0.451
Bilirubin (μmol/L)	12 ± 6	11 ± 6	21 ± 40	0.306
Albumin (g/L)	40 ± 4	39 ± 4	39 ± 4	0.748
INR	1.0 ± 0.2	1.0 ± 0.3	1.0 ± 0.3	0.808
Creatinine (μmol/L)	127 ± 65	132 ± 80	136 ± 133	0.959
Cyclosporine (ng/mL)*	463 ± 241	470 ± 429	356 ± 276	0.825
Tacrolimus (ng/mL)†	3.7 ± 1.7	3.8 ± 2.5	4.3 ± 2.2	0.732
Sirolimus (ng/mL)†	5.8 ± 3.2	4.4 ± 2.0	7.5 ± 4.7	0.180
Mycophenolate mofetil (ng/mL)†	3.4 ± 3.1	1.2 ± 0.6	0.8 ± 0.3	0.096

Abbreviations: ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; INR, international normalized ratio.
*Two-hour peak levels.
†Trough levels.

end-stage parenchymal liver disease often have low serum cholesterol levels because of impaired hepatic synthesis and lipid esterification,[15,16] whereas serum cholesterol may be high in cholestatic disorders[17] when parenchymal function is reasonably well preserved. Serum triglycerides may be elevated in obstructive jaundice and, less often, in parenchymal liver disease.[17]

Ezetimibe is the first lipid-lowering drug that inhibits intestinal uptake of dietary and biliary cholesterol without affecting the absorption of fat-soluble nutrients; it was approved by the US Food and Drug Administration in the fall of 2002 as therapy for hypercholesterolemia in combination with a statin or alone. This drug is rapidly absorbed and primarily metabolized in the small intestine and liver to its glucuronide, with little oxidative cytochrome P450–mediated metabolism.[18] Ezetimibe and its glucuronide undergo enterohepatic recycling and have a plasma half-life of approximately 22 hours in humans. Ezetimibe, the glucuronide metabolite, or both are excreted in feces (90%) and urine (10%).

The efficacy and safety of ezetimibe in the nontransplant patient population with primary hypercholesterolemia has been established in large studies.[19] Ezetimibe has also been proven to provide complementary efficacy for the management of hypercholesterolemia by its addition to ongoing statin therapy[20] as well as its coadministration with a statin.[21] Recently, the results of the ENHANCE study were published, confirming the safety of the combination of ezetimibe and simvastatin in further lowering LDL cholesterol.[22] However, the combination was no more effective in reducing atherosclerosis than simvastatin by itself. This negative finding was felt to be related to the relatively short duration of the study.

All trials that have examined the effectiveness and safety in heart[23,24] and kidney[8,25,26] transplant patients have concluded that ezetimibe is well tolerated and effective for the treatment of dyslipidemia in solid-organ transplant recipients, especially those with statin intolerance or resistance.

Statins are considered effective and safe in OLT patients.[7] Despite package-insert warnings, statins are used in chronic liver disease patients[27] and liver transplant recipients,[7] but control is suboptimal because of perceived adverse effects, especially by primary care providers. This retrospective study reflects local experience with the use of ezetimibe in a limited number of stable OLT recipients. Ezetimibe was shown to be effective in lowering LDL cholesterol, causing neither graft dysfunction nor significant alterations in the biochemical profiles of these subjects. There were also no adjustments required in the dosage of immunosuppression drugs because no significant variations were seen in cyclosporine 2-hour peak or tacrolimus trough levels. No serious adverse events were documented in the first 6 months of therapy with ezetimibe in these recipients. Although there have been rare case reports of jaundice, these occurred in subjects receiving ezetimibe together with multiple potentially hepatotoxic drugs.[28-31] In our case, we could not attribute to the drug the transient cholestatic hepatitis with jaundice in our patient 6 months after ezetimibe was started.

There were several limitations due to the retrospective nature of this observational study, relatively small number of subjects, and short period of therapy. However, our findings are important as they provide evidence that the use of ezetimibe helps this patient population reach its lipid goal with minimal adverse events. The results observed in our population may provide a safety net for physicians to consider ezetimibe either as monotherapy or in combination with a statin for the management of hyperlipidemia in OLT recipients. More importantly, this study provides support for future larger and long-term investigations of the role of ezetimibe, with or without statins, in the control of hyperlipidemia and reduction of cardiovascular risk in OLT recipients.

REFERENCES

1. Imagawa DK, Dawson S, Holt CD, Kirk PS, Kaldas FM, Shackleton CR, et al. Hyperlipidemia after liver transplantation: natural history and treatment with the hydroxymethylglutaryl-coenzyme A reductase inhibitor pravastatin. Transplantation 1996;62:934-942.
2. Munoz SJ. Hyperlipidemia and other coronary risk factors after orthotopic liver transplantation: pathogenesis, diagnosis and management. Liver Transpl Surg 1995;1(suppl 1):29-38.
3. Laryea M, Watt KD, Molinari M, Walsh MJ, McAlister VC, Marotta PJ, et al. Metabolic syndrome in liver transplant recipients: prevalence and association with major vascular events. Liver Transpl 2007;13:1109-1114.
4. Mells G, Neuberger J. Reducing the risks of cardiovascular disease in liver allograft recipients. Transplantation 2007; 83:1141-1150.
5. Taylor PJ, Kubler PA, Lynch SV, Allen J, Butler M, Pillans PI. Effect of atorvastatin on cyclosporine pharmacokinetics in liver transplant recipients. Ann Pharmacother 2004; 38:205-208.
6. Jacobson TA, Armani A, McKenney JM, Guyton JR. Safety considerations with gastrointestinally active lipid-lowering drugs. Am J Cardiol 2007;99:47C–55C.
7. Gazi IF, Liberopoulos EN, Athyros VG, Elisaf M, Mikhailidis DP. Statins and solid organ transplantation. Curr Pharm Des 2006;12:4771-4783.
8. Puthenparumpil JJ, Keough-Ryan T, Kiberd M, Lawen J, Kiberd BA. Treatment of hypercholesterolemia with ezetimibe in the kidney transplant population. Transplant Proc 2005;37:1033-1035.
9. Fodor JG, Frohlich JJ, Genest JJG Jr, McPherson PR. Recommendations for the management and treatment of dyslipidemia. Report of the Working Group on Hypercholesterolemia and Other Dyslipidemias. Can Med Assoc J 2000;162:1441-1447.
10. Roy A, Kneteman N, Lilly L, Marotta P, Peltekian K, Scudamore C, Tchervenkov J. Tacrolimus as intervention in the treatment of hyperlipidemia after liver transplant. Transplantation 2006;82:494-500.
11. Bergman AJ, Burke J, Larson P, Johnson-Levonas AO, Reyderman L, Statkevich P, et al. Interaction of single-dose ezetimibe and steady-state cyclosporine in renal transplant patients. J Clin Pharmacol 2006;46:328-336.
12. Mirabell R, Coucke P, Behrouz F, Blazek N, Mellinger M, Philipp S, et al. Nausea and vomiting in fractionated radiotherapy: a prospective on-demand trail of tropisetron rescue for non-responders to metoclopramide. Eur J Cancer 1995;31:1461-1464
13. Kobashigawa JA, Kasiske BL. Hyperlipidemia in solid organ transplantation. Transplantation 1997;63:331-338.
14. Miller LW. Allograft vascular disease: a disease not limited to hearts. J Heart Lung Transplant 1992;11(pt 2):S32–S37.
15. Munoz SJ, Doems RO, Moritz MJ, Martin P, Jarrell BE, Maddrey WC. Hyperlipidemia and obesity after orthotopic liver transplantation. Transplant Proc 1991;23:1480-1483.
16. Gisbert C, Prieto M, Berenguer M, Breto M, Carrasio D, deJuan M, et al. Hyperlipidemia in liver transplant recipients: prevalence and risk factors. Liver Transpl Surg 1997;3: 416-422.
17. Harry DS, McIntyre N. Plasma lipids and lipoproteins. In: Bircher J, Benhamou J-P, McIntyre N, Rizetto M, Rodes J, eds. Oxford Textbook of Clinical Hepatology. 2nd ed. Oxford, England: Oxford University Press; 1999:287-302.
18. Kosoglou T, Statkevich P, Johnson-Levonas OA, Paolini JF, Bergman AJ, Alton KB. Ezetimibe: a review of its metabolism, pharmacokinetics and drug interactions. Clin Pharmacokinet 2005;44:467-494.
19. Dujovne CA, Ettinger MP, McNeer JF, Lipka LJ, LeBeaut AP, Suresh R, et al. Efficacy and safety of a potent new selective cholesterol absorption inhibitor, ezetimibe, in patients with primary hypercholesterolemia. Am J Cardiol 2002;90:1092-1097.
20. Pearson TA, Denke MA, McBride PE, Battisti WP, Brady WE, Palmisano J. A community-based, randomized trial of ezetimibe added to statin therapy to attain NCEP ATP goals for LDL cholesterol in hypercholesterolemic patients: the ezetimibe add-on to statin for effectiveness (EASE) trial. Mayo Clin Proc 2005;80:587-595.
21. Melani L, Mills R, Hassman D, Lipetz R, Lipka L, LeBeaut A, et al. Efficacy and safety of ezetimibe coadministered with pravastatin in patients with primary hypercholesterolemia: a prospective, randomized, double-blind trial. Eur Heart J 2003;24:717-728.
22. Kastelein JJ, Akdim F, Stroes ES, Zwinderman AH, Bots ML, Stalenhoef AF, et al. Simvastatin with or without ezetimibe in familial hypercholesterolemia. N Engl J Med 2008;358:1431-1443.
23. Patel AR, Ambrose MS, Duffy GA, Cote H, DeNofrio D. Treatment of hypercholesterolemia with ezetimibe in cardiac transplant recipients. J Heart Lung Transplant 2007; 26:281-284.
24. Quarta CC, Potena L, Grigioni F, Scalone A, Magnani G, Coccolo F, et al. Safety and efficacy of ezetimibe with low doses of simvastatin in heart transplant recipients. J Heart Lung Transplant 2008;27:685-688.
25. Buchanan C, Smith L, Corbett J, Nelson E, Shihab F. A retrospective analysis of ezetimibe treatment in renal transplant recipients. Am J Transplant 2006;6:770-774.
26. Türk TR, Voropaeva E, Kohnle M, Nürnberger J, Philipp T, Kribben A, et al. Ezetimibe treatment in hypercholesterolemic kidney transplant patients is safe and effective and reduces the decline of renal allograft function: a pilot study. Nephrol Dial Transplant 2008;23:369-373.
27. Russo MW, Jacobson IM. How to use statins in patients with chronic liver disease. Clev Clin J 2004;71:58-62.
28. Stolk MF, Becx MC, Kuypers KC, Seldenrijk CA. Severe hepatic side effects of ezetimibe. Clin Gastroenterol Hepatol 2006;4:908-911.
29. Ritchie SR, Orr DW, Black PN. Severe jaundice following treatment with ezetimibe. Eur J Gastroenterol Hepatol 2008;20:572-573.
30. Tuteja S, Pyrsopoulos NT, Wolowich WR, Khanmoradi K, Levi DM, Selvaggi G, et al. Simvastatin-ezetimibe-induced hepatic failure necessitating liver transplantation. Pharmacotherapy 2008;28:1188-1193.
31. Castellote J, Ariza J, Rota R, Girbau A, Xiol X. Serious drug-induced liver disease secondary to ezetimibe. World J Gastroenterol 2008;14:5098-5099.