Marked Elevation of Liver Transaminases after High-dose Fluvastatin Unmasks Chronic Hepatitis C: Safety and Re-challenge

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Abstract- The statins, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase inhibitors, have emerged as the drugs of choice for patients with dyslipidemia and have been shown to reduce major cardiovascular adverse events in large-scale clinical trials for both primary and secondary prevention. Statins are generally safe; however, the results of clinical trials do demonstrate possibilities of significant adverse effects in liver and muscle. Moreover, the numbers from the trials may not reflect the real situation in daily practice because individuals at increased risk for hepatotoxicity are usually deliberately and carefully excluded in clinical trials. We presented an 85-year-old woman who had a marked elevation of ALT (up to 409 U/L) after treatment with fluvastatin 80 mg/day for 6 weeks. Hepatitis C was identified after this episode. The elevation of ALT resolved 10 weeks after discontinuation of fluvastatin. Re-institution of fluvastatin from 40 to 80 mg/day for 2 months only cause mild elevation of ALT. This case suggests that elevation of transaminases during statin therapy may not be solely ascribed to statins. Re-challenge with the same statin at lower doses or with other statins may help to identify the patients who can still be treated with drugs of this category.

Key Words: Hyperlipidemia, Hepatitis C, Statin, Safety

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INTRODUCTION

Statins are widely prescribed for the effectiveness in reducing risks of atherosclerotic vascular diseases in patients with dyslipidemia, and thus their safety is of great concern. The reported percentage of alanine aminotransferase (ALT) elevation of greater than 3 times the upper limit of normal (ULN) was around 0.1

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to 2.7% following statin treatment[1,2]. In contrast to the well-controlled situations in clinical trials, the general use of statins in clinical practice may be complicated by the interactions with concomitant medications and co-morbidities of the patients. The prevalence of viral hepatitis B and C is higher in Taiwan than in western countries[3-5], and carriers of the hepatitis viruses may necessitate more careful monitoring while receiving statins. This case report demonstrated a patient developed marked elevation of liver transaminases following high-dose fluvastatin therapy. Further investigation showed coexisting chronic hepatitis C, which may be associated with the elevation of liver enzymes. We further demonstrated the feasibility and safety of re-institution of the same statin from a lower dose.

CASE REPORT

This 85 year-old woman came to the out-patient clinic of Department of Neurology, Li-Shin Hospital in November, 2003, because of acute onset of vertigo. The physical and neurological examination revealed unremarkable results. Her fasting blood sugar was 184 mg/dL, total cholesterol (T-CHO) 271 mg/dL, triglyceride (TG) 291 mg/dL. The carotid and vertebral color-coded duplex sonography showed mild carotid atherosclerosis, but segmental stenosis of basilar artery was implicated in the transcranial color-coded sonography. Atorvastatin 10 mg qd and glimepiride 1 mg qd were prescribed from December, 2003 to April, 2005. According to the medical record, there are neither data of serum transaminases, nor examination of the markers of viral hepatitis before the treatment. The follow-up data of serum transaminases during atorvastatin treatment were within normal limits (Fig. 1, e.g. the ALT level was 16 U/L in Sep, 2004). The total duration of atorvastatin treatment was 17 months. During that period, she had also taken clopidogrel 75 mg qd and irbesartan 150 mg qd because of episodic attacks of vertigo and hypertension.

She was admitted to Li-Shin Hospital on 13th September, 2005 due to severe episodic vertigo and unsteady gait. The magnetic resonance image (MRI) of brain revealed segmental stenosis of the basilar artery. A clinical diagnosis of basilar artery stenosis with vertebro-basilar insufficiency was made based on her symptoms, neuroimaging and ultrasonographic findings. Abdominal ultrasonography showed fatty liver, and panendoscopy demonstrated multiple gastric ulcers with *Helicobacter pylori* infection. Fluvastatin 80 mg (extended release) qd was prescribed because of elevated T-CHO level of 221 mg/dL after confirmation of a normal ALT level (14 U/L). Esomeprazole 40 mg qd was also prescribed for eradication of *Helicobacter pylori*. On 19th October 2005, an elevated ALT level of 409 U/L was noted. Because that is more than 10 times ULN (36 U/L) in Li-Shin Hospital, fluvastatin was discontinued immediately, 6 weeks after it was first prescribed. In

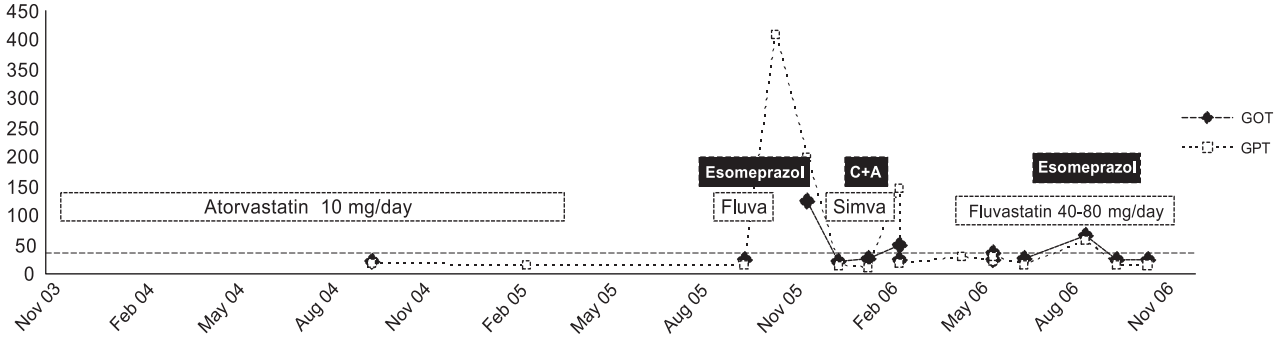

Figure 1. Correlation between the level of liver transaminases and different periods of statin treatment in the reported case. AST: Aspartate transaminases; ALT: Alanine aminotransferase; Fluva: Fluvastatin 80 mg/day; Simva: Simvastatin 10 mg/day; C+A: Clarithromycin and amoxicillin

the meanwhile, work-up of the markers of viral hepatitis revealed the following results: anti-hepatitis C virus (HCV) antibody (+), anti-hepatitis B surface antigen antibody (+), anti-hepatitis B surface core antibody (+), hepatitis B surface antigen (-). The ALT level returned to normal on 28th December 2005, 10 weeks after discontinuation of fluvastatin. Simvastatin 10 mg qd was then added back to her regimen. The concomitant medication included amoxicillin 1000 mg bid and clarithromycin 500 mg bid for one week to eradicate the *Helicobacter pylori* infection. However, simvastatin was also discontinued six weeks later, when the laboratory data showed elevated levels of ALT (144 U/L) and AST (48 U/L). The ALT and AST levels returned to the normal range 2 weeks after discontinuation of simvastatin.

Fluvastatin was reinstituted on 10th May 2006 with a starting dose of 40 mg per day (Atorvastatin was not considered because it could not reach the goal). The dose was increased to 80 mg 6 weeks later when the ALT level remained within normal limits. Only mild fluctuation of ALT levels (up to 65 U/L) was noted for the following 4 months of fluvastatin therapy.

DISCUSSION

We reported a case having very different response to three different statins in terms of serum levels of transaminases. This may be partly ascribable to the fact that the incidence of abnormal ALT elevation following treatment of statins is dose-related[6]. The incidence of such elevation with 10 mg atorvastatin qd is 0.2%, the same as that with 20 mg fluvastatin qd, but it increases to 2.7% with fluvastatin 80 mg qd[7]. On the other hand, this 85 year-old woman had chronic hepatitis C, which had never been known before the lipid-lowering treatment. Moreover, drug-drug interactions between clarithromycin and simvastatin may also contribute to the elevated serum transaminase levels. Being a potent inhibitor of cytochrome P450 3A4, clarithromycin will increase the serum level of statins significantly and should be used cautiously with simvastatin[8].

It is conceivable that some patients with chronic viral hepatitis in the endemic areas may need lipid-lowering drugs for prevention of cardiovascular events. Although statins in general have a good safety profile, the safety of long-term treatment in this particular hepatitis virus-infected population remains to be clarified. The estimated rate of acute liver failure associated with statins is roughly 0.2 case in 1 million patient-year[9], but this figure may not reflect the real prevalence of adverse events in clinical practice. In the well-controlled trials many subjects with co-mobidities such as

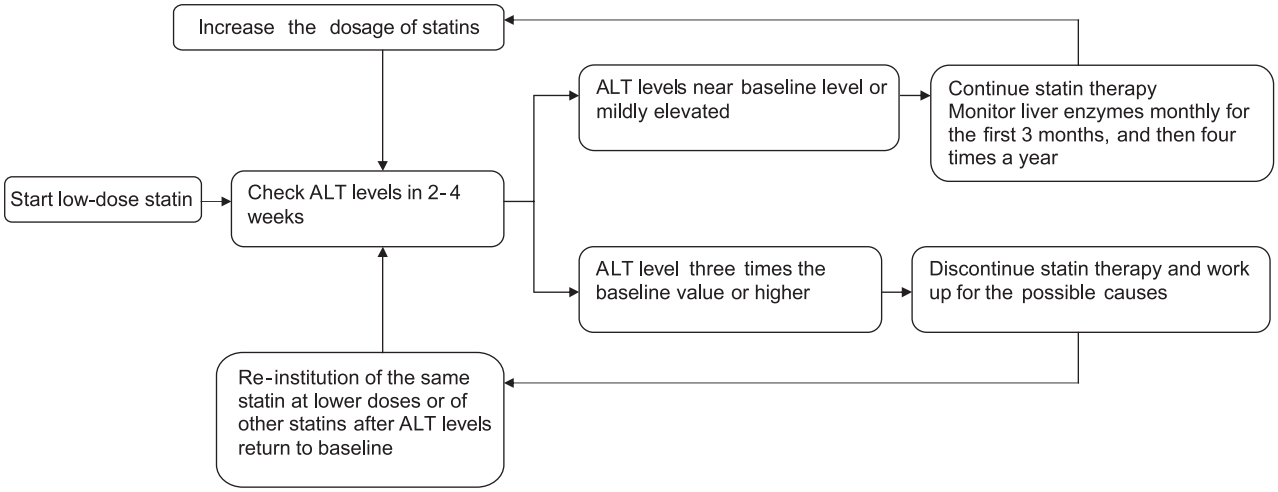

Figure 2. Proposed algorithm for statin use in patients with chronic liver disease and those at high risk for statin-related hepatic adverse events.

chronic viral hepatitis or abnormal liver functions are excluded[1,2]. Furthermore, interactions with other drugs are usually avoided as much as possible in the clinical trials. Some retrospective reviews of statin users in the primary care in the United States reported a percentage of 0.9-2.3% of elevated ALT more than 3 times ULN[10-12]. These prevalence rates are very close to those reported in the controlled trials[1,2]. However, it may not be so appropriate to apply the conclusions worldwidely, especially for the area where the people have higher percentages of chronic liver diseases or distinctive rates of metabolism of statins[13].

Subjects with chronic hepatitis should not be excluded from statin therapy, provided careful follow-up is exercised to recognize the onset of further liver damage in time[9]. Statins have not been shown to worsen the outcome in people with chronic transaminases elevations due to hepatitis B or C[14,15]. Gibson et al. reported the largest liver enzyme level elevation was 1.5 times ULN in a population of 219 patients with HCV infection and concluded that statins are not associated with significant liver enzyme elevations in patients with HCV infection[16]. Apparently, the conclusion of Gibson et al. could not be applied to the case reported here.

How could we prescribe statins safely in the areas where viral hepatitis is endemic, such as in Taiwan? The prevalence rate of positive hepatitis B surface antigen is 15-20%[3] and the seroprevalence of HCV infection is estimated to be 2-3% in urban areas and 20-60% in rural areas in Taiwan[4,5]. Our case supports the idea that ALT elevation may unmask the underlying chronic liver diseases[7]. The physicians in endemic areas of viral hepatitis should be cautious in the administration of statins. Starting from low dose and frequent monitoring of liver function in the beginning are warranted[14].

Another important issue is to avoid deleterious drug-drug interactions, which may account for as high as 81% (13/16) of the patients with abnormal ALT following statin treatment in the report of Charles et al.[12]. After elimination of the possible interacting drugs, it was reported that re-challenge with statins was associated with recurrence of ALT elevation in only 2/10 patients[12]. The elevated ALT after use of simvastatin in this case report may also be partly related to the concomitant use of clarithromycin.

Meticulous monitoring is mendatory for those at increased risk of statin-related adverse events, including elderly patients[17] and the patients on concomitant medications or with co-morbidities such as chronic viral hepatitis[7,12]. FDA in the United States now recommends that liver function tests to be performed before prescription of statins and during statin therapy (generally at 6- to 12-week intervals following the initiation of the therapy, depending on the specific agents used), and on elevation of the dosage. Similar suggestions are also noted in the basic product information of statins in Taiwan.

Based on the reported case and the experts' recommendation[14], we propose an algorithm for prescription of statins in patients with chronic viral hepatitis (Fig. 2). Detailed history taking about the liver conditions and pertinent tests are important before prescription. For patients at high risk, starting statins at low doses as well as frequent examinations of ALT levels (i.e. 2 weeks after initiation, then monthly for first 3 months and four times a year) is recommended. Once elevation of ALT more than three times ULN is noted, the statin should be discontinued and further investigation for the cause of such elevation is recommended. Trials of the same statins of lower doses or of another statin could be considered once ALT level returns to baseline.

In conclusion, we suggest the physicians in endemic areas of chronic viral hepatitis to start treatment with statins at lower doses than usual recommendations and to avoid possible drug-drug interactions. Elderly patients with co-morbid conditions and complicated medications, are especially at high risk for statin-related adverse events. It is prudent to follow the aforementioned suggestions strictly to avoid such events. If necessary, re-institution of the same statin from lower doses or of another statin could be considered once ALT level returns to baseline.

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