Rosuvastatin-Induced Thrombocytopenic Purpura
-A Case Report
Zheng-Wei Lin 1 Hsin-Chun Ho 1 Chih-Hsun Yang 2 Rosaline Chung-Yee Hui 2 Wen-Hung Chung 1

Many medications can cause thrombocytopenic purpura, including some hypolipidemic agents. This is the first case report of thrombocytopenic purpura due to the 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, rosvastatin. A 57-year-old Asian man developed multiple petechiae and purpura one month after receiving rosvastatin in a dosage of 20 mg/day. When the drug was stopped and the patient was treated with systemic methylprednisolone, 24 mg/day, his symptoms cleared within 4 weeks. The symptoms may have been due to an immune-mediated reaction. Also, since statins can alter antiplatelet and antithrombotic properties through significant inhibition of the activated platelet thrombin receptor (Proteinase-Activated Receptor-1), an overwhelming inhibition of platelet thrombin receptors might also have caused the thrombocytopenia. Because rosvastatin is used throughout the world to treat hyperlipidemia, and Asian patients have a twofold higher systemic exposure than do Caucasian patients, physicians should be familiar with its possible adverse effects, and use with caution when determining the starting dose, especially among Asian patients. (Dermatol Sinica 27: 235-240, 2009)

Key words: Rosuvastatin, Idiopathic thrombocytopenic purpura, Thrombotic thrombocytopenic purpura, Low-density lipoprotein, High-density lipoprotein

INTRODUCTION

Drug-induced thrombocytopenia is a serious side effect that can be caused by dozens of different medications, and that should be kept in mind when any patient presents with acute unexplained thrombocytopenia. 1 Rosuvastatin, a 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitor, is approved for the treatment of hyperlipidemia and is generally well tolerated. Although drug-induced purpura is a potential adverse effect of this agent, few reports have been published. 2 In this article, we describe a case of rosvastatin-induced thrombocytopenia, and review previous reports of statins-induced thrombocytopenia. We also discuss mechanisms that can lead to statins-induced thrombocytopenia.
A 57-year-old Taiwanese man came to our department on November 8, 2007 after developing multiple petechiae and purpura. He had no previous history of bleeding diathesis or associated thrombocytopenia. He was hypertensive and had been treated with losartan for more than one year. One month before his symptoms occurred, the patient’s family physician prescribed rosvastatin, 20 mg/day, after a general annual health examination revealed the patient had hypercholesterolemia. The patient’s complete blood count and platelet count were normal before he began treatment with rosvastatin. Nineteen days after he began taking rosvastatin, the patient developed generalized petechiae.

Physical examination showed widespread petechiae and several ecchymotic patches on his trunk and proximal limbs (Fig. 1A). No fever or lymphadenopathy was found. A complete blood cell count revealed a hemoglobin level of 14.4 g/dL (normal: 13.5-17.5 g/dL); a white blood cell count of 7.5 x 10^3/µL (normal: 3.9-10.6 x 10^3/µL) with hypereosinophilia (43%), and a decreased platelet count (105 x 10^9/L) (normal: 150-400 x 10^9/L). Coagulation values were normal (prothrombin time, 10.8 seconds [normal: < 11.2 seconds]; activated partial thromboplastin time, 22.8 seconds [normal: < 27.5 seconds]). The results of other laboratory studies were normal, including renal and liver function tests. Autoimmune serologic results were also normal (ANA negative). Other laboratory results included the following: profile of disseminated intravascular coagulation (fibrinogen, 267 mg/dL [normal: 190-380 mg/dL]; D-dimer, 174.85 ng/mL FEU [normal: < 500]; fibrin degradation product, < 10 µg/mL [normal: < 10 µg/mL]), profile of hemolysis (LDH 187 U/L [normal: 125-215 U/L]; reticulocytes, 1% [normal: 0.6%-1.9%]; haptoglobin, 178 mg/dL [normal: 45-243 mg/dL]; and total bilirubin, 0.5 mg/dL [normal: 0.1-1.3 mg/dL]). The results of these tests and the results of a direct Coombs’ test were all within normal ranges. There was also no serologic evidence of recent viral infections (negative results for cytomegalovirus,
Epstein-Barr virus, and viral hepatitis B and C). Urinalysis revealed no abnormalities. A peripheral blood smear showed no platelet clumping and no schistocytes.

Histopathologically, diffuse red blood cells extravasations were noted in the upper dermis (Fig. 1B). Rosuvastatin-induced thrombocytopenic purpura was diagnosed. The drug was discontinued and he was treated with oral methylprednisolone 24 mg divided into three times per day. Seven days after systemic methylprednisolone treatment was begun, the patient’s platelet count returned to 325 $\times$ 10$^9$/L, and the petechiae and purpuric lesions also disappeared rapidly. Systemic methylprednisolone was gradually tapered over the next 4 weeks, and the skin lesions and thrombocytopenia disappeared. Three months later, he remains symptom-free with a normal complete blood cell count. He was instructed to avoid rosuvastatin or other 3-hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors and his hypercholesterolemia was treated with fenofibrate.

DISCUSSION

This is a case report in the literature of thrombocytopenia associated with the use of rosuvastatin, and it reinforces the fact that statins may cause thrombocytopenia.

The diagnosis of drug-induced thrombocytopenia is often empiric and can be supported by prompt recovery of the platelet count when the suspected drug is withdrawn.\(^3\) Since laboratory tests for confirming drug-induced thrombocytopenia have not yet been established, other criteria are needed to make the diagnosis. George et al. proposed criteria for establishing a causative relationship in patients with drug-induced thrombocytopenic purpura.\(^1\) In our patient, therapy with rosuvastatin preceded thrombocytopenia, and recovery from thrombocytopenia was complete and sustained after the drug was discontinued. Other drugs were continued or reintroduced after discontinuation of therapy with rosuvastatin, and the patient’s platelet count remained normal; hence, we could exclude other causative agents of thrombocytopenia.

Several large clinical trials have demonstrated the beneficial effects of rosuvastatin in the primary and secondary prevention of coronary heart disease. However, the overall clinical benefits observed with statin therapy appear to be greater than what might be expected from changes in lipid profile alone. In fact, recent experimental and clinical evidence indicates that some of the cholesterol-independent effects of statins involve improving or restoring endothelial function, enhancing the stability of atherosclerotic plaques, and decreasing vascular inflammation.\(^4\)

Rosuvastatin has been shown to be highly effective for reducing low-density lipoprotein cholesterol levels, increasing high-density lipoprotein HDL cholesterol levels, and producing favorable modifications of other elements of the atherogenic lipid profile in a wide range of dyslipidemic patients.\(^2\) In patients with mild to moderate hypercholesterolemia, rosuvastatin has been shown to produce large decreases in LDL-C at starting doses, thus reducing the need for subsequent dose titration, and to allow greater percentages of patients to attain lipid goals, compared with available statins.\(^3\) Although rosuvastatin has a favorable risk-benefit profile, significant adverse reactions can include headache, constipation, anemia, dyspepsia, and myalgia.\(^2\)

Systemic exposure to rosuvastatin had been observed to be approximately twofold higher in Asian populations compared with Caucasian populations. The approximately twofold greater plasma exposure to rosuvastatin observed in Asian subjects did not appear to be the result of body weight or environmental factors. The mechanisms for this effect are not fully elucidated.\(^2\)
transporting polypeptides (OATPs) have also been shown to play a role in the uptake of statins in the liver. Genetic polymorphisms in the OATP1B1 gene was found to be associated with total and nonrenal clearance of pravastatin.\textsuperscript{7} SLC01B1 (the gene for OATP1B1) genotypes did not account for the observed pharmacokinetic differences between Asian and Caucasian subjects. The investigators raised the possibility that other genetic predisposition or environmental factors could account for the increased plasma exposure.\textsuperscript{6} As a result, the U.S. Food and Drug Administration has requested that the drug’s label be changed so that the starting dose is reduced to 5 mg for Asian patients. A higher starting dose, 20 mg per day, may have led to the development of thrombocytopenia in our patient.

There have been several reports of statins-induced thrombocytopenia.\textsuperscript{8-11} Most were reported with the use of simvastatin or atorvastatin. They were all Caucasians. In these reports, the onset of diffuse purpura ranged from 1 day to 11 months, and most clinical manifestations included diffuse petechiae, purpura or ecchymosis. A decrease in platelet count ranged from 3 to $10^5 \times 10^9/L$. Most cases were managed with transfusion of platelets and fresh-frozen plasma, doses of intravenous immune globulin, high doses of glucocorticoids, and plasma exchange. Recovery took from 5 days to 1 month.

The pathomechanism of statins-induced thrombocytopenia is unclear, but may involve accelerated immune-mediated platelet destruction or an idiosyncratic reaction. Our patient had hypereosinophilia (43%), and responded well to glucocorticoids, just as other patients have. This suggests that an immune-mediated reaction may play an important role. Additionally, statins have been shown to inhibit platelet structure, function, and aggregation.\textsuperscript{4} Potential mechanisms include a reduction in the production of thrombox-

ane A2 and modifications in the cholesterol content of platelet membranes.\textsuperscript{12} The cholesterol content of platelet and erythrocyte membranes is reduced in patients undergoing statin therapy. This may lead to a decrease in the thrombogenic potential of these cells. Indeed, in vitro experiments have demonstrated that statins possess antiplatelet and antithrombotic properties through significant inhibition of the activated platelet thrombin receptor (Proteinase-Activated Receptor-1).\textsuperscript{13} Therefore, overwhelming inhibition of platelet thrombin receptors should be also considered as a cause for the thrombocytopenia.

In patients with drug-induced thrombocytopenia, the most important step is removal of the offending agent(s). However, platelet transfusions are strongly indicated for those with symptomatic thrombocytopenia with platelet counts less than $20,000/mm^3$, or with bleeding.\textsuperscript{3} For patients with life-threatening bleeding, the optimal treatment strategies are comparable to those for treatment of patients with idiopathic thrombocytopenia purpura or thrombotic thrombocytopenic purpura, and should include intravenous immunoglobulin, high doses of glucocorticoids, and plasma exchange. And, finally, because rosuvastatin is used throughout the world to treat hyperlipidemia, physicians should be familiar with its possible adverse effects, and be cautious with the starting dose, especially among Asian patients.

REFERENCES


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Rosuvastatin-Induced Thrombocytopenic Purpura

Rosuvastatin誘發血小板減少性紫斑症
-病例報告

林政緯1 何信君1 楊志勛2 許仲瑤1 鍾文宏1
基隆長庚醫院皮膚科1 台北長庚醫院皮膚科2

引起血小板減少性紫斑症的藥物種類繁多，其中包括了降血脂藥。Rosuvastatin 為一透過抑制3-hydroxy-3-methylglutaryl-CoA還原的降血脂藥，過去並無文獻報告Rosuvastatin引起血小板減少性紫斑症，在此我們提出第一個病例報告。本文報告一位57歲男性，每日服用20毫克Rosuvastatin的一個月後，身上出現廣泛性的瘀點與紫斑。當病人停掉此藥且使用為期4週的口服類固醇methylprednisolone後，紫斑完全消失。此紫斑可能由免疫反應所引起。此外，因為statin類的降血脂藥物可以經由抑制活化的血小板血栓PAR-1受體，而具備抗血小板與抗血栓的特性，所以我們推測Rosuvastatin可能透過大量抑制血小板血栓受體而產生血小板減少性紫斑症。目前Rosuvastatin廣泛地被用來治療高血脂症，而藥物動力學研究結果發現與白種人相較，亞洲人Rosuvastatin的血中濃度為其2倍，因此臨床醫師應特別注意亞洲人的起始劑量且需熟悉藥物的副作用。（中華皮誌：27: 235-240, 2009）