Atorvastatin-Induced Refractory Thrombocytopenia

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Abstract

Drug-induced thrombocytopenia is rarely associated with statin medications. We describe the case of a 69-year-old woman who developed refractory thrombocytopenia following atorvastatin use. To our knowledge, this is the fourth reported case of atorvastatin-induced thrombocytopenia and the first reported case of atorvastatin-induced refractory thrombocytopenia. Additionally, we summarize the cases of statin-induced thrombocytopenia reported in the medical literature.

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Keywords: thrombocytopenia, refractory, atorvastatin, platelet, hyperlipidemia, petechiae, drug-induced thrombocytopenia, statin-induced, drug reaction, purpura

Introduction

Atorvastatin is used to treat dyslipidemia and the prevention of cardiovascular and cerebrovascular diseases, particularly in people who are unable to meet their lipid-lowering goals through lifestyle modifications [1-3]. It inhibits 3-hydroxy-3-methyl-glutaryl-coenzyme A reductase, a key enzyme in cholesterol synthesis. The most common adverse effects of statins are dyspepsia, constipation, abdominal pain, flatulence, headache, and myalgia [4]. Myopathy, rhabdomyolysis, and liver enzyme abnormalities are rare, but major side effects seen with statin use [5,6]. A few case reports of statin-induced thrombocytopenia, specifically with atorvastatin, rosuvastatin, and simvastatin [7-15].

Thrombocytopenia can be either inherited or acquired. Acquired causes include drug-induced thrombocytopenia (DIT), viral or bacterial infections, malignancy, liver failure, and hypersplenism. Several mechanisms are proposed for DIT, but the most recent hypothesis suggests that weakly reactive platelet autoantibodies develop an increased affinity for platelet glycoprotein epitopes in the presence of the sensitizing drug [16]. Patients present with epistaxis, bruising, and petechiae [16]. In this case report, we present a probable temporal relationship between atorvastatin initiation and the onset of refractory thrombocytopenia.

Case Presentation

A 69-year-old female with a history of hyperlipidemia presented to the hospital with atraumatic bruising, traumatic right knee hematoma, and multiple painless “blood blisters” on her buccal mucosa which she noticed one day prior. Her history was negative for bleeding disorders, anticoagulant use, and antiplatelet use. She started taking atorvastatin 20 mg daily about 10 weeks before presenting for hyperlipidemia. The patient’s baseline low-density lipoprotein was between 125 and 146 mg/dL (reference range: < 100 mg/dL) and high-density lipoprotein was between 66 and 72 mg/dL (reference range: > 40 mg/dL). The patient was found to have profound thrombocytopenia on this admission with a platelet count of 2,000/μL, and she was discharged home with close follow-up. She continued taking atorvastatin 20mg.

Two days after discharge, the patient returned to the hospital, presenting with worsening fatigue and purpura. She was found to have a platelet count of 1,000/μL and was readmitted. We discontinued her atorvastatin and started her on a regimen of IVIG for two days and prednisone 80mg for five days. Although
she responded to this regimen, we added rituximab given our high suspicion for refractory thrombocytopenia, indicated by the lack of response to two or more treatments. Our patient’s platelet count improved to 118,000/μL, and she was discharged home in stable condition with instructions to complete seven days of 60 mg of prednisone and weekly doses of rituximab. The patient was not restarted on atorvastatin or any other statin. At follow-up five months after her hospital discharge and after completing four doses of rituximab, our patient’s platelet count returned to baseline, and her purpura had resolved. A timeline of the variations in our patient’s platelet count is illustrated in Figure 1. She currently manages her hyperlipidemia with diet and exercise.

![Timeline of the Variations in Platelet Count in Relation to Exposure and Interventions](image)

**FIGURE 1: Temporal variations in platelet count after initiation of atorvastatin and response to interventions.**

IVIG- Intravenous immunoglobulin

**Discussion**

DIT presents with rapid symptomatic improvement following the discontinuation of the drug [16]. DIT has been associated with over 100 different medications [16]. Two major pathologic mechanisms behind drug-induced thrombocytopenia include decreased platelet production via marrow suppression and peripheral platelet clearance [10]. Patients are exposed to the implicated medication for at least a week before developing clinical signs of thrombocytopenia [16]. DIT is suggested by rapid recovery following discontinuation of the implicated medication and the temporal relationship between symptom onset and medication exposure [7]. It is common practice to discontinue the medication and treat with steroid, and IVIG and plasma exchange may be considered for refractory cases [16]. Our patient’s case was considered to be refractory given that she failed two or more treatments (steroids and IVIG), and the hematology-oncology consultant on the case agreed with this determination. We recognize that ITP may present similarly and that the resolution of our patient’s thrombocytopenia may be attributed to rituximab initiation, rather than atorvastatin discontinuation alone [17].

The Naranjo Algorithm is a validated standardized questionnaire of 10 question items designed to estimate the probability of a drug causing an adverse clinical event. Scores greater than 8 are considered a definite reaction, 5 to 8 considered probable, 1 to 4 considered possible, and less than 1 considered doubtful [18,19]. Our patient’s Naranjo algorithm score of 8 (Table 1) suggests a probable association between initiation of atorvastatin and the onset of thrombocytopenia in this case.
TABLE 1: The Naranjo Scale for assessing the association between atorvastatin use and the adverse drug reaction (ADR) of thrombocytopenia. Our patient had a probable ADR given a score of “8”. The reaction followed a reasonable temporal sequence after a drug, followed a recognized response to the suspected drug, was confirmed by withdrawal but not by exposure to the drug, and could not be reasonably explained by the known characteristics of the patient's clinical state [16].

| Naranjo Question Item                                                                 | Response | Score |
|-------------------------------------------------------------------------------------|----------|-------|
| 1. Are there previous conclusive reports on this reaction?                           | Yes      | 1     |
| 2. Did the adverse event appear after the suspected drug was given?                  | Yes      | 2     |
| 3. Did the adverse reaction improve when the drug was discontinued, or a specific antagonist was given? | Yes      | 1     |
| 4. Did the adverse reaction appear when the drug was re-administered?               | Yes      | 2     |
| 5. Are there alternative causes that could have caused the reaction?                | No       | 2     |
| 6. Did the reaction reappear when a placebo was given?                              | N/A      | 0     |
| 7. Was the drug detected in any body fluid in toxic concentrations?                 | N/A      | 0     |
| 8. Was the reaction more severe when the dose was increased, or less severe when the dose was decreased? | N/A      | 0     |
| 9. Did the patient have a similar reaction to the same or similar drugs in any previous exposure? | N/A      | 0     |
| 10. Was the adverse event confirmed by any objective evidence?                      | No       | 0     |
| Score                                                                               |          | 8     |

Lovastatin has been found to dose-dependently induce platelet apoptosis via mitochondrial caspase activation. In mouse models, lovastatin impairs platelet function and reduces circulating platelets in vivo, suggesting the possible pathogenesis of thrombocytopenia and hemorrhage in patients treated with statins [20]. Given these findings, it is interesting that lovastatin-induced thrombocytopenia has not yet been reported in the literature.

The reported cases of statin-induced thrombocytopenia are summarized in Table 2. It is difficult to draw conclusions from a small set of case reports; however, statin-induced thrombocytopenia has been associated with atorvastatin, rosuvastatin, and simvastatin in the literature, two of which are lipophilic molecules. Additionally, the lipophilic statin lovastatin has been demonstrated to cause platelet apoptosis in vivo. Atorvastatin-induced thrombocytopenia has been reported three times in the literature, however, our case reports a refractory presentation [9].
### TABLE 2: Table summarizing reported cases of statin-induced thrombocytopenia in the literature.

| Case | Drug     | Dose | Age / Gender | Length of statin treatment | Clinical Symptoms                               | Lowest platelet count | Treatment regimen | Time to resolution | Alternative treatment | Tolerated another statin? |
|------|----------|------|--------------|-----------------------------|-------------------------------------------------|----------------------|------------------|-------------------|----------------------|--------------------------|
| Present case | Atorvastatin | 10mg | 69/F         | 6 months                    | Diffuse petechial rash, purpura, oral mucosal bleeding, traumatic knee hematoma | 1,000                | Platelet transfusion, steroids, rituximab | 3 months           | Lifestyle modification | Yes, simvastatin            |
| Mcnair et al (2006) | Atorvastatin | 10mg | 66/M         | 6 days                      | Diffuse petechial rash, gingival bleeding         | 15,000               | Platelet transfusion, steroids, rituximab | 13 days           | Lifestyle modification | No                        |
| Castoria et al (2005) | Simvastatin | 20mg | 78/F         | 1 day                       | Generalized urticaria (immediate hypersensitivity reaction) | 85,000               | Steroids          | 12 days           | Unspecified            | No                        |
| Narayanan et al (2006) | Atorvastatin | 20mg | 68/M         | 6 months                    | Diffuse petechial rash, gingival bleeding         | 4,000                | Steroids          | Unspecified        | Rosuvastatin            | Yes, simvastatin            |
| Viret et al (2007) | Rosuvastatin | Unspecified | 65/F | 1 year | None | 31,000 | None (statin discontinuation only) | 6 months | Unspecified | No/unknown |
| Arnes et al (2006) | Simvastatin | 10mg | 63/M         | 2 months                    | None                                             | 120,000              | None (statin discontinuation only) | 1 month | Unspecified | No/unknown |
| Goeckelberg et al (2007) | Simvastatin | 10mg | 77/F         | 11 months                   | Epistaxis, easy bruising                          | 12,000               | None (statin discontinuation only) | 3 weeks | Unspecified | No/unknown |
| González-Ponte et al (2006) | Atorvastatin | 10mg | 46/M         | 2 months                    | Widespread purpura                               | 3,000                | Platelet transfusion, steroids, rituximab | 1 month | Unspecified | Yes, simvastatin |
| Yanada et al (2006) | Simvastatin | 5mg  | 75/F         | 2 years                     | Multiple purpura of extremities and trunk         | 2,000                | Platelet transfusion, steroids, rituximab | 2 months | Unspecified | No/unknown |
| Posandian et al (2007) | Simvastatin | 10mg | 64/F         | 1 year                      | Epistaxis, gingival bleeding, diffuse petechiae of trunk and limbs | 3,000                | Platelet transfusion, steroids, rituximab | 3 weeks | Lifestyle modification | No                        |

Conclusions

To our knowledge, this is the fourth reported case of atorvastatin-induced thrombocytopenia and the first reported case of atorvastatin-induced refractory thrombocytopenia. Clinicians need to be aware of this association and discontinue atorvastatin if thrombocytopenia develops. Future investigations into the relationship between statin medications and thrombocytopenia would prove useful to the medical literature.

Additional Information

Disclosures

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