

Statin-induced DRESS: Seldom Considered

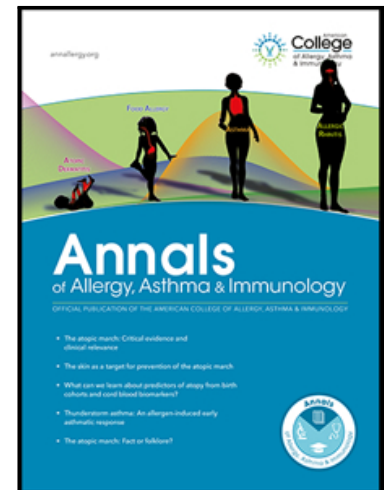
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PII: S1081-1206(21)01213-8
DOI: <https://doi.org/10.1016/j.anai.2021.10.027>
Reference: ANAI 3756

To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 20 September 2021
Revised date: 21 October 2021
Accepted date: 26 October 2021

Please cite this article as: Najeeb Khan MD , David Bernstein MD , Statin-induced DRESS: Seldom Considered, *Annals of Allergy, Asthma Immunology* (2021), doi: <https://doi.org/10.1016/j.anai.2021.10.027>



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Statin-induced DRESS: Seldom Considered

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Key words: Statin; induced; DRESS

Conflict of Interest disclosure statement: All authors have no conflicts to disclose.

Funding or financial support: No financial support needed

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Statin drugs are widely prescribed in clinical practice. Common side effects include elevated liver enzymes and muscle pain [1]. Although rare severe adverse reactions such as diffuse myositis and rhabdomyolysis occur [2], these risks are outweighed by the effectiveness of statin medications in preventing ischemic cardiovascular and cerebrovascular disease. Severe multisystemic hypersensitivity drug reactions to statins are uncommon [3,4]. Here we describe a recurrent life-threatening hypersensitivity drug reaction consistent with Drug Reaction with Eosinophilia and Systemic Symptoms syndrome (i.e., DRESS) manifested by skin rash, transaminitis, elevated muscle enzymes and acute interstitial nephritis following initiation of rosuvastatin which resolved following discontinuation. Causation was proven when inadvertent re-administration of rosuvastatin induced recurrence of all DRESS manifestations.

A 63-year-old Caucasian woman with Type 2 diabetes mellitus and hypertension presented with temperature of 38.9 C, heart rate of 104 bpm, eyelid edema and a diffuse maculopapular skin rash involving face, trunk and extremities. She had bilateral axillary lymphadenopathy. Five weeks

earlier, a 10-day course of clindamycin was initiated for right foot cellulitis and she was begun on 20 mg daily rosuvastatin for hyperlipidemia. Laboratory evaluation revealed WBC of 8,400/uL, Hgb of 13.2 g/dL, and elevated absolute eosinophil count of 1402 cells/uL. Creatinine was 5.2 mg/dL, ALT 444 U/L, AST 353 U/L and alkaline phosphatase 104 U/L (Figure1). Additional testing revealed a creatinine kinase of 8066 U/L, CRP of 4.6 mg/L and ESR of 38 mm/hr. Urinalysis was normal except for 5-6 white blood cells and 8-10 red blood cells per high power field without cellular casts; no urinary myoglobin.

The patient was admitted for management of acute hepatic and renal failure. Serology was negative for hepatitis A, B and C, HIV, EBV, HHV-6, HHV-8, CMV, HPV B-19, anti-smooth muscle and antimitochondrial antibodies, ANA, ANCA, anti-GB antibody, and ceruloplasmin. A hepatic duplex scan excluded portal vein thrombosis. There were no pulmonary infiltrates or pleural effusions on chest CT; bilateral axillary lymphadenopathy was noted. Abdominal ultrasound showed diffuse fatty infiltration of the liver and mildly enlarged kidneys. Transthoracic echocardiography was normal. A renal biopsy was performed revealing acute interstitial nephritis with eosinophilic and lymphocytic infiltration.

Clindamycin was suspected as the cause of DRESS and the drug discontinued. Rosuvastatin was withheld over concerns of transaminitis and elevated CK. After prednisone 60 mg q.d. was begun, AEC decreased to 206 u/L within 48 hours. Patient was discharged after day 5 on a tapering dose of prednisone.

At follow-up 2.5 months later, she was off corticosteroids with complete resolution of the rash; AEC was 30 cells/uL, CK 82 U/L, ALT 23U/L and the creatinine was 0.9 mg/dL. She was restarted on rosuvastatin and, three weeks later, the maculopapular rash recurred along with facial edema and fever of 39.2 C. Proximal muscle weakness was noted in both upper and lower extremities. Creatinine rose to 3.75 mg/dL and liver function tests, AEC increased to 1203 cells/uL and CK were again elevated (Figure 1). She was readmitted to the hospital with a diagnosis of DRESS. Rosuvastatin was discontinued and prednisone 60 mg q.d. was restarted followed by a gradual tapering schedule. Rosuvastatin was determined to be the most likely cause of the DRESS; lisinopril and insulin were the only concurrent medications. For 14 months since off prednisone and statins, there has been no recurrence of DRESS with normalization of AEC, CK,

ALT and creatinine values. (Figure 1). Data about cross-reactivity between statins pertaining to drug hypersensitivity reactions is lacking but the patient was advised to avoid all statin drugs in the future and, if possible, other high-risk drugs known to cause DRESS (e.g., allopurinol, carbamazepine).

DRESS syndrome is a serious hypersensitivity drug reaction characterized by fever, diffuse rash, eosinophilia, lymphadenopathy and visceral organ inflammation, primarily involving the liver, kidneys, heart and lungs. Mortality increases with multiple organ involvement [5]. Skin rash and involvement of organs vary, making diagnosis challenging. Clinical symptoms typically occur after 2–8 weeks of drug exposure. In this case, the onset of DRESS symptoms emerged 5 weeks after initiation of rosuvastatin, resolved after 2-3 months, and recurred 3 weeks after re-exposure to the statin. The RegiScar is a diagnostic scoring system used for DRESS. This patient had a RegiScar score of 7 consistent with definite DRESS (i.e., 1 point each for lymphadenopathy, AEC >700, atypical lymphocytes, organ involvement and exclusion of other causes; and 2 points for skin rash). Patch testing was not performed because the patient had been re-challenged to rosuvastatin and there was no ambiguity in terms of concurrent medications regarding causation of DRESS by the

statin. Patch testing has about 30-60% sensitivity for identifying DRESS and a negative test would not have excluded the diagnosis [6,7]. In this patient, acute renal insufficiency due to statin-induced rhabdomyolysis and ATN was considered but urinary myoglobin was absent and renal biopsy findings demonstrated acute interstitial nephritis with lymphocytic and eosinophilic infiltration [8]. Acute interstitial nephritis (AIN) occurs in 10 - 30 percent of DRESS patients and histopathological findings are like those identified in this patient [9].

In this case clindamycin was suspected as a more likely cause at initial presentation than the statin drug. Statins do not appear on published lists of causes of DRESS which could explain why treating physicians did not initially suspect rosuvastatin. Antiepileptics, sulfonamides, and allopurinol are the most common reported causes [5]. This case presented with acute kidney injury, transaminitis, peripheral eosinophilia and lymphadenopathy. To date, two additional cases of statin associated DRESS have been reported, one due to atorvastatin and one due to rosuvastatin [3,4]. The case of rosuvastatin induced DRESS was a 54-year-old male with acute onset fever and a generalized rash several weeks after starting rosuvastatin [3]. Prompt recognition and discontinuation of the offending medication are essential in the management of DRESS [10]. It is

important for clinicians to recognize that in addition to rhabdomyolysis and myositis, statin drugs can also present with DRESS. Failure to recognize unusual causes of DRESS can result in prolonged morbidity and possibly a fatal outcome.

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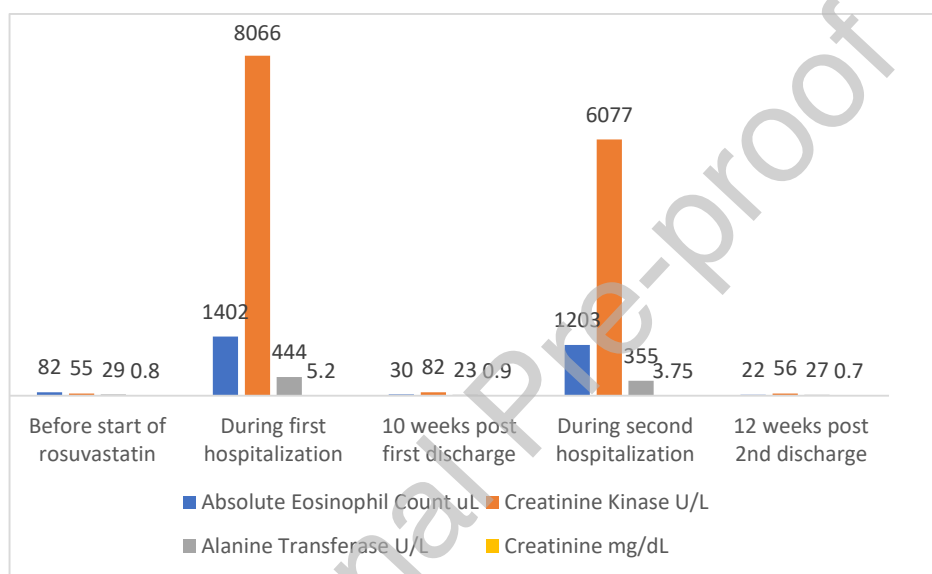


Fig.1 Laboratory data.