

Statin desensitization in a patient with probable familial hypercholesterolemia



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PROBLEM OVERVIEW: With cardiovascular disease being the leading cause of morbidity and mortality in the United States, cholesterol-lowering medications have become a prominent focus of medical management and cardiovascular risk reduction, including the use of statins making them the most widely prescribed class of medications in the United States and are the cornerstone of management of hyperlipidemia. This case report describes a 29-year-old female with probable familial hypercholesterolemia (FH) who had allergic reactions to statin therapy on two separate occasions. She required statin therapy based on her elevated carotid intima media thickness test, historic LDL-C ≥ 190 mg/dL, elevated Lp(a), and family history significant for premature coronary heart disease. In this report, we document a case of successful oral desensitization to rosuvastatin and propose a replicable statin desensitization protocol.

MAJOR MANAGEMENT: The patient was admitted for rosuvastatin desensitization following predetermined protocols, utilizing an interdisciplinary team, and monitored for 24 hours following completion of administration prior to discharge. She successfully completed desensitization to rosuvastatin 10mg by mouth daily without anaphylactic reaction. She continued to tolerate rosuvastatin 10mg daily through most recent follow-up, and with this addition, significant improvement in lipid levels was achieved.

CONCLUSION: This case report presented a patient with probable FH who was previously intolerant to other statin therapies that underwent successful desensitization to rosuvastatin with subsequent achievement of therapy goals.

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According to the World Health Organization, globally more than half of heart disease cases are associated with dyslipidemia resulting in more than 4 million deaths per

year.¹ With cardiovascular disease (CVD) being the leading cause of morbidity and mortality in the United States, cholesterol-lowering medications have become a prominent focus of medical management and cardiovascular risk reduction, including the use of statins (3-hydroxy-3-methyl-glutaryl-coenzyme A reductase inhibitors). Statins are the most widely prescribed class of medications in the United States and are the cornerstone of management of hyperlipidemia.² The 2013 American College of Cardiology/American Heart Association (ACC/AHA) Blood Cholesterol guidelines recommend that patients ≥ 21 years of age with low-density lipoprotein cholesterol

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(LDL-C) ≥ 190 mg/dL use high-intensity statin therapy unless contraindicated with intensification to achieve an LDL-C reduction of $\geq 50\%$.³

Statin intolerance has been described in the form of muscle-related symptoms, cognitive difficulties, hepatic transaminase level elevations, and new-onset diabetes mellitus. Management strategies vary and have been described in the literature. However, management of patients with an allergic reaction to statin therapy has been underreported. Only 1 case report of documented statin desensitization has been published to date. The patient was a 37-year-old man requiring statin therapy for secondary prevention with documented anaphylactic reactions to statins, including atorvastatin and simvastatin.⁴ Beyond this 1 case study, there is a lack of documentation of statin desensitization protocols and measured outcomes. In this report, we document a case of successful oral desensitization to rosuvastatin and propose a replicable statin desensitization protocol.

Case report

The patient is a 29-year-old woman marathon runner from South India who was referred to the lipid management clinic at an academic medical center heart hospital for management of LDL-C >190 mg/dL. Her medical history is significant for probable familial hypercholesterolemia (FH), elevated carotid intima media thickness (CIMT) in the 57th percentile at age 27 years that indicated her vascular age was 37 years, elevated lipoprotein (Lp) (a) level of 170, elevated LDL particle number (LDL-P) as high as 2791, and significant allergies to previous statin regimens.

Her family history is significant for premature coronary artery disease as a result of her mother passing away at the

age of 46 years from an acute myocardial infarction (MI) and father passing away from stroke at the age of 58 years. From her positive family history and elevated baseline LDL-C, patient can be diagnosed as probable FH per the Dutch Lipid Clinic Network Diagnostic Score and the Simone-Broome Register.^{5,6} With a baseline LDL-C ≥ 190 mg/dL, positive family history, elevated CIMT, and elevated Lp(a), she would benefit from statin therapy.

The patient reacted to statin therapy on 2 separate occasions. The first occurrence followed initiation of simvastatin 20 mg in October 2010. She subsequently developed urticaria with intense pruritus after the first dose of therapy, but continued until her third dose, when she developed subjective airway swelling. She treated herself with diphenhydramine and topical hydrocortisone, which relieved her symptoms, and simvastatin was discontinued.

Per historic records, the patient underwent allergy testing in India before moving to the United States. Her skin test revealed she was allergic to citrus fruits, cocoa, tomatoes, dust mites, and cats. Formal IgE-mediated testing has not been completed with regard to statin intolerances.

At her initial lipid clinic appointment in July 2012, because of her history with simvastatin, the patient was initiated on colesvelam and was titrated up to 3.75 g daily over the course of 3 mo and was referred to an allergist. At her following appointment in September 2012, she was initiated on niacin extended-release and successfully titrated to 1.5 g daily over a 3-mo period.

The second challenge was completed under medical supervision in August 2013 with a single dose of atorvastatin 5 mg. She was instructed to stop niacin extended-release and colesvelam 2 wk before retreatment of statin therapy. Approximately 75 min after the single dose of atorvastatin, she developed diffuse itching relieved by diphenhydramine, and atorvastatin was discontinued. The patient did not experience urticaria, facial or laryngeal

Table 1 Lipid results and corresponding therapy before desensitization

Date	TC (mg/dL)	HDL (mg/dL)	TG (mg/dL)	LDL-C (mg/dL)	Non-HDL (mg/dL)	Total LDL-P	Therapy
12-14-09	306	63	160	211	243		None
10-31-11	231	51	124	155	180	2002	None
04-06-12	237	47	137	163	190	2261	None
07-05-12	238	53	137	188	185	2791	None
08-24-12	262	50	154	181	212	2448	Colesevelam 1.25 g daily
10-19-12	204	60	101	124	144		Colesevelam 1.875 g daily, niacin extended-release 500 mg daily
01-25-13	188	73	74	100	115	1565	Colesevelam 3.75 g daily, niacin extended-release 1500 mg daily
07-29-13	301	87	44	205	214	2038	Colesevelam 3.75 g daily, niacin extended-release 1500 mg daily
11-01-13	159	59	51	90	100		Ezetimibe 10 mg daily, colesvelam 3.75 g daily, niacin extended-release 1500 mg daily

HDL, high-density lipoprotein; HDL-P, high-density lipoprotein particles; LDL, low-density lipoprotein; LDL-P, low-density lipoprotein particles; TC, total cholesterol; TG, triglycerides.

Table 2 Protocol for rapid rosuvastatin desensitization

Criteria	• Patients with a history of a reaction suggestive of an IgE-mediated hypersensitivity to rosuvastatin (ie, anaphylaxis, angioedema, urticarial, pruritus, flushing, dyspnea, hypotension) • Compelling indication for statin therapy (ie, secondary prevention, familial hyperlipidemia)
Preparation	• Consult allergy/immunology to determine the hypersensitivity status, whether desensitization is necessary, and how to perform the desensitization • Consider admission where patient can be closely monitored with one-to-one nursing • Desensitization should begin between the hours of 8 AM and 3 PM • If there is any interruption in the desensitization protocol or subsequent therapy, allergy/immunology must evaluate before proceeding • Allergy/immunology physician on-call must be available for problems or concerns during the desensitization procedure • Obtain signed consent • Discontinue medications which may mask signs or symptoms of allergy, as much in advance as possible • Examples: antihistamines, histamine-2 blockers (cimetidine, famotidine, nizatidine, ranitidine), phenothiazines (chlorpromazine, fluphenazine, perphenazine, prochlorperazine, promethazine, thioridazine), corticosteroids, tricyclic antidepressants, nonsteroidal anti-inflammatory agents, beta-blockers • Consider restarting any medications which may have been held after the desensitization • Respiratory therapy to instruct the patient on the use of the peak flow meter
Monitoring	• Nursing staff to monitor for and instruct patient to communicate any unusual symptoms (tingling in the lips or throat, difficulty breathing, hoarseness, swelling, itching) • Vital signs (blood pressure, heart rate, respirations, and O₂ saturation, peak flow meter) monitored every 30 min before each dose and every 30 min after the completion of the last dose of the protocol for 2 h
Rosuvastatin preparation and dosing schedule	• All oral syringes and doses should be labeled with dose number, medication name, concentration, and date and time of preparation • Suspension A: 0.5 mg/1 mL suspension: • Crush 2: rosuvastatin 10-mg tablets and mix with 20 mL of saline and add quantity sufficient of ora-sweet to reach 40 mL = final concentration of 20 mg/40 mL (0.5 mg/1 mL) • Suspension B: 0.1 mg/1 mL suspension: • Take 4 mL of suspension A and add quantity sufficient of ora-sweet to reach 20 mL = 2 mg/20 mL (0.1 mg/1 mL) • Suspension C: 0.01 mg/1 mL suspension: • Take 2 mL of suspension B and add quantity sufficient of ora-sweet to reach 20 mL = 0.2 mg/20 mL (0.01 mg/1 mL) • Follow dosing schedule in Table 3
Hypersensitivity reactions	• At bedside before desensitization: • Epinephrine 0.3 mg/0.3 mL prefilled syringe (Epi-Pen) • Diphenhydramine (Benadryl) 50-mg vial • Methylprednisolone sodium succinate (Solu-Medrol) 125-mg vial • Albuterol inhaler/nebulizer • Oxygen • Immediate reactions/anaphylaxis: • Notify medical emergency response team, anesthesia, primary team, and allergy/immunology • Administer epinephrine 0.3 mg/0.3 mL intramuscular injection in the lateral thigh (or deltoid) at least 5 min apart, diphenhydramine 50-mg vial intravenous push (IVP), methylprednisolone sodium succinate (Solu-Medrol) 125-mg vial IVP • Albuterol inhaler/nebulizer for wheezing

Table 3 Rosuvastatin desensitization dosing schedule*

Action	Formulation
Dose#1: 0.01 mg by mouth	Suspension C (0.01 mg/1 mL)
Dose#2: 0.02 mg by mouth	Suspension C (0.02 mg/2 mL)
Dose#3: 0.04 mg by mouth	Suspension C (0.04 mg/4 mL)
Dose#4: 0.08 mg by mouth	Suspension C (0.08 mg/8 mL)
Dose#5: 0.1 mg by mouth	Suspension B (0.1 mg/1 mL)
Dose#6: 0.2 mg by mouth	Suspension B (0.2 mg/2 mL)
Dose#7: 0.4 mg by mouth	Suspension B (0.4 mg/4 mL)
Dose#8: 0.8 mg by mouth	Suspension B (0.8 mg/8 mL)
Dose#9: 1 mg by mouth	Suspension A (1 mg/2 mL)
Dose#10: 2 mg by mouth	Suspension A (2 mg/4 mL)
Dose#11: 4 mg by mouth	Suspension A (4 mg/8 mL)
Dose#12: 8 mg by mouth	Suspension A (8 mg/16 mL)
Dose#13: 10 mg by mouth	One 10-mg tablet

*Doses given every 30 min.

swelling, or dyspnea with single dose of atorvastatin. She was restarted on colessevelam and niacin extended-release, as her LDL-C had been as low as 100 mg/dL on this regimen, and also initiated on ezetimibe 10 mg daily. When the patient was re-evaluated before desensitization, there were no significant changes to her laboratories after resumption of colessevelam and niacin extended-release with ezetimibe.

After the second failed trial of statin therapy, the decision was made to discuss statin desensitization with allergy/immunology in November 2013. At this visit, she was also instructed to stop her niacin extended-release while continuing her colessevelam and ezetimibe. [Table 1](#) depicts the patient's lipid results and the corresponding therapy.

[Table 2](#) depicts the statin desensitization protocol specific to rosuvastatin 10 mg, including monitoring parameters. Adequate monitoring of the patient is essential during the administration and at least for 2 h after completion. [Table 3](#) depicts the preparation and schedule of doses.

The patient was admitted January 23, 2014, for rosuvastatin desensitization following the protocols in [Tables 2 and 3](#). The dosing schedule ([Table 3](#)) that was followed mirrored that of the previously published case report. The

team consisted of nursing, respiratory therapy, pharmacy, cardiology, and allergy/immunology, who developed and executed an extensive protocol ([Table 2](#)) that details the patient criteria, preparation, monitoring, medication preparation, and directives to follow to prevent and alleviate hypersensitivity reactions. During the administration, the patient developed pruritus and flushing, requiring diphenhydramine 25-mg intravenous (IV) push after doses 2 and 5 and methylprednisolone sodium succinate 40-mg IV push after diphenhydramine after dose 5. The desensitization subsequently continued. Because of the patient's history of delayed reactions to statin therapy, she was monitored for 24 hr after completion of the administration. She received the second 10-mg rosuvastatin dose the day after desensitization. Within 2 hours of administration, she had complaints of flushing, coughing, and throat itching. Objective signs of bronchoconstriction were negative and there was not a significant change in her peak flow from baseline. She was initiated on daily cetirizine, which alleviated her symptoms and was continued outpatient. The patient successfully completed desensitization without anaphylactic reaction and was discharged home with a prescription for rosuvastatin 10 mg by mouth daily and cetirizine 10 mg by mouth daily. She was instructed if she missed more than 2 doses of rosuvastatin therapy to not take any further doses and contact her physician regarding repeating desensitization. She was continued on her previous cholesterol medications of colessevelam and ezetimibe.

Approximately 3 weeks after initiation of daily rosuvastatin 10 mg, the patient returned to the lipid clinic for evaluation on February 12, 2014. Since desensitization, her LDL-C decreased by 40% ([Table 4](#)) with the combination of colessevelam 3.75 g by mouth daily, ezetimibe 10 mg by mouth daily, and rosuvastatin 10 mg by mouth daily. She continued to tolerate the rosuvastatin. To assess maximal benefit of rosuvastatin, patient was continued on all 3 medications until further follow-up, with the possibility of discontinuing nonstatin therapies in the future. The patient may also benefit from increased dose of rosuvastatin to achieve high-intensity therapy and potentially discontinue nonstatin therapies. This increase in dose would not require readmission.

Table 4 Lipid results and corresponding therapy after desensitization

Date	TC (mg/dL)	HDL (mg/dL)	TG (mg/dL)	LDL-C (mg/dL)	Non-HDL (mg/dL)	Total LDL-P	Therapy
01-23-14	173	53	104	99	120		Colesevelam 3.75 g daily; ezetimibe 10 mg daily
02-12-14	125	55	62	59	71	1146	Colesevelam 3.75 g daily; ezetimibe 10 mg daily; rosuvastatin 10 mg daily
03-24-14	124	53	79	55	71	941	Colesevelam 3.75 g daily; ezetimibe 10 mg daily; rosuvastatin 10 mg daily

HDL, high-density lipoprotein; LDL, low-density lipoprotein; LDL-P, low-density lipoprotein particles; TC, total cholesterol; TG, triglycerides.

After another 6 wk of continued combination therapy, the patient was re-evaluated. Of note, throughout her course, LDL-P was discordant from LDL-C. When discordant, CVD outcomes are better predicted by LDL-P.⁷ Current laboratories revealed that her lipid panel remained stable while continuing to tolerate rosuvastatin and her LDL-P had decreased to <1000, which had not occurred while the patient was solely on nonstatin therapy (Table 4). Therefore, patient reached LDL-C of <100 mg/dL, achieved >50% reduction in LDL-C on moderate intensity statin, and reached LDL-P of <1000.

This primary prevention patient was successfully desensitized to rosuvastatin 10 mg by mouth daily. She required statin therapy based on her elevated CIMT, historic LDL-C ≥ 190 mg/dL, elevated Lp(a), and family history significant for premature coronary heart disease. Although she had several compelling indications for statin therapy, CIMT increase alone has been associated with increased risk of CVD. Nine prospective studies have been published each assessing the association of CIMT with CVD outcomes.⁸ CIMT is significantly correlated with risk for MI, stroke, coronary heart disease, death, or a combination of these outcomes. A 15% increased risk for MI and an 18% increased risk for stroke have been demonstrated with each 0.1-mm increase in CIMT.⁹

Despite minor reactions during the desensitization process, there was no significant reaction or evidence of bronchoconstriction, and she has continued to tolerate rosuvastatin through most recent follow-up.

This case report presented a primary prevention patient with probable FH who was previously intolerant to other

statin therapies that underwent successful desensitization to rosuvastatin with subsequent achievement of therapy goals. This article provided a protocol to replicate desensitization for high-risk cardiac patients with close monitoring within an inpatient medical setting.

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