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Case Report | Peer-Reviewed Article

A Case of Severe Myopathy

# Not All Statins are Equal – Environmental and Genetic Myotoxicity Risk Factors

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## Abstract

Dose-dependent statin-related myotoxicity (SRM) is a rare adverse effect of statin treatment. Differences in the pharmacokinetics and interactions with environmental and genetic factors constitute important risk factors for the development of SRM. We present the case of an 82-year-old female patient with severe simvastatin-related myotoxicity and several risk factors of SRM, namely a pharmacokinetic interaction with verapamil, a pharmacogenetic interaction with a SLCO1B1*1/*5 variant, high age, female gender and impaired renal function. A comprehensive evaluation of distinct pharmacokinetic and pharmacogenetic properties of different statins and a pharmacogenetic panel test guided the diagnosis and options for further clinical management. Inspired by this and other similar cases, we developed a pocket card as practical companion for statin prescribing in clinical practice and provide it as an addition to this report.

**Keywords:** Cholesterol-lowering therapy; statins; pharmacogenetics; SLCO1B1; CYP450; drug interactions; drug safety; clinical pharmacology

## Introduction

Statins are a cornerstone in the treatment of hypercholesterolemia, the primary and secondary prevention of ischemic vascular events and are among the most frequently prescribed medications worldwide [1]. Beyond lowering cholesterol, statins have also been associated with other beneficial properties including anti-inflammatory and plaque-stabilizing effects on atherosclerotic vessels [2]. However, statin-related myotoxicity (SRM) is a rare adverse effect of statins. The severity of SRM can range from subclinical muscle weakness and creatine kinase (CK) elevation to severe muscle pain and rhabdomyolysis. SRM shows intrinsic dose-dependency and can be distinguished from extremely rare idiosyncratic statin-related immune-mediated necrotizing myopathy [3]. SRM is considered a class effect of statins. Its dose-dependency implies that differences in the pharmacokinetics of various statins and their interactions with environmental and genetic factors constitute important risk factors for the development of SRM [3]. Therefore, the clinical prescribing of statins should account for these differences to lower the risk of SRM.

We present a case of severe simvastatin-induced myotoxicity and demonstrate how a comprehensive evaluation of statin-specific pharmacokinetics and patient-specific factors can guide personalized prescribing as well as the prevention and management of SRM. As an addition we developed a pocket card to guide statin prescribing in clinical practice.

## Case Presentation

A 82-year-old female of European descent (weight 74 kg, BMI 28.9 kg/m$^2$) with known type 2 diabetes, diabetic nephropathy and tachycardic atrial fibrillation presented to the emergency room after a sudden loss of consciousness at home. She reported having muscle weakness in her lower extremities for several weeks. Laboratory results showed marked elevations of CK (5779 U/l, norm. <171 U/l) and potassium (6.6 mmol/l, norm <5.3 mmol/l), and acute-on-chronic grade IV renal impairment (estimated glomerular filtration rate [eGFR] 26 ml/min/1.73 m$^2$). Medication upon hospitalization included simvastatin 40 mg/d for the primary prevention of ischemic vascular events in the presence of the risk factors type 2 diabetes and renal impairment, and verapamil 240 mg/d for hypertension and control of tachycardic atrial fibrillation. Both had been prescribed for more than a year. In the absence of other likely causes for the muscle symptoms and markedly elevated CK, a clinical diagnosis of SRM was made. Simvastatin was stopped immediately and intravenous fluids were administered. Within three days, muscle weakness improved, CK decreased to 1241 U/l, potassium to 4.6 mmol/l, eGFR increased to 38 ml/min/1.73 m$^2$ and the patient was discharged in good general condition.

Results of a pharmacogenetic panel test were available shortly after discharge. They showed one solute carrier organic anion transporter (SLCO) 1B1 non-functioning allele (*1/*5), indicating a decreased function of organic anion-transporting polypeptide (OATP) 1B1 transporter activity and also a cytochrome P450 (CYP) 2C9*1/*1 wild type, indicating normal CYP2C9 enzyme activity. According to standardized causality assessment based on WHO-UMC criteria (temporal relationship,

| | | Rosuvastatin | | | Atorvastatin | | | | Pitavastatin | | | Simvastatin | | | Pravastatin | | Fluvastatin | | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 mg | 10 mg | 20 mg | 10 mg | 20 mg | 40 mg | 80 mg | 1 mg | 2 mg | 4 mg | 20 mg | 40 mg | 80 mg | 20 mg | 40 mg | 20 mg | 40 mg | 80 mg |
| SLCO1B1 Polymorphism | Poor Function (*5/*5, *5/*15, *15/*15) | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] |
| | Decreased Function (*1/*5, *1/*15) | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] | [1] |
| Cytochrome P450 Inhibitors | Potent CYP3A4 Inhibitors (Itraconazole, Miconazole, Clarithromycin, Erythromycin) | [2], [3], C | [2], [3], C | [2], [3], C | [4], C | [4], C | [4], C | [4], C | C | C | C | [4], [5], C | [4], [5], C | [4], [5], C | [3], C | [3], C | [3], C | [3], C | [3], C |
| | Moderate CYP3A4 Inhibitors (Amiodarone, Verapamil, Diltiazem, Grapefruit Juice) | C | C | C | [6], [7], C | [6], [7], C | [6], [7], C | [6], [7], C | C | C | C | [6], [7], C | [6], [7], C | [6], [7], C | C | C | C | C | C |
| | Potent CYP2C9 Inhibitors (Fluconazole) | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | [8], C | [8], C | [8], C |
| | Moderate CYP2C9 Inhibitors (Valproate) | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | [8], C | [8], C | [8], C |
| Transpor t Inhib. | Ticagrelor (OATP1B1 and BCRP Inhibitor) | [9], [10], C | [9], [10], C | [9], [10], C | [9], [11], C | [9], [11], C | [9], [11], C | [9], [11], C | E* | E* | E* | [9], C | [9], C | [9], C | E* | E* | E* | E* | E* |
| Multi-Pathway Inhibitors (high risk drugs) | Protease Inhibitors with PK-Boosters (Ritonavir, Cobicistat) | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C | [12], [13], C |
| | Ciclosporine | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C | [14], C |
| | Gemfibrozil | [15], C | [15], C | [15], C | [15], C | [15], C | [15], C | [15], C | [16], E* | [16], E* | [16], E* | [15], C | [15], C | [15], C | [15], C | [15], C | [17], C | [17], C | [17], C |
| | Fusidic acid | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C | [18], C |
| Renal Failure | GFR < 30 ml/min | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C |
| | GFR 30 - < 60 ml/min | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C | C |

Traffic-Light Color Coding:

Stop: Contraindicated or strongly advised to avoid due to myotoxicity risk

Careful: Use with caution, monitoring myotoxicity risk (e.g., CK)

Go: No serious concerns regarding myotoxicity risk

**Table 1:** Table of statin-specific risk factors for statin-related myotoxicity (SRM).
A printed version for use as a clinical pocket card is available from the authors upon request.

1 Cooper-DeHoff RM, Niemi M, Ramsey LB, Luzum JA, Tarkiainen EK, Straka RJ, et al. The Clinical Pharmacogenetics Implementation Consortium Guideline for SLCO1B1, ABCG2, and CYP2C9 genotypes and Statin-Associated Musculoskeletal Symptoms. Clin Pharmacol Ther. 2022 May;111(5):1007–21.
2 Cooper KJ, Martin PD, Dane AL, Warwick MJ, Schneck DW, Cantarini MV. Effect of itraconazole on the pharmacokinetics of rosuvastatin. Clin Pharmacol Ther. 2003 Apr;73(4):322–9.
3 Li DQ, Kim R, McArthur E, Fleet JL, Bailey DG, Juurlink D, et al. Risk of adverse events among older adults following co-prescription of clarithromycin and statins not metabolized by cytochrome P450 3A4. CMAJ. 2015 Feb;187(3):174–80.
4 Dybro AM, Damkier P, Rasmussen TB, Hellfritzsch M. Statin-associated rhabdomyolysis triggered by drug-drug interaction with itraconazole. BMJ Case Rep. 2016 Sep;2016:bcr2016216457.
5 Page SR, Yee KC. Rhabdomyolysis in association with simvastatin and dosage increment in clarithromycin. Intern Med J. 2014 Jul;44(7):690–3.
6 Borders-Hemphill V. Concurrent use of statins and amiodarone. Consult Pharm. 2009 May;24(5):372–9.
7 Yeo KR, Yeo WW. Inhibitory effects of verapamil and diltiazem on simvastatin metabolism in human liver microsomes. Br J Clin Pharmacol. 2001 May;51(5):461–70.
8 Kantola T, Backman JT, Niemi M, Kivistö KT, Neuvonen PJ. Effect of fluconazole on plasma fluvastatin and pravastatin concentrations. Eur J Clin Pharmacol. 2000 Jun;56(3):225–9.
9 Danielak D, Karaźniewicz-Łada M, Główka F. Assessment of the Risk of Rhabdomyolysis and Myopathy During Concomitant Treatment with Ticagrelor and Statins. Drugs. 2018 Jul;78(11):1105–1112.
10 Lehtisalo M, Kiander W, Filppula AM, Deng F, Kidron H, Korhonen M, et al. Rhabdomyolysis during concomitant ticagrelor and rosuvastatin: A breast cancer resistance protein-mediated drug interaction? Br J Clin Pharmacol. 2023 Jul;89(7):2309–15.
11 Lau YY, Huang Y, Frassetto L, Benet LZ. effect of OATP1B transporter inhibition on the pharmacokinetics of atorvastatin in healthy volunteers. Clin Pharmacol Ther. 2007 Feb;81(2):194–201.
12 Rosenson RS, Colantonio LD, Burkholder GA, Chen L, Muntner P. Trends in Utilization of Statin Therapy and Contraindicated Statin Use in HIV – Infected Adults Treated With Antiretroviral Therapy From 2007 Through 2015. J Am Heart Assoc. 2018 Dec;7(24):e010345.
13 Liverpool Drug Interactions Group, University of Liverpool. Liverpool: HIV Drug Interactions; c2023. Available from: www.hiv-druginteractions.org.
14 Mo L, He J, Yue Q, Dong B, Huang X. Increased dosage of cyclosporine induces myopathy with increased seru creatine kinase in an elderly patient on chronic statin therapy. J Clin Pharm Ther. 2014 Dec;40(2):245–8.
15 Franssen R, Vergeer M, Stroes ES, Kastelein JJ. Combination statin-fibrate therapy: safety aspects. Diabetes Obes Metab. 2009 Feb;11(2):89–94.
16 Fujino H, Yamada I, Shimada S, Hirano M, Tsunenari Y, Kojima J. Interaction between fibrates and statins-metabolic interactions with gemfibrozil. Drug Metabol Drug Interact. 2003;19(3):161–76.
17 Vergoulas G, Miserlis G, Solonaki F, Imvrios G, Gakis D, Papanikolaou V, et al. Combined treatment of hypercholesterolemia of renal transplant allograft recipients with fluvastatin and gemfibrozil. Transpl Int. 2000;13 Suppl 1:S64–7.
18 Cowan R, Johnson PD, Urbancic K, Grayson ML. A timely reminder about the concomitant use of fusidic acid with statins. Clin Infect Dis. 2013 Jul;57(2):329–30.

C Swiss Summary of Product Characteristics (Compendium).
E* Author's impact estimation
GFR Glomerular filtration rate

other causes unlikely, positive rechallenge, extrinsic evidence), simvastatin can be classified as the "probable" cause for this patient's muscle symptoms and elevated CK levels.

## Further Clinical and Pharmacological Evaluation and Management

Assuming a multi-causal genesis of SRM in our patient, we systematically searched for potential drug-drug, drug-gene, drug-food and drug-disease interactions. First, simvastatin is primarily metabolized via CYP3A4, of which verapamil is a moderate inhibitor. A quantitative estimate of the resulting pharmacokinetic interaction predicts a 3.2× increase of simvastatin area under the curve caused by verapamil (https://www.ddi-predictor.org). In our patient this would correspond to a simvastatin exposure usually achieved with more than 120 mg/d, exceeding the maximum recommended dose of 80 mg/d. In addition, four other factors may have contributed to an even higher drug exposure: a further decreased metabolic capacity of CYP450 enzymes associated with high age and female sex, the decreased OATP1B1 transporter capacity related to the heterozygous SLCO1B1*1/*5 variant and the impaired renal function [3, 4]. Indeed, the clinical relevance of the SLCO1B1 variant is particularly well established for simvastatin, whereas it may play a lesser role for other statins [4, 5]. Further risk factors and acute triggers for SRM, including grapefruit juice consumption inhibiting the CYP3A4 enzyme and P-glycoprotein transporter activity, were actively searched in our patient but could not be identified.

Although the high-intensity statins rosuvastatin or atorvastatin are generally preferable, we concluded that the most suitable statin for our patient would be fluvastatin 20–40 mg/d, since it is not primarily metabolized via CYP3A4 but CYP2C9, for which our patient had no pharmacogenetic variant associated with an impaired function, and because fluvastatin is least affected by the SLCO1B1-variant and is therefore categorized as a low SRM-risk option [5]. On the other hand, in this elderly patient with several comorbidities, one should challenge the indication for statin therapy as primary prevention in the first place and eventually it was decided to discontinue any statin therapy.

## Discussion and Development of a Pocket Card as a Clinical Prescribing Companion

The presented patient developed typical symptoms of rhabdomyolysis during therapy with simvastatin and therefore a diagnosis of SRM was made despite the unusually long latency. A long latency time of several months or more has also been observed in clinical trials and other case reports of SRM [4]. The true incidence of SRM is uncertain, with reports ranging from 1.5 to 5% for randomized controlled trials (RCTs) and 10 to 33% in observational studies, depending on follow-up and definition of SRM [6]. All statins share the same mechanism of action, inhibition of the HMG-CoA reductase and all have the potential to cause myotoxicity. However, differences in the pharmacokinetic properties influence how statins interact with environmental and genetic factors, thereby either increasing or decreasing the risk of severe myotoxicity. Comprehensive information on this topic can be found in guidelines and position papers from the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) [7, 8], or the comprehensive review of relevant risk factors of SRM published by Turner and Pirmohamed [3]. This work also presents a well-structured overview of distinct pharmacokinetic features for all statins. Besides high statin dose, these can be separated into either environmental factors, including interactions with co-medication and diet, advanced age, female gender and co-morbidities, or genetic factors such as genetic variants of metabolizing enzymes and transporters. The identification of five risk factors in our patient emphasizes that a multi-causal model of disease likely applies as it does to most adverse drug reactions.

Consequently, an individual risk assessment before prescribing statins with a personalized statin selection would be desirable for each patient. A suboptimal statin choice might have pharmacokinetic interactions that may increase the patient's statin exposure causing an individually higher risk of SRM compared to another statin. For example, patients taking CYP3A4 inhibitors (e.g., clarithromycin, ciclosporin, verapamil or protease inhibitors) have an increased exposure of statins metabolized by CYP3A4 (simvastatin, atorvastatin, pitavastatin). In contrast, patients with CYP2C9 inhibitors (e.g., fluconazole) or CYP2C9 genetic variants with decreased activity have an increased exposure of fluvastatin, which is primarily metabolized by CYP2C9. Patients with chronic kidney disease (eGFR <30 ml/min) can have elevated levels of distinct statins that have a high renal elimination fraction (rosuvastatin and pravastatin) and a SLCO1B1 non-functioning variant (*5) likely affects simvastatin more than fluvastatin [4, 9]. This highlights the key message of our report, that while sharing the same mechanism of action, not all statins are equal, particularly regarding SRM risk and its attenuation by various factors.

The tabulated summaries cited above are most comprehensive but may not be pragmatic for daily use by the average physician. Therefore, to facilitate the implementation of personalized statin prescribing in clinical practice, we have compiled a detailed yet easy to use table of the most important clinical risk factors (table 1). The visualization helps to identify key information at one glance and was inspired by the CYP450 interaction tables first presented more than 20 years ago by our colleagues from Geneva [10]. We recommend using the table as a pocket card companion in clinical practice, as it can efficiently guide the selection and dosing of the most suitable statin for individual patients [3]. The table can be applied to all marketed statins in varying doses and includes individual risk factors via various mechanisms. Additionally, we aim to develop specialized algorithms integrated into electronic prescribing applications, particularly for hospitalized patients with statin therapy. Such proactive drug safety measures may identify patients at high risk for statin-induced myopathy and therefore support the prevention of SRM in the future.

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## Ethics Statement

We obtained written informed consent from the patient described in this case report to perform pharmacogenetic analyses and for the anonymized use of the patients data for scientific purposes.

## Conflict of Interest Statement

The authors have no potential conflicts of interest to declare.

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## Author Contributions

Conceptualization: AKS, VV, SR; laboratory analysis: SP; clinical patient care: AKS, SB, MB; writing, original draft preparation: AKS, VV, SP, SR; review and editing: all authors; design and content of table 1: VV, SR. All authors have read and agreed to the published version of the manuscript.

## References

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