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Rosuvastatin-induced rhabdomyolysis: case report and call for proactive multifactorial risk assessment and preventive management of statin therapy in high-risk patients

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ABSTRACT

Cholesterol-lowering statins are frequently prescribed for primary and secondary prevention of ischaemic vascular events. Whereas most patients tolerate statins without problems, statin-associated myopathy is well documented, as are several risk factors. We present a case report of an 80–90-year-old man with coronary artery disease who rapidly developed severe rhabdomyolysis during treatment with rosuvastatin while in intensive care. He had several concomitant risk factors for statin-induced myopathy including high dosage, old age, renal and hepatic impairment, and a pharmacogenetic SLCO1B1*1 a/*5 variant. Single known risk factors have a low predictive value for statin-induced myopathy and may therefore be underestimated in clinical practice. However, adverse drug reactions frequently involve the joint action of a multitude of environmental and genetic component causes, and statin-induced myopathy should be regarded as a multicausal event. We therefore advocate a proactive multifactorial risk assessment to guide and individualise statin therapy in high-risk patients.

BACKGROUND

Statins are competitive inhibitors of HMG-CoA-reductase and thereby reduce cholesterol synthesis. They are frequently prescribed as first-line drugs for the primary and secondary prevention of coronary, cerebral and peripheral ischaemic vascular events.[1 2]

Although effective and tolerated by most patients, myotoxicity is a rare but well-documented adverse effect of all statins that usually occurs within weeks or months. The mechanism of statin-associated myotoxicity is not entirely certain, but toxicity is dose-dependent and several risk factors have been identified. Indeed, any clinical case of statin-induced myotoxicity can be seen as multifactorial, and risk factors can be categorised as modifiable (also 'dynamic' or 'exogenous') versus non-modifiable (also 'static' or 'endogenous').[3–5]

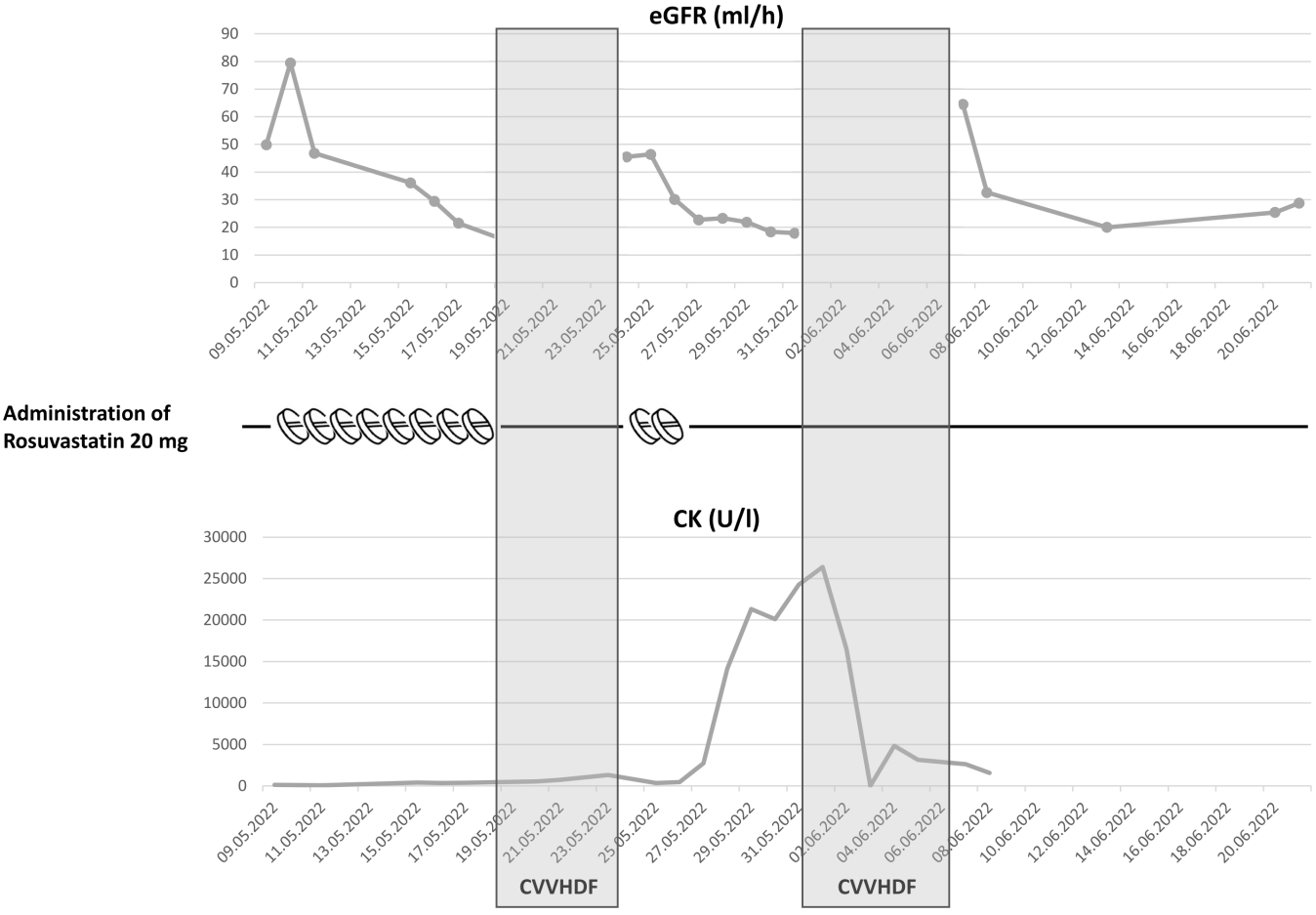
We present a case of severe rosuvastatin-induced rhabdomyolysis and discuss the interaction between various dynamic and static risk factors and their implication for the prevention, detection and clinical management of statin-associated myotoxicity.

CASE PRESENTATION

An 80–90-year-old Caucasian man presented to the emergency room with chest pain. He was admitted to the cardiology department with a primary diagnosis of unstable angina and, additionally, echocardiography revealed a mild pericardial effusion. Cardiac catheterisation was performed, showing three-vessel coronary artery disease with subtotal ostial stenosis of the right coronary artery. Angioplasty with placement of a drug-eluting stent was successful, and dual antiplatelet therapy plus rosuvastatin were initiated. Three days later the patient developed progressive dyspnoea and chest pain. He was admitted to the intensive care unit (ICU) with a diagnosis of multiorgan failure due to cardiogenic shock caused by pericardial tamponade with concurrent pre-existing perimyocarditis associated with a viral upper respiratory infection 3 weeks previously, and a pericardial drain was placed. Transaminases were markedly elevated (peak values: ASAT 5490 U/L, ALAT 2365 U/L), compatible with acute congestive liver disease. The patient also developed acute-on-chronic renal failure with estimated glomerular filtration rate (eGFR) decreasing from 36 to 15 mL/min/1.73 m^2 requiring continuous veno-venous haemodiafiltration (CVVHDF).

The course of rosuvastatin administration along with eGFR and creatine kinase (CK) values is shown in figure 1. Rosuvastatin 20 mg/day was administered after angioplasty for 8 days and stopped when CVVHDF was started. After stopping CVVHDF and a decrease in transaminases, rosuvastatin 20 mg/day was resumed and, after 2 days, CK rose steeply and eGFR declined again. CK reached a peak value of 26 399 U/L accompanied by a myoglobin level of >1000 µg/L. CVVHDF was resumed and methylprednisolone 125 mg/day administered. CK normalised, but renal function did not recover and the patient required ongoing intermittent haemodialysis.

A muscle biopsy showed acute necrotising myopathy compatible with statin-induced myotoxicity, and SLCO1B1 genotyping identified one non-functioning allele (*1a/*5) indicating decreased function of OATP1B1 transporter activity. Other hepatotoxic and nephrotoxic medications had been paused. CT imaging ruled out compartment syndrome and antibodies were negative, including anti HMG-CoA reductase.



eGFR = estimated Glomerular Filtration Rate (milliliter per hour), CK = Creatine Kinase (international units per liter), CVVHDF = Continuous Veno-Venous HaemoDiaFiltration

Figure 1 Administration of rosuvastatin, development of renal function and creatine kinase (CK) levels.

INVESTIGATIONS

The following investigations were undertaken:

- Pharmacogenetic panel test to determine the presence of pharmacogenetic variants predisposing for statin-induced myotoxicity.
- Muscle biopsy to determine the aetiology/nature of the rhabdomyolysis/myositis/vasculitis—that is, dermatomyositis, polymyositis and sporadic inclusion body myositis.

TREATMENT

Rosuvastatin was discontinued and CVVHDF initiated. 125 mg methylprednisolone once daily was administered intravenously for 1 week and then tapered to thwart the inflammatory component associated with the damaged muscle tissue. Subsequently, CK levels started to decrease.

OUTCOME AND FOLLOW-UP

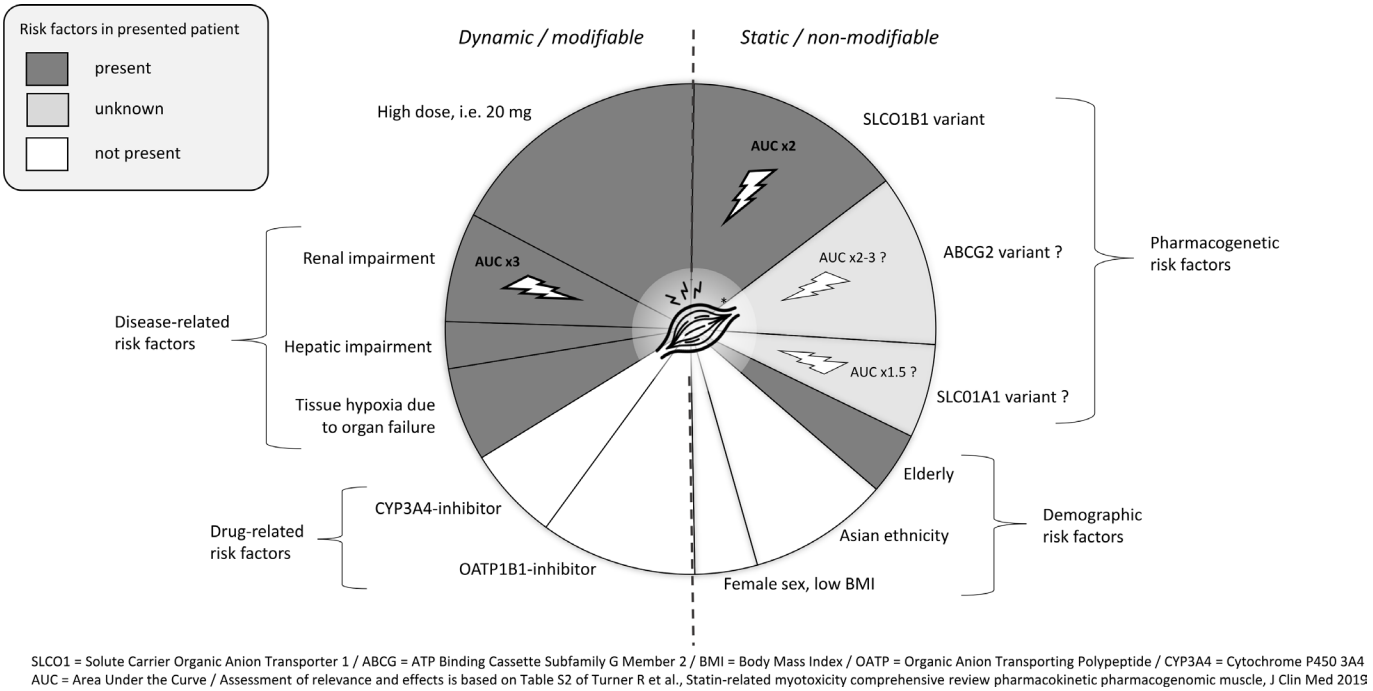
The patient's condition improved so that he could be transferred from the ICU to a normal ward and switch from CVVHDF to intermittent dialysis.

DISCUSSION

All statins share the same mechanisms of action and the potential to cause myotoxicity, but they have distinct pharmacokinetic profiles influencing their individual risk of drug–drug, drug–gene and drug–disease interactions, and thereby the risk for rhabdomyolysis.

The patient rapidly developed severe rhabdomyolysis associated with rosuvastatin therapy while suffering from acute renal failure. Although we were not able to obtain rosuvastatin plasma levels, even without such data, according to a standard semiquantitative causality assessment, rosuvastatin can be classified as the 'probable' cause of rhabdomyolysis in our patient.[6] Alternatively, one can approach this case with a 'causal pie' model, according to which a multitude of environmental and genetic component causes interact with each other and jointly act as a sufficient cause of disease.[7 8] Risk factors for statin-induced myopathy have been reported,[3–5] and several of these can indeed be identified in our patient and are presented in a causal pie model of statin-induced rhabdomyolysis (figure 2). While some are 'static' such as the pharmacokinetic properties of the statin or the patient's genetics, others such as renal function, co-medication with potential pharmacodynamic or pharmacokinetic interactions and co-morbidities may change acutely, especially in the setting of an ICU.

Rosuvastatin is primarily (about 90%) eliminated unchanged via the bile involving OATB1B1 and BCRP transporters but, in contrast to other statins, it is not prone to interactions via CYP450 enzymes and partially (about 10%) eliminated via the kidneys.[4] The latter may be the reason for its classification as having a low risk of myotoxicity, even in the presence of a SLCO1B1 variant with decreased OATB1B1 function.[9 10] However, rosuvastatin-induced



SLCO1 = Solute Carrier Organic Anion Transporter 1 / ABCG = ATP Binding Cassette Subfamily G Member 2 / BMI = Body Mass Index / OATP = Organic Anion Transporting Polypeptide / CYP3A4 = Cytochrome P450 3A4
AUC = Area Under the Curve / Assessment of relevance and effects is based on Table S2 of Turner R et al., Statin-related myotoxicity comprehensive review pharmacokinetic pharmacogenomic muscle, J Clin Med 2019

Figure 2 Relevance and effects of risk factors for rosuvastatin-induced myopathy in the presented case.

severe myotoxicity has previously been reported[11] and, in our patient, both elimination pathways—hepatic and renal—were likely impaired due to cardiac tamponade with resulting congestive liver disease and acute-on-chronic renal failure. Under these circumstances, the 'normal' elimination half-life of rosuvastatin of 19 hours may have been much longer, leading to accumulation with a peak after >3 half-lives, compatible with the observed delayed increase in CK. Indeed, severe renal impairment is expected to result on average in about a threefold higher exposure (AUC and C_{max}) to rosuvastatin,[12] and the SLCO1B1 variant, old age and tissue hypoxia in multiorgan failure were additional relevant risk factors for increased exposure and rhabdomyolysis in this case.[4] As an add-on, subsequent renal failure turns into a vicious cycle with further impairment of rosuvastatin elimination and increased toxicity.

Moreover, a recent comprehensive study provides evidence that pharmacogenetic variants significantly contribute to the large interindividual variation in a patient's rosuvastatin pharmacokinetics.[13] We postulate that our patient had an unfavourable genetic predisposition which, together with his acute renal failure, were the principal causes for the rapid onset of severe rhabdomyolysis.

Such a multicausal view has direct implications for the prevention and clinical management of statin-induced myopathy. Due to the distinct pharmacokinetic and interaction profile of different statins, the risk of statin-induced myotoxicity requires a personalised evaluation including the type of statin, individual co-medication and co-morbidities and, if available, information on SLCO1B1 and other relevant genes.

In our case, a proactive drug safety check by a clinical pharmacist first detected the increased risk of myotoxicity associated with rosuvastatin in this patient with acute renal failure. For that purpose, we recommend the routine use of detailed tables in the literature that compare the profiles and impact of different risk factors for different statins. They can guide the selection and dosing of the most suitable statin in individual patients and situations.[4 14] Furthermore, we have previously shown that automated electronic clinical decision support system algorithms can effectively identify and correct inappropriate prescriptions related to renal failure,[15] and we now aim to develop and implement specialised algorithms that can also identify multiple risk factors for myotoxicity in hospitalised patients with statin therapy. Such proactive drug safety measures may identify patients at high risk for statin-induced myopathy and therefore prevent comparable cases of myotoxicity in the future.

Learning points

- ⇒ Statin-induced rhabdomyolysis is a rare but severe adverse drug reaction with multiple static and dynamic risk factors. If a new dynamic risk factor—that is, acute renal failure—is added, rhabdomyolysis can develop rapidly, even in patients with previously well-tolerated statin therapy.
- ⇒ SLCO1B1 pharmacogenetics (analysis for heterozygous or homozygous non-functional genetic variants) without other risk factors have a low predictive value for statin-induced myotoxicity. However, with a better understanding of the significance of certain pharmacogenetic variants, they are recognised to play an important causal role as part of a sufficient component set of environmental and genetic causes in individual patients.
- ⇒ We advocate a systematic evaluation of static and dynamic risk factors for statin-induced myopathy in high-risk settings, and a consideration of the distinct pharmacokinetic profiles of different statins. Such an approach can then guide individualised selection and dosing of the most suitable statin for each patient and thereby reduce the risk of statin-induced myopathy.

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Contributors RL and MP are the principal treating physicians on the ICU and provided content regarding the patient's clinical course, interpretation of the laboratory data and the muscle biopsy. AS was the nephrologist in charge of the patient on the normal ward. SR was the initiator for the pharmacogenetic testing and interpretation of these results and provided the pharmacovigilance context and the multicausal view. DFN is guarantor, wrote the first draft, drew the figures, and came up with the concept for implementing automated alerts for the prevention of similar rosuvastatin-related cases of myotoxicity in patients with renal impairment.

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Ethics approval This is a case report and consent from the patient's next of kin was obtained after the occurrence of the adverse event.

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