

Case Report

Simvastatin-induced myoglobinuric acute kidney injury following ciclosporin treatment for alopecia universalis

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Abstract

Alopecia areata can affect the entire scalp (alopecia totalis) or cause loss of all body hair (alopecia universalis). Ciclosporin (CsA) has been suggested for its treatment, with controversial results. Concomitant use of statins and CsA may increase the risk of rhabdomyolysis due to drug–drug interactions.

Here we report the case of a 45-year-old woman treated with CsA for alopecia universalis, who presented a severe myoglobinuric acute kidney injury following the concomitant use of simvastatin. Upon admission to our unit, she was oligo-anuric. Her serum creatinine level was 13.8 mg/dl. CsA and simvastatin therapy were stopped, and haemodialysis treatment was started (eight daily dialysis sessions) until sufficient kidney function was regained. After 1 month, her serum creatinine level was 3.5 mg/dl; after 2 months and onwards (follow-up of 4 months), her serum creatinine level was 1.4 mg/dl and creatinine clearance was 43.2 ml/min.

In conclusion, physicians should be aware of the potential risks of the combined use of CsA and statins. Patients should be advised to report any muscle symptoms when they are on statins and CsA. The laboratory follow-up should include the monitoring of serum creatinine and muscle enzyme levels, blood CsA levels and liver function tests.

Keywords: acute kidney injury; ciclosporin; myoglobinuria; simvastatin

Introduction

Alopecia areata is a disorder in which there is loss of hair causing patches of baldness; it is one of the most frequent organ-restricted autoimmune diseases [1]. It can affect the entire scalp (alopecia totalis) or cause loss of all body hair (alopecia universalis). Few treatments for alopecia areata have been well evaluated in randomized trials, and no completely effective treatment has been established [2]. Hypertrichosis, one of the most common side effects of orally administered ciclosporin (CsA), encouraged a number of investigators to use this drug for the treatment of alopecia

areata; however, the reports on this subject have been controversial [3]. Co-administration of statins and CsA is often encountered in clinical practice since CsA itself can cause dyslipidaemia. CsA is a potent inhibitor of simvastatin metabolism and may therefore facilitate simvastatin-induced rhabdomyolysis [4].

Here we report the case of a 45-year-old woman treated with CsA for alopecia universalis, who presented a severe myoglobinuric acute kidney injury following the concomitant use of simvastatin.

Case report

On 5 August 2009, a 45-year-old Caucasian woman was admitted to our unit with severe oligo-anuric acute kidney injury. Her past medical history included three episodes of alopecia areata treated with minoxidil and undetermined topical therapy between 1995 and 2007. Her disease became acute in March 2007; she underwent steroid therapy and phototherapy without any improvement. She was admitted to the dermatology unit of another hospital in July 2008; a scalp biopsy was done, and the diagnosis of alopecia universalis was made. She was treated with weekly subcutaneous injections of efalizumab without any clinical benefit (August to December 2008). She started CsA (150 mg twice a day) and azathioprine (50 mg once a day) in January 2009. Her serum creatinine level was 0.62 mg/dl (estimated glomerular filtration rate by MDRD equation: 110.64 ml/min per 1.73 m²). After 1 month, the blood CsA level was 330 ng/ml and serum creatinine level was 0.8 mg/dl (Figure 1). It is worth noting that the attending dermatologist advised (erroneously) the patient to take only the morning dose of CsA on the day preceding the measurement of all blood CsA levels. CsA dosage was increased to 200 mg twice a day in March 2009. Blood CsA and serum creatinine levels were as follows, respectively: 588 ng/ml and 1.1 mg/dl in March, 720 ng/ml and 1.5 mg/dl in April, 459 ng/ml and 1.8 mg/dl in May, 467 ng/ml and 2.6 mg/dl in June. On 1 July 2009, the patient started treatment with simvastatin (20 mg a day) because of high levels of serum total cholesterol

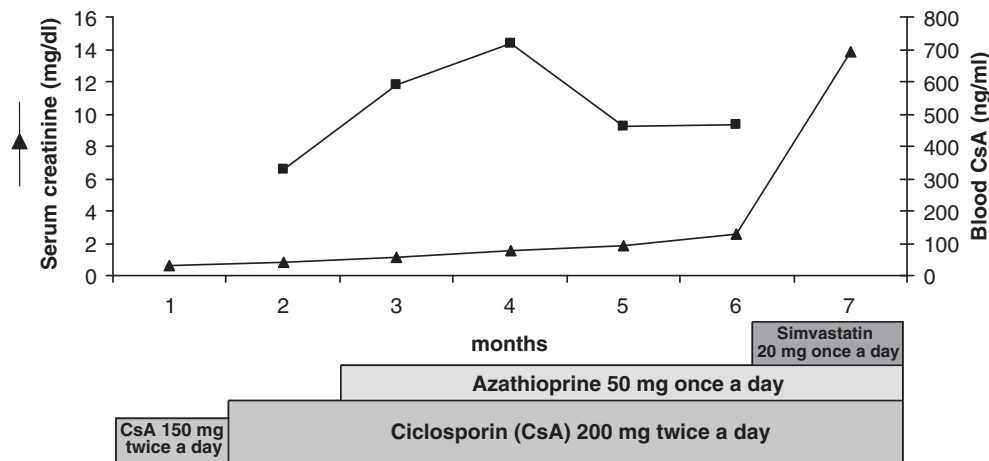


Fig. 1. Course of patient's renal function as depicted by her serum creatinine level plotted against time. The figure shows also blood CsA levels and the 7-month drug regimen of the patient.

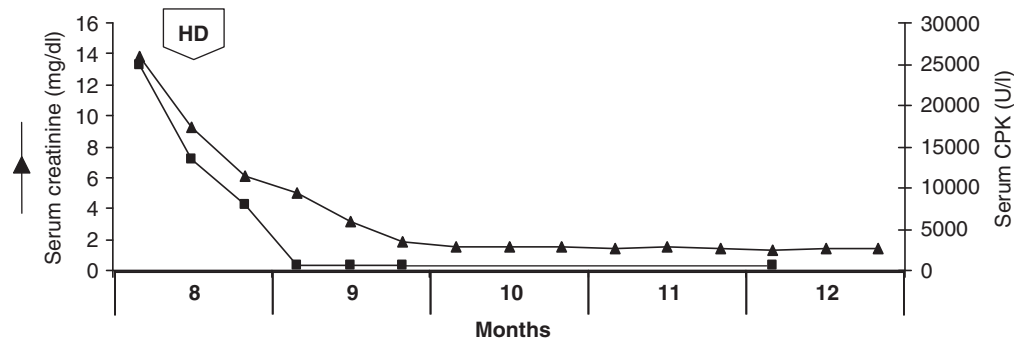


Fig. 2. Course of patient's renal function as depicted by her serum creatinine level plotted against time. The patient needed a total of eight consecutive daily haemodialysis sessions before the partial recovery of renal function. The highest serum total CPK level was 25 122 U/l on the first hospital day and gradually declined over time.

(286 mg/dl) (Figure 1). Upon admission to our division, the patient presented profound muscle pain and weakness with red/brown urine and a very low urine output. Her blood pressure was 135/75 mmHg, body temperature was 36.8°C, heart rate was 85 beats/min and body mass index was 27.7 kg/m². Also, her serum levels were as follows: creatinine 13.8 mg/dl (Figures 1 and 2), sodium 128 mmol/l, potassium 6.4 mmol/l, chloride 96 mmol/l, glucose 105 mg/dl, phosphorus 7.4 mg/dl, total bilirubin 0.9 mg/dl, uric acid 5.4 mg/dl, aspartate transaminase 1961 U/l (normal values 15–37), alanine transaminase 655 U/l (normal values 30–35) and alkaline phosphatase 90 U/l (normal values 50–136). Serum total creatine phosphokinase (CPK), serum myoglobin and serum lactate dehydrogenase levels were, respectively, 25 122 U/l (normal values 20–232) (Figure 2), 17 979 ng/ml (normal values 10–92) and 3209 U/l (normal values 100–190). Blood urea nitrogen was 170 mg/dl, haemoglobin 9 g/dl, haematocrit 26.9%, platelets 239 000/mm³ and white blood cell count 9500/mm³; prothrombin time and partial thromboplastin time were normal. Urinalysis showed no red or white blood cells and a positive dipstick for protein. Renal ultrasound showed normal kidney volume with normal thickness, a small increase of echogenicity, no hydronephrosis and a slightly increased intraparenchymal

resistance index, 73. The diagnosis was of oligo-anuric myoglobinuric acute kidney injury due to the concomitant use of simvastatin and CsA. Both drugs were withdrawn; the patient started haemodialysis treatment utilizing a central vein catheter inserted into the right femoral vein. She underwent eight consecutive daily dialysis sessions. On the ninth hospital day, her 24-hour urine output was 600 ml; haemodialysis was permanently discontinued; 2 days later urine output had increased to 1800 ml a day, although serum creatinine levels remained persistently increased. On 5 September 2009, serum levels were as follows: creatinine 3.5 mg/dl, sodium 140 mmol/l, potassium 5.2 mmol/l, glucose 100 mg/dl, phosphorus 3.7 mg/dl, aspartate transaminase 24 U/l, alanine transaminase 48 U/l, alkaline phosphatase 90 U/l, total CPK 56 U/l, myoglobin 108 ng/ml, bilirubin 0.7 mg/dl and uric acid 3.3 mg/dl; blood urea nitrogen was 48 mg/dl, haemoglobin 9.8 g/dl, haematocrit 30%, platelets 320 000/mm³ and white blood cell count 6800/mm³ (Figure 2). After 2 months and onwards (follow-up of 4 months), serum creatinine level was 1.4 mg/dl and creatinine clearance was 43.2 ml/min (Figure 2). The final diagnosis of chronic kidney disease was made consequent to an episode of severe oligo-anuric myoglobinuric acute kidney injury due to the concomitant use of simvastatin and CsA.

Discussion

Alopecia areata is one of the most frequent organ-restricted autoimmune diseases, yet its pathogenesis is still unclear [1]. Alopecia areata is a relatively common condition affecting 0.15% of the population [2]. Although in many cases it can be a self-limiting condition, hair loss can often have a severe social and emotional impact. Here we report the case of a 45-year-old woman treated with CsA for alopecia universalis, who presented a severe oligo-anuric myoglobinuric acute kidney injury following the concomitant use of simvastatin. She received an initial daily CsA dose of 4.0 mg/kg, which was increased to 5.3 mg/kg after 2 months. Blood CsA levels were always above the commonly accepted targets; they would have been much higher if the patient had taken the usual evening dose on the day preceding the measurement of all blood CsA levels. When the patient started simvastatin, serum creatinine level was 2.6 mg/dl. Nephrotoxicity is the major therapeutic limitation to the use of CsA. Acute nephrotoxicity of CsA is usually dose dependent; it is caused by afferent arteriolar vasoconstriction, which has been attributed to the activation of the renin-angiotensin system, to increased sympathetic activity and to altered balance between vasoconstrictor and vasodilator agents [5]. Acute renal toxicity may be reversible if the doses of CsA are reduced [6]. Chronic nephrotoxicity, characterized by prolonged arteriopathy that may lead to vascular occlusion with consequent striped interstitial fibrosis and tubular atrophy [6], is not reversible.

Simvastatin, a hydroxymethylglutaryl coenzyme A (HMG-CoA) reductase inhibitor, is an inactive hydrophobic lactone pro-drug which is metabolized in the liver by cytochrome P450 3A4 isoenzyme (CYP3A4) [7]. Drug-drug interactions between HMG-CoA reductase inhibitors and a given series of drugs most often result in increased plasma statin concentrations and related rhabdomyolysis [4]. The risk of statin-induced rhabdomyolysis is significantly increased when statins are used concomitantly with drugs such as fibrates, CsA, macrolide antibiotics, azole antifungals, digoxin, warfarin, verapamil, amiodarone or diltiazem [8]. Simvastatin interacts with CsA, both drugs being metabolized by the same hepatic enzyme system, CYP3A4; CsA is a potent inhibitor of simvastatin metabolism and may therefore facilitate simvastatin-induced rhabdomyolysis and myoglobinuric acute kidney injury. Co-administration of statins and CsA is, moreover, often encountered in the clinical practice since CsA itself can cause dyslipidaemia.

Cases of rhabdomyolysis in transplant recipient patients receiving simvastatin and CsA have been reported [9]. Therefore, some authors recommend not prescribing simvastatin at doses higher than 10 mg a day in patients treated with CsA because of the pharmacokinetic interaction between the two drugs [10]. Vanhaecke *et al.* demonstrated that even low simvastatin doses may induce adverse events

in CsA-treated patients with serum total CPK levels increased by 5–44 times the upper normal limit [11].

Fatal rhabdomyolysis after statins is very rare, with a reported rate of the Food and Drug Administration of 0.12 per 1 million prescriptions of simvastatin among all patients [12]; however, prognosis depends on severity and comorbid conditions, with a mortality of 52% in patients with acute kidney injury [13].

In conclusion, physicians should be aware of the potential risks of the combined use of CsA and statins. Patients should be advised to report any muscle symptoms when they are on statins and CsA. The laboratory follow-up should include the monitoring of serum creatinine and muscle enzyme levels, blood CsA levels and liver function tests.

Conflict of interest statement. None declared.

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