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Case Report

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Rhabdomyolysis and acute kidney injury induced by the association of rosuvastatin and abiraterone: A case report and review of the literature

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Abstract

Introduction: Abiraterone acetate is an inhibitor of androgens biosynthesis, approved as first-line treatment in castration-resistant prostate cancer and metastatic castration-sensitive prostate cancer. Abiraterone has been rarely associated with severe rhabdomyolysis, but the mechanism of muscle toxicity is unknown.

Case report: We hereby present a case of severe rhabdomyolysis resulting in acute on chronic kidney injury following abiraterone initiation in a patient previously under rosuvastatin.

Management and outcome: Rhabdomyolysis was resolutive after rosuvastatin and abiraterone discontinuation, and kidney function recovered. There was no recurrence of muscle toxicity after re-initiation of abiraterone alone.

Discussion: Abiraterone selectively inhibits CYP17 as well as the hepatic transporter OATP1B1. OATP1B1 is an efflux transporter, whose function is to extract several drugs from the portal blood, allowing them to undergo hepatic metabolism. We hypothesize that abiraterone-induced inhibition of plasmatic uptake of rosuvastatin by OATP1B1 increased plasmatic concentration of rosuvastatin, leading to toxicity on muscle cells. We therefore suggest that the association between rosuvastatin and abiraterone should be avoided.

Keywords

Abiraterone, rosuvastatin, rhabdomyolysis, acute kidney injury, OATP1B1, uptake transporter

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Introduction

Rhabdomyolysis is a syndrome of muscle injury defined as an increase in creatine kinase (CK) plasma level above 500 U/L.[1] Plasma levels higher than 5000 IU/L are well correlated with a risk of acute kidney injury (AKI). Furthermore, AKI consecutive to rhabdomyolysis is associated with mortality as high as 50% in some series.[2]

Rhabdomyolysis is usually caused by a specific event, most commonly traumatic injury, ischaemic stroke or the use of medications. Among those, statins have a higher risk to generate skeletal muscle side effects, alone or in combination with other drugs owing to interference at the level of uptake/transport or metabolisation. Besides, some risk factors are associated with drug-induced rhabdomyolysis: age >65 years, chronic kidney disease or diabetes mellitus.

Abiraterone acetate (hereafter referred to as abiraterone) is a selective and irreversible inhibitor of

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CYP17 that blocks synthesis of androgens in tissues such as prostate, tumour cells, adrenal glands and testes. In combination with prednisone, it has been shown to significantly increase overall survival[3] and provide additional clinical benefits in patients with metastatic, castration-resistant prostate cancer who have not received chemotherapy and in those who have received docetaxel.[4,5] More recently, the addition of abiraterone plus prednisone to androgen-deprivation therapy was also found to be associated with longer overall survival and longer radiographic progression-free survival than androgen-deprivation therapy alone in patients with newly diagnosed, metastatic castration-sensitive prostate cancer.[6] According to the American Urology Association guidelines,[7] abiraterone is now considered first-line treatment for metastatic prostate cancer. Given the high incidence of prostate cancer in the population, its use is expected to increase significantly in the next years.

Hereby, we report a case of rhabdomyolysis induced by the combination of rosuvastatin and abiraterone. We suggest an interaction mechanism, based on rosuvastatin uptake transporter OATP1B1, leading to severe toxicity.

Case report

A 74-year-old Caucasian man was admitted in the Emergency Department with complaints of weakness, diffuse muscle pain and loss of appetite for 10 days. The patient had a significant history of ischaemic cardiopathy, atrial fibrillation and chronic renal disease (stage IV). He was recently diagnosed with metastatic castration-resistant prostate cancer after trans-urethral resection of prostate with JJ stent placement. Androgenic deprivation therapy with degarelix acetate was then initiated. As extension work-up showed multiple bone metastasis, the patient began to take abiraterone (1000 mg/day) and prednisone (5 mg/day) two months prior his admission.

His current medications included rosuvastatin 40 mg/day, metoprolol 50 mg/day, acetylsalicylic acid 100 mg/day and degarelix acetate 80 mg/month. The only medications recently initiated were abiraterone and prednisone.

Physical examination in the emergency room was unremarkable.

Blood tests highlighted an acute renal failure with serum creatinine level at 9.12 mg/dL (normal value (NV): 0.6–1.3 mg/dL; last value measured at 2.37 mg/dL six weeks ago), urea level at 270 mg/dL (NV: 15–50 mg/dL), with mild acidosis (bicarbonate level at 11.9 mmol/L) and a rhabdomyolysis with CK level at 5763 U/L (NV: 20–200 IU/L), lactate dehydrogenase level at 411 IU/L (NV: <250 IU/L), aspartate aminotransferase level at 193 IU/L (NV: 19–48 IU/L) and alanine aminotransferase level at 46 IU/L (10–40 U/L). The rest of the routine analysis was unremarkable. Urinalysis showed a protein level at 1.8 g/g creatinine with a blood cell count at 203/field and a red cell numeration at 238/field without dysmorphism. The fraction of sodium excretion was calculated at 12.3%.

Urinary tract computed tomography showed no hydronephrosis.

Management and outcome

The diagnosis of drug-induced rhabdomyolysis leading to AKI was suspected. The patient was admitted to the intensive care unit (ICU) and rosuvastatin, prednisone and abiraterone were discontinued. Intravenous fluids were administered.

The patient responded well to fluid infusion and discontinuation of nephrotoxic medications with an immediate increase in urine output and a decrease in serum creatinine and CK value. He was discharged from the ICU to the nephrology ward 24 h later. CK values decreased gradually and reached normal values 10 days after admission. Serum creatinine reached its baseline value by hospital day 12. The patient was discharged home after 24 days.

One month later, because interaction between abiraterone and rosuvastatin was the suspected mechanism for muscle toxicity, abiraterone and prednisone were re-initiated under close monitoring. CK values remained strictly normal. A few weeks later, the patient developed a new episode of AKI, associated with hydronephrosis and attributed to JJ stent dysfunction. Renal function recovered after the replacement of the JJ stent. However, due to the progression of renal disease, and despite the fact that the latter AKI episode was related to obstructive nephropathy, abiraterone was discontinued and not re-initiated. Three months later, the patient remains progression-free under a sole degarelix treatment. The evolution of CK and creatinine values is shown in Figure 1.

Discussion

In clinical trials of abiraterone, the most common adverse events of any grade ($\geq$10%) were fatigue, arthralgia, hypertension, nausea, oedema, hot flush, diarrhoea, vomiting, upper respiratory infection, cough and headache. The most common laboratory abnormalities of any grade (>20%) were anaemia, elevated alkaline phosphatase, hypertriglyceridemia, lymphopenia, hypercholesterolemia, hyperglycaemia and hypokalemia.[3–6,8]

Few cases of abiraterone-induced rhabdomyolysis have been described since 2011.[9–13] Interestingly,

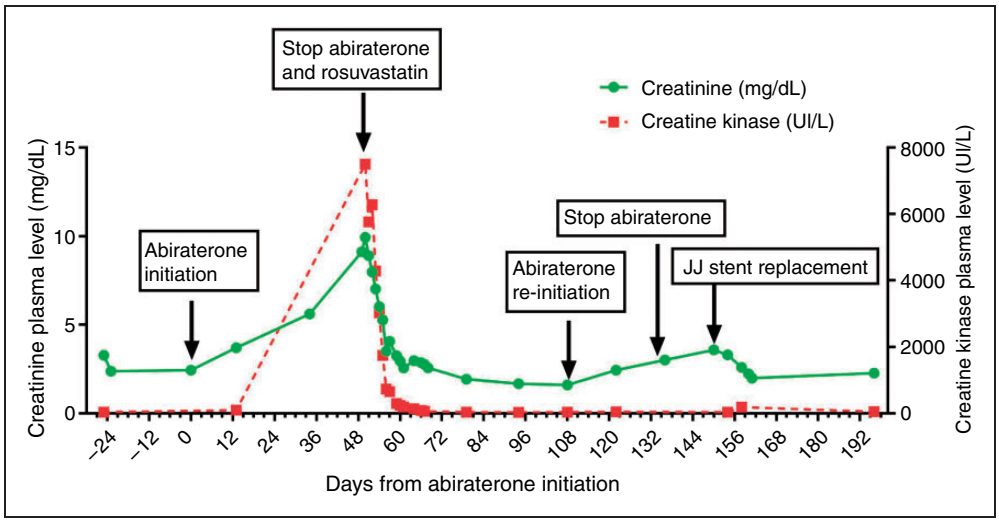

Figure 1. Time course of creatine kinase and creatinine plasma levels.

abiraterone was associated to rosuvastatin in nearly all the cases previously reported.[9,10,12]

Our patient was 74 years old, had chronic kidney disease and had been treated with high doses of rosuvastatin for a few years, all three factors being associated with statin muscular toxicity.[2] However, he had never experienced rhabdomyolysis before.

Based on temporal concordance (initiation of abiraterone and prednisone a few weeks before), we hypothesized that the interaction between abiraterone and rosuvastatin was the cause of rhabdomyolysis in our patient. The resolution of rhabdomyolysis after the discontinuation of abiraterone, rosuvastatin and prednisone, and the absence of recurrence after the re-initiation of abiraterone and prednisone support our hypothesis. The DIPS (Drug Interaction Probability Score) was used to assess the probability of drug interaction in our patient. It was qualified as 'probable', with a score of 5 (full scoring grid in Supplemental File).[14]

Rosuvastatin undergoes hepatic metabolism, with a low conversion into N-desmethylrosuvastatin through CYP2C9, 90% of the drug being eliminated in the bile without transformation. However, hepatic metabolism and elimination depend on the extraction of the drug from the portal blood by the liver, through uptake transporters.[15] Rosuvastatin is the substrate of the uptake transporter organic anion transporting polyprotein 1B1 (OATP1B1) and of the efflux transporter breast cancer resistance protein (BCRP).[16]

According to product information, abiraterone and its metabolites inhibit the hepatic uptake transporter OATP1B1.[17] Therefore, abiraterone could increase the plasma concentration of rosuvastatin through the inhibition of OATP1B1 and increase the risk of muscular toxicity.

The clinical importance of OATP1B1 in the pharmacokinetics of drugs has been suggested by several studies that focused on the effect of commonly occurring single-nucleotide polymorphisms in OATP1B1.[18] The OATP1B1*15 variant, found in 16–24% of the population in Europe and America is associated to a reduced transport activity and to increased plasma levels of certain OATP1B1 substrates.[19] Besides, the administration of other OATP1B1 inhibitors such as cyclosporine, gemfibrozil, cobicistat and several antidiabetic drugs (glimepiride, pioglitazone) has been shown to increase the serum concentrations of rosuvastatin, with clinically significant toxicity in some cases.[20]

After genetic testing, we determined that our patient was not a carrier of the OATP1B1*15 variant, leaving the toxic inhibition of OATP1B1 by abiraterone as the most likely hypothesis to explain the muscular toxicity of rosuvastatin. Unfortunately, we were not able to measure plasma concentrations of rosuvastatin in our patient and thus to prove this hypothesis.

In our case, the early recognition of drug-induced rhabdomyolysis and the immediate discontinuation of abiraterone and rosuvastatin were of paramount importance in order to avoid irreversible kidney injury. After normalization of kidney function, the careful re-initiation of abiraterone, without recurrence of rhabdomyolysis, supported the interaction-based hypothesis as to the origin of rhabdomyolysis and renal toxicity.

We present a case of rhabdomyolysis, a rare but potentially serious complication of combined treatment with abiraterone and rosuvastatin. We suggest a new interaction mechanism leading to rhabdomyolysis, through an abiraterone-induced inhibition of the plasmatic uptake of rosuvastatin by OATP1B1, leading to an increased plasmatic concentration of rosuvastatin

and to an increased risk of toxicity on muscle cells. Therefore, we suggest that the association of rosuvastatin and abiraterone should be avoided. Besides, our case highlights the importance of checking all the prescription drugs for potential interactions while faced with a case of possible drug toxicity.

Consent

The patient gave his consent for reporting the data presented in the manuscript.

Declaration of conflicting interests

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Supplemental material

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References

1. Bosch X, Poch E and Grau JM. Rhabdomyolysis and acute kidney injury. *N Engl J Med* 2009; 361: 62–72.
2. Zimmerman JL and Shen MC. Rhabdomyolysis. *Chest* 2013; 144: 1058–1065.
3. de Bono JS, Logothetis CJ, Molina A, et al. Abiraterone and increased survival in metastatic prostate cancer. *N Engl J Med* 2011; 364: 1995–2005.
4. Rathkopf DE, Smith MR, de Bono JS, et al. Updated interim efficacy analysis and long-term safety of abiraterone acetate in metastatic castration-resistant prostate cancer patients without prior chemotherapy (COU-AA-302). *Eur Urol* 2014; 66: 815–825.
5. Ryan CJ, Smith MR, de Bono JS, et al. Abiraterone in metastatic prostate cancer without previous chemotherapy. *N Engl J Med* 2013; 368: 138–148.
6. Fizazi K, Tran N, Fein L, et al. Abiraterone plus prednisone in metastatic, castration-sensitive prostate cancer. *N Engl J Med* 2017; 377: 352–360.
7. Lowrance WT, Murad MH, Oh WK, et al. Castration-resistant prostate cancer: AUA guideline amendment 2018. *J Urol* 2018; 200: 1264–1272.
8. Fizazi K, Scher HI, Molina A, et al. Abiraterone acetate for treatment of metastatic castration-resistant prostate cancer: final overall survival analysis of the COU-AA-301 randomised, double-blind, placebo-controlled phase 3 study. *Lancet Oncol* 2012; 13: 983–992.
9. Dineen M, Hansen E, Guancial E, et al. Abiraterone-induced rhabdomyolysis resulting in acute kidney injury: a case report and review of the literature. *J Oncol Pharm Pract* 2018; 24: 314–318.
10. Moore DC and Moore A. Abiraterone-induced rhabdomyolysis: a case report. *J Oncol Pharm Pract* 2017; 23: 148–151.
11. Moore DC and Ringley JT. Rhabdomyolysis with abiraterone exposure: a brief review of the Food and Drug Administration Adverse Event Reporting System (FAERS). *Ann Pharmacother* 2018; 52: 1160–1161.
12. Neyra JA, Rocha NA, Bhargava R, et al. Rhabdomyolysis-induced acute kidney injury in a cancer patient exposed to denosumab and abiraterone: a case report. *BMC Nephrol* 2015; 16: 118.
13. Ghafouri S and Drakaki A. Abiraterone-induced rhabdomyolysis in prostate cancer: a report of two cases and review of the literature. *Ann Clin Case Rep* 2018; 3: 1533.
14. Horn J, Hansten P and Chan LN. Proposal for a new tool to evaluate drug interaction cases. *Ann Pharmacother* 2007;41: 674–680.
15. Micromedex® (electronic version). IBM Watson Health, Greenwood Village, CO, USA, https://www.micromedexsolutions.com/ (accessed 21 April 2020).
16. Pasanen MK, Fredrikson H, Neuvonen PJ, et al. Different effects of SLCO1B1 polymorphism on the pharmacokinetics of atorvastatin and rosuvastatin. *Clin Pharmacol Ther* 2007; 82: 726–733.
17. Janssen Biotech Inc. Abiraterone acetate oral tablets. Product Information. Horsham, PA: FDA, 2014.
18. van de Steeg E, Greupink R, Schreurs M, et al. Drug-drug interactions between rosuvastatin and oral antidiabetic drugs occurring at the level of OATP1B1. *Drug Metab Dispos* 2013; 41: 592–601.
19. Pasanen MK, Miettinen TA, Gylling H, et al. Polymorphism of the hepatic influx transporter organic anion transporting polypeptide 1B1 is associated with increased cholesterol synthesis rate. *Pharmacogenet Genomics* 2008; 18: 921–926.
20. Farmer JA and Gotto AM Jr. Antihyperlipidaemic agents. Drug interactions of clinical significance. *Drug Saf* 1994; 11: 301–309.