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CASE REPORT

Rhabdomyolysis Induced by the Interaction Between Ribociclib and Statins- Case Report and Literature Review

Omar Badran[1], Mahmoud Abu Amna[1,2], Ilit Turgeman[1], Gil Bar-Sela[1,2]

[1]Department of Oncology, Emek Medical Center, Afula, Israel; [2]Technion Integrated Cancer Center, Faculty of Medicine, Technion, Haifa, Israel

Correspondence: Gil Bar-Sela, Oncology & Hematology Division, Emek Medical Center, Yitshak Rabin Boulevard 21, Afula, 1834111, Israel, Tel +972 04-6495725, Fax +972 04-6163992, Email gilbarsela1@gmail.com

Abstract: Cyclin-dependent kinase (CDK) 4/6 inhibitors given with endocrine therapy are standard of care for the treatment of women with advanced hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER-2) negative breast cancer. Ribociclib is a CDK 4/6 inhibitor with moderate to solid inhibition of CYP3A4, a member of the cytochrome P450 family oxidase system, which may lead to interactions with medicinal substrates that are metabolized via CYP3A4. Statins are among the most widely prescribed medications worldwide, predominantly metabolized by the CYP3A4 isoenzyme. Rhabdomyolysis is a known rare side effect of statins, commonly triggered by drug interactions. We report a case of a 73-year-old woman with metastatic HR-positive and HER-2 negative breast cancer who developed rhabdomyolysis and acute kidney injury due to interaction between simvastatin and ribociclib with a literature review.

Keywords: creatine kinase, CK. acute kidney injury, CYP3A4, drug interaction

Introduction

CDK 4/6 inhibitors have become an essential component in the treatment of hormone receptor (HR) positive and human epidermal growth factor receptor 2 (HER-2) negative breast cancer.[1] The three CDK 4/6 inhibitors used today are abemaciclib, palbociclib, and ribociclib. Ribociclib is approved for patients with advanced or metastatic breast cancer, in combination with an aromatase inhibitor (AI)[2,3] or fulvestrant.[4] Recent data with an extended follow-up of 6.6 years showed that adding ribociclib to AI improved overall survival (OS).[5] The drug may cause various side effects such as anemia, lymphocytopenia, neutropenia, increased liver enzymes, fatigue, arthralgia, increased serum creatinine, and rarely, prolonged QT interval on ECG.[2–4] In addition, ribociclib is a moderate to potent CYP3A4 inhibitor and may interact with medicinal substrates that are metabolized via CYP3A4, which can lead to the increased serum concentration of the concomitantly used medicinal product.[5]

Statins are usually selected as the first-line therapy to lower plasma levels of low-density lipoprotein cholesterol (LDL-C) and as part of the treatment of cardiovascular disease (CVD), to reduce the risk of myocardial infarction, stroke, and other CVD.[6–9]

In rare cases, the best recognized and most reported adverse effects (AEs) of statins are related to muscle injury, including muscle pain, fatigue, and rhabdomyolysis.[10,11] Rhabdomyolysis is the most feared complication of statins; it occurs when severe muscle damage leads to a marked elevation of creatinine kinase (CK), often accompanied by evidence of renal dysfunction and occasionally renal failure and death.[12,13] The most common etiologies of rhabdomyolysis include alcohol abuse, strenuous exercise, trauma, medicinal drug use, hyperthermia, toxins, ischemia, infections, inflammation, metabolic myopathies, and genetic factors.[13] Management of patients with rhabdomyolysis includes advanced life support (airway, breathing, and circulation), followed by measures to preserve renal function.[12,13] Simvastatin is metabolized predominantly by

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cytochrome P450 3A4 (CYP3A4, ie, family 3, subfamily A, polypeptide 4; encoded by the CYP3A4 gene).[14] Interactions with CYP3A4 inhibitors may be life-threatening.

We describe a case of a 73-year-old woman who developed rhabdomyolysis following a drug–drug interaction due to the concomitant use of simvastatin and ribociclib.

Case Report

The patient was a 73-year-old woman with a medical history of hypertension, atrial fibrillation, hyperlipidemia, and diabetes mellitus. Her chronic medications included bisoprolol 2.5 mg daily, apixaban 5 mg twice daily, glargine 32 units daily, valsartan-hydrochlorothiazide 160\25 mg, and simvastatin 40 mg, all of which she took daily for several years. In 2006, she was diagnosed with stage IIB left breast infiltrating carcinoma, which was HER-2 negative, and HR-positive. She underwent a lumpectomy and received adjuvant chemotherapy and radiation therapy. In July 2008, she initiated treatment with tamoxifen and, in October 2010, was switched to anastrozole until 2015.

Five years later, she noticed a mass in her left breast. Positron emission tomography-computed tomography (PET CT) scan revealed locally recurrent disease in the left breast and bone metastatic disease. Biopsy revealed a recurrence with the same pathologic characteristics. In August 2020, the patient began treatment with letrozole, and one month later, ribociclib was added to the treatment at a dose of 600 mg daily. An initial follow-up PET-CT scan in February 2021 revealed a partial response in the left breast and near complete metabolic resolution of the metastatic disease. The patient continued to receive ribociclib with letrozole while continuing simvastatin.

In January 2022, the patient presented with rectal bleeding attributed to internal hemorrhoids, and she complained of general weakness and muscle pain, especially in the lower extremities, and brown-colored urine. On presentation, she was afebrile, with a heart rate of 103 bpm, respiratory rate of 20, blood pressure of 91/58 mmHg, and normal oxygen saturation. Physical examination yielded only mild tachypnea. The patient denied recent physical activity, alcohol ingestion, or taking any over-the-counter supplements.

Initial laboratory findings revealed a creatinine of 2.06 mg/dL (baseline of 1.1 mg/dL), a glomerular filtration rate (GFR) of 14 mL/min, and a creatine kinase of 3070 units/L. Urine analysis showed a moderate amount of myoglobinuria. The ECG was unremarkable, and the chest X-ray showed the presence of left pleural effusion.

A diagnosis of acute kidney injury (AKI) secondary to rhabdomyolysis was made, and simvastatin and ribociclib were stopped following the diagnosis. After a fluid bolus, the patient was treated with crystalloids at 150–200 mL/h. Her urine output was monitored hourly. Fluids were titrated accordingly, and she did not require renal replacement therapy. Her renal functions were monitored daily. Her brown-colored urine (myoglobinuria) was slowly cleared to normal.

The patient gradually improved, and her creatinine gradually decreased to 1.3 mg/dL, GFR to 40.2 mL/min/1.73 m². Upon discharge, ribociclib was re-challenged with a dose of 200 mg daily. Simvastatin was permanently discontinued. As of the last follow-up with a PET-CT scan in March 2022, the patient continues to have non-avid metastatic disease.

Discussion

In ribociclib drug label, rhabdomyolysis is not explicitly listed as an adverse drug reaction, based on the pooled data set from the three Phase III pivotal clinical studies (MONALEESA-2, MONALEESA-3, and MONALEESA-7).[2–4]

The interaction between CDK 4/6 inhibitors like palbociclib or ribociclib with statins is associated with CK elevations of variable severity. However, rhabdomyolysis cases have rarely been reported.[15–17] Since ribociclib is a potent CYP3A4 inhibitor, caution is warranted in the case of concomitant use of other drugs with sensitive CYP3A4 substrates such as fentanyl, everolimus, alfuzosin, and amiodarone.[18]

To our knowledge, three previous case reports have described rhabdomyolysis caused by a combination of the CDK4/6 inhibitor and statins. The first case was a woman who developed necrotizing rhabdomyolysis with progression to death, the second was a 71-year-old woman who developed tetraparesis and rhabdomyolysis a few days after starting the first cycle of palbociclib therapy, and the third case was a 68-year-old woman who developed severe rhabdomyolysis 3 weeks after initiation of ribociclib.[15–17] In all the precedent case reports, the onset of rhabdomyolysis appeared to begin a few weeks after starting CDK4/6 inhibitors. Our patient was treated with statins for many years without developing symptoms of

rhabdomyolysis, since she developed signs of rhabdomyolysis after being treated with ribociclib, implicate that drug–drug interaction as the cause of rhabdomyolysis.

On the one hand, CDK4\6 inhibitors are a vital therapy for HR-positive metastatic breast cancer. On the other hand, statin therapy represents a substantial potential for safe, effective, and inexpensive primary prevention of CVD.[6–9] However, in elderly patients over 70 years, the risk of adverse effects associated with statins increases, particularly myopathy.[19] The benefit of statin drugs on frail patients is not well established. Frail patients are at increased risk for adverse effects and have a low chance of help from statins, mainly due to limited life expectancy.[20–22]

Furthermore, evidence of ribociclib rechallenge following rhabdomyolysis is lacking, and the safety of such a practice remains to be discovered.

In the current case, the treatment possibilities included stopping the CDK4/6 inhibitor, re-challenging the drug, or switching to another CDK4/6 inhibitor, considering the current GFR level. As for statins, the options were to change to other statin drugs or consider stopping statin therapy altogether, given that the benefits in older adults are not well established, especially in primary prevention in a patient with active cancer.

Taking these considerations together with a shared decision process with the patient and her family, ribociclib was re-challenged at a reduced dose, under close follow-up and monitoring.

Conclusion

Medical staff must learn about this interaction between ribociclib and statin treatment to prevent rhabdomyolysis.

Abbreviations

CDK, Cyclin-dependent kinase; HR, hormone receptor; HER-2, human epidermal growth factor receptor 2; CYP3A4, cytochrome P450 3A4; OS, overall survival; ECG, electrocardiogram; LDL-C, low-density lipoprotein cholesterol; CVD, cardiovascular disease; AEs, adverse effects; CK, creatinine kinase; PET CT, Positron emission tomography-computed tomography; GFR, glomerular filtration rate; AKI, acute kidney injury.

Ethics Statement

No institutional approval was required to publish the case details.

Consent Statement

The patient gave written informed consent to the publication of the case report.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis, and interpretation, or in all these areas; took part in drafting, revising, or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the report has been submitted, and agree to be accountable for all aspects of the work.

Disclosure

The authors report no conflicts of interest for this work.

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