

Rhabdomyolysis after transplantation: case report after allogeneic hematopoietic transplantation and review of literature

Abstract

We describe a case of flaccid paraparesis, intervening during treatment with simvastatin cyclosporine and low dose posaconazole, in a patient previously having undergone allogeneic hematopoietic transplantation. Final diagnosis was rhabdomyolysis related to statin. This is the first case reporting posaconazole as an agent favoring rhabdomyolysis when administered together with simvastatin and cyclosporine. In this patient, a low Vitamin D level may also have contributed to establishing rhabdomyolysis. Literature on rhabdomyolysis in transplanted patients is reviewed. Therapeutic choices in transplanted patients needing concomitant therapy with azole and statin are discussed.

Keywords: rhabdomyolysis, statin, hematopoietic stem cell transplantation, myopathy

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Leotta S, Piroso C, Cupri A, Martino E, Spadaro A, Milone Giuseppe

Department of Haematology, Azienda Policlinico Vittorio Emanuele Catania, Italy

Correspondence: Giuseppe Milone, BMT Unit, Department of Haematology, Azienda Policlinico Vittorio Emanuele Catania, Italy, Tel 0039095.7436158, Fax 0039095.7435913, Email Giuseppe.milone@gmail.com

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Abbreviations: VDR, vitamin d receptors; MINE, mesna, ifosfamide, mitoxantrone, and etoposide; PBPC, peripheral blood progenitor cell apheresis; GVHD, graft versus host disease; CSA, cyclosporine; CYP3A4, cytochrome p450 3a4 enzyme; PBPC, peripheral blood progenitor cell apheresis

Introduction

Rhabdomyolysis is a rare and potentially fatal condition.¹ After allogeneic hematopoietic stem cell transplantation, rhabdomyolysis has been reported in association with bacterial² and fungal³ infections, and has also occurred as a complication of sulfamethoxazole/trimethoprim⁴ and statin^{5,6} administration. The frequency of rhabdomyolysis increases during statin therapy concomitant with cyclosporine.^{5,7} The risk of this complication during statin therapy can increase further with the concomitant use of third agents such as macrolides and some azoles, such ketoconazole and itraconazole.⁸⁻¹¹

We here describe a patient who presented with flaccid paraparesis due to rhabdomyolysis, 2 months after having undergone allogeneic hematopoietic stem cell transplantation and during combined therapy with cyclosporine, statin and low dose posaconazole. This is the first case reporting posaconazole as an agent contributing to rhabdomyolysis together with simvastatin and cyclosporin.

Case report

The patient was diagnosed with non-Hodgkin lymphoma, mantle cell type, at the age of 51 years, on November 2007. He had stage IV-B by the Ann Arbor lymphoma staging system. He received for as first-line treatment R-CHOP (rituximab, vincristine cyclophosphamide, adriamycin and prednisolone), followed by HYPER-C-VAD (cyclophosphamide, vincristine, Adriamycin, and dexamethasone alternated with high-dose cytarabine and methotrexate) and showed a complete response, defined as complete disappearance of all lymphoma lesions that were present at diagnosis. The response was consolidated in February 2009 with high-dose BEAM (Bis-chloro-Nitrosurea, etoposide, cytarabine and melphalan) chemotherapy and

autologous peripheral blood stem cell transplantation. The patient relapsed 65 months later, on August 2014. The patient underwent chemotherapy consisting of 4 cycles of MINE (mesna, ifosfamide, mitoxantrone, and etoposide) followed by 2 cycles of ESHAP (etoposide, methylprednisolone, high-dose cytarabine, and cisplatin), and achieved a second complete remission. On October 26th, 2015, at the age of 60 years, while in his second complete remission, the patient received an allogeneic hematopoietic stem cell transplant from an 8/8 HLA-matched unrelated donor. The stem cell source was obtained by G-CSF mobilization and Peripheral Blood Progenitor Cell Apheresis (PBPC). A reduced-intensity conditioning regimen based on thiotepa, cyclophosphamide, and fludarabine was used, with antithymocyte globulin administered at a total dose of 5mg/Kg. Graft versus Host Disease (GVHD) prophylaxis consisted of cyclosporine (CSA) 3mg/Kg iv and short-term methotrexate administered iv for 4 doses, on days +1, +3, +6, +11.

On day +5, idiopathic pneumonia syndrome was diagnosed, and because of this lung toxicity, he was started on corticosteroids at 1.5mg/kg for 1 week, with rapid tapering. Neutrophil engraftment was achieved at day +11. On day +30, the patient was discharged on CSA at dose of 3.5mg/Kg/day po and prednisolone 0.5mg/kg po, posaconazole 200mg q 12 h po was also prescribed, as anti mould infection prophylaxis. Trough levels of CSA were assayed in whole blood weekly from the day of transplant to day +100 by chemiluminescent microparticle immunoassay (Abbot- DE), (therapeutic range: 200-400ng/ml) and dosage of CSA modified accordingly to blood level. On day +45, simvastatin 20mg/day po was added to the treatment regimen for hypertriglyceridemia (279mg/dL) and hypercholesterolemia (236mg/dL) revealed by routine monitoring. At start of simvastatin treatment no neurological or myopathy symptoms were present; CSA level was 279ng/ml (day +43), however, after 1 week, an increase of CSA level was noted (478ng/ml), no signs of liver, renal or neurological dysfunction were present, and a 30% decrease of cyclosporine dose was instituted, this promptly resulted in a CSA plasma level within therapeutic range.

After nine days of simvastatin treatment, on day +54 after transplantation, the patient complained of difficulty in walking. There was no fever, no headache, no abnormality of consciousness, neck was supple and no focal neurological defects were present, a bilateral hypo-asthenia in lower limbs was noticed, however, the patellar tendon reflex and sensitivity to tactile and pain stimuli were bilaterally intact. The patient was thought to suffer a corticosteroid associated myopathy and therefore prednisolone dose was reduced to 0.25mg/kg. However, 7 days later, on day +61, the hypo-asthenia had worsened and he was found unable to walk and to stand from the supine position. Again there was no sign of infection, no headache, no abnormality of consciousness, neck was supple and no focal neurological deficits were present, patellar tendon reflexes and sensitivity to tactile and pain stimuli in right and left legs and feet were found intact. On the same day he was admitted into hospital with clinical suspicion of rhabdomyolysis and a plasma CPK assay was immediately performed. At that time blood CSA level was found to be within therapeutic range (345ng/ml).

Laboratory findings on day +61 included the following: AST 2,617 IU/ml, normal values (nv) 0-50, ALT 925 IU/ml (nv: 0-50), CPK 111,460 U/mL (nv: 0-171), myoglobinuria, and proteinuria. Bilirubin, BUN, alkaline phosphatase, thyroid hormones and creatinine levels were all within normal ranges. The findings from brain computed tomography and nuclear magnetic resonance imaging, performed at day +62, were unremarkable. In blood drawn on day +61, patient's vitamin D level was found to be markedly reduced: 10mcg/ml (nv: >20mcg/ml).

Simvastatin and posaconazole were immediately discontinued (day +61); and the patient received intravenous hydration (3L/m²) and urine alkalinization by iv sodium bicarbonate. The patient's strength improved rapidly; and his CPK, ALT, and AST levels dropped over a few days. From day +70 he received a weekly Vitamin D supplementation (2000 IU, po). The patient was discharged two weeks later, on day +75. At the time of writing, he was +335 days after transplantation, with a Karnofsky score¹² of 80% and no sign of underlying disease. He was still receiving cyclosporine and a low-dose steroid for chronic GVHD involving his skin and mouth.

Discussion

Hypercholesterolemia and hypertriglyceridemia develop in 40%-70% of patients after transplantation of solid organs or hematopoietic stem cells¹³⁻¹⁵ and contribute to the high frequency of cardiovascular disease in transplant patients.^{16,17} In addition to the main risk factors seen for the general population, such as obesity, diabetes, hypogonadism, hypothyroidism and genetic factors, transplant patients have specific predisposing factors for hyperlipidemia, such as treatment with corticosteroids or immunosuppressive agents (cyclosporine, sirolimus, and to a lesser extent, tacrolimus). Acute and chronic GVHD are also important with regard to hyperlipidemia, independently of any treatment administered.¹³

Statins are effective for controlling the hypercholesterolemia and hypertriglyceridemia of patients who have received an allogeneic hematopoietic stem cell transplant¹³⁻¹⁷ or solid organ transplant.^{18,19} However, statins are pleiotropic compounds provided with anti-inflammatory, immunomodulatory, and antithrombotic effects. Based on such effects, statins have also been proposed after allogeneic transplantation as prophylaxis for reducing the risk of acute and chronic GVHD.^{20,21}

Myopathy is a known adverse event associated with statin treatment. Statin-associated myopathy is defined by muscle symptoms and in elevated CPK >10 above normal value. It occurs only rarely in the general population (0.1%).²² The more severe form of muscle damage, rhabdomyolysis, is defined as an elevation of CPK >50 fold that of normal value, myoglobinemia, myoglobinuria and myoglobin induced renal failure. Rhabdomyolysis during statin treatment has an incidence < 0.0001%.²²

After treatments using cyclosporine and statins, a total of 27 cases of rhabdomyolysis have been reported in the literature. Twenty cases of rhabdomyolysis have been reported after solid organ transplantation,²³⁻⁴² 2 cases after allogeneic hematopoietic stem cell transplantation^{5,6} while 5 cases of rhabdomyolysis occurred in patients assuming cyclosporine for other clinical reasons.^{7,43-46} In heart transplant recipients treated with statins, frequency of myopathy was estimated between 10% and 20%,⁴⁷ while in a retrospective study of patients who underwent marrow transplant and were treated with statins, myopathy was found in 1%.¹³ Since in transplanted heart recipients, as in hematopoietic transplant recipients, the frequency of myopathy after statin treatment is increased with respect to that found in the general population, an increased risk of rhabdomyolysis could be expected in transplanted patients. Indeed, in a retrospective study that examined the course of 20,366 patients who received renal transplantation, there were 62 individual cases of rhabdomyolysis with a cumulative incidence of 0.3%.⁴⁸ More data regarding the risk of statin-related rhabdomyolysis after various types of transplantation are required.

The increased incidence of myopathy in transplanted patients who are treated with cyclosporine and statins is thought to result from the fact that cyclosporine and most statins are metabolized by the cytochrome P450 3A4 enzyme (CYP3A4). Such agents, administered together, compete for the same metabolic pathway, leading to increased plasma levels of both drugs.⁴⁹ Inhibition of organic anion transporting polypeptide 1B1 (OATP1B1) by cyclosporine may also contribute to such pharmacological interactions, and cyclosporine inhibition of OATP1B1 can, in fact, lead to an increase in the area under the concentration-time curve (AUC) of statins.⁸ The incidence of rhabdomyolysis is also increased by the concomitant use of statins metabolized by CYP3A4 together with agents that inhibit CYP3A4, such as azoles, verapamil, diltiazem, amiodarone, protease inhibitors, fibrates, tricyclic antidepressants, midazolam, tamoxifen and macrolides.^{8,22}

Accordingly, in 9 out of the 22 case reports of myopathy occurring as an adverse effect of statins after transplantation,^{5,6,23-42} the patients receiving a statin and cyclosporine were also treated concomitantly with agents inhibiting CYP3A4, as follows: risperidone (1 case), verapamil (1 case), macrolides (1 case), itraconazole (1 case), clopidogrel (1 case), fibrate (1 case), fusidic acid (1 case), gemfibrozil (1 case) and multiple agents (1 case). In the other 13 cases, rhabdomyolysis was associated with the concomitant use only of cyclosporine and statins. The role that inhibitors of CYP3A4 play in statin-associated myopathy is well established, and the use of azoles together with statins is discouraged, independent of any use of cyclosporine.⁵⁰ Rhabdomyolysis occurred in our patient while he was taking simvastatin together with cyclosporine and posaconazole. We assume that posaconazole might have contributed, even though posaconazole has the lowest inhibitory activity of any azole against CYP3A4^{51,52} and although posaconazole was administered at low

dosage. Our case confirms that the use of simvastatin in a patient taking cyclosporine and posaconazole should be avoided.⁵³ However, posaconazole is widely used after allogeneic transplantation, because it is considered to be the first-line drug for antifungal prophylaxis for patients with GVHD who are being treated with cyclosporine and corticosteroids.⁵⁴ Indeed, the possibility to avoid a concomitant treatment with simvastatin and posaconazole is quite different in general population versus in transplanted patients.

In fact, in general population, a posaconazole treatment is commonly a short length situation and in this case the simvastatin can be easily withdrawn. On the contrary, in transplanted patients, posaconazole is frequently administered as anti-mould prophylaxis in patients treated by corticosteroids, and this treatment lasts usually for some months, therefore in this clinical situation avoidance of lipid lowering agent is not easily done. Furthermore, the patient needing posaconazole prophylactic treatment typically is the one affected by chronic GvHD and this type of patients has a great chance of developing hyperlipidemia and, therefore, is often in need of statin therapy.

Choosing an antilipidemic agent for patients treated with cyclosporine and possibly with an azole is problematic. Pravastatin, roxustatin, and pitavastatin are excreted unmodified and are not metabolized by CYP3A4.^{8,22} However, during treatment with cyclosporine, the pravastatin level has shown a 4- to 23-fold increase⁵⁵ because of the inhibitory activity of cyclosporine against the carrier-mediated biliary excretion of statins.

The metabolism of fluvastatin is independent of CYP3A4; it is metabolized primarily by CYP2C9. It is also unaffected by OATP1B1, and thus AUC of fluvastatin is not affected by cyclosporine. Therefore, fluvastatin may be a safer choice for patients treated with cyclosporine who need a statin.⁵⁶ Other agents that may be safe to use for hyperlipidemia in cases requiring concomitant cyclosporine treatment are fibrate and niacin.⁵³ In addition, if a patient on cyclosporine is prescribed simvastatin, its dosage should be reduced.⁵⁷

Since hyperlipidemia frequently occurs in patients after allogeneic hematopoietic stem cell transplantation, studies comparing the adverse effects of different antilipidemic agents in patients taking cyclosporine seem warranted. These studies might also be useful in identifying the factors predictive for rhabdomyolysis. A low vitamin D level may be involved. A reduced vitamin D level is frequently found after hematopoietic stem cell transplantation; and a low level, which was seen in our patient, seems to be important in statin-associated rhabdomyolysis.⁵⁸ In fact, vitamin D is thought to exert a direct trophic effect on skeletal muscle cells and vitamin D receptors (VDR) have been demonstrated on skeletal muscle cells.⁵⁹ In adults with vitamin D deficiency, atrophy of muscle fiber type II has been found.⁶⁰

Vitamin D exerts also an indirect beneficial effect on skeletal muscle through enhanced absorption of calcium and phosphate.⁶¹ Correcting the vitamin D levels in patients receiving a statin and cyclosporine is therefore indicated. Finally, knowledge of the pharmacological interactions between cyclosporine, statins, and azoles is of the utmost importance for the prevention and early recognition of rhabdomyolysis in the transplantation setting.

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Conflict of interest

The author declares no conflict of interest.

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