Case Report

SEVERE HYPERTRIGLYCERIDEMIA ASSOCIATED WITH EVEROLIMUS TREATMENT AFTER HEART TRANSPLANTATION

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ABSTRACT

Objective: Everolimus, a mammalian target-of-rapamycin (mTOR) inhibitor, is increasingly used post-transplantation due to favorable effects on renal function and malignancy risk when compared to other immunosuppressive treatments such as calcineurin inhibitors. However, it can confer adverse effects such as dyslipidemia, which is not underpinned by any long-term screening and management of dyslipidemia in heart transplant recipients treated with everolimus.

Methods: We report a case of severe hypertriglyceridemia which developed after commencement of everolimus in a heart transplant recipient with a background of Dunnigan-type familial partial lipodystrophy.

Results: The patient is a 36-year-old woman who underwent heart transplantation for dilated cardiomyopathy. About 11 weeks following commencement of everolimus as part of her antirejection medication regime, serum triglyceride level concentration peaked at 5,093 mg/dL (normal, 0.0 to 177.2 mg/dL). There were no clinical complications with triglycerides at this elevated level and it improved substantially following cessation of everolimus and initiation of a high dose intravenous insulin-dextrose infusion.

Conclusion: This case highlights dyslipidemia as a potential complication of everolimus treatment and that appropriate screening is important as lipid lowering medication can effectively control levels and minimize adverse outcomes. **(AACE Clinical Case Rep. 2020;6:e269-e272)**

Abbreviations:
FPLD = familial partial lipodystrophy; **LPL** = lipoprotein lipase; **MMF** = mycophenolate mofetil; **mTOR** = mammalian target-of-rapamycin

INTRODUCTION

Prognosis following heart transplantation continues to improve. Therefore, prevention of chronic post-transplant sequelae such as chronic kidney disease, transplant vasculopathy, and malignancy are increasingly important. Everolimus, a mammalian target-of-rapamycin (mTOR) inhibitor, is increasingly used for immunosuppression following heart transplantation. Its use permits moderation of calcineurin inhibitors and can attenuate adverse effects on renal function and risk of malignancy (1). However, everolimus has the potential for a unique constellation of adverse effects, including dyslipidemia (1), and at present no guidelines exist to inform long-term screening and management of dyslipidemia in heart transplant recipients treated with everolimus.

CASE REPORT

A 36-year-old woman with Dunnigan-type familial partial lipodystrophy (FPLD), glucose intolerance, hypertension, and nonalcoholic fatty liver disease underwent

Submitted for publication April 4, 2020
Accepted for publication June 15, 2020
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DOI: 10.4158/ACCR-2020-0191

heart transplantation for dilated cardiomyopathy. Her glucose intolerance, diagnosed 7 years prior to transplantation following an abnormal oral glucose tolerance test likely as part of her FPLD, was managed with metformin 1,000 mg daily.

Following the heart transplant, the initial immunosuppressive regimen consisted of tacrolimus, mycophenolate mofetil (MMF), and prednisolone. Due to hepatic and gastrointestinal adverse effects, everolimus was substituted for MMF at a dose of 0.25 mg twice daily. Prior to adjustment of antirejection medication, the lipid profile was suboptimal with total cholesterol of 228.2 mg/dL (normal, <232 mg/dL) and triglycerides of 699.7 mg/dL (normal, <177.2 mg/dL) despite treatment with pravastatin and gemfibrozil. One year prior, the total cholesterol was 224.3 mg/dL, triglycerides 389.7 mg/dL, and low-density-lipoprotein cholesterol (LDL-C) 119.9 mmol/L (normal, 154.7 mmol/L) on pravastatin alone. Eleven weeks post everolimus commencement, a plasma sample was noted to be markedly lipemic. Formal lipid studies demonstrated marked hypertriglyceridemia with serum triglycerides of 5,093 mg/dL and hyperlipidemia with total cholesterol elevated at 839.1 mg/dL. Everolimus level was in the therapeutic range at 4.6 μg/L (normal, 3.0 to 8.0 μg/L) and there were no clinical or biochemical features suggestive of pancreatitis (lipase 38 U/L [normal, 0 to 60 38 U/L]). Given the degree of triglyceride elevation, high dose intravenous insulin-dextrose infusion was commenced to rapidly lower serum triglyceride levels. Insulin doses were titrated to triglyceride levels with higher insulin doses supported by infusion of intravenous dextrose to prevent hypoglycemia. The dose response is illustrated in Figure 1, with greater than 13 units of insulin per hour required to effectively lower serum triglyceride concentrations. Please refer to the Supplementary Methods for the conversion of triglyceride and lipid levels from mmol/L to mg/dL, as they were initially recorded in mmol/L.

In conjunction with intravenous insulin, additional lipid lowering therapy was commenced including simvastatin 40 mg daily, fenofibrate 145 mg daily (substituted for gemfibrozil) and fish oil 1,000 mg twice daily. Subcutaneous insulin was continued on discharge with the aim to maintain tight glycemic control and suppression of lipolysis. Everolimus was discontinued and MMF was recommenced at a reduced dose of 750 mg twice daily. About 2 weeks following hospital discharge, triglyceride levels had improved to 779.5 mg/dL, with a total cholesterol level of 228.2 mg/dL. At around 7 months following discharge, total cholesterol remained at 228.2 mg/dL, triglycerides at 363.2 mmol/L, and LDL-C 116 mmol/L. As of August, 2019, with the addition of ezetimibe 10 mg daily to her lipid pharmacotherapy, her triglycerides and total cholesterol levels were 832.6 mg/dL and 251.4 mg/dL, respectively.

In regard to the patient's glycemic control, her HbA1c was 6.5% (48 mmol/mol) at 1 month following transplantation, thus confirming a formal diagnosis of type 2 diabetes mellitus. Alongside the continuation of metformin, insulin therapy (isophane insulin up to 46 units in the morning and insulin aspart pre-meals up to 22 units pre-lunch) was commenced to maintain adequate glycemic control. This is particularly due to frequent fasting blood glucose readings recorded at 216 mg/dL to 234 mg/dL, and prepprandial blood glucose readings recorded at up to 252 mg/dL, especially in the context of long-term immunosuppression with tacrolimus and prednisone therapy for low-grade chronic allograft rejection. Empagliflozin 25 mg daily was later commenced for persistently raised HbA1c readings of greater than 7% (53 mmol/mol; 7.3 to 7.6% [56 to 60 mmol/mol]) at least 10 months post-transplant. Following

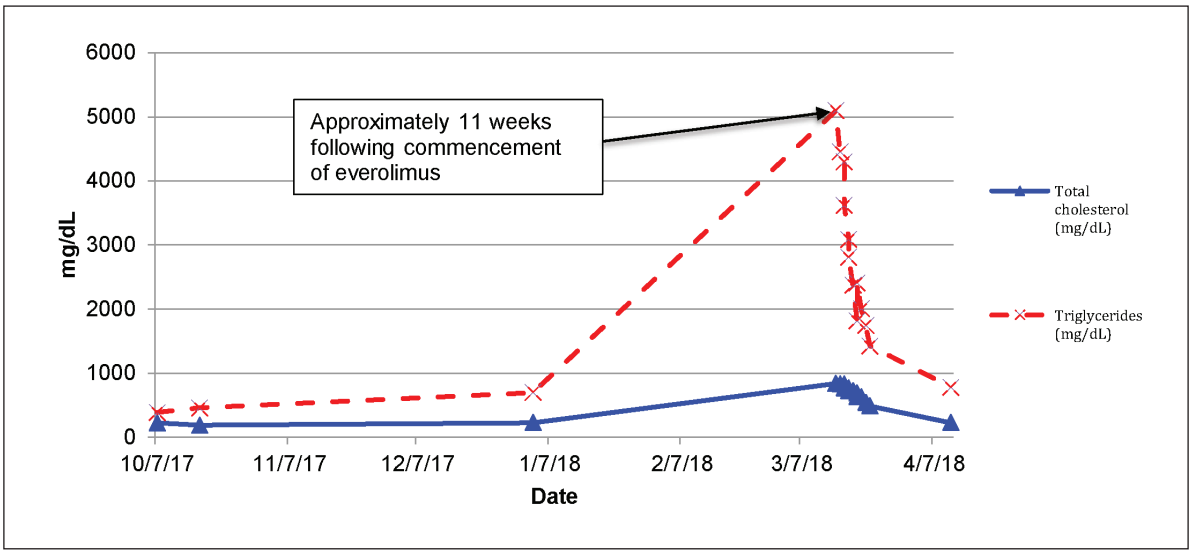

Fig. 1. Trends of triglycerides and total cholesterol.

the admission for hypertriglyceridemia as described above, the patient's pharmacotherapy for ongoing glycemic control was rationalized to metformin, and insulin aspart (rys) 30% plus insulin aspart (rys) 70% protamine suspension at 50 units in the morning and 10 units at night.

DISCUSSION

Everolimus has important effects in the prevention of graft rejection. However, everolimus use may have unintended adverse effects on lipid metabolism, which can culminate in dramatic increases in serum lipid concentrations such as those seen in our patient. Everolimus modulates the expression of enzymes involved in lipid metabolism such as lipoprotein lipase (LPL). LPL is required to hydrolyze lipoprotein-bound triglyceride and allow uptake and storage of triglycerides. As a result, the ability for adipose tissue to clear lipids from plasma is impaired (2,3). In observational studies, hyperlipidemia associated with the use of mTOR inhibitors is prevalent in up to 75% of those treated, although severe hypertriglyceridemia appears less common (2). Everolimus is generally associated with less severe hypertriglyceridemia when compared to other mTOR inhibitors, such as sirolimus (1,4).

Hypertriglyceridemia is the third most common etiology of acute pancreatitis following alcohol and gallstones, accounting for 1 to 4% of all cases. Fasting triglyceride levels greater than 885.7 mg/dL are often cited as the main trigger, but threshold values vary widely (5,6). Acute pancreatitis associated with everolimus in the presence of elevated triglyceride levels has been described in cases following renal transplantation, treatment of metastatic pancreatic neuroendocrine tumors and renal cell carcinoma (7-9). Despite a triglyceride level of 5,049 mg/dL, our case had no clinical or biochemical evidence of pancreatitis. The acute management of severe hypertriglyceridemia is not standardized and varies by center. Treatment modalities can include insulin, heparin, and/or apheresis in addition to standard lipid lowering agents such as statins, fibrates and others (10). In this patient, intravenous insulin was used to activate LPL and increase degradation of chylomicrons. Data pertaining to the efficacy of insulin in lowering triglyceride levels are limited to case reports or small case series (11,12). Since this practice is not universally advised, its use in an asymptomatic patient cannot be generalized.

This case is unique especially due to the underlying condition of FLPD. Furthermore, there are currently no specific guidelines to direct long-term hyperlipidemia management in heart transplant recipients prescribed mTOR inhibitors, let alone in patients with FLPD taking mTOR inhibitors. Published recommendations are generic and simply advise on strategies such as lifestyle optimization, increased physical activity, and consideration of common lipid-lowering pharmacotherapeutic agents such as statins, fibrates, fish oil, niacin ,and bile acid sequestrants (2). Nonetheless, statin therapy is considered first line in most cases. Pravastatin is typically chosen in the post-transplant setting given that it does not significantly interact with cytochromes P450, which regulates hepatic metabolism of several medications used following transplant, including everolimus which is metabolized by cytochrome P450, family 3, subfamily A (1).

An additional contributor to the cause of severe hypertriglyceridemia in this patient is her history of FPLD. The Dunnigan-type is the most common variety of FPLD and is due to lamin A/C (LMNA) mutations. The pathogenesis of dyslipidemia in partial lipodystrophy likely involves impaired adipocyte differentiation due to LMNA deficiency and the inability to properly store circulating lipids. Instead, dietary lipids are stored in nonadipose tissues such as the liver, and accumulation of hepatic triglycerides can precipitate very-low-density-lipoprotein secretion, which further exacerbates dyslipidemia associated with the condition (13). It is unclear whether patients affected by lipodystrophic syndromes are more susceptible to the dyslipidemic effects of mTOR inhibitors, but there is certainly biologic plausibility given their underlying propensity to dyslipidemia even in the nontransplant setting.

The link between hypertriglyceridemia and mTOR inhibitor use in this case can only be suspected given the pathologic predisposition and suggestive temporal relationship between events. Without a rechallenge to confirm the suspicion, other possible contributing factors that can lead to secondary hypertriglyceridemia must also be considered, including uncontrolled diabetes, alcohol consumption, hypothyroidism, end-stage renal disease, nephrotic syndrome, human immunodeficiency virus infection and other drugs such as estrogens, tacrolimus, thiazide diuretics, and sertraline (14). Another potential major contributor is noncompliance with medications such as statins. This could be due to several factors including perceptions of frequent side-effects to antihyperlipidemic treatments or lack of adequate explanation of the medications' benefits by physicians (15,16). However, there was no evidence to support the potential confounders above.

Given the potency of everolimus to increase serum triglyceride levels, we recommend that lipid profiles be closely monitored in all patients treated with mTOR inhibitors and that pharmacotherapy be started in all patients with elevation in serum triglyceride levels.

CONCLUSION

We present a patient with severe hypertriglyceridemia attributed to everolimus without clinical or biochemical evidence of pancreatitis. Hypertriglyceridemia developed over 11 weeks following commencement of everolimus, despite serum everolimus levels within the therapeutic reference range. Cessation of everolimus, high dose

intravenous insulin and introduction of multiple oral lipid lowering therapies resulted in rapid and sustained improvements in the serum lipid profile. Ideally, all heart transplant recipients should be screened for dyslipidemia. For those receiving everolimus, lipid levels should be monitored more regularly starting at baseline, 4 weeks after commencement and we would suggest 6-monthly thereafter to avoid preventable complications such as pancreatitis.

DISCLOSURE

P.S.M. served on the advisory board, received speaker fees, and received a research grant from Novartis. The other authors have no multiplicity of interest to disclose.

Supplementary Material

Supplementary Methods

The original lipid levels in this case reports were recorded in the units of mg/dL. They have been converted to mg/dL using the following conversion factors:

1. For total cholesterol and LDL-C: to get from mmol/L to mg/dL, multiply by 38.67.
2. For triglycerides: to get from mmol/L to mg/dL, multiply by 88.57.

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