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Case Presentation

Possible Drug-Induced Severe Hypertriglyceridemia in a Patient Co-Infected with Human Immunodeficiency Virus and Hepatitis C Virus

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Abstract

Lipid-related disturbances are commonly associated with Protease Inhibitor (PI) use; however, PI-sparing Human Immunodeficiency Virus (HIV) regimens are less frequently associated with increased lipids. A 53 year-old African American female, co-infected with Hepatitis C Virus (HCV) and HIV, maintained on a PI-sparing antiretroviral therapy, experienced a significant elevation in triglycerides following the initiation of HCV treatment with peginterferon Alfa-2a 180 mcg subcutaneously weekly, ribavirin 600 mg orally twice daily, and telaprevir 1125 mg orally three times daily. Two weeks after the start of treatment, a lipid panel was drawn with results: triglycerides (1678 mg/dL), high density lipoprotein-cholesterol (27 mg/dL), total cholesterol (257 mg/dL), and low density lipoprotein-cholesterol (not calculated). Fenofibrate 48mg orally daily was initiated 1 week later. After 7 weeks of fibrate therapy, the triglycerides remained elevated (1690 mg/dL). Marked triglyceride reduction (344 mg/dL) was achieved within 4 weeks of rosuvastatin 10 mg orally daily initiation.

Based on the Naranjo score of 4, it is possible that the patient's hypertriglyceridemia was drug-induced by peginterferon Alfa-2a. Statin selection is an important component of dyslipidemia management in co-infected HIV and HCV patients with baseline lipid abnormalities.

Keywords: Hepatitis C virus; HIV; Peginterferon Alfa-2a; Severe hypertriglyceridemia

Abbreviations

HIV: Human Immunodeficiency Virus; HCV: Hepatitis C Virus; PI: Protease Inhibitor; NNRTI: Non-Nucleoside Reverse Transcriptase Inhibitor; ART: Antiretroviral Therapy; CD4: Cluster of Differentiation 4; RNA: Ribonucleic Acid; IU: International Units; PO: By mouth; LDL-C: Low Density Lipoprotein-Cholesterol; HDL-C: High Density Lipoprotein-Cholesterol (HDL-C); CYP3A4: Cytochrome P450 3A4; AUC: Area Under The Curve; Cmin: Minimum Drug Concentration

Introduction

Of the people living with human immunodeficiency virus (HIV) in the United States, 25% are co-infected with hepatitis C virus (HCV) [1]. Treatment options suppress HIV and clear HCV infection. However, antiviral medications are not free of adverse effects or potential drug interactions. For example, marked triglyceride elevations are a frequently reported adverse effect associated with protease inhibitor (PI) use for HIV management, but uncommon with PI-sparing regimens [2-6].

Documented cases of dyslipidemia in patients co-infected with HCV Genotype 1a and HIV, who are receiving a PI-sparing regimen, are rare; particularly, given that reports indicate HCV may promote favorable lipid profiles and reduce rates of dyslipidemia [7,8]. We report a case of severe hypertriglyceridemia in a co-infected HCV and HIV patient on a concomitant PI-sparing, non-nucleoside reverse transcriptase inhibitor (NNRTI) based antiretroviral therapy (ART) regimen and HCV treatment.

Case Presentation

A primary care provider requested a pharmacist consult for a hypertriglyceridemia therapy recommendation following 10 weeks of HCV treatment in a 53 year-old, 66 kg African American female. The patient's medical history was significant for HCV Genotype 1a, diabetes mellitus type 2 (A1c of 5.8%, drawn 9 months prior to the start of HCV treatment), controlled hypertension, HIV (CD4 T cell count of 433 cells/uL and HIV RNA viral load of < 20 copies/mL, both drawn at the start of HCV treatment), and hypertriglyceridemia (triglycerides 430 mg/dL, drawn 9 months prior to the start of HCV treatment).There was no documentation of symptoms that may be associated with elevated triglycerides.

Table 1 contains the patient's medications at the time of pharmacy consultation. To confirm adherence, the pharmacist called the patient's community pharmacy to assess fill dates; compliance was deemed appropriate. No use of complementary and alternative medicine was noted, and the patient had no recorded drug allergies. Social history reported denial of current tobacco, alcohol, or illicit drug use, and the patient was employed as a residential assistant. Family history was not available. Adult vaccines, including influenza and Hepatitis A, were up-to-date.

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Table 1: Patient's drug therapy at the time of pharmacist consult.

Drug	Dose, Route of Administration, and Frequency
Efavirenz/emtricitabine/tenofovir	600 mg/200 mg/300 mg 1 tablet POdaily
Telaprevir	375 mg 3 tablets PO three times a day
Peginterferon Alfa-2a	180 mcg/0.5 mL subcutaneous solution, 180 mcg subcutaneously weekly
Ribavirin	Weeks 1 to 6 of treatment: 200 mg 3 capsules PO twice a day Weeks 7 to 12 of treatment: 200 mg 1 capsule PO twice a day Week 13+ of treatment: 200 mg 2 capsules PO twice a day
Fenofibrate	48 mg 1 tablet PO daily
Multivitamin	1 tablet PO daily
Ergocalciferol	50,000 units 1 capsule PO weekly

PO = by mouth

Table 2: Lipid panel results.

Date of Result	Total Cholesterol (mg/dL)	HDL-C(mg/dL)	Triglycerides (mg/dL)	LDL-C(mg/dL)
21months prior to starting HCV treatment	180	25	520	Unable to calculate
9 months prior to startingHCV treatment	137	31	430	Unable to calculate
2 weeks after startingHCV treatment (1 week prior to starting fenofibrate)	257	27	1678	Unable to calculate
6 weeks after starting HCV treatment (3 weeks after starting fenofibrate)	255	29	1516	Unable to calculate
10 weeks after starting HCV treatment (7 weeks after starting fenofibrate)	254	28	1690	Unable to calculate

HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol.

Lipid panel results, prior to and following HCV treatment initiation, are in Table 2. Other relevant laboratory results (drawn 4 weeks following initiation of HCV treatment) include: HCV RNA viral load of 249 IU/mL, aspartate aminotransferase of 48 IU/L (normal range 10-35 IU/L), and the following which are within normal limits: alanine aminotransferase of 28 IU/L, albumin of 4.1 g/dL, albumin: globulin ratio of 1.2, prothrombin time of 10.4 sec, and international normalized ratio of 1.0. The complete metabolic panel results were within normal limits. Creatinine clearance of 76 mL/min (serum creatinine of 0.75 mg/dL and ideal body weight of 55.3 kg) was calculated using the Cockcroft-Gault equation.

The patient started HCV treatment for Genotype 1a with peginterferon Alfa-2a 180 mcg subcutaneously weekly, ribavirin 600 mg PO twice daily, and telaprevir 1125 mg PO three times daily (education provided on fat consumption with use). At that time, treatment with telaprevir followed guideline recommendations. Telaprevir frequency was increased due to reduced concentrations when used concurrently with efavirenz [9,10]. HIV antiretroviral treatment (efavirenz/emtricitabine/tenofovir 600 mg/200 mg/300 mg PO daily) remained unchanged for nearly four years, and the patient's HIV was classified as stable.

Approximately 2 weeks after the initiation of HCV treatment, a lipid panel was drawn, indicating a triglyceride level of 1678 mg/dL (Table 2). One week after the receipt of the results, the patient started fenofibrate 48 mg PO daily, as prescribed by her physician. Following 7 weeks of fenofibrate therapy, a lipid panel was drawn with the following results: triglycerides of 1690 mg/dL, low density lipoprotein-cholesterol (LDL-C) could not be calculated, high density lipoprotein-cholesterol (HDL-C) of 28 mg/dL, and total cholesterol of 254 mg/dL. At this time, the pharmacist was consulted for a hypertriglyceridemia therapy recommendation. Following review of the collected information, the pharmacist recommended and the physician initiated rosuvastatin 10 mg PO daily and continued fenofibrate 48mg PO daily. In alignment with evidence-based guidelines, a statin was recommended rather than fibrate optimization given comorbid cholesterol elevations that fenofibrate would not have appreciably affected [11]. Atorvastatin and simvastatin were avoided due to metabolism through cytochrome P450 3A4 (CYP3A4), which telaprevir strongly inhibits. Additionally, efavirenz significantly reduces exposure to atorvastatin and pravastatin; therefore, rosuvastatin remained the only potent statin option available [9-12].

After 4 weeks of rosuvastatin treatment, a lipid panel was drawn with the following results: triglycerides of 344 mg/dL, LDL-C of 14 mg/dL, HDL-C of 29 mg/dL, and total cholesterol of 112 mg/dL. Additionally, during this time, telaprevir was discontinued after 12 consecutive weeks of use, and ribivirin and interferon therapy were continued as recommended.

Discussion

This case report details severely elevated triglycerides in a co-infected HIV and HCV patient following the initiation of peginterferon Alfa-2a, ribavirin, and telaprevir for HCV treatment. Despite not using a PI-based ART regimen for HIV management, hypertriglyceridemia was present in this patient prior to the start of HCV treatment, likely due to side effect profiles of the HIV medications. Efavirenz, a NNRTI, can cause triglycerides > 750 mg/dL in 6% to 11% of those treated [13]. Emtricitabine may also increase triglycerides, but to a lesser extent [13,14]. Tenofovir, unlike other antiviral agents, may have favorable effects on lipid profiles [15,16]. Noteworthy is 4% of those treated with combination therapy of efavirenz, emtricitabine and tenofovir, such as this patient, experience triglycerides > 750 mg/dL [14].

Ribavirin and peginterferon Alfa-2ainhibit HCV RNA replication and induce innate antiviral immune response, respectively [17,18].

Table 3: Naranjo adverse drug reaction probability scale.

Question	Yes	No	Do Not Know	Score
Are there previous *conclusive* reports on this reaction?	+1	0	0	+1
Did the adverse event appear after the suspected drug was administered?	+2	-1	0	+2
Did the adverse reaction improve when the drug was discontinued or a *specific* antagonist was administered?	+1	0	0	+1
Did the adverse reaction reappear when the drug was re-administered?	+2	-1	0	0
Are there alternative causes (other than the drug) that could on their own have caused the reaction?	-1	+2	0	-1
Did the reaction reappear when a placebo was given?	-1	+1	0	0
Was the drug detected in blood (or other fluids) in concentrations known to be toxic?	+1	0	0	0
Was the reaction more severe when the dose was increased or less severe when the dose was decreased?	+1	0	0	0
Did the patient have a similar reaction to the same or similar drugs in *any* previous exposure?	+1	0	0	0
Was the adverse event confirmed by any objective evidence?	+1	0	0	+1
Total Score:				4

Ribavirin is a nucleoside analogue not known to cause lipid abnormalities. However, in combination with peginterferon Alfa-2a, a recombinant pegylated alpha interferon, adverse reactions including elevated triglycerides (≥ 400 mg/dL) and severe hypertriglyceridemia (>1000 mg/dL) have occurred in up to 36% and 7% of co-infected HCV and HIV patients, respectively [18].

While this patient had elevated triglycerides prior to starting HCV treatment, use of peginterferon Alfa-2a, ribavirin, and telaprevir caused triglycerides to significantly increase within 2 weeks of therapy initiation. Interferon in various formulations, with and without ribavirin, has been found to cause elevated triglycerides early on during treatment of HCV infected patients [19-21]. Triglycerides typically decline before returning to normal limits following interferon dose reduction or discontinuation of therapy [19-21]. Unlike prior studies, this case report describes severe triglyceride elevation in a co-infected HIV and HCV patient who was receiving a newer formulation of interferon, peginterferon Alfa-2a, along with ribavirin, and an increased dose of telaprevir. The increased telaprevir dose of 1125 mg three times daily was indicated due the decrease in telaprevir's area under the curve (AUC) and minimum drug concentration (Cmin) by 26% and 47%, respectively, caused with co-administration of efavirenz [10,22,23]. A pharmacokinetic interaction between telaprevir and efavirenz could also have contributed to elevated triglyceride levels. Telaprevir inhibits CYP450 3A4, which may increase efavirenz exposure and the possibility of efavirenz-related adverse effects, including further triglyceride elevation. Telaprevir has not been shown to independently cause hypertriglyceridemia, but triglyceride elevations are a notable class effect of protease inhibitors [2]. Additionally, it is reasonable to consider that the dietary requirements of telaprevir consumption with fatty meals may increase total cholesterol, LDL, and potentially triglycerides [9].

Employing the Naranjo adverse drug reaction probability scale to evaluate this case (Table 3) yielded a score of 4, indicating a possible drug-induced adverse effect [24]. Lipid values, drawn 4 weeks following the initiation of rosuvastatin and just over 2 weeks following the discontinuation of telaprevir, indicate greatly reduced triglycerides. While telaprevir therapy was discontinued at week 12, peginterferon Alfa-2a and ribavirin were continued [11]. Previous studies support recovery to baseline triglycerides after 12-24 weeks of interferon treatment [20,21]. However, considering the magnitude of triglyceride elevation and insensitivity to initial fenofibrate lipid-lowering effect, we believe this patient's hypertriglyceridemia would have persisted beyond week 12 without statin initiation.

While ribavirin remains part of the recommended treatment regimens for multiple HCV genotypes, it is important to also recognize that guidelines continue to recommend treatment with peginterferon for genotypes 3, 4, 5, and 6. However, with the approval of new oral HCV therapies, telaprevir is no longer recommended for HCV treatment [25]. Considering treatment guidelines, the findings of this case report underscore the importance of advancing HCV treatment for both improved efficacy and safety, particularly regarding drug interactions with antiretrovirals and metabolic adverse effects such as hypertriglyceridemia.

Conclusion

The cause of severe hypertriglyceridemia in this case may be due to a combination of factors: peginterferon-induced hypertriglyceridemia, pharmacokinetic interaction between telaprevir and efavirenz resulting in increased risk of efavirenz-induced triglyceride elevation, and increased fatty meal consumption with telaprevir administration. Marked triglyceride reduction was achieved within 4 weeks following the initiation of rosuvastatin in a patient co-infected with HCV and HIV, who experienced a significant hypertriglyceridemia following the initiation of HCV treatment with peginterferon Alfa-2a, ribavirin, and telaprevir. Statin initiation in patients with baseline hypertriglyceridemia may be warranted for HIV co-infected patients initiating a hepatitis C treatment regimen including peginterferon. Clinician evaluation of the risk and benefit of antilipidemic therapy initiation must be considered in the context of patient specific characteristics. If therapy is not initiated, periodic lipid panel monitoring is warranted.

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