Case report

Severe dyslipidaemia after the addition of raltegravir to a lopinavir/ritonavir-containing regimen

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We describe a 55-year-old HIV-1-infected male who developed severe dyslipidaemia (total cholesterol 600 mg/dl, triglycerides >5,000 mg/dl, high density lipoprotein <5 mg/dl) after raltegravir was added to his lopinavir/ritonavir-containing regimen. To our knowledge, this is the first reported case of severe dyslipidaemia associated with the addition of raltegravir to a lopinavir/ritonavir-based regimen, suggestive of a possible drug interaction. The lipid profile quickly normalized following discontinuation of lopinavir/ritonavir and continuation of raltegravir, suggesting that lopinavir/ritonavir was the primary driver for the adverse event. With increasing interest in nucleoside-sparing regimens, knowledge of clinically significant adverse events such as this is important for HIV clinicians when selecting regimens for patients with highly resistant virus or drug tolerability issues.

Introduction

There are currently 24 FDA-approved antiretroviral medications for the treatment of HIV-1 infection, resulting in a vast number of potential drug combinations. More than half of these drugs are metabolized by hepatic cytochrome P450 enzymes, of which inhibition or induction can alter drug pharmacokinetics leading to subtherapeutic or supratherapeutic plasma concentrations. Although the pharmaceutical industry has been vigilant in conducting preclinical drug-interaction and safety studies, data are limited due to the small size of these studies and the intra- and inter-patient variability. Clinicians depend on post-marketing data and case reports to add to the body of literature regarding potential drug interactions and adverse events from antiretroviral medications.

We describe a patient who was diagnosed with lipaemia retinalis after a routine retinal exam. The acute onset of severe dyslipidaemia was evident after raltegravir (RAL) was added to his lopinavir/ritonavir (LPV/RTV)-containing regimen, suggesting a possible drug–drug interaction that led to the significant adverse event. To our knowledge, this is the first reported case of severe dyslipidaemia associated with the addition of RAL, an HIV-1 integrase inhibitor, to an LPV/RTV-based regimen.

Case report

A 55-year-old asymptomatic African American male with multidrug resistant HIV-1 infection developed breakthrough viraemia of 125 and 160 copies/ml on two consecutive clinic visits, over a 3 month interval, despite reported 100% adherence to antiretroviral therapy (ART). He previously had successful viral suppression for 3 years while receiving a regimen of LPV/RTV 400/100 mg twice daily, abacavir (ABC) 300 mg twice daily and tenofovir disoproxil fumarate (TDF) 300 mg once daily. Out of concern for evolving ABC resistance, given known history of multiple thymidine analogue mutations and the M184V mutation, ABC was discontinued and RAL was added. Emtricitabine (FTC) was also added as part of the fixed-dose combination of FTC/TDF to promote M184V-induced TDF hypersensitivity. He regained virological control to <48 copies/ml at the subsequent follow-up visit.

In addition to HIV, the patient’s medical history included dyslipidaemia, hypertension, benign prostatic hyperplasia, hypogonadism, cataracts and mild renal insufficiency (estimated creatinine clearance of 60 ml/min) and he was taking the following medications in addition to his ART: atorvastatin 10 mg daily,
ezetimibe 10 mg daily, fenofibrate 48 mg daily, hydrochlorothiazide (HCTZ)/triasterone 25/37.5 mg daily, feldopine ER 5 mg daily, tamsulosin 0.4 mg daily and testosterone patch 5 mg/24 h daily. Of note, no changes were made to these medications when his ART was changed.

Seven months after starting his new ART regimen, the patient presented to an ophthalmology clinic for a routine follow-up visit to assess his cataracts. Dilated fundoscopic exam revealed bilateral creamy arterioles (Figure 1A), consistent with a diagnosis of lipaemia retinalis due to severe hypertriglyceridaemia. During physical examination the patient denied chest pain, abdominal pain, dyspnea, nausea/vomiting or headache.

A stat lipid profile was obtained and the results confirmed the diagnosis of severe dyslipidaemia with total cholesterol 600 mg/dl, triglycerides 5,364 mg/dl and high-density lipoprotein (HDL) less than 5 mg/dl. A fasting lipid panel 48 h later confirmed the results with total cholesterol 515 mg/dl, triglycerides 5,168 mg/dl and HDL <5 mg/dl (Table 1). Of note, six weeks prior to the ART change, the patient’s total cholesterol was 143 mg/dl, triglycerides 193 mg/dl, HDL 36 mg/dl, and low-density lipoprotein (LDL) 68 mg/dl. Medication non-adherence and new alcoholism were ruled out as potential causes of the acute worsening of dyslipidaemia. Follow-up laboratory testing also ruled out new onset diabetes mellitus, hypothyroidism, pancreatitis and

Table 1. Lipid panel timeline in relation to changes in antiretroviral therapy

<table>
<thead>
<tr>
<th>Date</th>
<th>ART regimen</th>
<th>ART change</th>
<th>Cholesterol, mg/dl</th>
<th>Triglycerides, mg/dl</th>
<th>HDL, mg/dl</th>
<th>LDL, mg/dl</th>
</tr>
</thead>
<tbody>
<tr>
<td>28/12/06</td>
<td>ABC, TDF,</td>
<td>–</td>
<td>225</td>
<td>449</td>
<td>43</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>LPV/RTV</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>28/9/09</td>
<td>–</td>
<td>ABC stopped; LPV/RTV</td>
<td>143</td>
<td>193</td>
<td>68</td>
<td>NA</td>
</tr>
<tr>
<td>11/11/09</td>
<td>–</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1/6/10</td>
<td>TDF, FTC,</td>
<td>–</td>
<td>600&lt;sup&gt;a&lt;/sup&gt;</td>
<td>5,364</td>
<td>&lt;5</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td>LPV/RTV, RAL</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>3/6/10</td>
<td>–</td>
<td>LPV/RTV stopped; ETR added</td>
<td>515</td>
<td>5,168</td>
<td>&lt;5</td>
<td>NA</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>24/6/10</td>
<td>TDF, FTC, ETR, RAL</td>
<td>–</td>
<td>307</td>
<td>67</td>
<td>222</td>
<td>112</td>
</tr>
<tr>
<td>4/5/11</td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>

<sup>a</sup>Random lipid profile. All other lipid profiles listed are fasting. ABC, abacavir; ART, antiretroviral therapy; ETR, etravirine; FTC, emtricitabine; HDL, high-density lipoprotein; LDL, low-density lipoprotein; LPV/RTV, lopinavir/ritonavir; NA, not able to calculate; RAL, raltegravir; TDF, tenofovir disoproxil fumarate.
nephrotic syndrome as potential causes, with fasting glucose, haemoglobin A1c, thyroid stimulating hormone, lipase and random urine protein all within normal limits. Thus, the patient’s severe dyslipidaemia was believed to be due to the recent changes in his antiretroviral therapy. LPV/RTV was subsequently discontinued because it was felt to be the main driver of his lipid abnormalities and etravirine 200 mg twice daily was initiated. In addition, his fenofibrate was increased to 160 mg daily and he was started on omega-3 fatty acids 2 gm twice daily. The atorvastatin was held temporarily out of concern for increased risk of rhabdomyolysis when combined with high-dose fenofibrate. A repeat fasting lipid panel was performed two weeks later and his triglycerides had decreased to 90 mg/dl. His prior lipid-lowering regimen was resumed. The patient followed up with ophthalmology 4 months later and on exam the previous retinal findings had completely resolved (Figure 1B). Triglycerides, LDL-cholesterol and total cholesterol have remained well controlled since that time.

Discussion

Dyslipidaemia is a known side effect of RTV-boosted protease inhibitors (PI). The mechanism of action for PI-induced dyslipidaemia is not well understood. Genetics, prior use of PIs and boosting with RTV are thought to contribute to dyslipidaemia [1–3]. Some studies have shown a correlation between LPV concentrations and lipid abnormalities [4,5], however, a recent study did not find this association [6]. The onset of dyslipidaemia following initiation of LPV/RTV typically occurs during the first 2–3 months of therapy and stabilizes thereafter [7–9]. Our patient had significant dyslipidaemia during LPV/RTV initiation, which required three-drug therapy for management; however, this had been controlled with antilipidaemic medications for almost 3 years prior to the addition of RAL (Table 1).

Emtricitabine is not known to cause dyslipidaemia, but was added at the same time as RAL, so it cannot be excluded. However, it is an unlikely contributor, as his lipid profile remained within normal limits while on this medication, following the discontinuation of LPV/RTV. In reviewing his non-HIV medications, HCTZ has been reported to cause lipid increases, but elevations typically occur within the first two weeks of initiation [10]. Our patient had been taking HCTZ for several years without any side effects and thus it is unlikely that HCTZ was associated with the acute lipid changes.

The patient was never re-challenged with the LPV/RTV–RAL combination. However, the onset of dyslipidaemia after RAL initiation and rapid resolution following LPV/RTV cessation is suggestive of a combined effect of LPV/RTV and RAL on lipids. We believe that LPV/RTV was the main driver of our patient’s dyslipidaemia because his lipid profile rapidly normalized following discontinuation of LPV/RTV and continuation of RAL. Using the Naranjo Adverse Drug Reaction Probability Scale, a well-validated method for establishing causality of an adverse drug-related event, the calculated Naranjo score is 8, indicating a probable adverse drug event (definite adverse drug-related event defined as a score ≥9) [11]. The elevations in total cholesterol and triglycerides observed in our patient coincide with preliminary data from the PROGRESS Study, a safety and efficacy study comparing RAL plus LPV/RTV to LPV/RTV plus FTC/TDF in treatment-naive patients. Data at 48-weeks suggest that LPV/RTV in combination with RAL was associated with significant mean increases in triglycerides (99 versus 59 mg/dl; \( P=0.044 \)), total cholesterol (46 versus 29 mg/dl; \( P=0.008 \)) and HDL-cholesterol (12 versus 8 mg/dl; \( P=0.015 \)) from baseline in comparison to LPV/RTV plus FTC/TDF, an unexpected finding [12]. Our patient, however, experienced a significant decrease in HDL-cholesterol in contrast to the HDL increases reported in the PROGRESS study.

RAL has not been associated with hyperlipidaemia in large randomized clinical trials [13]. In the SWITCHMRK trials, patients who were switched from LPV/RTV to RAL had greater reductions in total cholesterol (-12.6% versus 1%), non-HDL cholesterol (-15% versus 2.6%) and triglycerides (-42.2% versus 6.2%) compared to patients that remained on regimens containing LPV/RTV (\( P<0.0001 \)) [14]. Lipid data from two other nucleoside-sparing studies comparing RAL plus a PI (either unboosted atazanavir or boosted darunavir) to RAL plus FTC/TDF were similar between study arms, suggesting that lipid elevations observed in the PROGRESS study are unique to LPV/RTV plus RAL [15,16].

The mechanism for the lipid elevations observed in our patient and in the PROGRESS study is unknown. LPV is a known substrate of CYP3A4 and RTV is a potent inhibitor of multiple cytochrome P450 enzymes [17]. However, RAL has not been shown to be an inhibitor of CYP3A4 or P-glycoprotein mediated transport, so it is unlikely that RAL-induced increases in plasma LPV/RTV concentrations would explain the effect seen [13]. It is plausible that RAL and LPV/RTV share an unknown efflux or uptake transport protein, which have been associated with unexpected interactions with other antiretrovirals [18,19]. If that is the case, then RAL could increase LPV/RTV levels through alternate pathways leading to the dyslipidaemia seen in our patient.

Of particular concern is that our patient was asymptomatic when diagnosed with lypaemia retinalis...
so it is unknown how quickly our patient’s lipids reached such dangerously elevated levels in relation to his regimen change. HIV infection and dyslipidaemia are both known risk factors for cardiovascular disease, which can lead to life-threatening acute coronary syndromes [20].

Conclusion

This is the first reported case of a possible drug interaction between RAL and LPV/RTV leading to severe dyslipidaemia. Clinicians should be alerted to the possibility that regimens containing this combination may greatly alter lipid profiles, even in patients that have tolerated LPV/RTV in the past. We recommend careful monitoring of fasting lipid profiles for patients on this antiretroviral combination. Further prospective safety studies with this antiretroviral combination are warranted.

Disclosure statement

The authors declare no competing interests.

References


Accepted 13 February 2012; published online 22 June 2012

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