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Complex Interactions of Darunavir in Patients with HIV and Multiple Comorbidities: Understanding Toxicity in Two Cases with Very Different Outcomes

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Abstract

Complex patients with multiple comorbidities are rarely included in large randomized studies. As a result, little is known about the optimal management of these cases. The following two cases occurred within a six month period in 2013 and were seen at Casey House, a community-based facility specializing in HIV/AIDS in Toronto, Canada. Both cases involved a serious assault to the liver believed to be drug induced liver injury (DILI) caused by darunavir. In the first case, Patient A, a 50 year-old male with a CD4 count of 454 cells/mm^3 presented with tense ascites, jaundice and pedal edema. He had recently started a new anti-retroviral (ARV) combination including darunavir. The ARV medications were stopped, liver function improved and his ascites was reduced with paracentesis and infusions of albumin. Chronic hepatitis B was identified. The patient was started on a new anti-retroviral regimen effective for hepatitis B. His liver failure resolved and he continues to live well in the community. In Patient B, a 49 year-old woman with CD4 count of 20 cells/mm^3 and *Mycobacterium Avium* Complex (MAC) and hepatitis C was started on a darunavir-based regimen. She developed abdominal pain, jaundice, elevated liver function tests and anemia. HIV medications were held, and then restarted. Her symptoms worsened. Eventually all medications were stopped. Although the patient's liver began to recover, her CD4 count remained very low and the patient developed pneumocystis pneumonia (PJP) and died. These cases are presented with a view to better understanding darunavir and its potential toxicity. The literature concerning darunavir toxicity in the setting of complex comorbidity will be reviewed.

Keywords HIV, darunavir, liver failure, adverse effects, comorbidities, hepatitis, case study

Introduction

We are just beginning to understand the complex interactions of medications in patients with HIV and multiple comorbidities, particularly hepatitis B/C. New complications associated with HIV and aging, combined with inflammation, immuno-compromise and immune reconstitution syndrome can make patient management challenging. Darunavir is a widely used and generally well tolerated anti-retroviral (ARV) medication [1]. Some studies suggest that it is safe to use even in the presence of hepatitis B/C [2-4]. However, in rare cases darunavir can cause severe hepatotoxicity and even death (FDA report, package insert). Co-infection with hepatitis B or C increases the risk of liver failure, as does a low CD4 count [5,6]. Although some drug trials for darunavir included patients with infectious hepatitis [3], patients with active AIDS defining illness, history of substance use, active liver disease, and cardiac dysfunction were excluded (see clinicaltrials.gov for a complete list of inclusion and exclusion criteria).

Here we discuss two cases of liver toxicity believed to be caused by darunavir. The patients were seen at Casey House, a community-based facility for patients with HIV/AIDS. The liver toxicity presented in a similar fashion with abdominal pain, jaundice and increased girth. Potentially due to the other comorbid conditions, the ultimate outcome of the two cases was different. One patient survived and went on to do well in the community. The other patient is now deceased.

Case Presentation

Patient A: A 50 year-old Caucasian male, diagnosed with HIV in 1993. CD4 count at admission was 454 cells/mm^3, with a viral load of 107 copies/ml. The patient had a number of complications of HIV, including peripheral neuropathy and history of oral candidiasis. At the time of admission the patient reported a history of untreated hepatitis C as well as a history of asthma and a seizure disorder not yet diagnosed.

He presented to Casey House with tense abdominal ascites, jaundice and pedal edema. He was not coping at home, and was unable to eat a full meal, or perform activities of daily living. Approximately 3 months previously the patient had started a new ARV regime with his community provider, including darunavir (600 mg BID), ritonavir, etravirine, maraviroc and tenofovir. Within a few days of starting these new medications the patient noticed abdominal bloating and discomfort. At a six week follow-up appointment, the patient was found to have jaundice, scleral icterus, abdominal pain, abdominal distension with ascites and enlarged spleen, as well as pedal

edema. The patient was sent to general hospital. Hospital laboratory investigations showed liver function tests (LFTs) as follows: bilirubin 221 μmol/L, alanine aminotransferase (ALT) 472 U/L, aspartate aminotransferase (AST) 182 U/L and an international normalized ratio (INR) of 2.4. He was diagnosed with a drug induced liver injury believed to be caused by darunavir. At that time his ARV medications were stopped. Gradually his jaundice began to resolve, and LFTs started to decrease. Because of ongoing tense ascites and edema he was unable to cope in the community and he was admitted to our facility.

Ascites began to resolve with paracentesis and the administration of albumin. In total, he received 4 transfusions of 25% albumin (200 ml). He was also treated with ceftriaxone 2 gr IV x 7 days for spontaneous bacterial peritonitis. He was diuresed with furosemide and spironolactone. Gradually he recovered. Over the course of months his condition improved. Ascites and edema resolved and he gradually resumed activities of daily living. His INR and bilirubin improved. LFTs also improved with AST 2-3 times the upper limit of normal (ULN) and ALT normal (Table 1).

Date*	INR (0.9-1.2)	Total bilirubin (0-23 μmol/L)	AST (7-40 U/L)	ALT (10-45 U/L)	ALP (35-125 U/L)
3/8/2013	2.30	83	143	75	131
3/20/2013	2.21	34	90	30	95
4/3/2013	1.99	35	143	43	114
4/12/2013	1.93	30	187	63	139
4/22/2013	1.93	27	217	81	118
5/2/2013	2.09	22	150	70	125
5/15/2013	2.02	20	162	68	130
6/25/2014	1.65	14	41	27	179

Table 1: Liver function test results over time for Patient A. *Patient A was not on darunavir at the time of admission. ARVs were stopped in mid-February 2013. ARV medications were restarted April 25, 2013 with: emticitibine/tenofovir (for hepatitis B), raltegravir and maraviroc.

Eventually results from public health indicated that Patient A had chronic hepatitis B infection (HBsAg positive, HBeAg positive, HBV DNA >1.70 × 10^8 IU/mL, ALT 30 U/L, AST 90 U/L). There was no evidence of hepatitis C (anti-HCV negative, HCV PCR negative). A new ARV regimen was devised for the patient, including emticitibine/tenofovir (for hepatitis B), raltegravir and maraviroc. While starting this regime the patient was monitored closely, but appeared to tolerate these medications well. His liver function tests resolved, and he was discharged, and now lives independently in the community.

Patient B: A 49-year-old Caucasian woman originally diagnosed with HIV in 1995. She reported poor tolerance to HAART due to nausea. Her CD4 count one month prior to admission was 20 cells/mm^3 (8%) with a viral load of 131, 318 copies/ml. About one month prior to admission this patient was seen in an ambulatory care clinic and found to have systemic *Mycobacterium avium* complex (MAC). She was started on ethambutol, rifampin and azithromycin with an intended course of treatment of at least 12 months. Anti-retroviral therapy was held to avoid immune reconstitution syndrome. She was known to have untreated hepatitis C, genotype 3A (viral load 2.68 × 10^5 IU/ml). The patient hoped to have this treated when her HIV was better controlled. The patient had a history of opioid use and was on methadone replacement therapy. At the time of admission she was noted to have chronic problems with pain in the back, and abdomen as well as chronic problems with urinary tract infection. At the time of admission her weight was 83.4 pounds. Reasons for her admission were to gain weight and strength, for support with medications, and to start ARV therapy.

Date*	INR (0.9-1.2)	Total Bilirubin (0-23 μmol/L)	AST (7-40 U/L)	ALT (10-45 U/L)	ALP (35-125 U/L)
01/10/2013	1.05	12	96	40	115
01/28/2013		106	159	76	73
02/13/2013	1.16	79	198	59	77
03/15/2013		45	132	39	115
03/27/2014	1.18		168	63	70
04/30/2013	1.47	121	136	64	69
05/15/2013	1.64	232	236	90	76
05/24/2013	1.86	365	366	130	77
06/04/2013	1.81	286	149	59	65
06/11/2013	2.16	170	91	17	55
06/22/2013	2.65	231	86	28	62
06/24/2013	4.05	306	140	40	52
06/25/2013	7.86	310	140	38	57
06/26/2013	3.25	268	1222	198	60

Table 2: Liver function test results over time for Patient B. *Patient B was on ARV therapy between January 9 and February 1, 2013 with: emtricitibine/tenofovir , darunavir and ritonavir. From April 19 until May 17th, 2013 the patient was on: 3TC, raltegravir, etravirine, darunavir and ritonavir.

Based on genotyping and consultation with the patient's infectious disease specialist, she was started on emtricitibine/tenofovir, darunavir (800 mg once daily) and ritonavir. Within 3 weeks, she developed worsening abdominal pain, with increased abdominal girth, jaundice, scleral icterus and peripheral edema. On laboratory testing she had elevated liver function tests (Table 2) as well as anemia (hemoglobin 65 g/L, mean corpuscular volume (MCV) 110 fL) and acute renal failure (serum creatinine of 124 μmol/L).

She was sent to the emergency room. All medications were stopped. She was transfused with 1 unit of packed red blood cells (PRBC) and gradually improved. MAC treatment was restarted after 19 days. Anti-retroviral therapy was reconsidered. Liver function tests did not resolve to baseline after MAC medications were restarted. It was believed that the elevated liver function tests were due to progression of her chronic liver disease. It was not possible at the time to treat for hepatitis C in the presence of untreated HIV and multiple comorbidities with the HCV antivirals available in 2013. Consultation

was made with nephrology and infectious disease and the following regimen for HIV was started 8 weeks later: 3TC, raltegravir, etravirine, darunavir (600 mg BID) and ritonavir. Within 2 weeks the patient again developed jaundice, abdominal pain and swelling, and pedal edema. Her LFTs showed AST of 136 U/L, bilirubin of 121 μmol/L and an INR of 1.47. The patient was seen by hepatology. She was given a diagnosis of darunavir toxicity, and a poor prognosis with 10-50 percent survival, "likely lower given comorbidities". At the time of this diagnosis AST was 5.9 x ULN and ALT was 2 x ULN. Total bilirubin was 10 x ULN.

She was treated with a course of N-acetyl cysteine, an unproven but non-toxic attempt to reduce liver toxicity. All other medications were stopped, except pain medications. At one point the patient experienced a very low level of consciousness, and a CADD pump was started. Throughout this time the patient's family continued to give lactulose, as they had been told it was to reduce confusion due to liver disease. For a brief time the patient improved. Unfortunately, her CD4 count, which had recovered only slightly to 48 cells/mm^3 declined after ARV therapy was stopped. She became acutely dyspneic with fever. The patient was transferred to hospital where a chest ×-ray and bronchoscopy revealed pneumocystis pneumonia (PJP). At the request of the patient's family, attempts were made to treat the PJP. The start of new medications caused the liver failure to worsen and the patient died in the ICU.

Discussion

As patients with HIV age, they experience an increasing number of medical comorbidities. The literature has commented on this extensively [7-9]. There is increased incidence of cardiovascular disease, kidney disease, endocrine disorders, as well as cognitive impairment [10-13]. There are also increased numbers of non-AIDS defining malignancies [14]. Because of the increasing numbers of comorbidities, patients are placed on more and more medications to treat these medical complications. With this increasing complexity combined with cognitive impairment patients may become confused about their condition and provide unreliable details about their medical history.

It is not uncommon to see aging patients with comorbidities on as many as 20 medications for their various disorders [15]. Quite often these medications interact, and doses or types of medication have to be adjusted to compensate. In addition, some patients are experienced with the treatment of HIV, and have resistant virus that requires additional HIV medication.

Frequently HIV/AIDS patients are co-infected with hepatitis B or C, viral illnesses which progress with time and may or may not be treated [16]. As in the case of Patient A, some patients go untreated because they are not aware of the presence of chronic hepatitis B. Hepatitis C patients may go untreated because until recently treatments for hepatitis C involved an extended course of interferon and ribavirin. These medications have poor efficacy and have serious side effects, including depression and pancytopenia as well as risk of liver failure in those with advanced cirrhosis. Also, the guidelines indicate that HIV should be optimally managed before hepatitis C treatment begins [17]. Patient B could not be treated for hepatitis C because she already had platelets <90 E9/L and albumin <30 g/L. Low platelets and low albumin are factors associated with serious side effects such as liver failure in those treated with pegylated interferon and ribavirin with or without first generation protease inhibitor - the best treatments available in 2013.

Other patients may have a long history of intolerance or non-adherence to ARV medications. These patients often present with very low CD4 counts, which increases the risk of Immune Reconstitution Inflammation Syndrome (IRIS). Their comorbidities can provide additional inflammation, which can exacerbate underlying medical conditions. Hepatitis B is known to flare during immune reconstitution. This can present with elevated transaminases, which resolve within weeks [18]. There are few guidelines about how best to manage these patients and frequently they have been excluded from the studies which might clarify this problem (see clinicaltrials.gov: NCT00650832). A case in point is darunavir, a protease inhibitor, widely used for the treatment of patients with HIV/AIDS. It has been on the market since 2007 (FDA approval in 2006). It was initially welcomed as a protease inhibitor for treatment experienced patients with drug resistant HIV. The drug is known to interact strongly with the protease enzyme [1]. The product monograph describes it as well-tolerated, with rash as the most common side effect in 7-10% of patients. Headache (3.8%), diarrhea, constipation and abdominal pain are also among the listed side effects. Many reports in the literature have indicated darunavir is generally well-tolerated with less overall toxicity than some anti-viral medications [1-4,18]. However, it should be noted that in the POWER studies, complex patients with comorbidities such as active AIDS defining illness, history of substance use, active liver disease, and cardiac dysfunction were excluded.

A subsequent letter to the FDA reported rare cases of hepatitis (0.5 percent), with liver failure and even death [19]. This is noted in the package insert. Darunavir toxicity initially manifests itself with low level transaminitis, with elevated levels of AST and ALT ranging from 2-5 times the upper limit of normal. Alkaline phosphatase (ALP) may be unaffected. If darunavir is left in place, further liver damage can occur resulting in actual changes to liver function including elevated bilirubin, decreased albumin and eventually elevated INR [5]. Clinically affected patients present with fatigue, anorexia, abdominal pain (generally in the right upper quadrant), inflammation of the liver, jaundice, dark urine, ascites and peripheral edema (package insert) [5].

Darunavir use has also been connected with other rare complications, including Stevens-Johnson syndrome [20]. There is one case report of an acute demyelinating polyneuropathy which was initiated after the start of darunvir/ritonavir and resolved after the cessation of the drugs [21].

It is well known that many ARV drugs are linked to drug induced liver injury (DILI) [5]. Following the start up of ARV therapy, laboratory abnormalities linked to hepatic function have occurred at an incidence rate of 24 per hundred person years, the second most common type of laboratory abnormality during this period [22] (the most common being lipid abnormalities). There are different patterns of hepatotoxicity including cholestatic injury, with elevated ALP, hepato-cellular injury (with elevated ALT relative to ALP) and also mixed cholestatic and hepato-cellular injury pictures. Several grading systems exist in the literature to rank the severity of the injury [5]. Much of the literature has focused on nevirapine and non-nucleoside reverse transcriptase inhibitors (NNRTIs); however, the darunavir package insert does explicitly state that darunavir/ritonavir can cause severe ALT elevation in 5.6-6.9% of cases. This is consistent with a hepato-cellular injury; ALT greater than 5 times the upper limit

of normal with bilirubin greater than 2 times the upper limit of normal and elevated INR, ascites, encephalopathy or other organ failure [5].

Quite often, during the initiation of ARV therapy, elevation of liver enzymes is mild, and lasts only a few weeks, thus not requiring a change in therapy. This is particularly true of newer agents such as darunavir [18]. However, some authors have suggested stratifying patients with increased risk of liver abnormalities, such as those infected with hepatitis B/C, and providing increased monitoring [22]. The standard of care is for follow-up of any ARV start within 2-8 weeks (aidsinfo.nih.gov), and includes blood work to check for transaminitis. Some have suggested that elevation of aminotransferases related to ARV interactions with hepatitis B/C may not occur for several months [22], requiring follow-up only every 3 months. However our cases show elevation of liver enzymes within weeks.

Severe liver toxicity on ARV medications appears linked to co-infection with hepatitis B and/or C [5,18,23,24]. Acute liver failure and death have been observed following some ARV starts, and there are reports of fatalities in HIV-HBV co-infected patients [6]. Severe elevation of liver enzymes (greater than 10 times the upper limit of normal) is not common, and acute liver failure is rare. If acute liver failure develops, the rate of mortality among HIV positive patients is high [6]. CD4 count also plays a role, since HIV-HBV co-infected patients are at risk for immune reconstitution and may experience a hepatitis flare as CD4 counts improve. It is difficult to separate this viral hepatitis-linked immune reconstitution from drug hepatotoxicity. Because of this, some liver experts have suggested initial treatment of hepatitis B with agents that do not have activity against HIV such as adefovir [6].

Conclusion

When treating patients with complex comorbidities associated with HIV, factors such as aging, multiple medications, co-infection with hepatitis B or C, and potential for immune reconstitution must be kept in mind. A history of viral hepatitis must be confirmed with lab test results. Clinicians should be mindful that a low level elevation of transaminases followed by jaundice can lead to liver failure and even death.

These cases highlight some of the additional complications involved in the medical management of complex HIV patients. Extra effort is required to communicate with a multidisciplinary team. When ARV medication is started in these complex patients, we recommend liver function be closely monitored- perhaps even twice weekly. Symptoms of abdominal pain, although sometimes vague should be regarded as serious. And drug toxicity even with generally well-tolerated agents such as darunavir must be considered.

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