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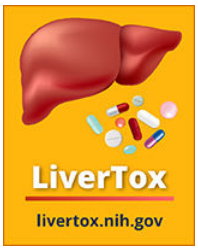

Lopinavir

Updated: September 1, 2017.

OVERVIEW

Introduction

Lopinavir is an antiretroviral protease inhibitor used in combination with ritonavir in the therapy and prevention of human immunodeficiency virus (HIV) infection and the acquired immunodeficiency syndrome (AIDS). Lopinavir can cause transient and usually asymptomatic elevations in serum aminotransferase levels and, rarely, clinically apparent, acute liver injury. In HBV or HCV coinfected patients, highly active antiretroviral therapy with lopinavir may result of an exacerbation of the underlying chronic hepatitis B or C.

Background

Lopinavir (loe pin' a vir) is a peptidomimetic HIV protease inhibitor that acts by binding to the catalytic site of the HIV protease, thereby preventing the cleavage of viral polyprotein precursors into mature, functional proteins that are necessary for viral replication. Lopinavir is usually given in combination with low "booster" doses of ritonavir which improves the pharmacokinetics of lopinavir by slowing its hepatic metabolism. Lopinavir was approved for use in the United States in 2000 for the treatment of HIV infection in adults and children. Lopinavir in fixed combination with ritonavir is available as tablets of 100 mg/25 mg and 200 mg/50 mg and as an oral solution (80/20 mg per mL) for pediatric use generically and under the brand name Kaletra. The recommended dosage of lopinavir in adults is 800 mg daily in combination with 200 mg of ritonavir, either once daily or in two divided doses. Pediatric doses are based upon body weight or body surface area. Common side effects include gastrointestinal upset, nausea, diarrhea, fatigue, headache, and, with long term therapy, dyslipidemia and lipodystrophy.

Hepatotoxicity

Some degree of serum aminotransferase elevations occur in a high proportion of patients taking lopinavir containing antiretroviral regimens. Moderate-to-severe elevations in serum aminotransferase levels (>5 times the upper limit of normal) are found in 3% to 10% of patients, although rates may be higher in patients with HIV-HCV coinfection. These elevations are usually asymptomatic and self-limited and can resolve even with continuation of the medication. Clinically apparent liver disease due to lopinavir/ritonavir occurs, but is rare. The latency to onset of symptoms or jaundice is usually 1 to 8 weeks and the pattern of serum enzyme elevations varies from hepatocellular to cholestatic or mixed. The injury is usually self-limited; however, fatal cases have been reported. In addition, initiation of lopinavir/ritonavir based highly active antiretroviral therapy can lead to exacerbation of an underlying chronic hepatitis B or C in coinfected individuals, typically arising 2 to 12 months after starting therapy, and associated with a hepatocellular pattern of serum enzyme elevations and increases in serum levels of hepatitis B virus (HBV) DNA or hepatitis C virus (HCV) RNA. Lopinavir therapy has not been

clearly linked to lactic acidosis and acute fatty liver that is reported in association with several nucleoside analogue reverse transcriptase inhibitors.

Likelihood score: D (possible, rare cause of clinically apparent liver injury).

Mechanism of Injury

The cause of the clinical hepatotoxicity from lopinavir may be due to its metabolism by the liver, which is largely by the cytochrome P450 system (CYP3A4), which may result in production of a toxic intermediate. In patients with HBV or HCV coinfection, initiation of highly active antiretroviral therapy including lopinavir may be associated with flares of the underlying chronic hepatitis which are thought to be the result of reconstitution of the immune system, viral interactions or a direct effect of the drug on the hepatitis virus.

Outcome and Management

The severity of liver injury ranges from mild enzyme elevations to acute liver failure. In typical cases, recovery occurs within 1 to 2 months of stopping lopinavir. Rechallenge may lead to recurrence and should be avoided. There does not appear to be cross reactivity to hepatic injury with other protease inhibitors or antiretroviral agents. The exacerbation of hepatitis B or C that can occur with lopinavir based antiretroviral therapies can be severe and lead to acute liver failure or progressive end stage liver disease. Patients with HCV or HBV coinfection should be monitored prospectively for viral and serum aminotransferase levels and appropriate therapy instituted if possible.

References to loprinavir are included with references to all the HIV protease inhibitors in the overview section of Protease Inhibitors (updated September 2017). Most of the HIV protease inhibitors in clinical use are proteinomimetic drugs and are structurally unrelated.

Drug Class: Antiviral Agents, Antiretroviral Agents

Other Drugs in the Subclass, Protease Inhibitors: Amprenavir, Atazanavir, Darunavir, Fosamprenavir, Indinavir, Nelfinavir, Ritonavir, Saquinavir, Tipranavir

CASE REPORTS

Case 1. Serum aminotransferase elevations during lopinavir/ritonavir therapy in a patient with HIV-HCV co-infection.

[Modified from: Kottilil S, Polis MA, Kovacs JA. HIV Infection, hepatitis C infection, and HAART: hard clinical choices. JAMA 2004; 292:243-50. PubMed Citation]

A patient with HIV and HCV coinfection was found to have elevations in serum aminotransferase levels 3 months after starting an antiretroviral regimen of abacavir, didanosine, and lopinavir/ritonavir. Aminotransferase levels had been near normal when therapy was started. He was asymptomatic and physical examination was normal, without fever, rash or jaundice. Laboratory tests showed ALT elevations of more than 5 times the upper limit of normal and at least five times baseline values (Table). All antiretroviral agents were stopped and ALT levels decreased. He was restarted on lamivudine, didanosine and lopinavir/ritonavir and serum enzymes remained unchanged. He tested positive for anti-HCV and HCV RNA levels were moderately high (780,000 IU/mL). A liver biopsy showed moderate necroinflammatory activity and bridging hepatic fibrosis. He was treated with peginterferon and ribavirin for 48 weeks in an attempt to eradicate the HCV infection, but serum aminotransferase and HCV RNA did not change. He was maintained on his four drug regimen for HIV infection and remained asymptomatic with CD4 counts above 300/μL and no opportunistic infections.

Key Points

Medication:	Lopinavir/ritonavir
Pattern:	Hepatocellular
Severity:	1+
Latency:	1 month
Recovery:	4 weeks
Other medications:	Didanosine, lamivudine, abacavir

Laboratory Values

Time After Starting	Time After Stopping	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	HCV RNA (IU/mL)
Pre		43	158	0.6	
Started abacavir, didanosine, and lopinavir/ritonavir					
12 weeks	0	286	158	1.1	
All antiretrovirals stopped					
16 weeks	14 weeks	76	105	0.7	
Restarted lamivudine, didanosine, and lopinavir/ritonavir					
4 weeks	0	197	123	1.1	780,000
12 months	0	117	114	1.4	772,571
Started peginterferon alfa-2b and ribavirin (48 weeks)					
13 months	0	54	122	1.9	
14 months	0	34	91	1.5	887,876
15 months	0	21	116	1.2	513,209
2 years	0	107	104	0.7	179,950
Peginterferon and ribavirin stopped					
1 year later		134	111	1.3	226,200
Normal Values		**<42**	**<116**	**<1.2**	

Comment

This patient had HIV-HCV coinfection and the chronic hepatitis C appeared to worsen when highly active antiretroviral therapy, which included lopinavir and low doses of ritonavir, was started. He did not, however, develop symptoms or jaundice. A liver biopsy revealed significant degrees of necroinflammatory activity and fibrosis, and he was treated with a 48 week course of peginterferon and ribavirin. While therapy of the hepatitis C led to transient improvements in serum aminotransferase levels, it had little effect on HCV RNA concentrations and no lasting effect on the disease activity. The worsening of hepatitis C with initiation of antiretroviral therapy has been attributed to reconstitution of the immune system. There is little evidence, however, that antiretroviral therapy leads to an increase in end stage liver disease or worse long term outcomes due to hepatitis C.

Case 2. Acute cholestatic hepatitis due to lopinavir/ritonavir therapy.

[Modified from: Zell SC. Clinical vignette in antiretroviral therapy: jaundice. J Int Assoc Physicians AIDS Care 2003; 2: 133-9. PubMed Citation]

A 35 year old man with long standing HIV infection developed jaundice and itching 17 months after starting a regimen including lopinavir/ritonavir, stavudine and lamivudine. He had been treated successfully for mycobacterium avium intracellulare (MAI) infection, and follow up cultures were negative after a prolonged course of clarithromycin and ethambutol, which had been stopped several months previously. Physical examination showed jaundice, without fever, rash or signs of chronic liver disease. Blood tests showed elevations in serum bilirubin (total 12.6 mg/dL, direct 8.5 mg/dL), alkaline phosphatase (435 U/L) and ALT (200 U/L) (Table). Tests for hepatitis A, B and C were negative. A contrast CT showed no evidence of biliary obstruction. All antiretroviral agents were stopped, but serum alkaline phosphatase levels continued to rise. A liver biopsy showed no evidence of MAI infection or extrahepatic obstruction. After a week, his liver tests begin to improve and he was restarted on antiretroviral therapy using stavudine, lamivudine and nelfinavir. Eight weeks after initial presentation, his serum bilirubin and aminotransferase levels had fallen to normal.

Key Points

Medication:	Lopinavir/ritonavir
Pattern:	Cholestatic (R=1.5)
Severity:	3+ (jaundice, hospitalization)
Latency:	17 months
Recovery:	2 months
Other medications:	Stavudine, lamivudine; previously ethambutol and clarithromycin

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
17 weeks	0	200	435	12.6	Antiretroviral therapy stopped
	1 week		958		Liver biopsy
	1.5 weeks	105	375	3.2	Discharged
Restarted lamivudine, stavudine, and nelfinavir					
19 weeks	8 weeks	25	319	1.1	
Normal Values		**<40**	**<130**	**<1.2**	

Comment

A cholestatic hepatitis arose during antiretroviral therapy, the most likely cause being lopinavir/ritonavir, rather than stavudine and lamivudine which had been tolerated for several years and which was restarted without recurrence of the liver injury. The liver biopsy did not show steatosis and features of mitochondrial injury that would be typical of stavudine. With no other competing diagnosis, the likelihood that this case represented lopinavir/ritonavir induced liver injury is high.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Lopinavir – Kaletra®

DRUG CLASS

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Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULA AND STRUCTURE

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Lopinavir	192725-17-0	C37-H48-N4-O5