

Medical Writers' Circle

June • 2006

a series of articles written by medical professionals about the management and treatment of hepatitis C

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2006 Series

Drug-associated Liver Disease during HAART: Impact of HCV Coinfection

Liver damage caused by medication ingestion—also known as drug-induced liver injury (DILI)—has become an important public health problem, contributing to more than 50% of acute liver failure cases, a fraction of which require urgent liver transplantation because of the irreversible damage to the liver. Cases of severe DILI are defined as liver enzyme elevations five or more times the normal limit.

Most drugs listed in the *Physician's Desk Reference* and a number of over-the-counter preparations have been associated with different degrees of liver enzyme elevations. Resulting liver toxicity is the number one cause for FDA non-approval or withdrawal of medications from the market. Fortunately most elevations are mild. Drug-induced liver injury (DILI) is often detected after a drug enters the market because animal models cannot always predict human

toxicity. For example, of 31 drugs that caused hepatotoxicity in humans, 13 showed no toxicity in animals. Conversely, of drugs associated with hepatotoxicity in animals, only one-third resulted in a rise in liver enzymes in humans.

In 2005, 8 new reports of drug-induced liver injury involving 8 medications or over-the-counter remedies were published in the literature. The NIH and AASLD conducted a special meeting in September 2005 to address these issues.

Causes of Drug Reactions

Why do people react negatively to drugs? The main issue is an individual's sensitivity (not necessarily allergic) to the drug or its metabolites. Reactions occur in .001 to 10 percent of exposed patients, depending on the medication. An individual's metabolic pathways may (by chance) lead to toxic compounds and we

know that specific enzymes are genetically determined. Mechanisms of detoxification (neutralization of toxic compounds) may also be associated with genetic variations: an individual's inefficient detoxification pathway may result in the occurrence of DILI.

Categories of patients at higher risk for DILI include:

- Females
- Obese individuals
- Elderly patients
- Viral illnesses (see below)
- Preexisting liver disease

Diagnosing Hepatotoxicity

Patients with drug-induced hepatotoxicity may be asymptomatic, with liver injury diagnosed during routine blood testing, while others develop symptoms including nausea, fatigue, itching and jaundice. The latter symptom is significant, as patients with jaundice (bilirubin >3-4) have a poorer outcome.¹

The diagnosis of drug hepatotoxicity in any patient is complicated by several factors. First, there are no satisfactory criteria for the positive diagnosis of DILI, and it is often a diagnosis of exclusion. Second, because patients often take several medications, teasing out the culprit can present challenges. Lastly, the histological expression of hepatotoxicity is extremely varied and, therefore, a liver biopsy is of limited use in making a positive diagnosis. However, hepatic histology is very useful for ruling out other causes of liver enzyme elevation and for establishing the 'signature' of a particular drug.¹

Therapy: The only therapy for drug-induced hepatotoxicity is immediate discontinuation of the offending medication. Because drugs taken together may cause toxicity, it is often useful to discontinue several medications as their combination may be the culprit. Acetaminophen toxicity is treated with N-acetylcysteine and this compound is being studied as a therapy for other drug injuries as well.¹ In cases of mitochondrial toxicity with lactic acidosis several agents (Vitamin B complex, carnitine, lipoic acid, coenzyme Q, and vitamin E) have been advocated, but none have been scrutinized in controlled trials. In selected cases of

liver failure, liver transplantation is indicated.

HIV and HCV coinfection: In patients with HIV, the term "hepatotoxicity" may be misleading because some of these elevated liver tests may not be directly caused by the medication in question. Instead, acute viral hepatitis, reactivation of chronic hepatitis B or C, and alcohol ingestion may all play a role in such events. Of note, patients often take alternative and complementary medicines in association with HAART and several of these have been associated with clear-cut DILI.² In addition, an elevation of transaminases is a sensitive signal for liver injury; however it may not be specific or even clinically relevant, as most instances of 'transaminitis' improve despite drug continuation.³ Most often (70-85%), these enzyme elevations are not accompanied by symptoms.³ On the other hand, a bilirubin elevation due to DILI is a more ominous finding as 10% of those with jaundice

die or need a liver transplant (the so-called Zimmerman's rule).^{1,16}

Patients with chronic viral illnesses such as HIV or HCV infection appear to be more prone to develop hepatotoxicity due to antituberculous medications or highly active antiretroviral therapy (HAART), possibly because of impaired hepatocyte defense mechanisms, e.g., glutathione.^{4,5} In addition, patients with HIV infection are very likely to ingest a cocktail of drugs for the control of their HIV infection. Therefore, they are at high risk for developing enzyme elevations during HAART. Liver injury associated with drugs is part of the spectrum of liver disease, and has the potential to greatly affect the lives of individuals living with HIV.⁶

Several earlier retrospective studies and case reports have associated liver enzyme elevations with specific HAART regimens. Sulkowski noted the highest percentages of World Health Organization (WHO) grade 3 enzyme

elevations with Ritonavir, in up to 30% of patients.⁴ Nevirapine is associated with such elevations in up to 13% of cases, however only 2.6% were symptomatic.¹⁸ In regimens with nucleoside analogues and non-ritonavir protease inhibitors (PIs), patients with hepatitis C had a three-fold higher chance of showing increased liver tests.¹ A Southwestern France cohort noted that 8% of patients had transaminase >200 IU/L at one year after initiating HAART.⁷ HCV was associated with a two- to three-fold chance of 'hepatotoxicity' in any HAART regimen.⁷ Regimens including two nucleoside analogs (NAs) led to enzyme elevations an average of 3 months later than PI-based regimens.⁷

As the evidence has accumulated in the HIV population, hepatitis C was confirmed to be a risk factor associated with a 3 to 5-fold chance of developing elevated transaminases during HAART, compared to HIV patients without

Table 1: Prospective studies of the impact of HCV coinfection on liver injury (transaminase elevations)

Study	N=CD4	Follow-up	Hep+	Hep-	Grade 3/4 Scale	Other associations
Martinez 2001	N=610 279	Q 3 mos	RR=2.5	--	no	Duration ART
Monforte 2001	N=1255 327	Q 3 mos @12 mos	7%	1%	no	Dizovudine Zalcitabine
Sulkowski 2000	N=298	Q 3 mos	RR=3.7	--	yes	---
Saves 1999	N=1253 144	Unknown @12 mos	13%	2%	no	---

*Abbreviations: ART, antiretroviral therapy; RR, relative risk

hepatitis. Between 7-13% of coinfecting patients develop grade 3 or 4 transaminase elevation as opposed to 1-2% in those with HIV alone.⁷⁻⁹ These studies were based on prospectively followed patient cohorts, where liver enzyme data were collected as a matter of protocol. **Table 1** clearly indicates that viral hepatitis (usually hepatitis C because of greater prevalence) is a risk factor

been clearly associated with the use of NA's. This type of systemic toxicity involves the liver as well as other organs, and may lead to liver failure and lactic acidosis.¹⁰

Mitochondrial DNA damage due to inhibition of gamma-polymerase is the accepted pathogenetic mechanism. The likelihood of such an event is associated with type of drug (greater with

think that GSH may protect against DILI. In fact, N-Acetylcysteine, a cysteine donor, repletes GSH stores and is the accepted therapy for acetaminophen-induced liver injury. HIV infection alone is also associated with depleted GSH stores, which can respond to therapy with NAC.¹³ HCV and HIV infection may result in a double jeopardy situation where the liver is unusually sensitive to

incorrect for several reasons. The chance of eradicating HCV in HIV coinfecting patients is lower than in non-HIV patients. Most enzyme elevations are moderate and not accompanied by jaundice. An elevated CD4 count is an important parameter for successful anti-HCV therapy. Therefore, HAART should be the first line of therapy in most instances of HIV/HCV coinfection.¹⁷

“In patients with HIV, the term “hepatotoxicity” may be misleading because some of these elevated liver tests may not be directly caused by the medication in question.”



for developing liver enzyme elevations.⁷⁻⁹ Some studies did not use grade 3 or 4 elevations as an endpoint; instead an arbitrary cutoff of >200 IU/L was used. In most laboratories, this represents 3.5 to 5 times the upper limit of normal.⁷⁻⁹ On the other hand, a more specific signal for hepatic injury, serum bilirubin elevation, is more rarely present. In those cases as well, the presence of hepatitis is associated with bilirubin elevation after initiation of HAART.⁴

Other well-established risk factors in the HIV cohorts are alcohol (6-fold risk), age (10% increased risk per year of age) and hepatitis B coinfection (3-fold risk).⁹ Mitochondrial toxicity has

D4T, ddI and combination) and duration of exposure (>1yr).¹¹ Thus, patients on chronic NA therapy need to be monitored over a prolonged time frame, longer than for other drugs.

The reason why HCV is associated with liver injury and HAART is unknown. Certainly, HCV infection can occasionally flare and directly result in elevated transaminases. However, HCV may also indirectly sensitize the liver to the toxic effects of certain drugs or medications. In vitro evidence suggests that the HCV core protein decreases intracellular glutathione (GSH) stores.¹² Knowing that GSH is a major antioxidant defense, it is reasonable to

oxidative stress. In addition, the HCV core protein has been implicated in the pathogenesis of liver steatosis and in mitochondrial injury.¹⁴ In turn, steatosis may lead to hepatic inflammation and fibrosis and result in enhanced sensitivity to the injurious effects of drugs.¹⁴ All of these putative effects of HCV are of course relevant to the pathogenesis of DILI in patients with HIV infection.

The strong association between hepatitis C and the chance of liver enzyme elevation during HAART has led some to propose treating all coinfecting patients with interferon and ribavirin before HAART. This may be

In summary, elevation of liver tests during HAART is common; more so in HCV coinfecting patients. Possibly, the profound GSH depletion seen in these patients is the major risk factor. Some medications have greater potential than others to elevate liver tests. Patients with HIV/HCV coinfection should not be denied a particular class of drug during HAART. Rather, they should be followed diligently with monthly liver tests and referred to specialists for grade 3 or 4 liver enzyme elevations.



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Dr. Bonacini is an investigator in a phase IV study comparing the efficacy of treatment with Copegus (ribavirin) 1000 or 1200 in combination with Pegasys (peginterferon alfa-2a (PEG-IFN alfa-2a) 180 µg to the approved regimen of Copegus 800 mg in combination with Pegasys 180 µg in patients with chronic hepatitis C genotype 1 virus coinfecting with HIV-1 treated for 48 weeks and followed for 24 weeks after treatment end (SVR). Enrollment in the study will begin in June or July 2006. For more information about this study visit www.cpmc.org/liver/ or call (415) 600-1026.

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A publication of the
Hepatitis C Support Project

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The Mission of the Hepatitis C Support Project is to offer support to those who are affected by the hepatitis C Virus (HCV), hepatitis B Virus (HBV) and HCV coinfections.

Support is provided broadly, through information and education, as well as access to support groups. The Project seeks to serve the HCV community as well as the general public.

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