

Medical Writers' Circle

a series of articles

written by medical professionals about the management and treatment of Hepatitis C

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

Liver damage caused by medication ingestion—also known as drug-induced hepatotoxicity or DIH—has become an important public health problem, contributing to more than 50% of acute liver failure cases., a fraction of whom require immediate transplantation because of the irreversible damage to their liver. Cases of severe drug-induced hepatotoxicity, are defined as liver enzymes 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 hepatotoxicity 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.

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 DIH.

Categories of patients at higher risk for DIH include:

- Females
- Obese individuals
- Elderly patients
- Viral illnesses (see below)
- Pre-existing 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 facts. First, there are no satisfactory criteria for the

positive diagnosis of DIH 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 to rule out other causes of liver enzyme elevation [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. 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 has been scrutinized in controlled trials. In selected cases of liver failure, liver transplantation may be 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, alcohol ingestion may all play a role in such events. Of note, patients often take alternative and complementary

Several earlier retrospective studies and case reports have associated liver enzyme elevations with specific HAART regimens. Sulkowski noted the highest percentages World Health Organization (WHO) grade 3 enzyme elevations (30%) with Ritonavir

to enzyme elevations an average of 3 months later than PI-based regimens [7].

As evidence had accumulated in the HIV population, hepatitis C has been confirmed to be a risk factor associated with a 3 to 5-fold chance of developing

developing liver enzyme elevations [7-9]. Some studies did not use grade 3 or 4 elevations as an endpoint; instead an arbitrary cut-off 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 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 D4T, ddI and combination) and duration of exposure (> 1yr) [11]. Thus, patients on chronic NAs therapy need to be

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medicines in association with HAART and several of those have been associated with clear-cut DIH [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%), those enzyme elevations are not accompanied by symptoms [3]. On the other hand, a bilirubin elevation due to DIH is a more ominous finding as 10% of those with jaundice die or need a liver transplant (the so-called Zimmerman's rule) [1].

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 toxicity associated with drugs is part of the spectrum of liver disease, and has the potential to impact the lives of individuals living with HIV [6].

[4]. In regimens with nucleoside analogues and non-ritonavir protease inhibitors (PIs), patients with hepatitis C had a three-fold higher chance to show 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

elevated transaminases during HAART, compared to HIV patients without 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 enzymes 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 for

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 months	*RR=2.5	—	No	Duration ART*
Monforte 2001	N=1255 327	Q 3 months @ 12 months	7%	1%	No	Zidovudine Zalcitabine
Sulkowski 2000	N=298	Q 3 months	*RR 3.7	—	Yes	—
Saves 1999	N=1253 144	Unknown @ 12 months	13%	2%	No	—

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

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 think that GSH may protect against DIH. 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 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 DIH 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 is probably wrong for several reasons:

1. The chance of eradicating HCV in HIV coinfecting patients is lower than in non-HIV patients.
2. Most enzyme elevations are moderate and not accompanied by jaundice
3. 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.

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.

Visit California Pacific Medical Center Liver Clinic Web Site at:

www.cpmc.org/liver

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