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Suspected Hy's Law- Fast, but not That Fast!

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Abstract

Drug-induced liver injury (DILI) is a major concern in clinical studies as well as in post-marketing surveillance. Several anti-infective drugs had development discontinued due to serious hepatic events- acute liver failure, including liver transplantation or death. The diagnosis of drug-induced liver injury necessitates an initial high degree of suspicion, based on circumstantial evidence. It is a step-by-step process of exclusion. Consequently, a patient in a clinical trial who experiences elevated LFTs that meet Hy's Law criteria should have causes other than study drug carefully excluded.

Keywords: Drug-induced liver injury (DILI); Hy's Law; Liver function tests (LFTs); Antibiotics; Congestive heart failure; Ischemic liver

Case Report

Drug-induced liver injury (DILI) is a major concern in clinical studies as well as in post-marketing surveillance. DILI is the most frequent reason cited for the withdrawal of approved drugs from the market and accounts for up to 15% of the cases of acute liver failure [1].

Before deciding to stop a global Phase 2, or 3 clinical trial and further development of a promising drug due to a suspected Hy's Law case, a pharmaceutical company must carefully consider the evidence. Patient safety comes first and foremost as stated by "Do No Harm," but to prematurely end a program that costs hundreds of millions of dollars also has consequences, especially with an unmet medical need for innovative drugs to treat the indication.

As per current international criteria, suspicion of Drug Induced Liver Injury (DILI) cases include: 1) alanine aminotransferase (ALT) ≥ 5 x ULN, or 2) alkaline phosphatase (ALP) ≥ 2 x ULN (particularly with accompanying elevations in concentrations of 5'-nucleotidase or GGT in the absence of known bone pathology driving the rise in ALP level), or 3) ALT ≥ 3 x ULN and simultaneous elevation of bilirubin concentration >2 x ULN1.

Hy's Law, a rule of thumb indicates a high risk of a fatal DILI if a patient receives a medication causing hepatocellular injury (not cholestatic injury) with jaundice. Liver function test (LFT) abnormalities include: alanine aminotransferase/aspartate aminotransferase (ALT/AST) >3 x ULN in combination with Total Bilirubin Level (TBL) >2 x ULN in the absence of cholestatic injury (ALP <2 x ULN) and no other cause identified. It serves as the basis for stopping rules in clinical trials and clinical practice. Abnormalities in these parameters require evidence for most likely or probable causality by the drug in question.

Prompt recognition of a culprit drug as the cause of liver injury, the most important aspect in hepatotoxicity management appears to decrease the risk of progression to acute liver failure or chronic liver failure.

The diagnosis of drug-induced liver injury necessitates an initial high degree of suspicion, based on circumstantial evidence. It is a step-by-step process of exclusion. Consequently, a patient in a clinical trial who experiences elevated LFTs that meet Hy's Law criteria should have causes other than study drug carefully excluded (Table 1) [2]. Abnormal aminotransferases signal the need to look closer to find the probable cause of liver dysfunction.

Alcohol Abuse
Viral hepatitis (A, B, C, D and E)
EBV and CMV
Bacterial or fungal sepsis
Autoimmune hepatitis
Inherited diseases (Wilson's Disease)
Congestive heart failure, ischemic liver
Primary or metastatic liver
Biliary tract or pancreatic carcinoma
Benign biliary obstruction

Table 1: Search for Non-Drug Causes.

Fluoroquinolones modestly increase serum ALT levels as a class effect. Fluoroquinolones among the most widely prescribed antibiotics due to ease of dosing and broad spectrum commonly cause idiosyncratic acute liver injury, including fatal instances of hepatic injury. For example, post-marketing safety surveillance revealed TROVAN®, trovafloxacin, a third generation fluoroquinolone, caused numerous cases of liver injury [3]. Within 2 years (with only 2.5 million patient exposures), 140 cases of serious hepatic events, including 14 cases of acute liver failure, 4 cases requiring liver transplantation and 5 deaths. The pattern of enzyme elevations is typically hepatocellular with serum aminotransferase levels >1000 U/

L. The drug was, therefore, restricted to serious and life- or limb-threatening infections [4].

Development of DX-619, a novel fluoroquinolone with activity against Methicillin-Resistant *Staphylococcus aureus* terminated after Ph 1 data showed severe hepatotoxicity-which an infectious diseases expert described as "worse than trovafloxacin, because it showed up in Ph 1" (Robert Moellering, M.D., personal communication) [4]. Fortuitous timing of this data resulted in cancelling a Ph 2 trial and prevented potential harm.

As with other macrolide antibiotics, telithromycin has a low rate (1% to 2%) of transient serum enzyme elevations during therapy. These elevations usually resolve even with drug continuation and a similar rate of serum enzyme elevations can occur with comparator agents. More importantly, subsequent to commercial launch in the USA, the ketolide KETEK®, telithromycin was implicated in at least 42 cases of clinically apparent liver injury reported to FDA between 2004-6; 26 were considered probable or highly likely and 16 as only possibly related to telithromycin, with four deaths and one liver transplant [5]. The pattern of enzyme elevations is typically hepatocellular and serum aminotransferase levels >1000 U/L. Clinical features were short latency (median, 10 days), abrupt onset of fever, abdominal pain and jaundice); this resulted in narrowing of its indication to the treatment of mild-moderate community-acquired pneumonia and acute exacerbation of chronic bronchitis (for the latter, only if the infection is caused by known or suspected β-lactam- and/or macrolide-resistant strains). Drugs within a therapeutic class differ regarding their hepatic liability, suggesting that physicochemical and toxicological drug properties affect DILI risk.

Case Studies

The following two subjects met Hy's Law clinical chemistry criteria during an anti-infective trial. However, neither subject was considered to be a Hy's Law case when other factors were considered, as described below.

Case 1: A 66- year-old White, non-Hispanic male was prescribed a 5-day blinded treatment of an oral ketolide vs oral moxifloxacin for community-acquired pneumonia. Medical history was significant for chronic cardiomyopathy, hypertension and hyperlipidemia.

Liver function tests are summarized in Table 2. Please note: ALT >3 x ULN at Day 3 with elevated TB >2 x ULN at EOT.

Between EOT and TOC, the subject experienced a non-serious adverse event (AE) of Neoplasma Malignum Bronchi Sive Pulmonis, Lobi Inferioris (MedDRA Preferred Term: Lung Neoplasm, Malignant).

This was not considered a Hy's Law case due to 1) a single episode of bilirubin elevation (at EOT) with normal levels shortly before (Days 3 and 5) and shortly after (TOC and Follow-Up), 2) bilirubin elevation at EOT only due to unconjugated bilirubin (conjugated bilirubin was normal), so likely due to an event of increased hemolysis in a patient with underlying bronchopulmonary malignancy. For the same reasons, this was not considered a DILI case.

Case 2: A 64 year-old African male was prescribed a 7-day blinded treatment of an oral ketolide vs oral moxifloxacin for community-acquired pneumonia. Medical history was significant for heavy smoking. No other drugs taken. At TOC, we received an automated alert for high aminotransferase and total bilirubin elevation that triggered the medical monitor to call the Principal Investigator to obtain addition information (Table 3).

Visit	Study Day	Test name	Result (units)	Reference range
Screening		ALT	34 (U/L)	0-44
		AST	23 (U/L)	14-39
		Total bilirubin	0.3	0.3- 1.2
Day 3	3	ALT	198 (U/L)	0-44
			4.5 x ULN	
		AST	109 (U/L)	14-39
Day 5		ALT	117	0-44
		AST	63	14-39
	5	ALP	125 (U/L)	53-129
End of Treatment	8	ALP	108 (U/L)	53-129
		Total bilirubin	2.7 (mg/dL); 2.25 x ULN	0.3 – 1.2
		Indirect bilirubin	2.01	0.2- 0.9
		Direct bilirubin	0.68	0.1- 0.4
Test of Cure	15	ALT	80 (U/L)	0-44

Table 2: Summary of Liver function test.

Visit	Study Day	Test name	Result (units)	Reference range
Screening		ALT	33 (U/L)	0-44
		AST	27 (U/L)	14-39
Day 5	5	ALP	143 (U/L)	53-129
End of Treatment	7	ALP	157 (U/L)	53-129
Test of Cure	15	ALT	213 (U/L); 4.8 x ULN	0-44
		ALP	217 (U/L)	53-129
		Total bilirubin	3.5 (mg/dL); 2.9 x ULN	0.3-1.2
		Direct bilirubin	1.52 (mg/dL);	0.1- 0.4
			3.8 x ULN	

Table 3: Aminotransferase and total bilirubin elevation.

DILI has 3 main biochemical injury patterns (hepatocellular, cholestatic, and mixed) by calculating the R value ([ALT value/ALT upper limit of normal (ULN)]/[ALP value/ALP ULN]). This patient's R value = 2.86, which corresponds to a mixed injury (2<R<5) [5].

The PI provided the following additional information. The patient complained of abdominal distention and right upper quadrant abdominal pain, cough productive of blood, dyspnea and weakness. Abdominal ultrasound showed numerous small cystic lesions in the liver. Since he lived in RSA and had cystic liver lesions, we considered cystic hydatid disease due to the dog tapeworm *Echinococcus granulosus*. However, a literature review revealed cystic liver lesions do not cause elevations of bilirubin and aspartate aminotransferase, as occurs in approximately 50% of patients with liver abscesses.

Further workup included: a cardiac echo that showed cardiomyopathy with LVEF 40%. The conclusion was symptoms caused by grade 3 cor pulmonale, grade 1 hypertrophic cardiomyopathy, chronic heart failure decompensation and most likely portal hypertension. The cystic lesions on abdominal ultrasound were probably dilated blood vessels. After treatment with digoxin, furosemide and nebulizers, the patient improved clinically and laboratory evaluation showed ALT 171 U/L, 3.9 x ULN, AST 68 U/L, 1.7 x ULN. This patient also is not a Hy's Law case. This wasn't hepatotoxicity, instead cardiomyopathy caused ischemic hepatopathy [6].

Discussion

Congestive hepatomegaly is due to chronically elevated hepatic venous pressure secondary to right-sided heart failure; it is often associated with impaired hepatic function with biochemical parameters usually moderately elevated 2-3 x ULN, including: ALT, AST, total bilirubin, LDH, GGT, and ALP [7]. Allen et.al analyzed liver function tests of 2679 patients with symptomatic chronic heart failure in the Candesartan in Heart Failure: Assessment of Reduction in Mortality and Morbidity (CHARM program) [8]. The analysis showed liver function test abnormalities were common in patients with chronic HF, ranging from ALT elevation in 3.1% of patients and total bilirubin elevated in 13% of patients. The proportion of patients with impaired left ventricular dysfunction (ejection fraction ≤ 0.40, n= 1594) who had elevations in total bilirubin (15.8%) was approximately double (9.4%) than that of patients with preserved left ventricular dysfunction (ejection fraction > 0.40); $p < 0.001$.

Conclusion

For DX-619, the sponsor did the right thing terminating the program quickly. The two cases presented, however, show the hazard of diagnosing Hy's Law from serum chemistries alone, without considering what might have caused the abnormalities. Terminating the trial would have been premature.

Patients with cardiovascular disease, especially right heart failure (cor pulmonale) and hypotension, or any cause of impaired oxygenation of the liver, may experience acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L) [7-11].

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