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Detection, Assessment and Management of DILI During Drug Development for HBV: The IQ DILI Initiative.

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Outline

- Background
- Risk of DILI in HBV patients
- Current Regulatory Guidelines
- Hy's law and HBV patients
- eDISH for databases of clinical trials for HBV
- Causality assessment: DILI versus HBV flare
- Hepatic stopping rules
- The IQ DILI Initiative
- Summary

Background of IQ Consortium

- The IQ Consortium (the International Consortium for Innovation and Quality in Pharmaceutical Development), composed of over 40 companies, is a leading science-focused organization with a mission to advance science and technology to augment the capability of member companies to bring transformational solutions that benefit patients, regulators and the broader R&D community.
- The IQ Consortium had been primarily focusing on CMC (Chemistry, Manufacturing, and Controls), and preclinical to early clinical trial topics (e.g. preclinical safety, drug metabolism, clinical pharmacology); however, it has an interest in expanding into the clinical space.

In June 2016, the IQ Board endorsed the establishment of an IQ initiative on clinical aspects of DILI; "The IQ DILI Initiative"

Gaps in Best Practices and Current Guidances

Patients with pre-existing liver diseases	Hepatitis B, C, metastatic liver disease, alcoholic liver disease, nonalcoholic steatohepatitis
Special populations	Pediatric, geriatric, oncology, immunosuppressed
Non-hepatocellular DILI	Cholestatic injury, steatohepatitis, hepatic vascular injury
Specific drug groups	Immunosuppressives, anti-virals, chemotherapy, cancer immunotherapy
Drug re-challenge	Is re-challenge with a drug implicated in DILI too dangerous? If not, criteria to define a positive re-challenge test
Biomarkers	Are there promising biomarkers for predicting idiosyncratic DILI that should be routinely incorporated into clinical protocols? Should prospective blood samples be banked for further study in subjects with liver signals?

DILI Background

- A major cause of terminated drug development and limited use*
- A leading cause of acute liver failure
- Most significant DILI events in the clinic are idiosyncratic
- Presently, there are no diagnostic or predictive DILI biomarkers
- ALT is a sensitive but nonspecific marker for hepatocellular DILI
- Animal studies generally do not predict idiosyncratic DILI
- DILI may be predicted by careful data collection and analysis in early phases of clinical development

**troglitazone, benoxaprofen, bromfenac, ticruynafen, ximelagatran, isoniazid, labetalol, trovafloxacin, felbamat, nefazodone, etc*

Risk of DILI in HBV patients

Are HBV patients susceptible to DILI?

Chronic Hepatitis B and DILI Risk

HEPATOLOGY Vol. 31, No. 1, 2000

Antituberculosis Drug-Related Liver Dysfunction in Chronic Hepatitis B Infection

WAI-MAN WONG,[1] PUI-CHEE WU,[2] MAN-FUNG YUEN,[1] CHI-CHUNG CHENG,[1] WING-WAI YEW,[3] POON-CHUEN WONG,[3] CHEUK-MING TAM,[4] CHI-CHIU LEUNG,[4] AND CHING-LUNG LAI[1]

Liver toxicity is a common side effect of antituberculosis (anti-TB) drugs. We studied the differences in liver dysfunction observed during anti-TB treatment between hepatitis B virus carriers (HBV) and noncarriers. Three hundred twenty-four patients on anti-TB drugs were recruited and followed up for 1 year. Forty-three patients with HBV and 276 non-HBV patients were included for analysis. Liver function tests and viral markers were monitored monthly. Liver biopsy was requested whenever the alanine transaminase (ALT) was persistently abnormal. Eighty-six HBV carriers who were not given anti-TB drugs were chosen as a second control and evaluated prospectively. The incidence of liver dysfunction was significantly higher in HBV carriers given anti-TB drugs (34.9%) when compared to noncarriers (9.4%, $P < .001$) and with HBV carriers not given anti-TB drugs (8.1%, $P < .001$). For patients given anti-TB drugs, HBV carriers who developed liver dysfunction were younger ($P = .011$) and had more severe liver injury compared with noncarriers ($P = .008$). By multiple logistic regression analysis, age ($P = .002$) and hepatitis B infection ($P < .001$) were the only 2 significant risk factors for hepatotoxicity related to anti-TB therapy. (HEPATOLOGY 2000;31:201-206.)

Chronic Hepatitis B and DILI Risk

Table 1. Prospective studies on the effect of hepatitis C virus (HCV) and hepatitis B virus (HBV) coinfection on severe liver injury (defined as transaminase elevations) in patients with HIV infection who are receiving HAART.

Study [reference]	No. of subjects	Average CD4 cell count, cells/mm^3	Follow-up	Relative risk of hepatitis, by infection status		Grade 3 or 4 transaminase elevation used as end point	Other associations
				Positive[a]	Negative		
Martinez et al. [14]	610	279	Every 3 months	2.5 (HCV)	1	Yes	Duration of therapy
Monforte et al. [15]	1255	327	Every 3 months	10.6 (HCV), 8.4 (HBV)	1	No	Zidovudine or zalcitabine therapy
Sulkowski et al. [1]	298	~200	Every 3 months	3.7[b]	1	Yes	—
Saves et al. [12]	1253	144	⩾1 test	3.2 (HCV) 3.0 (HBV)	1	No	—

- HBV coinfection is associated with a 3-8-fold increase in risk of developing elevated aminotransferase levels during HAART

M. Bonacini. CID 2004:38 (Suppl 2):S104-S108

Chronic Hepatitis B and DILI Risk

Kim *et al. BMC Infectious Diseases* (2016) 16:50
DOI 10.1186/s12879-016-1344-2

BMC Infectious Diseases

RESEARCH ARTICLE Open Access

Hepatitis C and not Hepatitis B virus is a risk factor for anti-tuberculosis drug induced liver injury

Wan Soo Kim[1], Sang Soo Lee[1], Chang Min Lee[1], Hong Jun Kim[1], Chang Yoon Ha[1], Hyun Jin Kim[1], Tae Hyo Kim[1], Woon Tae Jung[1], Ok Jae Lee[1], Jeong Woo Hong[1], Hyun Seon You[1*] and Hyun Chin Cho[2]

Risk of DILI in chronic HBV Patients

- Still a matter of debate due to scarce and mixed evidence.
- Generally, it is believed that chronic liver disease does not predispose to DILI[1-4]
- "*The often cited warning that drugs known to produce hepatic injury should not be given to patients with liver disease has little foundation in fact*"

Hyman Zimmerman

- Advanced pre-existing liver disease may lead to worse outcome when DILI occurs[5]

1. Zimmerman H. Hepatotoxicity: 2nd ed. Philadelphia, 1999.
2. Lewis JH. Expert Opin Drug Saf 2002;1:159–172.
3. Russo MW and Watkins PB. Gastroenterology 2004;126:1477–1480.
4. FDA Guidance for Industry 2009
5. Chalasani N. Gastroenterology 2015;148:1340–1352

Current Guidelines

What do current guidelines teach us about DILI in HBV clinical trials?

Current DILI Guidelines

- Presently, most drug makers rely on regulatory guidlines[1,2] and published position papers[3-5].
- Most published guidelines address comprehensively clinical trials enrolling patients with normal livers.
- However, they typically do not cover issues pertaining to patients with pre-existing liver diseases such as chronic hep B.
- As a result, approaches and practices of assessment of liver safety in HBV patients vary greatly between drug makers.

1. FDA. 2009. DILI: premarketing clinical evaluation. Guidance for industry.
2. Health Canada. 2012. Guidance document: pre-market evaluation of hepatotoxicity
3. Aithal et al. Clin Pharmacol Ther. 2011;89(6):806–15
4. Regev et al. Drug Saf;2014:37 (Suppl 1):S47–S56
5. Avigan et al. Drug Saf;2014:37 (Suppl 1):S19–S31

Guidance for Industry

Drug-Induced Liver Injury: Premarketing Clinical Evaluation

U.S. Department of Health and Human Services
Food and Drug Administration
Center for Drug Evaluation and Research (CDER)
Center for Biologics Evaluation and Research (CBER)

July 2009
Drug Safety

Hy's Law and chronic HBV patients

Should Hy's law be applied to NASH patients?

Hy's Law Criteria*

- ALT/AST ≥ 3X ULN
- Total bilirubin ≥ 2X ULN
- No initial cholestasis phosphatase < 2X ULN)
- No other cause of liver injury

Hyman Zimmerman
1914-1999

*as defined by FDA Guidance for Industry 2009

Hy's Law and DILI Prediction

- Hy's Law cases carry >10% risk of live transplant or death
- Two Hy's Law cases in a clinical trial of 1,000 subjects
  - → risk of liver transplant or death: **>2:10,000**
  - → risk post marketing: **>200 per million**

[3] This constellation of findings is the hallmark of a Hy's Law case. The predictive value of these three findings for a drug's potential to cause DILI may be different if these findings are identified in patients with preexisting liver disease, fatty liver disease such as NASH, chronic hepatitis C or B, or bilirubin metabolism abnormalities (Gilbert syndrome), or in patients on drugs that treat liver disease or that inhibit bilirubin glucuronidation, such as indinavir or atazanavir (Zhang and Chando et al. 2005).

FDA Guidance for Industry. July 2009

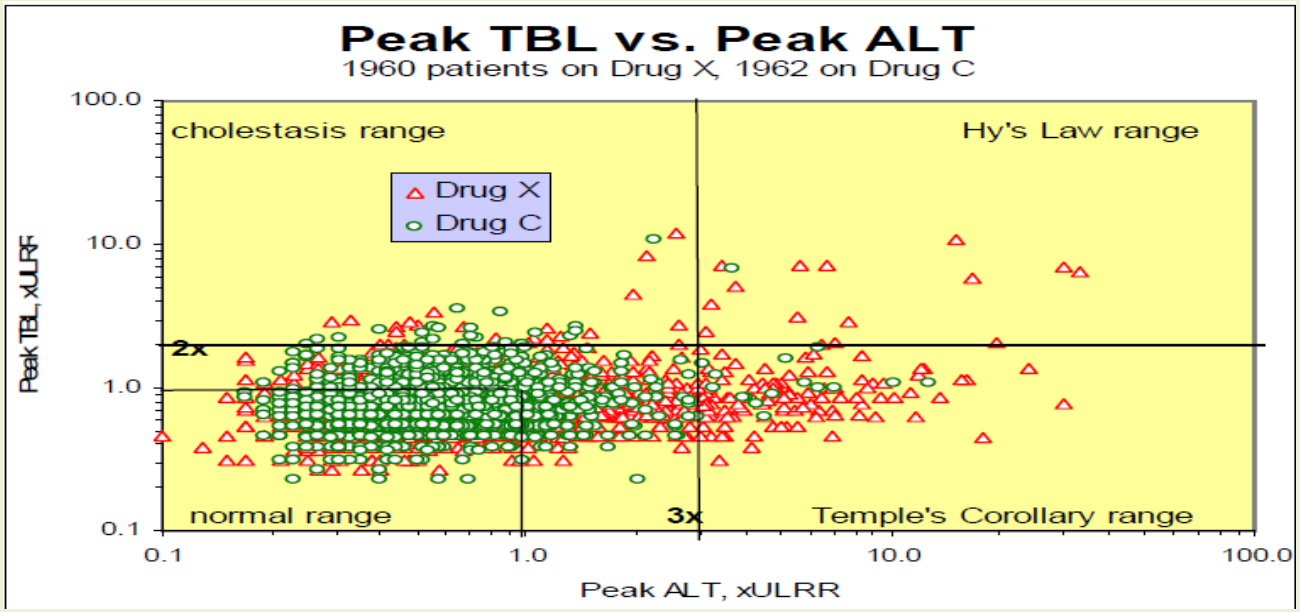
Hy's Law and chronic HBV patients

- Chronic HBV patients would often have elevated ALT or TBL at baseline, when enrolled in a clinical trial
- Can Hy's law be applied to HBV patients with baseline ALT> 3x ULN?
- Per definition, a case that has another cause for elevated ALT would not meet the full definition of HY's law.

eDISH for NASH Databases

Can eDISH be applied to HBV databases?

eDISH Plot (Evaluate Drug Induced Severe Hepatotoxicity)



ALT/AST Exclusion Criteria

Which ALT/AST level should be an exclusion criterion?

ALT/ AST Exclusion Criteria in NASH Clinical Trials

- "If the drug is intended to be prescribed or marketed to such patients after approval, they should be studied during controlled trials."[1]
- ALT> 200 U/L is often encountered in HBV patients.
- Inclusion of patients with high ALT levels may lead to difficulties in detection and monitoring of potential DILI

1. FDA Guidance for Industry. July 2009

Causality Assessment

How can DILI be differentiated from HBV reactivation/flare during drug development?

Causality Assessment

- There are still no diagnostic biomarkers for DILI
- Clinical manifestations of DILI may be similar to HBV reactivation or therapeutic flare
- Monitoring of HBV DNA levels may be helpful for differentiation from HBV reactivation but not from a therapeutic flare
- HDV infection has to be considered
- There is an unmet need for new diagnostic biomarkers

Hepatic Stopping Rules

When should the study drug be discontinued?

Hepatic Stopping Rules

Discontinuation of treatment should be considered if:[1]

- ALT or AST >8xULN
- ALT or AST >5xULN for more than 2 weeks
- ALT or AST >3xULN **and** (TBL >2xULN **or** INR >1.5)
- ALT or AST >3xULN with the appearance of fatigue, nausea, vomiting, right upper quadrant pain or tenderness, fever, rash, and/or eosinophilia (>5%)

- ❑ Discontinuing the drug too early may interfere with understanding the drug's hepatic safety profile, and would potentially increase the risk post-marketing
- ❑ Use of multiples of baseline of ALT may be superior to multiples of ULN as a threshold for discontinuation
- ❑ A new baseline may have to be established during the trial

1. FDA Guidance for Industry. 2009

Summary

- There is no clear evidence of increased risk of DILI in chronic HBV patients, however patients with advanced disease may have worse outcome when DILI occurs.
- Current regulatory guidelines do not address specific questions related to detection assessment and monitoring of DILI in HBV patients.
- Hy's law and eDISH may be difficult to apply to all HBV patients, especially those with baseline ALT>3x ULN.
- ALT/AST exclusion criteria may have important implications in HBV studies, and need to be pre-determined.
- Hepatic stopping rules may need to be adjusted based on baseline (or best pre-event) ALT/AST levels.
- Studies of large cross-pharma databases and new biomarkers will enable better understanding and improved approaches for detection and assessment of DILI in HBV clinical trials.

Thank you!

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Discussion

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