Diagnosing DILI in Patients with Active or Advanced Underlying Liver Disease (with a little help from Yogi)

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“Thank you for making this day necessary”
How to diagnose DILI in CLD?

“It’s déjà vu, all over again!”

You’ve got to be very careful if you don’t know where you’re going, because you might not get there.

Yogi Berra

WE'RE LOST, BUT WE'RE MAKING GOOD TIME.

Yogi Berra
Baseball Manager
(Born 1925)
Potential scenarios of DILI occurring in the setting of Active or Advanced CLD

- Chronic viral hepatitis
- Alcoholic liver disease
- Autoimmune hepatitis
- NAFL, NAFLD/NASH
- Chronic cholestatic disorders (PBC, PSC)
- Cirrhosis (all types)
- HCC, CholangioCa
- Hepatic metastases/infiltrative malignancy
- Extrahepatic biliary obstruction (benign or malignant)
Chronic Liver Diseases being treated in Clinical Trials vs Clinical Care

New drugs targeting CLD in clinical trials:
- PBC
- NASH
- Chronic hepatitis B, C

Acute and chronic liver diseases affecting clinical trials and post-marketing:
- HBV reactivation from DAAs, chemotherapy, immunosuppressive Tx
- Presence of NAFLD in diabetics
- Gallstones, hypoxic hepatitis, CHF and other benign conditions
- Hepatobiliary and pancreatic malignancy
Diagnosing DILI in CLD
Clinical Trials: Current Issues

- Many trials exclude ALT >1.5X ULN at enrollment
- Most trials exclude cirrhotics
- How to interpret natural fluctuations in liver tests?
- What monitoring interval should be in place? Weekly, monthly, q 3 monthly?
- Should monitoring be biochemical, clinical or both?
- Should unblinding be done for hepatic SAEs?
- What stopping rules should be applied? (higher or lower threshold?)
- Will a diagnostic biomarker for DILI become available?
Guidance from Regulatory Bodies

- 2009 FDA document on managing DILI in Pre-marketing studies was largely silent on specific diagnostic or stopping rules in CLD:
  
  “the implications of the 3 Hy’s Law findings [excess of ALT >3X ULN compared to controls; marked elevations of ALT >5X ULN vs controls, and bili >2X ULN in a setting of hepatocellular injury] may be different in patients with existing liver disease, and in patients on drugs that treat liver disease or inhibit bilirubin glucuronidation.”

  “patients are sometimes excluded from clinical trials because of baseline liver test abnormalities or a history of liver disease, but there is no well-established reason to do this, except perhaps to avoid confusion between the previous disease and the effect of the test drug. These patients generally should be included in at least the phase 3 trials because they are likely to be treated with the drug if it is marketed. Pre-existing liver disease is not known to make patients more susceptible to DILI (HJZ) but it may be that a diminished liver reserve or the ability to recover could make the consequences of injury worse, making it appear that such patients were more susceptible to severe DILI. .. It may be prudent to first determine if DILI occurs in people with previously normal livers before studying patients with well-characterized and stable chronic liver disease.”
DILI in CLD: Causality assessment
Questions that Need Answers

- Are flares in liver tests part of the expected course?
- Are there animal models of CLD for the drug under study?
- Should we use a modified RUCAM score or do we always need expert opinion in this setting?
- Hepatic Adjudication Committees – is there strength in numbers?
- Availability of published/unpublished clinical trial data?
- Do pharmacologic drug properties play a role (e.g. “Rule of 2” or others)?
Drug Properties for HCV DAA DILI: The Rule of 2

- Rule of 2 (dose >100mg/day and high lipophilicity logP>3) applied to 12 available HCV DAAs

<table>
<thead>
<tr>
<th>Class</th>
<th>Agent</th>
<th>daily dose (mg)</th>
<th>LogP</th>
<th>Model result</th>
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<tbody>
<tr>
<td>6 Ns3A/4A PIs :</td>
<td>Beceprevir</td>
<td>2400</td>
<td>1.93</td>
<td>negative</td>
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<tr>
<td></td>
<td>Telaprevir</td>
<td>2250</td>
<td>2.56</td>
<td>negative</td>
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<tr>
<td></td>
<td>Simeprevir</td>
<td>150</td>
<td>4.69</td>
<td>positive</td>
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<td></td>
<td>Paritaprevir</td>
<td>150</td>
<td>3.50</td>
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<tr>
<td></td>
<td>Asunaprevir</td>
<td>200</td>
<td>3.12</td>
<td>positive</td>
</tr>
<tr>
<td></td>
<td>Grazoprevir</td>
<td>100</td>
<td>2.94</td>
<td>negative</td>
</tr>
<tr>
<td>4 NS5A inhibitors:</td>
<td>Ledipasvir</td>
<td>90</td>
<td>5.57</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>Ombitasvir</td>
<td>25</td>
<td>5.60</td>
<td>negative</td>
</tr>
<tr>
<td></td>
<td>Daclatasvir</td>
<td>60</td>
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<tr>
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<td>Elbasvir</td>
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<tr>
<td>1 NS5B polymerase inhib- nuc:</td>
<td>Sofosbuvir</td>
<td>400</td>
<td>1.63</td>
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<tr>
<td>1 non-nuc NS5B polymerase inhib:</td>
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<td>CYP3A inhibitor:</td>
<td>ritonavir</td>
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<td>Nucleoside inhibitor:</td>
<td>ribavirin</td>
<td>1000/1200</td>
<td>-1.92</td>
<td>negative</td>
</tr>
</tbody>
</table>

*Mishra P, Chen M (FDA). Gastroenterology 2017;152:1270-4*
Is there Guidance relating to DILI from the literature?

Clinical trials can provide data on baseline values for liver tests in CLD

- PBC trials (e.g. obeticholic acid)
- Statin trials in patients with CLD
- NASH trials (FLINT etc)
- Diabetes (SGLT2 inhibitors etc)
- DILIN – 10% of cases were in CLD patients
“Normal Fluctuations“ of Liver Tests

Mean baseline ALT values of hepatocellular diseases in clinical trials

- CHBV* e Ag pos 140-150 IU (2-5X 60%; >5X 18-21%)
  e Ag neg 127-160 IU (2-5X 45%; >5X 15-26%)

- CHCV: non-cirrhotic ALT>AST
  cirrhotic AST>ALT

- NAFLD** ALT 64-83 IU, AST 45-61 IU

- autoimmune hepatitis***
  564 IU (220-1133) in pediatrics
  206 IU (25-1542) in adults

- alcoholic hepatitis: 2:1 ratio AST:ALT with AST <300 and ALT <100 IU

*Marcellin et al. NEJM 2008;359:2442
** Neuschwander-Tetri et al. Lancet 2015;385:956; Belfort et al NEJM 2006;355:2297
**Acute DILI vs Natural Progression of the Underlying Liver Disease**

<table>
<thead>
<tr>
<th>CLD</th>
<th>Favors DILI</th>
<th>Favors Nat’l Prog</th>
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</thead>
<tbody>
<tr>
<td>HBV</td>
<td>ALT rise w/ undetect DNA</td>
<td>ALT flare</td>
</tr>
<tr>
<td>HCV</td>
<td>ALT with undetectable HCV-RNA</td>
<td>mild fluctuations ALT with persistent viremia</td>
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<tr>
<td>NAFLD</td>
<td>acute ALT rise</td>
<td>mild fluctuations ALT</td>
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<tr>
<td>ETOH</td>
<td>ALT&gt;100 and &gt;AST</td>
<td>AST&lt;300 and ALT&lt;100</td>
</tr>
<tr>
<td>PBC</td>
<td>any acute rise in ALT/AST/AP</td>
<td>mild fluctuations in LTs</td>
</tr>
<tr>
<td>Cirrhosis</td>
<td>ALT&gt;AST</td>
<td>AST&gt;ALT</td>
</tr>
</tbody>
</table>

* Liver tests alone are not capable of making the determination – the clinical context, con meds, latency, etc must be factored in*
“Normal Fluctuations“ of Liver Tests in Cholestatic Liver Disease

- baseline liver test values in clinical trials for PBC:
  - AP expected to decline on therapy
  - Acute rise in AP, GGT, with or w/o ALT, bili might suggest DILI
  - Slowly progressive rise in AP, worsening of pruritus etc can be seen if the drug is not efficacious or patients are on placebo
AP in POISE Trial
Baseline and Subsequent Liver Tests in Hepatic Malignancy

- liver metastases in CRC: ALT/AST >ULN 9-12% [Hiwatshi et al J Cancer 2016;7:595]
- liver mets in breast Ca
- HCC
- pancreatic Ca (causing obstructive jaundice)
- Relatively few published data on liver tests (vs complete and partial tumor response, effects on survival, etc)
RUCAM in CLD?

- RUCAM is applicable only for acute liver injury, not for pre-existing chronic liver disease.
- RUCAM may require help from expert hepatologists when suspected DILI occurs on a complicated pre-existing liver disease.

Danan & Teschke. *Int J Mol Sci* 2016;17:14
Teschke et al. *Int J Mol Sci* 2017;18:803
RUCAM in a Clinical Trial Setting?

- Original RUCAM used to identify hepatotoxicity risk in ximelagatran trials
- 233 patients with elevated ALT (198 ximelagatran and 35 comparator anticoagulants)
- Possible or probable scores in 37% and 27% of the groups respectively
- Limitations: no rechallenges, unspecified use of alcohol, age >55, ambiguities in terms of the extent of the workup for other causes
- **RUCAM should be modified for drugs under development in clinical trials**

RUCAM elements used to diagnose acute DILI in CLD

- Latency
- Dechallenge response
- Exclusion of alternative causes
- Exclusion of hepatotoxic concomitant meds
- Rechallenge response (if done)

“You better cut the pizza in four pieces, because I’m not hungry enough to eat six”
- Yogi Berra
How Best to Utilize Expert opinion to distinguish Acute DILI from Underlying CLD Progression?

- Is there a clear deviation in the “normal” fluctuation of baseline liver tests?
- Is there an acute rise in viremia?
- Is the injury pattern (R value) similar or different from the underlying CLD?
- Is there any sign of hypersensitivity/immunoallergy?
- Are any co-morbidities a likely cause (e.g. right-heart failure, hypoxic hepatitis, gallbladder disease, etc)?
How Best to Utilize Expert opinion to distinguish Acute DILI from Underlying CLD Progression?

Additional Tricks of the Trade:

- Latency (time to onset): acute DILI rare after just a single dose or >12 months
- ALT:AST ratios (alcohol, muscle injury and cirrhosis have AST>ALT)
- Time course of improvement (or not) off the study drug (Dechallenge)
- Time course and clinical features of intentional or inadvertent Rechallenge
- Is the workup to exclude other causes adequate based on the height and pattern of the liver tests?
Where Expert Interpretation is also Needed

- Attributing drug tolerance/adaptation
- Interpreting ultra-short or long latency periods
- Diagnosing DILI after a drug has been discontinued
- Interpreting histological changes
- Evaluating the published literature
- Evaluating concomitant meds
- Taking the absolute height/fold increase into consideration
- Taking the AST:ALT ratio into account

Lewis JH. AASLD Clinical Liver Disease 2014;4(1):4-8
Challenges in Diagnosing DILI in CLD

- Does latency change for drugs causing acute DILI in CLD? How short or long is too short or long for acute DILI?
- Does alcohol or fatty liver increase the risk of DILI?
- How to factor in other hepatobiliary complications of the underlying CLD? (e.g. gallstone disease, HCC or CCA developing in diabetics)
- For cirrhotics, is an acute increase in MELD score a useful marker? (vs effects of sepsis, SBP, disease progression, PVT, HCC, etc on liver tests?)
Is it DILI in a Clinical Trial of CLD?

<table>
<thead>
<tr>
<th>Screen</th>
<th>day 1</th>
<th>wk 2</th>
<th>wk 4</th>
<th>wk 5*</th>
<th>wk 6</th>
<th>wk 7</th>
<th>wk 8</th>
<th>wk 9</th>
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<tr>
<td>ALT</td>
<td>71</td>
<td>69</td>
<td>60</td>
<td>156</td>
<td>576</td>
<td>463</td>
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<td>AST</td>
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<td>0.6</td>
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<td>67</td>
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<td>63</td>
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<tr>
<td>Eos%</td>
<td>1.1</td>
<td>0.7</td>
<td>1.3</td>
<td>5.3</td>
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<td>9.4</td>
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<td>HAV IgM/HEV IgM</td>
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<tr>
<td>HBsAg/HB core IgM</td>
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<td>antiHCV/HCV-RNA</td>
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<td>ANA,SMA,LKM-1</td>
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<td>CMV IgM</td>
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<tr>
<td>Acetaminophen/U tox</td>
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</table>

*study drug held

HAV IgM / HEV IgM: neg/neg
HBsAg/HB core IgM: neg/neg
antiHCV/HCV-RNA: neg/neg
ANA, SMA, LKM-1: neg/neg/neg
EBV VCA IgM: neg
CMV IgM: + 3.6
Acetaminophen/U tox: neg/neg

*study drug held
Another case: What’s to Blame?

- 64 WF with stage 2 PBC enrolled in a clinical trial
- Baseline AP 345 IU, AST 45, ALT 47, TB 0.7
- Has been on ursodiol 14mg/kg since the diagnosis 4 years ago along with vit D and calcium
- Week 60 of the trial develops acute epigastric and RUQ abdominal pain with nausea and vomiting – diagnosed with biliary colic with gallstones seen on ultrasound, with mild dilation of the CBD for which ERCP is performed and a biliary stent placed despite the absence of choledocholithiasis.
- Augmentin is given for 5 days. Study drug is continued
- On admission to the hospital: AP 268, AST 387, ALT 190, TB 1.9 mg%
- 6 wks later: AP 277, AST 45, ALT 60, TB 1.3 mg%, no further episodes of pain or nausea
Stopping Rules for Suspected DILI in CLD: Do we throw the baby out with the bathwater?

- Is a multiple of fold elevations the “new normal” for patients with elevated baseline liver tests?
- What threshold elevation should permitted? (e.g. doubling of BL, 5X BL, ??)
- Does Hy’s Law still apply?
- Do we use total or direct bilirubin?
- Should we be looking at other liver “function” tests (e.g. INR, albumin) for signs of impairment?
Patients allowed to enroll with elevated ALT Baseline values up to 5X ULN

Doubling of ALT During Pravastatin Treatment for Hypercholesterolemic pts with CLD (n=320)

Primary Safety: ALT Elevations

P = not significant at all weeks (wk 12 p=0.61; wk 24 p=0.095; wk32 p=0.076)

Non-DILI Causes of Jaundice and other acute hepatic events in clinical trials and post-marketing may be more common than we think

- Acute viral hepatitis
- Reactivation of chronic hepatitis B
- Cholecystitis, choledocholithiasis
- Malignant CBD obstruction (pancreatic Ca, CholangioCa)
- Hypoxic hepatitis (shock liver)
- Right heart failure
- Sepsis
- Multisystem organ failure
Concomitant medications in cirrhosis causing DILI

- Herbals and dietary/weight loss supplements used by 20-40% of patients with CLD
- HDS responsible for 20% of acute DILI in the US DILIN
- Antibiotics (azithromycin)
- APAP?
- HAART or antiTB drugs in pts with HBV, HCV, AIDS
How do we know that hepatico-pancreatic-biliary malignancy is not drug-related? Another role for HACs?

- Increased risk of HCC, pancreatic Ca, cholangioCa in diabetics
- Increased risk of HCC in HBV, HCV, PBC
- In short-term trials (<6 mo) the study drug is almost always excluded
- In medium length trials (6-12 mo) the S.D is considered unlikely
- In long-term trials (12 <24 mo) the S.D. is usually considered unlikely
- In extended long-term trials (>24 mo) is it the drug or the disease?

* Any signal of malignancy in animal studies?
The Ultimate Means to Diagnose DILI in CLD? The Quest for a Validated Biomarker Goes On!

"It ain't over 'til it's over"
— Yogi Berra