Detection and management of DILI in NASH/NAFLD subjects in drug development

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Why is this significant?

- Background prevalence of NAFLD is quite high (~ 20-35% of adult population)
- >150 clinical trials for NAFLD are registered at clinicaltrials.gov
- Elevated baseline aminotransferases and fluctuations are common.

Aminotransferases and NAFLD

- Two thirds of adults with NAFLD by MRI will have normal ALT and AST levels
- AST and ALT levels fluctuate, but typically stay under 200 U/L range
- Autoantibodies (e.g., ANA and ASMA) are common and are largely an epiphenomenon

NAFLD and risk for DILI

- No data to suggest that obesity or NAFLD are risk factors for all-cause DILI. May increase risk for liver damage from alcohol, methotrexate, or tamoxifen, but not well studied.
- DILI in patients with underlying liver disease may have worse outcomes

DILI in pre-existing liver disease

- In the DILIN prospective study, 10% had pre-existing liver disease
- Higher frequency of azithromycin DILI (5.6% vs.1.5%, p=0.02)

	Known pre-existing liver disease (n=89)	**No pre-existing liver disease (n=810)**	**P-value**
6 month Outcomes (%)			
- All-cause mortality	16	5.2	<0.001
- Liver-related mortality	9.1	2.4	0.04
- Transplant	3.4	4.1	1.0

Chalasani N, et al for the US DILIN. Gastroenterology 2015

Effect of NAFLD on Hepatic CYP3A activity

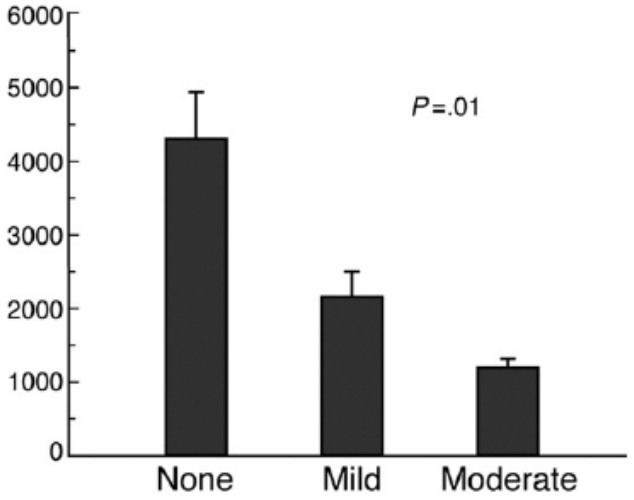


Figure 2. Relationship between hepatic CYP3A activity and severity of steatosis. Steatosis was categorized into none (n = 25), mild (≥5%–33% steatosis) (n = 20) or moderate steatosis (>33%) (n = 4). Data are shown as mean ± standard error.

Selected Characteristics of Normal Liver and Fatty Liver Groups

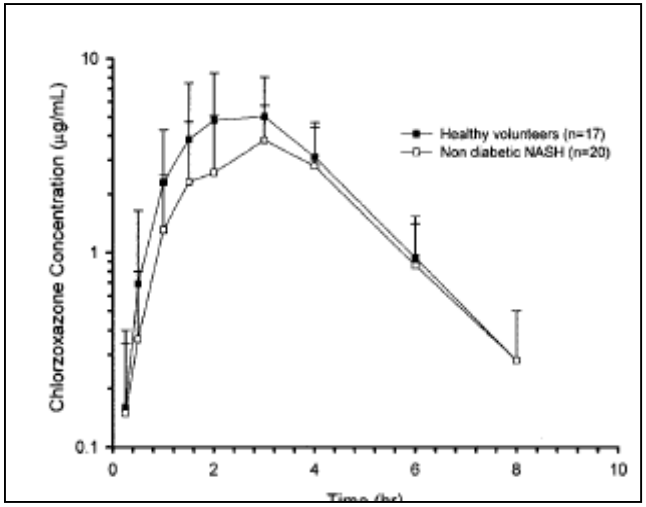
	Normal group (n = 25)	Fatty liver group (n = 24)
Age (*y*)	43 ± 20 (18–69)	47 ± 11 (14–69)
Male/female (%)	15/10	16/8
Race	11 white/3 black/1 Asian	18 white/1 Hispanic/1 Asian
% Receiving medications with potential for interaction with CYP3A	28	29
CYP3A4 mRNA[a]	5063 ± 1565 (23–24,162)	3071 ± 803 (9–12,886)
CYP3A5 wt mRNA[a]	390 ± 134 (2–2515)	171 ± 66 (9–1467)
CYP3A5 SV1 mRNA[a]	45 ± 7.5 (7–113)	49.5 ± 15 (2–319)
PXR mRNA[a]	5.5 ± 1.6 (0.3–37)	5.3 ± 2.9 (0.2–66)
CYP3A4 protein content (*pmol/mg* protein)	8.5 ± 2.2 (0.2–33.9)	6 ± 1.3 (0.5–25.7)
CYP3A activity ($pmol \cdot min^{-1} \cdot mg^{-1}$ of protein)	4287 ± 659 (1337–14,397)	1978 ± 299 (278–6676)[b]

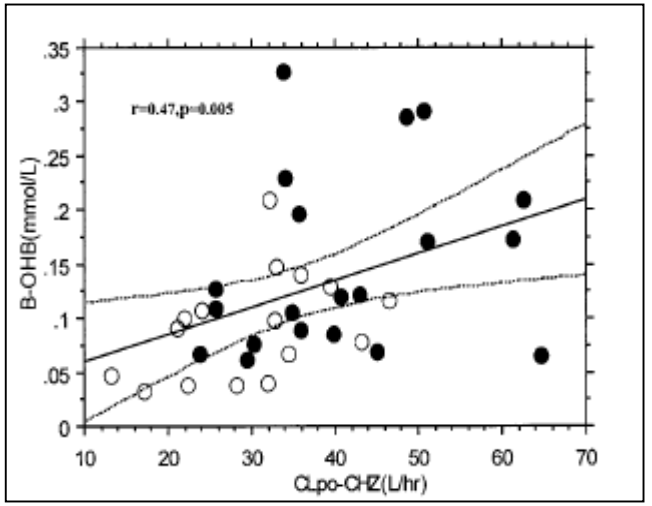
NOTE. Data are represented as mean ± standard error with ranges in parentheses unless indicated otherwise.
[a]mRNA values are in attograms/attograms after normalization to 18S RNA as a housekeeping gene.
[b]$P = .003$.

Vuppalanchi R, et al. Clin Gastro Hepatol 2007; 5: 388-393

Hepatic CYP2E1 activity in patients with NASH

- Hepatic CYP2E1 activity, as assessed by oral clearance of chlorzoxazone, was significantly higher in patients with NASH, compared to obese controls (41±12 vs. 33±16 L/h, p=0.03)
- Are patients with NAFLD more sensitive to acetaminophen?





Chalasani N, et al. Hepatology 2003; 37:544-550

Baseline ALT

- Since patients with NAFLD/NASH may have normal or elevated ALT, strategies to detect and manage DILI in NASH clinical trials should consider both patient's baseline (in case of elevated ALT) or ULN (in case of normal ALT)
- May need more than one ALT reading during the screening phase to establish a baseline for DILI monitoring

Drug-Induced Liver Injury in Patients With Preexisting Chronic Liver Disease in Drug Development: How to Identify and Manage?

Despite extensive research and considerable progress in recent decades, drug-induced liver injury (DILI) remains a major concern for patients, health care providers, and drug makers. Early prediction, diagnosis, and assessment of DILI during drug development continue to present major challenges to the drug industry, and hepatic safety concerns remain a leading cause for aborted development of new drugs. Presently, most drug makers rely during drug development

populations participating in late stage trials should generally mirror the real-world target population that will eventually be treated, which often include patients with CLD.[3] In addition there are a large number of clinical trials assessing drugs for CLD such as hepatitis B and C, NASH, PBC, and alcoholic liver disease.

It remains a matter of debate whether patients with CLD are more susceptible to DILI compared with patients with healthy livers. Despite some conflicting evidence in the published literature,[7–9] there is still a general belief that patients with CLD are not systematically prone to develop DILI.[9–11] However, it is also generally believed that patients with preexisting CLD are at higher risk for complicated course and adverse outcome from DILI.[3,9–11] A recent paper from the US Drug Induced Liver Injury Network showed that DILI in patients with preexisting liver disease was associated with significantly higher frequency of adverse outcomes,

has been suggested to use multiples of baseline of ALT rather than multiples of ULN as a threshold for suspecting DILI. The Food and Drug Administration (FDA) has recommended using ALT threshold values of >2× baseline in patients with elevated liver enzymes at enrolment[1]; however, others have suggested an increase of >3× baseline and >5× baseline as more appropriate for a hepatic safety signal.[4,14] In the absence of large prospective comparative data, there is little evidence to support one suggested threshold over the other and a combination of these approaches may be the most appropriate (Table 1).

How to determine the baseline ALT is also a matter of some debate. Because ALT levels can fluctuate even over a short period of time, especially in patients with CLD, a single measurement on a given day may not represent a true baseline. Therefore, it may be prudent to take at least 2 ALT measurements (and perhaps also 2

Chalasani N & Regev A. Gastroenterology 2016;151: 1046-1051

Suggested algorithm for monitoring and management of DILI in Phase 2-3 NASH studies in patients with normal or elevated baseline ALT

Treatment emergent ALT	Treatment emergent Total Bilirubin	Liver symptoms	Action
Normal baseline: **ALT>5x ULN** **Elevated baseline:** **ALT> 3 x baseline or >300 U/L (whichever occurs first)**	Normal Patients with Gilbert's syndrome: No change in baseline TBL	None	Repeat ALT, AST, ALP, TBL, in 2-5 days Follow-up for symptoms.
Normal baseline: **ALT>8x ULN** **Elevated baseline:** **ALT> 8x baseline or >500 U/L (whichever occurs first)**	Normal Patients with Gilbert's syndrome: No change in baseline TBL	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.

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Suggested algorithm for monitoring and management of DILI in Phase 2-3 NASH studies in patients with normal or elevated baseline ALT

Treatment emergent ALT	Treatment emergent Total Bilirubin	Liver symptoms	Action
Normal baseline: **ALT >5 ULN** **Elevated baseline:** **ALT> 5x baseline or >300 U/L (whichever occurs first)**	TBL>2x ULN Patients with Gilbert's syndrome: Doubling of direct bilirubin	None	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.
Normal baseline: **ALT >5 ULN** **Elevated baseline:** **ALT> 5x baseline or >300 U/L (whichever occurs first)**	Normal or elevated	Severe fatigue, nausea, vomiting, right upper quadrant pain	Interrupt study drug. Initiate close monitoring and workup for competing etiologies. Study drug can be restarted only if another etiology is identified and liver enzymes return to baseline.

Monitoring and Assessment of DILI in Patients with Advanced Liver Disease and Decompensated Cirrhosis

- Very close monitoring may be needed in early stage development
- Discontinuation criteria may have to be established for each clinical trial individually
- Unblinding of cases suspected to have DILI may be necessary in selected instances
- Concomitant administration of medications with high hepatotoxic potential may need to be avoided

Grading hepatotoxicity potential

- Category A ≥ 50 published reports (n=48)
- Category B 12-49 published reports (n=76)
- Category C 4-11 published reports (n=96)
- Category D 1-3 published reports (n=126)
- Category E None
- Category T Direct hepatotoxic (n=7, aspirin and salicylate, acetaminophen, niacin, vitamin A, intravenous methylprednisone, tetracycline, or buprenorphine)

Björnsson E & Hoofnagle J. Hepatology 2016; 63:590-603

Final thought: Should we mandate that certain medications be avoided in patients with CLD participating in clinical trials?

Top 10 therapeutic classes and individual agents to cause DILI in the USA

	Therapeutic Class	n		Individual agent	n
1	Antimicrobials	408	1	Amox-Clavulanate	91
2	Herbal and dietary	145	2	INH	48
3	CVS agent	88	3	Nitrofurantoin	42
4	CNS agents	82	4	TMP/SMX (Bactrim)	31
5	Anti-neoplastics	49	5	Minocycline	28
6	Analgesics	33	6	Cefazolin	20
7	Immunomodulatory	27	7	Azithromycin	18
8	Endocrine	20	8	Ciprofloxacin	16
9	Rheumatologic	13	9	Levofloxacin	13
10	Gastrointestinal	12	10	Diclofenac	12

Chalasani N, et al for the US DILIN. Gastroenterology June 2015