Berkeley Public Health

THE FORUM For Collaborative Research℠

Histology Series Session 5

Causality Assessment and the Role of Liver Biopsy in the Evaluation of Suspected DILI in NASH Clinical Trials

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Agenda

- Setting the stage
- IQ DILI Survey
- Case Examples of DILI Superimposed on NASH
- Panel Q and A

Setting the Stage

Challenges of DILI Assessment

- Causality assessment for suspected DILI is a major challenge during drug development, especially in NASH clinical trials where patients have baseline liver blood test elevations
- DILI has a varying clinical presentation that can mimic all known forms of acute and chronic liver disease
- No single test or biochemical signal exists to establish a definitive diagnosis. No gold standard for verification. The diagnosis is heavily dependent on exclusion of other causes of liver injury; and depends largely on clinical acumen
- Signs and symptoms of DILI vary with the pattern and severity of injury, which vary with the MOA of the suspect drug and the individual patient.
- Polypharmacy and the presence of comorbidities or intercurrent disease impede or complicate the diagnosis of DILI;
- Drug rechallenge often can provide definitive answers however, concerns associated with the risk of recurrence of severe DILI that may result in death or require liver transplantation prevents investigators from considering a rechallenge
- DILI is rare, which limits systematic clinical experience
- Finding DILI during drug development for NASH can contribute to the attrition of drugs advancing into later stage development

IQ DILI Survey [1]

- 13/14 companies responded to a blinded survey
- The importance of obtaining histology in the evaluation of a suspected DILI was ranked 6.4 on a scale of 1–10 (10 being most important).
  - Responses varied from as low as 2 to as high as 8
- 46.2% (6) of companies may utilize a liver biopsy for evaluation suspected DILI, with the caveat that it is dependent upon the protocol.
- 92.3% (12) of companies stated that liver biopsy/histology data was typically missing for DILI assessment
- 36.4% (4) of companies stated that they utilize histology results as part of their rechallenge decision-making process.

1. Hey-Hadavi, J, Seekins D, Palmer,M et al Overview of Causality Assessment for DILI in Clinical Trials: Drug Safety 1 February 2021

To Biopsy or not to Biopsy That is the Question

Benefits > risks of obtaining a liver biopsy

- the need to characterize injury patterns from a new drug or a new class of drugs not previously associated with DILI
- Instances in which worsening of liver blood tests occur during a clinical trial in a subject who had abnormal baseline liver blood tests
- to assist in differentiating disease progression from suspected DILI;
- The need to identify lesions that could have prognostic significance
- The onset of clinically important liver events, even in the background of normal ATs and TBIL
- the need to define the etiology of prolonged elevations in liver tests

DILIN study

- DILIN study n=249 suspected DILI cases
- Five most common histologic patterns of injury - acute and chronic hepatitis, acute and chronic cholestasis, and cholestatic hepatitis, observed on histology obtained from cases subsequently confirmed to have DILI, did not have any distinguishing characteristics from cases in which non-DILI diagnoses were felt to be more likely

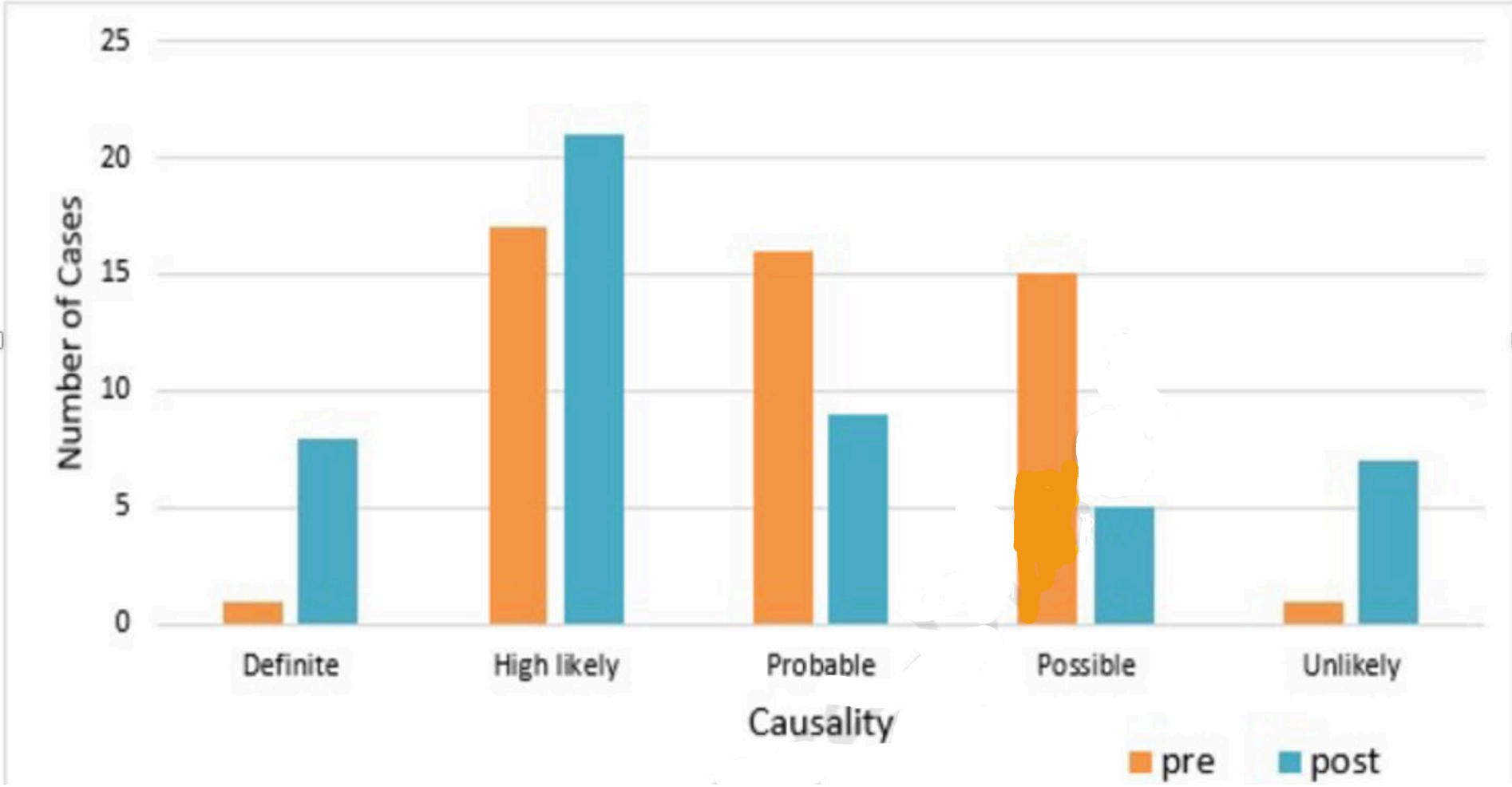
Kleiner DE, et al. Hepatic histological findings in DILI : systematic evaluation and clinical associations. Hepatology. 2014;59:661–70.

J Hepatol. 2022 Jan 21;S0168-8278(22)00014-9. doi: 10.1016/j.jhep.2021.12.043.
Online ahead of print.

Value of liver biopsy in the diagnosis of drug-induced liver injury

Jawad Ahmad [1], Huiman X Barnhart [2], Maurizio Bonacini [3], Marwan Ghabril [4], Paul H Hayashi [5], Joseph A Odin [6], Don C Rockey [7], Simona Rossi [8], Jose Serrano [9], Hans L Tillmann [10], David E Kleiner [11], Drug-Induced Liver Injury Network

Distribution of 50 simulated causality scores pre- and post-liver biopsy review



Results N=50

N= 42 High causality DILI Cases (1,2 or 3)

N=8 low causality cases (4,5)

After histology review

- biopsy was judged to have been helpful in 70%
- Causality score was changed in 68%
- Increase in DILI likelihood in 48%
- Decrease in 20%
- Changed diagnostic certainty from less certain(3 or 4) to highly certain (1,2 or 5) in 38% of patients

Conclusions

- Histology may help clarify the diagnosis of DILI
- Histology is particularly helpful in cholestatic or equivocal cases (possible or probable)

Are there histologic features that are diagnostic of DILI?

- Microvesicular steatosis
- demarcated perivenular necrosis
- minimal hepatitis with canalicular cholestasis
- poorly developed portal inflammatory reaction
- eosinophil infiltration
- epithelioid-cell granuloma

Are there histologic features that are prognostic?

- Only way to characterize the pattern, severity and distribution of hepatic injury
- Histologic findings may also predict outcome

- Meta-analysis of 570 case reports of DILI - Patients who had histologic eosinophilic infiltrates were statistically less likely to have a fatal outcome compared with patients without [1].
- An analysis of 461 liver biopsy samples from the Spanish DILI database
  - hepatocellular necrosis had a higher incidence of death than those with cholestatic or mixed cholestatic/hepatocellular damage on biopsy [2].
- DILIN experience 2014:
  - good outcome :granulomas and eosinophils
  - poor outcome: multiacinar or bridging necrosis and ductular reaction [3]

1. Bjornsson E, Aliment Pharmacol Ther. 2007;15(25):1411–21.
2. Andrade et al. Gastroenterology. 2005;129:512–21.
3. Kleiner DE, Hepatology. 2014;59:661–70.

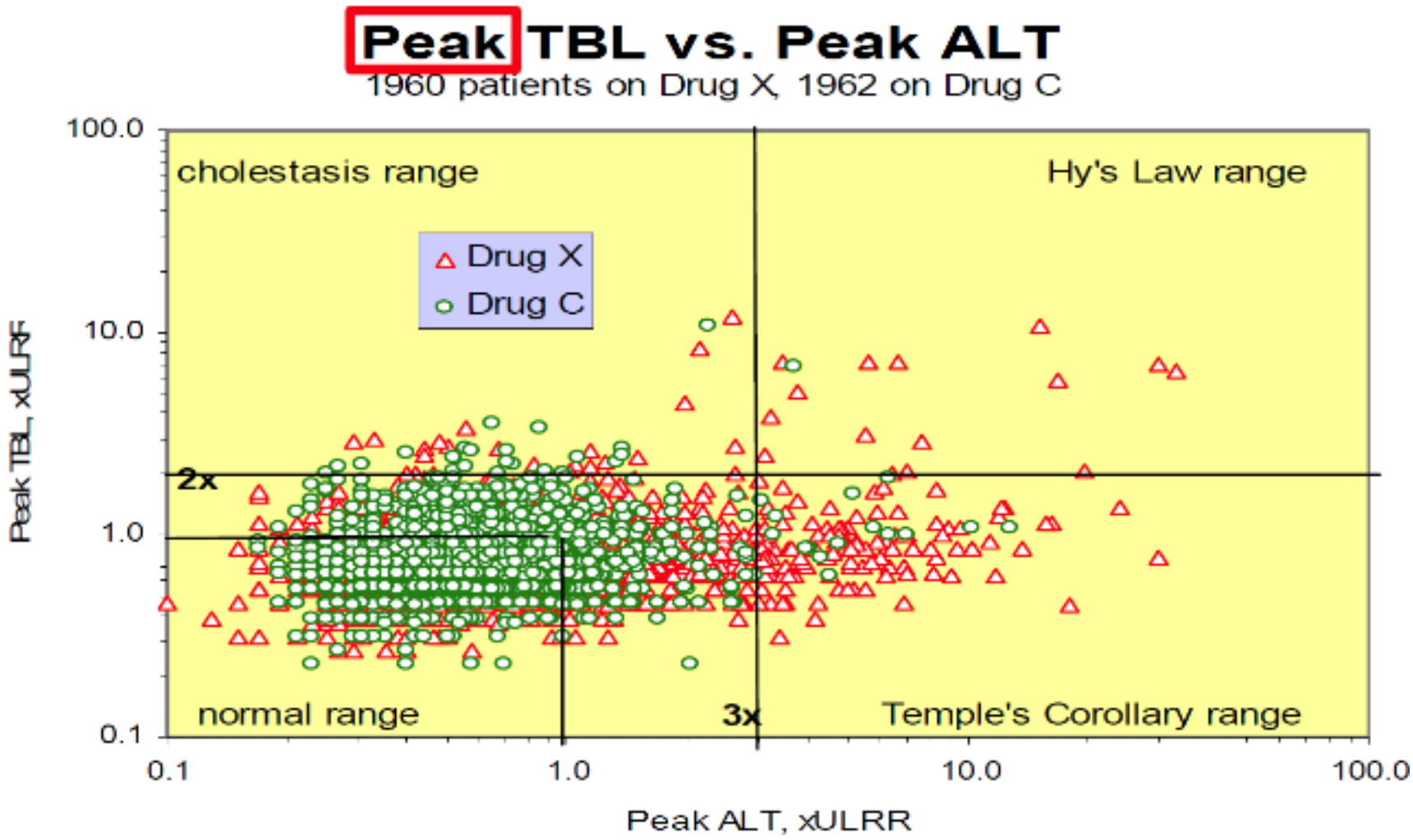
Autoimmune Findings

- **NAFLD/NASH**
  - Up to 30% of patients with may have low titers (<1:320) of ANA
  - NASH CRN elevated ANA ≥1:160 or ASMA ≥1:40 or both were present in 21% of 864 patients with biopsy-proven NAFLD, in the absence of AIH
  - epiphenomenon and does not correlate with grade or stage and no impact on long-term outcome

- **Idiopathic autoimmune hepatitis (iAIH)-** DILI can also be associated with high ANA, ASMA titers, and IgG levels, as drugs are known potential triggers

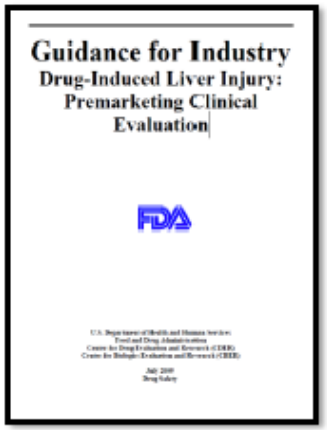
- **DI-AIH** - patients had pre-existing undiagnosed low-grade disease and/or a genetic predisposition to AIH that becomes overt after being triggered by a drug

Vuppalanchi R, et al. Clinical significance ofserum autoantibodies in patients with NAFLD: results from the NASH CRN. Hepatol Int. 2012;6:379-385.


Peak TBL vs. Peak ALT
1960 patients on Drug X, 1962 on Drug C
cholestasis range
Hy's Law range
Drug X
Drug C
2x
3x
normal range
Temple's Corollary range
100.0
10.0
1.0
0.1
0.1
1.0
10.0
100.0
Peak TBL, xULRR
Peak ALT, xULRR

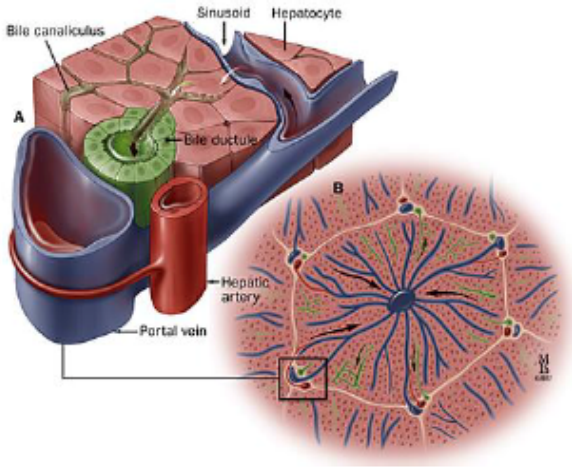
Hy's Law

1. The drug causes hepatocellular injury, generally shown by a higher incidence of 3-fold or greater elevations above the ULN of ALT or AST than the (nonhepatotoxic) control drug or placebo
2. Among trial subjects showing such AT elevations, often with ATs much greater than 3xULN, one or more also show elevation of serum TBL to >2xULN, without initial findings of cholestasis (elevated serum ALP)
3. No other reason can be found to explain the combination of increased AT and TBL, such as viral hepatitis A, B, or C; preexisting or acute liver disease; or another drug capable of causing the observed injury


Guidance for Industry
Drug-Induced Liver Injury: Premarketing Clinical Evaluation

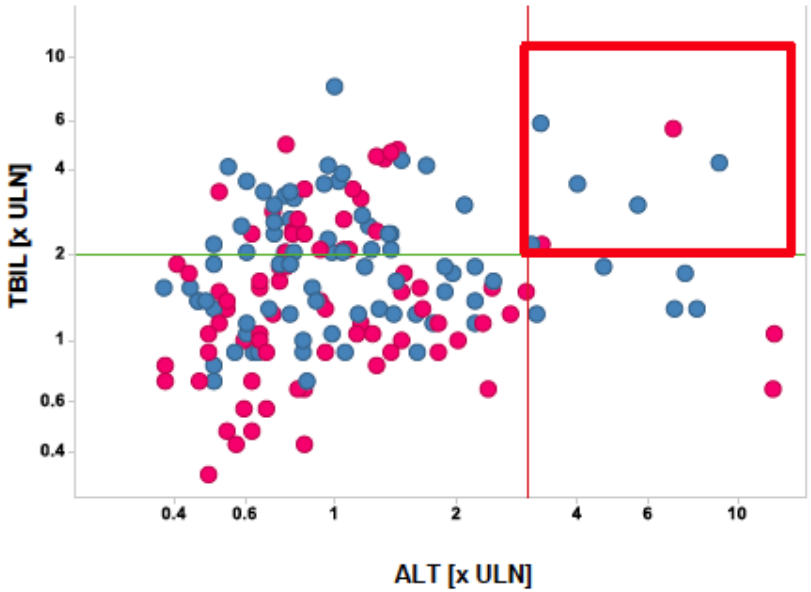
FDA

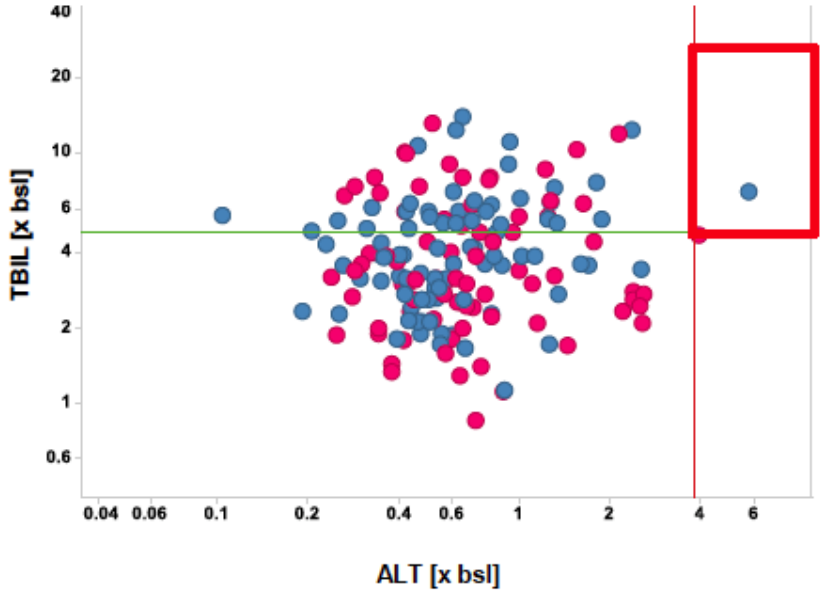
"Finding one Hy's Law case in the clinical trial database is worrisome; finding two is considered highly predictive that the drug has the potential to cause severe DILI when given to a larger population."



eDISH vs mDISH in practice

Color coding by gender





- Using multiples of baseline reduces false positives
- mDISH accounts for different baselines across different patient populations

6. Evaluating Data for Alternative Causes

An important purpose of close observation is to gather additional clinical information to seek other possible causes of the observed liver test abnormalities, such as one of the following common causes:

- **Acute viral hepatitis.** The usual onset of hepatocellular DILI is indistinguishable from acute viral hepatitis A or B. Hepatitis C is much less often acute in its onset and tends to be insidious, but it sometimes can resemble acute DILI. The presence of acute viral hepatitis A, B, and C should be evaluated by serological markers. Viral hepatitis D (requires concomitant hepatitis B infection) and E are relatively rare in the United States. Hepatitis E is more common in developing countries, including Southeast Asia, and should be considered in recent travelers to those countries and in patients in trials conducted in those countries. Also rare are hepatocellular liver injuries caused by Epstein-Barr virus, cytomegalovirus, herpes simplex virus, toxoplasmosis, varicella, and parvovirus, although these infections are seen more typically in immuno-suppressed individuals. Adolescent and young adult patients with possible DILI should be tested for Epstein-Barr virus. Hepatitis is common among transplant patients with cytomegalovirus disease.
- **Alcoholic and autoimmune hepatitis.** Acute alcoholic hepatitis usually is recurrent, with a history of binging exposure to alcohol preceding episodes, and it has some characteristic features, such as associated fever, leukocytosis, right upper quadrant pain and tenderness, hepatomegaly, and AST >ALT, that may help distinguish it from other causes of liver injury. Other features of the physical examination may include the presence of stigmata of cirrhosis, such as spider nevi, palmar erythema, estrogenic changes in males, and Dupuytren's contractures. Alcoholic and autoimmune hepatitis should be assessed by history, physical examination, and laboratory testing, including serologic testing (e.g., antinuclear or other antibodies).
- **Hepatobiliary disorders.** Biliary tract disease, such as migration of gallstones or intrahepatic lesions, more often causes cholestatic injury initially and should be investigated with gall bladder and ductal imaging studies, especially if ALP is increased. Malignant interruption of the biliary tract also should be considered.
- **NASH.** NASH may be seen in obese, hyperlipoproteinemic, and/or diabetic patients and may be associated with fluctuating aminotransferase levels, and hepatic and sometimes splenic enlargement. It is sometimes associated with cirrhosis and portal hypertension.
- **Cardiovascular causes.** Cardiovascular disease, especially right heart failure and hypotension or any cause of impaired oxygenation of the liver, may cause acute centrilobular hypoxic cell necrosis (*ischemic hepatitis*) with rapid and sometimes spectacular increases of serum AT (e.g., AT >10,000 U/L). Cardiovascular dysfunction or impaired liver oxygenation, including hypotension or right heart failure, should be assessed by physical examination and history.
- **Concomitant treatments.** It is critical to discover concomitant treatments, including exposure to nonprescription and dietary supplement products that might be responsible for injury. Many people take multiple drugs, perhaps less often in controlled clinical trials because of exclusion criteria, but subjects may not report taking disallowed drugs or other agents. The possible exposure to potentially toxic herbal or dietary supplement mixtures (sometimes of unknown composition), nonprescription medications such as acetaminophen, or to occupational chemical agents may not be volunteered unless subjects are specifically questioned.

Recommendations

1. Liver biopsy should be considered when the patient's benefit for continued treatment with the suspect drug exceeds risk.

2. Biopsy histology results must be used in combination with all other factors to assess causality.

3. Liver biopsy and histological assessment should be considered when it is important to distinguish AIH from DILI.

4. Histologic assessment should be performed by an expert hepatopathologist.

5. Evaluation of liver biopsy histology should occur at the time of or within a few days of the procedure. If unusual or unanticipated findings occur, an external blinded safety group should evaluate the findings and data should be unblinded if determined necessary. In this manner unexpected or unusual histologic findings can be evaluated promptly as part of safety monitoring.