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Abstract I-6_2017: Detection and Evaluation of DILI in Patients with Chronic Liver Disease.

The specific issue of detecting acute liver injury in patients with underlying chronic liver disease (CLD) and assigning causality to diagnose DILI remains challenging. The 2009 FDA Guidance FDA detecting and managing hepatotoxicity in patients in clinical trials did not provide any specifics in terms of dealing with patients with CLD. Recent clinical trials evaluating various therapies in patients with chronic hepatitis B, hepatitis C, NAFLD, PBC, malignancy (with hepatic metastases), among other disorders face the very real issue of assessing hepatic events in the setting of underlying liver disease, which brings with it a potentially different set of rules. As a result, clinicians and drug manufacturers have had to utilize what Dr Senior refers to as “medical reasoning” in order to determine if DILI has occurred, and how usual stopping rules should be modified using the currently available causality assessment methods.

The topic at hand can be divided into the historical past, the present and the future.

The Past:
Hy Zimmerman was confident in his clinical observation that most drugs could be used safely in patients with CLD; the only exceptions being the anti-TB drugs and HAART agents in patients with chronic hepatitis B or C; methimazole in hepatitis B, nefazadone, propoxyphene, valproate and vitamin A. However, he was also prescient in his caveat that should acute DILI occur in the setting of CLD, the consequences could be dire. Indeed, proof of his predictions was found in the US DILI Network registry where no significant differences appeared to exist between patients with and without CLD, with the exception of azithromycin. That particular drug was uniquely associated with both a higher risk of DILI in CLD (6.7% vs 1.5% in non-CLD patients); and was also the only agent to have a higher mortality associated with DILI (16% vs 5.2% in non-CLD patients). While relatively few drugs have been formally evaluated for their DILI potential in CLD, perhaps the best studied drug class in this setting can be found in the literature dealing with the statins. A number of retrospective reviews demonstrated their safety in CLD patients as did at least two randomized, prospective, controlled trials. High-dose pravastatin was evaluated for the possibility it could go OTC by studying asymptomatic hypercholesterolemic patients with underlying NAFLD, viral hepatitis or other CLD of which the patients themselves might be unaware. A safety endpoint was set as a doubling of their baseline ALT levels, with ALT levels up to 5X ULN permitted to be enrolled. To my knowledge, this was the first clinical trial to set stopping rules as a doubling of the patient’s baseline to this threshold. The results clearly demonstrated that patients on placebo had a higher risk of doubling their ALT baseline at all time points through the 36 week trial compared to subjects taking pravastatin. No serious hepatic AEs were reported and no Hy’s Law cases appeared. It was presumed that the statin, which had a significant salutatory effect on lipid parameters, also had a beneficial effect on hepatic inflammation from a possible reduction in fatty infiltration etc. RUCAM was not specifically designed to assess causality in patients with underlying liver disease, but is potentially useful if the hepatic event follows the same rules seen with DILI in patients without CLD. A positive dechallenge or rechallenge with elimination of other causes should be applicable, even when baseline liver tests are elevated.

The Present:
In the past, most clinical trials excluded patients with significant CLD from being enrolled. However, current clinical trials are in the process of comparing new therapies for NAFLD, PBC, and diabetes (with many subjects having underlying fatty liver and mildly elevated ALT permitted at baseline); most of whom have abnormal baseline liver chemistries. In such cases, sponsors are increasingly utilizing the expertise of clinicians skilled in the art of DILI adjudication to assess hepatic events in these settings. Being able to discern the natural fluctuations of liver chemistries and normal disease progression from acute drug injury can be especially challenging. Indeed, such patients have several potential confounders that can make DILI assessment more difficult, including the known increased risk of developing hepatobiliary malignancy (HCC, cholangiocarcinoma), especially among diabetics (8) and the development of acute or chronic cholecystitis and choledocholithiasis (with passage of gallstones in some cases) in long-term treatment studies. In diabetic outcome trials, the longer a patient remains in a clinical study, the more likely that an adverse cardiovascular or other event may occur—gallbladder disease, acute myocardial infarctions, strokes or other serious outcomes potentially cause hepatic events as well (e.g. shock liver, sepsis with multi-organ failure, passage of a gallstone, etc) that can confound the clinical assessment for possible DILI.

HAC Charters:
In the absence of a truly diagnostic DILI biomarker, hepatic adjudication committee charters (HAC) that are currently in use to assess possible DILI typically ask the following questions of the adjudicators:

1. is the injury pattern typical or atypical of the patient’s underlying liver disease?
2. is the injury pattern hepatocellular, cholestatic or mixed?
3. is the event representative of DILI?
4. what is the severity of the event?
5. is the possible DILI event due to the study drug alone; another concomitant medication alone; multiple drugs; or is it not possible to tell?
6. is the study medication causal for DILI?
7. if the answer is yes, what degree of medical certainty is present (e.g. highly likely, probable, possible)?
8. if the answer is no (unlikely), is there evidence to exclude the study drug?

DILI adjudicators should be knowledgeable and experienced with the CLD being treated so as to provide the best chance of assessing a wide variety of hepatic events in order to exclude acute DILI. For example, an acute hepatocellular injury pattern occurring in a PBC trial would be atypical of the underlying disease, as would acute cholestasis in a NAFLD trial, and DILI in those instances might be likely. However, several areas of potential difficulty remain, as listed below:

1. What if acute DILI mimics the natural disease progression of the CLD under study?
2. Do we have established longitudinal data on ALT values that permit a clear distinction between normal fluctuations, disease progression (on placebo?) and drug tolerance vs. acute DILI?
3. Passage of a gallstone is generally accompanied by acute abdominal pain, and occasional fever, leukocytosis, and the present of gallstones or CBD stones or ductal dilatation on imaging. ALT and AST can be significantly elevated, even in the absence of a significant rise in alkaline phosphatase. Once passed spontaneously, however, the event generally resolves quickly. In the absence of confirmatory imaging, or with no description of treatment with ERCP and stone extraction, etc to confirm the diagnosis, DILI cannot be excluded, although the clinical scenario, the latency and other factors may permit such circumstantial evidence to suggest DILI is unlikely.
4. The development of hepatobiliary malignancy in long-term treatment trials raises additional concerns – how can we be certain that the study drug is not in any way responsible? In most cases, if the malignancy develops within a relatively short timeframe (e.g. <6-12 months), it is usually considered unrelated. Although the increased risk of HCC in chronic viral hepatitis B, C, PBC, and NASH cirrhosis, etc is well-known, can we confidently exclude any contributory role of the study medication, especially in long-term trials?
5. Reactivation of hepatitis B with chemotherapy or with the use of DAAs in chronic hepatitis C needs to be differentiated from an ALT flare that often accompanies antiviral treatment of hepatitis B; the direct acute hepatotoxicity that has been described with DAAs; and the hepatic decompensation that has been seen with certain DAAs in advanced cirrhosis.
6. Liver biopsy is seldom performed in acute hepatic events that begin to resolve, and as a result, histologic clues that could help in the assessment of DILI are generally not available. While no specific pathognomonic findings for DILI have been found; histopathology may be useful to exclude other possible causes.
7. Knowledge of the potential of concomitant medications to cause hepatic injury is essential, along with the clinical signatures of such hepatotoxins in order to help differentiate the study drug from other agents.

What stopping rules are considered appropriate in patients with elevated baseline ALT?

The stopping rules for clinical trial subjects (ALT >8X ULN or ALT >5X ULN > 2 wks, or ALT >3X with bilirubin > 2X ULN) with no known CLD and normal ALT at baseline may not be appropriate for those with elevated ALT at baseline. A doubling of an elevated baseline ALT (enrolling up to 5X ULN) was shown to be safe in well-compensated CLD patients with NAFLD, and chronic viral hepatitis receiving high-dose pravastatin. This allowed for ALT to rise to 10X ULN. Such a threshold seems reasonable for patients with well-compensated liver disease (including CPT class A and B patients). Chalasani and Regev have proposed an algorithm with stopping rules for NAFLD trials based on similar principles. Patients with decompensated liver disease (CPT Class C) are regularly excluded from clinical trials, but not from clinical care. Close liver chemistry and liver function (INR, bilirubin, albumin) monitoring is generally performed in such patients outside of trials, and treatment proceeds according to
perceived benefit vs risk. “MELD purgatory” has been described for hepatitis C patients successfully treated with a DAA who still require a liver transplant but are disadvantaged from a lowering of their MELD score. With respect to DILI in the setting of decompensated liver disease, the crossing of a much lower threshold of hepatic impairment (perhaps a doubling of bilirubin to >3mg/dL or prolongation of INR to >1.5) should be invoked to stop the drug. In selected instances where confirmation of acute DILI is essential to ongoing patient safety, premature unblinding of study results (to see whether or not if the patient was on the suspect drug) can be considered.

The Future:
We await the development of several forms of DILI biomarkers/predictors to assist with causality assessment in patients with and without CLD:

1. an accurate predictive DILI biomarker (perhaps specific to an individual drug) that will alert the clinician to a risk of DILI prior to taking the drug (in which case the drug is not dispensed – akin the HLA-B*57-01 testing prior to the use of abacavir); or a biomarker that predicts development of liver injury prior to the usual markers of inflammation and necrosis (i.e. ALT) at the earliest possible point in time allowing for the drug to be stopped with minimal or no injury. To date, HLA testing or testing for metabolic polymorphisms are still limited in scope; microRNAs and other markers of necrosis, etc have relatively limited utility. It is expected that a truly predictive biomarker will eliminate the need for liver test monitoring, REMS programs, etc.

2. For patients in whom liver injury is suspected (with or without CLD), an accurate diagnostic biomarker, more sensitive than the currently used ALT and other liver chemistries, to confirm that a specific drug is responsible is anxiously awaited. This will eliminate the need to interrupt or permanently discontinue a useful therapy, as well as the costly evaluation looking for alternative viral, metabolic, autoimmune and other causes.

Conclusions:
1. Detection of acute DILI in CLD remains challenging at present, but expert opinion and “medical reasoning” seem capable of handling most hepatic events in clinical trials or the postmarketing setting with the current knowledge and expertise available.

2. Stopping rule for patients with elevated liver tests at baseline remain in evolution; allowing subjects to enroll with ALT up to 5X their elevated baseline (e.g. 10X ULN) for well-compensated individuals (up to CPT class A) seems reasonable; lower thresholds may need to be in place for patients with more advanced liver disease (CPT class B).

3. Stopping rules (thresholds) for patients with decompensated liver disease (CPT class C) are currently at the discretion of the sponsor and investigator/clinician. For drugs that are expected to treat and/or reverse the underlying liver disease (e.g. antivirals for Hepatitis B or C or drugs for NAFLD or PBC), improvement in hepatic synthetic function may permit a higher threshold during the treatment trial.

4. Avoiding concomitant potentially hepatotoxic medications with investigational agents may eliminate the concern over confounding agents in clinical trials or in the clinic in patients with CLD (13).

5. Breaking the blind prematurely in cases of special interest in clinical trials can exonerate the study drug (if it is not being given); but cannot eliminate causality if it turns out that it is being administered.

6. The usual evaluation to exclude other causes of liver injury should be carried out (as for patients with normal liver tests at baseline).

7. We anxiously await development of DILI markers that can either predict injury in a susceptible person (before the drug is taken) or confidently diagnose acute DILI at the earliest phase of injury (so the drug can be stopped prior to irreversible liver damage developing).

2158 words, without the 13 references