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MINIREVIEWS

Recent advances in the diagnosis of drug-induced liver injury

Taqwa Ahmed, Jawad Ahmad

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Abstract

Drug-induced liver injury (DILI) is a major problem in the United States, commonly leading to hospital admission. Diagnosing DILI is difficult as it is a diagnosis of exclusion requiring a temporal relationship between drug exposure and liver injury and a thorough work up for other causes. In addition, DILI has a very variable clinical and histologic presentation that can mimic many different etiologies of liver disease. Objective scoring systems can assess the probability that a drug caused the liver injury but liver biopsy findings are not part of the criteria used in these systems. This review will address some of the recent updates to the scoring systems and the role of liver biopsy in the diagnosis of DILI.

Key Words: Drug induced liver injury; Liver biopsy; Diagnosis; RUCAM; RECAM

Core Tip: Diagnosing drug induced liver injury (DILI) remains a challenge in the absence of a reliable biomarker. This review highlights some of the recent advances in causality assessment in DILI that will allow clinicians to be more certain in making a diagnosis.

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INTRODUCTION

Drug-induced liver injury (DILI) is a major problem in the United States, commonly leading to hospital admission. Diagnosing DILI is difficult as it is a diagnosis of exclusion requiring a temporal relationship between drug exposure and liver injury and a thorough work up for other causes. In addition, DILI has a very variable clinical and histologic presentation that can mimic many different etiologies of liver disease. Objective scoring systems can assess the probability that a drug caused the liver injury but liver biopsy findings are not part of the criteria used in these systems. This review will address some of the recent updates to the scoring systems and the role of liver biopsy in the diagnosis of DILI.

DIAGNOSING DILI

The diagnosis of DILI is challenging due to the lack of specific biomarkers and the variable presentation. DILI is a diagnosis of exclusion but there should be a temporal relationship to exposure to a drug, herbal product, or dietary supplement (HDS)[1-3]. DILI can essentially present as any type of liver disease so viral disease,autoimmune hepatitis, vascular liver disease, biliary tract disease and malignancy, all need to be excluded when assessing causality. Several society guidelines on DILI agree that to make a diagnosis of DILI, there should be thorough testing for other etiologies of liver disease[4-6]. The type of testing will vary depending on the clinical situation. In patients with hepatocellular injury, viral serology with hepatitis C viral RNA is indicated, even without an obvious risk factor[4,7]. Hepatitis E testing is important in older patients and in parts of the world where hepatitis E is endemic[8]. For cholestatic injury, imaging of the biliary tree is mandatory to exclude obstruction from gallstones or malignancy and to look for evidence of biliary disease such as primary sclerosing cholangitis (PSC)[4-6]. A recent study has suggested that DILI can present with a sclerosing cholangitis type picture[9], making differentiation with PSC difficult. Vascular imaging with computed tomography or Doppler ultrasound is indicated if Budd-Chiari or vascular compromise is suspected[4-6]. Autoimmune hepatitis (AIH) is a special situation as some drugs can lead to a drug-induced AIH and differentiating de novo AIH from drug-induced AIH can be difficult, even with autoimmune serology and liver biopsy[4]. Drugs associated with drug induced AIH include older agents such as nitrofurantoin, minocycline, hydralazine and methyldopa, but also several newer drugs, particularly immune checkpoint inhibitors[10]. In addition, a history of concomitant medications, latency (time from drug start/end to injury onset), dechallenge (improvement in liver tests after cessation of medication) and rechallenge are important factors[3,4,11].

National and international registries of DILI exist and typically employ expert consensus opinion to assess whether a drug caused a liver injury (*causality)*, such as in the Drug-Induced Liver Injury Network (DILIN). DILIN is funded by the National Institutes of Health in the United States and is an observational cohort study that enrolls patients with suspected DILI in multiple centers across the country. Causality is assessed based on a 5 point categorical scale but is undertaken 6 months after the onset of liver injury which allows interpretation of all the data. Experts review a clinical narrative summarizing the initial presentation and clinical and laboratory outcomes along with a summary of all available laboratory, radiological, and histological data[3]. Critically, this review is undertaken 6 months after the injury occurred and means there is plenty of time to review the course of the injury and various tests including serology and liver biopsy. When available, the liver biopsy is reviewed by an expert liver pathologist. This does not mirror the typical clinical situation where the diagnosis has to be made in real-time.

Practicing clinicians trying to make a diagnosis of DILI must rely on the history and local laboratory testing and abdominal imaging. If liver biopsy is performed it is unlikely to be reviewed by expert liver pathologists and expert hepatology opinion is rarely available. Fortunately, over the last 10 years, an online resource- livertox.nih.gov- has become a very valuable tool that details the typical liver injury from most prescription medications and many HDS[12]. The *livertox* database is regularly updated and provides an approximation to expert opinion.

DILI SCORING SYSTEMS

As well as *livertox*, a readily available online or digital tool for assessing DILI causality would be very useful. The Roussel Uclaf Causality Assessment Method (RUCAM) score (developed by the Council of International Organizations of Medical Sciences, an entity established by the World Health Organization and the United Nations Educational, Scientific and Cultural Organization was designed to be such a tool[13]. First introduced 30 years ago, the RUCAM score uses 8 factors in 7 domains (age over 55 years; presence of alcohol or pregnancy; latency (time from drug start to liver injury); time for dechallenge; exclusion of other causes; hepatoxicity (published or mentioned in the package insert; concomitant medications and positive rechallenge) and assigns points in each to produce an overall score. It has 5 categories based on the numerical score- highly probable (> 8), probable (6-8), possible (3-5), unlikely (1-2) and excluded (0 or less). Liver histology is not one of the domains included in the RUCAM score[13].

There are several criticisms of the RUCAM domains that suggest it may not be very accurate. RUCAM favors DILI if the temporal association to onset of injury is within 5-90 d from drug administration with initial treatment and within 15 d with subsequent exposure. The rate of decline of biochemical tests (the dechallenge) after discontinuation of the drug is also an important criteria with a decrease in alanine aminotransferase (ALT) > 50% from the upper limit of normal within 8 dwithout a subsequent uptrend in one month highly suggestive of DILI. Although uncommon, readministration or rechallenge of the drug with a two-fold increase in ALT favors DILI. However, evaluation of the latency period and the

dechallenge has changed with the recognition that certain drugs have a typically very short or long latency. The domain regarding the published literature of hepatotoxcity of the potential offending agent will inevitably change with time.

The points assigned in the age and alcohol domains were based on older literature and are not considered important today. Concomitant medications often present a problem as most drugs can cause DILI. In the case of polypharmacy it is often difficult to identify the offending agent, particularly if there are over the counter medications that are taken intermittently and the use of HDS is notorious for not being disclosed[14].

In addition, excluding other causes of liver disease involves more testing than was previously available, particularly with regards to viral hepatitis and the presence of underlying chronic liver disease is not taken into account in the RUCAM[4-6].

Comparing the RUCAM score with the structured expert opinion process which DILIN utilizes, demonstrated that the DILIN expert process yielded a higher overall causality consensus of DILI probability. Additionally, RUCAM assessment did not perform as well as expert opinion in cases restricted to a single implicated agent. This highlights the subjectivity of certain RUCAM criteria when even experts have difficulty agreeing, particularly as expert opinion is not available in routine practice[3].

An updated RUCAM version has been proposed with pre-scoring consideration for hepatocellular, cholestatic or mixed liver injury patterns[15]. This is determined with calculation of the R factor [ALT/alkaline phosphatase (ALP) on initial presentation and suspicion of DILI]. Hepatocellular injury is defined by $R \geq 5$, cholestatic injury with $R \leq 2$, and a mixed hepatic and cholestatic pattern with an $R > 2$ but < 5. The corresponding scoring method is then used based on the pattern of liver injury to aid causality assessment in DILI. Primary differences between the hepatocellular injury and cholestatic/mixed injury updated RUCAM is the percentage of improvement of ALT *vs* ALP, respectively, as discussed in criteria 2 of the original 1993 RUCAM. Similarly, criteria 7 measures any interval increase in ALT *vs* ALP in the hepatocellular *vs* cholestatic/mixed injury assessments, respectively, with re-exposure to the drug. Given the shortcomings of the RUCAM, the DILIN and the Spanish DILI Registry developed and validated a revised tool into an easily accessible electronic version termed the revised electronic causality assessment method (RECAM)[15]. Major changes included a much more detailed point-system regarding latency including time to injury after the drug was first taken and when stopped (domains 1a & 1b), dechallenge period standardized irrespective of R-value (domain 2), omission of risk factors (RUCAM criteria 3) and concomitant drugs (RUCAM criteria 4) since they are assessed separately. The major revision was the addition of domain 3 (literature supporting liver injury) using the National Institute of Diabetes and Digestive and Kidney Diseases LiverTox category for each drug[12]. Excluding other causes of liver disease such as viral hepatitis (including hepatitis A, B, C, and E), auto-immune disease, alcohol, biliary tract disease, infection/sepsis and ischemic liver injury encompasses domain 4 (former RUCAM criteria 5). Domain 5 was termed additional data with points awarded for several situations including rechallenge and liver biopsy findings (see below). Additional information, if available, is also included in domain 5 such as the presence of severe skin reactions, or atypical viral testing. Moreover, a warning is issued if a firm alternate diagnosis is suspected, or injury timing is inconsistent with DILI to the user making the diagnosis of DILI highly unlikely. Table 1 delineates the key differences between the original RUCAM and RECAM. Although more complex, incorporation of additional criteria make the RECAM a more accurate tool to assess causality in DILI.

The RECAM has the advantage of being adaptable to new findings, particularly in domain 3 as more reports of liver injury from certain drugs increases the likelihood category in LiverTox. This raises the possibility of newer domains being added. A good example of this is genetic risk factors that may affect the risk of DILI, especially variants in genes involved in drug metabolism or immune response. Multiple HLA and non-HLA polymorphisms have been described that can increase the risk of liver injury considerably but these are of limited clinical use currently as they are drug specific[10]. Recent examples include HLA-B35:01 for green tea extract associated DILI (7-fold increased risk)[16], HLA-B*53:01 for phenytoin associated DILI in African Americans (9-fold increase)[17], and HLA-DRB1*11:04 for nitrofurantoin DILI (4-fold increase)[18]. Newer genetic polymorphisms have been described, such as the PTPN22 gene, a gene associated with many immune-mediated diseases, that increase the risk of DILI for many drugs but only at a low level with an odds ratio of 2[19]. Since DILI is a rare event, even a 10 or 100 fold increased risk does not make the event common enough to warrant genetic testing prior to prescription.

LIVER BIOPSY

Half of all patients enrolled into DILIN undergo a liver biopsy. The liver biopsy is usually undertaken in a situation where the diagnosis is uncertain or in more severe cases[20]. For management decisions, the liver biopsy is performed early during the course of the injury as it may can determine if steroids are required or if the disease is very severe and there is a need to consider liver transplantation. Few diseases have a diagnostic pathologic finding but liver biopsy can support a diagnosis and can eliminate other causes of liver injury (such as autoimmune hepatitis and hemochromatosis) [21-23]. In DILI registries, hepatocellular injury is the most common presentation and pathologic changes can range from mild injury to confluent hepatocellular necrosis and in severe cases results in acute liver failure with massive necrosis. In 5-10% of cases, acute hepatocellular injury can progress to chronic injury mimicking alcoholic cirrhosis, autoimmune hepatitis, or chronic viral hepatitis. Several drugs are associated with this type of injury including TNF-alpha inhibitors [24] and antibiotics such as minocycline[25] and nitrofurantoin[18]. Similarly, certain drugs classically cause a cholestatic injury with characteristic findings on liver biopsy such as bland cholestasis with bile plugging and minimal hepatocellular injury mainly seen with oral contraceptives and anabolic steroids[26]. Mixed liver injury or cholestatic hepatitis has histologic findings of cholestasis with surrounding hepatocyte injury and portal inflammation that can be seen with

Table 1 Differences between The Roussel Uclaf Causality Assessment Method and revised electronic causality assessment method scores

RUCAM	RECAM
Criteria 1: Latency	Domain 1a: Latency from drug start
	Domain 1b: Latency from drug stop
Criteria 2: Dechallenge	Domain 2: Dechallenge
Different time cut-offs based on *R* value	Same time cut-offs regardless of *R* value
Criteria 3: Risk factors	Eliminated
Criteria 4: Concomitant drugs	Domain 3: Literature supporting drug toxicity (LiverTox)
Criteria 5: Exclusion of non-drug etiologies	Domain 4: Exclusion of non-drug etiologies
Criteria 6: Known hepato-toxicity of drug	Became domain 3
Criteria 7: Rechallenge response	Domain 5: Rechallenge response - both prospectively documented with lab testing and retrospective based on patient history. Includes additional data: Liver biopsy results, atypical viral testing, and presence of severe skin reactions

RUCAM: The Roussel Uclaf Causality Assessment Method; RECAM: Revised electronic causality assessment method.

use of amoxicillin-clavulanate, erythromycin, and herbal supplements[21-23].

It is not feasible to conduct a randomized clinical trial to determine the role liver biopsy plays in causality assessment in DILI. Selection bias is a problem when examining patients suspected of DILI that have already undergone a liver biopsy, as the result of the biopsy may have influenced subsequent management. To try and answer the question of how liver biopsy findings impact causality assessment, DILIN investigators in the United States assessed causality in a cohort of patients with suspected DILI, prior to obtaining a liver biopsy, and then repeated causality assessment after reviewing the liver biopsy[20]. All subjects in this study had been enrolled in the DILIN database and had had a liver biopsy performed within 60 d of DILI onset. Investigators reviewed data obtained before the liver biopsy was performed and assigned a causality score (the pre-score) and then reviewed the biopsy with an expert liver pathologist an assigned a post-biopsy causality score. The liver biopsy altered causality assessments in 68% of cases with an increase in DILI likelihood in 48% and made exclusion of DILI more certain in 20% of cases with a cumulative clinically meaningful change in 16% of cases. However, situations exist where the injury from DILI can be virtually indistinguishable such as differentiating AIH from drug-induced AIH[27].

A few caveats should be considered when considering the role of liver biopsy in support of a DILI diagnosis. While there is a suggested timing for DILI with temporal association between drug use and onset of symptoms, there is no suggested timing for obtaining liver biopsies with suspected DILI. The liver injury in DILI can evolve from initially hepatocellular to cholestatic later in the course and the degree of jaundice can worsen. Additionally, when a patient is biopsied, the zone of hepatocellular or cholestatic injury may not be found in the particular lobe or segment from which the biopsy is obtained as seen with acute zonal hepatocellular DILI[22,23]. Biopsies are often inadequate without enough portal tracts or poorly stained. Similar to the updated RUCAM score which is reliant on expert opinion, a biopsy read is pathologist-dependent, often read by community pathologists without much liver pathology experience. Kleiner *et al*[23] described an approach for evaluating hepatic histological findings in patients with suspected DILI correlating pathology with causality and clinical outcome. Up to 10 sections of liver biopsies were obtained from each patient for various staining and reviewed by the same blinded hepatic pathologist. Causality assessment as definite, very likely, probable, possible, or unlikely was assigned to each case. Biopsies in the definite to probable criteria had statistically significant increase in eosinophils (P = 0.04), decreased ductal reaction (P = 0.04), and decreased hepatocellular iron accumulation (P = 0.0008). Nearly 70% of the reviewed samples were implicated with a single agent, while the remaining samples were involved 2 or more hepatotoxic agents. Most common associated drugs included antibiotics such amoxillicin-clavulanate, nitrofurantoin, and sulfamethaxazole-trimethoprim. However, this again highlights some of the limitations of biopsy as these samples met strict criteria in terms of the size and number of portal tracts and were all reviewed by a very experienced liver pathologist. In addition, the drugs that were associated with liver injury in this study are the most common prescription drugs associated with DILI in the United States, suggesting the pre-biopsy likelihood of DILI was already quite high.

Liver biopsy may be helpful in prognosticating the severity and possible course or recovery of DILI. Composite data of patients enrolled in DILIN revealed favorable clinical outcomes in patients with hepatic eosinophil infiltration and eosinophilia[23]. However, hepatocyte drop-out or necrosis, microvesicular steatosis, and fibrosis were seen in severe or fatal cases. It is worth noting that although eosinophilia is associated with hypersensitivity features of fever and rash as seen in drug reaction with eosinophilia and systemic symptoms syndrome, these symptoms were seldom seen in the included patients with high suspicion for DILI. Although fibrosis can be seen with amiodarone or nitrofurantoin use, it may indicate undiagnosed underlying chronic hepatic disease and limit response to injury. Micro and macrovesicular

steatosis reflect mitochondrial injury secondary to fatty acid oxidation and is usually associated with higher clinical severity as seen in acute fatty liver of pregnancy[23,28].

Society guidelines on DILI have recommendations on when to perform liver biopsy in DILI but are hampered by low quality evidence so are not very definitive. The American College of Gastroenterology guideline suggests liver biopsy in situations where AIH is on the differential diagnosis and immunosuppression is being contemplated; if the injury is not improving; and if the injury persists for more than 180 d[4]. The Asia Pacific Association of Study of Liver guideline is more general and states to consider liver biopsy if an alternative diagnosis needs to be ruled out or if patients fail to respond after the suspected offending agent is stopped[6]. The European Association for the Study of the Liver guideline are similar, suggesting liver biopsy in selected patients; if AIH is suspected; and if the liver injury persists or worsens[5].

The conclusion from these guidelines are that liver biopsy can be considered in patients where the diagnosis is not certain, particularly if the injury is not improving and if AIH is on the differential diagnosis.

The diagnosis of DILI continues to be a clinical challenge due to several confounding variables that albeit known, undisclosed, or undiagnosed at the time of initial clinical evaluation, affect attributing a correct diagnosis of DILI. A recent review of patients enrolled in DILIN reported 1.5% of cases from 2004-2016 were found to have acute hepatitis C in the 6 month follow up period from enrollment[7]. At enrollment, serologic assessment was done to exclude other causes of hepatic injury including testing for viral hepatitis. Routinely, anti-hepatitis C antibodies were collected, however, hepatitis C virus (HCV) RNA was sent at the discretion of the investigator at that time. At the 6-month follow up period, stored serum samples were retrospectively analyzed for HCV RNA if this had not been initially tested, revealing 23 cases of acute hepatitis C with varying initial degrees of suspicion for DILI from highly probable to unlikely. As with any diagnosis of exclusion, cumulative and complete data with a possible temporal advantage helps illuminate missed underlying diagnoses. However, it is important to note that uncovering acute hepatitis C in these patients was possible due to stored sera from which is not routinely possible in every clinical encounter. Other retrospective studies evaluated the presence of acute hepatitis E in patients enrolled in DILIN[8,29]. Stored sera were tested for anti-hepatitis E antibody (anti-HEV), HEV IgM, HEV IgG, and HEV RNA levels. The results revealed 1.5% of patients with active hepatitis E at the time of suspected DILI. These were predominantly older men almost all of whom presented with typical acute viral hepatitis-like symptoms including fatigue, nausea, abdominal pain, and jaundice. Similarly, this study reiterates the difficulty and importance to differentiate whether an acute hepatic injury is attribute to another etiology rather than DILI.

CONCLUSION

In conclusion, while the diagnosis of DILI remains challenging for clinicians due to the absence of a standardized diagnostic criteria or a specific biomarker, recent literature has reiterated the importance of complete exclusion of other etiologies for hepatic injury as seen in uncovered cases of acute hepatitis C and E with repeat serologies or liver biopsy results that significantly changed expert opinion regarding DILI likelihood. Additionally, the revision and digitalization of RUCAM into RECAM facilitates the diagnostic evaluation and probability of a DILI diagnosis. While a liver biopsy is not necessary for establishing a DILI diagnosis, histologic findings can augment or exclude DILI in certain patients and help to differentiate AIH from DILI and the need for immunosuppression.

FOOTNOTES

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