

Idiosyncratic Drug-Induced Liver Injury: A Short Review

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Idiosyncratic drug-induced liver injury (iDILI) is a rare adverse drug reaction that occasionally leads to acute liver failure or even death. An aging population that uses more drugs, a constant influx of newly developed drugs, and a growing risk from herbal and dietary supplements of uncertain quality can lead to an increase in iDILI. Antimicrobials, central nervous system agents, and herbal and dietary supplements are the most common causes of iDILI in developed countries. iDILI is still a diagnosis of exclusion, and thus careful history taking and thorough work-ups for competing etiologies, such as acute viral hepatitis, autoimmune hepatitis, and others, are essential. The pathogenesis of iDILI is not clear and includes a mix of host reactions, drug metabolites, and environmental factors. Immediate cessation of the suspected offending drug is key to preventing or minimizing progressive damage. No definitive therapies for iDILI are available, and the treatments remain largely supportive. (*Hepatology Communications* 2017;1:494–500)

Introduction

In developed countries, idiosyncratic drug-induced liver injury (iDILI) remains the leading cause of acute liver failure (ALF).⁽¹⁾ The wide range of clinical presentations and causative drugs and the lack of objective diagnostic markers for iDILI make its diagnosis and management particularly difficult. Despite its low incidence of 19 in 100,000 in the general population,⁽²⁾ physicians must always consider the possibility of iDILI in patients with unexplained liver injury. Moreover, the incidence of iDILI is considered to increase with age; therefore, the incidence of iDILI will rise in countries with aging populations. Many herbal and dietary supplements (HDSs) can cause iDILI, and thus they must always be considered as a possible cause in cases of iDILI.

One useful characterization of iDILI cases is to separate them from the intrinsic type. *N*-Acetyl-*p*-aminophenol (acetaminophen; APAP) is perhaps the best-known drug that causes intrinsic DILI. iDILI is less common, affects only susceptible patients, has a less consistent relationship to dose, and is more varied in its clinical presentations.

Diagnosis of iDILI

RISK FACTORS

Many host, environmental, and compound-specific risk factors have been described as causing iDILI, but there is no variable that can be a major risk factor for all-cause iDILI. Certain variables, such as age, sex, obesity, alcohol consumption, diabetes mellitus, and

Abbreviations: AIH, autoimmune hepatitis; ALF, acute liver failure; ALT, alanine aminotransferase; APAP, acetaminophen; CLD, chronic liver disease; DILIN, Drug-Induced Liver Injury Network; FDA, U.S. Food and Drug Administration; HCV, hepatitis C virus; HDS, herbal and dietary supplement; HEV, hepatitis E virus; HLA, human leukocyte antigen; iDILI, idiosyncratic drug-induced liver injury; Ig, immunoglobulin; NAC, *N*-acetylcysteine; ULN, upper limit of normal.

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chronic liver disease (CLD), can increase the risk of iDILI in a drug-specific manner.⁽²⁾

Age increases the overall risk of iDILI, in part due to the polypharmacy. A few drugs, such as isoniazid, flucloxacillin, halothane, amoxicillin/clavulanate, and nitrofurantoin, were reported to increase the risk of iDILI in older individuals.⁽³⁻⁷⁾ In female patients, there are some trends in the patterns of injury, with hepatocellular as well as autoimmune-like injury being common.⁽⁸⁾ Patients with CLD are hypothesized to be at higher risk of iDILI because of the inherent altered pharmacokinetics of drugs metabolized by the liver. However, the laboratory data for this population are mixed and hindered by the competing causes of the elevation of liver biochemistries.⁽⁸⁻¹⁰⁾ There are no data to show that underlying CLD is a major risk factor for all-cause iDILI, but it may increase the risk in selected drugs. Patients with chronic hepatitis (A, B, or C) may be more prone to developing iDILI in combination with specific drugs, such as isoniazid and antiretroviral drugs, and may experience worse outcomes.⁽⁸⁾

Several human leukocyte antigen (HLA) serotypes have been identified as risk factors for iDILI in combination with specific drugs (e.g., amoxicillin/clavulanate and flucloxacillin), suggesting that the immunologic reaction is also important in iDILI. Interestingly, drugs whose daily dose is over 50 mg account for over 70% to 80% of iDILI cases.⁽¹¹⁾ These data suggest that iDILI may still have a dose-dependent component similar to APAP.^(12,13) The lipophilicity of drugs has also been shown to be a strong predictor of iDILI. In fact, when drugs have both a dosage over 100 mg per day and lipophilicity, there is a markedly increased risk of iDILI.⁽¹⁴⁾

Drug-drug interactions and polypharmacy are often invoked as risk factors for iDILI; however, there is scant evidence to show that they are key risk factors for all-cause iDILI. Drug interactions may potentially exacerbate the risk of iDILI associated with

antituberculosis drugs and anticonvulsants, such as valproate.

DIAGNOSIS AND CAUSALITY ASSESSMENT IN iDILI

Clinical symptoms usually consist of nonspecific symptoms (fatigue, nausea, and abdominal pain), and occasionally liver-specific symptoms in severe cases (jaundice, ascites, and encephalopathy). The most important clue for the timely diagnosis of iDILI is a suspicion of the presence of iDILI in patients with elevated liver enzymes. An accurate clinical history related to drug exposure and the onset of abnormalities should be obtained when iDILI is suspected. History taking is greatly enhanced by the knowledge of the most common and most rarely implicated iDILI drugs. Overall, antibiotics and antiepileptics account for >60% of iDILI cases, whereas antihypertensive and diabetic drugs are less common causes of iDILI.^(15,16) There are increasing reports of iDILI due to HDSs, and thus close questioning regarding HDS consumption is crucial.⁽¹⁷⁾

Table 1 lists the most notorious and commonly prescribed drugs associated with iDILI, and the patterns of liver injury and typical latencies are also provided. Harnessing knowledge of rare or newly reported cases of iDILI is also important. The LiverTox website (<http://www.livertox.nih.gov/>), a free and helpful online iDILI resource containing detailed information on more than 1,200 drugs, is very useful.⁽¹⁸⁾

iDILI is a diagnosis of exclusion, and thus appropriate competing etiologies should be excluded using blood tests, hepatobiliary imaging, and occasionally liver biopsy. The diagnostic algorithms available to clinicians are based on clinical scoring systems, such as the Roussel Uclaf Causality Assessment Method.^(8,19-21) Although such systems can help organize the clinician's history and testing by providing a diagnostic

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TABLE 1. MOST COMMON OR WELL-DESCRIBED DILI DRUGS

Drugs	Pattern of Injury	Latency
<i>Antibiotics</i>		
Isoniazid	Hepatocellular, resembling viral hepatitis	Moderate
Amoxicillin/clavulanate	Cholestatic, more hepatocellular in children	Short
Macrolides	Hepatocellular, but can be cholestatic	Short
Minocycline	Hepatocellular, often resembling autoimmune hepatitis	Moderate
<i>Anti-epileptics</i>		
Phenytoin	Hepatocellular, Mixed, or Cholestatic, immune-allergic	Short
Carbamazepin	Hepatocellular, Mixed, or Cholestatic, immune-allergic	Moderate
Valproic acid	Hepatocellular, rise in ammonia, sometimes acidosis	Moderate
<i>Analgesics</i>		
NSAIDs	Hepatocellular	Moderate
<i>Lipid-lowering agents</i>		
Statins	Hepatocellular, Cholestatic, or Mixed, autoimmune like	Moderate
<i>Immune modulators</i>		
Anti-TNF agent	Hepatocellular, with autoimmune hepatitis features	Moderate
Azathioprine	Cholestatic, Hepatocellular, with portal hypertension	Moderate
<i>Herbals and dietary supplements</i>		
Green tea extract	Hepatocellular	Short
Anabolic steroid	Cholestatic	Moderate
Pyrolizidine alkaloids	Sinusoidal obstruction/veno-occlusive disease	Moderate
Flavocoxib	Mixed, or Cholestatic	Short
<i>Miscellaneous</i>		
Methotrexate	Fatty liver, with fibrosis	Long
Proton pump inhibitor	Hepatocellular, very rare	Short
Allopurinol	Hepatocellular or Mixed, Granulomas often present on biopsy.	Short
Amidarone	Hepatocellular, Mixed, or Cholestatic, with steatohepatitis	Moderate

Short, 3-30 days; moderate, 30-90 days; long, >90 days.

Abbreviations: NSAID, nonsteroidal anti-inflammatory agent; TNF, tumor necrosis factor.

framework, they still lack clarity and proven accuracy.⁽²²⁾

The pattern of liver injury in iDILI is categorized by the "R value"⁽²³⁾: $R = (\text{alanine aminotransferase [ALT]}/\text{upper limit of normal [ULN]})/(\text{alkaline phosphatase/ULN})$. iDILI can be categorized by R value into hepatocellular ($R > 5$), cholestatic ($R < 2$), and mixed ($R = 2-5$) types. The pattern of liver injury provides a useful framework that allows us to focus on differential diagnoses. However, the same drug can present varying R values and clinical features in different individuals with iDILI.⁽⁸⁾

In patients with suspected hepatocellular or mixed iDILI, acute viral hepatitis (A, B, and C) and autoimmune hepatitis (AIH) should be excluded with standard blood tests. The diagnosis of acute hepatitis C can be challenging because anti-hepatitis C virus (anti-HCV) antibodies may initially be negative. In the initial report of the DILI Network (DILIN) prospective study, acute HCV infection masqueraded as iDILI in 1.3% of cases; therefore, that report recommended that acute HCV infection should be excluded by HCV RNA testing.⁽¹⁶⁾ Another published report from the DILIN showed that 3% of patients with suspected iDILI were positive for anti-hepatitis E virus (anti-

HEV) immunoglobulin (Ig) M, and it was concluded that blood testing for acute HEV infection should be performed, especially if the clinical features are compatible with acute viral hepatitis.⁽²⁴⁾ However, routine anti-HEV IgM testing cannot be recommended owing to the uncertain performance of the currently available commercial tests.⁽²⁵⁾ This testing should be considered in patients who have recently traveled in an HEV-endemic area. Testing for acute cytomegalovirus, acute Epstein-Barr virus, or acute herpes simplex virus infections should be undertaken if classical viral hepatitis has been excluded or if clinical features, such as atypical lymphocytosis and lymphadenopathy, suggest such causes.

AIH should be considered as a differential diagnosis for all types of iDILI. In fact, it is well known that some drugs, such as minocycline and nitrofurantoin, have a high propensity to cause autoimmune-like iDILI.⁽²⁶⁾ Serum autoantibodies (anti-nuclear antibody and anti-smooth muscle antibody) and IgG levels should be obtained, and a liver biopsy may be considered in selected patients. Wilson's disease in patients younger than 40 years and Budd-Chiari syndrome in patients with tender hepatomegaly and/or ascites should also be considered as differential diagnoses of iDILI.

In patients with cholestatic iDILI, abdominal imaging (ultrasound or computed tomography scan) should be performed to exclude biliary tract diseases. Blood testing for primary biliary cirrhosis should be limited to those with no evidence of obvious biliary tract pathology on such abdominal imaging. Endoscopic retrograde cholangiography should be limited to patients in whom routine imaging is unable to exclude impacted common bile duct stones, primary sclerosing cholangitis, or pancreaticobiliary malignancy.

Liver biopsy is not mandatory in the evaluation of iDILI. A liver biopsy should be considered if AIH remains a competing etiology and immunosuppressive therapy is contemplated.⁽²⁵⁾ In addition, liver biopsy is recommended if there is an unrelenting rise in liver biochemistries or if there are signs of worsening liver function despite stoppage of the suspected offending drug.⁽⁸⁾

The hepatitis pattern of iDILI is not static; a hepatocellular pattern at initiation may evolve into a cholestatic pattern in the course of the disease.^(16,23) Therefore, the liver biochemical pattern at the time of initial presentation should be considered to define the pattern of iDILI.⁽²⁷⁾

Management of iDILI

PROGNOSIS

Of great importance in the short-term prognosis of iDILI is the presence of jaundice (total bilirubin > 3 mg/dL), which entails some risk of mortality. Hy's law, which has been defined by the U.S. Food and Drug Administration (FDA) as total bilirubin > 2 times ULN and aspartate aminotransferase or ALT > 3 times ULN, suggests that there is a 10% risk of mortality if this criterion is met.⁽²⁸⁾ Hy's law has been corroborated in several studies, including a recent single-center study from India that found a mortality rate of 21.5% in a setting where transplantation was not available.⁽²⁹⁾

Once a diagnosis of iDILI is suspected, the suspected offending drugs should be discontinued. A vast majority of iDILI will subside with the cessation of the offending drug. In general, the outcomes of iDILI are good, with only 10% or fewer patients reaching ALF. The outcome is less favorable in patients with severe symptoms, such as jaundice, ascites, or encephalopathy. Patients with advanced iDILI should be transferred to advanced centers for intensive care or liver transplantation should be undertaken. Transplant-free

survival for ALF due to DILI was found to be 23%, with 40% undergoing liver transplantation and 42% dying of this episode.⁽⁸⁾ Results of liver transplantation for iDILI are similar to those of other cases of ALF, with an overall survival of 58%.

TREATMENT

Currently, no definitive therapies for iDILI are available. Most clinicians use antihistamines for symptomatic pruritus. In addition, as many as 30% of patients enrolled in the DILIN prospective study were given ursodeoxycholic acid, but its efficacy in iDILI is not established.⁽¹⁶⁾ Corticosteroid therapy has been proposed as a treatment for iDILI in the ALF setting; however, there is little evidence supporting its efficacy. N-Acetylcysteine (NAC), the proven antidote for APAP overdose, may also be considered in adults with early stage ALF, given its good safety profile and some evidence for its efficacy in early coma-stage patients.⁽³⁰⁾ For those with an etiology of DILI within the NAC trial,⁽³¹⁾ transplant-free survival was 58% for those who received NAC versus 27% for those who did not receive NAC. However, the use of NAC in children with non-APAP ALF demonstrated a lower rate of survival at 1 year; therefore, NAC is not recommended for children with severe iDILI leading to ALF.⁽³²⁾ To date, the FDA has not approved NAC for the treatment of non-APAP ALF. Intravenous carnitine has been shown to be useful in valproic-acid-induced hepatotoxicity. In a case-controlled study of patients with valproate-induced hepatotoxicity, patients treated with L-carnitine showed significantly higher survival rates compared to patients treated with supportive care (42% versus 10%, $P < 0.001$).⁽³³⁾

RECHALLENGE

Rechallenge with the suspected offending drug is best avoided, especially if the initial injury was associated with a significant ALT elevation over 5 times ULN, matching to Hy's law, or jaundice.⁽⁸⁾ In some patients in whom the causal relationship is uncertain or the prior history is unknown and/or when the drug is considered very important, rechallenge has been undertaken. Rechallenging with a drug in this context may be associated with a more rapid injury than initially experienced and a more severe and possibly fatal reaction, even when the first instance was relatively mild. Rechallenge may occur and may even be done intentionally with recognition of the risks; however, it

is generally discouraged in all but the most life-threatening situations where no suitable alternative is available.⁽³⁴⁾ Clinicians who have recognized a toxic reaction should be careful to educate the patient regarding the name of the suspected drug, encourage the patient to use Medic Alert bracelets and cards, and remind the patient that rechallenge with that drug may have even more deleterious effects.

FOLLOW-UP

Patients with any acute hepatic illness should be followed up to its complete resolution whenever possible. In those experiencing iDILI, recent data suggest that chronicity occurs in approximately 13.6% of cases.⁽¹⁶⁾ Patients who presented with cholestatic iDILI were more likely to develop chronic iDILI compared to those who presented with hepatocellular iDILI.⁽³⁵⁾ Chronic iDILI may resemble AIH and might respond to corticosteroids, provided that blood markers and biopsy findings are suggestive of this diagnosis. Late development to cirrhosis and its complications have been observed but are quite rare in iDILI.

Future Perspectives on iDILI

iDILI research is poised to make significant discoveries that will translate into improved clinical practice over the next decade. Several iDILI registries are now growing and maturing worldwide⁽³⁶⁾ and will provide rich data for translational and clinical research. Based on the clinical data alone in these registries, newer diagnostic algorithms to improve the Roussel Uclaf Causality Assessment Method will be developed. The emergence of large medical groups and systems in the United States along with the use of large amounts of electronic medical records will be rich sources of data for pharmacoepidemiologic studies that will help determine accurate incidence and risk factors for iDILI.

With the increasing availability of tissue and blood from well-defined iDILI cases, the chance of identifying accurate biomarkers for the diagnosis of iDILI will increase. New biomarkers, such as microRNA-122, high mortality group box-1, and macrophage colony-stimulating factor receptor 1, have recently received regulatory support from the European Medicines Agency and the FDA for more systemic use in an exploratory developing setting; this will ultimately

enable full qualification of the most promising markers.^(22,37) Once qualified in well-controlled trials, regulatory guidance will then also have to account for the new markers and incorporate them into existing guidelines.

Genome-wide association studies are already providing insight into the pathophysiology of iDILI.⁽³⁸⁾ Several HLA associations with iDILI from a variety of drugs strongly suggest an immune system component to the liver injury.^(39,40) In a recent genome-wide study of persons of European descent with iDILI, HLA-A*33:01 was reported to be associated with iDILI from statins as well as two nondrug specific risk factors.⁽⁴¹⁾

Such an immune system component as the so-called drug-peptide complex or drug-specific T cells may lend itself to target therapies that may truncate iDILI and prevent ALF. Metushi et al.⁽⁴²⁾ recently reported the treatment of PD-1^{-/-} mice with amodiaquine and anticytotoxic T lymphocyte antigen 4 led to liver injury similar to human iDILI. This model suggested that immune tolerance would have an important role in the development of iDILI.⁽⁴³⁾ Other genetic and drug metabolism markers, such as N-acetyltransferase 2 or uridine diphosphate glucuronosyltransferase 2B7, also show promise. Next-generation sequencing technology and increasing sample sizes will identify markers for use in diagnostic testing and risk assessment for iDILI in the years to come.⁽⁴⁴⁾

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