Idiosyncratic drug-induced liver injury (DILI) is an underreported and underestimated adverse drug reaction. A recent population-based study found a crude incidence of approximately 19 cases per 100,000 a year. Amoxicillin-clavulanate continues to be the most commonly implicated agent in most Western countries, reported to occur in approximately 1 of 2300 users. In patients with drug-induced autoimmune hepatitis, liver tests often do not normalize with cessation of the drugs and require corticosteroids. DILI associated with jaundice can lead to death from liver failure or require liver transplantation in at least 10% of cases.

Identification of genetic predisposition to drug-induced liver injury (DILI) is of paramount importance. Early candidate gene studies have identified various polymorphisms in drug-metabolizing genes that infer increased DILI susceptibility. Few of these have been confirmed in more recent genome-wide association studies, which have identified several specific human leukocyte antigen (HLA) alleles. The low incidence rate of DILI, however, leads to a low positive predictive value for currently identified genetic variations, making them unsuitable for pre-prescription screening. HLA screening incorporated into clinical practice can aid the diagnostic process resulting in enhanced diagnostic accuracy and confidence.

Drug-induced liver injury is a diagnosis that relies on the patterns of injury associated with specific medications and toxins. The process by which a clinician determines which agent is the likely culprit of the liver injury is called causality assessment. The Roussel Uclaf Causality Assessment Method (RUCAM) and additional causality assessment methods have been developed with the goal of providing a more standardized, less subjective approach to causality assessment. RUCAM remains the most used standardized method, however many physicians continue to rely on their experience for causality assessment.
Frequent Offenders and Patterns of Injury

Jinyu Zhang and Deepak Venkat

Given the liver’s role in drug metabolism, it is uniquely sensitive to potential drug-induced liver injury (DILI) despite inherent protective mechanisms. In this article, we focus on the most common causes of DILI and their patterns of injury. Although not comprehensive, we attempt to cover several classes of commonly used drugs, and their associated patterns of injury and management.

Quantitative Systems Toxicology Approaches to Understand and Predict Drug-Induced Liver Injury

Paul B. Watkins

The DILI-sim Initiative is a public-private partnership using quantitative systems toxicology to build a model (DILIsym) capable of understanding and predicting liver safety liabilities in drug candidates. The effort has provided insights into mechanisms underlying dose-dependent drug-induced liver injury (DILI) and interpatient differences in susceptibility to dose-dependent DILI. DILIsym may be useful in identifying drugs capable of causing idiosyncratic hepatotoxicity. DILIsym is used to optimize interpretation of traditional and newer serum biomarkers of DILI. DILIsym results are considered in drug development decisions. In the future, it may be possible to use DILIsym predictions to justify reduction in size of some clinical trials.

Liver Histology: Diagnostic and Prognostic Features

Billel Gasmi and David E. Kleiner

When patients with suspected drug-induced liver injury (DILI) undergo liver biopsy, the pathologist can provide a wealth of information on the morphologic changes. The most common histologic patterns of DILI include mimics of acute and chronic hepatitis as well as acute cholestasis, chronic cholestasis, and a mixed pattern that combines hepatitis with cholestasis. The pattern may suggest etiologies of injury or correlate with reported patterns of injury for specific agents. Biopsy may exonerate or indict particular drugs as causal agents of injury and provide specific information on severity of injury and specific types of changes related to various outcomes.

Acute Liver Failure Secondary to Drug-Induced Liver Injury

Maneerat Chayanupatkul and Thomas D. Schiano

Drug-induced liver injury (DILI) is the most common cause of acute liver failure (ALF) in Western countries. Without liver transplantation, the mortality rate for ALF approaches greater than 80%. Acetaminophen-related ALF may be associated with a rapid progression but fortunately has a high chance for spontaneous survival compared with idiosyncratic DILI–related ALF. Several prognostic scoring systems for severe DILI have been developed to aid clinicians in selecting patients who require urgent liver transplantation. Patients who undergo liver transplantation for ALF are at risk for early graft loss and death and should be closely followed.
Drug-Induced Liver Injury in the Setting of Chronic Liver Disease
Nicholas A. Hoppmann, Meagan E. Gray, and Brendan M. McGuire

Drug-induced liver injury (DILI) is an uncommon but significant cause of liver injury and need for liver transplant. DILI in the setting of chronic liver disease (CLD) is poorly understood. Clinical features of patients presenting with DILI in the setting of CLD are similar to those without CLD with the exception of a higher incidence of diabetes among those with CLD and DILI. Diagnosis of DILI in CLD is difficult because there are no objective biomarkers and current causality assessments have not been studied in this population. Differentiating DILI from exacerbation of underlying liver disease is even more challenging.

Drug-Induced Liver Injury from Statins
Lindsay Meurer and Stanley Martin Cohen

The hydroxymethyglutaryl-coenzyme A reductase inhibitors (statins) are a commonly prescribed class of medication for the treatment of hyperlipidemia and coronary artery disease. This class of medication has several proven benefits, including reduction of mortality related to coronary artery disease. A major consideration when prescribing these drugs are the potential for adverse effects, mainly myalgias, myopathy, and hepatotoxicity. In this article, we summarize current data on statin-associated hepatotoxicity and highlight that the risk of clinically significant idiosyncratic drug-induced liver injury is actually quite small. We also review preclinical data suggesting potential hepatoprotective effects of statin therapy.

Drug-Induced Liver Injury in the Setting of Analgesic Use
Umar Darr and Norman Leslie Sussman

No professional society has created guidelines to aid clinicians in the management of analgesics in the setting of hepatic injury. Acetaminophen overdose is the most common cause of acute liver failure in the United States. In the setting of acetaminophen toxicity, N-acetylcysteine remains the standard of care. Other analgesics including nonsteroidal antiinflammatory drugs, opiates, tricyclic antidepressants, and anticonvulsants rarely cause liver injury.

Drug-Induced Liver Injury Resources and Reporting for the Clinician
Marisa Isaacson and Michael Babich

Although many risk factors for developing drug-induced liver injury (DILI) have been identified and more than 1000 medications and herbal and dietary supplements are known to cause liver dysfunction, idiosyncratic drug reactions remain unpredictable and erratic. Varying effects of individual drugs on the event cascade and patient genetic polymorphisms lead to different clinical presentations. Mechanisms and causality scales have been developed to guide the clinician in diagnosis, and several databases and registries are available for reference and reporting. We identify and summarize the resources available to clinicians to help diagnose, manage, and report DILI and to identify hepatotoxic drugs.
The use of herbal and dietary supplements (HDS) is increasing in the United States and worldwide. Its significant association with liver injury has become a concern, particularly because rates of hepatotoxicity caused by HDS are increasing. There are a variety of HDS available, ranging from multi-ingredient substances, to anabolic steroids for bodybuilding purposes, to individual ingredients for purposes of supplementing a diet. This article reviews the impact of liver injury caused by HDS and explores the hepatotoxic potential of such products and their individual ingredients.