Drug-Induced Liver Disease
Clinical Course

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KEYWORDS

• Drug-induced liver injury • Acute liver failure • Chronic drug-induced liver injury

KEY POINTS

- Most patients with suspected drug-induced liver injury (DILI) have uneventful recovery after the withdrawal of implicated agent.
- Approximately 10% of patients with DILI progress to acute liver failure leading to death or liver transplantation.
- 5% to 20% of patients with DILI will have persistent abnormalities at 6 months.
- Cirrhosis as a result of DILI is rare but described and can be associated with decompensated disease and liver-related death months to years after DILI is recognized.

INTRODUCTION

Despite the crucial role of the liver in the metabolism of many medications, drug-induced liver injury (DILI) is a relatively infrequent event. DILI accounts for less than 1% of patients hospitalized for jaundice.[1] However, DILI is a leading cause of medications not making it to the market during the investigational stage. Population-based studies from France and Iceland have estimated an incidence rate of 13.9 and 19 per 100,000 persons.[2,3]

DILI can range from mild elevation of transaminases detected on routine blood work to acute liver failure (ALF) requiring liver transplantation or death. Many drugs can cause mild elevation of liver enzymes that resolve with continued exposure by a process of adaptation. Idiosyncratic DILI is a result of complex interaction between a drug or metabolites and host immune response. Defective adaptation potentially related to T-cell response can lead to severe liver injury.[4] Idiosyncratic DILI differs from intrinsic DILI, which occurs in a predictable fashion from known hepatotoxins, such as acetaminophen. Chronic liver enzyme elevation may result from DILI, and in rare cases, cirrhosis and its complications can develop with resultant liver-related morbidity and mortality.[5–7]

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Most information on the clinical course of DILI has come from the Drug-Induced Liver Injury Network in the United States (DILIN) and the Spanish Group for the Study of Drug-Induced Liver Injury in Europe. Each of these networks has prospectively collected data on the natural history of DILI. In addition, there is a large cohort of patients that were reported to the Swedish Adverse Drug Reactions Committee that has provided insight into the natural history of DILI through retrospective review. Data from these networks are reviewed in this article, with a focus on the clinical course of idiosyncratic DILI. **Table 1** describes the outcomes from each of the 3 large DILI cohorts.

DISCUSSION

Diagnosis

The diagnosis of DILI can be quite difficult to make, although it only requires evidence that liver injury resulted from a drug or herbal supplement. Several challenges to making the diagnosis are described in later discussion. **Fig. 1** outlines the steps to make the diagnosis of DILI, including a reasonable diagnostic workup to rule out alternative causes of liver injury.

DILI may be found incidentally on routine blood work; however, patients that develop severe DILI generally present with symptoms such as jaundice, pruritus, abdominal pain, nausea/vomiting, and malaise. Fever, rash, and eosinophilia may be seen in cases of hypersensitivity reactions.

An accurate diagnosis of DILI depends on an accurate list of all prescription medications (PMs), over-the-counter medications, and herbal/dietary supplements that the patient is taking. The diagnosis of DILI can be limited by patient history and may require corroboration from family members or a phone call to the patient's pharmacy to obtain accurate records. A good understanding of the most common offending agents, latency periods, and pattern of injury can help determine which drug caused the episode. However, many drugs and herbal/dietary supplements can cause DILI, so it may be necessary for the clinician to examine the literature for cases of DILI for each medication that a patient is taking. The National Institutes of Health has developed a

Table 1
Results of drug-induced liver injury registries

Study	Total Number of Cases[a]	Pattern of Injury (%)			ALF (%)		Chronic DILI (%)[b]
		Hepatocellular	Mixed	Cholestatic	Death	LT	
US DILI Network	899	53	22	23	6	4	18.9
Spanish DILI Registry	805	61	16	20	2.5	1.5	5.7
Swedish Adverse Drug Reactions Committee	784	52	22	26	7.5	1.7	3.4

Numbers were taken from the most recent publication as of May 2016 for each group.

Abbreviation: LT, liver transplantation.

[a] Only cases determined to be possible, probable, or highly probable were included in the study analyses.

[b] The definition of Chronic DILI varied by study. In the US DILIN, chronic DILI was defined as elevation of ALT, AST, ALP, or bilirubin, histologic or radiologic findings that persisted for more than 6 months from the original DILI episode. The Spanish DILI registry defined chronic hepatocellular injury as elevated enzymes 3 months after the original DILI episode and chronic cholestatic injury as elevated enzymes 6 months after the original DILI episode. The Swedish Registry did not use a predefined definition of DILI; this number reflects the number of patients hospitalized with a diagnosis of liver disease after the original episode of DILI.