Nonacetaminophen Drug-Induced Acute Liver Failure

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KEYWORDS

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

KEY POINTS

- Nonacetaminophen drug injury represents 11% of all acute liver failure cases in a large acute liver failure dataset in the United States.
- Females and African Americans are disproportionally affected, with the latter having worse outcomes.
- Nearly all drugs implicated in global registries of non–acetaminophen-induced acute liver failure are older compounds that have been available for decades, but remain on the market owing to their clinical efficacy and the lack of alternative agents.
- *N*-Acetylcysteine has shown some benefit for non–acetaminophen-induced acute liver failure, particularly if given when patients have early stage coma grades.
- Future work is poised to elucidate potential host genetic factors that make drug-induced acute liver failure more likely and discover biomarkers that can diagnose it earlier.

INTRODUCTION

Acute liver failure (ALF) of all causes is diagnosed in between 2000 and 2500 patients annually in the United States. Although multiple etiologies are responsible, drug-induced ALF (DI-ALF) is the leading cause of ALF, accounting for more than 50% of cases overall. Even though acetaminophen (APAP), both from intentional self-harm as well as unintentional overdose, is the cause in most instances of drug-related cases, non-APAP drug injury represents 11% of all cases in the latest registry from the US ALF Study Group (US ALF SG).[1] Although rare, the development of ALF is clinically dramatic when it occurs, and requires a multidisciplinary approach to

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management. In contrast with APAP ALF, non-APAP DI-ALF has a more ominous prognosis with a lower transplant-free survival and a higher rate of chronic liver disease. DI-ALF also has had an important influence on the drug development process, with several agents having been withdrawn after approval, abandoned in the United States or not approved at all owing to the risk of ALF (**Table 1**).[2] No specific antidote is available to treat or reverse the hepatic injury from these agents, although NAC may have a role in those with early grade coma and liver support devices, such as the molecular adsorbent reticulating system (MARS; Baxter International, Deerfield, IL), have been used in some cases. Liver transplant remains the definitive therapy, but its availability remains an issue.

In this article, we summarize the recent advances in the diagnosis and management of non-APAP DI-ALF. APAP ALF is discussed in Chalermrat Bunchorntavakul and K. Rajender Reddy's article, "Acetaminophen (APAP or N-acetyl-p-aminophenol) and Acute Liver Failure," and ALF owing to nondrug causes is reviewed in Pavan Patel and colleagues' article, "Future Approaches and Therapeutic Modalities for Acute Liver Failure," both in this issue.

GLOBAL EPIDEMIOLOGY

In the United States, the US ALF SG has prospectively collected cases of all forms of ALF since 1998. In the initial decade of the study, 133 of 1198 subjects (11%) were suspected to have drug-induced liver injury (DILI), by expert opinion.[1] This dataset found that 70% of the subjects were female, and minorities were overrepresented (**Table 2**). Whereas APAP caused almost one-half of all cases, non-APAP DILI was the second largest group, on par with ALF owing to viral hepatitis.

In the US Drug-Induced Liver Injury Network (US DILIN), a prospective registry of patients with DILI beginning in 2004, 107 of 1089 patients died within 2 years of onset of DILI.[3] Analysis of these 107 patients who died showed that DILI had a primary role in 68 (64%) patients. Nearly three-quarters of these patients fulfilled criteria for ALF. Thirteen percent had either acute-on-chronic liver failure or acute cholestatic failure.

In an analysis of Kaiser Permanente Northern California (KPNC) admissions from 2004 to 2010, 669 patients had diagnostic and laboratory criteria suggesting ALF.[4]

Table 1
Drugs withdrawn, abandoned, or not approved in the United States owing to hepatotoxicity

Withdrawn	Abandoned	Not Approved
Iproniazid	Chloroform	Benoxaprofen
Ticrynafen	Cinchophen	Oxmetidine
Ibufenac	Phenurone	Ebrotidine
Suprofen	Phenindione	Dilevalol
Zoxazolamine	Fenclozic acid	Ajmaline
Chenodeoxycholic acid	Isoxepac	Ximelagatran
Pemoline	Thorium dioxide	Clometacine
Oxyphenisatin	Suprofen	Nimesulide
Troglitazone	Carbutamide	Lumiracoxib
Bromfenac	Metahexamide	
	Halothane (limited use elsewhere)	
	Erythromycin estolate (limited use elsewhere)	
	Phenylbutazone	

Adapted from Lewis JH. The art and science of diagnosing and managing drug-induced liver injury in 2015 and beyond. Clin Gastroenterol Hepatol 2015;13:2173–89; with permission.