Incidence and Outcomes of DILI in Western Patients

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Several recent studies have improved our understanding of the epidemiology of drug-induced liver injury (DILI). In its most severe form, DILI can lead to acute liver failure, with associated mortality and need for liver transplantation. However, most patients with DILI have a favorable outcome. In many cases, the liver injury is associated with considerable morbidity, hospitalization, and costs. Most previous cohort studies have been retrospective and likely underestimate this difficult-to-diagnose adverse drug reaction. In this short report, the findings of the largest and most recent studies on the etiologies and outcomes of DILI in Western countries are highlighted.

Multicenter Cohort Studies

A number of recent studies with a large number of patients with DILI have illustrated the clinical characteristics of patients, the major drug classes leading to DILI, and the prognosis of these patients (Table 1).[1-3] The major classes of drugs associated with DILI were similar in these studies, with antibiotics being the most commonly implicated agents.[1-3] Patients with drug-induced jaundice have an approximately 10% risk of death or liver transplantation.[1-3] The results regarding prognosis of drug-induced jaundice have been remarkably similar across the different studies.[1-3] None of these studies[1-3] was population-based, and it is unclear how many patients are at risk of DILI among those patients who are prescribed potentially hepatotoxic drugs.

Incidence of DILI

A few retrospective studies have attempted to ascertain the incidence of DILI. Crude incidence of DILI in the United Kingdom based on the General Practice Research Database (GPRD) was found to be 2.4 per 100,000 per year.[4] A study in an outpatient hepatology clinic setting from a single center in Sweden showed similar results with 2.3 cases per 100,000 inhabitants annually.[5] As most previous studies have been either retrospective or have originated from tertiary referral centers, the incidence of DILI in the general population has been largely unknown. The first population-based study on DILI was from a city in the northern part of France.[6] A careful prospective survey of DILI was performed.[6] All new cases of symptomatic DILIs were collected by physicians—general practitioners as well as gastroenterologists trained for this task in order to assess the incidence and the seriousness of DILI in a defined population over a 3-year period.[6] The incidence of DILI was found to be approximately 14 per 100,000 patient-years.[6] The number of hepatic adverse effects due to drugs was 16 times greater than the number of cases reported to the French authorities.[6] Among the cases of DILI detected, 6% died and 12% required hospitalization.[6] Thus, spontaneous reporting systems clearly underestimate the frequency of DILI. This should come as no surprise because adverse effects associated with the use of drugs in general are underreported.[7,8] Only approximately 5% of real cases of adverse drug reactions out of the total number of serious drug reactions leading to hospitalization were identified by spontaneous reporting in a given population in France.[7]

A recent population-based study from the whole country of Iceland during a 2-year study period demonstrated an incidence of 19 cases per 100,000 patient-years.[9] These results showed similar, although somewhat higher, incidence than the French population-based study.[4] In a total of 96 patients (56% females), DILI was caused by a single prescription medication in 75% of the cases, dietary supplements in 16% of the cases, and multiple agents in 9%.[9] The median duration of therapy was 20 days (range, 8-77); 27% and 23% were hospitalized for a median of 5 days (range, 2-8), and 1 patient died as a result of the liver

Abbreviations: DILI, drug-induced liver injury; GPRD, General Practice Research Database; HDS, herbal and dietary supplements; NSAIDs, nonsteroidal anti-inflammatory drug.

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TABLE 1 Incidence and Outcomes of DILI in Western Patients

	Iceland[9]	France[6]	United States[3]	Spain[1]
Recruitment method	Prospective population-based	Prospective population-based	Prospective registry	Prospective registry
Years of study	2010-2012	1997-2000	2003-2007	1994-2004
Number of cases	96	34	300	461
Duration of patient follow-up	13 months	–	6 months	6 months
% female	56%	65%	60%	49%
% died (liver-related death)	11.5% (9.1%)	5.8% (100%)	8% (44%)	5.2% (75%, including transplants)
Major implicated agents	Antibiotics, antiinflammatory drugs, NSAIDs, and HDS	Antibiotics, psychotropic drugs, hypolipidemic agents, and NSAIDs	Antibiotics, central nervous system agents, and HDS	Antibiotics, central nervous system agents, NSAIDs

Abbreviation: NSAIDs, nonsteroidal anti-inflammatory drug; HDS, herbal and dietary supplements.

injury.[9] The most commonly implicated drugs were amoxicillin/clavulanate (22%), diclofenac (6%), azathioprine (4%), infliximab (4%), and nitrofurantoin (4%).

For most drugs used in clinical practice, *idiosyncratic* DILI is rare. In previous review articles on DILI, the frequency of DILI has ranged from 1 per 10,000 to 1 per 100,000 of those exposed—or even lower risk for many drugs.[10-12] However, except within the scope of clinical trials, the individuals exposed to drugs in the general population are unknown. Thus, the denominator of drug exposure has been largely unknown, and the true incidence of DILI has not been provided. Some previous retrospective studies have attempted to define the absolute and relative risk of DILI associated with use of drugs.[4,13,14] These pharmacoepidemiologic studies have tried to quantify the absolute risk of DILI among those who are exposed to specific drugs (data obtained from the GPRD) in the United Kingdom.[4,13] A computerized search was performed in the GPRD to identify patients who were referred to a consultant or hospitalized for a liver-related diagnosis. Retrieved cases were then reviewed manually.[4] The most frequently implicated agents were chlorpromazine, amoxicillin/clavulanic acid, flucloxacillin, macrolides, tetracyclines, metochlopramide, chlorpheniramine, betahistine, sulphasalazine, azathioprine, diclofenac, and antiepileptics. The highest crude incidence rates were found for chlorpromazine, 1 per 739 users; followed by azathioprine, 1 per 1103 users; sulphasalazine, approximately 1 per 1000 users; and amoxicillin-clavulanate, 1 per 11,688 users. The limitations of this study included its retrospective nature, lack of complete diagnostic workup, and unavailable medical records for those who died.[4] Finally, drugs purchased over the counter and agents such as herbal and dietary supplements (HDS) were not recorded systematically.[4] In the Icelandic study, all patients fulfilling the predefined criteria were connected to a nationwide pharmaceutical database (Icelandic Medicines Registry) and to a hospital pharmaceutical database that record all prescriptions issued outside hospitals and within hospitals in Iceland, respectively.[9] These pharmaceutical databases allowed the investigators to assess the risk of DILI among all users of these drugs during the study period. The results revealed much higher incidence rates for DILI than were previously reported. The highest risks for individual agents were 1 out of 133 for azathioprine and 1 out of 148 for infliximab.[9] The risk of DILI was also found to be 1 per 2350 users of amoxicillin/clavulanate.[9] The incidence rates for amoxicillin/clavulanate were higher among inpatients, 1 per 729 users versus 1 per 2350 among outpatients. Although this probably reflects more routine testing of liver biochemistry in the hospital, it cannot be ruled out that sicker patients might be more vulnerable to the potential hepatotoxicity of the drug.

Summary

DILI has become increasingly prevalent among Western patients, showing incidence to be 14 per 100,000 and 19 per 100,000, respectively, in prospective studies. Much higher incidence rates of DILI associated with the use of individual drugs have recently been demonstrated than previously reported.■

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