Outcome of Acute Idiosyncratic Drug-Induced Liver Injury: Long-Term Follow-up in a Hepatotoxicity Registry

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A chronic adverse reaction may occur in some instances of drug-induced liver injury (DILI), even despite drug cessation. In our study, we obtained records from a Spanish registry and evaluated cases of DILI with biochemical evidence of long-term damage. Chronic outcome was defined as a persistent biochemical abnormality of hepatocellular pattern of damage more than 3 months after drug withdrawal or more than 6 months after cholestatic/mixed damage. Data on 28 patients with a chronic clinical evolution (mean follow-up 20 months) between November 1995 and October 2005 were retrieved (18 female; overall mean age 55 yr) and accounted for 5.7% of total idiosyncratic DILI cases (n = 493) submitted to the registry. The main drug classes were cardiovascular and central nervous system (28.5% and 25%, respectively), which, in contrast, represented only 9.8% and 13%, respectively, of all DILI cases. The most frequent causative drugs were amoxicillin–clavulanate (4 of 69 cases), bentazepam (3 of 7 cases), atorvastatin (2 of 7 cases), and captopril (2 of 5 cases). Patients with cholestatic/mixed injury (18 of 194 cases [9%]) were more prone to chronicity than patients with hepatocellular injury (10 of 240 cases; P < .031). In the case of chronic hepatocellular injury, 3 patients progressed to cirrhosis and 2 to chronic hepatitis. In the cholestatic/mixed group, liver biopsy indicated cirrhosis in 1 patient and ductal lesions in 3 patients. In conclusion, cholestatic/mixed type of damage is more prone to become chronic while, in the hepatocellular pattern, the severity is greater. Cardiovascular and central nervous system drugs are the main groups leading to chronic liver damage. (HEPATOLOGY 2006;44:1581-1588.)
The hepatotoxic potential of common therapeutic drugs, along with herbal remedies and dietary supplements, is widely recognized as an increasingly important health problem. Illustrating this issue, drugs (excluding paracetamol) account for 13% to 17% of cases of acute liver failure, and hepatotoxicity remains the leading cause for regulatory measures after drug approval. An unresolved issue is the identification of patients who are more susceptible to this unpredictable, idiosyncratic form of injury.

The consequences of drug-induced liver injury may be devastating, leading to death or liver transplantation. Recently, two studies reported that variables such as female sex, hepatocellular damage, total bilirubin, and aspartate aminotransferase levels were associated with fulminant liver failure and were strongly predictive of short-term outcome. Complete recovery following the drug’s withdrawal appears to be the rule in less-severe cases of drug-induced liver injury. However, despite cessation of the drug, chronic liver injury including cirrhosis may ensue in a relatively small number of cases. There is a dearth of prospective studies with a long-term follow-up and, hence, data on chronic damage is scarce and often based on anecdotal individual reports or series containing limited numbers of cases. The impact of persistent damage with respect to physical and psychological disability—as well as the need for long-term surveillance in these patients—is at present unknown. Furthermore, the type of hepatic reactions that are more likely to become chronic, and the factors underlying such an outcome, remain to be elucidated.

In a recent retrospective study of a small series of patients with idiosyncratic hepatotoxicity (mainly due to the administration of antibiotics and nonsteroidal anti-inflammatory drugs) who had received a liver biopsy, approximately one third (13 of 33) showed signs of chronic liver disease (evidenced by biochemical and/or scan abnormalities). These cases have been scrutinized long after the initial clinical presentation. However, because the design of the study had not excluded concurrent diseases, the high frequency of chronic sequelae might be an over-representation.

In our study, we analyzed cases of idiosyncratic liver injury recorded in a registry of hepatotoxicity. The cases selected had biochemical evidence of long-term damage. We attempted to characterize patterns of damage that would appear to be more prone to chronic clinical evolution and assessed the drugs and host-dependent risk factors that may have been associated with this outcome.

**Patients and Methods**

Cases of chronic idiosyncratic liver disease were selected from those submitted to the Registry of Hepatotoxicity in Southern Spain since its foundation in April 1994, and coordinated by two of the present authors (R. J. A. and M. I. L.). The operational structure of the registry, data recording, and case ascertainment has been reported elsewhere.

Cases of hepatocellular pattern of damage were defined as chronic if liver tests showed persistent abnormality more than 3 months after stopping drug therapy. In the case of cholestatic/mixed type of injury the abnormality needed to be persistent for more than 6 months following drug withdrawal. Cases were defined as having been resolved when liver tests values returned to within laboratory reference ranges within this time period. Outcomes were assessed by clinical, laboratory, and imaging tests together with liver histology when available.

A detailed history was obtained from all patients regarding antecedents of liver or biliary tract disease, drug addiction, and alcohol abuse, transfusion of blood products, or surgery within the 6 months preceding the onset of hepatitis. A thorough check for present and previous use of drugs, herbal remedies, and over-the-counter medications was performed by questioning patients and relatives. A structured report form was used to record the patient’s data, the details of which relate to: (1) the time lapse between the commencement of the medication and the onset of the liver disease, and between the discontinuation of suspected agent and improvement in, or recovery from, liver dysfunction; (2) serology and specific biochemistry to rule out viral hepatitis, autoimmune and metabolic liver disorders, and appropriate imaging tests to exclude bile duct disease; (3) the presence of known risk factors of hepatotoxicity such as pregnancy, alcohol intake (measured as standard drink units of 10 g for all alcohol-containing beverages); and (4) the outcome of the liver damage. Only cases considered as being drug-related according to the clinical judgment of experts were then assessed using the Council for International Organizations of Medical Sciences (CIOMS) scale, and only when the cases were classified as definite or highly probable, probable, or possible were the data incorporated into the database.

Excluded from the present analyses were cases of hepatic damage that were clearly secondary to drug overdose (acetaminophen), those resulting from occupational exposure to toxins, and patients with an underlying liver disease. Patients who presented with a chronic outcome were considered eligible only if they scored as “definite or probable.”
The pattern of liver injury and the chronological relationship between the drug and the onset of hepatitis were defined according to the criteria of the International Consensus Meeting for Drug-induced Liver Injury (DILI). Liver damage was based on liver biopsy findings, when available. The drugs considered to be implicated in the liver damage were classified according to the Anatomical Therapeutic Classification of the World Health Organization—Europe. Cases were considered immunoallergic in nature if they presented with any of the classical clinical or laboratory features of allergy (fever, rash, serum eosinophilia, cytopenia, or detectable titers of autoantibodies) and/or there were accompanying histopathological findings (eosinophil-rich inflammatory infiltrate and/or granuloma formation). In the remaining cases, the mechanism was presumed to be metabolic idiosyncrasy.

The control group used for comparison purposes contained a cohort of cases recorded in the registry in whom symptoms and biochemical abnormalities were resolved within 3 months for hepatocellular injury (\(n = 230\) cases) and within 6 months for cholestatic/mixed injury (\(n = 176\) cases), respectively. This acute outcome group totaled 406 patients. In 17 patients there was insufficient follow-up to ascertain outcome: 4 patients were lost to follow-up, the attending physician was unable to report final data on 8 cases, and 5 patients were still recovering from the index episode.

Excluded from the analyses were those patients who had died within the time period established for chronic disease status (\(n = 24\)), had fulminant liver failure at presentation (\(n = 18\)), or had insufficient follow-up (\(n = 17\)). The study protocol was approved by the Local Ethics Committee of the Co-ordinating Centre at the Virgen de la Victoria University Hospital in Málaga.

Data were analyzed with SPSS version 12.0 for Windows. Variables were examined using descriptive statistics. Bivariate associations were measured using Student t test for continuous variables and chi-square test for categorical items. ANOVA was used for comparisons of groups. Nonparametric analyses (Kruskal-Wallis test) were performed when variables followed a nonnormal (skewed) distribution. Differences were reported as statistically significant if the P value was less than .05.

**Results**

There were 28 patients (mean age 55 yr) with a chronic clinical evolution (mean follow-up 20 months [range 5-74]) of whom 18 were women reported between November 1995 and October 2005. These accounted for 5.7% of the total cases of toxic liver damage submitted to the registry (\(n = 493\)). CIOMS ratings generated for 32 drugs (in 4 cases there was more than 1 drug implicated) were classified as definite in 15 (47%) and probable in 17 (53%) cases; 4 cases were excluded because they did not fulfill the time lapse criteria with 2 cases having features of autoimmune hepatitis which improved following the introduction of corticosteroids.

Cholestatic/mixed type of damage (18 of 194 cases [9%]) was more prone to chronic outcome than hepatocellular injury (10 of 240 cases [4%]; \(P < .031\)). Clinical and biochemical details of these patients are summarized in Table 1 (hepatocellular damage cases) and Table 2 (cholestatic/mixed cases). Of the 10 cases with chronic hepatocellular type damage, 8 underwent a liver biopsy, 3 had cirrhosis (1 subsequently underwent liver transplantation), and 2 had chronic hepatitis. The case of chronic hepatitis attributed to bentazepam (case 4, Table 1) showed inflammatory infiltrate in portal tracts, piecemeal necrosis, bile duct proliferation, and extensive portal-to-portal fibrosis delineating occasional regenerative nodules. The case attributed to diclofenac (case 5) showed portal inflammatory infiltrate with piecemeal necrosis and moderate portal fibrosis with disruption of the lobular architecture. All but 1 of the cases developed jaundice. Hypersensitivity features or positive titers of autoantibodies were detected in 4 cases. The episode could be ascribed to a single drug except for 1 case in which 2 drugs had been administered simultaneously. Complete normalization of liver tests was achieved only in 1 patient after 26 months of follow-up. Of note, 2 patients in the hepatocellular-type injury group who had a slight increase in serum bilirubin (case 3) or a minimally raised \(\gamma\)-glutamyltranspeptidase (case 8) at the end of follow-up had cirrhosis and portal hypertension. It took 12 and 4 months, respectively, for alanine aminotransferase values in these patients to return to within the laboratory reference range.

In the protracted cholestatic/mixed cases, only 1 of the 7 patients biopsied had cirrhosis. There were 3 patients with ductal lesions (1 bile duct proliferation, 1 mild ductopenia, and 1 vanishing bile duct syndrome). In 3 cases, 2 putative culprit drugs were noted and, hence, the episode was ascribed to both drugs. Recovery was achieved in 3 cases after a mean follow-up of 15 months.

In none of the patients with histological evidence of chronic damage could an alternative etiology be found despite an appropriate workup. Furthermore, in 2 hepatocellular cases with cirrhosis, baseline liver tests values were within the reference range. In the remaining case of a young female in whom cirrhosis was attributable to ebrotidine, baseline liver tests were unavailable, but there was no clinical or sonographic evidence of chronic liver disease or portal hypertension. In addition, neither risk factors nor echographic evidence of nonalcoholic fatty
Liver disease was found in the 2 patients in this group who had not undergone a liver biopsy.

In 6 of 10 cases of hepatocellular damage, continued exposure to the putative drug was documented despite the development of symptoms of DILI over a median period of 23.5 days (range 1-127 d); 1 patient was documented to have increased aminotransferases as well. However, the patient who continued taking the drug for a longer period (127 d) recovered. Similarly, 10 of 18 patients (56%) with cholestatic/mixed damage continued the drug after the symptoms had appeared (median 36 d [range 1-620 d]). Of note, 2 patients in whom the drugs were inappropriately used continued taking the drug for a longer period (127 d) and recovered. Similarly, 10 of 18 patients (56%) with cholestatic/mixed damage continued the drug after the symptoms had appeared (median 36 d [range 1-620 d]).

### Table 1. Clinical Details and Biochemical Parameters of the 10 Patients With Hepatocellular Damage Who Developed Chronic Idiosyncratic Hepatotoxicity

<table>
<thead>
<tr>
<th>Case No.</th>
<th>Sex/Age, yr (BMI)</th>
<th>Drug Present</th>
<th>Duration of Therapy (d)</th>
<th>Time to Onset (d)</th>
<th>Biochemical Variables Index Episode/End Follow-Up</th>
<th>Pattern of Hepatitis</th>
<th>Outcome (Follow-Up)</th>
<th>Comments*</th>
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<tr>
<td>1</td>
<td>F/53</td>
<td>Captopril</td>
<td>8</td>
<td>8</td>
<td>TB&lt;sub&gt;0&lt;/sub&gt;/TB&lt;sub&gt;1&lt;/sub&gt; (mg/dL) 18/1.4</td>
<td>10.4/2.5</td>
<td>1.4/2.0</td>
<td>12.5/9.6</td>
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<tr>
<td>2</td>
<td>F/51 (26)</td>
<td>Bentazepam</td>
<td>28</td>
<td>152</td>
<td>ALT&lt;sub&gt;0&lt;/sub&gt;/ALT&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 0.8/0.5</td>
<td>7.7/0.7</td>
<td>0.9/1</td>
<td>3.0/1.9</td>
</tr>
<tr>
<td>3</td>
<td>F/55</td>
<td>Ebrotidine</td>
<td>58</td>
<td>59</td>
<td>ALP&lt;sub&gt;0&lt;/sub&gt;/ALP&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 10.6/0.8</td>
<td>71.1/0.7</td>
<td>1.6/1.1</td>
<td>9.8/1.1</td>
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<td>4</td>
<td>F/60</td>
<td>Bentazepam</td>
<td>150</td>
<td>277</td>
<td>GGT&lt;sub&gt;0&lt;/sub&gt;/GGT&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 4.6/0.7</td>
<td>26.3/0.4</td>
<td>0.6/0.8</td>
<td>6.7/0.5</td>
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<td>5</td>
<td>F/56</td>
<td>Diclofenac</td>
<td>700</td>
<td>743</td>
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<td>39.8/0.8</td>
<td>3.5/1.1</td>
<td>7.8/3.6</td>
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<tr>
<td>6</td>
<td>M/56 (28)</td>
<td>Irbesartan</td>
<td>5</td>
<td>8</td>
<td>TB&lt;sub&gt;0&lt;/sub&gt;/TB&lt;sub&gt;1&lt;/sub&gt; (mg/dL) 9.6/1.2</td>
<td>60.3/0.5</td>
<td>2.4/0.8</td>
<td>6.3/2.3</td>
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<td>M/41 (28)</td>
<td>Amoxicillin-</td>
<td>35</td>
<td>5</td>
<td>ALT&lt;sub&gt;0&lt;/sub&gt;/ALT&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 10.2/11.8</td>
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<td>F/69 (25)</td>
<td>Ebrotidine</td>
<td>366</td>
<td>366</td>
<td>ALT&lt;sub&gt;0&lt;/sub&gt;/ALT&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 18.5/1.8</td>
<td>14.0/0.5</td>
<td>2.2/0.5</td>
<td>2.0/0.3</td>
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<tr>
<td>9</td>
<td>M/35</td>
<td>Indomethacin/</td>
<td>216</td>
<td>216</td>
<td>ALT&lt;sub&gt;0&lt;/sub&gt;/ALT&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 1.8/1.4</td>
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<tr>
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<td>M/60 (28)</td>
<td>Clopidogrel</td>
<td>6</td>
<td>27</td>
<td>ALT&lt;sub&gt;0&lt;/sub&gt;/ALT&lt;sub&gt;1&lt;/sub&gt; (&lt;x&gt;ULN) 6.9/9</td>
<td>47.9/2</td>
<td>2.5/1.8</td>
<td>26.4/19.8</td>
</tr>
</tbody>
</table>

ALT values are those at presentation, whereas TB values are the peak.

*Hypersensitivity features include presence of fever, rash, and/or eosinophilia.

†Liver biopsy (time after presentation).

Abbreviations: BMI, body mass index; TB, total bilirubin; ALT, alanine aminotransferase; ALP, alkaline phosphatase; GGT, gamma-glutamyltranspeptidase; TB/ALT/ALP/GGT, initial values at index episode; TB/ALT/ALP/GGT<sub>1</sub>, values at end of follow-up; <x>ULN, multiples of the upper limit of normal.
ate continued for 125 and 620 days ultimately resolved following drug withdrawal. The other patient who had resolved had received the drug for 7 days after the symptoms had appeared.

Comparisons of the demographic characteristics and clinical and laboratory findings according to the type of liver injury are summarized in Table 3. Patients with the cholestatic-type injury were older (P < .028). Most patients in the hepatocellular injury group presented with jaundice (90%), and required hospitalization (80%). The only case that required liver transplantation belonged to this group. Jaundice was less frequent in the cholestatic/mixed group (61%). A chronic course was evident in the hepatocellular cases after a mean follow-up time of 14 months, while the corresponding figures for the cholestatic and mixed cases were 28 and 17 months, respectively. The duration of treatment did not differ between chronic and self-limited cases, in either the hepatocellular or cholestatic/mixed groups.

Segregation of the data according to outcome did not reveal any demographic, clinical, or laboratory findings that were predictive of a chronic evolution.

### Therapeutic Groups Involved in Chronic Damage.

The main pharmacological groups of drugs involved in chronic damage (Table 4) were cardiovascular (28.5%) (encompassing angiotensin-converting enzyme inhibitors, angiotensin II inhibitors, statins, and fibrates) and central nervous system drugs (25%), followed by anti-
infectious (21%), musculoskeletal medications (14%), and gastrointestinal drugs (11%) (represented by histamine 2 antagonists). In contrast, the cardiovascular drug group (n/H11005/40) represented only 9.8% of all self-limited DILI cases, whereas anti-infectious (n/H11005/134 [33%]), musculoskeletal (n/H11005/56 [14%]), and central nervous system (n/H11005/54 [13%]) were the most prevalent therapeutic groups with acute self-limited outcomes.

The drugs most frequently associated with a chronic outcome were amoxicillin–clavulanate (4 of 69 cases), bentazepam (3 of 7 cases), atorvastatin (2 of 7 cases), captopril (2 of 5 cases), and ebrotidine (2 of 22 cases).

**Discussion**

DILI can be severe in the short-term. Despite a few anecdotal reports or case series describing instances of chronic liver disease despite withdrawal of the culprit drug, data on the long-term outcome of DILI is scarce.
This study represents the largest prospective follow-up of toxic idiosyncratic liver injury patients with long-term abnormalities of liver tests. The cases were drawn from a Spanish registry of hepatotoxicity\(^3\) which included almost 500 patients and which was not restricted to specific agents. Thus, the data provide an overview of the problem as encountered in standard clinical practice while minimizing the risk of selection bias typical of retrospective analysis of case records.

Our definition of chronic DILI follows the International Criteria\(^10\) which defines chronic liver injury as abnormal liver tests for a period of more than 3 months. Other investigators have suggested that this period should be 6 months.\(^15\) Evidence from several case reports\(^16-18\) and general consensus suggest that cholestatic/mixed lesions subside slower than hepatocellular injury. To alleviate this concern, we analyzed the two types separately. Indeed, the dechallenge scoring of the CIOMS/Roussel Uclaf Causality Assessment Method scale\(^9\) has a very different time sequence related to the type of damage (1 month for hepatocellular injury and up to 6 months for the cholestatic/mixed type damage). One concern is reliance on CIOMS/Roussel Uclaf Causality Assessment Method score (definite or probable) for inclusion of chronic cases, because such criteria might weigh against attribution to the culprit drug. However, in contrast to the situation in fulminant cases, which continue to worsen from the presentation, chronic cases received a high score because of an initial improvement once the drug was removed.

Our surveillance period, although uneven, far exceeded the cut-off time period used in the definition of chronic status in the majority of patients. Importantly, the liver tests were near normal in two patients in whom cirrhosis and portal hypertension developed. This suggests that the true incidence of chronic liver injury as sequelae of idiosyncratic hepatocellular liver damage could be underestimated if only laboratory parameters are used as markers of persistent disease (e.g., severe chronic inactive hepatic disease may be present).\(^7\) A liver biopsy was performed in 8 of the 10 patients in the group with hepatocellular-type injury. The histological results indicated cirrhosis in 3 cases and chronic hepatitis in 2 cases. Of note, in the latter 2 cases, the liver biopsy specimens were obtained at 1 and 2 months after clinical presentation of liver damage and do not represent end-of-follow-up assessment; the aminotransferases returned to within the reference range values in these 2 cases at 9 and 3 months, respectively.

The severity of the chronic outcome in this expression of hepatotoxicity is thus unquestionable, because underlying cirrhosis could confidently be excluded in our series of patients. Two cases of cirrhosis were related to ebrotilidine (a histamine 2 receptor antagonist), the use of which has been discontinued in Spain since 1998 because of its hepatotoxic potential.\(^19\) A rapid progression to cirrhosis has been reported in ebrotilidine-associated hepatotoxicity.\(^5\) The third case of cirrhosis in our group of patients with hepatocellular damage was related to unintentional re-exposure to amoxicillin–clavulanate. The only instance of cirrhosis in the cholestatic/mixed group involved a case of tamoxifen-associated hepatotoxicity with voluntary positive rechallenge.

The long-term prognosis in patients with chronic severe toxicity-associated liver damage is at present unclear. However, our findings support the need for regular follow-up of these patients because of clinical, psychological, and legal implications.

A chronic outcome of DILI is more difficult to prove in the hepatocellular-injury group, because the residual alanine aminotransferase abnormalities might reflect a baseline impairment resulting from a common underlying condition in the adult population such as nonalcoholic fatty liver disease. However, the culprit drugs more likely to be prescribed for subjects with risk of nonalcoholic fatty liver disease, such as statins and antihypertensive agents, induced a cholestatic or mixed pattern of chronic damage rather than hepatocellular injury; the only exception was a patient who had hepatocellular injury related to the intake of irbesartan. This patient had an isolated increase in γ-glutamyltranspeptidase at the end of follow-up (15 months), whereas elevated alkaline phosphatase was noted 12 months after presentation (data not shown). This tendency of some hepatocellular injury cases to convert to cholestatic-type pattern during the follow-up is a curious finding of the present study for which we do not have a clear explanation but may be related to the differences in the faster rate of improvement of alanine aminotransferase versus alkaline phosphatase or γ-glutamyltranspeptidase following drug withdrawal.

Approximately 40% of patients in the overall series showed hypersensitivity features, with no significant differences between hepatocellular and cholestatic/mixed patterns of injury. Interestingly, in a large cohort of patients with drug-induced idiosyncratic liver disease,\(^20\) a link between HLA class II and cholestatic/mixed injury has been reported. This would suggest that the majority of cholestatic/mixed injury cases may have a genetically based allergy component. This is less certain in hepatocellular injury cases with hypersensitivity features.\(^21\)

In approximately 60% of the hepatocellular and cholestatic/mixed cases in our series, continued exposure to the drug was documented after the onset of symptoms. Continuing therapy with a hepatotoxic drug that causes jaundice was suggested by Zimmerman\(^22\) to be an important risk factor in the development of acute liver failure, a
proposition which has been confirmed by others.23 However, this factor was also predictive of persistence of liver test abnormalities in the study of Aithal and Day7 and highlights the importance of prompt cessation of drug therapy in cases of suspected DILI. Of further note is that central nervous system and cardiovascular therapeutic groups were more frequently represented among chronic cases than self-limited cases. Thus, bentazepam, captopril, and atorvastatin more frequently lead to chronic liver damage. Awareness of drugs that are more likely to cause chronic damage should be considered in determining follow-up after DILI has been recognized and use of the drug has been discontinued.

In conclusion, cholestatic and mixed-type damage in drug induced liver injury are more prone to a chronic outcome than hepatocellular-type injury, albeit the severity appears to be greater in the latter. Drugs prescribed for cardiovascular disease and central nervous system disorders are more prone to lead to a chronic outcome of DILI. A more detailed prospective study on the natural history of DILI by our collaborative group of investigators is currently underway.

References