

# A focus on epidemiology of drug-induced liver injury: analysis of a prospective cohort

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**Abstract.** – **OBJECTIVE:** Drug-induced liver injury (DILI) is more often a challenge even for expert clinicians. Presently, there are limited data about the epidemiology, because the real incidence and prevalence of the disorder are underestimated, and further, sometimes the pharmacovigilance chain is unsuccessful as cases are largely underreported. We review available literature data and discuss our clinical experience regarding a prospective cohort of 185 patients with a diagnosis of DILI.

**MATERIALS AND METHODS:** Significant papers were identified by literature search, and selected based on content including the epidemiology of DILI. By analyzing our prospective cohort, consecutively collected since January 2000 to December 2016 at our tertiary referral center for liver disease, we report the frequency of different drug classes involved in DILI and their related clinical outcomes.

**RESULTS:** In our cohort of 185 patients, 56% were females and 44% males; the mean age was 53 years, even if about 70% of patients were 40 years old; only 2% had a previous chronic liver disease. At clinical presentation, 57.8% showed a hepatocellular pattern, whereas 18.3% a cholestatic and 23.2% a mixed one. Antibiotics were involved for 23.4%, NSAIDs for 35.5%, immunosuppressants for 10.9%, statins for 4.3%, anti-platelets and anti-psychiatric drugs for 7.6%, and other drugs for 9%. Regarding the evolution, antibiotics, NSAIDs, and immunosuppressant were frequently responsible for chronicity, whereas statins, anti-psychiatric and anti-platelets drugs were not.

**CONCLUSIONS:** In this review, we discuss our clinical experience in the field of DILI, in which many efforts are required to reinforce the attention of a physician to the possibility that a patient with the acute liver disease could be diagnosed as a patient with DILI.

Key Words:

Drug hepatotoxicity, Epidemiology, DILI, Prospective cohort.

for acute liver failure (ALF), and, consequently, urgent liver transplant<sup>1</sup>. Although the American College of Gastroenterology (AGA) yielded guidelines on Diagnosis and Management of Idiosyncratic Drug-Induced Liver Injury (DILI)<sup>2</sup>, providing indications regarding clinical presentation, diagnosis, and management of DILI, the European Countries are yet to formulate appropriate rules. Because the diagnosis is still of exclusion, another important help comes from the use of website. The Liver Tox website (available at <http://livertox.nlm.nih.gov>) is an useful help for the diagnosis of DILI. It provides information on documented hepatotoxicity of certain drugs, herbal remedies and dietary supplements (HSD). In Europe, many projects are going on with the final proposal of formulating appropriate guidelines to help clinicians in the management of this still-debated issue.

Potentially, all drugs can be involved, but liver damage is commonly caused by antibiotics, NSAIDs, statins, anti-platelets, immunosuppressants and HSD. However, liver injury caused by drugs is the most frequent cause of failure entry in the marketing phase, because the drug is blocked among preclinical stages of experimental trials, or withdrawn in the post-marketing phase<sup>1,3,4</sup>.

In this review, we aim to focus our attention on the main epidemiological data of DILI available from the literature. Moreover, we wish to share our clinical experience, which we experienced in a single tertiary referral center of chronic liver disease since January 2000, in which we prospectively collected a cohort of almost 185 patients, who have been diagnosed as suffering from DILI and whose clinical outcomes were recorded. By an epidemiological point of view, we analyzed this prospective cohort aiming to assess the frequency of usage of different drug classes involved in DILI.

## Introduction

Drug induced liver injury (DILI) is not a common condition, which sometimes is responsible

## Definition of Dili, Clinical Approach and Prognosis

DILI is defined as liver damage caused by drugs, dietary supplements and herbal products, at

normal dose<sup>1</sup>. It is a diagnosis of exclusion, made when all common causes of liver damage are ruled out.

In 1989, in Paris, an international meeting of experts (CIOMS – Council of International Organization of Medical Scientists), in an attempt to define liver damage induced by drugs, considered referral parameters: the increase of aminotransferases (ALT/AST), alkaline phosphatase (AP) and bilirubin of at least 2 times the normal value. After this, Roussel Uclaf Causality Assessment Method (RUCAM)<sup>5</sup> scores introduced the concept of latency as the temporal relationship between drug intake and clinical presentation; the dechallenge as the clinical course after drug discontinuation, and finally, the rechallenge as the reiteration of drug<sup>6,7</sup>. Following this, Maria & Victorino added parameters of exclusion of alternative causes and the presence of coexistent extrahepatic and immune-allergic manifestations<sup>8</sup>. Finally, in 2011, criteria for diagnosis of DILI were upgraded and revised, the cut-off of aminotransferases have been increased up to 5 times the upper normal limit, of alkaline phosphatase (AP) up to 2 times its normal limit, or with a combination of 3 times normal for ALT e and 2 times for total bilirubin<sup>9</sup>.

According to the Guidelines of American College of Gastroenterology (ACG) of 2014, the diagnosis is made by evaluating the alteration of liver enzymes, clinical history and physical examination of the patient. The pattern of liver injury assessed by the ratio  $R = (ALT/UNL)/(ALP/UNL)$  allows us to define if the DILI has a hepatocellular pattern ( $R > 5$ ), a cholestatic pattern ( $R < 2$ ) or a mixed pattern ( $2 < R < 5$ )<sup>2</sup>.

The diagnosis is provided through a detailed evaluation of serological, instrumental and histological aspects, as well. To assess the patient with DILI, biochemically we usually need to know: 1. Liver function tests (LFTs) allow to assess hepatocellular, cholestatic and mixed liver injury; 2. Extra-hepatic manifestations such as pruritus, rash, fever, and eosinophilia; 3. Mayor hepatotropic viruses (HAV, HBV, and HCV) and possibly minor (CMV, EBV, and HSV); 4. Non-organ specific autoantibodies (ANA, AMA, ASMA, and LKM). To complete the diagnostic evaluation, we need to perform imaging investigation such as abdominal ultrasound, liver stiffness measurement by TE, and finally, a liver biopsy that still represents the golden standard to definitely assess liver damage by drugs (fibrosis, steatosis, necroinflammation, granulomas, lipofuscin, and cholestasis). Sometimes, computed tomography (CT) scan and

magnetic resonance (MR) could help in the diagnosis<sup>2-10</sup>. Assessment of DILI patient is reported in Figure 1.

Clinical course is varying by asymptomatic disease (diagnosis made as a result of examinations routinely performed) to acute clinical presentation with typical symptoms such as jaundice, acholic stools, itching, malaise, nausea, skin rash and in most severe cases signs of hepatic encephalopathy, altered coagulative parameters which can lead to death or need for an urgent liver transplant.

According to the indications for transplantation, fulminant hepatitis is the highest priority (status 1) requiring transplantation within hours and organ allocation of National basis. Actually, ALF due to drugs (paracetamol and non-paracetamol related, nimesulide, NSAIDs) represents the most frequent cause of liver transplant in the USA and European Countries<sup>11</sup>.

The prognosis is generally good, and only 10% have ALF with coagulopathy and encephalopathy. In these rare cases, the prognosis results are poor, with a need for transplantation in 40% of cases or death of the patient<sup>2</sup>.

### Epidemiology of DILI

Despite a low incidence, the probability of DILI should always be considered when there is an acute liver injury, and all other possible etiologies have been excluded.

DILI incidence according to previous published data was between 1 in 10,000 and 1 in 100,000. However, more recent studies<sup>1-12</sup> reported a higher incidence. There are several registries both in Western<sup>13-16</sup> and in Asian<sup>17</sup> countries, which have provided useful information as regards the etiology, pathogenesis as well as the clinical presenta-

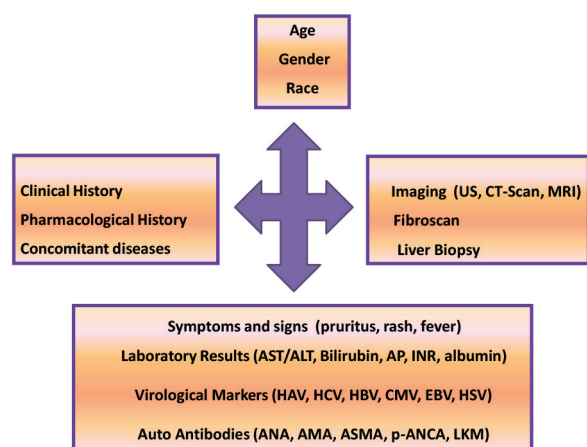


Figure 1. Clinical assessment of DILI.

tion, diagnosis, and management of DILI. Some population studies, in fact, have shown an annual incidence of 19.1 cases per 100,000 inhabitants in Iceland<sup>16</sup>, and of 13.9 cases per 100,000 inhabitants in France, with hospitalization of 12% and mortality of 6% (500 deaths per year in French general population)<sup>14</sup>. Several drugs potentially cause a DILI, but the most frequently involved are antibiotics, which according to the DILI Network in the USA, represents about 46% of the DILI cases<sup>18</sup>; similar results have been stemmed from Spanish and Icelandic registries<sup>15,16</sup>.

In an Italian case-control study the annual incidence of DILI was 4.1 cases per 100,000 inhabitants. About half of the patients received NSAIDs. These data are partially in agreement with Swedish and English studies and with the population based studies from Björnsson et al<sup>16</sup> and Sgro et al<sup>14</sup>. Probably, these results reflect some differences between the study methodology: some used database of primary source information, whereas others were based on participation of specialists; another difference was the type of patients recruited (in- or outpatients) and the period of recruitments, ranging from 2 to 10 years<sup>19</sup>.

There are few studies and reports pertaining to some drugs, for some others an extensive literature is available. There also occurs an ethnic difference, for example, in India drugs more involved in episodes of DILI are the anti-tuberculosis drugs (58%), followed by anti-epileptics (11%). In addition, the mortality associated with anti-tubercular drugs is 2 times greater than other medications<sup>20</sup>. Differences are also connected with the registration and the prescription of drugs in different parts of the world<sup>21</sup>, because some drugs are more frequently used in some parts than in others. From a database of general practitioners in the United Kingdom (General Practice Research Database – GPRD), which assessed a large population between 1994 and 1999, the risk of DILI appears to be more than 100 of 100,000 cases for isoniazid and chlorpromazine; more than 10 cases of 100,000 for amoxicillin-clavulanic acid and cimetidine; and fewer than 10 cases per 100,000 for other drugs<sup>22</sup>.

The elderly are more affected than the youth, probably because they receive multiple drugs, have low tolerability and low compliance to therapy<sup>23,24</sup>. DILI is also frequent in children owing to high use of antibiotics in childhood. As for gender, women are more affected than men. There is also a difference by socio-economic status, and the wealthier classes are affected more because

of the spread of HSD, which should be purchased via Internet without any prescription or medical supervision. The use of supplements, hormonal products, is frequent among body builders who gym. Particular attention must be given to pregnant women whose use of certain drugs may be deleterious. According to the Food and Drug Administration (FDA), drugs are divided into different categories (A, B, C, D, X) based on the potential damage caused by them (drugs of X category must be avoided)<sup>25</sup>. There is also an increased use of HSD in pregnant women, which are considered as natural and safe to use, but sometimes harmful and even abortive.

### ***Analysis of a Prospective Cohort***

In our tertiary referral center, we evaluated a cohort of 185 patients, in the time period between January 2000 and December 2016, with the diagnosis of DILI according to ACG Guide Lines. The patients, mostly hospitalized, were regularly followed after discharge at 3 months intervals for at least the first year.

Of the 185 patients, (104/185) 56% were females and 44% males; the mean average age was 53 years, even if about 70% of patients were 40 years old; only 2% had a previous chronic liver disease. At clinical presentation, 57.8% showed a hepatocellular pattern, 18.3% a cholestatic pattern, 23.2% a mixed one. Among the different classes of drugs, antibiotics were involved for 23.4%, NSAIDs for 35.5%, immunosuppressants for 10.9%, statins for 4.3%, anti-platelets and anti-psychiatric drugs for 7.6%, and other drugs for 9% (Table I, Figure 2). In 25% of cases, two or more drugs are involved simultaneously.

### ***Antibiotics***

Antibiotics are the class of drugs most commonly implicated in DILI, and amoxicillin-clavulanic acid appears as the major exponent. It is often associated with a cholestatic pattern caused mostly by the clavulanic component<sup>26</sup>. Usually, it affects women, aged >65 years and with reported previous use of this drug. In the clinical setting, presentations could be mild or severe, leading to ALF or urgent liver transplantation<sup>27</sup>. Another antibiotic responsible for cholestatic damage in 60% of cases, due to the sulfonamide component, is the trimethoprim sulfamethoxazole<sup>18-21</sup>.

Asymptomatic, mild and transient elevations in liver enzymes might occur in 2-3% of patients treated with fluoroquinolones, whereas jaundice and hepatitis are much less common. In addition,

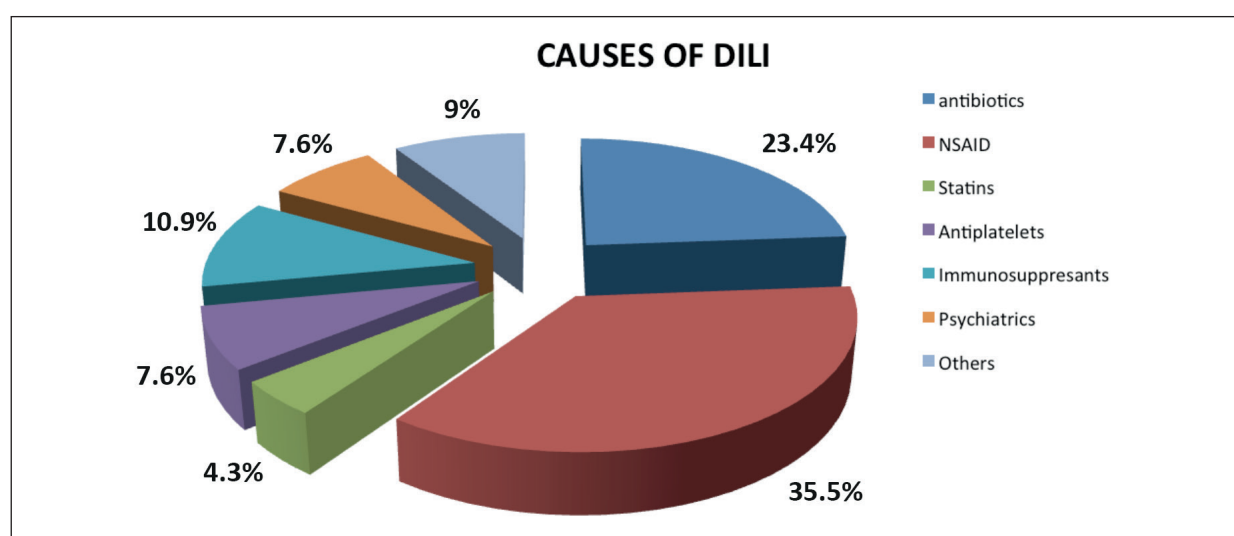
**Table 1.** Clinical features of 185 patients with drug induced liver injury seen at our tertiary referral center.

All drugs (185)	
Age	53.1 ± 17.87
Length of drug intake	51.43 ± 110.72
Sex (Males)	81 (44%)
Latency	27.9 ± 36.7
HE at diagnosis	5 (2.7%)
Jaundice	87 (47%)
Pattern of DILI	
Hepatocellular	107 (57.8%)
Cholestatic	34 (18.3%)
Mixed	43 (23.2%)
ALT	540 ± 871.7
AP	273.3 ± 315.4
Stiffness (69 pts)	11.5 ± 8.4
Chronicity	16 (%)
Days at hospital	7.8 ± 8.0
Hospitalization	
Ward	114 (%)
DH	57(%)

ALF reporting rates using FDA data per 10 million prescriptions have been found to be 2.1 for levofloxacin, 6.6 for moxifloxacin, 6.0 for gatifloxacin and 58 for trovafloxacin. The reviewed cases suggest that the phenotype and clinical presentation of liver injury due to fluoroquinolones are similar with different agents. However, some differences may be explained, at least in part, by the structural characteristics of certain molecules of quinolones. The main feature of the hepatic

damage was the short latency and rapid onset of injury. Severe hepatotoxicity usually occurred within 14 days of the start of therapy, and most cases occurred within 6 days. The reported hepatotoxic reactions showed a temporal relationship between the consumption of the culprit drug and the onset of the effects: up to 90% of the patients reported taking fluoroquinolones for a period between 1 day and 3 months, and this time period can be considered to be “suggestive” in the causality assessment according to RUCAM. Dechallenge was always positive. The occurrence of hepatotoxicity and the majority of fatal reports were significantly higher in patients more than 65 years of age. Both hepatocellular and cholestatic patterns of liver injury have been reported with fluoroquinolones. The pattern of injury was mostly hepatocellular<sup>28</sup>.

In our series, antibiotics were involved in (44/185) 23.4% of cases. Amoxicillin was alone involved in 44% of cases, plus clavulanic acid in 35%, whereas in 25.5% in combination with an NSAID; in 55% of cases was another type of antibiotic. The most common pattern reported associated with the use of antibiotics was hepatocellular in 64% of cases. Women were affected more than men (55% vs. 45%); the most affected were subjects aged more than 40-years-old (88%). Jaundice occurs in 58% of cases, ALF in 4.6%, and in all these cases encephalopathy was observed. A pre-existing chronic liver disease was present in 30% of cases. Comorbidities were present in 53.4% of cases, and other concurrent therapy in 34.8% of cases. These patients were mostly hospitalized (66%) for the severity of liver damage,

**Figure 2.** Drugs most commonly involved as causes of drug induced liver injury (DILI) in a cohort of 185 patients prospectively followed at our tertiary referral center.

with positive outcomes in 100% of cases; 14% of cases developed a chronic DILI (Figure 3).

### **NSAIDs**

NSAIDs are analgesic drugs used worldwide<sup>29</sup>. Although the most frequent adverse events are gastrointestinal, renal and cardiovascular, there is a certain percentage of idiosyncratic hepatotoxicity with serious effects, sometimes even fatal. This caused withdrawal of some drugs of this class from the market<sup>30,31</sup>. A peculiar case is that of nimesulide, which has never been marketed in some countries and withdrawn from the market in others (previously in Finland and Spain, then Ireland and Argentina)<sup>32-35</sup>. According to European Medicine Agency (EMA) although the assessment of the benefit/risk ratio of nimesulide showed a favorable profile, restrictions regarding indications, formulations and the length of treatment (maximum 100 mg twice daily) have been enforced<sup>36</sup>.

A recent Italian multicenter study found that the incidence of DILI is about 4 cases per 100,000 inhabitants, half of which is due to use of NSAIDs<sup>19</sup>. The increased risk is linked with the use of nimesulide, followed by ibuprofen and high doses of ketoprofen. NSAIDs are a class of drugs largely used, often self-managed in the indications and dosages, not always requiring a medical prescription. This leads to a high risk of adverse effects, including the risk of liver injury<sup>19</sup>.

The number of patients with elevated aminotransferases during treatment with nimesulide is increasing, and cases of fulminant and subacute hepatitis, sometimes fatal, are shown. Two different pathological patterns of nimesulide-induced DILI (i.e. hepatocellular necrosis and pure cholestasis) have been described, which seem to be related to the gender of the patient.

In our series, NSAIDs were involved in (65/185) 35.5% of cases. Nimesulide was responsible for 38.5% of cases, whereas ketoprofen for 34%, diclofenac for 15%, ibuprofen for about 7%; NSAIDs were used in combination with an antibiotic in 17%. Almost 50% were women, with a higher frequency of hepatocellular and a lower frequency of cholestatic patterns as compare with that in males. Advanced age may affect the likelihood of adverse hepatic reactions to the drug in general. In fact, the majority of our nimesulide cases were above the age of 40 years. Furthermore, nimesulide-induced DILI may have a severe outcome; in fact, in our previous study<sup>37</sup>, the only 3 patients with hepatic failure, encephalopathy, and ascites due to DILI belonged to the nimesuli-

de group, and one of them died, whereas another was on waiting list for orthotopic liver transplantation (OLT).

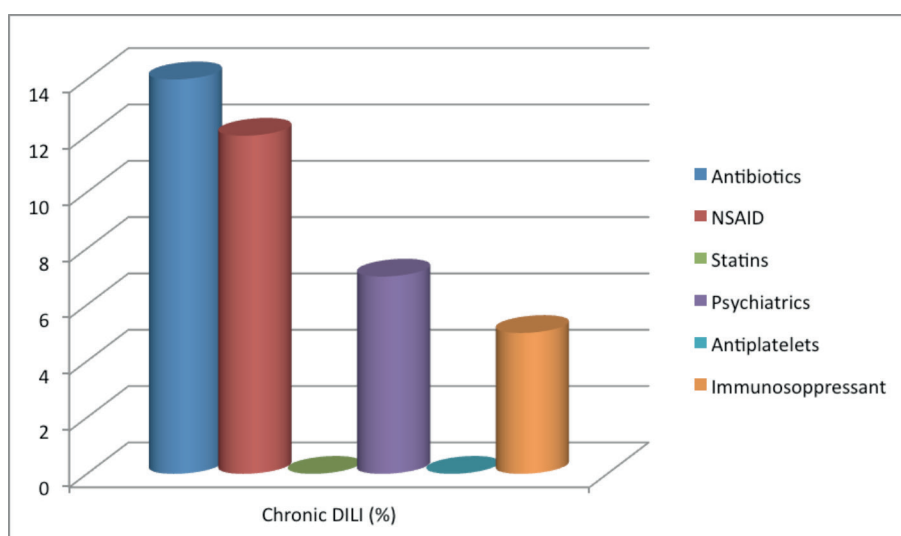
However, in the NSAIDs series, pre-existing chronic liver disease was found in 26% of cases. The period of drug intake was of a mean time of 49.9 days, with a mean latency of 18.8 days for the manifestation of the symptoms. Comorbidities were present in 49% of cases, with concurrent therapy in 50% of cases. Regarding the hospitalization, most patients were hospitalized (71%) with one case of death for ALF; 12% of cases existed in chronic DILI (Figure 3). In our series, paracetamol was present in 9 cases, all in combination with other NSAIDs or antibiotics.

### **Statins**

Statins rarely cause DILI, but the data are approximate due to the heterogeneity of existing studies, the type of statin used and the sample size. In a Swedish retrospective study that considers patients with jaundice, statins were evaluated as the suspected cause of DILI only in 1%. In the Spanish registry for hepatotoxicity, statins were involved in DILI in 3% of cases, above all atorvastatin and simvastatin<sup>15</sup>. The largest study was, instead, Swedish, and the diagnosis of DILI was considered only when transaminases overcome 5 times the normal limit and alkaline phosphatase 2 times the normal limit, a situation that occurred in more than half the cases in males aged more than 65 years. The statins involved were atorvastatin and simvastatin. About 35% had jaundice, with two cases of ALF and transplantation.

Despite the fact that statins rarely cause DILI, they have a poor prognosis, and the rechallenge causes a recurrence of injury with a similar pattern<sup>38-39</sup>. Liver damage caused by statins is often an idiosyncratic form and may be associated with genetic variants for the genes coding for enzymes involved in the metabolism (CYP 450) and for genes that code for certain transporters<sup>40</sup>.

In our series, statins (simvastatin, rosuvastatin, atorvastatin, fluvastatin and pravastatin) were involved in 4.3% of patients (8/185). In 37.5% of cases, it was atorvastatin. The pattern was equally hepatocellular and cholestatic ( $p = 0.032$ ). Women were more affected than men (62% vs. 38%), the most affected subjects were aged >40 years (100%) with a mean age of 68.8 years (vs. 52.7 of other drugs) ( $p = 0.004$ ). Jaundice occurs in 37.5% of cases; none showed encephalopathy or other signs of ALF. A pre-existing chronic liver disease was reported in 12% of cases. The mean



**Figure 3.** Chronic evolution of DILI according classes of drugs.

length of drug intake was 66.3 days, with a mean latency of 37.5 days for the manifestation of the symptoms. Comorbidities were present in all cases, with concurrent therapy in 87.5% of cases. Only 50% of the patients were hospitalized and discharged with positive outcomes and without chronic evolution.

### **Psychiatric Drugs**

Anti-depressant and/or anti-epileptic drugs are largely used in the treatment of anxiety disorders, depression, and other psychiatric illnesses. Even at therapeutic doses, these medications could be responsible for hepatotoxicity. Paroxetine, citalopram, and venlafaxine show a reversible liver injury on discontinuation of drug. The onset of antidepressant-associated hepatotoxicity ranges from 5 days to six months. Although data are scarce, 0.5%-3% of patients treated with anti-depressants may develop asymptomatic and mild elevation of LFTs. Antidepressants induce hepatotoxicity, especially in elderly patients and those with polypharmacy<sup>41,42</sup>.

In our series, (14/185) 7.6% were diagnosed as suffering from DILI related to psychiatric drugs; in about half of the cases, benzodiazepines were involved alone or in combination with other psychiatric drugs (anti-depressants). The most common pattern reported was the mixed one (42.8%). Women and men were affected by the same percentage, mostly were aged more than 40 years (65%) with a mean age of 48.4 years. Jaundice occurs in 36% of cases; no cases of ALF

or encephalopathy were reported. A pre-existing chronic liver disease was present in 7% of cases. The mean length of 75.3 days, with a mean latency of 28.6 days for the manifestation of the symptoms. Comorbidities and concurrent therapy were present in 85%. Most patients were hospitalized (80%), with positive outcomes and a chronic evolution in 7% of cases (Figure 3).

### **Anti-Platelets**

The novel oral anti-coagulants (NOACs) have been commonly prescribed for the primary and secondary prevention and treatment of thromboembolic disorders. Safety studies regarding the use of these new drugs are underway. In addition, Pharmacosurveillance screening programs should be undertaken to better define DILI by rivaroxaban<sup>43</sup>.

In our series, the anti-platelets drugs were involved in (14/185) 7.6% cases. Ticlopidine was responsible for 70% of the cases, clopidogrel, and rivaroxaban in 14% each. The most common pattern was the mixed one (43%). Women were more affected than men (64% vs. 36%). Jaundice occurs in 28.5% of cases; no cases of ALF or encephalopathy were found. A pre-existing chronic liver disease was found in 21.4% of cases. The mean period of drug intake was 98.6 days, with a mean latency of 70 days (vs. 22.9 of other drugs) ( $p = 0.016$ ) for the manifestation of the symptoms. Comorbidities and concurrent therapy were present in 93%. Most patients were hospitalized (86% vs. 59% of other drugs), with positive outcomes and without chronic evolution.

### ***Immunosuppressants***

Among immunosuppressants, the main content responsible for hepatotoxicity seems to be azathioprine (AZA). It is used in rheumatology (e.g. for rheumatoid arthritis), gastroenterology (for inflammatory bowel diseases-IBD) and to prevent rejection post organ transplantation<sup>44-46</sup>. There are many potential side effects, including liver damage<sup>47,48</sup>, estimated as an increase of aminotransferases 2 times the normal values<sup>49</sup>. In a prospective cohort study about the use of AZA in rheumatoid or psoriatic arthritis, the incidence of DILI was around 2%<sup>50</sup>. AZA possibly causes DILI through the activation of the immune system with an inflammatory mechanism, triggered by oxidative stress (oxidation of 6-mercaptopurine, metabolite of AZA by xanthine oxidase)<sup>51</sup>. In patients with IBD who use aminosaliculates, the prevalence of LFT abnormalities is relatively high, associated to a cholestatic pattern, but the development of severe injury is exceptional. The alterations spontaneously return to normal values<sup>52</sup>.

In our series, immunosuppressive drugs were involved only in 10.9% of cases (20/185), divided as follows: 75% of the cases involved azathioprine, and 25% involved methotrexate. The most common pattern was the mixed one (45%) ( $p = 0.016$ ). Women and men were equally affected with a mean age of 49.6 years. Jaundice occurs in 30% of cases; no cases of ALF or encephalopathy were reported. A pre-existing chronic liver disease was present in 10% of the cases. The mean length of drug intake was 69.4 days, with a mean latency of 21.7 days for the manifestation of the symptoms. Comorbidities and concurrent therapy were present in 40% of the cases. Patients were mostly hospitalized for day hospital (55%). Outcomes were positive with only one chronic evolution.

### ***Herbal and Dietary Supplements (HDS)***

Hepatotoxicity due to herbal products and dietary supplements is already well-recognized, but evidence regarding the actual impacts are lacking. In the Eastern world, the incidence is very high-reaching peaks of 70%<sup>53</sup>, as compared with Western countries where it is lower (2-5%)<sup>15</sup>. In the US, among patients undergoing liver transplantation for DILI other than paracetamol, it is estimated that about 12% may be due to HSD<sup>54</sup>. The DILI reported a percentage higher, up to 20% in the last 10 years<sup>55</sup>.

They are not considered as real drugs, so do not follow the pre-marketing phases, designed to

evaluate safety, efficacy, and tolerability. Adverse effects are recorded only in the post-marketing phase. However, there are no databases for monitoring side effects, which makes it difficult to obtain the real impact of the burden of this debated issue. Often, they are mixtures of plants (seed, leaves, barks and roots) contaminated with aflatoxins, pesticides, metals, and microorganisms, increasing the risk of toxicity<sup>56,57</sup>. There are several uses: well-being enhancer (to strengthen the immune system, to improve memory), neuropsychiatric, gastrointestinal disorders, to relieve menopausal symptoms and finally for weight loss. In a certain percentage of the cases, hormonal products are also used for muscle building, and can cause jaundice with a favorable prognosis compared with other cases (green tea extract as slimming aids) that affect middle-aged women with an unfavorable outcome and the need for liver transplantation<sup>55,58</sup>.

In our series, we found only four cases of liver damage from HDS, half of them in combination with other drugs in two cases alone, in the other cases in combination with other drugs. In one of these cases, the patient who disclosed the use of such substances for gastrointestinal disorders, had a preexisting undiagnosed cirrhosis post Non-alcoholic Steatohepatitis (NASH) and following the complication of chronic liver disease, died for hepatic insufficiency; the other one developed a chronic DILI with drug-induced autoimmune hepatitis (DIAIH) and the need for steroidal therapy.

### **Conclusions**

In this review, we focused on the epidemiology of DILI together with features of our prospective consecutive cohort of 185 patients, collected at our tertiary referral center according to ACG guidelines, since January 2000 to December 2016, suffering from DILI.

Antibiotics showed an onset after a shorter exposure and latency than other drugs, and there was a higher risk of transformation in chronic DILI. Also, in our series, DILI could be associated with DIAIH, which occur mainly in women, with positivity of auto-antibodies, high levels of transaminases and gamma globulin, features of liver histology such as interface hepatitis, lymphoplasmacytic infiltrate, rosettes and cholestasis, and with a better prognosis<sup>59</sup> as compared with AIH (Autoimmune Hepatitis) properly defined. Recent data suggest an association with cer-

tain HLA gene variants, with alteration of specific cytokines<sup>60</sup> and inhibition of some hepatobiliary transporters<sup>61</sup>.

Acute liver disease induced by NSAIDs represented an important cause of hospitalization with severe clinical events such as hepatic encephalopathy or death. The most frequent pattern was that of the hepatocellular, with higher ALT values than those in other groups. Statins were rarely the cause of DILI, frequently in older subjects with mild clinical manifestation and lower stiffness values than in others. Also, psychiatric drugs were rarely the cause of severe DILI with low risk of complication or chronic transformation. Anti-platelets causes DILI in older subjects, with better prognosis than other drugs (longer latency and lower need for hospitalization). Immunosuppressants were responsible for DILI with a mixed pattern, low risk of complication or chronic transformation.

Finally, this report represents a snapshot of our clinical experience in the field of DILI, in which many efforts are required to reinforce the attention of physicians to the possibility that a patient suffering from acute liver disease could be diagnosed as a patient with DILI.

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#### Conflict of interest

None of the authors have any financial or other relations that could lead to a conflict of interest.

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