**Systematic review: ibuprofen-induced liver injury**

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**SUMMARY**

Background: Nonsteroidal anti-inflammatory drugs (NSAIDs) are a leading cause of drug-induced liver injury (DILI) across the world. Ibuprofen is one of the most commonly used and safest NSAIDs, nevertheless reports on ibuprofen-induced hepatotoxicity are available.

Aim: To analyse previously published information on ibuprofen-induced liver injury for a better characterisation of its phenotypic expression.

Method: A systematic search was performed and information on ibuprofen-induced liver injury included in case series and case reports, in terms of demographic, clinical, biochemical and outcome data, was analysed.

Results: Twenty-two idiosyncratic ibuprofen hepatotoxicity cases were identified in the literature, suggesting a very low prevalence of this type of DILI. These patients had a mean age of 31 years and 55% were females. Mean cumulative dose of ibuprofen and time to onset were 30 g and 12 days, respectively. Hepatocellular injury was the most frequently involved liver injury pattern. Six cases developed vanishing bile duct syndrome. Full recovery occurred in 11 patients after a mean time of 14 weeks, whereas five cases evolved to acute liver failure leading to death/liver transplantation.

Conclusions: When assessing potential hepatotoxicity cases, physicians should keep in mind that ibuprofen has been associated with hepatotoxicity in the literature. Ibuprofen-associated DILI presents commonly as hepatocellular damage after a short latency period. Published reports on ibuprofen hepatotoxicity leading to liver failure resulting in liver transplantation or death are available. However, due to the apparent low absolute risk of ibuprofen-induced liver complications, ibuprofen can be regarded as an efficacious and safe NSAID.

## INTRODUCTION

Nonsteroidal anti-inflammatory drugs (NSAIDs) belong to a group of chemically heterogeneous compounds, and their therapeutic effect relies on the strong anti-cyclooxygenase activity and ability to block pro-inflammatory substance formation. The main indications for NSAID therapy range from mild/moderate forms of pain to chronic inflammatory processes.[1, 2]

In the United States, 6% of the population declared taking at least one prescription NSAID a month and over 30 million people around the world take NSAIDs daily.[3] Conventional NSAIDs are generally well tolerated, but adverse effects, such as cardiovascular, gastrointestinal and renal events may occur in a small proportion of users.[4] NSAID-associated hepatotoxicity is considered rare and the incidence is estimated to be 1-23 cases per 100 000 patient-years.[5] In addition, previous systematic reviews have found low level of liver-related hospitalisation involving NSAID intake.[6,7] Nevertheless, the common use of NSAIDs emphasises the importance of understanding NSAID-associated liver toxicity, which is responsible for approximately 10% of drug-induced liver injury (DILI) cases in developed countries.[8-10] Interestingly reports from prospective DILI cohorts around the world demonstrate differences in relative frequency of individual NSAIDs responsible for DILI (Table 1). Diclofenac was the most common causative NSAID in the United States (63%) and Iceland (100%), while nimesulide more frequently caused DILI in Latin America (38%) and Italy (39%).[10-13] Ibuprofen, on the other hand, was the NSAID responsible for most DILI cases in the Spanish DILI Registry (29%) and was also highly represented in an Indian DILI study (25%), although the latter study presented a more equal distribution between different NSAIDs than the former study.[12,14] Caution should however be taken when interpreting these results due to lack of sales/prescription data.

Ibuprofen is a propionic acid derivative available under medical prescription and as an over-the-counter medication. It has been available in the UK since 1969 and was introduced on markets worldwide during the 1970s. It is currently the most frequently prescribed NSAID with over 20 million prescriptions per year in the USA, apart from its vast self-medication use.[11] The recommended therapeutic dose for adults varies from 800 to 1200 mg per day for over-the-counter self-medication use and 1800-2400 mg per day for chronic treatments under medical supervision.

Short plasma half-life and absence of prolonged retention in the organism contribute to a better gastrointestinal safety profile of ibuprofen compared to other NSAIDs.[15]

Nevertheless, ibuprofen has been linked to instances of clinically apparent liver injury with injury patterns varying from moderate elevations of aminotransferases to vanishing bile duct syndrome (VBDS) and even acute liver failure (ALF) resulting in death.[16-34] While most reported ibuprofen-induced hepatotoxicity cases to date are idiosyncratic, some cases of liver injury due to ibuprofen overdose have also been described.[35-37]

The large consumption of ibuprofen worldwide together with the fact that only limited information is available on ibuprofen-induced hepatotoxicity to date, prompted us to look deeper into the phenotypic presentation of this type of DILI. In the present study, we aimed to review previously reported cases of ibuprofen-induced liver injury in the literature in order to enhance the understanding of ibuprofen hepatotoxicity with regard to frequency and phenotypic expression.

## METHODS

A systematic literature review was conducted in accordance with the "Preferred Reporting Items for Systematic Reviews and Meta-Analyses" (PRISMA) guidelines, in order to identify all preexisting studies on ibuprofen-induced liver injury to date.

### *Systematic database search*

Systematic electronic searches of PubMed, Cochrane and Web of Science were performed to obtain case reports and case series of ibuprofen-induced liver injury published up to December 2018. The searches were conducted using the terms "hepatotoxicity", "drug-induced liver injury" and "ibuprofen". An elevated number of ibuprofen-induced hepatotoxicity events related to the term "vanishing bile duct syndrome" was also observed. Thus, this term was included in a new search. Only articles published in English were considered. No other restrictions were applied.

### *Eligibility criteria*

After removing duplicates, titles and abstracts were screened independently for eligibility by two reviewers (MEZ and CS). Any disagreements were resolved by discussion between the two reviewers. Full articles corresponding to the selected abstracts and/or titles were obtained and assessed against eligibility criteria. Only cases where ibuprofen was judged as the single culprit drug causing a liver reaction were considered for our analysis. References cited by the selected articles were also reviewed to identify other potentially eligible studies not captured in the initial electronic database search.

*Data collection*

Demographic, clinical, histological, laboratory and outcome information corresponding to exposure to ibuprofen resulting in hepatotoxicity was retrieved from the articles and analysed. The pattern of liver injury was classified based on R value calculations from the first available blood test after DILI recognition.[38] For those cases without complete analytical information at DILI recognition, histological findings from liver biopsies were carefully reviewed. Presentations considered as hypersensitivity features included fever, rash, eosinophilia and lymphopenia.

## RESULTS

The applied search strategy led to a total number of 131 published works, which were obtained from the above described databases. Of these, 14 reports were found to be duplicates and another five did not meet the language criteria, and thus were immediately removed. In the next step, 59 records were selected due to being of potential interest for the present analysis based on article titles and abstracts (53 records were excluded as their content fell outside the scope of the current study). Of the 59 full articles, which were carefully assessed, 22 were considered for inclusion in our systematic review. The 37 omitted articles did not include data on human ibuprofen-induced liver injury useful for performing analyses of phenotypic characterisation. The 22 selected articles consisted of 17 case reports and two case series on idiosyncratic ibuprofen-induced liver injury and three additional case reports on ibuprofen overdose-related liver injury, which were all included and thoroughly analysed in the present work (Figure 1).

*Demographic characteristics of idiosyncratic ibuprofen-induced hepatotoxicity*

Seventeen published case reports and two case series of idiosyncratic ibuprofen-derived liver injury from 1976 to 2018 were retrieved, carefully analysed and summarised in Tables 2 and S1.[16-34] Of the 22 identified cases, 12 involved females (55%) and the mean patient age was 31 years (range 7 months—59 years). Thirteen patients (59%) had underlying chronic conditions, which were mainly related to rheumatic disorders (three patients with systemic lupus erythematous, one with juvenile rheumatic arthritis and one with polyarthritis) and hepatic disorders (four patients with hepatitis C virus infection). Ibuprofen was the only administered medication in six cases (27%), whereas it was administered simultaneously with other medications in twelve additional cases. In the

remaining four cases, the authors did not provide information on concomitant treatments. The cumulative ibuprofen doses ranged from 0.4 to 180 g (mean 30 g) over a time period of 1-42 days with a mean ibuprofen treatment duration of 14 days. The mean time to onset of the DILI episode was 12 days (range 1-42 days; Table S1).

*Clinical, biochemical and histological profile of idiosyncratic ibuprofen-induced liver injury*

Eighteen patients presented clinical manifestations at onset. The most prevalent symptoms were rash (56%), fever (56%), jaundice (50%), choluria (39%), vomiting (39%) and abdominal pain (22%). In addition, four patients were asymptomatic, and the diagnosis of liver injury was based on routine blood tests (Table S1).

The mean values for peak liver tests were as follows: total bilirubin (TBL) 7.6 mg/dL, aspartate aminotransferase (AST) 986 IU/L, alanine aminotransferase (ALT) 968 IU/L and alkaline phosphatase (ALP) 610 IU/L (Table 2). To depict an overview of potential severity of the ibuprofen cases, peak ALT and TBL values were graphed for 13 of the 22 cases (cases 2-5, 9, 11-16, 20 and 22) with available information (Figure 2). This figure also includes 25 ibuprofen-induced hepatotoxicity cases from the Spanish DILI Registry and Latin-American DILI Network, for comparative purposes. These cases, which do not form part of the current systematic review, have been published previously as a cohort study, but not as case reports.[12] Detailed information on these cases can therefore be found in Table S2. Figure 2 shows that a large proportion of cases from both groups had a TBL and ALT level >2 and >5 times the upper limit of normal, respectively, indicating a higher risk of severe outcome (Hy's law). The cases included in the current study, however, demonstrate a higher proportion of worst outcome cases compared to the Spanish/Latin-American cases (31% vs 12%).

Fourteen of the 22 patients (cases 1-3, 5, 10-13, 15, 17-18, 20-22) had hypersensitivity features (fever, rash and/or eosinophilia). However, hypersensitivity features are not specific to DILI and must therefore be considered in the comorbid context of each patient. Only eight of the patients (cases 3, 5, 10-12, 15, 20 and 22) had hypersensitivity features most likely related to the DILI episode.

Liver histology information was available for 15 of the analysed patients (Table S1). These patients had their initial liver biopsies performed 10-63 days after DILI recognition. The primary findings were necrosis in three cases (cases 9, 10 and 22), cholestasis in five cases (cases 3, 5, 10, 11 and 14) and fatty changes were present in three cases (cases 1,

10 and 17). A total of seven cases had bile duct injury with significant bile duct loss in five cases (cases 5, 11, 12, 16 and 20). Mixed inflammatory infiltrate was detected in six cases (cases 5, 10, 11, 15, 20 and 22), while lymphocytic infiltrate predominated in cases 12, 20 and 22, and eosinophilic infiltrate was observed in case 13.

Hepatocellular pattern of liver injury was the most frequently observed injury pattern, with 11 cases presenting biochemical and/or histopathological criteria of hepatocellular injury, while three cases presented cholestatic and three cases mixed liver injury. The remaining five cases provided insufficient data to assess type of liver injury (Table 2). Six of the patients were diagnosed with VBDS after confirmation of compatible hepatic histology (cases 4, 5, 11, 12, 16, 20). In addition, several patients developed clinical manifestations that were associated with drug reaction with eosinophilia and systemic symptoms (DRESS; case 22), Stevens-Johnson syndrome (SJS; cases 3 and 5), or toxic epidermal necrolysis (TEN; cases 12 and 20).

*Outcome and follow-up information on idiosyncratic ibuprofen-induced liver injury*

Eleven of the analysed ibuprofen-induced liver injury patients fully recovered from the DILI episode (50%) and the mean time to resolution was 15 weeks (range 2-32 weeks). In addition, four patients with underlying HCV infections (cases 6-8 and 19) also recovered from the DILI episode, and liver injury markers returned to baseline values (ALT 105-119 IU/L, elevations due to the underlying chronic condition present prior to the DILI episode) within a mean time of 10 weeks (range 8-12 weeks). Patient follow-up visits ceased prior to complete normalisation for case 16 and no outcome information was available for case 18. One patient had a fatal outcome after suffering massive hepatic fatty metamorphosis and pleural effusion, and died 1 week after onset (case 1), whilst two patients (cases 9 and 22) had ALF and underwent liver transplantation within 10 weeks from onset. Two patients, who developed VBDS and remained deeply jaundiced 12 months after onset despite pharmacological therapy with immunosuppressive agents, were finally referred for liver transplantation (patients 4 and 5). Three cases (patients 6, 17 and 21) had an inadvertent rechallenge to ibuprofen, which triggered a new flare of aminotransferase elevations. These additional episodes subsided after ibuprofen dechallenge and the patients recovered (complete liver profile normalisation for patients 17 and 21, while patient 6 returned to baseline values; Table S1).

*Intrinsic ibuprofen-induced hepatotoxicity*

Three case reports were also found describing liver damage following ibuprofen overdose (cases 23-25).35-37 Two of the events (case 23 and 25) were suicide attempts with a single ibuprofen intake of 20 and 60 g, while the reason for a single intake of 9.6 g of ibuprofen in case 24 remains unknown. In terms of outcome, one case developed ALF and underwent liver transplantation 4 weeks after onset, one case fully recovered (time to resolution unknown) and the outcome of the third case is unknown as follow-up was lost after 2 weeks (Tables 2 and S1).

## DISCUSSION

Despite being considered as one of the safest NSAIDs in terms of the hepatic profile,[4,6,7] ibuprofen can cause hepatotoxicity. The prevalence of ibuprofen hepatotoxicity, however, appears to be relatively low considering the widespread use of this medication. In fact, vascular and gastrointestinal complications are probably more commonly associated with ibuprofen than hepatotoxicity.[39] The search for idiosyncratic ibuprofen-induced hepatotoxicity information in the literature resulted in 22 identified cases. Overall, ibuprofen-derived liver injury occurred after a relatively short time from treatment initiation with a mean time to onset of 12 days. With regard to sex, we noted a trend towards women more frequently developing ibuprofen hepatotoxicity than men. This was not the case in our previous report on ibuprofen hepatotoxicity cases in Spain and Latin-America, with similar frequency of male and female subjects, although a slightly higher proportion of women was observed in DILI due to other NSAIDs.[12] A possible explanation for this finding could be that 23% of the patients in the current study had underlying rheumatic disorders, which are more prevalent in women.[40] In addition, a recent study analysing the trends of NSAID use in US adults found that women are more likely to use NSAIDs.[41] Hence, a higher use of NSAIDs and a higher prevalence of rheumatic disorders requiring NSAID treatments may be the reasons behind the observed increase in females in published ibuprofen hepatotoxicity case reports rather than females being biologically more susceptible to this form of DILI than men.

We previously found a predominance of hepatocellular pattern of liver injury in Spanish and Latin-American DILI cases caused by ibuprofen.[12] The same observation holds for the cases obtained from the literature in the current study with 65% of the cases, with sufficient information to determine pattern of liver injury, presenting hepatocellular type of liver injury. Thus, the most common pattern of liver injury associated with ibuprofen-

induced hepatotoxicity appears to have a hepatocellular character, although cholestatic/mixed liver injury can also occur.

Vanishing bile duct syndrome is characterised by bile duct injury and ductopenia, and occurred in six of the 22 idiosyncratic cases. Although rarely, VBDS can occur in DILI patients with progressive cholestasis potentially leading to liver failure and death or liver transplantation. It has been associated with causative drugs such as azathioprine, androgens, amoxicillin-clavulanate, carbamazepine, chlorpromazine, erythromycin, estradiol, flucloxacillin, phenytoin and co-trimoxazole.[42] A study of 363 DILI cases with biopsy data found that 7.2% of the cases had bile duct loss based on histopathological interpretations, of which 54% exhibited moderate to severe ductopenia with bile duct loss in more than 50% of the portal tracts.[43] However, it has been suggested that this incidence may be overestimated compared to observations in population-based studies due to the fact that the cases were recruited from tertiary referral centres, which are likely to see more severe cases.[44] Two of the case reports with VBDS in the current study had bile duct loss in more than 50% of portal tracts,[24, 29] while the level of bile duct loss was not provided for the remaining four VBDS cases.

Four of the identified cases in the current study developed serious cutaneous reactions (progressive xanthomatosis, SJS or TEN) in addition to VBDS. The concurrence of VBDS and cutaneous reactions was similarly found in the aforementioned study of North American DILI cases, and suggests an aberrant hypersensitivity reaction affecting cholangiocytes and keratinocytes, potentially due to shared immunogenic proteins and cell surface presentation of drug-protein adducts or immunogenic drug metabolites.[43] Interestingly, one of the US cases with VBDS and TEN had taken ibuprofen prior to the liver reaction. The case was, however, adjudicated as DILI most likely caused by azithromycin, and only possibly due to ibuprofen.[43] Nevertheless, a role for ibuprofen cannot be completely ruled out in this case in terms of DILI development and clinical presentation.

Cutaneous reactions were not limited to those cases that developed VBDS. Our literature search also revealed three ibuprofen hepatotoxicity cases with cutaneous reactions (case 3, 15 and 22), but not VBDS. Cutaneous hypersensitivity reactions to ibuprofen are well known.45 These reactions are often allergic in nature, mostly mild, occur rapidly after drug exposure and rarely contain hepatic involvement. In contrast, DRESS syndrome often presents with concurrent cutaneous and hepatic reactions.[46] However, ibuprofen

does not appear to be a major cause of DRESS (with liver involvement) as we only identified one case in our literature search.

Our findings support that ibuprofen-induced liver injury has a wide clinical spectrum rather than a homogeneous signature. However, it should be noted that the analysed cases were all obtained from published case series and case reports and might therefore have been subjected to publication bias, as reports with severe or novel presentations tend to be preferred for publication compared to cases with mild and uncomplicated clinical courses. This may have contributed to the high proportion of identified ibuprofen hepatotoxicity cases with VBDS, SJS and TEN in the current study.

A severe clinical progression was identified in five idiosyncratic cases (one death, two liver transplantations and two liver transplantation referrals with unknown outcome) as well as one case involving a single ibuprofen overdose that led to liver transplantation. Similarly, the prospective ibuprofen-induced hepatotoxicity cohort previously reported from the Spanish DILI Registry demonstrated a concerning proportion of fatal/liver transplantation patients, which was higher than the proportion for DILI caused by other NSAIDs or non-NSAID agents.[12] These findings demonstrate that ibuprofen, although rarely, can be associated with worst outcome DILI. However, further studies involving a high number of carefully diagnosed ibuprofen hepatotoxicity cases are needed to confirm this and to determine the true incidence rate of worst outcome for this type of DILI.

Our study is based on a comprehensive database search to answer an unmet need for a better understanding of ibuprofen DILI, but it also has limitations. The availability of sufficient information to establish causality varied between cases. For example, presence of concomitant medications was not reported for some cases, which could reduce the diagnostic reliability of these cases. This highlights the importance of implementing and adhering to strict guidelines for DILI case reporting. The DILI criteria and diagnostic process may also have varied as the reporting period spanned across more than 40 years. Moreover, the distinction between hepatotoxicity and hypersensitivity with hepatic manifestation is not well defined. Furthermore, we cannot rule out publication bias and consequently under-representation of less striking cases. The low number of cases retrieved from the literature also implies that limited conclusions on the clinical presentation and outcome of ibuprofen hepatotoxicity can be drawn. Further evidence is required for more reliable conclusions.

In conclusion, ibuprofen-induced liver injury can occur, but the absolute risk of hepatotoxicity associated with ibuprofen is probably very low. It is in fact probably lower

than the absolute risks of vascular and gastrointestinal complications. Ibuprofen-induced hepatotoxicity presents mainly as hepatocellular type of liver injury after a short latency period, but other presentations (including hypersensitivity features, cholestatic damage and VBDS) are known to occur. We found a relatively large proportion of patients in our study that died or required liver transplantation. However, the relatively high prevalence of underlying comorbidities including chronic liver disease causes uncertainties with regard to prognosis and causality of the liver failure/mortality cases. Additional studies including a substantial number of carefully diagnosed ibuprofen hepatotoxicity cases are therefore needed. Nevertheless, clinicians should not overlook ibuprofen intake when assessing a suspicion of hepatotoxicity, but be aware that ibuprofen has been associated with DILI in the literature. In line with other forms of DILI, careful follow-up and monitoring of patients suspected of having ibuprofen-induced liver injury is recommended until recovery. Although further studies are required to fully understand the role of ibuprofen in DILI, ibuprofen can be regarded as a safe and efficacious widely available NSAID.

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## FIGURE LEGENDS

**FIGURE 1.** Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram of the report selection in the current study

**FIGURE 2.** Idiosyncratic ibuprofen-induced liver injury events depicted according to peak alanine aminotransferase (ALT) and total bilirubin (TBL) levels. The hepatotoxicity cases include 13 cases identified from the literature (part of the current study) that are compared with 25 cases from the Spanish and Latin-American DILI Registries that are not included in the current study (case details can be found in Table S2).
Worst outcome: death or liver transplantation; ULN: upper limit of normal.

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**Table 1.** Prevalence of NSAID hepatotoxicity in large prospective DILI cohorts worldwide

| | **Spanish DILI Registry**[12] | **Latin DILI Network**[12] | **US DILIN**[11] | **Iceland**[10] | **India**[14] | **Italy**[13] |
|---|---|---|---|---|---|---|
| Year | 1994-2015 | 2012-2015 | 2004-2013 | 2010-2011 | 1997-2008 | 2000-2016 |
| Type of registry | National | Multinational | National | Population-based study | Single-center study | Single-center study |
| Total number of DILI cases, n | 871 | 200 | 1221 | 96 | 313 | 185 |
| Musculo-skeletal drugs, n (%) | 96 (11) | 36 (18) | N/A | N/A | N/A | N/A |
| NSAIDs, n (%) | 73 (9 | 29 (10) | 30 (3) | 6 (6) | 8 (3) | 65 (36) |
| Most frequent NSAIDs, n (% of total NSAIDs) | Ibuprofen 21 (29)<br>Diclofenac 13 (18)<br>Nimesulide[§] 9 (12)<br>Piroxicam 5 (7)<br>Droxicam 4 (5)<br>Naproxen 4 (5) | Nimesulide[§] 11 (38)<br>Diclofenac 10 (34)<br>Ibuprofen 5 (17)<br>Piroxicam 1 (3)<br>Ketoclorac 1 (3)<br>Ketoptofen 1 (3) | Diclofenac[¶] 16 (53)<br>Meloxicam3 (10)<br>Celecoxib 3 (10)<br>Ibuprofen 2 (7)<br>Etodolac 2 (7)<br>Oxaprozin 2 (7)<br>Sulinadac 1 (3)<br>Valdecoxib 1 (3) | Diclofenac 6 (100) | Nimesulide 2 (25)<br>Diclofenac 1 (13)<br>Ibuprofen 2 (25)<br>Celexocib 2 (25)<br>Piroxicam 1 (13) | Nimesulide 25 (39)<br>Ketoprofen 22 (34)<br>Diclofenac 10 (15)<br>Ibuprofen 4 (7) |

Abbreviations: N/A, not available; NSAID, nonsteroidal anti-inflammatory drug;
[§]Withdrawn from the market in Spain in 2002 and Argetina in 2009, but still commercialized in other countries;
[¶]alone or in combined formulation

**Table 2.** Biochemical parameters (at the time of peak ALT), liver injury pattern and additional information on ibuprofen-induced liver injury (n = 25)

| Case | TBL (mg/dL) | AST (IU/L) | ALT (IU/L) | ALP (IU/L) | Type of injury | Additional information | Ref |
|---|---|---|---|---|---|---|---|
| **Idiosyncratic DILI cases** | | | | | | | |
| 1 | 2 | 6200 | N/A | 760 | Hep | ANA+ (1:4096) | 16 |
| 2 | 1 | 2200 | 1245 | N/A | Hep | - | 17 |
| 3 | 14 | N/A | 441 | 238 | Chol | Developed acute-onset SJS | 18 |
| 4 | 6.5 | 404 | 488 | 309 | Mix | Developed VBDS and severe progressive xanthomatosis | 19 |
| 5 | 3.3 | 582 | 649 | 519 | N/A | Developed acute-onset VBDS and SJS; ANA+ (1:40) | 20 |
| 6 | N/A | 459 | 1209 | N/A | Hep | - | 21 |
| 7 | N/A | 523 | 1238 | N/A | Hep | - | 21 |
| 8 | N/A | 597 | 1577 | N/A | Hep | - | 21 |
| 9 | 30 | 2260 | 2099 | N/A | Hep | - | 22 |
| 10 | N/A | N/A | N/A | N/A | N/A | - | 23 |
| 11 | 5.4 | 333 | 639 | 1697 | Hep | Developed acute VBDS | 24 |
| 12 | 8.5 | 879 | 723 | 890 | N/A | Developed acute VBDS and TEN | 25 |
| 13 | 0.4 | 383 | 464 | 36 | Hep | Developed meningitis; ASMA+ (1:20) | 26 |
| 14 | 3.9 | 99 | 182 | N/A | Chol | ASMA+ (1:80) | 27 |
| 15 | 15 | 1492 | 1860 | 323 | Hep | Developed multiform exudative erythema; DLST+ for ibuprofen; | 28 |
| 16 | 6 | 247 | 207 | 1598 | Chol | Developed VBDS and hyperlipidemia; ANA+ (1:320) | 29 |
| 17 | N/A | 105 | 255 | 155 | Mix | ANA+ | 30 |
| 18 | N/A | 185 | N/A | N/A | N/A | - | 30 |
| 19 | N/A | 355 | 1093 | N/A | Hep | - | 31 |
| 20 | 8.1 | 186 | 419 | 700 | Mix | Developed VBDS and TEN | 32 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 21 | N/A | 147 U/mL[§] | N/A | N/A | N/A | ANA+ (1:80) | 33 |
| 22 | 2.9 | 1168 | 2154 | 90 | Hep | Developed DRESS syndrome | 34 |
| **Mean** (range) | **7.6** (0.4-30) | **986** (99-6200) | **968** (182-2154) | **610** (36-1697) | | | |
| **Intrinsic DILI cases** | | | | | | | |
| 23 | 5 | >717 | 1873 | 135 | Hep | ANA+ , ASMA+ | 35 |
| 24 | 19 | N/A | 2301 | 109 | Hep | - | 36 |
| 25 | N/A | 291 | N/A | 245 | N/A | - | 37 |

Abbreviations: TBL, total bilirubin; AST, aspartate aminotransferase; ALT, alanine aminotransferase; ALP, alkaline phosphatase; N/A, not available; Hep, hepatocellular; Mix, mixed; Chol, cholestatic; SJS, Stevens-Johnson syndrome; VBDS, vanishing bile duct syndrome; TEN, toxic epidermal necrolysis; DLST, drug lymphocyte stimulation test; DRESS, drug rash with eosinophilia and systemic symptoms; Ref, bibliographic reference;

*Type of liver injury was deduced from R values based on initial blood analysis values when presented, or biopsy findings in the absence of analytical information;

[§]normal, <47 U/mL;

**Figure 1**

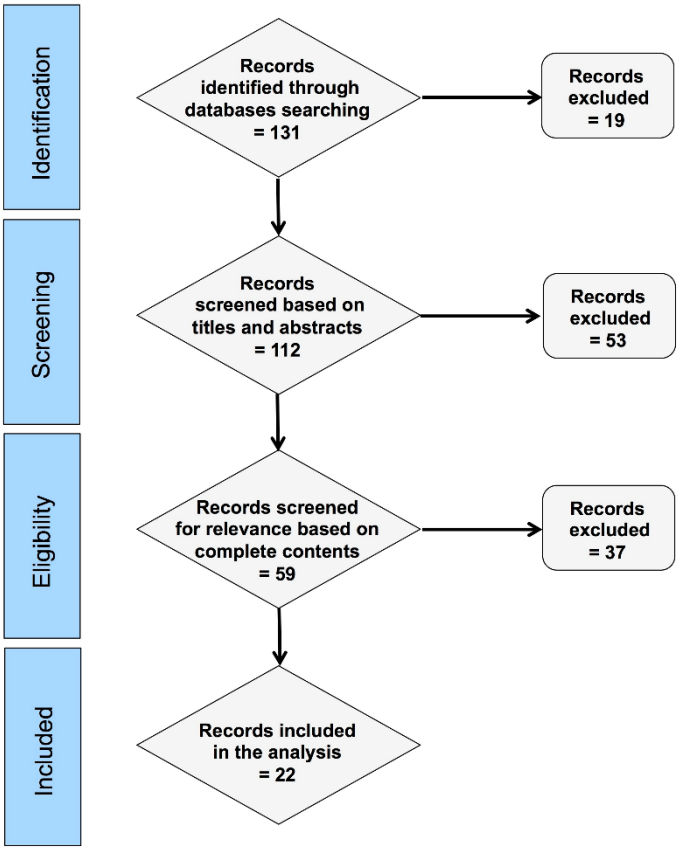
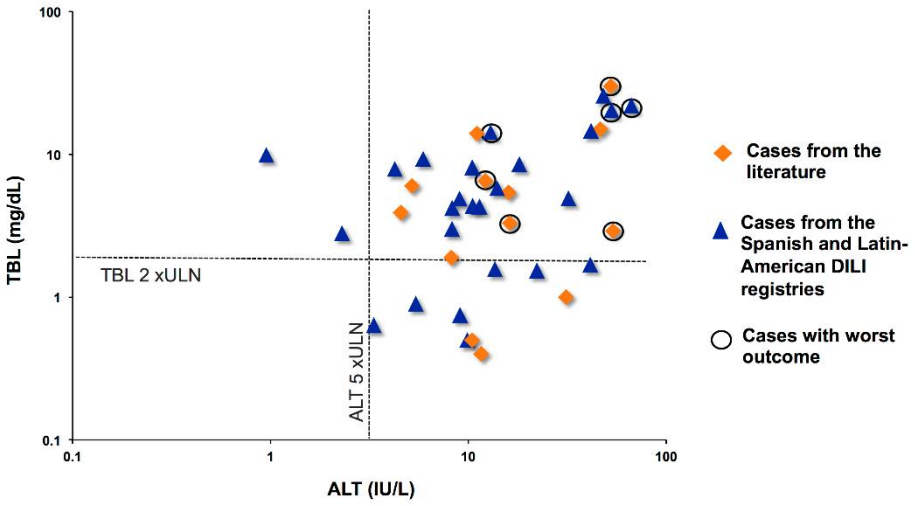

Identification
Screening
Eligibility
Included
Records identified through databases searching = 131
Records excluded = 19
Records screened based on titles and abstracts = 112
Records excluded = 53
Records screened for relevance based on complete contents = 59
Records excluded = 37
Records included in the analysis = 22

**Figure 2**


100
10
1
0.1
TBL (mg/dL)
TBL 2 xULN
ALT 5 xULN
0.1
1
10
100
ALT (IU/L)
Cases from the literature
Cases from the Spanish and Latin-American DILI registries
Cases with worst outcome

**Supplementary table 1. Demographic, clinical, histological and outcome information of ibuprofen-induced liver injury events reviewed in the literature (n=25)**

| Case | Age / sex | Ibuprofen daily dose mg (duration, d) | Time to onset, d | Clinical presentation | Pre-existing conditions | Concomitant medications | Time to resolu-tion, w | Liver biopsy (Time after recognition) | Outcome | Ref |
|---|---|---|---|---|---|---|---|---|---|---|
| **Idiosyncratic DILI cases** | | | | | | | | | | |
| 1 | 48/F | 2400 (N/A) | 15 | Fever, nausea, vomiting, | Polyarthritis, Raynauds's phenomeneon, potentially mixed connective tissue disease | Ampicillin, aspirin | - | 90% of hepatocytes replaced by fatty material with no areas of parenchymal collapse; minimal portal chronic inflammation (autopsy; 3 d) | Exitus (3 days after hospital admission) | 16 |
| 2 | 12/F | 1200 (15) + 1500 (2) | 17 | Fever, malaise, anorexia, vomiting, weakness | Juvenile rheumatoid arthritis | Aspirin | 2 | - | Complete recovery | 17 |
| 3 | 44/M | 1200 (8) + 400 [7 days later] | 8 | Fever, rash, severe sore throat, eosinophilia, jaundice | None | Penicillin | 28 | Cholestatic hepatitis (N/A) | Required corticosteroid treatment. Complete recovery | 18 |
| 4 | 29/M | 600 (21) | 21 | Jaundice, pruritus, nausea, vomiting, abdominal pain, choluria, acholia | Childhood asthma, allergic rhinitis | Hypoallergenic injections | - | 1. Damaged bile ducts with neutrophil and eosinophil infiltrates; mononuclear infiltrate in portal zones; canalicular cholestasis (11 d)<br>2. Less portal inflammation, but more cholestasis and obliteration of bile ducts (42 d)<br>3. Bile duct paucity (6 mo) | Required prednisone, antihistamines, choles-tyramine and ursodiol treatments. Deeply jaundiced 12 months after ibuprofen ingestion→referred for LTx evaluation (1 year after first presentation) | 19 |
| 5 | 9/F | <30 mg/kg (6) | 6 | Jaundice, pruritus, anorexia, fever, fatigue, choluria, rash, acholia | None | APAP occasionally | - | 1. Moderately severe cholestasis; portal inflammation; interlobular bile duct damage and loss (45 d) | Required UDCA, prednisone and tacrolimus treatments. Referred for LTx (6 months after detection) | 20 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 2. Absence of bile ducts and cirrhosis without active inflammation (5 mo) | | |
| 6 | 33/M | 800 (3) | 3 | Asymptomatic | HCV | N/A | 12 | - | Return to baseline values (Positive inadvertent re-exposure 6 months later→return to baseline values after 3 months) | 21 |
| 7 | 44/M | 4800/week (N/A) | N/A | Asymptomatic | HCV | N/A | 8 | - | Return to baseline values | 21 |
| 8 | 34/M | 1600 (N/A) | N/A | Asymptomatic | HCV | N/A | 8 | - | Return to baseline values | 21 |
| 9 | 59/F | 1800 (10) | 5 | Jaundice, choluria, fatigue | Insufficient peripheral venous blood flow | Dobesilate | - | Submassive hepatic necrosis (explant; 70 d) | Subacute liver failure →LTx (70 days after dection) | 22 |
| 10 | 35/M | 400 (single dose) | 7[#] | Rash, pruritus, jaundice[#] | None | Tetanus toxoid injection | 28 | Inflammation; marked cholestasis; spotty necrosis of hepatocytes with focal areas of ballooning and fatty changes (2 mo) | Required antihistaminics and UDCA treatments. Complete recovery | 23 |
| 11 | 10/F | <30 mg/kg (2+4 [8 days later]) | 14 | Jaundice, choluria, acholia, cheilitis, arthralgia, pruriginous rash | None | None | 28 | Centrolobular cholestasis; loss of interlobular bile ducts in 50% of portal tracts; bile duct injury in the remainder; portal polymorphous infiltrate with eosinophils (48 d) | Required UDCA and rifampicin treatments. Complete recovery | 24 |
| 12 | 0[˚]/F | <30 mg/kg (2)[**] | 2 | Rash | None | None | 16 | Lymphocyte infiltration; marked degeneration of interlobular bile duct epithelium; destructive narrowing of ducts in portal tracts; no intralobular bile ducts in at least 10 portal areas (20 d) | Required UDCA treatment. Complete recovery | 25 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 13 | 38/F | 600 (7) + 800 (2) when needed | 7 | Generalized body aches, vomiting, fever | None | None | 2 | Mild lobular hepatitis with eosinophilic infiltrate (N/A) | Complete recovery | 26 |
| 14 | 16/M | 1200 (14) + 200-400 (28) when needed | 42 | Jaundice, choluria | Chronic shoulder pain | None | 12 | Centrilobular intrahepatic + canalicular cholestasis; cytoplasmic changes in bile duct epithelium compatible with mild duct damage (18 d) | Required UDCA, diphenhydramine, rifampin and vitamin K supplement treatments. Complete recovery | 27 |
| 15 | 36/F | 300 (20) | 25 | Fever, choluria, rash (erythema) | None | Famotidine, azulene sodium sulfonate, dompreidone | 4 | Collapse of hepatocytes primarily around centrilobular areas with infiltration of inflammatory cells (9 d) | Required intravenous methylprednisolone and and oral corticosteroid treatment treatment. Complete recovery | 28 |
| 16 | 40+/F | 600, 2-3 days/month (over a time period of 365 days) | N/A | Jaundice, fatigue, choluria | Diabetes type II, adenomyosis | Acarbose, metformin | >45§ | 1. Biliary injury and absence of small terminal bile ducts around hepatic arteries affecting >50% of sampled portal tracts (28 d) 2. Absence of small terminal bile ducts, interstitial fibrous tissue hyperplasia, bile salt deposition in peripheral liver cells, lymphocytes with small amount of plasma cell infiltration (7 mo) | Required polyene phosphatidylcholine, silibinin, GSH and UDCA therapies. Loss of followup prior to complete recovery | 29 |
| 17 | 54/F | 1200 (10) + 400 (< 3) a few days later | 10 | Fever, rash, vomit, abdominal pain | SLE | N/A | 2 | Minimal fatty changes (10 d)§§ | Positive inadvertent re-exposure 8 days later. Required chloroquine therapy. Complete recovery | 30 |
| 18 | 15/F | 1200 (6) | 6 | Abdominal pain, fever, vomiting, rash | SLE | Aurothio-glucose | N/A | - | N/A | 30 |
| 19 | 57/M | 1200 (30) | 30 | Asymptomatic | HCV | None | 12 | - | Return to baseline values | 31 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 20 | 7/M | <30 mg/kg (3) | 2 | Jaundice, rash | None | None | 32 | Lymphocyte infiltration; marked degeneration of interlobular bile duct epithelium; absence of intralobular bile ducts in at least 10 portal areas (21 d) | Required treatment with methylprednisolone and UCDA.<br>Complete recovery | 32 |
| 21 | 36/F | 2000 (10) | 7 | Epigastric pain, fever, nausea, vomiting | SLE | Aspirin | N/A | - | Complete recovery (Positive controlled re-exposure 3 weeks later → new episode → prednisone therapy → complete recovery) | 33 |
| 22 | 22/M | 1200 (N/A) | 1 | Fever, rash, eosinophilia | Kawasaki disease at age 14 | Metamizole, codeine, APAP | - | Submassive confluent necrosis with inflammatory polymorphous reaction, hypereosinophilia and phlebitis (explant, 3 d) | Liver failure and encephalopathy → LTx (3 days after initial symptoms) | 34 |
| **Intrinsic DILI cases** | | | | | | | | | | |
| 23 | 29/F | 60000 (single dose) | 1 | Altered mental status, lethargy, jaundice | Depression, asthma, prior alcohol and drug abuse | - | >2 | - | Liver profile normalizing, but loss of followúp prior to complete recovery | 35 |
| 24 | 55/F | 9600 (single dose) | 8 | Jaundice, asthenia | Arterial hyper-tension, alcohol abuse | Amlodipine | - | Large areas of confluent necrosis and zones of confluent collapses of zone 3, both infiltrated with mononuclear cells, leucocytes and macrophages (6 d) | Liver failure and stage III encephalopathy → LTx (22 days after detection) | 36 |

| | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| 25 | 48/M | 20000 (single dose) | 1 | Depressed conciuosness, severe metabolic acidosis | Alcohol abuse | - | >3 | - | Complete recovery | 37 |

Abbreviations: APAP, acetaminophen; d, days; DILI, drug-indcued liver injury; GSH, glutathione; HCV, hepatitis C virus infection; LTx, liver transplantation; mo, months; N/A, not available; Ref, bibliographic reference;UDCA, ursodeoxycholic acid; w, weeks.

[#]Treatment cessation due to maculopapular skin rash appearing 2 hours after ibuprofen intake. Jaundice appeared 7 days later; [*]7-month-old infant; [**]a single-dose of ibuprofen, 10mg/kg, was given three months earlier; [§]Last follow-up; [§§]two days after ibuprofen re-exposition during hospitalization (day 8)

**Supplementary table 2. Description of demographic and clinical characteristics in 25 Spanish Latin American ibuprofen-induced liver injury cases**

| Patient | Gender | Age, y | Time to onset, d | Comorbid conditions | Type of liver injury | Additional information | Severity |
|---|---|---|---|---|---|---|---|
| 1 | F | 21 | 15* | None | Hep | - | Mild |
| 2 | M | 43 | 25 | None | Mix | Jaundice | Moderate |
| 3 | M | 77 | 4 | Osteoarthritis, arteritis, COPD, peptic ulcer | Mix | Jaundice, rash | Moderate |
| 4 | M | 30 | 66 | None | Mix | Jaundice | Moderate |
| 5 | M | 75 | 3 | COPD, pneumothorax | Mix | Jaundice | Moderate |
| 6 | F | 69 | 21 | Diabetes mellitus | Hep | Jaundice, eosinophilia | Moderate |
| 7 | M | 43 | 8 | None | Hep | Jaundice | Moderate |
| 8 | M | 18 | 3 | None | Mix | Jaundice, lymphopenia | Moderate |
| 9 | F | 47 | 68 | None | Mix | Eosinophilia | Mild |
| 10 | F | 41 | 3 | None | Hep | - | Mild |
| 11 | F | 64 | 11 | Diabetes mellitus, hypertension | Mix | Jaundice, ASMA+ | Moderate |
| 12 | F | 59 | 4 | osteoarthritis, peripheral vascular disease | Hep | Jaundice, lymphopenia, ANA+ | LTx |
| 13 | F | 44 | 8 | Depression, breast cancer | Mix | Jaundice | Fatal |
| 14 | F | 49 | 10 | None | Hep | Jaundice, eosinophilia | Moderate |
| 15 | F | 57 | 31 | Goitre, diabetes mellitus, dyslipidemia, psoriasis | Chol | Jaundice | Moderate |
| 16 | F | 71 | 30 | Diabetes mellitus, dyslipidemia, hypertension | Mix | Jaundice, lymphopenia | Moderate |
| 17 | M | 40 | 1767§ | None | Chol | Eosinophilia | Mild |
| 18 | F | 60 | 27 | Obesity, depression | Hep | Eosinophilia, ANA+, ASMA+ | Mild |
| 19 | M | 40 | 38 | Sclerosing cholangitis, ulcerative colitis, pancreatitis | Hep | Jaundice | Moderate |
| 20 | M | 56 | 15 | None | Hep | Jaundice, ASMA+ | Moderate |
| 21 | F | 48 | 14 | Diabetes mellitus, rheumatoid arthritis | Hep | Eosinophilia | Mild |
| 22 | F | 42 | 40 | Hypothyroidism, depression | Hep | Lymphopenia | Mild |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 23 | M | 62 | 11 | None | Hep | Jaundice, ASMA+ | Fatal |
| 24 | M | 37 | 96 | None | Hep | - | Mild |
| 25 | M | 64 | 6 | Colorectal cancer, diabetes mellitus, hyperlipidemia, myocardial infarction | Hep | Jaundice, ASMA+ | Moderate |

*Asymptomatic episode, time to onset is based on first detection in routine blood analysis, §on-demand intake
Abbreviations: Chol, cholestatic; ANA+, positive antinuclear antibody titers; ASMA+, positive anti-smooth muscle antibody titers; COPD, chronic obstructive pulmonary disease; d, days; F, female; Hep, hepatocellular; LTx, liver transplantation; M, male; Mix, mixed; y, years