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An update on drug-induced liver injury—What's new?

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Drug-induced liver injury (DILI) is an important medical condition. Recently, development of novel causality assessment tools has improved the diagnostic accuracy of *idiosyncratic* DILI, particularly RECAM (Revised Electronic Version of Roussel Uclaf Causality Assessment [RUCAM]). RECAM was found to be better than RUCAM in difficult cases and increased the precision of the DILI diagnosis but needs further refinement. In recent years, there has been an increased incidence of DILI with drugs, such as oncological drugs and herbal and dietary supplements (HDSs). DILI is commonly associated with checkpoint-induced liver injury. Treatment with corticosteroids has been the standard of care in this type of liver injury, but its use is controversial and potentially harmful. With the help of liver biopsy, 60% of subjects can avoid corticosteroids. In recent years, a number of dietary supplements have been found to lead to DILI, such as turmeric, *Garcinia cambogia*, kratom and ashwagandha. HLA-B*35:01 has been identified as a risk factor for green tea extract-induced liver injury. International collaborative efforts have tried to find candidate biomarkers, but no biomarker has yet demonstrated superior performance to standard liver tests. FDA has recently approved the use of serum glutamate dehydrogenase (GLDH) as a biomarker to distinguish liver injury from muscle injury. Serum GLDH should be used alongside standard liver injury monitoring in patients without pre-existing liver disease. In the current review, recent findings in DILI are presented on diagnostic strategies, new agents such as checkpoint inhibitors and HDSs leading to DILI, biomarkers and new therapies.

Keywords: DILI, drug-induced autoimmune hepatitis, hepatotoxicity, secondary sclerosing cholangitis

Introduction

DILI (drug-induced liver injury) can mimic almost all known liver disorders and is always a part of the differential diagnoses among patients without an obvious cause of jaundice or liver enzyme elevations. *Idiosyncratic* DILI is, together with paracetamol toxicity, the most common cause of acute liver failure (ALF) in westernized countries. Although DILI associated with the use of most drugs is rare, DILI is a relatively common aetiology in unselected patients presenting with abnormal liver tests. In a recent nationwide prospective study from Iceland, in patients with hepatocellular and cholestatic liver injury, DILI was found among 8% of patients, with a similar frequency as hepatobiliary cancer and more common than viral hepatitis, but less common than choledocholithiasis and ischaemic hepatitis [1].

The development of safer medications over the past two decades, such as in the treatment of epilepsy, has reduced the risk of DILI [2]. In a recent study on DILI associated with antiepileptic drugs (AED) in the US, the frequency of AED liver injury significantly decreased over the last two decades [2]. This is most likely due to increased use of newer AEDs marketed in the US, and newer AEDs were less likely to have unfavourable compound characteristics that increase the risk of DILI, such as lipophilicity, aromaticity, and reactive metabolite formation [2].

However, other novel therapies such as anti-TNF alpha inhibitors and checkpoint inhibitors have been associated with a relatively high frequency of DILI [3, 4]. DILI has been reported to occur in approximately 1% (1 out of 120) of infliximab (IFX) users [3] and up to 9% in users of checkpoint

inhibitors, which is a high rate for an *idiosyncratic* reaction (see below in sections on new drugs causing DILI).

Thus, given the importance of immune-related therapies in the treatment of immunological disorders and malignancies, associated DILI has become a major challenge in the management of these patients. The management of patients with suspected DILI is frequently in the hands of experts in other fields of medicine than gastroenterologists and hepatologists. Thus, management of patients with suspected DILI is often undertaken by clinicians from specialties other than gastroenterology or hepatology. Therefore, it is very important for the former group to have a broad understanding of the main principles of the diagnosis of DILI, the most common aetiologies, assessing the severity of the liver injury, when to refer to a specialist, and tackling potential complications. In the last two decades, knowledge of various aspects of *idiosyncratic* DILI has increased significantly.

For initiation of most drugs, DILI is so rare that it is not considered cost-effective to follow liver tests on a regular basis in order to detect liver injury. However, for certain agents such as tuberculostatics, both liver tests and/or development of new symptoms that might be associated with DILI are followed. Moreover, in treatment with other drugs such as disulfiram, liver tests are controlled after a few weeks, and in treatment with checkpoint inhibitors, liver tests are usually controlled prior to each cycle of infusion. If liver enzymes are elevated above the traditional DILI threshold, that is, ALT $>5 \times$ upper limit of normal (ULN) and/or ALP$>2 \times$ ULN, a detailed history should be obtained. Is the patient symptomatic? Is there fever or recent hypotension and/or hypoxia? Is upper abdominal pain associated with liver enzyme elevations? Is there alcohol overconsumption, use of over-the-counter drugs, or herbal and dietary supplements (HDSs)? If these questions are negative and no obvious cause of liver injury is found on hepatobiliary imaging, answers to further questions are needed. When was the suspected drug started? What was the dose? Has the dose been increased? What is the documentation of hepatotoxicity, for example, in LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/)? If the liver tests are increasing and/or jaundice develops, the discontinuation of the implicated drugs should be considered early, and at the same time, the causality assessment process started. There are several causality assessment tools available, such as Roussel Uclaf Causality Assessment (RUCAM), expert opinion and RECAM, which includes checklists that are helpful in excluding competing aetiologies, as discussed below [5–8].

In the current narrative review, emphasis is on the development of new knowledge of the study of DILI over the last 5 years. Important publications from 2020 to 2026 will be the main focus. The main fields to be explored are advances in diagnostic strategies, new etiological agents leading to DILI (including a variety of HDS), new phenotypes of DILI associated with antibiotic use, new biomarkers intended to improve diagnosis and prognosis, recent advances in the understanding of DILI due to checkpoint inhibitors and novel therapies for DILI.

New diagnostic strategies of DILI

Establishing a diagnosis of DILI has been called the Achilles heel of the study of DILI. Unfortunately, there is no gold standard or reliable biomarkers to establish the diagnosis of DILI, and sometimes the diagnosis of DILI can be very difficult. However, recent intake of drugs and/or HDS known to have hepatoxicity potentially increases the likelihood of the DILI diagnosis with concomitant exclusion of competing aetiologies (Fig. 1). Various methods have been used to assist in the diagnosis of DILI in the past. The causality assessment instrument, most commonly used in clinical research, has been the RUCAM scale developed by the Council of International Organization of Medical Sciences from the early 1990s [5, 6]. This consists of a checklist covering important parameters that need to be taken into consideration in a patient with suspected DILI, such as time to onset, course of liver injury after cessation of the drug, exclusion of competing causes and previous documented hepatotoxicity. However, there are several limitations of the RUCAM scale, such as the lack of clear operating instructions, leading to interobserver variability, unclear validity and several other weaknesses. The group drug-induced liver injury network (DILIN) from the US has instead used expert opinion in the causality assessment process [7]. Expert opinion is not an objective methodology, although clinical judgment of experienced hepatologists is an important assessment of suspected DILI. In the Prospective European DILI Network (PRO-EURO-DILI-NET), RUCAM has been utilized together with expert opinion. However, there is a need for a

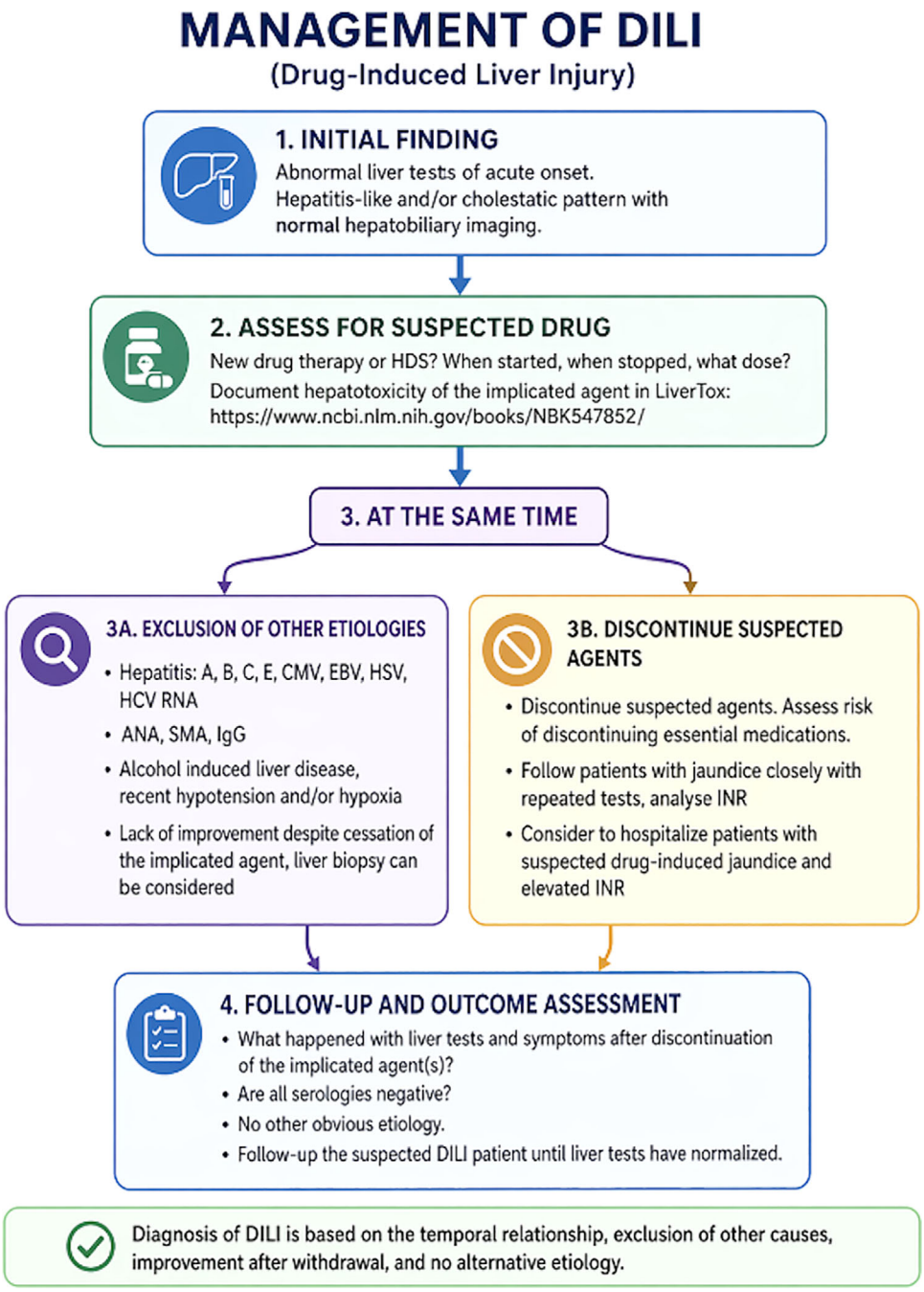

Fig. 1 *The management of drug-induced liver injury (DILI) is illustrated, from initial findings in a patient with suspected DILI: based on assessment of the implicated agent, exclusion of competing aetiologies, stopping the therapy and assessment of severity and follow-up. HCV, hepatitis C virus; HDS, herbal and dietary supplement; INR, international normalized ratio.*

refined methodology to assist and improve the diagnostic accuracy of patients with suspected DILI. Recently, in an international collaboration between DILI experts with data from the DILIN and the Spanish DILI Registry, a Revised Electronic Version of RUCAM for the Diagnosis of DILI, called RECAM, was developed (https://dilirecam.com/). The aim was to design an objective, online version in the public domain with a simplified scoring system, for wider use in clinical practice [8]. RECAM is linked to LiverTox (https://www.ncbi.nlm.nih.gov/books/NBK547852/), improving access to the documentation of DILI of prescription drugs. RECAM was found to be better than RUCAM in difficult cases (diagnostic extremes), had increased objectivity, and was found to increase the precision of the DILI diagnosis [8]. This causality assessment tool spans a dynamic scoring range of −6 to +20 points. However, as pointed out by the authors of the RECAM publication, further refinement and validation in other cohorts are needed [8]. It has pointed out that in RECAM, causality assessment of anti-tuberculosis (TB) drugs is flawed [9]. Anti-TB drugs are important causes of DILI in Asian countries, such as India [10] and China [11], but also in the Spanish DILI registry [12]. RECAM was based on analysis of single drugs, validated through individual drugs in the DILI registries [7, 12] and in LiverTox, whereas isoniazid, rifampicin and pyrazinamide are given together, and performing causality assessment in combination regimens is very challenging [9]. Devarbhavi et al. also highlighted that negative rechallenge might be excessively penalized within RECAM, as for example, anti-TB DILI positive rechallenge does not occur in around 90% of patients [13]. Interestingly, according to the RECAM instrument, the distinction between cholestatic/mixed and hepatocellular type of injury was not found to be necessary for the latency of the drug reaction, as in RUCAM [8]. Being an electronic instrument, RECAM includes unique features that remind the user of testing for important aetiologies, some of which are quite rare causes of acute liver injury, at least in some countries, such as hepatitis E and acute HCV (hepatitis C virus), measured with PCR [8]. Several recent studies have tried to validate RECAM. A Japanese study used a modified approach of RECAM to identify DILI in a retrospective analysis [14]. By omitting aetiologies in RECAM rarely found in Japan, such as PCR for HCV and hepatitis E, the sum of highly probable DILI cases was approximately 80% [14]. Thus, the modified version of RECAM, the Japanese version (RECAM-J 2023), follows RECAM's scoring system, except for Domain 4. In a recent study from China, the RUCAM and RECAM causality assessment scales were compared [15]. A total of 481 DILI patients and 100 controls with alternative diagnoses were included, with a single prescription drug in 63% and 37% due to HDS. Better diagnostic performance was found with RECAM, with a significantly higher area under the curve (AUC) than for RUCAM [15]. This was found for all DILI cases with AUC 0.947 versus 0.867 ($p = 0.0016$), with similar significant differences in AUC for conventional prescription drugs and also for HDS [15]. Moreover, causality assessment was also found to be adequate for liver injury due to HDS [15]. In a single-centre study from the US, RUCAM and RECAM were compared on 120 suspected DILI cases identified by a search for ICD-10 diagnostic codes for toxic liver disease [16]. RUCAM was found to have better agreement with DILIN expert opinion scores versus RECAM [16]. However, similar to the Japanese experience [14], making HCV RNA and anti-HEV IgM optional significantly improved agreement between DILIN expert opinion scores and RECAM [16]. It is unclear why the RECAM seemed to work better in the Chinese than in the US cohort. However, case identification was different in the Chinese study, not with ICD-10 codes but by conventional methods of diagnoses in agreement with international guidelines. Thus, there was a greater intrinsic difference in the control (non-DILI) cases compared with the DILI cases with probable causality, which might explain a better discrimination with the RECAM causality assessment tool [16]. Both acute HCV and acute HEV are very rare in many countries, and depending on the incidence of these infections, their place in the assessment of competing aetiologies should be variable, depending on the clinical context, and not mandatory in all patients with suspected DILI. RECAM will require an update when this has been validated in separate DILI cohorts [17–19].

The importance of liver biopsy in the causality assessment of DILI is controversial. There are no pathognomic histological features that prove DILI. In a recent study, a review of histology was found to change the causality score in 68% of patients, and increased the DILI likelihood score in 48% and decreased it in 20% [20]. In a minority of patients (16%), there was a clinically meaningful change in the causality score [20]. Interestingly, a biopsy performed in patients taking drugs with a well-documented DILI—such as

amoxicillin–clavulanate, trimethoprim–sulfamethoxazole, minocycline and nitrofurantoin—was unlikely to be helpful. Limitations of the study were the retrospective approach in patients who had already undergone a liver biopsy, which can be associated with a selection bias [20]. In a study from China, the timing of biopsy—within a month, 1–3 months and >3 months—was found to impact the liver pathology findings in DILI patients [21]. Acute cholestatic hepatitis dominated in the group having a biopsy within 1 month [21]. Septic shock or ischaemic hepatitis are important differential diagnoses in patients with suspected DILI that are included as exclusions in RUCAM and RECAM. In a recent study from the US comparing RUCAM and RECAM, with identification of DILI patients with ICD-10 codes, the most frequently identified alternative cause of liver injury was ischaemic hepatitis in approximately 30% of cases [16]. Moreover, in a Korean study, the most common reason for exclusion of patients with suspected DILI was ischaemic hepatitis, partly due to septic shock [22]. Until recently, studies trying to find distinguishing features between patients with DILI and sepsis have been lacking. In a recent comparative study between sepsis-induced liver injury (SILI) and DILI patients, some distinguishing features between these two conditions were identified [23]. Marked elevation of AST and rapid resolution with an HC pattern of liver injury favours the diagnosis of SILI [23]. Cholestatic/mixed SILI also resolves rapidly in contrast to CS/mixed DILI that is associated with markers of more pronounced liver injury [23].

New herbal and dietary supplements

Liver injury associated with HDS continues to grow, as shown in several different hepatotoxicity registries [12, 24–26]. Indeed, from 2020 to 2025, important new ingredients, classified as HDS, have been found to lead to liver injury.

The popularity of various HDS varies across countries. In a recent study from China on the evaluation of different causality assessment methods of DILI, mentioned above, single prescription drugs were identified in 63% of cases and HDS in 37% [15]. Among the HDS culprit agents overall 21% were associated with *Polygonum multiflorum* [15]. This herbal preparation has been reported in a few isolated case reports in the West. A recent report from San Francisco in the US described a 48-year-old woman who developed hepatocellular jaundice after drinking tea containing *P. multiflorum* [27]. In India, during the COVID-19 pandemic, many cases of liver injury were identified due to *Tinospora cordifolia* [28–30]. *T. cordifolia* is a widely grown shrub that has been commonly used in India's traditional system of Ayurveda and is considered to have immune-boosting properties. In two case series from India, the relationship with the intake of *T. cordifolia* was convincing and, interestingly, the most common phenotype was drug-induced autoimmune-like hepatitis (DI-ALH). In the largest series, 43 patients were identified, of whom more than half were women, with a latency of 46 days [28]. Most commonly, patients presented with antinuclear antibodies (ANA) elevation, and among those having a liver biopsy, autoimmune features were observed with acute hepatitis and hepatocyte and canalicular cholestasis [28]. In both series, it was evident that *T. cordifolia* consumption seems to induce an autoimmune-like hepatitis or unmask an underlying autoimmune liver disease, which might support its immune 'booster' mechanism [28, 29]. However, limited information was given in the general management, and whether those who received corticosteroids were found to have a relapse after stopping corticosteroids, which would support the role of *T. cordifolia*. As was pointed out in a letter to the editor, a distinctive feature that separates DI-AIH from classical AIH is that of absence of relapse in patients with DI-AIH or progression to cirrhosis, whereas with classical AIH, relapse is almost universal [30].

Case reports from other countries have provided further documentation of the hepatotoxicity potential of *T. cordifolia* [31–33]. From the Latin-American registry, a recent report revealed that 29/367 (8%) identified DILI cases were associated with the use of HDS [24]. *Camellia sinensis*, in some Herbalife products and *Garcinia cambogia*, were the most commonly implicated agents and mostly used for weight loss [24]. The median latency was 1 month, mostly with hepatocellular injury (83%) and jaundice (66%). Five cases (17%) developed ALF. Severity was more pronounced among the HDS cases, with fatal/liver transplantation outcomes (21% vs. 12%; $p = 0.005$) [24]. In the recent PRO-EURO-DILI-NET cohort study, 7% of cases were due to HDS and weight-loss supplements and/or supplements containing green tea extracts [25]. In a landmark paper from Hoofnagle et al., the main genetic risk factor for liver injury associated with the use of green tea extract was reported [34]. Among approximately 1400 cases within the DILIN cohort at that time,

40 supplements contained and were attributed to green tea, with a distinct biochemical phenotype, being hepatocellular in 95% of cases [34]. The liver injury was severe in 35% of cases, requiring liver transplantation in 8%. Interestingly, HLA typing demonstrated a high prevalence of HLA-B*35:01, observed in 72% of green tea cases, but only 15% among cases due to other supplements and 12% attributed to other drugs, which was similar to population controls (11%). Thus, the study by Hoofnagle et al. explains that many of the supplements used mainly for weight-loss with green-tea extract among the ingredients are the cause of liver injury in genetically susceptible individuals. Two identical twins developed liver injury from the same HDS brand (Hydroxycut), containing green tea, 18 years apart, with a remarkably similar biochemical phenotype with hepatocellular jaundice [35]. Both had the genotype HLA-B 35:01 allele, a risk factor for green-tea extract-induced liver injury, which was included in both Hydroxycut products [35]. According to recent publications from the DILIN, the most common ingredients causing liver injury in the US, apart from green tea, are turmeric, *G. cambogia*, kratom and ashwagandha [36–39]. In the study by Halegoua-DeMarzio et al., HLA-B 35:01 was also found to be a risk factor for turmeric-induced HILI, as in the case of green tea extract-induced liver injury [36]. The most common reasons reported for turmeric use—which was used for a median of 86 days—were arthritis, pain relief and general health or well-being [36]. A coating with synthetic emulsifiers in turmeric supplements might account for higher curcumin bioavailability, which has been suggested to be a risk factor for hepatotoxicity [40]. Emulsifiers have been shown to alter gut microbiota, which has been found to be associated with downregulation of the hepatic mitochondrial function, and an increase in hepatic key enzymatic, inflammation and cell-activation pathways in an animal model [41]. Other reports from Italy are in agreement with the US study [42]. However, the pharmaceutical preparation of the turmeric supplements has not been reported or investigated in detail [37, 43]. One of the HDS that has been shown to have a well-documented hepatotoxicity in recent years is *G. cambogia* [37, 43]. Green tea extract, turmeric and *G. cambogia* all seem to cause predominantly hepatocellular liver injury within 1–4 months [34, 36, 37]. In a recent meta-analysis on a botanical dietary supplement from the fruit of the tree *Garcinia gummi-gutta*, commonly known as *G. cambogia*, a total of 34 hepatotoxicity reports were identified [43]. Overall, nine liver transplantations were required among these patients, and one died of ALF [43]. Causality was performed with a positive rechallenge in one case [43]. Other recently identified HDS ashwagandha and kratom—in contrast with green tea extract, turmeric and *G. cambogia*, associated with hepatocellular injury—are associated with cholestatic or mixed type of liver injury, with a shorter latency [38–40]. Ashwagandha (*Withania somnifera*) is widely used in Indian Ayurvedic medicine, and multiple dietary supplements containing ashwagandha are marketed in the US and Europe. In the first series describing suspected liver injury due to ashwagandha, with three cases from Iceland and two from DILIN, there were considerable similarities in the clinical and biochemical profiles [38]. All developed jaundice and pruritus with cholestatic or mixed type of liver injury, after a latency of 2–12 weeks [38]. Other reports have found a very similar pattern of liver injury after intake of ashwagandha and typically histological features of cholestatic hepatitis [44, 45]. In a series from India, 23 patients developed liver injury after intake of ashwagandha, and of those who had taken a single-ingredient formulation of ashwagandha, cholestatic hepatitis was the most common presentation. A total of three patients with underlying liver disease developed acute-on-chronic liver injury, and three died on follow-up [46]. It is not clear why reports of ashwagandha have been appearing during the last 5 years, although widely used in ancient Ayurvedic Indian medicine. It is likely that the dose of ashwagandha has been higher in marketed products in the West and also in India, although this has not been convincingly shown in recent studies. Lastly, kratom, which is a botanical product used as an opium substitute with abuse potential, has recently been associated with liver injury [39, 47].

Kratom (*Mitragyna speciosa*) leaves contain the mu opioid partial agonists mitragynine and 7-hydroxymitragynine [47]. It is known as 'ketum' in Malaysia and 'kratom' in Thailand and is illegal in many countries. A literature review was undertaken of cases with liver injury associated with the use of kratom, and causality assessment was undertaken [47]. The authors found strong evidence of DILI associated with this product, originating from multiple sources, such as case reports, FDA databases and from the DILIN [47]. The DILIN study group reported their experience recently with 11 cases found to be due to kratom [39]. The

majority were of male gender with a median age of 40 years, who presented with jaundice after a latency of only 2 weeks. No patient died from liver failure due to kratom-induced hepatotoxicity, and no transplants were required. Interestingly, 10 of the 11 patients were homozygous for the PTPN22 G allele, which has been found to be a non-HLA, genetic risk factor for DILI across a great variety of drugs [48].

Not only has liver injury due to HDS increased over the last decade in most countries, but ALF due to HDS has been shown to lead more frequently to liver transplantation or death than ALF due to prescription drugs, 83% versus 66% [49, 50]. In another recent study from the US, patients with HDS-related liver injury were more likely to die or require LT than those with ALF due to conventional drugs [51]. The more serious hepatic consequences associated with the use of HDS have been called the elephant in the room [52].

DILI and antibiotics

In the vast majority of previous DILI studies, antibiotics have been shown to be the most common type of drug leading to DILI [1, 2, 7, 12, 25].

Ten years ago, the DILIN group described a novel syndrome of cholestatic liver disease with a latency of 1–3 weeks after a single dose of cefazolin [53]. This was met with a lot of skepticism, even by leading Figures in the field of DILI. This adverse reaction occurred after a single dose, and the latency was often 2–3 weeks [53]. In a recent study from DILIN, a total of 58 cases of cefalosporin-induced liver injury were reported, around 70% with cefazolin as the implicated agent [54]. The median treatment duration of cefalosporin therapy was 1 day (range 1–15 days), and similar clinical and biochemical features were noted in patients receiving a single prophylactic dose and multiple doses for infection [54]. Novel genetic information was provided, showing HLA-A*02:01 to increase the risk of DILI, OR 2.5–2.7 (p value <0.0001) [54].

Recently, in a population-based study from Iceland among patients with DILI due to antibiotics, seven patients with liver injury due to cefazolin were reported [55]. Very similar biochemical and clinical features were observed as in previous studies on cefazolin [53, 54], with a latency up to 30 days after two doses [55]. Thus, the previous observations in cefazolin-induced DILI were reproduced in the Icelandic study. Therefore, these recently published studies demonstrate convincingly that cefazolin-induced liver injury can occur after a single dose, with cholestatic liver injury developing after 2–3 weeks. In a recent study from Spain, antibiotics were the second most common cause of DILI, after antineoplastic drugs (mostly checkpoint inhibitors), which were the most common types of drug leading to DILI [56]. Together with checkpoint inhibitors, several other drug types other than antibiotics have been found to increasingly lead to DILI.

New drugs leading to DILI

IFX, one of the biological therapies that has revolutionized treatment of a number of autoimmune diseases, has been shown in recent years to have a well-documented hepatotoxicity [3]. IFX belongs to category A in LiverTox, with more than 100 cases reported [57].

IFX-induced liver injury has a distinct clinical and biochemical phenotype, which in the majority of cases is associated with hepatocellular injury, occurring after 4–5 infusions, and approximately 50% seem to require corticosteroids in order to hasten recovery [3]. IFX has been reported to be associated with DI-ALH [3, 58]. IFX was, after antibiotics, the most common cause of a single prescription drug in Iceland, and IFX is the 11th most common drug in DILIN [17]. In most cases, the prognosis of patients who develop DILI due to IFX is favourable. However, a total of 12 cases of IFX-induced liver injury have been reported to lead to severe ALF, most of them requiring a liver transplantation [59]. Of interest are the accumulating reports of DILI due to intravenous (iv) methylprednisolone (MP) [60–64]. These reports demonstrate that hepatocellular injury often predominates with autoimmune features. Moreover, positive rechallenge has been frequently reported, occurring after a few weeks, and mortality from liver injury has been observed [61–64]. However, there are many unanswered questions regarding this type of DILI, as has been pointed out [65]. It is unclear why only MP and not other corticosteroids given intravenously such as hydrocortisone, betamethasone and dexamethasone have not been reported to cause DILI and why MP seems to occur mainly in patients with multiple sclerosis [65].

Among other new drugs that have recently been associated with DILI are CDK4/6 inhibitors,

Table 1. Drugs and herbal and dietary supplements (HDSs) that have newly been recognized and documented to have the potential to cause drug-induced liver injury (DILI), mainly reported during the last 5 years.

Drugs/HDS	Median latency	Median age (years)	Female (%)	Biochemical features	Prognosis
Infliximab (Ref. [3])	110 days	46	78	HC 64%, mixed 33%, CS 3%	Favourable, but liver transplants reported
Check point inhibitors (Ref. [79])	3.5–4.9[a] infusion cycles	63	47	HC 39%, mixed 37%, CS 24%	Mild 62%, moderate in 45 in 39%. No acute liver failure
Green tea extract (Ref. [34])	72 days	40	74	Hepatocellular 95%	Liver transplants 8%
Covid vaccines (Ref. [70])	73 days	40	63	Hepatocellular 84%	One liver transplant
Turmeric (Ref. [36])	86 days	56	80	Hepatocellular 90%	One died of liver failure
Kratom (Ref. [39])	14 days	40	18	HC 27%, mixed 55%, CS 27%	No transplants or deaths
Ashwaganda (Ref. [38])	14 days	39	43	Mixed 60%, hepatocellular 40%	All had jaundice, no deaths or transplants
Tinospora cordifola (Ref. [28])	46 days	50	54	Hepatocellular, DI-ALH features	4 deaths and two transplants

Note: Median latency: duration in days from the start of the implicated drug to the detection of the liver injury.
Abbreviation: DI-ALH, drug-induced autoimmune like hepatitis.
[a]Mean of infusion cycles, in hepatocellular, mixed and cholestatic.

oncological agents mainly used against breast cancer [66, 67]. In a retrospective study from France and Belgium, 22 DILI cases were induced by CDK4/6 inhibitors (ribociclib, $n = 19$ and abemaciclib, $n = 3$). Around 40% of patients had autoimmune features and were treated with corticosteroids for the resolution of hepatitis [67]. Finally, the definition of DI-ALH was recently established in an international workshop [68]. Apart from well-documented drugs leading to DI-ALH such as nitrofurantoin, methyldopa, hydralazine, minocycline and IFX, other drugs have been shown to be able to induce DI-ALH [69, 70]. Although most drugs leading to DI-ALH do not relapse after immunosuppressive therapy, relapse of ALH has also been demonstrated in patients considered to have DI-ALH, particularly with a long-term follow-up [71]. In Table 1, new drugs and HDS causing DILI that have been identified are demonstrated.

New types of liver injury due to checkpoint inhibitors

Immune checkpoint inhibitors (ICIs) are a class of drugs that have transformed the prognosis of many cancer patients, particularly those with advanced malignant tumours. ICIs target the checkpoints that prevent aberrant immune responses, such as programmed cell death protein-1 (PD-1), PD ligand 1 (PDL-1) and cytotoxic T-lymphocyte-associated protein-4 (CTLA-4), which are overexpressed in cancer. By doing so, ICIs block the pathways that tumour cells use to evade the immune system. However, this mechanism is inevitably associated with immune-related adverse events affecting multiple organs, including immune checkpoint-induced liver injury (ChILI). The exact mechanisms are not fully understood. However, it is thought that the activation of cytotoxic T-cells that inadvertently target liver cells is a major driver of hepatotoxicity caused by these compounds, with probable participation of other immune cells, such as B cells, FoxP3+ Tregs, T helper cells and cells from the innate immunity, such as macrophages and dendritic cells [72]. Indeed, ChILI is a specific type of hepatotoxicity called indirect hepatotoxicity, which does not align with *idiosyncratic* DILI. This is because the mechanism of liver injury relates to the drug's pharmacological action, that

is, 'what the drug does rather than what the drug is' [73]. Consequently, ChILI occurs more frequently than *idiosyncratic* DILI, with a prevalence ranging from 1%–15%, depending on whether a CTLA-4 or PD-1/PDL-1 antagonist is used in monotherapy or in combination. The latter poses a higher risk of hepatotoxicity (9.2%) [74, 75]. The incidence of ChILI is highest when combination therapy includes ipilimumab and nivolumab, particularly in patients being treated for hepatocellular carcinoma (42%) [76]. Although the data are not yet conclusive, the type of immunotherapy and the fact that the cancer being treated is hepatocellular carcinoma are not the only suggested risk factors for the appearance of ChILI. Other factors include female sex, younger age, a history of immune-mediated diseases, and some genetic variants [77]. A study by DILIN found that the carriage of several genes was associated with ChILI [78]. These included the EDIL3 gene, which is associated with various autoimmune diseases, and the SAMA5A gene, which is expressed in and activates regulatory T cells. Other identified genes were GABRP and SMAD3, which are involved in tumour immune responses, and SLCO1B1, a gene expressed in hepatocytes with variants that alter transport function. These genes all increased the odds of ChILI with a modest effect size (OR: 2.08–2.4, $p < 0.01$) [78]. The clinical presentation of ChILI is heterogeneous, with variable latency ranging from 2 to 3 weeks to more than 4 months, and the predominant pattern is hepatocellular. However, cholestatic and mixed injury accounted for 62% of cases in a large French/Belgian cohort [79]. In order to assess causality in ChILI, alternative causes of liver damage must be excluded. In that clinical context—as well as ruling out common causes such as viral hepatitis—metastatic infiltration of the liver and alcohol abuse (including alcohol biomarkers in suspected cases) should be actively investigated. The presence of serum ANAs, smooth muscle antibodies and hypergammaglobulinaemia is uncommon, occurring in only 10%–20% of cases, and does not impact disease severity or outcomes [80]. The use of liver biopsy to assess ChILI is problematic, as there are no pathognomonic features of immune-mediated liver injury. Besides, the timing of liver biopsies in relation to the discontinuation of ICIs varies, and patients are often receiving steroids at the time of biopsy [81]. In fact, liver biopsies were performed on 95 out of 107 ChILI patients in a study, and 59% of these patients had received steroids at the time of biopsy [82]. The histology findings reported in patients with ChILI include granulomatous hepatitis with fibrin deposits and microgranulomas, as well as lobular hepatitis and periportal inflammation with varying degrees of necrosis [83–85]. In the diagnostic evaluation of suspected ChILI, the liver biopsy does not occupy a hierarchical position. The first step should be a contrast-enhanced CT or MRI scan of the liver to exclude liver metastases and/or pancreaticobiliary disease. Referral to a hepatologist is then recommended for further medical evaluation and consideration of a liver biopsy, either at the same time as or before the initiation of high-dose corticosteroids and before antimetabolite therapy. In cases where suspected ChILI does not resolve, a liver biopsy may provide prognostic information and help avoid excessive immunosuppression in patients with an alternative cause of liver injury [81]. Severity of ChILI is usually assessed in clinical practice by the Common Terminology Criteria for Adverse Events criteria. However, these criteria may overestimate the severity, as high ALT values (>20 × ULN), which correspond to a grade 4, do not correlate well with clinical outcome and mortality [75]. Instead, the criteria of the International DILI Expert Working Group—which incorporate synthetic liver parameters, bilirubin and international normalized ratio (INR)—provide a better discrimination between mild-moderate and severe ChILI cases [86]. Nevertheless, mortality from ChILI is rare. A systematic review and meta-analysis estimated the incidence of fulminant hepatitis to be 0.07% [87]. An emerging phenotype of ChILI is secondary sclerosing cholangitis, with an increasing number of case reports and case series being published [88]. Sclerosing cholangitis related to ICIs can be difficult to distinguish from primary sclerosing cholangitis. Indeed, although secondary sclerosing cholangitis is rarely diagnosed, its frequency may be underestimated, as a multicentre French/Belgian study involving 117 patients found that eight (6.8%) had biliary stenosis [79]. Compared to ChILI without involvement of the biliary tract, secondary sclerosing cholangitis related to ICIs occurred after a greater number of ICI cycles and with a longer latency [89]. It most often presents as cholestatic injury, with very high alkaline phosphatase levels, and is typically associated with antiPD-1 agents such as pembrolizumab or nivolumab [90]. Up to 27% of cases in a French pharmacovigilance series manifested hyperbilirubinemia, which was associated with a worse prognosis [91]. Although the use of systemic steroids is recommended in the guidelines for the management of most grade 2 or higher irAEs,

including ChILI [92], uncertainties remain regarding the required grade of ChILI at which to initiate immunosuppression, the timing of this initiation and the optimal dosage. In a retrospective study of the largest cohort to date of patients (mostly males) who received or did not receive steroids for irAEs, the development of irAEs was found to be associated with improved survival. The use of steroids was not found to be associated with worse overall survival. However, early initiation of steroids (within the first 2 months) was shown to reduce irAE-associated survival benefits, even with continued ICI treatment [93]. A recent study of 44 patients with grade 3 ChILI showed that an approach involving discontinuing ICI followed by a liver biopsy in cases where liver biochemistry failed to improve allowed over 50% of subjects to avoid corticosteroids, those who did not have severe inflammation [94]. Furthermore, ICI-related secondary sclerosing cholangitis responds poorly to corticosteroids and often progresses to bile duct loss [88].

New biomarkers

Genetic biomarkers. DILI is often a complex clinical scenario. Causality assessment is based on evidence of exposure to a drug or HDS within a compatible timeframe, and careful exclusion of alternative causes. This is because there are no specific biomarkers that can distinguish DILI from other causes of liver injury. Although serum aminotransferases (ALT and AST) are markers of liver injury, their specificity is very low as they are also elevated in muscle injury and other liver disorders. Serum bilirubin and the INR, on the other hand, are markers of hepatic function. In recent years, several international initiatives have been undertaken to discover and qualify DILI biomarkers [95]. According to their context of use, DILI biomarkers can be classified as either susceptibility or prediction (genetic) biomarkers, or safety/monitoring, mechanistic and prognostic biomarkers. The latter generally uses a proteomic approach.

Genome-wide association studies have identified genetic variants associated with DILI for many, but not all, common causative drugs. These are mainly HLA alleles and haplotypes, which generally differ for specific drugs [96]. However, in some cases, the same HLA allele is shared by two agents belonging to different drug classes with different mechanisms of action. An example of this is amoxicillin clavulanate and lumiracoxib, for which the risk of hepatotoxicity is associated with the HLA class II allele *DRB1*15:01* [97]. Although the discovery of genetic associations with DILI risk offered hope for risk stratification, the positive predictive value of genetic association in DILI is very low, unlike in other clinical scenarios, owing to the rarity of *idiosyncratic* DILI. This is illustrated by the *HLA-B*57:01* allele, which markedly increases the risk of flucoxacillin-induced hepatotoxicity [98]. Individuals who carry this allele have an 80-fold increased risk of developing hepatotoxicity when exposed to this antibiotic compared to individuals who do not carry the allele, which is the strongest genetic association with DILI so far. However, it is estimated that only one in every 500 carriers of this HLA allele will develop DILI when taking this antibiotic. By contrast, one in every two patients carrying *B*57:01* will develop serious hypersensitivity when abacavir is administered, making genetic testing mandatory to prevent abacavir hypersensitivity reactions. Recent data suggest that DILI related to certain drugs (i.e., amoxicillin–clavulanate) may involve a polygenic risk score comprising not only HLA variants but also other genes such as *PTPN22* (a general non-HLA genetic risk factor) and an *ERAP2* variant that results in diminished function. *ERAP2* codes for an enzyme that trims peptides for presentation by class 1 HLA proteins. The presence of all these factors further increases the risk of amoxicillin–clavulanate hepatotoxicity [99]. However, only around one in 100 carriers of this polygenic risk score will develop DILI when the antibiotic is administered, which limits the value of pre-prescription testing. This is because susceptibility to DILI is likely to involve not only genetic factors but also other factors that increase the drug concentrations. However, the high negative predictive value of the genetic association could help to diagnose DILI caused by a specific drug and could be used to prevent further exposures to that drug [100]. Ultimately, an increased knowledge of genetic risk factors should help to improve the understanding of the underlying mechanisms of DILI and improve methods for identifying hepatotoxic drugs at an early stage of development [101]. Novel genetic risk factors in idiosyncratic DILI since 2020 are illustrated in Table 2.

Non-genetic biomarkers. An improved DILI biomarker should either be more specific for liver injury than ALT or more sensitive in detecting hepatocellular dysfunction than bilirubin. Other desirable advantages would be providing

Table 2. Novel genetic risk factors in idiosyncratic drug-induced liver injury (DILI) since 2020.

Drug and HDS	Number of patients	Genetic risk factor	Odds ratio	Year of publication
Isoniazid (Ref. [113])	125	rs117491755	4.37	2021
Isoniazid (Ref. [113])	125	HLA-B*52:01	2.67	2021
Trimethoprim–sulfamethoxazole (Ref. [114])	51	HLA-A*34:02	47.52	2021
Trimethoprim–sulfamethoxazole (Ref. [114])	51	HLA-B*27:02	13.53	2021
Trimethoprim–sulfamethoxazole (Ref [114])	51	HLA-B*35:01	9.20	2021
Trimethoprim–sulfamethoxazole (Ref [114])	51	HLA-C*08:02	3.78	2021
Infliximab (Ref. [3])	36	DQB1*02:01 and HLA-DRB1*03:01	2.65	2022
Dapson (Ref. [115])	4	B*13:01	NC (100%)	2022
Nitrofurantoin (Ref. [2])	78	HLA-DRB1*11:04	4.3	2022
Nitrofurantoin (Ref. [116])	26	HLA-A*33:01	10.93	2023
Nitrofurantoin (Ref. [116])	26	HLA-A*30:02	5.56	2023
Nitrofurantoin (Ref. [116])	26	HLA-DPB1*16:01	4.84	2023
Amoxicillin-clav. (Ref. [99])	444	HLA-B*15:18	3.61	2023
Azithromycin (Ref. [117])	30	HLA-DQA1*03:01	3.44	2024
Vancomycin (Ref. [118])	9	HLA-A∗32:01	NC (78%)	2024
Green tea extract (Ref. [34])	40	HLA-B*35:01	NC (70%)	2020
Polygonum multiflorum (Ref. [119])	73	HLA-B*35:01	11.11	2020
Kampo products (Ref. [120])	19	HLA-B*35:01	9.56	2023

Note: Odds ratio represents the increased risk of developing DILI compared to different control group used in the various studies.
Abbreviations: HDS, herbal and dieteary supplements; NC, not calculated, (*x*%) = of participants.

information on the mechanisms of DILI and being more accurate than INR at predicting clinical outcomes in DILI patients at an earlier stage. A panel of promising biomarkers of liver injury—glutamate dehydrogenase (GLDH), cytokeratin-18 (K18), caspase-cleaved K18 (ccK18), osteopontin, macrophage colony-stimulating factor (MCSF), MCSF receptor and microRNA-122 (miR-122)—was evaluated in 175 patients with acetaminophen hepatotoxicity, individually and as a multivariate model, with GLDH, K18 and miR-122 [102]. The multivariate model could accurately predict patients with liver injury compared with healthy volunteers or patients with damage to muscle, pancreas, gastrointestinal tract and kidney [102]. However, despite several previous international collaborative efforts in discovering and qualifying candidate biomarkers for *idiosyncratic* DILI [95], no alternative biomarker has yet demonstrated superior performance to the standard panel of serum liver tests for use in clinical practice. In a collaborative European study, including 133 *idiosyncratic* DILI cases, a panel of fructose-1,6-bisphosphatase 1, alone or in combination with glutathione *S*-transferase A1 and leukocyte cell-derived chemotaxin 2, could potentially assist in clinical diagnosis by distinguishing DILI at onset from other aetiologies of acute liver injury, such as viral hepatitis and autoimmune hepatitis (AUC range: 0.65–0.78) [103]. The proposed strategy would involve a 'screen and confirm' approach, using conventional biomarkers such as liver enzymes to 'screen' for initial signals, followed by the use of new biomarkers for in-depth investigations to 'confirm' DILI [103]. However, further technical and clinical validation of these candidate biomarkers is needed before they can be implemented in clinical practice.

A recent small retrospective nested case–control study involving the proteomic profiling of pre-treatment plasma from 24 patients (12 with anti-tuberculosis-induced liver injury (ATB-DILI) and 12 controls) identified several differentially expressed proteins: antithrombin III, apolipoprotein D, carboxypeptidase B2, chromogranin A and retinol-binding protein 4 [104]. These proteins were validated by ELISA in an independent cohort of 35 ATB-DILI patients and 37 controls. A random forest model built using these pre-treatment biomarkers demonstrated robust predictive performance in the test set (AUC = 0.94, sensitivity = 90.0%, specificity = 90.0% and accuracy = 0.90) [104]. The authors also used multiple machine-learning approaches (GBDT, SVM, GBM etc.), which confirmed the stability and generalizability of this protein signature (inter-model AUC range: 0.85–0.96). Although promising, this panel of proteins requires further validation in independent studies, and its applicability would be limited to ATB-DILI.

A Japanese study used a metabolomics approach to analyse serum samples from 45 patients with DILI and 60 healthy volunteers. Three metabolites were identified that demonstrated a high and similar ability to differentiate between patients with mixed and cholestatic DILI, and those who had recovered from DILI (ROC-AUC > 0.9): pyroglutamylglycine (pyroGluGly), phenylalanine (Phe) and phenylalanyltryptophan (PheTrp) [105]. Some or all of these metabolites demonstrated a substantially high discriminative ability (ROC-AUC > 0.8) in patients with mixed/cholestatic DILI, compared to patients with other liver diseases (except for obstructive jaundice) [105]. Further external validation of this preliminary study is also warranted.

In a recent prospective, nested case–control observational European study, 22 molecular bile acid (BA) species were determined by liquid chromatography tandem mass spectrometry in 120 patients adjudicated as DILI, in 49 subjects with non-DILI acute liver injury and 25 healthy volunteers. In DILI patients, higher values of total, primary and conjugated BAs at presentation were associated with liver injury that was likely to progress in severity. The ratios of primary-to-secondary BAs and (cholic acid + deoxycholic acid) to (chenodeoxycholic acid + lithocholic acid) improved the prognostic value of the MELD score [106]. However, further research in independent longitudinal studies is needed to validate this biomarker.

Even though new biomarkers have not yet been adopted in daily clinical practice, the FDA has recently approved the use of serum GLDH as a safety biomarker in clinical trials for participants with elevated serum transaminases due to muscle injury or degeneration, when DILI is being considered. GLDH should be used alongside standard liver injury monitoring biomarkers (ALT, AST, GGT, ALP and bilirubin) in patients without pre-existing liver disease [107].

New therapies for DILI

Prevention and treatment of DILI. *Idiosyncratic* DILI is a liver disorder for which there is no specific therapy. Overall, most cases of DILI recover when the implicated drug is discontinued and supportive care is provided. However, a small proportion of cases progress to liver failure, requiring intensive care and emergency liver transplantation. Randomized clinical trials (RCTs) in acute DILI are difficult to design and conduct because the condition often resolves spontaneously, making it unrealistic to define a robust endpoint (e.g., transplant-free survival). Therefore, weaker endpoints such as length of hospital stay or time to ALT normalization are used instead, which makes the potential clinical benefit of therapy uncertain.

This is illustrated by a randomized, placebo-controlled trial of intravenous *N*-acetylcysteine (NAC), which explored the efficacy of NAC in managing anti-tuberculosis-DILI in 102 patients [108]. NAC had to be discontinued for five subjects due to adverse events. There was no difference in the primary endpoint (time to reduce ALT to <100 U/L) between the two groups, but NAC significantly reduced hospital stay ($p = 0.09$). Overall mortality (14%) did not differ between groups. It should be noted that 87% of the subjects in this study had concomitant HIV, which may prevent the results from being generalized [108].

Although corticosteroids are frequently used to mitigate ChILI, the recommendations for their use are based on clinical experience rather than well-designed and conducted prospective studies. Likewise, there is insufficient evidence to support the use of corticosteroids in patients with severe DILI or even drug-induced ALF. However, when empirically indicated in severe DILI, a propensity matching score analysis showed that they were not associated with worse outcomes, and there is a greater rate of normalization of liver enzymes [109]. A

potential role of corticosteroids has been investigated in chronic DILI. In a Chinese randomized open-label trial, 70 patients with chronic DILI (predominantly hepatocellular) as defined by biochemical and/or histological abnormalities that persisted 6 months after the onset of DILI were given either MP plus glycyrrhizin or glycyrrhizin alone over 48 weeks. In the steroid plus glycyrrhizin group, there was a higher proportion of patients with sustained biochemical response (94% vs. 71%, $p = 0.023$) and a shorter time to biochemical normalization as well as a decrease in histological activity and fibrosis [110]. The same authors later conducted another randomized open-label study in 90 patients with chronic DILI showing that a shorter 36-week tapering steroid regimen was as effective as a 48-week regimen [111]. It is worth noting that 41% of patients had the DI-ALH phenotype, and the response rate of this subtype did not differ from that of the rest of the chronic DILI group. However, the fact that such a high rate of chronic DILI has never been reported in western DILI series, coupled with the finding that more than half of the events in this trial were attributed to herbal compounds, would limit the validation and generalizability of the results.

In Asia, particularly in China, a number of agents have been used to treat and prevent DILI and other causes of liver injury. A recent systematic review included 22 RCTs of various compounds—including silymarin (8 studies), bicyclol [4], magnesium isoglycyrrhizinate [3], NAC [3], tiopronin [1], L-carnitine [1] and traditional Chinese medicines [2]—which were tested in the intervention arm, whereas the control arm mostly received standard supportive care or placebo. Although safety was good, there was evident heterogeneity among the studies in terms of DILI case qualification and methodological quality. The RCTs performed demonstrated the limited efficacy of the specific intervention [112]. There is an unmet need for international research initiatives to establish a framework for the design of RCTs and therapeutic endpoints in DILI.

Conclusion and future prospects

Over the last two decades, advances in DILI research have led to the identification of newer hepatotoxic agents and more reliable diagnostic tools. They have also revealed genetic variants that increase susceptibility to DILI, as well as new biomarkers that, while not specific to DILI, can enhance diagnostic certainty in some cases. International collaborations have been instrumental in these advances. The pharmaceutical industry's efforts to implement preclinical models to improve the assessment and prediction of hepatotoxicity in humans, in order to guide future drug safety testing, can now benefit from the growth of artificial intelligence. Indeed, artificial intelligence will also raise awareness of DILI among prescribers and help DILI investigators manage and process the vast amount of clinical information generated in recent years, creating new models for predicting, diagnosing and prognosing DILI.

Author contributions

Einar S. Björnsson: Conceptualization; writing—original draft; methodology; validation. **Raul J. Andrade**: Conceptualization; writing—original draft; methodology; validation.

Conflict of interest statement

The authors declare no conflicts of interest.

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Data availability statement

The data that support the findings of this study are available on request from the corresponding author. The data are not publicly available due to privacy or ethical restrictions.

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