Drug Induced Liver Injury: Is there an Indication for Ursodeoxycholic Acid Use?

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Abstract: Drug induced liver injury (DILI) is one of the most conflicting diagnoses for hepatologists. DILI is defined as an acute or chronic liver injury, manifested by alteration of liver function tests, due to the consumption of medications, herbal or dietary supplements, after excluding other etiologies of liver disease. Several facts contribute to DILI; among them, host related factors, as age, sex, alcohol consumption and underlying chronic diseases; and drug related, as dose, lipophilicity, drug metabolism and interactions. Few treatments for DILI are actually recommended in current guidelines. Ursodeoxycholic acid (UDCA) use for DILI is debated, because of the lack of clinical trials proving its efficacy. Hence, in several case reports UDCA has been used for DILI with good results preventing the progression of the disease and the need of liver transplantation. Small series have also described the resolution or amelioration of DILI with the use of UDCA. Nonetheless, current guidelines do not support its wide use. The aim of this review is to discuss the current knowledge of DILI and the mechanisms of action and facts of the use of UDCA in DILI, making UDCA a promising alternative for the treatment of DILI.

Keywords: Drug-induced liver injury, Ursodeoxycholic acid, biliary transporters, vanishing bile duct syndrome, cholestasis.

1. INTRODUCTION

DILI is the manifestation of acute or chronic liver injury due to unexpected adverse reaction to drugs or herbal products [1-3]. This damage is eventually precipitated by drug related factors such as metabolism, drugs-interactions, and the dose and duration of the treatment, but also by host associated facts such as age and gender. Even though, the vast majority of DILI are idiosyncratic [1,4]. Several hepatic transporters and enzymes could be involved in the development of DILI, it has been described that the pathophysiology of DILI is associated first, to the metabolism and transport of the drug within the liver; second, to the direct toxic effect of the medication causing oxidative stress and the triggering of inflammatory pathways; or third, by the coaction of host and drug factors [4].

This review attempts to analyze and discuss various characteristics of DILI and focuses on the mechanism of action of UDCA and its protective effect on DILI by preserving cholangiocytes and hepatocytes from bile acid induced apoptosis. UDCA might represent an interesting therapy for treating DILI [5-7]. Nevertheless, clinical trials are needed to confirm UDCA's beneficial effect.

2. ETIOLOGY OF DILI

DILI is a wide term used to describe the hepatic injury caused by drugs and recently the term herbal induced liver injury (HILI) has been proposed; nevertheless, DILI includes both terms. The main drugs reported to cause DILI are antimicrobials with 45% of the cases, after that herbal and dietary supplements (HDS), cardiovascular drugs, anticonvulsants, antineoplastic drugs and nonsteroidal anti-inflammatory drugs (NSAID). Among the antimicrobials, the most frequently described is amoxicillin-clavulanate in 22%; afterwards anti-TB drugs, mainly isoniazid, and nitrofurantoin [3].

In the US network, the most frequent causative drugs were amoxicillin-clavulanate, isoniazid, trimethoprim-sulfamethoxazole (TMP-SMZ), antifungals, anticonvulsants, NSAID and nitrofurantoin [8].

For the hepatocellular DILI, the most common agents described are isoniazid, macrolides,

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minocycline, nitrofurantoin, inhaled anesthetics, anticonvulsants, amiodarone, allopurinol, NSAIDS and fluoroquinolones. For the cholestatic injury, the drugs with higher risk of hepatotoxicity are amoxicillin-clavulanate, TMP-SMZ, anabolic containing steroids, azathioprine, amiodarone, sulfalazine, and anticonvulsants as phenytoin and carbamazepine [3].

Classified by intrinsic or idiosyncratic DILI: For intrinsic damage the most common causative medications were acetaminophen, amiodarone, anabolic steroids, antimetabolites, cyclosporine, anticonvulsants, HAART drugs and statins; for idiosyncratic injury were allopurinol, amiodarone, amoxicillin-clavulanate, bosentan, NSAID, fibrates, fluoroquinolones, anti-TB drugs (such as isoniazid), antifungals (such as ketoconazole and terbinafine), cardiovascular drugs (such as lisinopril, methyldopa and statins), other antibiotics (such as nitrofurantoin and minocycline), and inhaled anesthetics [1].

There are also new drugs that have potential hepatotoxicity; among them, tumor necrosis factor-alpha antagonists, tyrosine kinase inhibitors and other anti-neoplastic drugs [9].

The Latin America DILI group described that HDS are a common cause of hepatotoxicity. Among the HDS, the most common were Camellia sinensis and garcinia cambogia [10]. Other HDS with reported HILI in Mexico are Scoparia dulcis L, Citrus aurantium L, Prunus Persica, Rosmarinus officinalis, equisetum hyemale and Tilia Mexicana [11].

3. EPIDEMIOLOGY

The annual incidence of DILI varies among countries, as well as its severity. In Europe it is described as an incidence of 14 to 19 for 100,000 habitants [12]. In France, it has been reported an annual incidence of DILI of 13.9 +/- 2.4 per 100,000 inhabitants [13].

In the US, the reported incidence of DILI is 2.7 per 100,000 habitants in 2014 [14].

China's DILI annual incidence disclosed in general population was of 23.8 per 100,000 persons. China has recorded a higher incidence of DILI compared to that expressed in Western countries; probably due to the use of Traditional Chinese medicines (TCM) that represent herb induced liver injury (HILI) rather than DILI [15]. Nevertheless, this fact has been debated; Cong *et al*. discuss these results arguing that TCM and HDS are not the main cause of DILI in China because the Shen study grouped all TCM in the same category, contributing considerably to the high proportion of DILI caused by TCM [16].

In the Latin America DILI network, they reported 206 cases of DILI from which 59% were women with mean age of 51 years old, hepatocellular presentation was in 54% of the cases and the main drugs involved were amoxicillin-clavulanate, diclofenac, nimesulide, nitrofurantoin, cyproterone acetate, and anticonvulsants [17].

The global incidence of DILI reported in the US was of 19 to 20 cases per 100,000 persons a year and the most common drug responsible was amoxicillin-clavulanate with approximately one of 2300 users [8]. DILI contributes to the development of acute liver failure (ALF) in 13% of the cases mainly due to acetaminophen in 39%, but also to isoniazid, nitrofurantoin and sulfur antibiotics [9]. DILI was found to be significantly more common in patients with underlying liver disease with 16% compared to 5.2% in patients without preexisting liver disease [18].

It has also been reported that older patients (>65 years old) tend to present predominantly with a cholestatic injury compared to younger; nonetheless, the need of LT or mortality was not higher in >65 years old patients compared to younger patients [19].

In children antimicrobial drugs are the principal agents that cause idiosyncratic DILI manifesting with hepatocellular pattern damage, at a mean age of 14 years old and more frequently in girls. Mortality in children due to DILI is rare [20].

4. RISK FACTORS FOR DILI

4.1. Host Factors

Several host factors have been described to increase patient's susceptibility to develop DILI. Among these factors is age, DILI is 5 times more common in patients older than 70 years old [3], having an incidence rate of 41/100,000 patients [1], adverse effects of several medications increase with age, suggesting a probable mitochondrial functional impairment as the causative factor [1]. Even the scale for the causality assessment of DILI gives extra points if the patient is older than 55 years old [2], as well as for alcohol consumption; that might increase hepatotoxicity of certain drugs as isoniazid and methotrexate [1]. Gender is another host risk factors

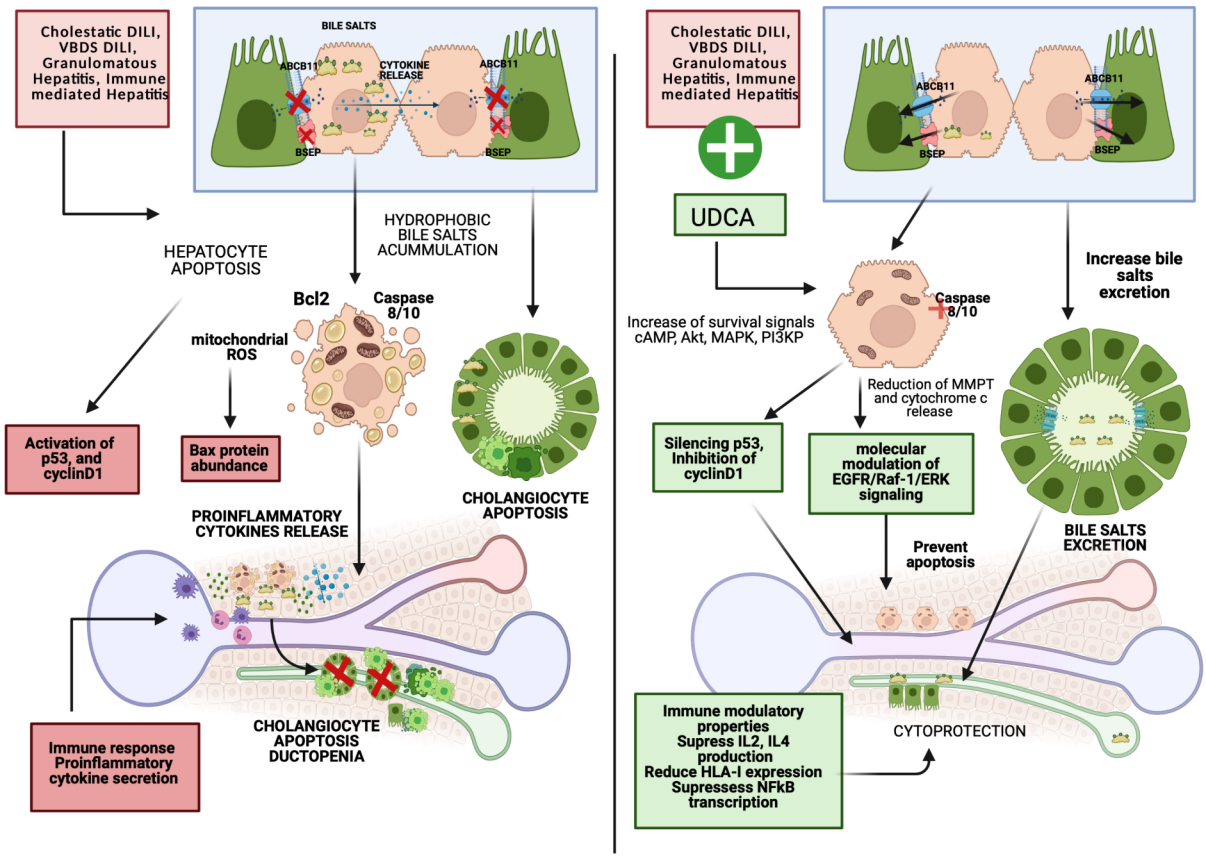

Figure 1: Mechanisms of Action of ursodeoxycholic Acid. 1) Protection of cholangiocytes and hepatocytes against bile acid induced apoptosis. Reduction of mitochondrial Membrane Permeability transition (MMPT) and cytochrome c realease. Inflection of immune response and pro inflammatory cytokine release. Immunomodulatory effect by the suppression of IL2, IL4 production, reducing concavalinA proliferation. Suppressing NFkB transcription. Reducing the level of HLA-I expression. Reduce secretion of mitochondrial ROS and Bax protein. Silencing of p53 and cyclin D1, molecular modulation of EGFR/Raf-1/ERK signaling 2) Increase bile acid excretion via protein kinase dependent mechanism. 3) Cholangiocytes protection against hydrophobic bile acids [5-7,73-75].

reported; being females more susceptible to DILI, and in some cases, supporting the fact, the women have higher risk to develop DILI-related ALF [1,2]. Ethnicity trends to be another host related risk factor to DILI development with certain drugs, suggesting a variation of drug metabolizing enzymes polymorphisms among races.

The human leukocyte antigen (HLA) allele expression has also been associated to DILI; HLA-DRB1*15:02-DRB1*06:01 have been reported as risk factor for amoxicillin clavulanate ALF DILI, HLA-A*33:03 to ticlopidine DILI, HLA-A*33:01 as a frequent allele present in DILI patients, HLA-B*57:01 for abacavir and flucloxacillin DILI and HLA DRB1*01:01 and B*14:02 for nevirapine [21-23]. Pregnancy has also been described to increase hepatotoxicity of certain drugs, especially after HAART therapy [24].

Underlying comorbidities as preexisting liver disease, Type 2 diabetes, and HIV infection have been reported to be risk factors for the development of DILI, these due to drug transporters as bile salt transporters (BSEP), macrophage inflammatory protein 2 (MRP2), and Multidrug resistance protein 3 (MDR3) and also because of disturbed immunological response [25].

4.2. Related to the Drug

After oral administration, medications pass through portal blood into the liver which perform its metabolism and excretion. The drug enters to the hepatocyte by divers systems including passive diffusion or facilitated diffusion by sinusoidal membrane transporters, once in the hepatocyte, the drug is metabolize by hepatic cytochrome P450 (CYP) isoforms or by several enzymes, including monoamino oxidase, alcohol dehydrogenase among others. After the oxidation, reduction and transformation of the drug, the drug and its metabolites are excreted by the hepatocyte to the small bile duct or through hepatocyte canalicular transporters [26].

As previously discussed, CYP enzymes are fundamental for the metabolism of most drugs, being that 61.1% are metabolized by CYP isoforms mainly by CYP3A4/5 in 49.6% and by CYP2C9 in 24.6% [26]. According to this, it has been reported that daily drug dosing is a risk factor to the development of DILI [12,27], an assumption disputed by others [26]. This dosing related hepatotoxicity was considered as being closely linked to the hepatic metabolism of the drug and the availability of CYP enzymes [1,25]. It could explain a genetic variability in liver enzymes that metabolize drugs as CYP3A4/5, CYP2C9, CYP 2C19, CYP 3A, CYP2D6 and CYP2E1, thereby predisposing some individuals to DILI [1, 25]. Besides the drug daily dosing the cumulative drug dose might also play a role in dose related toxicity [26].

Lipophilicity of certain drugs was also described as a drug related risk factor, but only if it is associated with a high daily dose, because lipophilic drugs need imperatively a hepatic metabolism to be eliminated [1], conditions that remain overall debated [26]. Drug interactions represent another drug related factor; this is mainly due to the assessment and induction of CYP enzymes and also to the metabolization and detoxification of the drugs within the liver [25].

5. PATHOPHYSIOLOGY AND DIAGNOSIS

5.1. Pathophysiology

Hepatocellular damage secondary to DILI is the result of the combination of the pharmacological properties of the metabolite, the host's own factors, and environmental conditions [27].

The established response mechanism depends mainly on two interrelated axes:

- The drug or substance exposed to liver metabolism and the toxicity threshold it reaches.
- The immune response of the host damage associated molecular pattern molecules (DAMPs), drug-induced tissue damage, activation of signaling pathways that induce oxidative stress and its capacity for cell regeneration [28,29].

5.1.1. Cell Damage

Most drugs when ingested are metabolized in the liver through different phases. Phase I makes the metabolite more soluble, Phase II facilitates excretion by hepatic transporters, and phase III forms active metabolites with conjugation capacity with other cells or macromolecules. At the end of the whole process, if the dose threshold to efficiently metabolize the drug is reached, or the transporter system involved in the clearance of drugs such as MDR1 or MDR3 is altered [30]; consequently, oxidative stress is increased. Hepatocytes have a defense system against oxidative stress, the main one is the activation of the nuclear factor erythroid 2-relatd factor 2 (Nrf2). This factor is released from Kelch-like ECH-associated protein 1 (Keap1) in the cytoplasm and translocate to the nucleus and binds to the antioxidant response element (ARE) that induce defense gene expression [31].

There are data that suggest that diet influences the homeostasis of cellular oxidative stress, since there are food compounds with binding affinity to Keap1 and the consequent activation of Nrf2 [32]. However, if the regulatory mechanisms of oxidative stress are exceeded, multiple signaling pathways of mitochondrial damage are activated, such as c-Jun N-terminal kinase (JNK), associated with direct mitochondrial damage produced by the drug [33-35].

Although it is described that the liver is relatively resistant to cellular stress and is able to adapt to the damage induced by oxidative stress [36], there are other forms of direct cellular damage such as toxicity caused by the accumulation of bile. The latter occurs when there is dysfunction or inhibition of the BSEP. The BSEP are predominant bile salt efflux system of hepatocytes and mediates the cellular excretion of numerous conjugated bile salts such as taurine- or glycine conjugated [37]. These transporters are located in the apical and basolateral membrane of the cholangiocytes [38].

The BSEP and transporters involved with hepatic drug clearance belong to different members of the ABC transporter superfamily: MDR1 (ABCB1), MDR3 (ABCB4) and BSEP (ABCB11). Also belonging to this superfamily are protein 2 associated transporters involved in the resistance of multiple drugs MRP2 (ABCC2) [39], also is the main driving force for bile salt–independent bile flow through canalicular excretion of reduced glutathione and transports drug substrates such as cancer chemotherapeutic agents, uricosurics, and antibiotics [40]. The importance of the knowledge of these transporters is because genetic polymorphisms have been found to provoke changes in drug transporters expression and function that could increase susceptibility to cholestatic drug reactions [41].

5.1.2. Immune Response

The same drug metabolites act as haptens and neoantigens, that bind to the HLA system and are presented to defense cells, through antigen presenting cells (APC), which are recognized by T lymphocytes [42].

This causes the established response to vary between each drug and in different individuals. For this reason, two main types of response have been established: intrinsic and idiosyncratic. However, there are authors who have identified a third category called indirect [43,44] (Table **1**).

Intrinsic response refers to the direct damage caused by the drug, directly due to high toxic levels. While an idiosyncratic response, refers to liver injury caused by the interaction of the drug, at a recommended dose, with the host. This response can be mediated by immune and non-immune response mechanisms [45].

The indirect type seeks to explain that liver damage is caused by the actions that the drug induces on the cell, differentiating itself from the drug's own toxicity. For example, drugs that act on immune checkpoints known as target therapy in the oncology field. However, this definition remains unclear and some authors consider it an idiosyncratic response [46].

Finally, the above types of response manifest with different phenotypes of clinical and laboratory characteristics.

5.2. Diagnosis and Phenotypes of DILI

The diagnosis of DILI becomes emergent since it is essential to give an adequate and prompt management that leads to the suspension of the medication that caused the inflammation [1]. However, due to the different types of response that can occur, due to the different presentation phenotypes and the lack of specific tests, algorithms have been designed taking into account the factors involved in the pathogenesis such as the characteristics of the drug, time of onset of the condition, etc. Currently there are scales that add these factors and try to guide causality.

The steps to be evaluated according to the latest updates made by the American Association for the Study of Liver Diseases (AASLD), European Association for the Study of the Liver /EASL), Asian Pacific Association for the Study for the Live (APASL), Latin American Association for the Study of the Liver (LAASL) and other revisions updated to 2021 will be described below [1-3,17].

5.2.1. Clinical Suspicion

The clinical presentations of DILI have different patterns of presentation known as phenotypes and can mimic other liver diseases, making diagnosis problematic. Initially, the clinical suspicion is based on the clinical data such as: age, consumption of drugs, herbs, date of beginning and end of consumption. It is also important to note medications even after years of starting their use, for example amiodarone, statins, nitrofurantoin [19]; as well as personal history, recent alcohol consumption, visits to endemic areas [47]. Another important antecedent is to know that patients with DILI/HILI resolve the inflammatory process after 3 months of stopping the drug, but there is a small group that can become chronic or evolve into autoimmune hepatitis. [48]. Once the condition is suspected, liver enzymes are measured.

5.2.2. Measurement of Liver Function Tests and Assessment of the Type of Phenotype

In 2011, Aithal *et al.* [49] defined a case of DILI when it presents one of the following points:

a. Alanine aminotransferase (ALT) ≥ 5 × upper limit of normal (ULN)

b. Alkaline phosphatase (ALP) ≥ 2 × ULN (especially with an elevation of gamma-glutamyl

Table 1: Types of DILI/HILI [42,43]

Characteristic	DILI/HILI INTRINSIC	DILI /HILI IDIOSYNCRATIC	DILI /HILI INDIRECT
Frequency	Rare. Example Paracetamol Toxicity	More frequent	Intermediate
Response prediction	Predicable. Dose-dependent, direct hepatotoxicity up to toxicity threshold	Unpredictable, not dependent on drug dose	Partially
Latency	1-5 Days	5 to 90 days or years	A few days to several weeks
Type of damage	direct	Immune and non-immune	Immune-mediated

transferase (GGT) or after ruling out primary bone pathology in cases of isolated elevation of ALP)

There are three main phenotypes described according to the pattern of elevation of transaminases and alkaline phosphate. The way to categorize is done by calculating the R ratio, to determine if the damage is hepatocellular, cholestatic or mixed, the use of R value is recommended in DILI guidelines [1-3]. The major diagnostic drawback of the causation of liver injury is the existence of drugs that can cause more than the same phenotype pattern [50]. Previous authors have clearly described specific sub-classifications that refer to the pathogenesis and evolution of the damage [52,56].

There are special cases where AST levels can be used for diagnosis if ALT is not available and there is no other etiology that explains the elevation of AST, such as muscle disease [48]. GGT cannot be used as a replacement for ALP due to its low sensitivity [54].

In conjunction with the evaluation of liver enzymes, the severity of liver damage should be assessed by measuring the levels of INR, albumin, and bilirubin. The elevation of transaminases and/or ALP alone cannot clearly establish the degree of liver involvement [52].

5.2.3. Assessments of Causality

Causality assessments such as RUCAM are used to assess the relationship between the timing of drug exposure and the development of DILI or HILI in order to be able to accurately remove the drug that likely caused the injury. This reduces the probability of withdrawing medications necessary for the management of any specific pathology of the patient [55].

The Roussel Uclaf Causality Assessment Method (RUCAM), first described in 1993 [52] and formerly termed erroneously as CIOMS (Council for International Organizations of Medical Sciences) scale [56], represents an algorithm that evaluates the causality of DILI and is the most widely used DILI causality assessment scale [52,56-58].

This RUCAM scale consists of evaluating seven domains: onset, evolution, risk factors, drugs used concomitantly, non-pharmacological causes, prior information on the drug's potential for hepatotoxicity, and response to drug re-administration. The points obtained are added and the probability of presenting DILI is evaluated according to this: Excluded (<1 point), unlikely (1-2 points), possible (3-5 points), probable (6-8 points) or highly probable (>8 points) and its application is recommended by the AASLD, EASL, APASL and LAASL [1-4,17]. The latest update to the RUCAM scale reduces interobserver variability and facilitates its application by asking less ambiguous questions [56] while preserving the same 7 domains, but with more specific items for its application in specific liver domains and hepatotoxicity with scored items [45,56].

One of the advantages that the implementation of RUCAM has brought worldwide for the diagnosis of DILI and HILI was to identify that more than 61% of the drugs that cause idiosyncratic DILI are drugs metabolized by cytochrome P450 isoforms. Although there is no consistent evidence, it could suggest the type of CYP isoform involved in a specific drug metabolism as a risk factor [57].

Another scale used is the Clinical diagnostic scale (CDS) it evaluates 5 domains: temporal relationship between drug intake and the onset of clinical picture, exclusion of alternative causes, extrahepatic manifestations, intentional or accidental re-exposure to the drug and previously published report in the literature of cases of DILI associated with the drug. The obtained score is interpreted as follows: excluded <6, unlikely 6–9, possible 10–13, probable 14–17, and definite >17 points [59]. Lucena *et al.* [60], compared the RUCAM scale with CDS, showing that CDS had a lower discriminative power in patients with longer or chronic latency.

5.2.4. Complementary Tests and Differential Diagnosis

The type of pattern found helps to guide the complementary tests to be carried out.

The hepatocellular pattern should request complete serological studies to rule out acute viral hepatitis A, B, C and E and AIH. In immunocompromised patients or with extrahepatic manifestations testing for cytomegalovirus, Epstein – Barr virus and herpes simplex virus should be added. In patients younger than 40 years, Wilson's disease should be ruled out [55]. If hepatomegaly is found, with or without ascites, Budd-Chiari syndrome or hepatic sinusoidal obstruction syndrome should be discarded.

In a cholestatic pattern, an ultrasound of the liver must be requested to rule out pathologies that cause

bile duct dilatation, if bile duct dilatation is ruled out primary biliary cholangitis (PBC) should be suspected [55].

The mixed pattern guides the performance of all the aforementioned studies. The performance of another type of test will depend on the suspected differential diagnosis.

5.2.5. Biopsy

In general, the diagnosis of DILI does not require a liver biopsy, but it serves to exclude other pathologies [61]. It defines the specific histological characteristics of the type of liver injury, adequately classifying the phenotype and causality of DILI / HILI and is very useful to differentiate cases of chronic liver injury [62-65].

The type of indirect response triggered by biological drugs presents a distinctive histological pattern characterized by ring granuloma and endotheliosis, where biopsy plays a decisive role in clearly establishing this type of response [66].

5.2.6. New Biomarkers

New non-invasive biomarkers have been sought to increase the sensitivity and specificity in the early diagnosis of DILI [67,68], but major caveats were presented [67]. Biomarkers have been classified as diagnostic and prognostic [68]; nonetheless, they are now under major critical consideration because regulatory support by EMA (European Medicines Agency) was withdrawn due to falsified study results provided by an external group [67]. Details focused previously on glutamate dehydrogenase located in the mitochondria of centrilobular hepatocytes, high mobility group 1 box protein, keratin-18 and microRNA (mainly miR-122) because they tend to be more specific for liver injury [68], conditions that are now obsolete due to retracted support by EMA [67].

MicroRNA-122 (miR-122) is released from damaged hepatocytes reflecting liver necrosis [68] and is a hepatocyte-specific miRNA that is elevated in patient plasma within hours after an overdose with some medications [69]. Other MicroRNA that reflect hepatocyte damage is micro-RNA 192 that is under validation [68].

Total High mobility protein-1 (HMGB1) and cytokeratin-18 have been shown to be biomarkers of necrotic cell death; hence, this death is not exclusive to liver cells. Cytokeratine-18 has been classified as a prognostic biomarker, its fragments reflect also cell death by apoptosis via caspase pathway. Acetylated HMGB1 manifest liver injury via innate immune activation but persists not specific to the liver [68].

Integrin beta 3 (ITGB3) is a membrane adhesion molecule that is needed for the interaction between leucocytes and other cell types with the extracellular matrix [70]. This biomarker has been evaluated for DILI diagnosis although the recommendation for its use is premature due to lacking firm data [67].

Elevation of macrophage colony stimulating factor receptor 1 (MCSFR1) and osteopontin were observed in some patients diagnosed with DILI, their elevation were associated with unfavorable prognoses [71].

The combination of these markers added to the existing scoring systems could improve the predictive values of each test [72].

6. CURRENT TREATMENT MODALITIES FOR DILI

The first approach in a case of DILI is to identify the offending drugs and to suspend their use; in certain cases, it will be advised the use of the antidote that might stop or reverse the hepatic damage caused by the drug [1-3,56].

Charcoal might be used if the medication was taken within the last 3 to 4 hours while the drug remains in the stomach to avoid further absorption. This is mainly used in case of high dose paracetamol intake [1].

N-acetyl cysteine (NAC) is a promising treatment used for paracetamol and non-paracetamol DILI with beneficial effects [1]; AASLD and APASL describe that NAC even in non-paracetamol liver injury offers better transplant free survival rates [2,3].

Cholestyramine has also been used to increase the depuration and elimination of certain drugs as terbinafine and teriflunomide. Carnitine is indicated as the antidote of valproate induced DILI [2,3].

Corticosteroids have also been used with limited beneficial effects. Their use might be more effective in DILI with hypersensitivity features in which steroids have shown some benefit, in this setting, guidelines recommend their use [1-3].

UDCA prescription might represent an interesting option for the treatment of DILI; thereby we will further

discuss the mechanisms of action and current facts describing its potential beneficial effect not only as treatment of DILI but also as a hepatoprotective treatment.

6.1. General Aspects of UDCA Mechanism of Action

UDCA is a hydrophilic bile acid absorbed by passive diffusion mostly in the small intestine by solubilization in micelles with other bile acids. (Figure **1**) Absorbed UDCA pass to the colon and converts to lithocholic acid by intestinal bacteria. In the liver, UDCA conjugates and is secreted into the bile. The beneficial effects of UDCA seems to be in reducing hydrophobic bile acids, by stimulating its hepatobiliary secretion into the bile by the upregulation and activation of transporters; protecting cholangiocytes and hepatocytes against apoptosis due to the accumulation of hydrophobic bile acids, and reducing the secretion of proinflammatory cytokines and chemokines, thereby reducing the persistence of the injury and apoptosis [7].

6.2. Reducing Hydrophobic Bile Acids/Role of Bile Acid Transporters

The accumulation of hydrophobic bile acids within the liver drives to the alteration of bile formation and the consequent cholangiocyte and hepatocyte apoptosis. Part of the beneficial effects of UDCA is in reducing the concentration of toxic substances from the hepatocytes [7]. UDCA has demonstrated to decrease hydrophobic bile acids concentration [73], by stimulating the expression of transporter proteins for biliary secretion as (ABCB1, MRP2, BSEP) and basolateral carriers as (MRP3 and 4) [74], reducing cytotoxicity to cholangiocytes and hepatocytes [75], by silencing p53, inhibiting cyclin D1, inhibiting caspase 8 to 10 cascades, downregulating extracellular signal regulated kinase (ERK), and modulating EGFR/Raf/ERK signaling [6].

Thus, UDCA exerts various beneficial effects in this point; among them, increasing endogenous secretion of bile acids, enhancing bile flow and immunomodulation, as well as a hepatoprotective effect by increasing the biliary secretion of phospholipids [75].

6.3. Reducing the Secretion of Proinflammatory Cytokines and Chemokines

Divers beneficial effects have been described of UDCA; first it exerts immunomodulatory effects, in animal models, it has shown to reduce antigenic T cells stimulation by reducing HLA I expression, and reducing aberrant major histocompatibility complex (MHC) class I antigens. UDCA also has shown to reduce cytokine secretion of peripheral monocytes[75], downregulation of NFkB and the reduction of the secretion of proinflammatory cytokines among them TNFα [76], IL6, TGF-β [76], IL2 and IL4 [74], also reducing the expression of several proinflammatory chemokines as MCP1 [77] and MIP2 [78]; all these might contribute to the UDCA anti-inflammatory effects. UDCA also modulate cytokine production and the secretion of immunoglobulins by B-cells and further UDCA has shown to inhibit the epithelial oxide synthase with might act in cytoprotection [79].

6.4. Modulating Apoptosis by Regulation of Bcl2 and by MMPT Reduction

Hydrophilic UDCA and its conjugated form with taurine (TUDCA) show profound cytoprotective properties, acting as potent inhibitors of apoptosis pathways [80].

Apoptosis, beyond being the cell death program, play a regulatory role in cell homeostasis; therefore, defects in the physiological pathways of apoptosis contribute to the development of numerous diseases such as T-cell depletion, neural and hepatocellular degeneration [81].

Two main routes trigger apoptosis; the intrinsic one that involves the mitochondria causing a permeability of the mitochondrial membrane that releases proteins that activate the layers and lead to cell death [82]. There is a second pathway called extrinsic that is activated through stimulation of cell membrane receptors [83,84]. The activation of these receptors belonging to the Bcl2 family forms channels located in the mitochondrial membrane in order to regulate both negatively and positively cell death. The pro-apoptotic proteins are Bcl-2, Bcl-xL and Bcl-w located in the outer membrane of the mitochondria and the antiapoptotic proteins are located in the cytosol and are Bax and Bak [85].

Apoptosis in cholestatic diseases seems to be induced by the activation of the Fas death receptor, and the activation of caspase 3, 8,[75,76] Bid and Bax; increasing mitochondrial membrane permeability transition (MMPT) causing mitochondrial permeability delivering cytochrome c with activation of caspase 9 and 10. UDCA inhibit apoptosis by the down-regulation of Bax gene, Bcl2 and caspase 3 expression, [75] and likewise UDCA has shown to reduce MMPT and cytochrome c leaking.

Further UDCA increase survival signal pathways as epidermal growth factor receptor, [75] cyclic Adenosine monophosphate (cAMP), Mitogen-activated protein kinases, (MAPK) [7] and phosphaditil-inositol 3-kinase mediated kinase pathways (PI3KP) [82] So UDCA also acts in cytoprotection and survival of cholangiocytes and hepatocytes [5,76].

The protective effect of UDCA on hepatocytes has been demonstrated, since it prevents apoptosis by inhibiting the translocation of pro-apoptotic proteins such as BAX and thus prevents the formation of oxygen free radicals [86]. This modulating effect has not only been evidenced in liver cells but in other types of cells [87].

7. HEPATOPROTECTIVE EFFECT OF UDCA

7.1. Basic Considerations

It has been widely discussed the hepatoprotective role of UDCA against several drug induced liver toxicity. Among these effects, it has been characterized that UDCA reduce proinflammatory cytokines secretion, to reduce hepatocyte apoptosis and necrosis, to diminish oxidative stress and to decrease the concentration of hydrophobic bile acids that are cytotoxic to the hepatocytes [73] It has being described that UDCA offers a hepatoprotective effect against methotrexate induced hepatotoxicity, preventing hepatocyte necrosis [88]. In this same line, it has also been described the hepatoprotective effect of UDCA against liver dysfunction induced by amoxicillin-clavulanic acid [89]. In patients that receive anticonvulsant drugs as valproic acid and phenobarbital, it has also been shown a reduction in hepatotoxicity [90]. In Concavalin-A liver injury it has been reported the hepatoprotective effect of UDCA, reducing the secretion of proinflammatory cytokines as TNF-alpha, IL6 and MIP2 [91]. Another study showed the same effect of UDCA reducing the proinflammatory cytokines secretion confirming its liver protection effect against inflammation and apoptosis [92]. Other hepatoprotective effect of UDCA has been depicted against hepatic damage with bosentan, preventing liver

Table 2: Case Reports of the Use of UDCA in DILI and Results Obtained after its Usage [93, 101-111]

Author	Year	Case	Drug	Dose of UDCA	Type of DILI	Duration of UDCA use	Results
Cicognani *et al*. [101]	1996	Case report	Flutamide	12mg/kg/d	hepatocellular	5 months	Resolution without LT
Barrio *et al*. [102]	1998	2 cases report	Amox-Clav	300mg bid	Cholestatic	1 month	Resolution without LT
Malnick *et al*. [103]	2002	Case report	Isoflurane	600mg/d	Cholestatic hepatitis	2 weeks	Resolution without LT
Zapata Garrido *et al*. [104]	2003	Case report	Terbinafine	NE	Heptocellular	6 months	Resolution without LT
Agca *et al*. [105]	2004	Case report	Terbinafine	1000mg/d	Cholestatic hepatitis	8 weeks	Resolution without LT
Valente *et al*. [106]	2010	Case Report	Herbal medicines	NE	Cholestatic	2 months	Resolution without LT
Chaabane *et al*. [107]	2011	Case report	Amoxicillin	NE	Cholestatic hepatitis	8 weeks	Resolution without LT
Mason *et al*. [108]	2014	Case report	Temozolomide	750mg/d	VBDS	129 days	Resolution without LT
Ito *et al*. [93]	2014	2 cases report	Bosentan	600mg/d	Cholestasic	1.preventive 4mo 2.treatment 4 months	Resolution without LT
Adike *et al*. [109]	2016	Case report	Hydroxicut	NE	VBDS	NE	Resolution without LT
Ikeda *et al*. [110]	2017	Case report	Itraconazole	NE	cholestatic	2.5 months	Resolution without LT
Fernandes *et al*. [111]	2019	Case Report	Herbal Supplements (Kratom)	600mg tid	Cholestatic	6 weeks	Resolution without LT

Table 3: Case Reports of the Use of UDCA Associated with Prednisone in DILI and Results Obtained after its Usage [112- 120]

Author	Year	Case	Drug	Dose of UDCA	Type of DILI	Duration of PDN use	Duration of UDCA use	Results
Elefsiniotis *et al*. [112]	2007	Case report	Herbicide Quizalofop-p-ethyl	750mg/d	mixed	2 months	2 months	Resolution without LT
Farah *et al*. [113]	2008	Case report	etanercept	500mg bid	Granulomatous Hepatitis	6 months	6 months	Resolution without LT
Herrero-Herrero *et al*. [114]	2010	Case report	Amox/clav	13mg/kg/d	Cholestatic	10 weeks	10 weeks	Resolution without LT
Studniarz *et al*. [115]	2012	Case report	Amox/Clav	20mg/kg/d	Cholestatic	3 days	3 months	Resolution without re-LT
Abenavoli *et al*. [116]	2013	Case report	Cyproterone acetate	1250mg/d initially 750mg/d after M2	Hepatocellular	180 days	180days	Resolution without LT
Paiwah *et al*. [117]	2019	Case report	Pexidartinib (PLX3397) and paclitaxel	1200mg/d	VBDS	1 week	13 months	LT
Greca *et al*. [118]	2020	Case report	Garcinia, horsetail and ketoprofen	NE	Cholestatic and VBDS	NE	NE	Resolution without LT
Díaz-García *et al*. [119]	2020	Case report	Anabolics	15mg/kg/day	Cholestatic	7 days	4 months	Resolution without LT
DeJonghe *et al*. [120]	2021	Case report	Atabecestat	500mg	Hepatocellular Immune mediated hepatitis	9 days	116 days	Resolution without LT

toxicity [93], as well as in the use of anti-TB drugs, as isoniazid and rifampicin, UDCA have shown to reduce oxidative stress and apoptotic anti-TB effects, exerting a hepatoprotective role [94]. Nonetheless, in anti-TB drugs, Saito *et al.* did not found that the use of UDCA accelerate the normalization of liver enzymes in DILI [95].

7.2. Use and Indication of UDCA in DILI

UDCA benefit has been proven in multiple indications, among them PBC, intrahepatic cholestasis of pregnancy, primary sclerosing cholangitis (PSC) and other cholestatic liver diseases, graft-versus host disease (GVHD) after bone marrow transplantation (BMT), cholestasis secondary to total parenteral nutrition, veno-occlusive disease of the liver, hepatic allograft rejection, polycystic liver disease, cystic fibrosis, lipid metabolism, and DILI; although, in the latter diseases its effectiveness remain insufficiently proven [7, 75, 96-100].

Several case reports have been published describing the use of UDCA in DILI (Table **2**) [93, 101-111], with or without prednisone, showing the potential beneficial effect of UDCA in the resolution of the damage caused by DILI without the need of liver transplantation (LT) (Table **3**) [112-120]. However, RUCAM based cases were available in two reports published by Abenavoli *et al.* [116] and Diaz-García *et al.* [119].

UDCA has been used in DILI with cholestatic injury, vanishing bile duct syndrome (VBDS), granulomatous hepatitis, even in hepatocellular immune mediated hepatitis.

The beneficial effect of UDCA has also been shown to mitigate or prevent damage caused by several drugs, as antiTB and bosentan [93, 121].

Nevertheless due to contradicting results and lack of clinical trials proving it efficacy; current EASL guidelines leave the recommendation of UDCA use in DILI as a drug with effectiveness inconclusive, leaving UDCA prescription to the physician decision [1]. AASLD guidelines described that UDCA might be used

as preemptive prophylactic treatment in patients that will undergo BMT and do not pronounce its recommendation in usage as treatment of DILI [121]. APASL guidelines describe that UDCA has reported to improve DILI in some case reports; hence, clinical trials are needed to prove its benefit [122].

8. CONCLUSION

DILI is becoming a frequent cause of liver injury. UDCA use might represent an interesting option of treatment to these patients based on it mechanisms of action. Currently available cases reports describe the prevention of the progression of DILI avoiding the need of liver transplantation, supporting the fact that UDCA might represent an alternative of treatment for patients with DILI.

AUTHOR CONTRIBUTIONS

NMPL, JCG, NMS contributed to the conceptualization and the Writing of the manuscript.

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ABBREVIATIONS

DILI = Drug induced liver injury

UDCA = Ursodeoxycholic acid

HILI = Herb induced liver injury

HDS = herbal and dietary supplements

NSAID = nonsteroidal anti-inflammatory drugs

TMP-SMZ = trimethoprim-sulfamethoxazole

antiTB = antituberculosis drugs

HAART = high activity antiretroviral drugs

TCM = Traditional Chinese medicines

ALF = acute liver failure

HLA = human leukocyte antigen

BSEP = Bile salt export pump

MRP2 = macrophage inflammatory protein 2

MDR3 = Multidrug resistance protein 3

CYP = hepatic cyto-chrome P450

DAMPS = damage associated molecular pattern molecules

Keap 1 = Kelch-like ECH-associated protein 1

Nrf2 = nuclear factor erythroid 2-relatd factor 2

ARE = antioxidant response element

JNK = c-Jun N-terminal kinase

ABC = ATP-binding cassette

ABCB4 = ATP-binding cassette sub-family B member 4

MIP2 = Macro-phage inflammatory protein 2

AASLD = American Association for the Study of Liver Diseases

EASL = European Association for the Study of the Liver

APASL = Asian Pacific Association for the Study for the Liver

LAASL = Latin American Association for the Study of the Liver

ALT = Alanine ami-notransferase

ALP = Alkaline phosphatase

GGT = Gamma-glutamyl transferase

RUCAM = Roussel Uclaf Causality Assessment Method

CIOMS = Council for International Organizations of Medical Sciences

CDS = clinical diagnostic scale

PBC = primary biliary cholangitis

AIH = autoimmune hepatitis

HMGB1 = High mobility protein-1

MCSFR1 = macrophage colony stimulating factor receptor 1

ERK = extracellular signal regulated kinase

TUDCA = Taurine conjugated ursodeoxycholic acid

MMPT = mitochondrial membrane permeability transition

MAPK = mitogen-activated protein kinase

PI3KP = phosphatidyl inositol 3-kinase–mediated kinase pathways

VBDS = Vanishing bile duct syndromes

T2DM = type 2 diabetes mellitus

PSC = primary sclerosing cholangitis

LT = liver transplantation

PI3KP = phosphaditil inositol 3-kinase mediated kinase pathways

cAMP = cyclic Adenosine monophosphate

BMT = bone marrow transplantation

GVHD = graft versus host disease

APC = antigen presenting cell

amox/clav = amoxicillin/clavulanate

ITGB3 = Integrin beta 3

NAC = N-acetyl cysteine.

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