Review Article

DRUG-INDUCED LIVER DISEASE

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Abstract. *Liver impairment can be caused by a significant number of foreign compounds (xenobiotics); prescribed drugs, 'over the counter' (OTC) drugs, herbal and alternative medicines. Hepatotoxicity caused by drugs used for therapeutic, recreational or nutritional purposes as well as drugs of abuse is a drug-induced liver disease (DILD). Over 300 agents in use have been connected with causing DILD. Factors associated with increased susceptibility to DILD are: age, gender, genetic predisposition, dose, other drug reactions, concomitant use of drugs, excessive use of alcohol, nutritional status, liver disease and other diseases. Drugs may cause liver injury in a predictable, dose-dependant manner (intrinsic DILD), or in an unpredictable, non-dose-dependant manner (idiosyncratic DILD). Xenobiotics that cause liver impairment provide a wide range of lesions resembling many other liver diseases. Acute hepatocellular damage can be cytotoxic (hepatocellular necrosis), cholestatic (associated with the interrupted flow of bile), or mixed. Clinical expressions of DILD range from nonspecific abnormalities of liver tests, to cholestasis, acute hepatitis and acute liver failure. Nodular hyperplasias, chronic hepatitis, autoimmune hepatitis, fibrosis, NASH, cirrhosis, benign and malignant liver tumours have been reported. Diagnosis of DILD is based on history, blood tests, imaging examination of hepatobiliary tract and, if applicable, liver biopsy. Clinical and laboratory findings in DILDs are not always in line with liver pathology. Histologic changes can be minor compared to biochemical findings. Liver enzymes are not synonym of liver damage.*

Key words: *liver, injury, drugs.*

Introduction

Significant increase of scientific studies investigating drug-induced liver disease (DILD) in the last few years is making DILD an emerging safety issue that requires attention by medical professionals in clinical practice, regulatory authorities, pharmaceutical companies and academic institutions [1]. Liver impairment can be caused by a significant number of foreign compounds (xenobiotics); prescribed drugs, 'over the counter' (OTC) drugs, herbal and alternative medicines. Chemical agents widely used in households, drugs of abuse, pesticides, herbicides may have toxic and/or carcinogenic properties. Hepatotoxicity caused by drugs used for therapeutic, recreational or nutritional purposes as well as drugs of abuse is a drug-induced liver disease (DILD). About 14-19 per 100 000 inhabitants in general population is the reported frequency of DILD. Health care system records the incidence of about 30-32 per 100 000 persons [2,3]. According to available data, 462 medicinal products were withdrawn from the market between 1953 and 2013. Hepatotoxicity was the most reported adverse drug reaction causing post marketing drug withdrawal (81 cases; 18%). Withdrawals were significantly less common in Africa than in Asia, Europe, and America [4].

In the largest number of reports, DILD is unpredictable because of its idiosyncratic nature. Accurate underlying mechanisms (mitochondrial injury, reactive metabolites, biliary transport inhibition, and immune responses) have been identified rarely. DILD can occur in case of accidental or intentional overdose or during the use of a drug for therapeutic purposes in certain clinical circumstances, as in the case of paracetamol in patients who regularly consume alcohol [5]. Paracetamol is the leading cause of acute liver failure, whereas chlorpromazine, halothane, sulpiride and amoxicillin-clavulanate were found as most common drugs leading to hepatotoxicity in all prospective studies [6]. The list of top 10 drugs implicated in DILD consists of antibiotics, statins, antitumor necrosis factor antagonists (infliximab as leading); herbal and dietary supplements (most frequent causes of serious hepatotoxicity are weight loss and bodybuilding products) [7].

Risk Factors for Incidence and Severity of DILD

Factors associated with increased susceptibility to DILD are: age, gender, genetic predisposition, dose, other drug reactions, concomitant use of drugs, excessive use of alcohol, nutritional status, liver disease and other diseases. Age more than 60 increases the frequency and severity of DILD caused by isoniazid and halothane. Children are more commonly affected by salicylates. Women are at an increased risk of developing hepatotoxicity from halothane, nitrofurantoin and men from amoxicillin-clavulanate and azathioprine. Concomitant use of acetaminophen and isoniazid, zidovudine and phenytoin lower the hepatotoxic dose and increase severity of DILD. Obesity increases the risk of liver injury by halothane, methotrexate and tamoxifen, while malnutrition increases the risk of liver injury by acetaminophen. Genetic variation at human leukocyte antigen (HLA) class I & II loci has been shown to be associated with amoxicillin–clavulanate DILD. The strongest association thus far identified is at a single nucleotide polymorphism in the gene encoding the class II HLA-DRB1* 1501-DQB1* 0602 allele [8,9]. Variations of genes for mitochondrial DNA polymerase gamma are associated with valproate hepatotoxicity [10].

Mechanisms of Drug Injury

Drugs may cause liver injury in a predictable, dose-dependant manner (intrinsic DILD), or in an unpredictable, non-dose-dependant manner (idiosyncratic DILD).

In most cases of the drug induced liver injury, the same happens in an unpredictable manner and only in susceptible individuals (idiosyncrasy or hypersensitivity). Impairment may appear from toxic metabolites which affect cell proteins. Toxic metabolites cause necrosis (metabolic idiosyncrasy) or form antigen (drug hapten) complexes which stimulate T cells, inducing an immune reaction and causing hepatic impairment (hypersensitivity or drug allergy). Drug-induced hypersensitivity reactions are commonly merged with systemic reactions, such as fever, rash and eosinophilia. They have a fixed latent period and prompt response to a repeated provocation. This reflects an underlying immunological mechanism. Vice versa, atypical metabolism of a drug which leads to formation of toxic metabolites, generally does not cause systemic allergic manifestations and it has a long or variable latency period and frequently a late response to a repeated provocation [11,12,13]. The most common causes of idiosyncratic damage are amoxicillin-clavulanate, nitrofurantoin, co-trimoxazole, ciprofloxacin, isoniazid, tyrosine kinase inhibitors [14].

A very small number of currently used medicinal products cause liver injury as a result of intrinsic toxicity or toxicity of one or more of their metabolites (predictable or intrinsic hepatotoxicity) [15]. Paracetamol is hepatotoxic due to production of the toxic metabolite as a result of accidental or intentional overdose or when used in recommended doses in circumstances of chronic use or alcohol abuse or starvation. The actual cause of damage to hepatocytes or cell death is damage or destruction of cell membranes or covalent binding of toxic metabolites to liver macromolecules causing a disturbance in calcium homeostasis, mitochondrial dysfunction or decay of other cell systems.

Acetaminophen (paracetamol) accounts for 50% of all drug-induced acute liver damage. Its metabolite, N-acetyl-p-benzoquinone imine (NAPQI), is created in hepatocytes. This toxic metabolite is reduced by glutathione. Reduced capacity of glutathione leads to impairment of vital processes in the cells and to their death. Paracetamol induced liver disease is treated with n-acetyl cysteine, in the first 8 hours of introduction of the drug [16].

Nimesulide, diclofenac, ibuprofen are non-steroidal anti-inflammatory drugs (NSAIDs) widely used in therapy of most rheumatological disorders, as analgesics and antipyretics, as prescription drugs and over the counter drugs. Nearly all NSAIDs are associated with hepatotoxicity; several NSAIDs have been withdrawn from the market (amphenac, ibufenac, phenylbutazone, fluproquazone). The new more selective COX-2 inhibitors (e.g. celecoxib, rofecoxib, nimesulide) are also connected with hepatotoxicity. Pathogenic mechanisms include oxidative stress alone or in combination with mitochondrial injury [17].

Oral contraceptive steroids and 17-alkylated anabolic steroids are associated with cholestasis, vascular lesions and hepatic neoplasms.

Drugs of abuse like cocaine or 3,4 methyenediomatamphetamine ("ecstasy") are related to hepatotoxicity. Cocaine toxicity is related to P450 catalysed N-demethylation to norcocaine, converted to N-hydroxynorcocaine. The latter redoxcycles to norcocaine nitroxide by receipt of an electron from NADPH, and transfers electrons to O2, generating oxidative stress [17].

The frequency of hepatic injury with antiretroviral drugs is at least 10%. Hepatic failure has been reported in patients taking zidovudine, but didanosine and stavudine have been most often involved in severe hepatotoxicity due to mitochondrial damage. Nevaripine has been implicated in causing severe hepatotoxicity. Ritonavir, Indinavir, Saquinavir, Nelfinavir have been reported for hepatotoxicity. Anti-retrovirals can induce direct toxicity in the liver, mitochondrial toxicity; hypersensitivity reactions have been reported relatively often with nevirapine and abacavir. Newer anti-HIV drugs like raltegravir, maraviroc and enfuvirtide have not been associated with significant hepatotoxicity [18].

The frequency of the DILD with recently introduced drugs will be known after larger studies. Nature of liver injury is presented in Table 1 [18].

Xenobiotics that cause liver impairment provide a wide range of lesions resembling many other liver diseases. Acute hepatocellular damage can be cytotoxic (hepatocellular necrosis), cholestatic (associated with the interrupted flow of bile), or mixed. In addition to

Table 1 Histologic pattern and clinical expressions of DILD

Drug	Liver injury
Alfuzosin	Hepatocellular od mixed hepatocellular-cholestatic injury
Beta interferon	Liver injury rare, autoimmune hepatitis
Bosentan, sitaxsentan	Acute hepatitis
Imatinib mesilate and other tyrosine kinase inhibitors	Acute hepatitis, massive or submissive hepatic necrosis(rare); acute liver failure with sunitinib
Leukotriene antagonists (zafurlukast, montelukast)	Massive or submissive hepatic necrosis (zafirlukast), acute hepatitis, cholestitis hepatitis (montelukast)
Infliximab and other tumor necrosis factor antagonists	Cholestasis, cholestatic hepatitis, hepatic granuloma, autoimmune hepatitis
Ximelagatran	Acute liver failure (not finally proven)

hepatocellular necrosis or cholestasis, other types of liver lesions could be induced by xenobiotics. Fatty change of the liver (steatosis) is common. Macrovesicular steatosis refers to large drops of fat and the core is replaced by a large intracytoplasmic lipid globule. Microvesicular steatosis is characterized by small drops of fat within the cytoplasm that do not suppress the core. Some drugs are associated with the formation of Mallory's bodies. Hepatic granulomas are a typical damage caused by certain drugs. Various forms of chronic liver impairment resembling chronic active hepatitis, chronic cholestasis and cirrhosis can be caused by xenobiotics.

Vascular disorders of the liver caused by medicinal products include a venous-occlusive disease, very similar to Budd-Chiari's syndrome. Peliosis hepatis is formation of blood cysts within the liver. Several drugs disrupt lipid metabolism in the hepatocytes by inhibiting phospholipase, which gives a foamy texture cytoplasm and characteristic ultrastructural liposomal appearance (phospholipidosis). Finally, certain drugs and chemicals are associated with hepatic neoplasia. Benign hepatic adenomas appear after the introduction of oral contraceptive steroids.

Clinical Expressions of DILD

Clinical expressions of DILD range from nonspecific abnormalities of liver tests, to cholestasis, acute

hepatitis and acute liver failure. The most common form of presentation of DILD is an acute viral "hepatitis-like" syndrome, with jaundice, nausea, fatigue and abdominal discomfort or pain. DILI can virtually mimic any other liver disease such as chronic hepatitis, autoimmune hepatitis, fibrosis, NASH, cirrhosis, benign and even malignant liver tumours [19].

Clinicopathological classification of DILD is presented in Table 2.

Biochemical Classification

Biochemical classification of liver damage caused by drugs include hepatocellular, cholestatic and mixed pattern. R value is calculated to assist in diagnosis and management of DILD. In case there is evidence of drug or supplement use in previous 6 months, and elevated liver enzymes are detected, R value is calculated as follows:

R = (ALT value / ALT ULN) / (ALP value / ALP ULN)

If R < 2 cholestatic damage is susceptible. Ultrasound of abdomen should be done and MRI/MRCP are to be considered. If R is between 2 and 5 mixed pattern and R > 5 hepatocelular liver damage is suggested. In these cases testing for hepatitis A, B, C and E should be done, as well as ultrasound imaging. In consideration are testing for EBV, HSV, autoimmune hepatitis etc.

Table 2 Clinicopathological classification of DILD

Damage type	Drug
▪ Acute hepatocellular injur	Isoniazid, aspirin, sulphonamide
▪ Autoimmune hepatitis	Nitrofurantoin, minocycline, ipilimumab
▪ Pure cholestasis	Anabolic steroid, oestrogens
▪ Macrovesicular steatosis	Tetracycline, steroids, gold, 5-fluorouracil, methotrexate, tamoxifen
▪ Microvesicular steatosis	Tetracycline, steroids, gold, 5-fluorouracil, methotrexate, tamoxifen,
▪ Cholestasis hepatitis	Phenytoin, AC, fluoroquinolones, macrolides, azithromycin
▪ Granulomatous hepatitis	Isoniazid, interferon, phenytoin, allopurinol
▪ Chronic hepatitis	Phenytoin, AC, fluoroquinolones, macrolides, azithromycin
▪ Non-Alcohol fatty liver	Tamoxifen, Amiodarone
▪ Fibrosis/cirrhosis	Metotrexate, amiodarone
▪ Liver Adenoma	Oral contraceptives
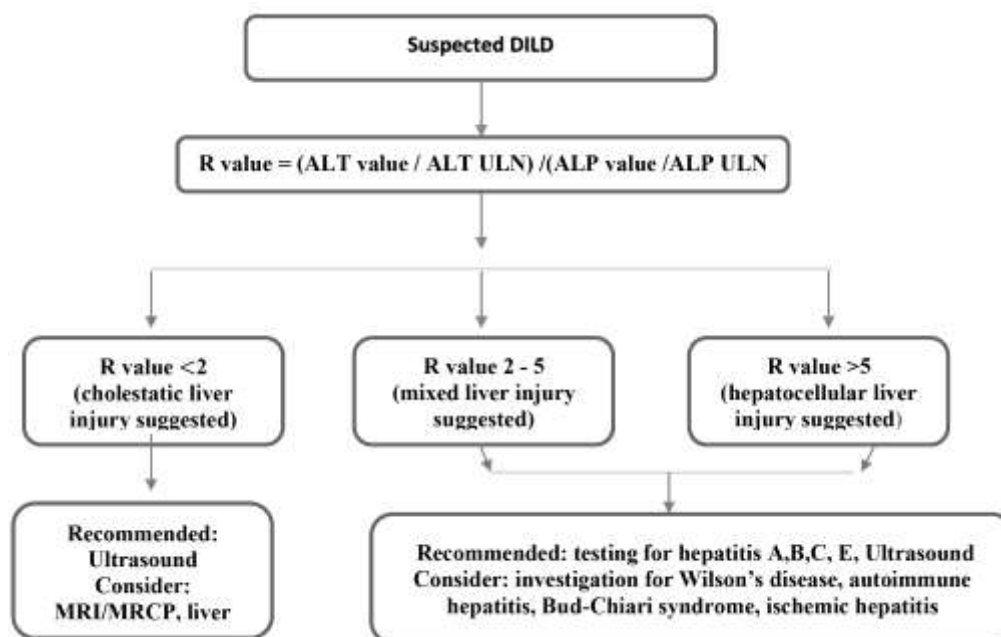
Fig 1 Calculation of R value and use in DILD management [15]

Diagnosis of DILD

Diagnosis of DILD is based on history, blood tests, imaging examination of hepatobiliary tract and, if applicable, liver biopsy. There are no specific laboratory tests, histological presentations, or clinical signs and symptoms enabling the diagnosis of DILD. Signs and symptoms vary with the drug, host, and severity of injury [20].

Some situations where the probability of the existence of DILD is likely are summarized in Table 3 [18].

The diagnostic evaluation of DILD usually includes evaluation of data summarized in Table 4
Liver biopsy is indicated in cases in which liver disease remains in doubt and this uncomfortable and risky procedure will make a difference in management of the injury. Liver biopsy is reasonable in case when continued use or re-challenge with a suspected drug is clinically necessary. For patients receiving methotrexate there are guidelines for biopsy [21,22]. Other situations where liver biopsy could be recommended are:

exacerbation of liver function in spite of stopping drug exposure, unexpected decreases of ALT within 30-60 days in hepatocellular or ALP within 180 days in cholestatic DILDs despite termination of use of the suspected drug [13].

Table 4 The diagnostic evaluation

- history (use of drugs, herbal or dietary supplements; possibility of drug interaction; exposure time/latency, alcohol intake, chronic liver disease, concomitant diseases (diabetes, heart failure))
- signs and symptoms (weakness, fatigue, fever, yellow urine, nausea, vomiting, abdominal pain, abdominal bleeding, rash, pruritus, icterus, ascites)
- initial laboratory tests (compete blood count (eosinophilia), liver function testing (AST, ALT, GGT, R value)
- routine serological tests (Acute viral hepatitis A, B, C (Anti –HAV IgM, HbsAg, anti-HBc IgM, anti – HCV, HCV RNA, autoimmune hepatitis (ANA, IgG level))
- serological tests by patients history (hepatitis E (anti hepatitis E virus IgM), CMV, EBV, HSV)
- other investigations (for Wilson's disease, etc.)
- imaging studies (Ultrasound, CT, MRCT)

ALP (alkaline phosphatase); ALT (alanine aminotransferase); ANA (antinuclear antibody); CMV (cytomegalovirus), CT (computed tomography), EBV (Epstein Bar virus); GGT (gamma –glutamyl transferase, HAV (Hepatitis A virus); HBc (Hepatitis B core antigen); HBsAg (Hepatitis B surface antigen); HCV (Hepatitis C virus) ; HSV (hepatitis C virus); HSV (herpes simplex virus); IgG (immunoglobin G); IgM (immunoglobin M); MRCP (magnetic resonance imaging, RNA (ribonucleic acid); ULN (upper limit of normal range).

Table 3 Situations in which the existence of DILD is likely

- Introduction of a new therapy in the last 3-6 months;
- Evidence of extrahepatic manifestations like rash, eosinophilia, lymphadenopathy;
- Acute hepatitis not connected to hepatitis viruses, other infections, metabolic, immunologic disorders;
- Mixed hepatocellular and cholestatic injury;
- Hepatitis with microvesicular steatosis;
- Cholestasis with normal bile duct imaging;
- Chronic hepatitis without antibodies;
- Liver disease after years of taking steroids, immunosuppressive or other drugs, etc.

The Council for International Organizations of Medical Sciences has created a CIOMS/RUCAM questionnaire. Score count is based on timing of exposure and liver biochemistry washout, competing medications and diagnoses, re-challenge of data and risk factors for DILI. Additional methods have been developed. One of them is Naranjo Adverse Drug Reaction Probability Scale (NADRPS). The CIOMS/RUCAM is widely used and considered the best assessment method respecting sensitivity and predictive value. Likelihood levels are: 'highly probable' (> 8), 'probable' (6 – 8), 'possible' (3 – 5), 'unlikely' (1 – 2), and 'excluded' (score < = 0). RUCAM score system is separated into hepatocellular injuries; cholestatic or mixed injuries form [23].

Prevention

Liver function testing is recommended before starting the treatment along with safety monitoring during therapy with agents with known hepatotoxicity and in case treatment extends for longer than 2-4 weeks. However, with respect to the costs of such screening, it is difficult to define the threshold at which the drug should be discontinued especially in case of absence of symptoms.

Generally, it is recommended that the drug should be stopped if ALT level exceeds five times ULN. Abnormal bilirubin level, albumin concentration, prothrombin time and symptoms are clear indications to stop the therapy.

The monitoring of the liver tests is strongly recommended in case of treatment with the following agents: methotrexate, isoniazid, retinoids, ketoconazole, anticancer drugs, and minocycline in prolonged time [18,24].

Treatment of DILD

There are varied presentations and multiple possible drug causes. The treatment of all cases is withdrawal of the suspecting agent. If a DILD is caused by acetaminophen or in case of Amanita mushrooms intoxication, appropriate therapy should be administered. All patients can now be considered for NAC therapy, especially adults with early-stage of ALF (acute liver failure). Patients should be monitored for normalization of biochemical tests. In cases when it is recognized as lifesaving, Early liver transplantation is recommended in cases where it is recognized as a lifesaving procedure [25].

Prognosis

The prognosis is highly variable depending on the clinical presentation and degree of liver damage. In general, outcomes of idiosyncratic DILI are good, with about 10% reaching the ALF (coagulopathy and encephalopathy). The outcome of acute liver failure is determined by aetiology, the degree of hepatic encephalopathy, and complications such as infections. DILI developing to ALF carries a poor prognosis. Mortality rate of DILD is 9 to 12%. Only 20% to 25% of patients with acute idiosyncratic fulminant hepatic failure survive 3 weeks without liver transplantation. The causes of death include cerebral oedema, sepsis, multiple organs insufficiency, cardiac and respiratory failure [13,15]. In cases with existing liver disease, increased morbidity and mortality have been reported. Prognosis is worse the longer a patient is exposed to hepatotoxin.

Mixed type of liver damage often progresses into a chronic form with cirrhosis. Immune type of damage (eosinophils and granulomas on biopsy) has a better prognosis. Pure hepatocellular necrosis in biopsy has a worse prognosis [14].

Categorisation of the Probability of DILD

According to the Drug-Induced Liver Injury Network (DILIN) assessment causality of probability to induce liver injury, drugs are classified in five categories of probability to induce DILD. This assessment is based on published data and is more precise for widely prolonged use of medicines than nearly approved drugs or herbal products [26].

Table 5 Categorisation of the probability of DILD

Category A. Medicines from this category are well known, well described, well reported to cause either direct or idiosyncratic liver injury. The number of described cases is more than 50

Category B. Known or highly likely drugs reported to cause idiosyncratic liver injury. The number of described cases is between 12 and 50 cases including small case series.

Category C. Probably linked drugs to induce idiosyncratic liver injury, reported uncommonly. The number of identified cases is less than 12 without significant case series.

Category D. Possible hepatotoxic drugs that rarely cause liver injury. The number of identified cases is less than 3.

Category E. Drugs with no evidence that has caused liver injury. Mostly inconclusive single case reports have been published.

Category E*. Agents with reported DILD in extensive clinical studies, but with insufficient supportive causality data. Hepatotoxicity is unproven, but suspected.

Category X. Medicines quite recently presented or seldom used in clinical practice with luck of data on risk for developing of DILD ("unknown" category).

A [HD], B [HD], C [HD] or D [HD] category. Medicines that induce liver damage in cases of overdose. Most common used agents from this category are aspirin, acetaminophen, naicin and vitamin A.

Liver disease associated with particular drugs

Amoxicillin-clavulanate

The incidence of DILD is 1.7 per 10,000 prescriptions. It is more common in the elderly with a concomitant therapy. It occurs more frequently in individuals who are

heterozygous for a mutant form of the gene for glutathione-S-transferase. The injury starts within 6 weeks of therapy with amoxicillin-clavulanate. Cholestatic type of damage is common and other forms are possible, as well.

Recovery period is 3-6 months. About 3% of injured finished with acute renal insufficiency or progression to cirrhosis [13].

Fluoroquinolones

The latency period is short (from 2 to 9 days). Common type of injury is immune damage. Prognosis is better than in case of DILD induced by amoxicillin-clavulanate. It is more common in people who are allergic to fluoroquinolones. Liver damage is a 'class effect' of fluoroquinolones [15].

Tyrosine kinase inhibitors

Liver damage occurs in the first 8 weeks after initiation of therapy. It can be manifested as a mild form - only an increase in transaminases, which passes spontaneously after discontinuation of medication. The severe form is presented as hepatocellular injury, and the incidence is 2-3% of total number of treated patients [13].

Direct-acting oral anticoagulants (DOACs)

Liver damage during administration of therapeutic doses of direct-acting oral anticoagulants has been reported in the past few years. Post marketed data reported rivaroxaban as the agent with the highest risk in the group. A pharmacological and chemical characteristic of direct-acting anticoagulants seems to be associated with drug-induced liver injury risk. Rivaroxaban, dabigatran and apixaban contain structural elements connected to metabolism and/or reactive metabolites connected to DILD occurrence in humans. Host factors seem to have influence on DILD occurrence. DILD induced by DOACs therapy of venous thromboembolism in surgical patients is reported more frequently then atrial fibrillation [27].

Herbal and Dietary supplement-induced liver injury

The increasing use of alternative medicines has led to many reports of toxicity. The spectrum of liver disease is wide. Herbal and Dietary supplements do not pass preclinical and clinical toxicology safety testing or clinical trials for safety. A dietary supplement consists of vitamins, minerals, amino acids, enzymes, tissues extracts, metabolites, etc. Herbal and Dietary Supplements (HDS) are widely consumed and in most cases without medical observation. Some of these products have been reported to induce liver injury. First of all, body-building products, which contain anabolic steroids are associated with an initial cholestatic hepatitis followed by prolonged jaundice [28]. Pyrrolizidine alkaloids can induce sinusoidal obstruction syndrome [29]. In some cases, flavocoxid, has been associated with severe liver injury [30]. The same diagnostic approach for DILI is applicable to suspected HDS hepatotoxicity. Patients should stop using HDS products and be monitored until hepatotoxicity has been resolved.

Individual susceptibility is important for herbal-induced drug injury. Kava, anxiolytic agent is connected to hepatotoxicity in Caucasians with low expression of CYP2D6. Some herbs initiate immunoallergic liver injury (jin bu huan). Rarely, herbal medicines may trigger latent liver disease (dai-saiko–to, black cohosh). Herbal hepatotoxicity could be presented as acute hepatitis, steatosis, fibrosis to submassive and massive hepatic necrosis (chaparral leaf). Some herbal agents and dietary supplements implicated as causing toxic liver injury are presented in Table 6 [13].

Discussion/Conclusion

Clinical and laboratory findings in DILDs are not always in line with liver pathology. There are significant differences between categories. Histologic changes can be minor compared to biochemical findings. Liver enzymes are not synonym of liver damage. Some drugs, like estrogens, are associated with high levels of AT and mild cholestasis on biopsy can be recorded.

Drugs like methotrexate, arsenic can cause cirrhosis with minimal changes in laboratory tests. Model of liver tests is nonspecific and often mixed. Various forms of injury can be seen: steatohepatitis, cholestatic hepatitis, chronic hepatitis, minor nonspecific liver injury.

Most cases of drug-induced dysfunction are reversible. In general, discontinuation of hepatotoxin results in rapid reversal of signs and symptoms if the

Table 6 Herbal agents and dietary supplements implicated as causing toxic liver injury

Herbal remedy	Indication	Pattern of liver injury
Atractylis gummifera	Purgative, diuretic	Acute liver failure
Black cohosh	Menopausal symptoms	Acute liver failure, could trigger autoimmune hepatitis
Chinese herbal medicines	Multiple use	Liver injury, Acute hepatitis
Germander tea and capsules	Weight reduction, health tonic	Acute and chronic hepatitis, acute liver failure, hepatic fibrosis
"Green juice"	Dietary supplement	Granulomatous hepatitis
Herbalife®	Health supplement	Acute hepatitis, Cholestasis
Kava	Anxiety disorder	Diffuse hepatocellular necrosis, Cholestatic hepatitis
Kombucha	Health tonic	Acute hepatitis
LipoKinetix®	Slimming aid	Acute hepatitis, acute liver failure
Shark cartilage	Food supplement	Abnormal liver tests

injury is mild to moderate. A 50% reduction of hepatic-associated enzymes can be expected within 1 week if the injury is hepatocellular, but this degree of improvement may take 6 months or longer if the injury is cholestatic.

In most cases, management of drug-induced liver dysfunction is limited to supportive care, as therapeutic treatment is applicable in only a small number of situations.

Liver function testing before starting of the treatment and safety monitoring during the therapy with agents with known hepatotoxicity and in case treatment will extend for longer than 2-4 week is recommended. Monitoring of the liver tests is strongly recommended in case of treatment with the following agents: methotrexate, isoniazid, retinoids, ketoconazole, anticancer drugs, and minocycline in prolonged time. Herbal and Dietary Supplements (HDS) are widely consumed and in most cases without medical observation. Some of these products have been reported to induce liver injury. Patients should stop using HDS products and they should be monitored until hepatotoxicity has been resolved.

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