Review Article

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A REVIEW ON DRUG INDUCED LIVER INJURY: A RETROSPECTION

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ABSTRACT

Drug-induced liver injury (DILI) is an infrequent condition but can become potentially dangerous due to various factors. The triggering factors of liver disease are often associated with Over the Counter (OTC) medicines, prescription medications, and herbal and dietary supplements (HDS). DILI are of two types: intrinsic and idiosyncratic. Risk factors for idiosyncratic DILI (IDILI) are frequently associated with multiple hosts, environmental and compound factors. The formation of international syndicates for the registry made it advantageous for conducting the study of individual predispositions to DILI. Recent data highlight antibiotics, central nervous system agents, anti-tubercular drugs, herbal/dietary supplements and immunomodulatory agents as the most common causes of DILI. Female patients are often affected by this disorder. Treatment modalities range from the use of nanotechnology to provide hepatoprotective agents directly to the liver, up to polyherbal formulations. Future areas of research include the identification of predisposing factors in the patients at highest risk for DILI.

Keywords: Drug – Induced Liver Injury (DILI), Registries, Herbal Medications, Risk Factors

INTRODUCTION

Liver often plays an important role in the metabolism of drugs and xenobiotics, steering to atypical risk of toxic effects. Drug-induced liver injury (DILI) defined as liver injury triggered by exposure to a drug or non-infectious toxic agent and is allied with different levels of organ dysfunction[1]. More than 900 drugs, toxins, and herbs have been reported to cause liver injury and drugs account for 20-40% of all instances of sudden and severe hepatic failure[2]. DILI can be pharmacologically classified into two: dose-dependent and dose independent or idiosyncratic. Dose-dependent DILI, also known as direct toxicity, occurs after the consumption of a dose beyond a known toxic threshold. It is predictable, reproducible and develops with short dormancy; whereas, in Idiosyncratic DILI, it is unpredictable and usually develops at therapeutic doses. The damage extent is not always proportional to administered dose and the period of damage's onset can fluctuate broadly[1].

Epidemiology

Almost all idiosyncratic DILI concluded in liver transplant or death. This was mainly due to unawareness of patients, failed reporting system and diagnosis. The cause of DILI varies from one country to another, based on their system of medicine. For example, antimicrobials are the most common reason behind DILI in European countries, paracetamol in western world and TB drugs in India[3]. The consumption of unregulated herbal and dietary supplements has introduced new challenges in epidemiologic assessment and management of DILI.

Guidelines and Registries

The Drug-Induced Liver Injury Network (DILIN) is one of the most reliable DILI registries in the world which was founded in the US by the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK). This registry was created owing to the rarity of DILI and for the better understanding of the problem and analysis of all reported cases. For this reason, various epidemiological registries have been formed all over the world[3] such as the Regional Registry of Hepatotoxicity in southern Spain, the U.S. Acute Liver Failure Study Group (ALFSG), south-east Asian registries and registries in Australia, Iceland, India, South Korea, and Serbia.

In April 2012, in addition to DILIN and the other national databases, the United States National Institutes of Health and National Library of Medicine launched Liver Tox (https://livertox. nlm.nih.gov/)[3]. This provides up-to-date, precise information on the diagnosis, frequency, cause, patterns, and management of liver injury due to prescription and nonprescription medications, herbals and dietary supplements. Liver tox also contain a case registry that will facilitate scientific analysis and enhanced description of the clinical patterns of liver injury. European registry and USA DILIN reported antibiotics as the first class of involved drug in DILI. But in South East Asian registries there is the high incidence of herbal and dietary supplements related DILI[1].

Risk factors

The risk factors arise from three diverse aspects: (1) Clinical host-related; (2) Environmental; and (3) Drug-related. Non-modifiable risk factors include Age and Gender[3];
The following are some of the risk factors attributable to DILI.

Host Factor

Based on the reports on the registries, female have been predominantly identified with DILI, studies from United States,

India, Spain and France shows an incidence of 49% to 60% of females with DILI. Males have been indicated as high-risk patients for DILI associated with systemic anti viral, whereas liver injury and ALF has been reported with higher frequency in children[3,4].

Alcohol

Alcohol is believed to be a risk factor for DILI, due to the synergetic effect with anti tubercular medications, anti viral and antibiotics with the patients leading to hepatotoxic effects. In some studies, alcohol increases the probability score of DILI. In the Roussel Clef Causality Assessment Model (RUCAM) a causality instrument, data pertaining to addition of alcohol as a risk factor was relatively inadequate[1,5]. According to Harshad D *et al*., chronic use of alcohol particularly with under nutrition depletes glutathione stores but a definite link between alcoholism is lacking. In the DILIN study, alcohol was a negative predictor for DILI[3].

Herbal medications, Dietary supplements (HDS) and Poly pharmacy

According to WHO; in 1998, eighty percentage of world population is exclusively using herbs for therapeutic purposes. Herbal formulations even though they are not clearly recognized as medicines, they can have pharmacological properties and different potency based on the soil, season, altitude etc. So, they cannot only be beneficial but also can produce toxic effects. Herbal liver toxicity can be varying from herb–herb, herb-drug interactions, toxic effects from contaminants, adulteration with heavy metals, microbes, traditional drug, pesticides, botanical misidentification, mislabeling and variability in the collection and extraction processes has been reported in various literatures[4].

Hepatotoxicity induced by the herbal products is a major challenge for clinicians to diagnose the cause of the hepatotoxicity due to the reluctance of the patients to open up about the herbal medicines they use. These products contain different herbs of different dosages which make it difficult for clinicians to point out the toxicity of a single herb. According to DILIN registry, 76% of DILI are occurring due to this reason. The amount of the herbs consumed by patients, interactions between different herbs and allopathic medicines, the synergistic hepatotoxicity of herbal preparations, and risk factors of patients have to be considered[1]. A wide variety of herbs from China, India and Korea such as *Aegle marmelosa, Artemisia herba-alba, Larrea tridentata, Ephedra sinica, Teucrium Chamaedrys, Actaea racemosa, Viscum album, Mentha puligeum*, some flower plants containing pyrrolizidine alkaloids, green tea extract, *Mitragyna speciosa*, and *Garcinia cambogia* have been reported to cause liver injury[4]. Liver transplant registries note that 5% of liver transplants are because of the consequences of HDS-induced ILIDI[6]. Another area of growing concern is the use of herbal and dietary products for the weight loss, body building and erectile dysfunction. Epidemic of obesity in developed countries increases the frequency of this type hepatotoxicity[6]. Fact to consider is that most of these herbal or dietary supplements are not regulated by governmental agencies, including the U.S. Food and Drug Administration (FDA). A study done by Estes *et al*., showed that 50% of patients suffered with acute liver failure (ALF) due to the intake of potentially toxic hepatotoxic herbs or supplements for weight loss[7-9].

Age

Generally, it was believed that older age, especially greater than 55 years old people are at risk of DILI. But various reports show that the age is not a factor in DILI. Studies from India reported that the young adults and children (8.7%) are more prone to DILI. Concomitant uses of anti tuberculosis and anti epileptics' medications were found to be the leading causes of DILI in children[3].

Human Immunodeficiency Virus

HIV infected patients are more susceptible for DILI, due to the fact that they are on multiple medicines for both HIV infections and opportunistic infections such as pneumonia, tuberculosis, salmonella infections, candidiasis, toxoplasmosis, pneumocystis carinii infections and concomitant hepatitis B and C infections. This can induce liver injury on their own from both drug–drug and drug–disease interaction[3].

Hepatitis B and Hepatitis C

Chronic infectious diseases like Hepatitis B and Hepatitis C are associated with a higher incidence of hepatoxicity induced by several drugs such as anti tuberculosis drugs, isoniazid, rifampicin etc. Moreover, patients with these diseases have poorer effect than healthy individual which in turn progress into DILI[3].

Genetic Factors

The major group of enzymes in the liver that metabolize drugs can be isolated in a sub-cellular fraction termed the microsomes. The largest and most important of these enzymes are the cytochrome P450 family of enzymes, which is encoded by a unique gene. Genetic polymorphism of this enzyme can result in abnormal reactions to drugs and idiosyncratic reactions leading to DILI[2].

Dose

In a study conducted by Lammert *et al*., on exposed dose of a drug and hepatotoxicity find out that any drug administered in doses greater than 50 mg and also drugs with more than 50% hepatic metabolism are at higher risk of hepatotoxicity. Additionally, drugs metabolized by the liver with its excretion in biliary canaliculi appear to enhance the risk of DILI. Long-acting drugs may cause more injury than shorter-acting drugs[2,5,10].

Common drugs leading to liver injury

The most commonly implicated drugs involved in liver injury and their disease patterns are summarized in Table 1.[11,12]

Table 1: Commonly-reported drugs associated with drug induced liver injury (DILI)

Anesthetic	Halothane
	Isoflurane
Analgesic	Flupirtine
Anti anginal	Perhexiline
Anti Arrhythmia	Amiodarone
	Propafenone
Antibiotic	Amoxicillin-clavulanate
	Minocycline
	Nitrofurantoin
	Amoxicillin/ clavulanate (augmentin)
	Vancomycin
	Minocycline
	Flucloxacillin
	Erythromycin
	Ciprofoxacin
	Ornidazole
	Telithromycin
	Trovafloxacin
Anti diabetic	Acarbose
	Troglitazone
Antiepileptic	Carbamazepine
	Phenytoin
	Carbamazepine
	Valproic acid
	Bentazepam
	Lamotrigine
	Phenytoin
Antifungal	Ketoconazole
	Fluconazole
	Itraconazole
Anti hemorrhagic agent	Benzarone
Anti hypertensive	Hydralazine
	Methyldopa
	Enalapril
	Didanosine
	Efavirenz
	Erythromycin
	Flucloxacillin
	Interferon alpha/Peginterferon
	Nevirapine
Anti neoplastic	Floxuridine
	Flutamide
	Etoposide
	Imatinib
	Ipilimumab
	Oxaliplatin
	Temozolomide
	Thioguanine
	Tamoxifen
	Busulfan
	Everolimus
	Methotrexate
Anti parkinsonism	Tolcapone
Anti retroviral	Ritonavir
Anti spasmodic	Papaverine
Anti tuberculosis	Isoniazid
	Rifampicin
	Pyrazinamide
	Isoniazid
Birth control	Contraceptives
Body building	Anabolic steroids
Gout prophylaxis	Allopurinol
Hyperthyroidism	Propylthiouracil
Immuno Modulator	Glatiramer
Immunosuppressive agent	Mercaptopurine
	Gold salts
	Infliximab
	Methotrexate
	Azathioprine
	Cyclophosphamide

	Sodium Aurothiomalate
Lipid lowering agent	Atorvastatin
	Ezetimibe
Multiple Sclerosis	Interferon beta
Muscle relaxant	Dantrolene
Muscle relaxant/ Sedative & hypnotic	Clomethiazole
NSAID	Diclofenac
	Ibuprofen
	Nimesulide
	Naproxen
	Acetaminophen
	Lumiracoxib
Opoid Analgesics	Buprenorphine
	Dextropropoxyphene
Psychosis	Chlorpromazine
	Chlorpromazine
	Paroxetine
Respiratory stimulant	Doxapram Hydrochloride
Steroids	Anabolic steroids
	Cyproterone acetate
	Methylprednisolone
Substance abuse agent	Disulfiram
Vitamin	Vitamin A (retinol)[11,12]

Treatment

Symptoms of DILI range from biochemical abnormalities to hepatitis and severe jaundice. The standard treatment of DILI is the sudden discontinuation of the offending drug and thereby preventing the development of ALF. But in some cases, medicines taken for even two or three days may lead to serious outcome. For ALF due to idiosyncratic DILI, there is no approved antidote[13].

For immune-mediated reactions, corticosteroid therapy was considered as treatment for DILI in the ALF and Ursodeoxycholic acid (UDCA) for cholestatic liver injury, but data pertaining to their use is meagre. According to American College of Gastroenterology Clinical Guidelines, no controlled trials of steroid therapy for DILI have been performed[8]. Tawfik K *et al*; reported that steroids failed to prove its beneficial effect in two ALF trials (which consist of 104 patients of whom 12 had DILI). Conversely even the patients with DILI, shows a worse prognosis towards steroid therapy. Since UDCA has a good safety profile, a combination treatment of UDCA and oral steroids was found to be beneficial in a retrospective study of 300 patients with DILI with acute liver failure. For severe DILI, antioxidants have been used as treatment of choice. For example, N-acetylcysteine (NAC) is the antidote for the treatment for acetaminophen-induced liver injury and also seems to be beneficial for patients with acute liver failure caused by herbal agents[13]. Complicated DILI should be managed by the clinical pharmacist joining with a hepatologist and on further complications with liver failure immediate referral to a liver transplant unit is recommended[8].

Plasma exchange is another therapeutic approach for the treatment of acute liver failure. In this method the protein bound toxin molecules accumulated in the liver due to hepatic failure, nitrogenous waste products such as ammonia and urea, inflammatory cytokines are removed and adding up of coagulation factors to correct the coagulopathy from liver injury and improving encephalopathy in patients with acute liver failure was taking place. Studies demonstrated that plasma exchange exerts beneficial effects on patients with acute liver failure with residual liver functional capacity. Patients with chronic disease have only minor survival benefits in this treatment modality[13].

Novel treatment options for hepatic failure are molecular adsorbent re circulating system (MARS) and fractionated plasma separation and adsorption system (PFSA). Even these treatment modalities also not assuring beneficial survival effect in randomized control trials (RCTs) of patients with acute and chronic liver failure. MARS and PFSA have decreased risk of infections and allergic reactions[14]. So the treatment modalities range from the use of nanotechnology to provide hepatoprotective agents directly to the liver up to the polyherbal formulations [10].

Prevention

The proverb says, “prevention is better than cure”, and in case of DILI this proverb is appropriate. Drugs which are causing DILI often carries a label to reduce the dose for the patients with hepatic disease, but data reveals that this does not reduce the risk of DILI. It is challenging to predict, when and which drug will develop DILI during treatment. So rational drug prescribing and use of it is the best method to prevent or minimize DILI especially for patients with risk factors[15].

So the practitioners and pharmacist should have a thorough knowledge about drug–drug interaction and drug–disease interaction. Caution should be exercised whenever minor a symptom of early onset of DILI emerges. Proper counseling should be given for both patients and caregivers regarding the symptoms such as jaundice, pruritus, anorexia, vomiting, dark urine, and anorexia and right quadrant abdominal pain. Patients should be educated regarding the importance of cessation of the drug at the slightest suspicion of DILI and also the significance of conducting liver injury test for the patient who are on the hepatotoxic drugs. It is also important to educate them regarding the health; especially for obese patients with co morbid disease, people who are using herbal medicines for various purposes etc. in order to avoid these risk factors to prevent DILI. Consider a hepatologist’s advice whenever a query rises against the medications or symptoms for the individual with chronic liver disease. Patients should be encouraged to report use of HDS to their healthcare providers and be reminded that supplements are not subjected to the same rigorous testing for safety and efficacy as are prescription medications[8,15].

CONCLUSION

DILI remains one of the most common causes of acute liver failure. The upcoming challenge is to identify the predisposing

factors of the individuals and thereby customizing the medication therapy to suit the patient's need and decrease the incidence of DILI. The formation of international syndicates for the registry made it advantageous for conducting the study of individual predispositions to DILI. In India, there is a lack of active reporting or surveillance systems. Recent data highlight antibiotics, central nervous system agents, anti-tubercular drugs, herbal/dietary supplements and immunomodulatory agents as the most common causes of DILI. The hallmark of treatment options is the elimination of the causative drug, and still we are up against the wall and in need of further advances.

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