3rd GLOBAL LIVER HEALTH FORUM

DIAGNOSIS AND TREATMENT OF DRUG-INDUCED LIVER INJURY: GUIDELINES AND PRACTICE

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Epidemiology, types, and causes of DILI

DILI is a rare condition within the general population; however, the prevalence of the condition is gradually increasing in hospitalised patients.[1] Among patients with unexplained liver conditions such as hepatic biochemical abnormalities, jaundice or ALF, DILI is a common aetiology.[1] In the USA, most cases of DILI in patients with new onset non-alcoholic jaundice are attributed to APAP, with a prevalence of ~4%. The proportion of DILI within the ALF population is also increasing; for example, in the USA, DILI caused by APAP and (i)DILI accounts or >50% of all cases of ALF.[1]

DILI is typically classified as direct hepatotoxicity (a frequent, predictable and dose-related condition), idiosyncratic hepatotoxicity (a rare form of liver injury that is neither predictable nor dose-related), or indirect hepatotoxicity (a non-dose-related condition that can be predicted in some cases). Indirect DILI presents a new therapeutic challenge due to its dose-agnostic nature, as the condition is thought to be caused by the indirect action of an agent on the liver or immune system. It has a delayed onset and is more common than idiosyncratic hepatotoxicity but less common than direct hepatotoxicity.[2]

Many different causes of DILI have been identified and the leading cause typically varies from country to country. In Spain and France, the leading cause of DILI is anti-infectious agents, while antibiotics, antimicrobial drugs and anti-inflammatory drugs are the leading causes in Iceland, the USA and Japan, respectively. Conversely, in Korea the leading cause of DILI is herbal medications, in Singapore it's Chinese traditional CAM, in India it's anti-TB drugs, and TCM or HDS are the leading causes of DILI in China.[1] In general, Asia-Pacific regions show a higher incidence of HDS-induced liver injury in DILI than Europe and the USA.[1]

Factors contributing to the development of DILI

A variety of risk factors that are considered to contribute to the risk of DILI have been identified; however, not all-cause risk factors have been confirmed.[3] DILI events tend to result from combined effects of the first exposure from potential hepatotoxic drugs, genetic and non-genetic risk factors, and adaptive injury repair mechanisms.[1] More recently, due to the consideration of genome-wide association studies, key HLA alleles that influence the susceptibility to DILI caused by specific drugs have been identified. Clinically, the negative predictive value of HLA alleles could be used to exclude certain drugs as a cause of DILI.[1]

ACG-DILI guidelines for the diagnosis of DILI

Internationally, there are different DILI clinical guidelines which cover multiple types of DILI. DILI is diagnosed by exclusion, through a careful assessment of other aetiologies of liver disease.[1] Other possible causes of liver injury are excluded based on: clinical history, including a thorough history of the patients intake of drugs and HDS; serum biochemical tests; liver imaging; and/or biopsy.[1,4] When obtaining history on the indication and use of drugs and HDS, it is important to have a complete list of all agents, exposure times of each agent and also gather washout data by conducting liver biochemistries.[4] The ACG-DILI guidelines recommends differential diagnostic strategies for suspected DILI. Liver biopsies are recommended to assist diagnosis in many different circumstances, including cases of DILI where there has been continued use or re-exposure to the implicated agent.[4]

Recommendations for treatment of DILI, according to different guidelines

It is widely agreed across the many different guidelines for DILI treatment strategies, that the most important management strategy when DILI is suspected is to discontinue the offending agent.[4–9] However, guidelines often provide differing recommendations regarding other treatment strategies. Both the ACG (2021)[4] and the CIOMS (2020)[6] guidelines recommend the use of corticosteroids in DILI patients with AIH-like features, whereas CSH guidelines (2015) recommend corticosteroids for the treatment of patients with immuno-allergic or autoimmune features.[8] A retrospective analysis study investigating the use of steroids in ALF in 361 ALF cases, including 131 of the aetiology DILI, from 1998 to 2007 found that corticosteroids did not improve overall survival or spontaneous survival (survival without transplant) in drug-induced ALF.[10] In an open-label, controlled study in 150 patients with solid malignant tumours, lower incidence of liver dysfunction with adjunctive EPL treatment after chemotherapy (16.8% vs 44.2%, p<0.0001) and lower hepatoxicity grade (2.5% vs 13.9%, p<0.0001) were observed.[11]

The relationship between DILI and COVID-19

Patients with COVID-19 often show abnormalities in liver tests, though the cause of this is currently unknown. A systematic review was conducted to characterise the role of conventional drugs in causing DILI using data from 393 patients with DILI and COVID-19; the results of the review showed that the most common cause of DILI was anti-viral drugs given empirically for their known therapeutic efficacy in other viral infections.[12] In addition, for patients with MAFLD, the risk of DILI in patients with COVID-19 is increased, as they are much more likely to be hospitalised and receive antiviral agents to treat severe systemic inflammation.[13]

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ACG, American Society of Gastroenterology; AIH, autoimmune hepatitis; ALF, acute liver failure; APAP, acetaminophen; CAM, complementary and alternative medicines; CIOMS, Council for International Organizations of Medical Sciences; COVID-19, coronavirus disease 2019; CSH, Chinese Society of Hepatology; (i)DILI, (idiosyncratic) drug-induced liver injury; EPL, essential phospholipids; HDS, herbal and dietary supplements; HLA, human leucocyte antigen; MAFLD, metabolic-dysfunction associated fatty liver disease; TB, tuberculosis; TCM, traditional Chinese Medicine.

Learning objectives:

- Explore the leading causes of DILI, its diagnosis and treatment
- Explore the difference between DILI in the East and the West, including HDS-induced liver injury and treatment options
- Discussion on the difficulty of COVID-19 and DILI including an overview that the liver injury seen with COVID-19 may be due to DILI, pre-existing liver diseases or viral infection

Main takeaways:

- The prevalence of DILI tends to be higher in hospitalised patients compared with patients with liver disease in the general population
- In general, Asia-Pacific regions show a higher incidence of HDS-induced liver injury in DILI than Europe and the USA
- The widespread use of genome-wide association studies has helped to identify both HLA alleles and non-HLA variants that influence the susceptibility to DILI caused by specific drugs
- The most important management strategy when DILI is suspected, is to discontinue the offending agent; however, regarding other treatment strategies, guidelines often provide differing recommendations
- EPL have been investigated in DILI with chemotherapeutic and antitubercular agents
- Treatment with EPL in patients with DILI could improve clinical outcomes
- Patients with MAFLD have increased risk of DILI after COVID-19 infection as they are more likely to be hospitalised and receive antiviral agents to treat systemic inflammation

COVID-19, coronavirus disease 2019; DILI, drug-induced liver injury; EPL, essential phospholipids; HDS, herbal and dietary supplements; HLA, human leucocyte antigen; MAFLD, metabolic-dysfunction associated fatty liver disease.

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