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Drug Induced cholestasis: A Review

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ABSTRACT:
Healthcare system may have difficulties dealing with cholestatic drug-induced liver damage (DILI). This is an uncommon event in which there are estimated to be 14 to 19 incidences annually for every 100,000 patients. Acute illness that quickly goes away when the offending medications are removed. Additionally, the majority of individuals are susceptible to persistent jaundice, pruritis, fever, nausea, and vomiting. It is associated with risk factors like advanced age, genetic factors, and the characteristics of certain medications. Although a number of additional drugs have been linked to cholestatic DILI, antibiotics—especially amoxicillin and clavulanate - continue to be the principal cause of the illness. This study aims to provide an overview of drug-induced cholestatic liver damage, including its clinical manifestations, pathophysiology, associated medications, and treatment**.**

Keywords: Drug induced liver injury (DILI), Drug induced cholestasis (DIC), drug development, serum transferases

I. INTRODUCTION

An adverse drug response to a variety of medications often observed in clinical settings, as well as to herbal remedies and nutritional products, is known as drug-induced liver damage (DILI). Typically, DILI has been determined as either idiosyncratic (no dose-related) or direct (dose-dependent). However, indirect liver damage has developed as a third kind of DILI [1].

After preclinical research, DILI is among the many common reasons for drug development discontinuation for otherwise promising therapeutic medicines. Drug withdrawals soon after their release from the market are mostly due to the significant drug safety concern known as DILI (2).

The abnormal hepatic and/or systemic accumulation of bile acids (BAs) and their conjugate bile salts is a hallmark of cholestasis, which is characterized by impaired bile secretion and flow (3) Cholestatic hepatitis, vanishing bile duct syndrome (VBDS), acute and chronic cholestasis, and immune checkpoint inhibitor-related cholangiopathies are the principal histological signs of DIC. In fact, cholangitis of the large and small ducts and cholecystitis have been studied among the immune-related hepatobiliary disorders associated with anti-programmed death-ligand 1/anti-programmed cell death protein 1 (anti-PD-L1-1/Anti-PD-1).

By excreting lipophilic medicines and their metabolites into the bile, the liver is crucial to the systemic clearance of these substances. Cholestasis is brought on by the interaction of many drugs with liver transporters. Curiously, alterations in bile transporters and allergic immunological systems are involved in its cause of DIC: ductular variants of iDILI, like VBDS, are incidents of this, in which an immune reaction to biliary cells is triggered by a medication or its metabolite (4).

DIC may give rise to either acute or chronic liver disease. It can be intrahepatic or, less frequently, extrahepatic. Acute drug-induced cholestasis can be treated with medication and can be cured when the symptoms go away, but more persistent signs of chronic cholestasis persist for a minimum of six months following the beginning of cholestasis insult. Clinical signs such as skin yellowing are completely gone when the medication is stopped.

Further clinical features might potentially exacerbate hyper bilirubinaemia and raise blood levels of alanine aminotransferase, 5'-nucleotidase, aspartate aminotransferase, and alkaline phosphate ϒ-glutamyl transpeptidase [5].

30 to 40% of IDILI cases are caused by DIC, and liver disease resolves more slowly than hepatocellular damage following medication withdrawal.

II. PATHOPHYSIOLOGY

Bile, a yellowish green fluid, is secreted by the liver. The liver breaks down cholesterol to produce bile acids. There are two forms of bile acids. The primary bile acids are formed from classical pathway and constitute 70% of the bile acid. Bacteria in the intestinal lumen create the secondary bile acids- deoxycholic acid (DCA),

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lithocholic acid (LCA), and Ursodeoxycholic acid (UDCA). Biliary BAs goes into the small intestine from the gallbladder, where they function as signalling molecules and detergents. The apical sodium-dependent bile acid transporter (ASBT) effectively absorbs luminal bile acid after it traverses through the small intestine and reaches the distal ileum. Reabsorbed bile acids (BAs) are transported back to the liver through the portal vein and are then received by hepatocytes by the action of the sinusoidal sodium- taurocholate co-transporting polypeptide (NTCP), which initiates the enterohepatic circulation(6).

A main feature of DIC is the potentially harmful build up of bile acids due to a disturbance of bile flow caused by drug exposure, either mechanically or metabolically, in the liver (7) There are three different categories of triggers that might cause drug-induced cholestasis.

- **transporter alterations**: decreased expression, functional inhibition, and/or abnormal subcellular localization
- **hepatocellular alterations**: reduced membrane fluidity, cytoskeletal architecture impairment, and rupture of tight junctions
- Changes in either the dilation or the constriction of the bile canaliculi (5).

III. CLINICAL FEATURES

Depending on how severe the liver damage is, people with DILI present different medically. Mild DILI patients may have normal general bilirubin levels, no symptoms, or nonspecific symptoms along with elevated levels of aspartate aminotransferase , alanine aminotransferase , or alkaline phosphate (or a mix of these). Within a few months, a number of medications induce slight, clinically inconsequential, and temporary elevations in liver enzyme levels. These elevated levels often signify an adaptive reaction to the medication and do not need to stop the agent's therapy. Usually, clinically significant DILI can occur when a patient's bilirubin levels is 2.5 mg/dl or more, the liver enzyme level increases by greater than 3 to 5 times the ULRR, or decreased liver function. Medication which could be the reason for such symptoms should be discontinued immediately. (1)

Persistent jaundice, ascites, coagulopathy, encephalopathy, moderately general symptoms (weakness, tiredness, anorexia, right upper quadrant discomfort, vomiting, fever, chills, pruritus, etc.), and others are possible clinical signs of cholestatic DILI.(8) A thorough medical history that includes exposure to all medications, herbal remedies, and nutritional supplements should serve as the basis for clinical suspicion. A DILI diagnosis can be supported by looking for two things: improvements following medication withdrawal (dechallenge) and worsening of the drug (rechallenge), which frequently occurs unintentionally. It is necessary to look at additional circumstances that might lead to cholestasis, including as alcohol usage, complete parental nourishment, or hepatic ischemia (heart failure, sepsis, or hypotension).

IV. GENETIC DETERMINANTS

There is a dearth of information regarding the hepatic injury are mediated via basolateral drug transporters. However, there is conjecture that elevated expression levels of some drugs may enhance hepatic concentrations through organic anion transporting peptides (OATP) and other drug uptake transport proteins. Consequently predisposing the individual to cholestatic reactions (9).

ABCB4 gene mutation can potentially cause cholestasis since tissue culture studies indicate that xenobiotic can inhibit P-glycoproteins. Additionally. This canalicular export protein is a contributing factor to DIC because drug metabolites are MRP2 substrates. (4).

Patients with amoxicillin/clavulanate-induced DILI have been seen to have the corresponding human leukocyte antigen (HLA) haplotypes HLA B1*1501-DRB5*0101 DQB1*0602,149 . Flucloxacillin-induced DIC was found have significant association with the genotype HLA-B*5701[10].

V. DIAGNOSIS

Unfortunately, there are no confirmed tests to diagnose drug-induced liver injury (DILI), therefore the diagnosis is still based on clinical suspicion and the exclusion of other causes. The biochemistry of the liver is essential for identifying and categorising damage (11).

The most frequently performed tests are of serum levels of bile salts and conjugated bilirubin. The blockade may be in the bile ducts (extrahepatic cholestasis) or the liver (intrahepatic cholestasis) (3). A rise in alkaline phosphatase (ALP) more than two times the upper limit of normal (ULN) and/or a ratio of alanine aminotransferase (ALT)/ALP of less than two are markers for drug-induced cholestasis. Another option is by computing the R value, which is equal to (ALT/ULN of normal

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ALT)/ (ALP 3 ULN of normal ALT), one can distinguish between hepatocellular and cholestatic DILI. The clinician should apply the ULN for ALT and ALP calculated by the local laboratory when applying this formula (2).

VI. DRUGS THAT INDUCE CHOLESTASIS [10][12]

The drugs that are commonly associated with inducing cholestasis are described in the below Table (1):

Drugs	Class	Time of onset	Indication	Incidence
Amoxicillin/clavulanate	Penicillin	Within 4 weeks	Pneumonia, UTI, Acute otitis media, etc.,	0.1% - 3%
Chlorpromazine, tricyclic antidepressant Serotonin reuptake inhibitor	Psychotropic drugs	Within 6 months	Depression, Anxiety disorder, mania, schizophrenia etc.,	0.1%
Diclofenac, Ibuprofen, Allopurinol, Azathioprine	Anti-inflammatory drugs	Within 3 months	Arthritis, Pain, Auto immune disorder etc.,	1.4% - 10%
Trimethoprim/sulfamethoxazole	Sulfonamides	Within 4 weeks	UTI, otitis media, travelers' diarrhea, bacillary dysentery etc.,	4.3%
Erythromycin, telithromycin, clarithromycin, and azithromycin	Macrolides	Within 10 to 20 days	atypical community acquired pneumonia, H. Pylori, chlamydia and acute non-specific urethritis etc.,	0.036%
Doxycycline, minocycline, and tigecycline	Tetracycline	Within 60 days	infections of skin, eye, lymphatic, intestinal, genital and urinary systems etc.,	0.013%
Terbinafine, griseofulvin, ketoconazole, and itraconazole	Antifungals	Within 4 weeks	Candidiasis, vaginitis, yeast infection etc.,	0.001%
Androgens, anabolic steroids, estrogen supplements	Oral contraceptives	Within 1 to 2 weeks	menstrual pain, irregular menstruation, fibroids, etc.,	1%

Table (1)

VII. MANAGEMENT

The primary management for DIC is the withdrawal of the suspected drug and treat the patient symptomatically. The causal drug should not be considered for rechallenge [13]. If the patient indicates serious liver damage as demonstrated by jaundice or increase in serum aminotransferases, immediate cessation of the suspected drug should be done.

Ursodeoxycholic acid is the drug of choice for pharmacotherapy of cholestatic liver injury because it protects against cytotoxicity from toxic bile salts, stimulates hepatobiliary secretion, has antioxidant properties, raises glutathione levels,

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and inhibits liver cell apoptosis [14]. However, the data on ursodeoxycholic acids therapeutic efficacy on treatment of cholestatic DILI is inadequate. Pruritis secondary to severe cholestasis can be treated by cholestyramine, antihistamines, rifampin, phenobarbital and opioid analogues that resolves pruritis. In case of failed medical therapy, the patient can be given alternate therapy such as ultraviolet B phototherapy and plasmapheresis [15].

VIII. CONCLUSION

A main reason for drug development's cessation is drug-induced liver damage (DILI). Drug induced cholestasis contributes to being one of the main causes for DILI, and consequently, to withdrawal of drugs from post market surveillance. This review discussed about the pathophysiology, diagnostic and management aspects of the disorder. While termination of drugs causing DIC may treat the condition, there are few cases where DIC has proven to be fatal, which calls for stringent adverse effect reporting of new drugs.

Conflict of interest

The authors had no conflict of interest during the course of performing the review.

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