

LITERATURE REVIEW

Tuberculosis Drug-Induced Liver Injury

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ABSTRACT

Effective tuberculosis (TB) treatment requires a combination of bactericidal and/or bacteriostatic TB drugs. The combination of these regimens is the standard therapy recommended by World Health Organization (WHO). The standard therapy consists of 5 first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin). TB drugs have mild to severe side effects. Side effects that arise not only cause mortality and morbidity but also cause the cessation of treatment with the effect of not achieving cure, even arising drug resistance. Drug-induced liver injury (DILI) is a form of side effect that causes the cessation of TB treatment or regimen changes due to treatment failure, relapse, and drug resistance. DILI increases the problem, covering more than 7% of all side effects. DILI is also one of the concerns in the treatment of TB.

INTRODUCTION

Effective tuberculosis (TB) treatment requires a combination of bactericidal and/or bacteriostatic TB drugs. The combination of these regimens is the standard therapy recommended by World Health Organization (WHO). The standard therapy consists of 5 first-line anti-TB drugs (isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin). TB drugs have mild to severe side effects. Side effects that arise not only cause mortality and morbidity but also cause the cessation of treatment with the effect of not achieving cure, even arising drug resistance. Drug-induced liver injury (DILI) is a form of side effect that causes the cessation of TB treatment or regimen changes due to treatment failure, relapse, and drug resistance. DILI increases the problem, covering more than 7% of all side effects. DILI is also one of the concerns in the treatment of TB.¹⁻³

TB DILI is a disorder of liver function due to the use of antituberculosis drugs (ATD). DILI due to ATD occurs within 2 months after administration and the highest incidence occurs in the first 2 weeks. The incidence of DILI is difficult to predict, there are several risk factors for the occurrence of DILI during administration of ATD. Some risk factors are body mass index (BMI), isoniazid (INH) metabolic acetylator status, age, sex, metabolic factors, drug interactions, and alcohol consumption.²⁻⁵

A study shows that there are pathological processes in Bridging necrosis and multilobular necrosis in the use of INH. Acetylhydrazine is an INH metabolite

that causes liver damage in adults. Age is the most important risk factor for DILI due to INH. Liver damage is rare in patients under the age of 20 years old, complications occur in 0.3% of patients aged 20 to 34 years old, and the incidence is increasing to 1.2% in people aged 35 to 49 years old and 2.3% in people aged over 50 years old. 12% of patients who received INH showed increased plasma aspartate and alanine transaminase activity.^{2,6}

The use of rifampicin orally is absorbed by the gastrointestinal. After being absorbed, rifampicin will be eliminated quickly in the bile and enterohepatic circulation occurs. The half-life of rifampicin ranges from 1.5 to 5 hours and increases when there is liver dysfunction. A study shows the process of rifampicin hepatotoxicity can originate from oxidative stress on mitochondria, cholestasis, and accumulation of fat cells in the liver.^{2,6-8}

After administration of pyrazinamide, sign and symptoms of liver disease will occur in 15% of patients, accompanied by jaundice in 2-3% and death due to liver necrosis in some cases. Increased alanine and aspartate aminotransferase in plasma are the earliest symptoms of abnormality caused by this drug. Pyrazinamide should not be given to people who experience abnormalities of liver function at any level unless there is absolutely no other route.^{2,3}

RISK FACTORS

Effective TB treatment uses rifampicin, isoniazid, pyrazinamide, and ethambutol. The use of these drugs has a risk of hepatotoxic side effects. There

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are several risk factors that can be used to predict the occurrence of hepatotoxicity that causes DILI, namely BMI, INH metabolic acetylator status, age, sex, metabolic factors, drug interactions, and alcohol consumption (Figure 1).^{3,9}

Body Mass Index (BMI)

It has long been believed that a low body mass index (BMI) in TB patients due to malnutrition increases the risk of developing DILI. Weight loss, low albumin value, and low nutritional status are associated with an increased risk of hepatotoxicity due to drug administration. A research conducted at Dr. Soetomo General Hospital found a significant correlation between BMI with the onset of DILI in general. In that study, it was found that there was a significant correlation of low BMI increasing the risk of developing a moderate degree DILI.^{3,10}

Acetylator Status

The body has a gene for INH metabolism called NAT2 gene (N-acetyltransferase2). In TB treatment using INH, NAT2 gene codes for enzyme acetyltransferase has a function in the process of acetylation of INH in the liver enzyme system. Through the initialization process by NAT2, INH undergoes an acetylation process which turns into acetyl-isoniazid and then hydrolyzed rapidly to acetylhydrazine. Acetylhydrazine can be oxidized by cytochrome P450 enzymes isoform 2E1 (CYP2E1) to toxic reactive metabolites or acetylation to diacetyl hydrazine. In patients who have a slow acetylator response (slow NAT2 gene) acetyl hydracin is not detoxified rapidly, thereby increasing the oxidation time by CYP2E1 enzyme forming toxic reactive metabolites. From the research conducted at Dr. Soetomo General Hospital, it was found that the status of acetylators did not have a significant correlation with the onset of DILI in general, but a significant correlation occurred between slow acetylators and moderate degree of DILI events.^{3,11}

Age

Age is a risk factor for DILI in some drugs. The mechanism of the occurrence of DILI based on age is still unclear. Some experts say in elderly a decline in kidney function will cause an increase in drug concentration in the liver. In the treatment of TB using INH increases the risk of TB DILI. Cholestasis type DILI is more common in elderly, while in young adults there is more hepatocellular type. Studies in the United States say the incidence of hepatotoxic due to isoniazid is 4.4 per 1,000 patients aged 25-34 years old and increased to 20.83 per 1,000 patients aged 50 years old or more.^{6,10}

Sex

Female patients with hepatocellular type DILI will experience a worse prognosis than men. A study

shows that women and men have a different risk of DILI depending on the type of drugs used, for example, women are more likely to have DILI in the use of halothane, INH, and chlorpromazine. The study by Lucena reported that out of 603 patients with DILI, 51% were male and 49% were female. In the study, it was said that there was a significant increase in cases of hepatocellular DILI in women if they were less than 60 years old. In studies by Shapiro and Lewis, there were no differences in sex as a cause of DILI.^{6,12,13}

Metabolic Factors

More than 50% of drugs are metabolized in the liver and cause DILI without jaundice. Studies also show that the majority of drugs that are not metabolized in the liver very rarely cause DILI. Drugs that excrete through the gallbladder tend to have jaundice compared to drugs that are not excreted through the gall bladder.^{6,10,14}

Drug Interaction

There are 20 or even more types of cytochrome P450 (CYP) variations found in the liver CYP system. This enzyme is responsible for mediating the reaction of metabolites in phase I and these metabolites are more numerous in the centrilobular zone than the periportal zone. Some drugs can modify DILI potential of other drugs through enzyme induction mechanisms, which in some instances cause metabolite reactions such as rifampicin, phenytoin, INH, ethanol, and smoking.^{6,10,14,15}

Alcohol Consumption

Alcohol consumption is known to cause acute or chronic liver disorders. Acute DILI reactions to alcohol consumption occur in patients taking methotrexate, INH, or halothane. Hepatotoxicity due to alcohol consumption is likely due to alcohol inducing CYP2E1 which causes toxic metabolites in the liver. A study in Pakistan found that alcohol consumption increases the risk of hepatotoxicity in 25% patients.^{6,11,16}

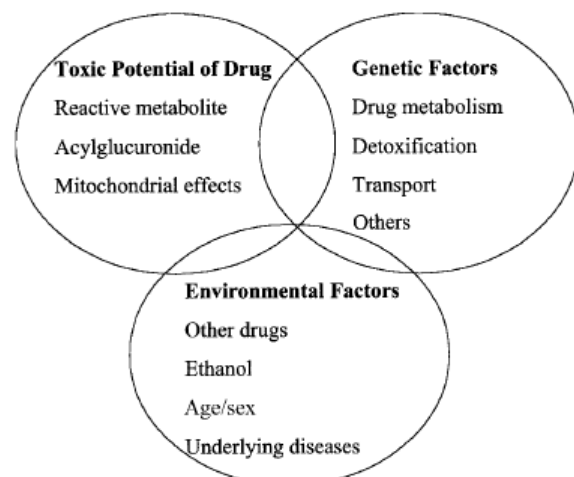


Figure 1. Risk factors for susceptibility to DILI.¹⁶

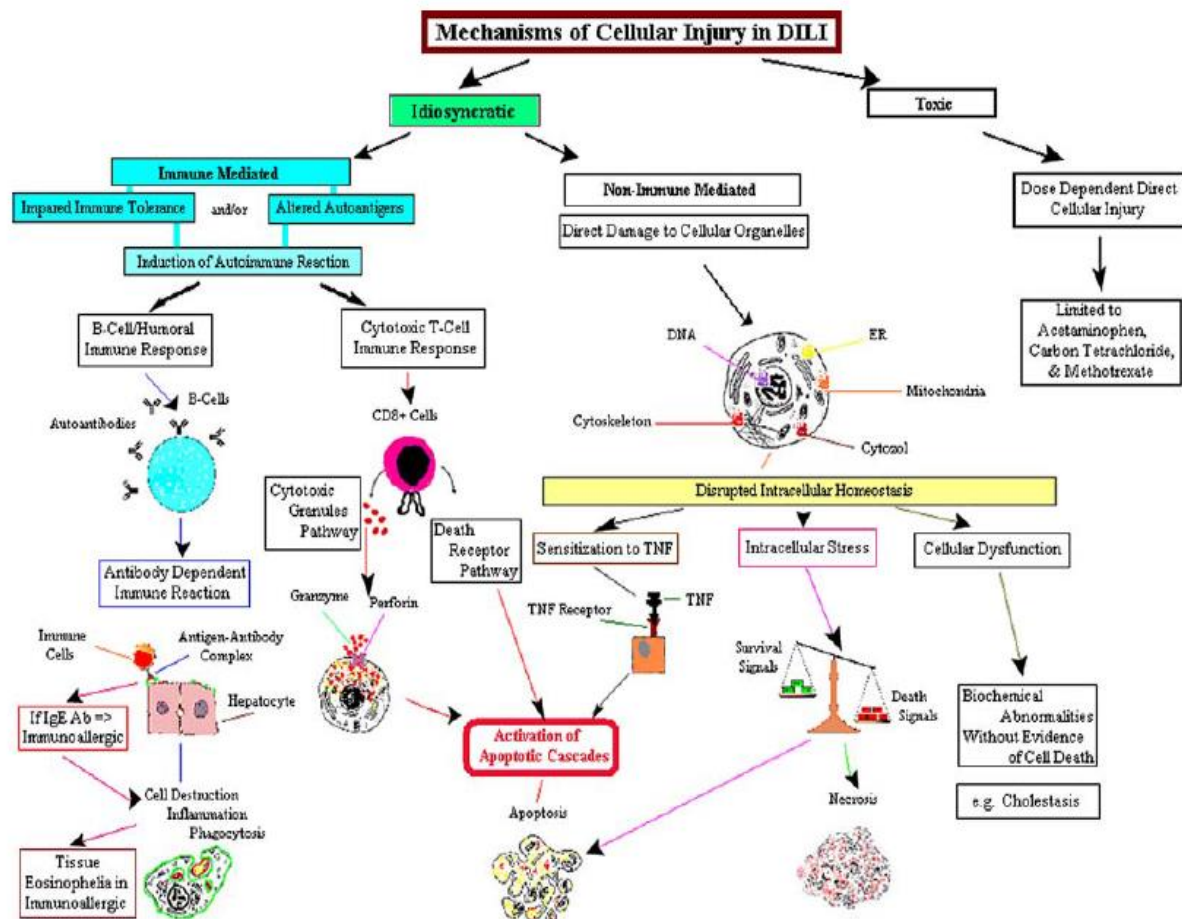


Figure 2. Schematic figure demonstrates the different mechanisms of cellular damage in DILI.¹⁶

Pathological Mechanism

There are several mechanisms that cause liver damage. Some drugs such as acetaminophen and methotrexate are known to cause direct poisoning to the liver depending on the dose and duration of use. Some DILI are idiosyncratic processes. This mechanism can have an effect on one liver cell or several different types of liver cells, such as: hepatocytes, bile gland cells, sinusoid epithelial cells, stellate cells, and Kupffer cells.¹⁶⁻¹⁹

Idiosyncratic reactions can occur metabolically or mediated by immunity to different degrees. Metabolic idiosyncratic develops when a drug or one of the metabolites of the drug is bound by cellular proteins, DNA or other parts of molecular cells which in turn causes cellular dysfunction. Other mechanisms involve glutathione depletion, changes in oxidation reduction, or initiation of intracellular oxidative stress. Impaired balance between life and death signals in cells by influencing proapoptotic factors that initiate cascades from intracellular reactions that cause loss of viability. Other mechanisms involve liver cell sensitization to cytokines, such as tumor necrosis factor (TNF) which can cause apoptosis or necrosis (Figure 2).^{16,18,20-23}

In DILI mediated by immunity, a portion of the drug or metabolite covalently binds to cellular protein to

form hapten-carrier conjugation. This phenomenon is known as "haptization". MHC type 2 - haptized peptide is raised to the surface by Kupffer cells pioneering the formation of antigen-recognizing helper and cytotoxic T cells. Other antigens raised by hepatocytes that are in conjunction with MHC type 1 activate humoral and cellular immunity causing responses that cause liver damage. Inflammatory reactions are mainly mediated by a number of proinflammatory cytokines including TNF, FasL, NO, IFN- γ , and others. TNF triggers a cascade of caspase pathways, including Bim and Bmf, resulting in apoptosis. In many cases, DILI has allergic manifestations such as fever, redness, interstitial nephritis, peripheral eosinophilia, and eosinophil infiltration in liver parenchyma.^{21,22,24-28}

Liver damage due to immunity develops secondary to defects in the immune tolerance mechanism. The liver has a unique ability to induce tolerance to large numbers of foreign antigens, which are sent through the portal system. Kupffer cells mediate this process by inducing apoptosis through T cell activation, immune deviation, and active suppression. Disturbances in the process of immune tolerance will cause immune toxicity and autoimmune responses (Figure 2).^{21,22,24-28}

Idiosyncratic reactions can develop easily in some individuals but not in others. An explanation of idiosyncratic reactions is that liver enzymes, especially P450, are responsible for the metabolism of foreign substances including drugs, have expression of gene variability and catalytic activity which cause large phenotypic variations between individuals. Patients experience idiosyncratic reactions to certain drugs through unique pathways or lack of certain neutralizing enzymes to protect cells from the formation of reactive metabolites.^{26,29}

Many drugs cause a temporary increase in enzyme aminotransferase, usually three to five times the normal value. This increase stops even though drug use continues. The exact mechanism of the process of adaptation to the drug that causes the damage is not yet known. Patients who experienced a temporary increase in liver function were considered in the small group (5-10%) of all DILI patients. For example, transaminitis is present in 3% of patients taking statins, which usually return to normal within the first 3 months after therapy. The liver returns to normal after a temporary increase in liver function without sequelae.^{16,30,31}

CLINICAL SYMPTOMS OF TB DILI

Clinical symptoms of TB DILI are the same as acute and chronic symptoms of hepatobiliary disease, with dominant symptoms appearing as jaundice in acute hepatitis or cholestatic liver disease. Jaundice in acute hepatitis is more dangerous and has a mortality rate of 10%, regardless of the type of drug that causes it. Jaundice in acute hepatitis is accompanied by an increase in serum transaminases and a minimal increase in serum alkaline phosphatase. In dangerous cases, symptoms of coagulopathy and encephalopathy are more common. Cholestasis (also called cholestatic hepatitis) is usually not life-threatening. Cholestasis of hepatitis has symptoms of jaundice, pruritus, and an increase in serum alkaline phosphatase, with a mild increase in serum alanine transferase (ALT). Mixed symptoms with increased ALT and alkaline phosphatase show atypical hepatitis or granulomatous hepatitis. In rare cases, DILI and gallbladder disease appear after stopping drugs that cause impaired liver function.^{6,15,32,33}

Clinical symptoms of liver disease may not appear, but hepatotoxic drugs in individuals can cause typical clinical symptoms accompanied by pathological symptoms and latent periods. Mostly the same as acute hepatitis, cholestasis or mixed symptoms appear. Drugs that cause immune-mediated liver damage cause an excessive immune response, causing symptoms of hepatitis, cholestasis, or mixed. Some drugs are known to cause more than one symptom of the disease.^{2,6}

Acute Liver Failure in Consequence of Tuberculosis Drug

TB treatment is a major cause of acute liver failure in the Asian region. A study involving 1,223 patients who experienced cases of acute liver failure in India reported that there were 5.7% of patients undergoing TB treatment with 1.2% experiencing acute liver failure due to viral hepatitis. Most patients experienced hyperacute symptoms with an average use of ATD for 30 days until symptoms of acute liver failure appeared. The use of 1st category of ATD INH, rifampicin, and pyrazinamide has been known to have hepatotoxic effects ranging from mild symptoms with increased transaminases to symptoms of acute liver failure. Patients with acute liver failure often show increased serum transaminases.^{15,33,34}

In acute liver failure, the clinical symptoms may not appear as specific as loss of appetite, fatigue, abdominal pain, fever, and jaundice. The patient needs to be asked about the history of infection, drug use, family history of liver pain, history of previous liver disease, history of travel to endemic areas. In acute liver failure a physical examination is needed to determine the occurrence of jaundice, mental status, and signs of coagulopathy. Enlarged liver rarely occurs in acute liver failure, but minimal enlargement can be an early sign of acute viral hepatitis. Significant enlargement of the liver can be a sign of the emergence of congestive hepatomegaly due to heart problems, Budd-Chiari syndrome or infiltrative disease. Laboratory tests are performed to see the presence or absence of coagulopathy and ensure the emergence of acute liver failure and disease prognosis.^{15,33,34}

Table 1. Drug-induced liver injury category⁶

Grade	Definition
A Mild	There are elevations in serum ALT and/or ALP levels, but the total serum bilirubin level is <2.5 mg/dL and INR is <1.5.
B Moderate	There are elevations in serum ALT and/or ALP levels, and the serum bilirubin level is >2.5 mg/dL or INR is >1.5.
C Moderate-severe	There are elevations in serum ALT, ALP, and bilirubin or INR levels, and hospitalization or ongoing hospitalization is prolonged because of a DILI episode.
D Severe	There are elevations in serum ALT and/or ALP levels, and the total serum bilirubin level is ≥2.5 mg/dL, and there is at least one of the following: <ul style="list-style-type: none"> • Hepatic failure (INR ≥1.5, ascites or encephalopathy) • Other organ failure believed to be due to a DILI event (i.e. renal or pulmonary)
E Fatal	Death or liver transplantation from DILI episode.

Notes: DILI (*Drug-induced liver injury*); ALT (*Alanine aminotransferase*); ALP (*Alkaline phosphatase*); INR (*International normalized ratio*)

TB DILI Treatment

Effective treatment is only minimal in cases of TB DILI except in DILI due to acetaminophen which has effective therapy, N-acetylcysteine (NAC). The most important management of DILI is the cessation of drugs that cause it and initiating symptomatic and supportive therapy. DILI can heal spontaneously in most patients, but has different variability. In some patients, DILI can be prolonged as in the case of DILI cholestasis and some patients may have acute liver failure. Because there is no specific therapy for DILI, experts try steroid therapy in cases of idiosyncratic and ursodeoxycholic acid (UDCA) in patients with DILI cholestasis and some antioxidants even though the literature on these therapies is still controversial.^{6,35}

Steroid

Steroid function in DILI was reported in a retrospective study of idiosyncratic DILI cases with autoimmune symptoms or hypersensitivity reactions. For example, the use of steroids in DILI due to the use of diclofenac, phenytoin, drugs containing sulfa, methyl dopa, and propylthiouracil. Some experts also recommend the use of steroids in cases where DILI symptoms still appear after 4-5 days of stopping the drug that is suspected as the cause. In TB, the use of steroids is used as adjunctive therapy in TB meningitis and acute period of TB pericarditis, not as a DILI treatment.^{6,36}

Ursodeoxycholic Acid (UDCA)

Ursodeoxycholic acid (UDCA) has anti-oxidant effects and is safe to use for a long time. This drug is known to be effective in the treatment of primary biliary cirrhosis and possibly in primary sclerosing cholangitis (PSC). The mechanism proposed in DILI cholestasis case is still not fully understood, but it is thought that UDCA prevents cholestatic damage by replacing toxic effects with nontoxic bile fluids by reducing the histocompatibility of antigens arising from hepatocytes or cholangiocytes or direct mechanism of cytoprotective effects. Although based on the results, the evidence of the successful use of UDCA still varies in DILI cholestasis type. The dosage of use for DILI cholestasis is 13-15mg/kg BW. Because there is no definitive therapy for the treatment of DILI, experts decide that currently the best DILI treatment is prevention. In the event of DILI, experts suggest stopping drugs that are suspected of being the originators of DILI. Patients who are given drugs that are known to be potentially hepatotoxic are being told if they experience nausea, vomiting, right upper abdominal pain, weakness, lethargy or fever which cannot be explained when taking the drug should immediately notify the doctor.^{6,18}

In Patients with TB Treatment

TB treatment is discontinued in patients who have DILI symptoms, jaundice, nausea, and vomiting, as well as the patients who have symptoms of DILI with

SGOT and SGPT functions more or equal to 3 times the normal value. TB treatment is also discontinued in patients who have no clinical symptoms but the results of laboratory tests for bilirubin are more than 2. If there are no clinical symptoms of DILI but the results of the SGOT/SGPT laboratory examination are more than 5 times the normal value, then the TB treatment is discontinued too. If there are no clinical symptoms of DILI with an increase in SGOT/SGPT more than or equal to 3 times the normal value then the TB treatment is continued by conducting close supervision.^{4,37}

TB treatment is discontinued while waiting for liver function to return to normal and clinical symptoms (nausea and abdominal pain) to disappear. If liver function tests cannot be performed, then TB medication is given 2 weeks after the patient is not jaundice and does not experience abdominal pain. If DILI has been completed, TB treatment can be tried one by one starting with rifampicin which is less common in hepatotoxic than INH or pyrazinamide. After 3-7 days, the patient can be given INH. Patients who have had a history of jaundice can still receive rifampicin and INH but should no longer be given pyrazinamide.^{4,37}

SUMMARY

DILI is a liver function disorder due to the use of hepatotoxic drugs such as ATD. DILI due to ATD occurs within 2 months after administration of ATD begins and the highest incidence is in the first 2 weeks. DILI symptoms vary from mild symptoms such as loss of appetite, fatigue, abdominal pain, fever, and jaundice with an increase in transaminases to symptoms of acute liver failure. Factors that can cause DILI include BMI, INH metabolic acetylator status, age, sex, metabolic factors, drug interactions, and alcohol consumption. TB treatments that are known to cause DILI are INH, rifampicin, and pyrazinamide. If it occurs during TB treatment then the treatment is discontinued until clinical symptoms disappear for 2 weeks and liver function returns to normal. Pyrazinamide is not used for subsequent treatment.

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