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Drug-Induced Hepatotoxicity - Case Report of an Anti-Tuberculosis Drug-induced Liver Injury with Comorbid of Diabetic Nephropathy

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Abstract: ***Anti-tuberculosis drug-induced liver injury (ATLI) has already known as one of several essential and critical drug unexpected events found in as much as 7% of all drug adverse event cases. Nowadays, the appropriate ATLI mechanism has not yet been acknowledged. Hepatotoxicity incidence is still a complicated issue to be counted, due to the abundance of drug combinations in anti-tuberculosis therapy. This case report described ATLI diagnosis and exposed the management of several complications related to diabetes mellitus and chronic kidney disease as comorbidities.***

Keywords: Tuberculosis , Drug Induced Liver Injury, Diabetic Nephropaty, Hepatotoxicity, Anti-Tuberculosis Drug

1. Introduction

Tuberculosis is one of the most lethal and increasing issues in the majority of the developing countries in the world. Approximately, a third of tuberculosis global prevalence was found in the Southeast Asia region (1). Tuberculosis is one of the primary curable transmittable diseases with a high mortality rate. 9 million recent tuberculosis cases were found in 2004, and 1.7 million people were unable to survive in tuberculosis cases (2). The triple drug combination of pyrazinamide (PZA), isoniazid (INH) and rifampicin (RMP), followed by RMP and INH are the utilized regimen that included the most effective short course of TB treatment (6 months course). Those regimens are shown to be effective in eradicating *Mycobacterium tuberculosis*. Unfortunately, those regiments also induced enormous unexpected issues, including hepatic damage, reaction of the skin, neurological issues, and gastrointestinal disturbances. Anti-tuberculosis drug-induced liver injury(ATLI) counts on 7% of all essential and life threatening adverse events (3).

There is no definitive mechanism of ATLI described. Hepatotoxicity incidence estimation is still a challenging problem due to drug combination in anti-tuberculosis therapy (4). The key events that protrude the process are related to particular pathways provoked by specific drugs or their metabolites. Aggravation of liver cells has occurred as the result of detoxification failure or phase I metabolism, therefore increasing the formation of active metabolites. IgE mediated reaction and reactive metabolite syndromes are induced then by the process. those reactions are dose-dependent in susceptible individuals (5).

INH is highly involved in drug toxicity. A few series have shown isoniazid-induced hepatotoxicity in a monotherapy setting (4). INH was hypothesized to have a role in the inhibition of mycolic acid synthesis as a major constituent of the wall of mycobacterial (6). INH is metabolized and expelled by the hepatic system. Acetylation by NAT2 enzyme is the main pathway in metabolism of this medicine. Monoacetyl hydrazine (MAH) is stated to be the highest toxicity of all INH metabolites. Additionally, reactive oxygen species (ROS) formation also alter hepatic system (2).

Covalent bond is formed by INH metabolites with toxic nature with biologically formed macromolecules. Hepatic damaged induced by INH is proved by the increasing level of lipid alteration and peroxidation (4). Liver toxicity was highly correlated with isoniazid in a study (odds ratio (OR) 1.6) as monotherapy. Administration of rifampicin and isoniazid as a combination increases the likelihood of hepatoxicity (OR 2.6), if compared with other monotherapies (7).

As a drug which poses an antimicrobial effect, RMP or Rifampicin is included in semi-synthetic category that produced by *Streptomyces meditteranei*(6). DNA-dependent RNA polymerase elaborate with RMP in producing enzymatic complex which then inhibit the activity of the complex. Antibiotic is absorbed and converted to diacetyl RMP in the cells of liver by the enzyme esterase, then expelled through faeces. This medicine is also acknowledged as a strong inducer of metabolizing enzymes (4). Its combination with other drugs induced metabolism which then resulting in the accumulation of metabolites. In the end, liver injury is provoked by the toxic nature and induction of immune response (5). Rifampicin can cause impaired bilirubin uptake, resulting in temporary unconjugated hyperbilirubinemia without any damage to the liver cells. Inhibition of the bile salt exporting pump contributes to conjugated hyperbilirubinemia followed by altered eradication of bilirubin (4).

PZA or Pyrazinamide is a synthetic ATD that is often given as adjunctive therapy along with INH and RMP. This drug is derived from nicotinic acid. This medicine is also metabolized in the liver to pyrazinoic acid. Then, these metabolites undergo an oxidation process by xanthine oxidase resulting in the production of 5-hydroxy pyrazinoic acid (6). Pyrazinoic acid possesses a direct toxic effect that is related to the hepatotoxicity nature of PZA. Higher doses than 40 – 50 mg/kg is more likely to cause hepatotoxicity

(8). This metabolite runs a function in the inhibition of CYP45058 activity and alteration of NAD59 levels which are associated with liver toxicity mediated by free radical species (9). Diagnosis is made by evaluating the presence of liver damage manifestation, such as pain in the abdominal, nauseous feeling, jaundice, asthenia and vomiting. Unfortunately, these symptoms are inadequate to indicate the damaged hepatic system (3). An increase in aspartate aminotransferase (AST) and/or elevation of alanine aminotransferase (ALT) levels up to three fold of its normal level and/or an increase in total bilirubin to > 1.5 mg/dL (25 mol/L), occurring at least five days after starting anti-TB drugs in the absence of other abnormal LFT cause (10). Interruption of treatment causes relief in ATLI complain. Late in stopping the medicine can result in lethal condition (10).

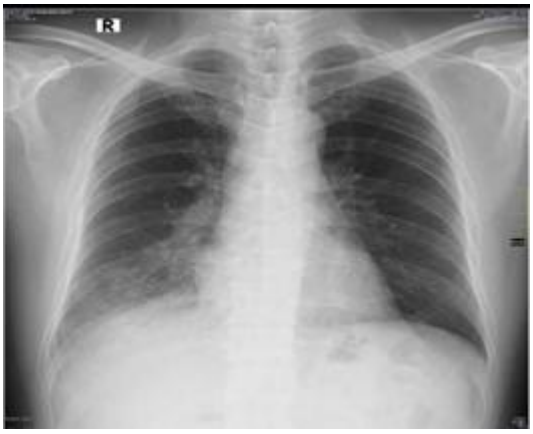
In cases with extensive disease, hepatotoxicity case is significantly higher. Comorbidity with several diseases is common in cases of hepatotoxicity (11).

A study showed that 19.1% in patient with TB history had liver injury. Higher ATLI possibility was found in 8% of patient with hepatitis history. It can be caused by infection of virus, accompanied by the presence of jaundice. The previous history of diabetes mellitus was identified in 16.8% and chronic renal failure was found in 6.1% of cases (10). Diabetes mellitus is also associated with higher time needed for a treatment to be effective, increased level of failure or recurrence of tuberculosis, and toxicity, failure, and recurrent TB (12). Close supervision is needed in anti-tuberculosis treatment, especially in patients with a combination of DM and TB. Patients with this condition have a significant risk in the interactions of drugs and unexpected effects, therefore it is necessary to adjust the dose or drug regimen (13). Complications of diabetes mellitus, especially diabetic nephropathy, possess clinical importance in worsening TB treatment (14). Diabetic nephropathy (DN) or kidney diabetes is diabetic condition that presented with impaired excretory process of urinary albumin, lesions of glomerular, and altered glomerular filtration rate (GFR) (14). When compared with patients posing normal renal function, patients with comorbid kidney disease are highly possible of presenting with unexpected event of drug for anti-tuberculosis (15)

The liver is also the site of rifampicin metabolism. Rifampicin formyl which is metabolically inactive is excreted in the urine. Deacetyl-rifampin as the main metabolite is excreted in the bile. Likewise with Pyrazinamide, this drug also undergoes metabolism in the liver. 3-4% of the drug is excreted through the kidneys in an unchanged form (16). Ethambutol undergoes 80% unchanged renal excretion. Therefore, decreased level of ethambutol is excreted after 15 mg/kg intake in person with chronic kidney disease comorbidity (17). The excretion of some drugs is found to be 80% unchanged in the urine, such as streptomycin, kanamycin, amikacin, and capreomycin. compared with other aminoglycosides, vestibular toxicity with less nephrotoxicity was observed with streptomycin (15).

2. Case Report

A 58 years old man presenting to the emergency room with cough for 2 months, accompanied with blood on the sputum within the last 2 weeks. The patient does not have any symptom of definitive weight loss, however there is fever that occur repeatedly every evening for the last 2 weeks. Past medical history shows that patient had diagnosed with non-insulin dependent diabetes mellitus since 13 years ago, along with chronic kidney disease. Previous history of hepatitis was denied. From the physical examination, patient had rhonchi on the right lung thus followed by extended examination for tuberculosis. Laboratory examination on patient sputum shows the result of TCM positive with MTB detected medium, PA view of chest X ray radiograph examination shown infiltrate on basal of the right lung.



Patient was treated with fixed dose Anti-Tuberculosis Drug Category 1 2 (R HZE)/4(HR) 3: RMP, INH, PZA and ethambutol (EMB) given every day for 2 months followed by RMP plus INH three times a week for 4 months. After one week of administering the medicine, patient felt nauseous and experiencing vomiting after every meal, and also had difficulty ingesting diet orally. Furthermore liver function examination shows that there is elevation on liver serum with AST: 194 U/L and ALT: 257 U/L, and renal function also showed elevated ureum: 46 mg/dl and serum creatinine: 1.6 mg/dl. This table describes liver function test and renal function test before and after using Anti Tuberculosis Drug. In this case, it was seel that this patient did have chronic kidney disease since before using Anti Tuberculosis Drug.

is	27/11/2020	13/08/2020	03/01/2022	11/01/2022	18/01/2022
AST	34	28	194	29	46
ALT	44	34	257	120	50
Ureum	24	41	46	28	45
Creatinine Serum	1,4	1,4	1,8	1,5	1,8

The administration of anti-tuberculosis on patient will be discontinued temporarily, and afterwards will be given hepatin 1 x 1 daily as hepatoprotective agent. The result in doing so after 2 weeks, there is a significant reduction of liver serum with AST: 46 U/L and ALT: 50 U/L, while renal function staus relatively the same with BUN: 45 U/L and SC: 1.8 U/L. at the moment, patient was undergoing anti-tuberculosis drugs challenge with administration direction as

follows, administration of RMP 1 x 200 mg on the first day, 1 x 300 mg on the second day, 1 x 450 mg on the third day, and 1 x 600 mg on the fourth and fifth day. After the RMP challenge, patient did not feel nausea or vomiting. For the second challenge, INH 1 x 100 mg on the first day, 1 x 150 mg on the second day, 1 x 225 mg on the third day and 1 x 300 mg on the fourth and fifth day. Because there were absolutely no complaints of nausea and vomiting in patient, then we got the third challenge which used ethambutol 1 x 250 mg on the first day, 1 x 500 mg on the second day, 1 x 750 mg on the third day and 1 x 1000 mg on the fourth and fifth day. Finally, there are no complaints of nausea and vomiting, so we can conclude that the patient was allergic to PZA. Currently, we are using Anti Tuberculosis Drugs with a loose dose INH 1 x 300 mg, RMP 1 x 600 mg, and ethambutol 1 x 1000 mg. Now the patient is feeling comfortable with these drugs without any complaint of nausea or vomiting and without an increase in AST and ALT test.

3. Discussion

The risk factors found in patients receiving antituberculosis drugs have varied prevalence in the world. Several major risk factors have been reported that lead to hepatotoxicity (6). The combination of isoniazid and rifampin has shown its significant efficacy in tuberculosis eradication, but has side effects such as hepatotoxicity (8).

Several causes of medication provoked liver injury (DILI) are still challenging in the incidence determination, including unknown denominators of individuals administered with the drug, inadequate number of reliable tests for defining DILI, restricted research about liver marker alteration that constitutes DILI, difficulty in determining a single cause on many drugs, and systematic reporting (18). In several studies discussing epidemiology, it is stated that antibiotics, anti-tuberculosis antibiotics, nitrofurain, and sulfur-based antibiotics, are classes of drugs that cause acute liver failure as a result of medicine provoked liver damage (15).35% of patients taking antituberculosis drugs reported an incidence of hepatotoxicity. according to the formal guidelines published by the American Thoracic Society, cases of hepatotoxicity improved after discontinuation of the drug, whereas continued treatment could lead to severe hepatotoxicity to acute liver failure.

The combination of RMP and INH is the most effective combination in the management of TB. RMP with 100% sensitivity and INH with 97% sensitivity, and 100% specificity for both drugs (18). Hepatotoxicity effects of the triple combination are known, whereas streptomycin and ethambutol are included as non-toxic to liver. Unfortunately, the incidence of ATLI is often ignored, so patients still have to take antituberculosis drugs (10).

Several enzymes are known to suppress hepatotoxicity, namely P4502E1 cytochrome microsomal enzyme (CYP2E1) and N-acetyltransferase 2 (NAT2). The latter enzyme is responsible for the metabolism of INH to acetyl isoniazid, which happens to undergo hydrolyzation into acetyl hydrazine. followed by oxidation by CYP2E1 resulting in the formation of N-hydroxy-acetyl hydrazine. These metabolites then undergo dehydration and form acetyl diazine. if acetyl diazine breaks down into reactive acetyl onium ions, acetyl radicals and ketenes, then liver injury can occur as a result of covalent binding of these metabolites with liver macromolecules (4).

The NAT2 enzyme also plays a role in the alteration process of acetyl hydrazine to diacetyl hydrazine. This form has no toxic nature. The acetylation process produce mono-acetyl hydrazine and the parent compound. Isoniazid hydrolysis directly results in hydrazine which can injured the liver (19)

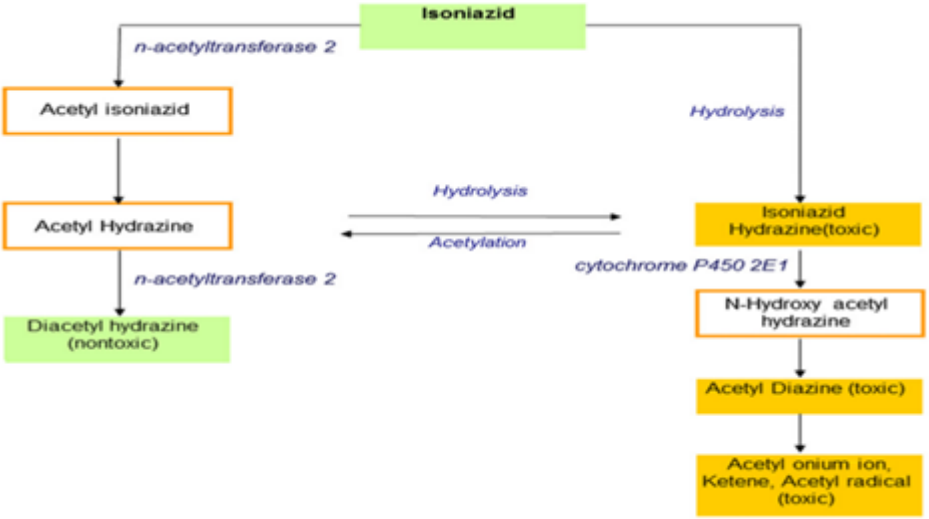


Figure 1 Pathways involved in the metabolism of isoniazid.

Thereisatenfold increase in INH acetylation in INH metabolism in minor pathways, particularly those associated with rifampicin. In human, polymorphic is the form of NAT2. The finding of two NAT2 gene allele variants is related to the phenotype of slow acetylation. In fast acetylators, several wild type NAT2"4 alleles can be seen. Patients with the NAT2 genotype have a fourfold increased risk of INH-induced hepatotoxicity (4).

More severe hepatotoxicity is often seen with slow acetylators than with fast acetylators. Inhibition of CYP2E1 gene activity occurred on INH administration. in the presence of this effect, enzyme activity was found increased in subjects homozygous for the CYP2E1 c1 allele (wild type). A series with 318 people undergoing treatment for tuberculosis concluded that there was a 2.5 times increased likelihood of hepatotoxicity in subjects with CYP2E1 c1 /c1. there is a 7-fold increase in the risk of hepatotoxicity when a combination of CYP2E1 c1/c1 is found in a slow acetylator status (20).

Glutathione also has an essential protective role in scavenging intracellular free radicals conjugated with metabolites which is reactive and toxic in nature resulting from the xenobiotics and drugs biotransformation. Homozygous null mutation on GSTT1 and GSTM loci decrease the activity of GST, triggers modulation of liver injury provoked by xenobiotic and drug susceptibility. GSTM1 and GSTT1 null mutations and recorded null mutations of GSTM1 were more often to be found in DILI cases due to anti TB therapy (4).

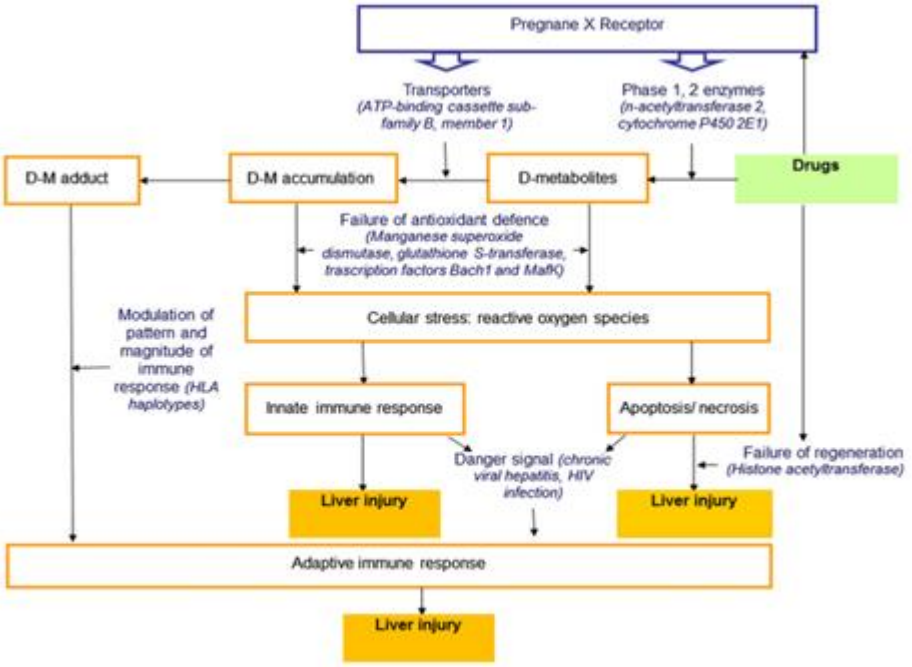


Figure 2 Hypothetical model of DILI due to anti-TB agents with potential drug and host related factors (in blue) involved in the pathogenesis.

Isoniazid is metabolized through the hepatic system forming less active metabolites. These are going through the kidneys to be expelled out of the body. Several studies have shown that INH is largely cleared via hepatic metabolism. there is a series giving isoniazid in double doses three times weekly followed by dialysis sessions; however, more occurrences was found for neurotoxicity results from INH's high peak concentrations (16). Therefore, this treatment is not recommended to be carried out routinely. Until now, there are still no adequate data regarding the elimination of isoniazid in peritoneal dialysis (4).

Rifampicin goes through several stages in its metabolism in hepatic cell, including desacetyl rifampicin formation through desacetylation and a different hydrolysis step which then forms 3-formyl rifampin. More polar properties is detected in desacetyl rifampicin compared to its active parent compound. Antibacterial activity in bile is produced by this metabolite. Rifampicin also undergoes secretion via bile and urine. The metabolite of rifampicin is not toxic, but is associated with a hepatocellular pattern of DILI (4). Additionally, rifampicin is capable of modulating liver toxic effect of several anti TB medicine. Some literature states that rifampin has the ability to act as a strong inducer of the CYP3A4 or the cytochrome P450 system through hepatocyte PXR. Rifampicin is also capable of activating the pregnane X receptor xeno-sensing (PXR). As the nuclear receptor superfamily member, activated PXR forms a bond in order to affect elements in the promoter. It also controls phase I and II transcription of enzymes functioning in drug metabolism, includes: glutathione S transferases (GST), transporter (related to phase III), and cytochrome P450 (CYP)s. Isoniazid hydrolase is also induced by rifampin. as a result, there is an increase in the production of hydrazine in slow acetylators. In the presence of isoniazid in combination, this condition results in increased toxicity (4). On the other hand, rifampin is able to affect bilirubin uptake. this produces temporary unconjugated hyperbilirubinemia, with no damage to liver cells. However, the bilirubin uptake, highly seen, forming the conjugated compound by meddling on the excretory process of bilirubin, especially the inhibition of bile salt-exporting pump (BSEP) (2).

Figure 2 Metabolism of pyrazinamide

Adverse events reported in patients with comorbid CKD or dialysis were not significantly increased. In some literature, sometimes acute renal failure can be found in patients taking rifampin. With this statement, it has been agreed that there is no need to change the dose of rifampin or monitor drug levels in patients with comorbid renal impairment.

Pyrazinamide conversion becoming its acid form, pyrazinoic acid, is followed by an oxidation process catalyzed by xanthine oxidase into 5-hydroxypyrazinoic acid. Excretion of these metabolites is carried out by the kidneys. in patients with hepatic impairment, pyrazinamide poses longer half-life (8). Concomitant use of pyrazinamide with xanthine oxidase inhibitor, e.g. allopurinol, also results in a prolongation of the half-life. However, treatment duration doesn't affect pyrazinamide half-life, so it can be concluded that the induction of metabolic enzymes was not induced by pyrazinamide (4). Free radical-mediated hepatotoxicity associated with ingestion of pyrazinamide in rats resulted from inhibition of CYP45058 activity and changes in NAD59 levels. In another human study, it was found that pyrazinamide did not inhibit the CYP450 isoenzyme (9).

The liver is the organ that carries out the metabolism of pyrazinamide. Only 3-4% is excreted through the kidneys in an unchanged form. No changes in the pharmacokinetics of this drug were found in patients with renal failure. A study showed that elimination of this drug was detectable as long as 48 hours after ingestion. This drug can cause uric acid retention, so cases of hyperuricemia are common. Hemodialysis can eliminate pyrazinamide and its metabolites, 45% of the elimination process can be found in the dialysate. Until now there is not enough data related to peritoneal dialysis. It is necessary to change the dosing interval in patients with stage 4 and 5 CKD because of the probability of delayed elimination (16).

Approximately 80% of ethambutol excreted in the kidneys remains unchanged. The excretion of ethambutol in cases of renal failure has decreased significantly, even in the consumption of 15 mg/kg. In some cases, dose-related ocular toxicity has been found. Ethambutol is also found in the dialysate. Increased effectiveness occurs with high doses at less frequent intervals than daily low doses. It is necessary to monitor serum with a target of below 1.0 mg/ml during 24 hours after dosage of no dialysis (16).

Table 1: Dose recommendation for anti-tuberculosis therapy with CKD comorbidity

	Stage 1e3 CKD*	Stage 4 and 5 CKD*	Ɨrecipient of renaltransplantation
Isoniazid	300 mg/day	300 mg/day or 15 mg/kg max 900 mg 33/week	300 mg/day
Rifampicin	< 50 kg: 450 mg/day ≥ 50 kg: 600 mg/day	< 50 kg: 450 mg/day ≥ 50 kg: 600 mg/day	< 50 kg: 450 mg/day ≥ 50 kg: 600 mg/day
Pyrazinamide ‡	< 50 kg: 1,5 g daily ≥ 50 kg: 2 g each day	25-30 mg/kg 3 x week	< 50 kg: 1,5 g each day ≥ 50 kg: 2 g daily
Ethambutol§	15 mg/kg/day	15-25 mg/kg 33 x/week (max 2.5 g)	15 mg/kg/day
Moxifloxacin	400 mg each day	Not appropriate in 33 weekly regimen	400 mg each day

Each anti-tuberculosis drug has different pharmacological properties. These properties then affect its administration in patients with renal failure, especially with regard to the clearance of dialysis and immunosuppressive drugs in kidney transplantation (16).

Improved detection, diagnosis and prevention of acute idiosyncratic DILI helps better management. Although the management of DILI remains focused on discontinuing the causative drug immediately (14). This raises a dilemma in the therapy of tuberculosis. Therefore, an alternative and adjuvant is needed that can function to replace the causative agent of DILI without interfering with therapy (14).

Adherence to DOTS is main factor of focus in the management of active TB. Changes in anti-TB have resulted in a decrease in the optimization and effectiveness of treatment. In comparison of patient without ATLI, 9.25-fold (95% CI, 5.69-15.05) increased probability of developing failure of treatment outcome was found in ATLI patient (3). Patients with ATLI also undergo an additional intensive care phase. No change in treatment resulted in improved recovery compared to cases with discontinued anti-TB (3).

Appropriate diagnosis, causative drug evaluation and its discontinuation are the basic treatment of DILI (21). Discontinuation statement of drug administration should be determined by considering liver enzyme level. Several indications for stopping anti-tuberculosis drugs include: 1) ALT level is more than 8 fold of upper normal threshold (ULN), 2) ALT level is above 5 times of ULN for three consecutive weeks, 3) ALT more than 3 times of ULN, accompanied by bilirubin level of more than 2 fold of ULN, 4) the ratio of prothrombin time/international normalized (PT-INR) is more than 1.5 times of ULN or 5) manifestation of signs and clinical symptoms of hepatic impairment (14).

Discontinuation of the drug can result in mixed outcomes that range from complete resolution to death (14). Currently, the anti-TB challenge test is a controversial issue. It is feared that the challenge test may result in a more severe reaction, such as ALF or death, so this test is not generally recommended. This challenge test is only performed in cases where there is no other adequate therapy for the life-threatening condition, so recovery methods should still be tried.

The recommended anti-tuberculosis treatment for patients with comorbid DM is still the same. However, patients with DM often experience anti-TB drug resistance, delayed response to treatment and an increased risk of toxicity, failure and recurrent TB. Adjustments to the duration of anti-tuberculosis consumption have been carried out in several countries such as China. In Taiwan, a large retrospective cohort study involving 9 months of TB treatment was conducted. in this study it was concluded that 9 months of TB therapy showed a lower rate of recurrent TB than the use of 6 months of therapy (HR 0.76, 95% CI 0.59-0.97) (12).

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