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Anti-tubercular drugs, predisposing factors and management of drug-induced hepatotoxicity: A concise and up-to-date review

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Abstract

Tuberculosis remains a leading cause of death in developing countries. In India antitubercular treatment was effective from the 1950s and has been engaged for more than 50 years. Hepatotoxicity secondary to antitubercular drug treatment is a major threat to tuberculosis. Anti-tubercular drugs like isoniazid, rifampicin, and pyrazinamide are potentially hepatotoxic and their adverse reactions are based on dose or hypersensitivity. Hepatotoxicity can occur within a few weeks of initiating intensive phase and elevation of serum transaminase levels with signs and symptoms are considered as the diagnostic criteria. The variations in the incidence of anti-tubercular drug-induced hepatotoxicity may be due to differences in patient characteristics, regimen used, type of monitoring and the diagnostic criteria defining hepatotoxicity. Predisposing factors associated with anti-tubercular drug-induced hepatotoxicity include advanced age, gender, nutritional status, alcohol intake, extensive TB, indiscriminate use of various drugs, ethnic factors, chronic liver disease and concomitant infections. There are no evidence-based guidelines that are accessible for the management of these patients. Management of hepatotoxicity generally involves withholding the anti-tubercular drugs and reintroduction after normalization of biochemical markers of liver injury.

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INTRODUCTION

Hepatotoxicity or liver injury is triggered by hepatotoxins, which comprises of pharmaceutical drugs, dietary supplements, chemicals, and medicinal plants (Thompson *et al.*, 2017). Tuberculosis (TB), a bacterial infection caused by *Mycobacterium tuberculosis*, affects over fifty million people worldwide. India is a developing country who actively participates in the TB control program, yet TB continues to be India's severest health crisis. TB kills an estimated 480,000 Indians annually (Khaparde, 2019). It arises because most of the population is undernourished, which leads to a weakened immune system. Major risk factors of TB are human immunodeficiency virus (HIV), malnutrition, diabetes, alcohol, use of immunosuppressive drugs, indoor air pollution and smoking. Behavioural and socio-economic factors also play a significant role in enhancing TB infection (Narasimhan *et al.*, 2013). Delayed diagnosis, inadequate and costly treatment are the challenges facing TB control program of

India. WHO recommends for pulmonary TB, a two month intensive phase of isoniazid (INH), pyrazinamide (Z), rifampicin (R) and ethambutol (E) and a continuation phase for another four months during which a combination of isoniazid and rifampicin (2RHZE/4RH regimen) are given (WHO, 2016). According to the Global tuberculosis report 2018, 54 million lives were saved by TB treatment, and the mortality rate fell by 42% globally between 2000 and 2017 (WHO, 2018). The adverse effects of anti-tubercular treatment include hepatotoxicity, skin reactions, immunological reactions, gastrointestinal, and neurological disorders, among which anti-tubercular drug-induced hepatotoxicity is the most significant one.

Hepatotoxicity is defined as - toxin injury to the liver due to a medication, chemical, herbal or dietary supplement; another term for drug-induced liver injury (Hoofnagle *et al.*, 2013). It causes high morbidity and mortality and also weakens anti-TB treatment effectiveness owing to non-adherence. First-line anti-tubercular drugs like isoniazid, rifampin and pyrazinamide are potentially hepatotoxic and metabolized by the liver.

Combination therapy of TB enhances the liver damage. Hepatotoxicity secondary to anti-TB drugs ranges from an asymptomatic elevation of transaminases to hepatic failure. Predisposing factors for anti-TB drug-induced hepatotoxicity (DIH) include advanced age, malnutrition, chronic alcoholism, viral hepatitis, autoimmune disease, shock, septicemia, cardiac failure and concomitant use of other hepatotoxic drug have been reported. Asian populations have been reported at a higher risk of hepatotoxicity than Western society.

The clinical and genetic factors have a strong influence on hepatotoxicity due to anti-tubercular treatment. The genetic impact is coupled with the MHC class II region, particularly the DQ locus acts an imperative role in the development of DIH (Sharma *et al.*, 2002). Anti-TB-DIH usually occurs within the initial weeks of the intensive phase of chemotherapy. If there is an elevation in the transaminase level, withdrawal of the drug is necessary, and reintroduction can be performed when liver function tests return to normal but not if there has been symptomatic evidence of liver impairment.

Elevation of liver enzymes was common during antituberculous treatment, especially in the intensive phase. Hence its early identification would avert complications such as therapeutic failure or relapse. Patients with atypical liver function tests at baseline or liver cirrhosis should be closely monitored (Sun *et al.*, 2009). One controversial aspect of anti-tuberculosis treatment is the frequency of follow-up required during the treatment period. The review aims to study the incidence, underlying mechanisms of hepatotoxic anti-tubercular drugs, predisposing factors, and management of hepatotoxicity.

INCIDENCE AND EPIDEMIOLOGICAL TREND

Wide variations have been found in the incidence of hepatotoxicity secondary to anti-tubercular therapy and it may vary worldwide. Developing countries have a higher incidence rate than the developed countries.

Data from western and Asian countries suggest that 2.4-19% and 5.3-18.2% of incidence was reported within 15- 60 days of onset of therapy. In India, the incidence of anti-tubercular drug-induced hepatotoxicity varies from 2.0-16.2% (WHO, 2018; Sharma *et al.*, 2002; Sun *et al.*, 2009). The Comparison of the incidence of hepatotoxicity during anti-tubercular treatment between studies is given in Table 1 .

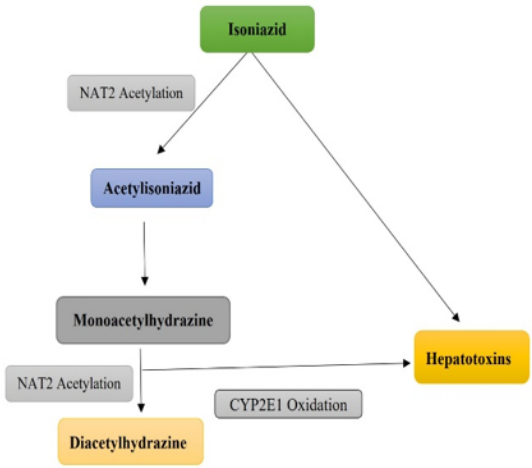

Figure 1: Mechanistic metabolic pathway of isoniazidleading to the formation of hepatotoxins.

DIAGNOSTIC CRITERIA FOR DRUG INDUCED HEPATOTOXICITY

Based on American thoracic society guideline (Saukkonen *et al.*, 2006),

1. Serum transaminase (AST, ALT, Alk P) concentrations are > five times the U.L.N. (with or without symptoms) or
2. >3 times the ULN with jaundice and/or hepatitis symptoms.

Table 1: Comparison of incidence of hepatotoxicity duringantitubercular treatment between studies

Authors	Country	Study Period	Incidence rate of hepatitis
Agal *et al.* (2005)	India	June 2001 to December 2002	10.5% (21 patients out of 200)
Saha *et al.* (2016)	India	January 2008 to December 2012	9.48% (24/253)
Dawra *et al.* (2019)	India	-	7.1% (10/141)
Gaude *et al.* (2015)	India	2009 to 2013	3.8% (150/ 3900)
Abera *et al.* (2016)	South Ethiopia	May 2014 to October 2014	8% (10/124).
Shakya *et al.* (2004)	Nepal	December 2001 to November 2002.	8% (4/50)
Jeong *et al.* (2015)	Korea	-	8.7% (17/195)
Abbara *et al.* (2017)	UK	April 2010 and May 2014	6.9% (105/ 1529)
Makhlouf *et al.* (2008)	Egypt	October 2004 to January 2005	15% (15 /100)
Sun *et al.* (2009)	Taiwan	July 2000 to July 2001	16.1% (42/ 261)

Table 2: The weight band for a standard first-line regimen for TB in adults

Weight category (2019)	Number of tablets (FDCs)	
	Intensive phase-4FDC (HRZE) 75/ 150/ 400/ 275	Continuation phase-3FDC (HRE) 75/150/275
25-34	2	2
35-49	3	3
50-64	4	4
65-75	5	5
>75Kg*	6	6

Tables show the newly introduced weight band regimen for standard tuberculosis treatment—F.D.C.s- Fixed-dose combinations, H-Isoniazid, R- Rifampicin, Z- Pyrazinamide, E-Ethambutol. *patients >75 Kg may receive five tablets/day if they do not tolerate this dose.

ANTI-TUBERCULAR DRUGS AND HEPATOTOXICITY

The current TB chemotherapy advanced from various experimental and clinical examinations primarily conducted between the 1950s and 1970s (Saukkonen *et al.*, 2006). Anti-tubercular agents are of two categories, first-line oral anti-tubercular drugs include isoniazid, rifampin, ethambutol, pyrazinamide, rifapentine, and second-line injectable anti-TB agents include streptomycin, kanamycin, amikacin, capreomycin, para-aminosalicylic acid, levofloxacin and moxifloxacin.

The currently suggested standard TB chemotherapy is called directly observed treatment short-course (DOTS), and the treatment period is up to six months, including two months of intensive and six months of continuation phases. The intensive phase comprised of isoniazid, rifampicin, ethambutol, and pyrazinamide, or streptomycin. But the continuation phase comprises of INH and RIF. A novel medication, bedaquiline, for the treatment of TB was approved for use in the United States in 2012. Many other marketed drugs have the potential to cause hepatotoxicity. They include A.C.E. inhibitors, acetaminophen, alkylating agents, alpha-1 adrenergic receptor antagonists, aminoglycosides, anabolic steroids, analgesics, anaesthetics, antiarrhythmic agents, antidepressant agents, antidiabetic agents, antifungal agents, antihistamines, antigout agents, anti-tuberculosis agents, anti-infective agents and so on. Several anti-tubercular agents have been con-

sidered as being hepatotoxic. The isoniazid (particularly in association with rifampicin) and pyrazinamide cause hepatic dysfunction more frequently than ethambutol and streptomycin. The revised weight band for standard first-line regimen for TB in adults is given in Table 2.

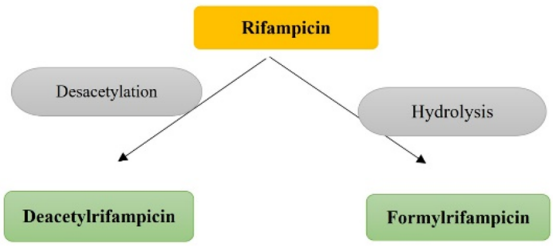

Figure 2: Metabolic derivatives of rifampicin. The deacetylated derivative of rifampicin possesses antibacterial activity.

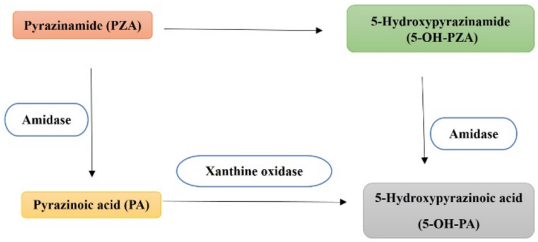

Figure 3: Metabolic pathway of pyrazinamide (PZA).

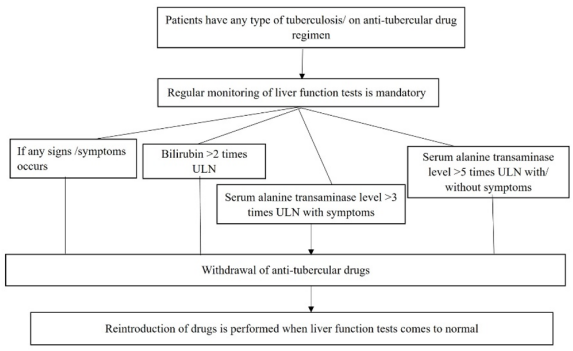

Figure 4: Flow chart of diagnostic criteria and managementof drug-induced hepatotoxicity.

Isoniazid (INH: Isonicotinic acid hydrazide)

Isoniazid (INH) is a potent antibacterial agent used predominantly for tuberculosis. INH is available as 100 and 300 mg tablets, used in combination with either pyrazinamide or rifampicin, or both. Specifically, activation is associated with the reduction of the mycobacterial ferric Kat G catalyse-peroxidase by hydrazine and reaction with oxygen to form an oxyferrous enzyme complex and inhibits the synthesis of mycolic acid. The oxidation of INH followed by metabolism via acetylation by the hepatic enzyme N-acetyltransferase 2 (NAT2). The various metabolic products include acetyl hydrazine (AcHz), hydrazine (Hz) and isonicotinic acid, which have been suggested as being hepatotoxic. The patients with slow acetylator phenotypes have greater prevalence of INH induced hepatotoxicity than rapid acetylators because slow acetylators have significantly greater serum aminotransferase levels and higher concentrations of the AcHz metabolite than rapid acetylators (Parthasarathy *et al.*, 1986). Elevations in serum transaminases may begin from one week to nine months after starting treatment with INH. Various risk factors are advanced age, chronic alcohol use, malnutrition, cirrhosis, slow acetylators, underlying chronic hepatitis B and C. Patients taking INH alone reported an overall incidence of 1% in the United States Public Health Service (USPHS) study of hepatotoxicity related to isoniazid in 1978.

In contrast, the incidence and severity of hepatotoxicity may enhance with the concomitant use of rifampicin (Rajani Shakya, R. 2006). Side effects of INH include nausea, rash, fever, numbness in the hands and feet, increased blood levels of liver enzymes, peripheral neuropathy. The metabolic pathway of isoniazid, leading to the formation of hepatotoxins is shown in Figure 1.

Rifampicin (Rifampin)

Rifampicin is a semisynthetic derivative of rifamycin, used in combination with other agents for tuberculosis therapy. Its broad spectrum of activity hinders DNA- dependent RNA polymerase enzyme in susceptible bacteria. The usual dose is 10mg/kg/day once every day. Fixed-dose combinations of rifampicin (300mg), isoniazid(150mg) and both isoniazid(50mg) and pyrazinamide(300mg) are available in market. During repeated administration, rifampicin undergo self-induced metabolism, which leads to decreased concentration of rifampicin in blood with a consequent reduction in half-life. Minor transient elevation in serum aminotransferase may occur during long term treatment in 10-20% of patients, this typically does not require any dose modification or cessation. Drug-induced liver injury, coupled with rifampicin, may range from hyperbilirubinemia without hepatocellular injury to reasonable

elevations in transaminases or, clinically significant hepatitis. Rifampicin is widely distributed in body fluids and tissues, including cerebrospinal fluid. Rifampicin undergoes deacetylation and hydrolysis to form desacetyl rifampicin and formyl rifampicin respectively. Desacetyl rifampicin is microbiologically active and highly polar than the parent compound (Ataç *et al.*, 2001). The onset of hepatotoxicity due to rifampicin ranges from one and six weeks. Compared to INH, the pattern of injury is usually hepatocellular at the onset of injury, but can cholestatic or mixed. Rifampicin clearance can be impaired by liver failure, thereby enhancing the serum levels of the drug. It should be included in the tubercular regimen by considering its important role, with the provison that the patients be closely monitored through frequent clinical evaluations and laboratory tests. Rifampicin can also be used for chemoprophylaxis of meningococcal disease and meningitis due to H.influenza. Adverse reactions include decreased blood pressure, flushing, shock, vasculitis, pruritis, abdominal cramps, diarrhoea, anorexia, heartburn, renal insufficiency, conjunctivitis, etc. The metabolic derivatives of rifampicin are shown in Figure 2.

Pyrazinamide (PZA)

Pyrazinamide **(**PZA) is a nicotinic acid derivative act as an active inhibitor of *Mycobacterium tuberculosis.* The recommended dosage form of pyrazinamide is 15 to 30 mg/kg daily. The onset of hepatotoxicity due to pyrazinamide ranges from 4 to 8 weeks. Responsible enzymes for PZA metabolic pathways are amidase and xanthine oxidase. Pyrazanoic acid (PA) is the principal metabolite of PZA, which is produced by liver microsomal amidase. Xanthine oxidase then hydroxylates PA to 5-hydroxy pyrazinoic acid (Huang, 2002). PZA is well absorbed from the gastrointestinal tract and is widely distributed throughout the body. It is metabolized by the liver and excreted by the kidneys (Kopanoff *et al.*, 1978). In U.S. pyrazinamide is reserved for combination use in patients infected with drug-resistant strains. The serum enzyme pattern is usually hepatocellular like isoniazid hepatotoxicity. Pyrazinamide shou,ld be used when the nearby perception of the patient is conceivable. Intolerance of PZA was associated with the same risk factors as the like history of hepatitis and age $\geq$60 years as intolerance of entire standard therapy. The most important side effect of pyrazinamide was exanthema which developed directly after the first dose and arthralgia (Singh *et al.*, 1995). The metabolic pathway of PZA is shown in Figure 3.

PZA induced hepatotoxicity is dose dependent and is the most hepatotoxic drug, especially treatment, is more than > 30mg/kg/day. Rechallenge with the responsible drug should be avoided once hepatotoxicity occurs, as it increases the risk of recurrence (Singh *et al.*, 1995; Walker, 1999). Asians had a higher risk of adverse events, especially due to PZA (Narasimhan *et al.*, 2013; Walker, 1999).

Fluoroquinolones

Fluoroquinolones are bactericidal antibiotics with numerous valuable pharmacokinetic properties including high oral bioavailability, an enormous volume of distribution and broad-spectrum antimicrobial activity. Fluoroquinolones inhibit bacterial DNA gyrase and topoisomerase, enzymes essential for bacterial DNA replication (Tost *et al.*, 2005; Andrade and Tulkens, 2011). Examples of fluoroquinolones are Ciprofloxacin, delafloxacin, gemifloxacin, levofloxacin, moxifloxacin, norfloxacin, and ofloxacin. Ciprofloxacin is a second-generation fluoroquinolone antibiotic is available in multiple oral formulations of 100, 250, 500 and 750mg tablets. Fluoroquinolone antibiotics also have a potential risk of hepatotoxicity. Mild transient aminotransferase elevations may occur, however uncompromising hepatotoxicity hypothetically associated with fluoroquinolone use is quite uncommon (Yee *et al.*, 2003). Peripheral eosinophilia and fever are often associated with hypersensitivity reactions (Gurumurthy *et al.*, 1984). The onset of injury ranges from 2 days to 2 weeks. Trovafloxacin was withdrawn from the marketplace because of a tough association with fatal acute liver failure. Patients exposed to fluoroquinolones had a 20% increased probability of developing hepatotoxicity comparative with the control group.

Ethambutol (EMB)

Ethambutol is an ethylenediamine derivative having bacteriostatic antimycobacterial activity and used as a first-line anti-tubercular agent effective against mycobacterium tuberculosis. Its mechanism is inhibition of arabinosyl transferase, an enzyme that polymerizes arabinose into arabinan and then arabinogalactan, a mycobacterial cell wall constituent. Ethambutol is available as 800mg tablet and dose may increase according to body weight. Optic neuritis is the most significant potential side effects of ethambutol (Shih *et al.*, 2013).

PREDISPOSING FACTORS OF HEPATOTOXICITY SECONDARY TO ANTI-TUBERCULAR DRUG

Predisposing factors associated with anti-tubercular drug-induced hepatotoxicity are advanced age, gender, acetylator phenotype, nutritional status, alcohol intake, extensive TB, indiscriminate use of various drugs, ethnic factors,

chronic liver disease and concomitant infections like chronic viral hepatitis B, C, and HIV.

Advanced age

Advanced age >60 years has been associated with an enhanced risk of hepatic injury (Saukkonen *et al.*, 2006). The threat of hepatotoxicity secondary anti-tuberculosis treatment increments with age, and the highest incidence occurs in individuals above 50 years (Ho *et al.*, 2009).

Gender

Females are more prone to anti-tubercular drug-induced hepatotoxicity than males. Previous studies also concluded that hepatotoxicity was seen more in females than males and with presumed recent infections (Abera *et al.*, 2016; Alshammari *et al.*, 2014).

Acetylators phenotype A hypothesis existed that rapid acetylators are prone to develop isoniazid induced hepatotoxicity than slow acetylators and studies proved that acetylator phenotype either rapid or slow is not a predisposing factor for ATT induced hepatotoxicity (Gurumurthy *et al.*, 1984; Wong *et al.*, 2000).

Malnutrition

Poor nutritional status perceived as one component that enhanced hepatotoxicity in developing countries. Patients having pretreated hypoalbuminemia had a two-fold higher risk of developing hepatotoxicity. In malnutrition, there is a depletion of glutathione stores that makes one vulnerable to oxidative injuries (Forget and Menzies, 2006).

Chronic alcoholism

Alcoholism (which is defined as consuming >35 units and >28 units of alcohol per week for at least ten years for men and women, respectively) was found to be significantly associated with the incidence of anti-TB-DIH (Andrade and Tulkens, 2011).

Concomitant drugs

Concomitant acetaminophen intake of more than 2g daily lead to antitubercular drug induced hepatotoxicity in 33.8% of patients and its concomitant use predisposes for hepatic injury (Ataç *et al.*, 2001; Bao *et al.*, 2018). Concurrent antiretrovirals like nevirapine, stavudine, efavirenz are known to enhance hepatotoxicity (Lee *et al.*, 2002) (Saukkonen *et al.*, 2006).

Concomitant infections

Patients with chronic hepatitis B co-infection (HBV) have a higher prevalence of liver failure than those with TB mono-infection. A cumulative drift in HBV-DNA levels were seen in patients after anti-TB therapy. ALT elevations were associated with an increase in HBV-DNA levels irrespective of HBeAg status (Ataç *et al.*, 2001; Shakya *et al.*, 2004). Nucleotide analogue ought to be administered for the patients with dynamic HBV-DNA replication before anti-TB treatment to avoid the development of hepatic failure (Li *et al.*, 2013; Acocella, 1978; Mahmood *et al.*, 2007). Studies have proved that patients who were co-infected with both hepatitis C and HIV infections, have a 14.4 fold relative risk of developing DIH (Jeong *et al.*, 2015; Bavikatte *et al.*, 2017).

Genetic factors

Genetics factors have an impact on anti-tubercular drug-induced hepatotoxicity. After co-treatment with isoniazid and rifampicin, there is a cumulative risk of antitubercular drug induced hepatotoxicity (ATT DIH) is coupled with the accumulation of protoporphyrin IX in the liver, which is regulated by PXR in the heme biosynthesis pathway (Chen *et al.*, 2018; Sharma *et al.*, 2010; Schaberg *et al.*, 1996). The individual's susceptibility to anti-TB DIH is due to a surplus formation and/or accumulation of reactive metabolites or condensed clearance. Association of genetic polymorphism in other genes includes CYP7A1, B.S.E.P., UGT1A1, P.X.R., H.L.A.'s, TNF-α, TXNRD1, and SOD1 also contribute anti-TB DIH (Li *et al.*, 2013). The baseline serum drug concentration of patients with anti-TB drugs did not differ significantly from those of anti-TB drug-induced hepatotoxicity (Gaude *et al.*, 2015).

MANAGEMENT

Anti-tubercular drug-induced hepatotoxicity was common in the intensive phase of tuberculosis treatment. No evidence-based guidelines are accessible for the management of these patients. Elevations of serum transaminase (AST, ALT) levels may occur, elevations more than three times upper limit of normal with signs and symptoms, then known hepatotoxic agents like isoniazid, rifampicin, and pyrazinamide should be withheld in patients. Reintroduction is done when all biochemical markers of liver injury have returned to normal (Chen *et al.*, 2018). Sequential reintroduction of isoniazid, pyrazinamide, and rifampicin based on weight-based regimen should be carried out in all anti-tubercular drug-induced hepatotoxic patients (Sharma *et al.*, 2002). Patients with severe or prolonged hepatotoxicity can tolerate the reintroduction of rifampin and isoniazid, but pyrazinamide is hazardous (Koul, 2015; Lampertico *et al.*, 2017). Certain studies revealed that the recurrence of hepatotoxicity is related to reintroduction with a full-dose regimen of pyrazinamide (Sun *et al.*, 2009; Pande *et al.*, 1996). Liver function tests

were monitored periodically in 2 weeks during the initiation phase to determine anti-tubercular tolerance. Patients with liver cirrhosis should be closely monitored (Laoveeravat *et al.*, 2019). Early diagnosis, treatment, and identification of the predominant factors for drug-induced hepatotoxicity are most important to prevent hepatitis induced mortality (Ungo *et al.*, 1998). The patient should also be educated about the occurrence of symptoms and the significance of clinical and laboratory surveillance (Gupta *et al.*, 2009). The management of anti-tubercular drug-induced hepatotoxicity is shown in Figure 4.

PATIENT EDUCATION

Patients should be made aware of various side effects regarding the use of anti-tubercular drugs. It should be given as printed leaflets, counselling, and awareness classes. Patients are advised to monitor their liver functions weekly during the initial treatment period. Patients have to be informed about signs and symptoms of hepatotoxicity like nausea, vomiting, abdominal discomfort, fatigue, and withdrawal of the drugs immediately. The patient should be warned about the concomitant use of other hepatotoxic drugs and alcohol use.

CONCLUSION

The hepatotoxicity secondary to anti-tubercular treatment is quite common. The systematic monitoring of liver function during anti-TB treatment can lead to prevention of hepatotoxicity to a certain extend. Clinicians should be more vigilant regarding the diagnosis part of drug-induced hepatotoxicity by considering the diagnosis of exclusion. Particular attention should be given to patients who have elevated serum transaminases at baseline and chronic liver diseases. The criteria for the diagnosis of drug-induced hepatotoxicity may vary between treatment centers and there are no well-established guidelines for management. Further research is required, especially in developing countries where TB are endemic.

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Conflict of interest

All authors have no conflicts of interest to declare.

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