ORIGINAL RESEARCH PAPER

Medical Science

ANTI- TUBERCULAR DRUG-INDUCED HEPATITIS IN TUBERCULOSIS PATIENTS ATTENDING TERTIARY CARE CENTRE

KEY WORDS: Tuberculosis, Hepatitis, Bilirubin, Pulmonary, Extra pulmonary

Dr. Suman Kumar Panda Senior consultant, Department of General Medicine, TMH, Jamshedpur

Dr. Bhagyalakshmi Satyanarayan* Consultant, Department of General Medicine, TMH, Jamshedpur. *Corresponding Author

Dr. Zaid Md. Nafe Registrar, Department of Gastroenterology, TMH, Jamshedpur

Dr. Sarita Kumari Senior registrar, Department of General Medicine, TMH, Jamshedpur

Dr. Ashok Sunder Head of Department, Department of General Medicine, TMH, Jamshedpur.

ABSTRACT

Background: Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). . In this study, we aimed to study the clinical profile and outcome in patients with Anti- tuberculosis drug induced hepatitis over a period of 1 year. **Material and methods:** A prospective observational study conducted in Tata Main Hospital in patients with tuberculosis on Anti- tubercular treatment (ATT) over a period of 1 year i.e. April 2020 - Mar 2021 on 533 tuberculosis patients. Results: Patients in the DIH group were significantly older than those in the non-DIH group, but other parameters, including the male/female ratio, measures of nutritional status and erythrocyte sedimentation rate were more or less similar in both groups. During the treatment period, 14.3% (36/533) patients developed anti-TB-DIH, which was detected by clinical examination and confirmed by liver function parameters. Pre-treatment level of ALT and AST were almost similar in patients with and without DIH (ALT=28.17 ± 4.25 versus 25.61 ± 3.87, $p < 0.0001$; AST=29.24 ± 6.41 versus 26.14 ± 5.37, P=0.0027). Whereas, during the treatment period, all patients developing DIH showed significant higher (P<0.0001) level of ALT, AST and bilirubin as compared to patients without DIH (ALT=153.57 ± 28.11 versus 35.21 ± 08.41; AST=155.78 ± 22.38 versus 33.52 ± 09.82; bilirubin=1.32 ± 0.45 versus 0.81 ± 0.53). Conclusion: Our study indicates that TB patients with male gender (69.44%), high body mass index (77.78%), pulmonary involvement (75%) and ≤ 35 years (69.44%) were at higher risk for anti-TB-DIH. Thus, there is a need for a regular biochemical and clinical follow-up for those patients who are at higher risk. Close clinical monitoring and liver function tests might be helpful in the early diagnosis of anti-TB-DIH, which is crucial to prevent progression of severe liver injury.

Introduction:

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). TB is caused by the bacillus Mycobacterium tuberculosis, which is spread when people who are sick with TB expel bacteria into the air; for example, by coughing. The disease typically affects the lungs (pulmonary TB) but can also affect other sites (extra pulmonary TB). About a quarter of the world's population is infected with M. tuberculosis [1].

Globally, an estimated 10.0 million (range, 8.9–11.0 million) people fell ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million (range, 1.1– 1.3 million) TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208 000 deaths (range, 177 000–242 000) among HIV-positive people (a reduction from 678 000 in 2000). Men (aged ≥15 years) accounted for 56% of the people who developed TB in 2019; women accounted for 32% and children (aged < 15 years) for 12%. Among all those affected 8.2% were people living with HIV [2].

Geographically, most people who developed TB in 2019 were in the WHO regions of South-East Asia (44%), Africa (25%) and the Western Pacific (18%), with smaller percentages in the Eastern Mediterranean (8.2%), the Americas (2.9%) and Europe (2.5%). Eight countries accounted for two thirds of the global total: India (26%), Indonesia (8.5%), China (8.4%), the Philippines (6.0%), Pakistan (5.7%), Nigeria (4.4%), Bangladesh (3.6%) and South Africa (3.6%). The other 22 other countries in WHO's list of 30 high TB burden countries accounted for 21% of the global total [2].

SDG Target 3.3 shows by 2030 end the epidemics of AIDS, TB, malaria and neglected tropical diseases, and combat hepatitis, water-borne diseases and other communicable diseases [2].

The most effective TB treatment currently available is the 6-month short-course regimen utilizing isoniazid (INH), rifampicin (RMP), ethambutol (ETB) and pyrazinamide (PZA) in the intensive phase, followed by RMP, INH and ETB in the continuation phase. This regimen is capable of curing almost all patients with TB due to drug-sensitive organisms, assuming patient compliance. Unfortunately, however, anti-tuberculosis medications have various adverse effects, one of which is drug-induced hepatotoxicity (DIH). DIH is usually related to changes in treatment regimens, the use of less effective second-line treatments and prolonged hospitalization. The reported incidence of hepatotoxicity in controlled trials of anti-TB chemotherapy that included INH, RMP and PZA ranged from 0.6% to 3% [3].

Hepatotoxicity is one of the important side-effects of anti-TB drugs especially during the initial intensive period, and monitoring is crucial during this period, but may be costly. Awareness of the risk groups may decrease the cost as well as the incidence of serious drug-related adverse effects. In this study, we aimed to study the clinical profile and outcome in patients with Anti- tuberculosis drug induced hepatitis over a period of 1 year.

Material And Methods: A prospective observational study conducted in Tata Main Hospital in patients with tuberculosis on Anti- tubercular treatment (ATT) over a period of 1 year i.e. April 2020 - Mar 2021 on 533 tuberculosis patients.

Definition of ATT induced hepatitis: An increase 5 times the upper limit of the normal levels (50 IU/l) of serum AST and/or ALT or >3 times the upper limit of normal (>150 IU/l) on 3 consecutive occasions or an increase in serum total bilirubin >1.5 mg/dl or any increase in serum AST and or ALT level above pre-treatment values + anorexia, nausea, vomiting, and jaundice or improvement in liver function test results (serum bilirubin level <1 mg/dl; AST and ALT level <100 IU/l) after withdrawal of anti-tuberculosis drugs [4].

Inclusion criteria: Patients of either sex, >12 years of age & fulfilling the criteria

Exclusion criteria: Serological evidence of acute viral hepatitis, concomitant consumption of other potentially hepatotoxic drugs (e.g. methotrexate, phenytoin, valproate, and fluconazole, chronic liver disease & negative serologic tests for hepatitis A, B, C, and E, and for HIV.

In case of drug-induced hepatotoxicity (DIH), ATT was immediately stopped and modified ATT- Ethambutol, Streptomycin and Levofloxacin were added and the patients were followed up at weekly intervals until the clinical and biochemical parameters of acute liver injury stabilized.

After stabilization of liver functions, drugs were administered in a manner similar to that recommended in the American Thoracic Society guidelines for reintroduction: Rifampicin at a maximum dosage from day 1, Isoniazid at a maximum dosage from day 8 & Pyrazinamide at a maximum dosage from day 15.

Drug dosages: The drug dosages were calculated in relation to the weight of the patients as follows [5]:
Streptomycin: 0.75 gm IM (<50 years) and 0.50 gm (>50 years)

Rifampicin: Body weight <450 mg/day; >50 kg – 600 mg
Isoniazid: 600 mg (10–15mg/kg)
Ethambutol: 1200 mg (30 mg/kg)
Pyrazinamide: 1500 mg (30–35mg/kg).

Results and observation: A prospective observational study on 533 tuberculosis patients on ATT in a tertiary care centre.

Table 1: Characteristics of DIH and Non-DIH Tuberculosis Patients

Characteristics	DIH	Non- DIH	p-value
Mean age in years	36.24 ± 06.87	32.61 ± 08.35	0.0112S
Gender M/F	25/11	311/186	------
Height m	1.47 ± 0.78	1.62 ± 0.82	0.2882NS
Weight kg	52.31 ± 10.91	49.71 ± 11.34	0.1835NS
BMI, kg/m2	18.67 ± 03.68	18.25 ± 03.39	0.4758NS
ESR	43.21 ± 19.24	40.11 ± 21.37	0.3981NS

Patients in the DIH group were significantly older than those in the non-DIH group, but other parameters, including the male/female ratio, measures of nutritional status and erythrocyte sedimentation rate were more or less similar in both groups.

Table 2: Level of liver function parameters in patients with and without DIH at different stages i.e. before and during the treatment period

Parameters	Patients with DIH (n= 36)	Patients without DIH (n=497)	t and p-value
ALT (IU/L)			
Before treatment	28.47 ± 04.25	25.61 ± 03.87	t = 4.2530, < 0.0001HS
During treatment (Peak value)	153.57 ± 28.11	35.21 ± 08.41	t = 63.0893, < 0.0001HS
AST (IU/L)			
Before treatment	29.24 ± 06.41	26.14 ± 05.37	t = 3.0115, 0.0027HS
During treatment (Peak value)	155.78 ± 22.38	33.52 ± 09.82	t = 63.8468, < 0.0001HS
Bilirubin (mg/dl)			
Before treatment	0.62 ± 0.11	0.64 ± 0.21	t = 0.5655, 0.5720NS
During treatment (Peak value)	1.32 ± 0.45	0.81 ± 0.53	t = 5.6272, < 0.0001HS

During the treatment period, 14.3% (36/533) patients developed anti-TB-DIH, which was detected by clinical examination and confirmed by liver function parameters. As shown in Table 2 pre-treatment level of ALT and AST were almost similar in patients with and without DIH (ALT=28.17 ± 4.25 versus 25.61 ± 3.87, p < 0.0001; AST=29.24 ± 6.41 versus 26.14 ± 5.37, P=0.0027). Whereas, during the treatment period, all patients developing DIH showed significant higher (P<0.0001) level of ALT, AST and bilirubin as compared to patients without DIH (ALT=153.57 ± 28.11 versus 35.21 ± 08.41; AST=155.78 ± 22.38 versus 33.52 ± 09.82; bilirubin=1.32 ± 0.45 versus 0.81 ± 0.53).

Table 3: Risk factors for anti-tuberculosis drug-induced hepatotoxicity by univariate analysis

Characteristics	No. of patients	Patients with DIH (n= 36)	Patients without DIH (n=497)	p-value
Age in years				
≤ 35 years	297 (55.72%)	25 (69.44%)	272 (51.03%)	0.086066NS
> 35 years	236 (44.28%)	11 (30.56%)	225 (48.97%)	
Gender				
Male	330 (61.91%)	25 (69.44%)	305 (57.22%)	0.335246NS
Females	203 (38.09%)	11 (30.56%)	192 (42.78%)	
Disease classification				
Pulmonary	394 (73.92%)	27 (75.0%)	367 (68.85%)	0.87866NS
Extra pulmonary	139 (26.08%)	09 (25.0%)	130 (31.15%)	
Body mass index (kg/m^2)				
<18.5	86 (16.13%)	08 (22.22%)	78 (14.63%)	0.30386NS
≥18.5	447 (83.87%)	28 (77.78%)	419 (85.37%)	

In reference to table no.3, it was found that in risk factors age less than 35 years i.e. 297 (55.72%) having more cases with DIH 25 (69.44%) in comparison to non-DIH cases i.e. 272 (51.03%) respectively. Similarly males i.e. 394 (73.92%) having more DIH cases i.e. 25 (69.44%) in comparison to females 203 (38.09%) i.e. 11 (30.56%) respectively. Also more cases were pulmonary 394 (73.92%) and having more DIH cases i.e. 27 (75.0%) with respect to extra-pulmonary cases 139 (26.08%) i.e. 09 (25.0%). <18.5 kg/m2 body mass index 86 (16.13%) have less DIH cases i.e. 08 (22.22%) in comparison to ≥18.5 kg/m2 body mass index 447 (83.87%) with greater DIH cases i.e. 77.78% respectively.

Table 4: Extra-pulmonary classification of studied cases

Extra-pulmonary classification	No. of patients (n=139)	Patients with DIH (n=9)	p-value
Cervical lymphadenopathy	47 (33.81%)	03 (33.33%)	Chi-square statistic is 0.6872. The p-value is 0.876216NS
Pleural effusion	39 (28.07%)	03 (33.33%)	
Gastro-intestinal	23 (16.54%)	02 (22.22%)	
Bone	18 (12.94%)	01 (11.11%)	
Genito-urinary	12 (08.63%)	00 (00.00%)	

Table 4 shows that most number of extra pulmonary cases were cervical lymph adenopathy i.e. 47 (33.81%) & pleural effusion 39 (28.07%) with more DIH cases i.e. 03 (33.33%) each followed by gastrointestinal cases i.e. 23 (16.54%) with two DIH cases only. Rest were bone & genitourinary i.e. 18 (12.94%) & 12 (08.63%) with one and no DIH cases seen.

Discussion:

Drug-induced liver injury (DILI) is ultimately a clinical diagnosis of exclusion. The time of onset to acute injury is within months of initiating a drug. Rechallenge with the suspected offending agent with more than twofold ALT elevation, and discontinuation leading to a fall in ALT, is the strongest confirmation of the diagnosis. Risk factors include advanced age, pregnancy, alcohol intake, female sex, slow acetylator status, malnutrition, HIV and pre-existent liver disease [10]. Incidence ranges between 2% and 28%. Anti tubercular drug regime includes Isoniazid (INH), rifampicin (RMP), pyrazinamide (PZA), and ethambutol (EMB) for 2 months followed by 4 months of INH, RMP and EMB. These drugs are metabolized in liver. Hepatotoxicity is greater with pyrazinamide.

ATT- Drug induced hepatitis may reduce treatment effectiveness by compromising treatment regimens. To take decisions, therapeutic drug monitoring during treatment may be needed in cases with slow response to treatment, drug-resistant TB, drug-drug interaction risks and severe underlying diseases. With pyrazinamide induced hepatotoxicity, it is recommended to reduce the standard dose.

INH is generally known to be one of the major causes of DIH in the treatment of TB, and is metabolized to hepatotoxic intermediates mainly by N-acetyltransferase (NAT). Reports linking polymorphic NAT acetylator status with DIH have been published and have indicated that slow acetylators are a risk factor for anti-TB DIH and that patients are prone to developing more severe hepatotoxicity than with rapid acetylators [10].

Most common non-infectious causes of hepatitis are alcohol, cholestatic drugs and toxic materials. The most common mode that leads to liver injuries is antituberculosis drug-induced hepatitis. The severity of drug-induced liver injury varies from minor nonspecific changes in hepatic structure to fulminant hepatic failure, cirrhosis and liver cancer. Patients receiving antitubercular drug frequently develop acute or chronic hepatitis. The time required for the metabolites to reach hepatotoxic levels is much earlier with isoniazid plus rifampicin treatment than isoniazid alone and this has been shown to be synergistic rather than additive. Antituberculosis drug (ATT)-inducible cytochrome P-4502E1 (CYP2E1) is constitutively expressed in the liver. Recent studies show that polymorphism of the N-acetyltransferase 2 (NAT2) genes and glutathione-S-transferase (GST) are the major susceptibility risk factors for ATT-induced hepatitis. The hepatic NAT and GST are involved in the metabolism of several carcinogenic arylamines and drugs. The NAT2 enzyme has a genetic polymorphism in human. N-acetyltransferase 2 genes (NAT2) have been identified to be responsible for genetic polymorphism of slow and rapid acetylation in humans. Slow acetylators of NAT2 prove to develop more severe hepatotoxicity than rapid acetylators making it a significant risk factor. Deficiency of GST activity, because of homozygous null mutations at GSTM1 and GSTT1 loci, may modulate susceptibility to drug induced hepatotoxicity. [12]

This was a retrospective observational study conducted in an industrial hospital on 533 patients with tuberculosis either pulmonary or extra pulmonary having Anti- tubercular treatment over a period of 1 year.

Present study shows that cases with DIH were significantly older than those in the non-DIH cases, but other parameters, including the male/female ratio, measures of nutritional status and erythrocyte sedimentation rate were more or less similar in both groups. Similar results were also seen in Sharma SK et al [6] study. Gaude GS et al [7], also show similar results with respect to age distribution i.e. < 40 years with more number 50 (33.33%) followed by 40-60 years 54 (36.0%) respectively. Also Ambreen K et al [8] study found that ≤35 years there were 179 cases out of that 31 i.e. 17.3% showing DIH.

Ambreen K et al [8] study found <18.5 BMI were 50 cases i.e. 20.5% with respect to ≥18.5 BMI i.e. 194 (79.5%) and also pulmonary cases were 129 (52.9%) with that of extra pulmonary cases were 115 (47.1%) respectively. Which were very comparable to present study.

During the treatment period, 14.3% (36/533) patients developed anti-TB-DIH, which was detected by clinical examination and confirmed by liver function parameters. Pre-treatment level of ALT and AST were almost similar in patients with and without DIH (ALT=28.17 ± 4.25 versus 25.61 ± 3.87, p < 0.0001; AST=29.24 ± 6.41 versus 26.14 ± 5.37, P=0.0027). Whereas, during the treatment period, all patients developing DIH showed significant higher (P<0.0001) level of ALT, AST and bilirubin as compared to patients without DIH (ALT=153.57 ± 28.11 versus 35.21 ± 08.41; AST=155.78 ± 22.38 versus 33.52 ± 09.82; bilirubin=1.32 ± 0.45 versus 0.81 ± 0.53).

Similarly Ambreen K et al [8] also found comparable results i.e. pretreatment level of ALT and AST were almost similar in patients with and without DIH (ALT=27.17±4.02 versus 26.60±3.82, p=0.42; AST=28.83±3.40 versus 29.33±2.64, P=0.32). Whereas, during the treatment period, all patients developing DIH showed significant higher (P<0.0001) level of ALT, AST and bilirubin as compared to patients without DIH (ALT=144.03±24.35 versus 30.02±4.46; AST=141.63±21.02 versus 32.53±3.18; bilirubin=1.27±0.36 versus 0.79±0.14). However, we also found that pretreatment bilirubin level was already significantly higher (P<0.02) in patients without DIH as compared to patients with DIH (0.66±0.18 versus 0.59±0.09).

Present study found that in risk factors age less than 35 years i.e. 297 (55.72%) having more cases with DIH 25 (69.44%) in comparison to non-DIH cases i.e. 272 (51.03%) respectively. Similarly males i.e. 394 (73.92%) having more DIH cases i.e. 25 (69.44%) in comparison to females 203 (38.09%) i.e. 11 (30.56%) respectively. Also more cases were pulmonary 394 (73.92%) and having more DIH cases i.e. 27 (75.0%) with respect to extra-pulmonary cases 139 (26.08%) i.e. 09 (25.0%). <18.5 kg/m2 body mass index 86 (16.13%) have less DIH cases i.e. 08 (22.22%) in comparison to ≥18.5 kg/m2 body mass index 447 (83.87%) with greater DIH cases i.e. 77.78% respectively. Similarly Ambreen K et al [8] also found in univariate analysis indicated that the prevalence of anti-TB-DIH was significantly (P=0.03) higher in younger age group (≤35 years) as compared to older (RR=2.81, 95% CI=1.03-7.66). Females were more (p=0.005) affected with anti-TB-DIH

as compared to males (RR=0.39, 95%CI=0.20-0.78). The prevalence of anti-TB-DIH was significantly (P=0.002) higher in low BMI (<18.5) than BMI ≥18.5 (RR=2.59, 95% CI=1.42-4.72). Also, pulmonary patients were found to be at 59% lower risk (P=0.006) for anti-TB-DIH as compared to extra pulmonary patients (RR=0.41, 95s%CI=0.21- 0.80). Saha A et al [9] also found similar findings and can be comparable with present study.

Present study found that most number of extra pulmonary cases were cervical lymph adenopathy i.e. 47 (33.81%) & pleural effusion 39 (28.07%) with more DIH cases i.e. 03 (33.33%) each followed by gastrointestinal cases i.e. 23 (16.54%) with two DIH cases only. Rest were bone & genitourinary i.e. 18 (12.94%) & 12 (08.63%) with one and no DIH cases seen. Ambreen K et al [8] et al also shown cervical lymphadenopathy were more i.e. 45 (39.1%) followed by pleural effusion i.e. 28 (24.3%) respectively.

Patients developed DIH after around 2 weeks of ATT initiation. Liver fnction tests (LFT) normalization time varied between 8 days to >45 days. Four patients required second line ATT.

Figure 1: Diagnostic criteria for tuberculosis

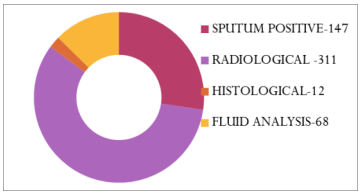

Figure 2: Diagnostic criteria in ATT induced hepatitis patients

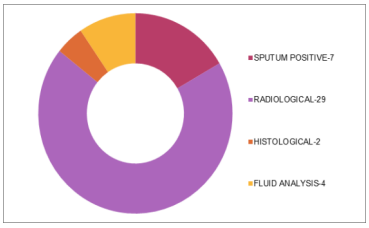

Table 5: Site of tuberculosis in patients with drug induced hepatitis

Site of TB	Number of patients
Tubercular Pleural effusion	3
Tubercular Ascites	1
Tubercular meningitis	1
Tubercular lymphadenitis	1
Spinal tuberculosis (Quadriparesis)	1
Miliary tuberculosis	1
Rectal tuberculosis	1
Pulmonary tuberculosis	27
Total	36

Table 6: Other comorbidities in patients with drug induced hepatitis

Comorbidities	Number of patients
Type II diabetes Milletus	12
Essential Hypertension	3
Chronic kidney disease	2
Alcoholic	2
Wegener's Granulomatosis	1
Systemic Lupus Erthythematosus	1
Chronic Liver Disease	0
Malignancy	1
Ischemic heart Disease	1

Maximum ALT and AST were 1518.6 IU/L and 3864.2 IU/L respectively. Maximum International Normalised Ratio (INR) was 4.04, maximum bilirubin was 20.15 mg/dl. One patient expired and two patients developed encephalopathy.

Table7: Comparison Between Jeoung I, et al and our study

	Jeoung I et al [10]	Our study
Total	195	533
DIH	12 (6.15%)	36 (6.75%)
Period of study	January 2006 to February 2010	April 2020 to March 2021
Death	6 (other causes)	1
Maximum AST	249	3864.2
Maximum ALT	249	1518.6
Median interval between the initiation of anti-TB therapy and onset of hepatotoxicity	41 days (Range 13 to 263 days)	14 days

Table 8: Comparison between Abbara et al and our study DIH: Drug induced Hepatitis

	Abbara et al [11]	Our study
Total	1529	533
DIH	105 (6.9%)	36 (6.75%)
Period of study	April 2010 and May 2014	April 2020- March 2021
Death	4	1
Males	53.3%	71.42%
Pulmonary	20%	80%
Extra-pulmonary	58.1%	20%

In a study by Abbara et al, risk factors for DILI (Drug Induced Liver Injury) were: low patient weight, HIV-1 co-infection, higher baseline ALP, and alcohol intake. [11]

Table 9: Comparison of recurrence rates of tuberculosis and drug induced hepatitis in our study and other studies

DIH: Drug induced Hepatitis

	Recurrence Rate of Tuberculosis	DIH
Our study	11%	6.75%
Overall studies	7%	
Singh et al [13]	6.8%	
Telman et al [14]	6.3%	5.3%

CONCLUSION:

In conclusion, our study indicates that TB patients with male gender, high body mass index, pulmonary involvement and ≤ 35 years were at higher risk for anti-TB-DIH. Thus, there is a need for a regular biochemical and clinical follow-up for those patients who are at higher risk. Close monitoring through liver function tests might be helpful in the early diagnosis of anti-TB-DIH, which is crucial to prevent progression of severe liver injury.

ATT induced hepatitis is not very uncommon. Baseline liver function tests must be done. Liver function test should be done on monthly basis after initiation of ATT. Suspected cases of DIH must be investigated for viral hepatitis and all hepatotoxic drugs must be stopped. At least three non-hepatotoxic drug regimens must be started. Daily monitoring of patient's condition and liver function tests every 3 days should be done. After complete resolution of transaminitis, most ATT drugs can be safely started in phased manner.

REFERENCES:

1. Devarbhavi H. Antituberculous drug-induced liver injury: current perspective. Tropical Gastroenterology. 2011 Nov 22;32(3):167-74.
2. Shu CC, Lee CH, Lee MC, Wang JY, Yu CJ, Lee LN. Hepatotoxicity due to first-line anti-tuberculosis drugs: a five-year experience in a Taiwan medical centre. The International journal of tuberculosis and lung disease. 2013 Jul

1;17(7):934-9.
3. Tostmann A, Boeree MJ, Aarnoutse RE, De Lange WC, Van Der Ven AJ, Dekhuijzen R. Antituberculosis drug-induced hepatotoxicity: concise up-to-date review. Journal of gastroenterology and hepatology. 2008 Feb;23(2):192-202.
4. Kishore PV, Palaian S, Paudel R, Mishra P, Prabhu M, Shankar PR. Drug induced hepatitis with anti-tubercular chemotherapy: Challenges and difficulties in treatment. Kathmandu Univ Med J. 2007 Apr 1;5(2):256-60.
5. Girling DJ. Singapore Tuberculosis Services/British Medical Research Council study of intermittent rifampicin plus isoniazid for pulmonary tuberculosis: Interim results at 12 months. Tubercle. 1975 Sep 1;56(3):246-7.
6. Sharma SK, Balamurugan A, Saha PK, Pandey RM, Mehra NK. Evaluation of clinical and immunogenetic risk factors for the development of hepatotoxicity during antituberculosis treatment. American journal of respiratory and critical care medicine. 2002 Oct 1;166(7):916-9.
7. Gaude GS, Chaudhury A, Hattiholi J. Drug-induced hepatitis and the risk factors for liver injury in pulmonary tuberculosis patients. Journal of family medicine and primary care. 2015 Apr;4(2):238.
8. Ambreen K, Sharma R, Singh KP, Khan FH, Kumar S. Risk factors for antituberculosis drug-induced hepatotoxicity and its association with oxidative stress in North Indian population. Annals of Tropical Medicine and Public Health. 2012 Nov 1;5(6):574.
9. Saha A, Shanthi FX M, Winston A B, Das S, Kumar A, Michael JS, Balamugesh T. Prevalence of hepatotoxicity from antituberculosis therapy: a five-year experience from South India. Journal of primary care & community health. 2016 Jul;7(3):171-4.
10. Jeong I, Park JS, Cho YJ, Yoon HI, Song J, Lee CT, Lee JH. Drug-induced hepatotoxicity of anti-tuberculosis drugs and their serum levels. Journal of Korean medical science. 2015 Feb 1;30(2):167-72.
11. Abbara A, Chitty S, Roe JK, Ghani R, Collin SM, Ritchie A, Kon OM, Dzvova J, Davidson H, Edwards TE, Hateley C. Drug-induced liver injury from antituberculous treatment: a retrospective study from a large TB centre in the UK. BMC Infectious Diseases. 2017 Dec;17(1):1-9.
12. Hussain Z, Kar P, Husain S A. Antituberculosis drug-induced hepatitis: risk factors, prevention and management. Ind J Exp Biol 2003; 41: 1226–1232.
13. Singh J, Garg PK, Tandon RK. Hepatotoxicity due to antituberculous therapy: clinical profile and reintroduction of therapy. J clin gastroenterol 1996; 22: 211-214.
14. Teleman MD, Chee CB, Earnest A, Wang YT. Hepatotoxicity of tuberculosis chemotherapy under general programme conditions in Singapore. Int J Tuberc Lung Dis 2002; 6:699-705.