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NON-STANDARDISED ATT REGIMENS IN DRUG SENSITIVE TB PATIENTS WITH DILI

Pulmonary Medicine

Dr Rajeev Tandon Professor, Dept. Of Respiratory Medicine, SRMS, IMS.

Dr Gauri Goswami JR- 3, Dept. Of Respiratory Medicine, SRMS, IMS.

Dr Pradeep Nirala Associate Professor, Dept. Of Respiratory Medicine, TMU.

Dr Lalit Singh Professor and HOD, Dept. Of Respiratory Medicine, SRMS, IMS.

ABSTRACT

A number of conditions predispose to anti-TB drugs-induced hepatotoxicity. These include advanced age, female sex, poor nutritional status, preexisting chronic liver disease, extensive pulmonary disease or serious type of tuberculosis e.g. meningitis and high dosages of drugs like Pyrazinamide Tuberculosis treatment in patients with preexisting advanced liver disease poses significant challenges. The likelihood of drug-induced hepatitis is increased with prior advanced liver disease, liver transplant, or hepatitis C infection. Abnormal baseline aminotransferases alone are an independent risk factor for drug induced liver injury , In our study of 79 patients maximum number of patients belonged to age group of 21 to 60, with more males that is 64.3% being affected by DILI. Most of these patients belonged to the lower middle class with majority having lower BMI. 37.3% had history of alcohol intake whereas 31.1% were smokers and 10% had other addictions. .7 percent were patients of disseminated TB, 68.2% were suffering from PTB and 27% had EPTB. 4% had PTB with TB. All these patients showed deranged LFT and their ATT was modified in accordance and the most commonly prescribed non standardised regimen were HRE, E-LEVO, SE-LEVO. At the end of IP phase 57 patients reported improvement, 19 had persisting complains, 1 patient dies and 2 were lost to f/u. Radiological follow up showed that, most patients reported with consolidation at the beginning, out of which 34 reported resolution at end of IP phase. Patients with miliary pattern, effusion and pneumothorax mostly improved radiologically. 2 patients had fibrotic change. All patients in whom reintroduction of ATT drugs was successfully done , were excluded from the study . It was concluded that the most toxic first line drug was pyrazinamide and could not be given in patients of DILI. Most of the patients showed improvement at the end of intensive phase. No patient developed any intolerance or reaction to the modified regimen

KEYWORDS

INTRODUCTION

- In many impoverished countries, tuberculosis is still a serious infectious illness. It has a heavy socioeconomic cost on the person and society. India is the nation with the biggest TB burden, accounting for one-fifth (21%) of the global TB population. [1] As per the Global TB Report 2021, the estimated incidence of all forms of TB in India for the year 2020 was188 per 100,000 population. The first-line medications discovered more than 5 decades ago continue to remain the basis of pharmaceuticals used in the treatment of TB, despite the fact that newer and safer treatments are constantly being sought for and employed to treat TB. These include ethambutol (EMB), pyrazinamide (PZY), rifampicin (RIF), and isoniazid(INH). Although the great majority of patients tolerate the medications, some do have side effects, the most notable of which is hepatotoxicity.

Twenty percent of patients experience asymptomatic elevation of liver enzymes, which in the majority of cases resolves on its own [2,3,4,5]. However, the prognosis may be less promising for patients who experience jaundice, ascites, encephalopathy, or acute liver failure. Hepatotoxicity also has adverse consequences such as treatment interruption with potential for treatment extension, the development of drug resistance, and treatment failure. Antituberculosis drug-induced liver injury (DILI), also known as hepatotoxicity, refers to a broad range of liver damage ranging from asymptomatic minor increase of liver enzymes to severe liver failure, which often results in death or liver transplantation. In fact, it is a major contributor to drug-induced liver damage and drug-induced acute liver failure that results in mortality in India (DIALF). Contrarily, the most frequent causes of DILI and drug-induced ALF in western nations are non-TB antibiotics and paracetamol

Due to its status as the second-leading cause of infectious disease-related mortality globally, tuberculosis (TB) continues to be a serious issue for global health. This is true even when there are excellent treatments available. Treatment discontinuation brought on by negative medication responses is a significant contributor to poor outcomes.

DILI

Inconsistencies in the rise of transaminase numerical levels required for a DILI diagnosis plagued earlier classifications. The criteria used to diagnose DILI, particularly TB DILI, are now quite consistent. As long as competing causes like acute viral hepatitis, autoimmune hepatitis, and other liver diseases are ruled out, elevation of transaminases up to 5 times the upper limit of normal (ULN) in the absence of symptoms and up to 3 times the ULN or twice the ULN of bilirubin in the presence of symptoms constitute DILI[1]. Recent investigations have highlighted the significance of concurrent viral hepatitis A-E as a cause for increase in liver biochemical tests, despite the fact that clinicians often consider elevation of transaminases or bilirubin as the default criterion for diagnosing TB DILI.

Incidence, Interactive Toxicity And Mechanism Of Toxicity

The prevalence of TB DILI in the general population is unknown and likely unrecognized Both primary prophylaxis (preventive therapy) and TB treatment may result in toxicity, which is influenced by drug dynamics, drug-disease dynamics, and drug-host dynamics.

Among the first-line drugs (isoniazid, rifampicin, pyrazinamide and ethambutol), the first three have the potential for hepatotoxicity with pyrazinamide being the most hepatotoxic followed by isoniazid and rifampicin. [6] Though transient hepatic enzyme elevations have been seen in but they return to normal in majority on continuation of therapy. The hepatotoxic effects of Rifampicin and Isoniazid are additive[6]. Pyrazinamide induced hepatic damage is dose and duration related. However , it is hard to determine how much each medicine contributes to DILI when it develops after the administration of a 4-drug combination regimen.

Pathogenesis And Mechanisms

Most cases of DILI are idiosyncratic in nature, meaning it is the characteristics of the host and not the characteristic of the drug which are responsible for the liver injury. Idiosyncratic reactions may be hypersensitive or metabolic. Hypersensitive idiosyncrasy is often associated with skin rashes, fever, eosinophilia and/or lymphadenopathy. This is uncommon in anti-TB drugs, being more common with antiepileptics and sulfonomides. More commonly, TB DILI is due to metabolic idiosyncrasy due to the metabolites released or accumulated during the metabolic process. This may be facilitated by genetic factors or polymorphism of drug metabolizing enzymes

Presentation, Adaptation And Clinical Evaluation Of DILI

Antituberculosis DILI has a wide spectrum of presentations, ranging from asymptomatic mild rise in liver biochemical tests to acute hepatitis and acute liver failure. The mild increase in amino-

transferases experienced by ~20% of patients is usually asymptomatic. Clinical hepatitis is seen in 1-6% of patients taking isoniazid prophylaxis or combination drugs. A feature peculiar to anti-TB drugs is the development of adaptation or tolerance to the drugs. Indeed, adaptation during INH or anti- TB use is an illustrative example for adaptation. This is defined as elevation of transaminases and or bilirubin, without any symptoms, which resolves with continuation of the drugs. Rarely, despite marked rise in transaminases and bilirubin, patients may still be asymptomatic.

When elevated liver enzymes are noted in a TB patient on ATT, the major challenge for the treating physician is to determine whether the elevation is a sign of adaptation or a sign of incipient liver injury.

Risk Factors For TB DILI

A number of conditions predispose to anti-TB drugs-induced hepatotoxicity. These include advanced age, female sex, poor nutritional status, preexisting chronic liver disease, extensive pulmonary disease or serious type of tuberculosis e.g. meningitis and high dosages of drugs like Pyrazinamide[6]

Tuberculosis treatment in patients with preexisting advanced liver disease poses significant challenges. The likelihood of drug-induced hepatitis is increased with prior advanced liver disease, liver transplant, or hepatitis C infection . Abnormal baseline amino-transferases alone are an independent risk factor for drug induced liver injury [7][8]

Majority of studies support the view that chronic hepatitis B virus carriers, chronic alcoholics and patients with past history of acute viral hepatitis do not predispose to increased hepatotoxicity with anti TB drugs and usual treatment can be given in these patients [6],though one has to be extra vigilant about occurrence of hepato-toxicity in these cases.

In patients with established chronic liver disease, Pyrazinamide is contraindicated. The half -life of Pyrazinamide, which is 9-10 hours in persons with normal hepatic and renal functions, is prolonged in patients having impaired hepatic functions. [9]

According to technical and operative guidelines 2016-following regimens are suggested in conditions with deranged liver functions: -

- Containing two hepatotoxic drugs:
- INH + Rifampicin + Ethambutol for 9 months or
- INH + Rifampicin + Ethambutol + Streptomycin for 2 months followed by INH and Rifampicin for 7 months or
- Rifampicin + Ethambutol + Pyrazinamide for 6–9 months.
- Containing one hepatotoxic drug
- INH + Ethambutol + Streptomycin for 2 months followed by INH + Ethambutol for 10 months
- Containing no hepatotoxic drugs
- Streptomycin + Ethambutol + FQ for 18–24 months.

METHODOLOGY

Prospective analysis-Outdoor and Indoor patients

The study was undertaken after obtaining approval from the hospital ethical committee and was conducted from January 2021 to June 2022 over a period of 18 months in OPD and IPD of Respiratory medicine in tertiary health care centre, fulfilling the inclusion and exclusion criteria.

Type Of Study: Prospective and Observational Study

METHODOLOGY: Data was collected using a pre tested pro forma which included demographic details of the patient, vitals, presenting signs and symptoms, clinical examination addictions, socioeconomic factor, education levels, along with specific diagnostic test for TB like CBNAAT, AFB, and other investigations, CBC, RBS, LFT, KFT, radiological diagnostic like X-RAY and serological test like ADA and histopathology/cytological examination.

Inclusion Criteria

All patients of tuberculosis, pulmonary and extra pulmonary attending OPD /IPD of tertiary care centre, either confirmed as DS-TB by CBNAAT or do not fall in case definition of presumptive DR-TB. All new TB cases were defined as patients who have never been treated for TB or have taken anti-TB drugs for less than 1 month

Exclusion Criteria

- Confirmed/Presumptive DR-TB case
- All patients in whom ATT was successfully reintroduced
- Previously treated patients
- Patients who were diagnosed with HIV
- Patients of pediatric age group
- Patients not willing to participate in the study

Data Analysis

1. Demography

Demographic parameters		DILI	
		n	%
AGE	<= 20	9	11.4%
	21 - 40	26	32.9%
	41 - 60	26	32.9%
	61+	18	22.8%
SEX	F	28	36.7%
	M	51	64.3%
BMI	< 18.5 (Underweight)	37	46.8%
	18.5 - 22.9 (Normal)	33	41.8%
	23.0 - 24.9 (Overweight)	7	8.9%
	> 25.0 (Obese)	2	2.5%
SOCIO ECONOMIC STATUS	I (UPPER)	4	5.1%
	II (UPPER MIDDLE)	27	34.2%
	III (LOWER MIDDLE)	46	58.2%
	IV (UPPER LOWER)	2	2.5%
EDUCATIONAL STATUS	ILLITERATE	6	7.6%
	5TH PASS	12	15.2%
	8TH PASS	12	15.2%
	10TH PASS	8	10.1%
	12TH PASS	15	19.0%
	GRADUATE	26	32.9%
RESIDENCE	R	57	72.2%
	U	22	27.8%
Total		79	100.0%

2. Addictions

ADDICTIONS	Frequency	Percent
ALCOHOL INTAKE	55	37.3
SMOKER	46	31.1
ADDICTION (OTHERS LIKE – TOBACCO, MARIJUANA)	15	10.0

3. Microbiology

		Frequency	Percent
EPTB/TB	DISSEMINATED TB	1	.7
	EPTB	21	27.0
	EPTB+PTB	4	4.1
	PTB	53	68.2
AFB1	NEGATIVE	12	16.2
	SCANTY	7	10.1
	1+	6	8.8
	2+	10	14.2
	3+	5	7.4
	4+	1	.7
	NA	38	42.6
AFB2	NEGATIVE	3	4.1
	SCANTY	2	3.4
	1+	4	5.4
	2+	3	4.7
	3+	3	4.7
	NA	64	77.7
CBNAAT	MTB DETECTED R SENSITIVE	15	20.3
	NOT PERFORMED	64	4.1
Total		79	100.0

4. LEFT

LFT		DILI	
		n	%
Total Bilirubin	≤ 1.0	41	51.9%
	1.1 - 3.0	24	30.4%
	3.1 - 5.0	6	7.6%
	> 5.0	8	10.1%
SGOT	≤ 35.0	6	7.6%
	35.1 - 105.0	28	35.4%
	105.1 - 175.0	20	25.3%

	> 175.0	25	31.6%
SGPT	≤ 35.0	11	13.9%
	35.1 - 105.0	32	40.5%
	105.1 - 175.0	13	16.5%
	> 175.0	23	29.1%
SAP	≤ 140	34	43.0%
	141 - 420	42	53.2%
	> 420	3	3.8%
Albumin	≤ 1.5	0	0.00%
	1.5 - 2.5	24	36.40%
	2.5 - 3.5	39	59.10%
	> 3.5	3	4.50%
Total		79	100.0%

5. Alternate Regimens

	Alternate Regimen												total
	E-levo		H E Levo		Hre		Re-levo		S E Levo		Other		
	n	%	n	%	n	%	n	%	n	%	n	%	n
DILI	19	24	11	16%	20	25%	0	0.0%	15	18.0%	14	17%	79

6. End Of IP Phase

DO INITIAL CLINICAL SYMPS PERSIST (AFTER 2 MTHS)	Frequency	Percent
DEATH	1	2.0
LOST TO FOLLOW UP	2	2.7
asymptomatic	57	71.6
symptomatic	19	23..6
Total	79	100.0

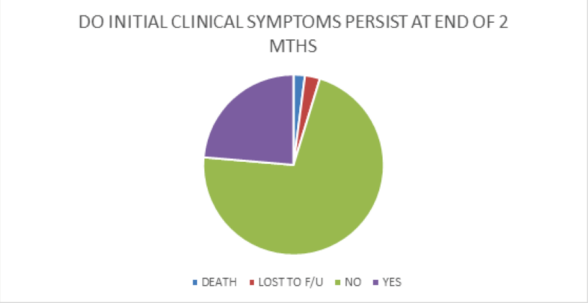
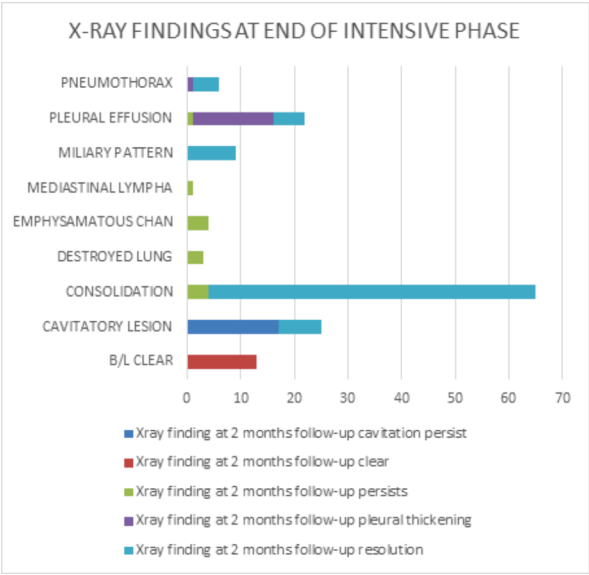


Fig 1. End Of Ip Phase

7. X-ray Findings And Changes At End O

		Xray finding at 2 months follow-up										Total	
		cavitation persists		Clear		persists		pleural thick-ening		re-solution			
		n	%	n	%	n	%	n	%	n	%	n	%
Xray findings at the time of pre-senta-tion	B/l Clear	0	0.0	6	100.0	0	0.0	0	0.0	0	0.0	6	
	Cavi-tatory Lesion	9	68.0	0	0.0	0	0.0	0	0.0	4	32.0	13	
	Consoli-dation	0	0.0	0	0.0	2	6.2	0	0.0	34	93.8	36	
	Des-troyed Lung	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	1	
	Emphys ematous Chan	0	0.0	0	0.0	2	100.0	0	0.0	0	0.0	2	
	Media-stinal Lympha deno-pathy	0	0.0	0	0.0	1	100.0	0	0.0	0	0.0	1	
	Miliary Pattern	0	0.0	0	0.0	0	0.0	0	0.0	5	100.0	5	
	Pleural Effusion	0	0.0	0	0.0	1	4.5	7	68.2	3	27.3	11	
	Pneumot horax	0	0.0	0	0.0	0	0.0	1	16.7	2	83.3	3	



In our study maximum number of patients belonged to age group of 21 to 60, with more males that is 64.3% being affected by DILI. Most of these patients belonged to the lower middle class with majority having lower BMI. 37.3% had history of alcohol intake whereas 31.1% were smokers and 10% had other addictions. .7 percent were patients of disseminated TB, 68.2% were suffering from PTB and 27% had EPTB. 4% had PTB with TB. All these patients showed deranged LFT and their ATT was modified in accordance and the most commonly prescribed non standardised regimen were HRE, E-LEVO, SE-LEVO. At the end of IP phase 57 patients reported improvement, 19 had persisting complains, 1 patient dies and 2 were lost to f/u. Radiological follow up showed that, most patients reported with consolidation at the beginning, out of which 34 reported resolution at end of IP phase. Patients with miliary pattern, effusion and pneumothorax mostly improved radiologically. 2 patients had fibrotic change.

DISCUSSION

All the patients in our study were switched to Non- standardized ATT within a period of one month of being diagnosed with TB

Age

In our study, mean age was 45.9 ±18.3 years. Comparable to the study of interruption of ATT due to various side effects 46.9% of the defaulters were in the age group of 20-35 years, followed by 31.3% in the age group of 36-50 years [11].

In other studies of incidence of serious side effects from first line antituberculosis drugs among patients treated for active tuberculosis between 1990 to 1999 resulting in discontinuation or modification of therapy the age group most affected was 60 years and above which was higher as compared to our study[12]

Similarly in a study by Huang-Shen Lin et al it was concluded by comparison between different age groups, that the older age group more frequently had hepatitis, gastrointestinal upset, and unfavorable outcomes highlighting higher rates of adverse drug reactions and unfavorable outcomes [13]

Gender

In the present study, 36.7 percent patients were females and 64.3% patients were males. Comparable to incidence of serious side effects of ATT in the study by Daphne Yee et al where 65% affected patients were male and 35% patients were female [12]

Female gender has been related with development of drug-induced hepatitis in two studies [14, 15] but not in other two studies [16, 17]. These contradictory observations, though inconclusive, suggest that closer monitoring of females during antituberculosis therapy is needed

BMI and Addiction

46.8% of the patients presenting with DILI had a mean BMI of less than 18.5. 44% of the patients who presented with DILI had history of alcohol consumption. Most of the patients presenting with DILI in our study had higher ALP, with 57% having ALP > 140. Abbara, Aula et al

concluded that Risk factors for DILI were: low patient weight, HIV-1 co-infection, higher baseline ALP, and alcohol intake.[18]

Radiography

Chest x-ray done in our study were suggestive of consolidation seen in 36 patients, cavitatory lesion in 13, effusion in 11, miliary pattern in 5, and pneumothorax in 3, destroyed lung in 1, mediastinal lymphadenopathy in 1 patient.

DILI

In our study Non- Standardised ATT was started on basis of the deranged lab tests

The criteria used to diagnose DILI- elevation of transaminases up to 5 times the upper limit of normal (ULN) in the absence of symptoms and up to 3 times the ULN or twice the ULN of bilirubin in the presence of symptoms [l]

In our study 7.6% patients had bilirubin 3 times the ULN, 10.1% patients presented with bilirubin >5mg/dl. 25% had SGOT thrice the ULN, and 31.6% had it five times the ULN. 13% patients had SGPT three times the ULN, whereas 29% presented with SGPT five times the ULN

In a study carried out by Dhiman RK et al in 2012 demonstrated that the greatest challenge in the patient with CLD or liver cirrhosis and tuberculosis is managing the therapy since the best first-line anti-tuberculosis drugs are hepatotoxic and baseline liver function is often deranged. It was concluded that that pyrazinamide should be avoided in ATT being given to patients with hepatotoxicity [19]

As seen our study the alternate regimen of levofloxacin, and ethambutol was started after the development of DILI in 19 patients (24 %), 20 patients were started on HRE (25%), 15 patients on SE LEVO (18%)

In a study conducted by Udwadia et al (reference)about tuberculosis management by private practitioners in Mumbai, HRE, SHRE, HREZ+ Levofloxacin were some of the non -standardized regimens prescribed, that were also few of the regimens prescribed in our patients [20]

Our study included patients in whom ATT could not be reintroduced successfully.

In a similar study of Daphne Yee et al rechallenge with possibly responsible drugs was attempted 21 times. “Only 3 of the 12 patients with hepatitis were rechallenged—none successfully, compared with 11 of 21 with rash/drug fever—1 successfully, and 7 of 11 with GI intolerance—2 successfully” [21]

CONCLUSION

HRE was the most common non-Standardised regimen that was prescribed, followed by Emb-Lfx, and Sm-Emb-Lfx. The most toxic first line drug was pyrazinamide that could not be given in patients of DILI. Most of the patients showed resolution in both symptoms and X-Ray findings at the end of intensive phase. No patient developed any intolerance or reaction to the modified regimen

Future Directions

The study has potential to give valuable information to health system, policy makers in India to use the information for development of ATT guidelines, especially in terms of number of drugs to be given, follow up schedule, and optimum duration of therapy in patients subjected to treatment with non standardised ATT Patient should be followed up for full length of treatment -radiologically and microbiologically to decide the optimum time of treatment in all such non standardised regimens, moreover there is need for expert group recommendation regarding treatment completion in such cases

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