OUTCOME OF MODIFICATION OF REINTRODUCTION THERAPY IN PATIENTS WITH ANTI-TUBERCULOSIS DRUG INDUCED HEPATOTOXICITY

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ABSTRACT

Anti-tuberculosis drug induced hepatotoxicity (ATDH) is a significant problem in the developing countries as well as in Myanmar owing to high disease burden of tuberculosis, limited facilities for diagnosis and monitoring methods. This study aimed to find out the outcome of modification of reintroduced standard anti-TB drug regimen in patients with anti-TB drug induced hepatotoxicity. In a hospital based prospective interventional study, a total of 62 patients who fulfilled the criteria of ATDH were enrolled. All hepatotoxic anti-TB drugs were stopped. Once the study population were recovered from hepatotoxicity, standard anti-TB drugs were reintroduced sequentially in accordance with American Thoracic Society guideline, 2006. Pattern of hepatotoxicity, severity of liver injury and outcome of ATDH were evaluated. Hepatocellular pattern of liver injury was predominant in 50% of studied subjects. Almost all patients (98.4%) had moderate severity index of liver injury. All the participants (100%) were fully recovered from liver injury after withholding their anti-TB drugs ($p < 0.001$). Eighty point six percent of the study population was tolerated to sequential reintroduction of standard anti-TB drugs, however, recurrence of hepatotoxicity was identified in 19.4% of patients. This study highlighted that (1) standard anti-TB drugs with a potential to cause hepatitis could be safely reintroduced in most of the studied patients after recovery from ATDH, (2) sequential reintroduction of standard anti-TB drugs per ATS guideline could be one of the treatment option for ATDH.

Keywords: ATDH, Reintroduction therapy, Outcome

INTRODUCTION

Tuberculosis (TB) has existed for centuries and remains a major cause of morbidity and mortality worldwide despite significant improvement in socioeconomic and medical sciences. Around 10 million people fall ill with the disease each year, and TB is one of the top 10 causes of death. With the devastating social and economic impact, Myanmar has TB incidence of 358 per 100 000 populations and 51 per 100 000 population dying of TB in 2017[1]. The mainstay of TB treatment includes isoniazid (INH), rifampicin (RIF), pyrazinamide (PZA) and ethambutol (ETB) identified more than 3-4 decades ago. Six-month combination treatment of these standard drugs achieved high efficacy in cure rates around 95%[2]. However, some adverse events attributable to anti-TB treatment pose serious threat to the patients.

Of which, hepatotoxicity is the most significant, leading to drug discontinuation in 11% of patients[3] or treatment has been changed to non-hepatotoxic anti-TB regimens, but efficacy of which have not been tested systematically[4]. Despite decades of experience in the use of anti-TB drugs, treatment of underlying TB after the development of hepatitis continues to be bothersome. There are a broad range of

guidelines such as British Thoracic Society (BTS, 1998)[5], American Thoracic Society (ATS, 2006)[4] and National Institute for Clinical Excellence (NICE, 2011)[6], that recommend reintroduction of standard anti-TB drugs after ATDH is resolved. The present study applies ATS protocol in which anti-TB drugs are reintroduced sequentially with the advantage of ease of administration, identification of causative agent in the event of hepatotoxicity recurrence and possibility of mitigating the risk of recurrence through hepatic adaptation. Along with this effort, this study aimed to demonstrate more favorable outcome and provide some information for future studies to develop safer management of tuberculosis.

MATERIALS AND METHODS

This study was hospital based prospective interventional study conducted at Department of Tropical and Infectious Diseases, Yangon General Hospital during the period from January 2018 to April 2019. A total of 62 patients ≥ 18 years of age who had given written informed consent and who developed hepatotoxicity within 2 months of standard anti-TB treatment were involved in the study. Patients with acute viral hepatitis (Hepatitis A, B and C), chronic hepatitis or cirrhosis of liver on ultrasound, those who did not recover from hepatotoxicity more than 4 weeks after stopping anti-TB drugs, pregnancy, HIV patients taking ART and prophylactic treatment for opportunistic infection, patients with abnormal liver function tests before initiation of anti-TB drugs were excluded from the study. Thorough history taking and physical examination were recorded on the proforma.

Radiology and laboratory tests

Chronic hepatitis and cirrhosis of liver were excluded by Ultrasound examination. Blood tests were done to determine serum bilirubin, AST (aspartate aminotransferase) and ALT (alanine aminotransferase), ALP (alkaline phosphatase), international normalized ratio (INR), serum albumin, serology for hepatitis B surface antigen, hepatitis A, C and HIV antibody.

Criteria for ATDH **(a**s defined by American Thoracic Society, 2006[4])

For labeling ATDH, any one of the following criteria should be met:

- Rise in ALT ≥ fivefold increase from upper limit of normal without symptoms
- ≥ threefold rises in ALT concentration in the presence of hepatitis symptoms and/or jaundice
- Increase in bilirubin concentration > 1.5 mg/dl

Patterns of ATDH **(**criteria proposed by International DILI Expert Working Group[7])

Patterns are defined by using R-value where R = ALT activity/ALP activity.

- ALT activity = patient's ALT/upper limit of normal (ULN);
- ALP activity = patient's ALP/ULN;
- Hepatocellular pattern = R ≥ 5.
- Mixed pattern = R > 2 and < 5.
- Cholestatic pattern = R ≤ 2

Severity Index of ATDH **(**graded in accordance with International DILI Expert Working Group[7])

- Mild: Elevated ALT or ALP concentration reaching criteria for ATDH but bilirubin concentration < 2× upper limit of normal (ULN)
- Moderate: Elevated ALT or ALP concentration reaching criteria for ATDH and bilirubin concentration ≥2× ULN, or symptomatic hepatitis.
- Severe: Elevated ALT or ALP concentration reaching criteria for ATDH and bilirubin concentration ≥2× ULN, and at least one of the following:
  - INR ≥ 1.5.

- Ascites and/or encephalopathy, disease duration <26 weeks
- Other organ failure considered to be caused by drug induced liver injury.

- Fatal: Death or liver transplantation for drug induced liver injury

Reintroduction strategy of anti-TB treatment according to ATS, 2006

Treatment of INH, RIF, and PZA was immediately stopped in patients with ATDH. They were managed with non-hepatotoxic drugs comprising of ethambutol, streptomycin and levofloxacin. Patients with moderate and severe ATDH were admitted to hospital. Clinical monitoring and weekly LFT were done till acute liver injury stabilized. Reintroduction was started with rifampicin with maximum dose as per body weight on day 1 followed by isoniazid on day 8 and adding pyrazinamide on day 15. Before introducing each drug, ALT was checked. If symptoms of hepatitis recur or ALT increases, the last drug added was stopped. After complete reintroduction, regular monitoring of LFT every week for the first month, every 2 weeks for the second month were done.

Data were collected and analyzed using SPSS statistical software version 16. Description of categorical data was expressed as frequency percent. Appropriate statistical test like Fisher exact test or Paired t test or Wilcoxon signed ranked test was used in data analysis. Information of patients were kept confidential. The study was started after approval by Research and Ethics Committee of University of Medicine-1, Yangon, Myanmar.

RESULTS

Pattern and Severity of ATDH

Among 62 subjects, majority of patients had hepatocellular pattern (50%) in 31 patients whereas mixed and cholestatic patterns represented (33.9%) in 21 patients and (16.1%) in 10 patients respectively (Figure 1). Only mild and moderate severity were determined in this study. 1 (1.6%) out of 62 patients had mild hepatotoxicity while 61 (98.4%) patients had moderately severe hepatotoxicity (Figure 2).

Recovery of ATDH

Mean serum bilirubin, AST, ALT& ALP at baseline (at the time of ATDH) and after stabilization were shown in Table (1). All the patients were fully stabilized and recovered from ATDH ($p < 0.001$).

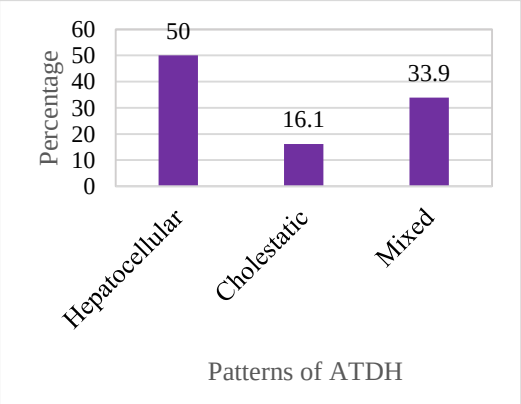

Figure (1) Patterns of liver injury among patients with ATDH

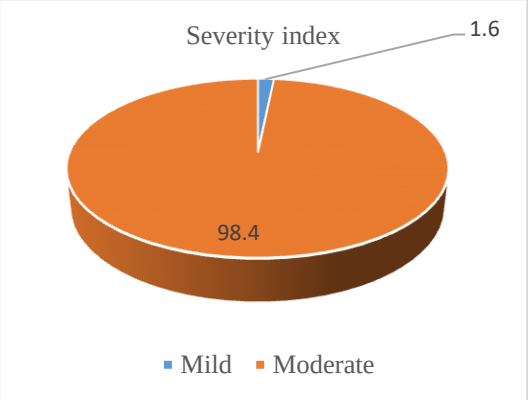

Figure (2) Severity index among patients with ATDH

Table (1) Comparison of liver function tests between baseline and after stabilization prior to reintroduction of anti-tuberculosis drugs

Parameters of liver function test	Baseline (at the time of ATDH)	After stabilization	Paired t test (p value)
	Mean ± SD	Mean ± SD	
Serum Bilirubin	3.9±3.4	0.78±0.28	<0.001
Serum AST	310.1±248.8	27.3±7.2	<0.001
Serum ALT	241.3±159.4	22.2±6.8	<0.001
Serum ALP	205.1±143.7	110.3±44.4	<0.001

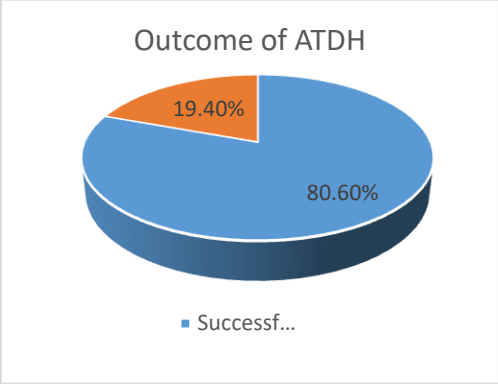

Figure (3) Outcome of ATDH after complete reintroduction of anti-TB drugs

Comparison of mean serum ALT between stabilization and after reintroduction of each anti-TB drugs

Among successful and recurrent cases of ATDH, mean serum ALT one week after reintroduction of RIF was not significantly different from stabilization (20.8 U/L VS 22.2 U/L). On rechallenge with combination of RIF and INH, reintroduction was successful in 55 out of 62 patients. In the remaining 7 patients, hepatotoxicity was reappeared as mean serum ALT one week after combined drugs was found out to be 187.2 U/L VS 24.6 U/L. Mean serum ALT in the 55 successful cases was 42.7 (±53.3) U/L. Furthermore, when 55 patients were reintroduced with combination of RIF, INH and PZA, all drugs were safely reinstituted in 50 out of 55 patients. Mean serum ALT in 5 recurrent cases was significantly raised (141.2 U/L VS 24.3 U/L) whereas in 50 successful cases, it was found to be 34.5 (±35.4) U/L. Successful group was followed up for 2 months, in which mean serum ALT was 22.2 (±8.5) U/L (Figure 4).

Outcome of ATDH

Successful outcome which was defined by the absence of recurrence of hepatotoxicity within 2 months was figured out in 50 out of 62 (80.6%) studied subjects. Recurrent hepatotoxicity was identified in 12 out of 62 (19.4%) patients (Figure 3).

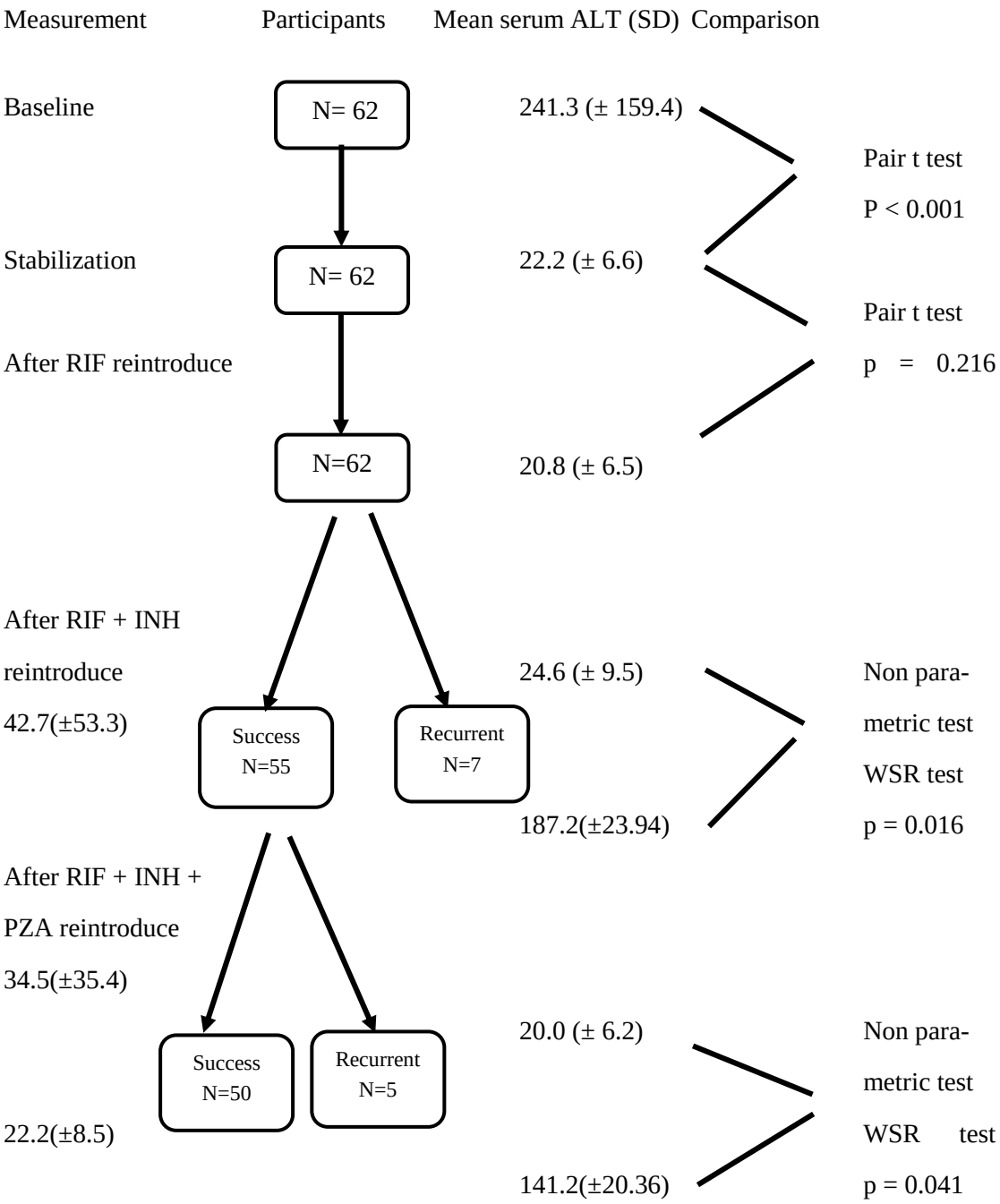

Figure (4) Serum ALT between baseline, stabilization, after reintroduction of each antiTB drugs among successful and recurrent cases

DISCUSSION

Most cases of ATDH are thought to be an idiosyncratic reaction due to the metabolites released during the metabolic process. Idiosyncratic mechanism of liver damage can manifest as direct hepatocellular damage, cholestatic pattern of liver injury, steatosis/steatohepatitis, granulomatous hepatitis, autoimmune hepatitis, fibrosis, oncogenesis, immunoallergic and vascular collapse[8].

All three major patterns of ATDH were present in this study. Most prevalent pattern was hepatocellular followed by mixed and cholestatic type that was in accordance with the findings from Pakistan study[9]. Although calculated pattern of injury does not always match the histologic picture, recognizing them can help narrow down the list of competing diagnoses that need to be considered when liver biopsy is not readily feasible.

In the present study, only mild and moderate severity was observed, however, other studies[10,11] have shown mild, moderate, severe and very severe hepatotoxicity with anti-TB treatment. The discrepancy was owing to different classification system used in those studies, prior exclusion of acute and chronic liver diseases, and also small sample size of the present study.

In agreement with previous studies[12,13], all patients have fully recovered from liver injury since withdrawal of anti-TB drugs. No patients experienced worsening of their clinical condition while awaiting recovery from liver injury. Hence outpatient follow up approach can be adopted for monitoring of these patients.

After the development of ATDH, treatment of underlying tuberculosis is rather difficult, whether these patients should leave their tuberculosis untreated or treat them with either non-hepatotoxic anti-TB drugs, or reintroduction of effective but potentially hepatotoxic drugs. There is dramatic difference in cost, efficacy and length of therapy between first line and second line anti-TB drugs that underlies positive efforts to maintain and reintroduce first line drugs.

Successful outcome was identified in 80.6% of patients whereas recurrent hepatotoxicity was identified in 19.4% of study populations. Tolerance of rechallenge in similar way was recognized in former studies as well [9,12,13,14,15]. In fact, hepatitis should recur on rechallenge with same agents in most of the patients, but it didn't. A possible explanation could be their improved general wellbeing and nutritional status after they had received anti-TB treatment for some time and sequential reintroduction might reduce the risk of recurrence through the process of hepatic adaptation.

In the reintroduction process, rifampicin was relatively a safe drug in comparison with isoniazid considering all cases were tolerant to rifampicin. It rarely causes serious liver injury, instead it can lead to increase in serum conjugated bilirubin levels due to interference in the transport process[16]. However, addition of isoniazid led to recurrence of hepatotoxicity in 11.3% (7 out of 62) of patients in the present study. One study[17] showed development of hepatotoxicity in 0.6% patients with isoniazid alone and 2.55% with regimen containing isoniazid and rifampicin.

Finally, inclusion of pyrazinamide in the reintroduction regimen causes hepatotoxicity (9.09%) of all the remaining patients (5 out of 55). In the study conducted in Turkey[18], there was no recurrence of hepatotoxicity on reintroduction of anti-TB drugs excluding pyrazinamide. Additionally, combination of

isoniazid, rifampicin and pyrazinamide increases the risk of anti-TB drug induced hepatotoxicity[19]. In the present study, management after recurrence of ATDH was individualized and second re-challenge was not attempted.

Overall, 19.4% recurrence of ATDH was documented in this study which was slightly higher than previous studies[9,12,13]. The higher frequency of recurrence in the present study might be due to smaller sample size of the study and the possibility of alternative diagnosis like autoimmune hepatitis, acute hepatitis E infection and genetic factors could not be ruled out.

Conclusion

Managing anti-tuberculosis drug induced hepatotoxicity is challenging for clinicians although it is a frequently reported clinical problem in daily practice. This study highlighted that (1) standard anti-TB drugs with a potential to cause hepatitis could be safely reintroduced in most of the studied patients after recovery from ATDH, (2) sequential reintroduction of standard anti-TB drugs per ATS guideline could be one of the treatment option for ATDH and (3) balance should be made between recurrence of liver injury and re-challenge of anti-TB drugs.

CONFLICT OF INTERESTS

The authors had no conflict of interests.

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