ORIGINAL ARTICLE

Comparison of British Thoracic Society and American Thoracic Society reintroduction guidelines for anti-tuberculous therapy induced liver injury

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Abstract

Objective: To compare the efficacy of British Thoracic Society and American Thoracic Society guidelines for re-introduction of anti-tuberculous therapy after drug-induced liver injury, and to assess the ease of administration of each guideline on a scale of 1-10.

Methods: The randomised prospective interventional study was conducted at the Department of Medicine and Pulmonology, Dow University of Health Sciences, Karachi, from December 2011 to November 2013. Patients with anti-tuberculous therapy drug-induced liver injury were selected. Hepatotoxic anti-tuberculous therapy was stopped and modified anti-tuberculous therapy was started. Patients were followed weekly till clinical and biochemical parameters got stabilised. After stabilisation, the patients were randomised to one of the two groups to receive re-introduction of anti-tuberculous therapy under the guidelines of British Thoracic Society (Group I) or those of American Thoracic Society (Group II). Means of the groups were analysed by Student's t test and proportions were compared by chi-square test. Multivariate analysis was done for age, body mass index and serum albumin for recurrence of drug-induced liver injury after the re-introduction. P value <0.05 was taken as significant.

Results: Of the total 325 patients, 163(50.15%) were in Group I, while 162(49.84%) were in Group II. The frequency of recurrence of drug-induced liver injury in Group I was 16 (9.8%) and in Group II it was 18 (11.1%). There was no statistically significant difference between the two groups (p<0.7). Age was positively related with drug-induced liver injury, while body mass index and serum albumin were negatively associated.

Conclusion: There was no significant difference between the two major guidelines though the American Thoracic Society guideline was easier to follow.

Keywords: Drug Induced Hepatitis, DILI, Anti-tuberculous drugs, ATT re-introduction. (JPMA 64: 896; 2014)

Introduction

Tuberculosis (TB) is still an important cause of morbidity and mortality in Pakistan with Multi Drug Resistant (MDR) TB rate of 2.4% in new cases and with a steady increasing trend for resistance.[1,2] About 9.4 million people develop TB every year around the world out of which approximately 297000 are in Pakistan.[3] Worldwide number of deaths due to TB is about 2 million per year.[4] With a large proportion of population suffering from TB, problem of Drug Induced Liver Injury (DILI) due to Anti-Tuberculous Therapy (ATT) is also evident.[5] It has been reported that about a quarter of patients on ATT develop DILI during the course of ATT with a mortality rate of 22.7%.[6] The mortality is higher in patients who develop ascites or encephalopathy.[6] Although ATT-DILI is reported more frequently in males, but it carries higher mortality in females.[7]

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DILI is a diagnosis of exclusion. The time of onset is usually within weeks of the start of the offending drug, with resolution of disease on withdrawal of the offending drug.[8] There are many mechanisms for pathogenesis of DILI, but mostly the exact mechanism remains unclear. These include direct toxicity of the compound or its metabolite, free radicals, immune mediated injury and hypersensitivity reactions.[9] With the 'First Pass' circulation that delivers ingested drugs from splanchnic circulation directly to the liver, major brunt of the injury is borne by the liver. This is followed by the Phase-I pathway which is carried out principally by cytochrome P450. In Phase-I major processes employed are oxidation, reduction or hydrolysis. Phase-II pathway causes conjugation making compound that could be excreted readily. In this phase major processes used are of glucuronidation, sulphation, acetylation and glutathione conjugation. This is followed by Phase-III pathway in which cellular transport proteins facilitate excretion of these compounds via bile or systemic circulation.[10] Three of the first-line drugs are hepatotoxic, pyrazinamide is the most toxic followed by isonicotiny lhydrazine (INH) and rifampicin.[11] Combination of rifampicin with pyrazinamide is more toxic than with INH.[12,13]

Treating ATT-DILI properly is very important for proper management and re-introduction of ATT. There are several guidelines by different societies and organisations having different protocols for the re-introduction of ATT after DILI.[10,14,15] These guidelines recommend protocols that differ with each other and one wonders which one to follow. The current study was designed to compare two re-introduction regimes as advised by British Thoracic Society (BTS) and the American Thoracic Society (ATS) in terms of efficacy and ease of administration and follow-up. This will enable the doctors to make a well-informed choice for which recommendation to follow in the patients.

Patients and Methods

The randomised prospective interventional study was conducted using consecutive sampling technique at the Department of Medicine and Pulmonology, Dow University of Health Sciences (DUHS), Karachi, from December 2011 to November 2013. Patients of either gender of age 18-60 years with ATT-related DILI were selected and informed consent was obtained from them. The sample size was calculated using reported 10.9% occurrence of DILI after ATT and keeping confidence interval (CI) of 95% and precision of 0.05. The required sample size was 150 patients.[16] The sample size was also calculated using the means of outcome, but as it was smaller than 150, it was not used.

DILI was defined if any one of the three criteria was satisfied: increase in Alanine transaminase (ALT) of $\geq$5 times the upper normal limit (UNL) on one occasion; increase in ALT of $\geq$3 times UNL on 3 consecutive occasions; and increase in Bilirubin of >1.5mg/dl.

Those who were excluded from the study were cases with serological evidence of acute viral hepatitis; ultrasonic evidence of chronic liver disease; Human immunodeficiency virus (HIV) positive; consumption of >48g of alcohol/day for the preceding one year; concomitant use of hepatotoxic drugs (methotrexate, phenytoin, valproate, fluconazole); pregnancy; mono and multi drug resistant TB; and category-II TB.

Hepatotoxic ATT [(Isoniazid (H), Rifampicin (R) and Pyrazinamide (Z)] were stopped, and modified ATT consisting of Streptomycin, Ethambutol and Quinolone-Moxifloxacin (SEQ) was started. Patients were followed up weekly till clinical and biochemical parameters were stabilised. This period was termed normalisation period. Stabilisation was defined as: bilirubin<1 mg/dl; ALT <100 IU/L.

After stabilisation patients were randomised using random tables to one of the two groups to receive re-introduction of ATT by BTS Group I or ATS Group II. During re-introduction of ATT, liver function tests (LFTs) were done before the introduction of the new drug. After re-introduction, LFTs were repeated on weeks 1, 2, 3, 4, 6, 8 and12.

Group I received the re-introduction as H=100mg/day from day 1, maximum dose from day 4; R=150 mg/day from day 8, maximum from day 11; and Z=500 mg/day from 15, maximum from day 18.

Group II received the re-introduction as R=maximum dose from day 1, H=maximum dose from day 8, Z=maximum dose from day 15.

Care-givers were also asked to rank ease of administration of the re-introduction of both schedules on a scale of 1-10; 1 being the easy while 10 being the difficult.

Means of groups were analysed by Student's t-test. The proportions were compared by chi-square test. Continuous variables with skewed distributions were compared by Mann-Whitney Test. Univariate analysis was done to identify variables having significant effect on relapse of DILI after the re-introduction of ATT. Variables identified as significant were then analysed by multivariate linear regression analysis to see if the variables significantly related with relapse of DILI. P<0.05 was taken as significant. SPSS version 22.0 was used for analysis.

Results

Of the 327consecutive patients selected for study, 2(0.6%) refused to follow the study protocol before randomisation into groups, and thus the final study sample comprised 325 patients. Group I consisted of 163(50.15%) patients, while Group II had 162(49.84%). Demographic details of the subjects were noted (Table-1) and no significant difference was found in any parameter between the two groups. The mean stabilisation time in Group I was 3.3±1.6

Table-1: Comparison of demographic details.

	Group		P value
	Group-I (BTS) Mean±SD	Group-II (ATS) Mean±SD	
Age (years)	35.9±9.9	33.9±9.3	0.26
BMI	18.5±0.7	18.4±0.7	0.46
Stabilisation (weeks)	3.3±1.6	3.2±1.2	0.35
Bilirubin (mg/dl)	0.82±0.1	0.84±0.08	0.133
ALT (IU/ml)*	55.5±14.0	53.8±14.0	0.296
Albumin (mg/dl)	3.3±0.4	3.1±0.3	0.72

*Mann-Whitney Test applied.
BMI: Body mass index.
ALT: Alanine transaminase.

Table-2: Univariate analysis.

Variable	Adjusted R Squared	F (df)	Sig.
Age	0.345	171.47 (1)	< 0.001*
Stabilisation weeks	0.418	233.76 (1)	< 0.001*
Bilirubin	0.002	1.73 (1)	0.19
ALT	0.337	185.37 (1)	< 0.001*
BMI	0.201	82.35 (1)	< 0.001*
Albumin	0.332	154.97 (1)	< 0.001*

P < 0.05.
ALT: Alanine transaminase.
BMI: Body mass index.

Table-3: Multivariate Linear Regression Analysis.

Variables	Standardized Coefficients	T	Sig.
Age	0.109	2.036	0.043
Stabilisation	0.456	9.158	< 0.001
BMI	-0.059	-1.110	0.268
Albumin	-0.326	-5892	< 0.001

BMI: Body mass index.

weeks while that in Group II was 3.2±1.2 weeks. The difference was not significant. The frequency of recurrence of DILI in Group I was 16 (9.8%) and in Group II it was 18(11.1%) (p<0.17).

Details of relapse of DILI after the re-introduction in Group I was H (1), R (4), Z (11) and that in Group II was R (5), H (1) and Z (12). The most common symptoms at relapse were nausea 32 (94.1%), vomiting 22 (67.3%), abdominal pain 10 (29.4%) and jaundice 17 (50%).

Opinion about ease of administration regarding the two re-introduction regimens was significantly in favour for ATS guidelines. Mean score of ATS guideline was 2.1±0.9 and that for BTS was 7.3±1.1 (p<0.001).

To see the impact of age, bilirubin, ALT, body mass index (BMI), serum albumin and duration of weeks taken for stabilisation; a univariate analysis was done to identify the factors having individual relation with relapse. Multivariate analysis of age, bilirubin, ALT, BMI and serum albumin with relapse of DILI was also done (Table-2). Factors identified having significant effect on relapse of DILI after the re-introduction of ATT on multivariate linear regression were age (p<0.043), stabilisation weeks (p<0.001) and serum albumin (p<0.001), while BMI did not show any significant impact (Table-3).

Discussion

DILI is essentially a clinical diagnosis of exclusion. Aggravation of liver enzymes after the re-introduction is diagnostic, but at the same time could be lethal. Other tests are inconclusive and liver biopsy is rarely done in such cases. Avoidance of the offending drug is curative in most cases. The presence of lymphocytic infiltrates in liver points to a role of immune mediated mechanism for DILI.[17] Pathogenesis involves drug or its metabolite that induces injury either by immune related mechanisms or by directly affecting the biochemistry of cell, leading to its death that in turn causes the symptoms.[9] A feature characteristic of ATT is the development of tolerance which is manifested by the elevation of ALT and bilirubin without any symptoms and their resolution with continued therapy.[18] This phenomenon should be recognised to prevent inadvertent stoppage of ATT.

The current study did not find any significant difference between the re-introduction regimen by BTS and ATS guidelines. In a similar study conducted in India, comparisons were made with different re-introduction regimens and it also did not find any significant difference.[16] It reported a relapse rate of 10.9% which is also similar to our findings. The frequency of symptoms in our study was slightly higher in our study compared to the Indian study. This could be due to slightly less BMI of our patients (18.5) than the Indian subjects (19.5).[16] BMI and albumin are negatively correlated with the occurrence of DILI.

As identified by our study also, alcohol consumption and presence of cirrhosis are risk factors for DILI that have been identified by other studies.[7] Recently Horita N, et al. reported decreased activity of normal living as a strong independent risk factor for the development of ATT-DILI.[19] High international normalised ratio (INR), presence of ascites and encephalopathy have been identified as poor prognostic markers.[7] In our study it was also noted that recurrence of DILI was most frequently reported by pyrazinamide in both groups followed by rifampicin. It has been reported earlier that both these drugs are most hepatotoxic.[20,21]

Role of liver biopsy to improve accuracy of diagnosis in possible cases of DILI is unknown. Suzuki et al. conducted a study using diagnosed cases of DILI and auto-immune hepatitis from Spanish and Mayo clinic databases and took opinion from four expert histopathologists who were blinded to the clinical and lab findings. Unanimous diagnosis for DILI was achieved in only 28% of cases and that for auto-immune hepatitis in 50% of cases.[22,23] Another important confounder is acute hepatitis E infection which in many ways may mimic DILI and has to be excluded.[23] Search for a reliable biomarker for predicting DILI is still unfruitful, but apolipo protein E has shown some promise in recent studies.[24]

The BTS and ATS guidelines for the re-introduction of ATT after DILI differ. While BTS takes a slow gradual incremental dose approach, ATS is easy to follow with step-wise re-introduction of drugs. In our study there was no significant difference between the frequencies of relapse of DILI in the two groups.

Conclusions

Diagnosis of DILI is still clinical and of exclusion. The re-introduction after ATT-DILI is to be taken with care and the study did not find any significant difference between the two major guidelines, but ATS was perceived to be easier to follow.

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