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RESEARCH ARTICLE

Adverse drug reaction monitoring of antitubercular drugs during intensive phase at tertiary care medical college hospital: A prospective study

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ABSTRACT

Background: Tuberculosis (TB) an infectious disease can cause serious economic burden to the country and to the patients. About quarter of the world TB cases are reported in India. As many newer and newer drugs emerge it creates newer and rare side effects which may lead to the discontinuation of the drug and finally end up in multi-drug resistant TB. Hence, monitoring of these related adverse drug reactions (ADRs) is very essential wherein the drug causing ADR can be detected and appropriate therapeutic regimen can be tailored to the patient and thus reduce the economic burden. **Aim and Objective:** The aim of the study was to assess the rate of prevalence of ADR with antitubercular drugs during intensive phase of treatment in Tirunelveli Medical College Hospital (TVMCH). **Materials and Methods:** The sample size of 100 patients who were diagnosed with pulmonary TB and undergoing treatment in TVMCH was observed for any adverse effects. The observed adverse effects were recorded using "Adverse Drug Reactions reporting form." The casualty and the severity assessment were done using WHO-Uppsala Monitoring Centre Criteria and Hartwig-Siegel Scale, respectively. **Results:** Among 100 pulmonary TB patients receiving fixed-dose combination pills the most commonly observed adverse effects are Nausea (20 cases), hepatitis (19 cases), gastritis (15 cases), and other side effects such as pruritus, abdominal cramps, and diarrhea. **Conclusion:** Early identification, reporting, and management of ADRs remain key factors in the treatment of a newly diagnosed TB patients. It can be revised even more to lower the severity levels and achieve elimination of TB.

KEY WORDS: Adverse Effects; Casualty Assessment; Severity Assessment; Hartwig-Siegel Scale; WHO- Uppsala Monitoring Centre criteria

INTRODUCTION

Tuberculosis (TB) is caused by an acid-fast bacilli *Mycobacterium tuberculosis*.[1-3] TB ranks the top among the infectious diseases with most deaths.[1,3] *M. tuberculosis* most often affects the lungs but also it affects almost all the other organs. Transmission of the disease is mainly through the droplets laden with the infectious *M. tuberculosis* expelled from the infected TB patients. The acid fastness of the bacteria is mainly because of the cell wall contents. The cell wall contains mainly mycolic acid, long chain cross-linked fatty acids, arabinogalactan and peptidoglycan. This makes the bacterial cell wall to be less permeable to antibiotics thus reducing the effectiveness.[1,2,4] This unique property of the bacteria creates a great challenge to produce effective antibiotics. According to WHO 95% of the world TB cases are mostly observed in developing countries which creates an economic burden in these countries impairing it's development. Another challenge which reduces the effectiveness of the antibiotics is resistance

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of the bacteria towards the antibiotics. Discontinuing or withdrawing the drug even for a short period, the bacteria may develop resistance against the drug which makes the condition even worse.

India is the country with the highest burden of TB, according to the World Health Organization statistics for year 2013 with an estimated incidence of 2.1 million cases of TB for India, out of a global incidence of 9 million with estimated TB prevalent cases of 2.6 million.[5] About 40% of the Indian population is infected with TB bacteria, the vast majority of whom have latent rather than active TB.[6] Recently, the burden of resistant TB is again emerging as a big challenge to India and by considering this, government of India announces TB as a notifiable disease in year 2012.[7]

At the beginning of 2020, the TB control program Revised National TB Control Program has been converted to National TB Elimination Program (NTEP) with a target of eliminating TB in India by 2025.[8] So the research on the obstacles which hinder us to reach the elimination status of TB becomes inevitable.

Due to the advancement of modern medicine TB disease can be cured with proper and continuous treatment. But if the patient takes the medicines irregularly which is mainly due to the side effects of the Anti-Tubercular treatment which lead to poor patient compliance and lead to the development of resistance and finally the rise of multi-drug-resistant (MDR) TB and extensively drug-resistant (XDR TB).[1,2] So the need to identify the adverse effects and precautions to reduce the side effects become very essential to raise the patients compliance and thereby reducing the drug resistant forms TB.

This study was aimed to disseminate the profile of adverse drug reactions (ADRs) in newly diagnosed TB patients under DOTS therapy for early diagnosis and immediate action for further improving the compliance of patient and complete cure of TB.

Objectives of the Study

The objectives of the study were to assess the rate of prevalence of ADRs with antitubercular drugs during intensive phase of treatment in Tirunelveli Medical College Hospital.

MATERIALS AND METHODS

Study Design

This study was prospective observational study.

Study Sample

100.

Study Duration

The study duration was 5 months.

Study Place

This study was conducted in the Department of Thoracic Medicine, Tirunelveli Medical College and Hospital, Tirunelveli.

Inclusion Criteria

The following criteria were included in the study:

- All new cases of pulmonary TB patients in intensive phase were included
- Patients of either sex visiting tertiary care hospital and diagnosed with pulmonary TB.

Exclusion Criteria

The following criteria were excluded from the study:

- MDR TB and XDR TB patients
- Patients with comorbid medical or surgical conditions were excluded except HIV infection.

Ethical Consideration

The study was approved by the Institutional Ethics Committee of Government Tirunelveli Medical College (TVMC) Tirunelveli.

Methodology

Institutional ethical committee approval was obtained. Patients of either sex visiting the tertiary care hospital and diagnosed with pulmonary TB were included in this study. They were treated with fixed dose combination (FDC) pills according to the current regimen given by RNTCP. These patients were continuously monitored for any side effects. Side effects due to the drugs were observed and recorded. System wise distribution of ADRs was tabulated by detailed clinical history; patient examination, relevant lab investigations, and correlation between the drug intake and onset of ADRs were noted. The occurrence of the side effects was statistically analyzed and presented in a pictorial representation. The system wise distribution of the adverse effects was presented in a bar graph.

WHO-Uppsala Monitoring Centre (UMC) causality assessment systems were used to categorize ADR as possible and probable.[9] The severity assessments were done by using modified Hartwig and Siegel scale.[10] The frequency and the percentage of the serious reaction were pictorially represented in a pie diagram. Then, the precautions taken on the basis of the observed side effects were also recorded and pictorially represented in a pie chart.

Statistical Analysis

Data analysis was done using SPSS software version and results were analyzed by descriptive statistics and expressed in percentage.

RESULTS

Among the 100 patients who are involved in the study 67 were male and 33 were female. Most of the patients fall under the age group of 41–55 (37%) followed by 26–40 (25%) and so on [Table 1].

Most of the observed side effects were due to gastrointestinal (GI) systems. The results of the observed side effects were as follows Nausea (20%), hepatitis (19%), gastritis (15%), vomiting (13%), diarrhea (9%), abdominal cramps (9%), Pruritus (9%), arthralgia (6%), headache (4%), and giddiness (3%). Hyperuricemia and rashes were seen in very minimal cases [Figure 1]

Table 1: Baseline characteristics

Characteristics	Percentage
Sex	
Male	67
Female	33
Age in years	
10–25	15
26–40	25
41–55	37
56–70	23
FDC pills/day	
2 pill/day	8
3 pill/day	61
4 pill/day	28
5 pill/day	2
6 pill/day	1

FDC: Fixed-dose combination

According to the WHO-UMC criteria, the frequency of the probable and the possible side effects was 47 and 66, respectively. The percentage of the probable and the possible side effects was 41.5% and 58.4%, respectively [Figure 2].

According to Hartwig-Siegel Scale, the seriousness of the reaction was about 20.3% and the reactions which were less severe were about 79.6% [Figure 3].

Frequency of system-organ classes involved in ADR induced by anti-TB drug was graphically depicted in Figure 4. In about 23% of the cases, the treatment regimen has been modified and in the remaining 77% of the cases the regimen was still continued with symptomatic therapy [Figure 5].

DISCUSSION

These results suggest that anti-TB drugs may cause more serious ADRs resulting in hospitalization compared with other drug classes used in infectious and general wards. Hepatitis was the most serious reaction observed in 19% which was mainly due to rifampicin or isoniazid. Those with altered liver transaminases either had their Antitubercular treatment (ATT) altered or were monitored closely depending on physician preference. Other serious ADR observed were hyperuricemia (2%) which was mainly due to pyrazinamide and elevated renal parameters

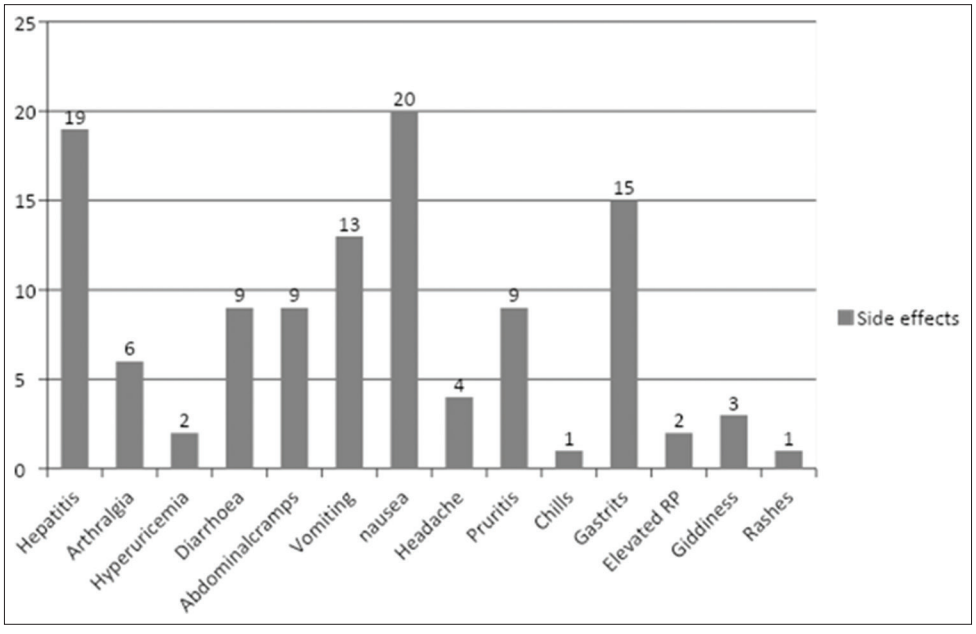

Figure 1: Side effects reported

(2%) which was mainly due to rifampicin. Others are GI side effects which can be managed by symptomatic therapy. No need to alter the ATT regimen due to these minor side effects. Hence, in this study, 23% patients need regimen modification and in 77% patients the regimen was continued with symptomatic therapy.

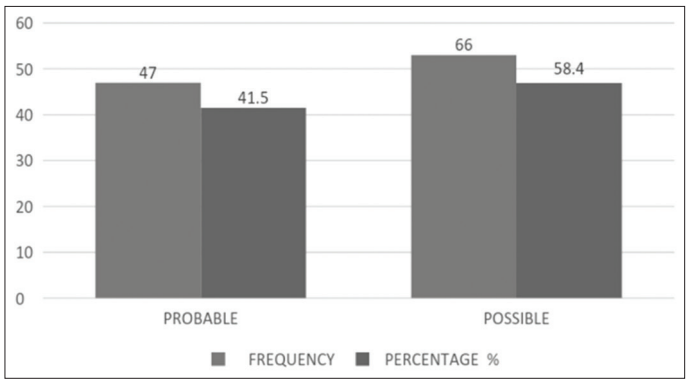

Figure 2: WHO-Uppsala Monitoring Centre causality scale

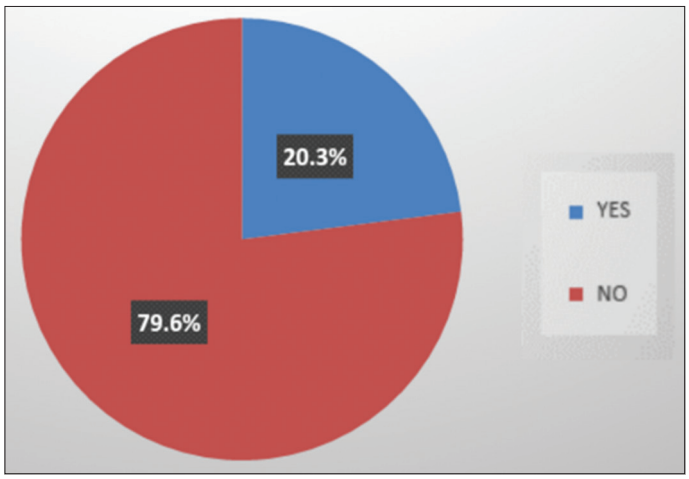

Figure 3: Seriousness of reaction

In the present study, TB was seen more in males compared to females which is similar to Bai *et al*. study.[11] Furthermore, the percentage of male patients was greater, 61.32% than female patients, 38.68% in a study conducted Patil *et al*.[12] and Vishakha and Sanjay[13] also reported higher percentage of male, 63.49% than female, 36.51%. A study conducted by Abideen *et al*.[14] reveals that, GI system, liver and biliary system was the most frequent organ system affected by ADRs which is similar to our study. While comparing the old weekly regimen study by Nanda *et al*.[15] and Törün *et al*.[16] to the present study of daily regimen, there was no visual or hearing problem. Kurniawati *et al*.[17] observed that majority of the cases of ADRs were skin related, present in 51 (7.8%) patients followed by hepatotoxicity in 17 (2.6%) patients, then GI reactions in 16 (2.5%) patients whereas in our study majority of cases were GI tract (GIT) related 66 (58.4%) followed by hepatotoxicity 19 (16.8%). Furin *et al*.[18] and Vishakha and Sanjay[13] have reported hepatotoxicity in single case (1.7% and 1.58%, respectively).

ADRs to the drugs used are one of the major reasons for the default of treatment. These events may incur substantial additional costs because of added outpatient visits, tests, and in more serious instances hospitalizations. Onset of the ADRs is an important factor helpful in early detection of the ADRs. It is essential for the health-care professionals to counsel the patients regarding the early identification of ADRs in the first few weeks. At the start of 2020, the central government has renamed the Revised National TB Control Programme as the NTEP,[11] achieving the sustainable development goal of ending TB by 2025.

Limitations

Data were obtained from patients attended outpatient and also inpatients in a tertiary care hospital mainly coming from rural area.

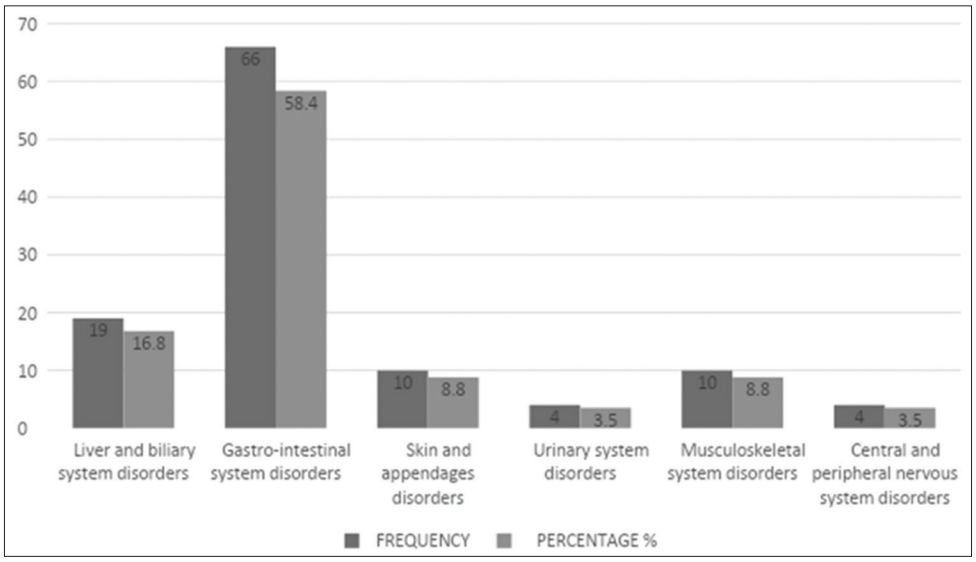

Figure 4: Frequency of system organ classes involved in adverse drug reactions induced by anti-tuberculosis drug

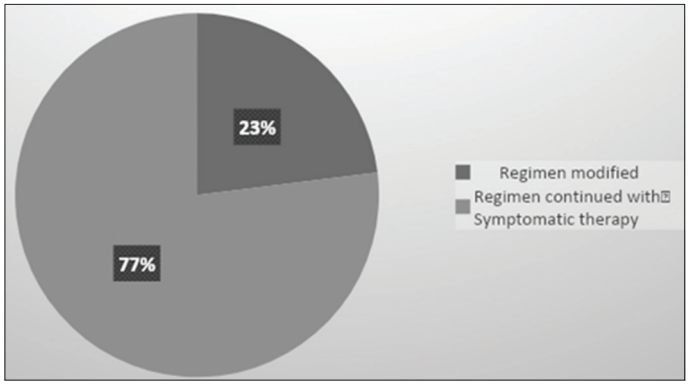

Figure 5: Action taken due to adverse drug reactions induced by anti-tuberculosis drugs

CONCLUSION

Anti-TB drugs could cause significant adverse effects both in quantity and severity. Hence, pharmacovigilance of antitubercular drugs is very much essential for successful treatment of TB and its elimination. Most of the adverse effects observed due to the FDC of ATT are GIT related adverse effects. These adverse effects can be overcome by symptomatic therapy, resulting in increasing the overall patient compliance.

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