RESEARCH ARTICLE

Adverse reaction monitoring in drug resistance tuberculosis patients in a Northern Karnataka district

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ABSTRACT

Background: Drug resistance tuberculosis (DRTB) is an important concern in India as it accounts, one-fourth of global burden. DRTB regimen is associated with adverse drug reactions (ADRs) accounting for significant mortality, non-adherence, and treatment discontinuation. Hence, the present study emphasis to be vigilant about these ADRs. Aims and Objectives: The aim of the study was to estimate the incidence, various types, and risk factors associated with adverse reactions in DRTB in Northern Karnataka district. Materials and Methods: A Prospective observational cohort study was conducted at Nodal DRTB center. All diagnosed and treatment initiated pulmonary DRTB patients during January–March 2021 aged ≥18 years of either sex were included, which constituted 70 patients. A pre-designed case report form was used to collect details like sociodemographic information, past history, personal history, and drug regimen along with their contact information of the DRTB patients. Results: Of 70 study participants, 64% were males and mean age was 36.7 ± 14.5 years with majority being resistant to rifampicin (52%). Incidence of ADR was 32 (46%) and commonly reported ADR were nausea (30%), gastritis (24%), vomiting (21%), arthralgia (9%), and peripheral neuropathy (9%). Causality assessment was done using “Naranjo algorithm,” majority were probable (79.01%) and as per the modified Hartwig and Siegel severity scale most ADR were mild (87.65%). The past history of TB and exposure to ATT was the major risk factor associated and was statistically significant ($P = 0.009$). Conclusion: ADRs are common in DRTB regimen early recognition and appropriate management might determine treatment adherence, prevent complications, and improve overall treatment outcome.

KEY WORDS: Adverse Reactions Monitoring; Multidrug Resistance Tuberculosis; Risk Factors

INTRODUCTION

Tuberculosis (TB) is a common communicable infectious disease caused by Mycobacterium tuberculosis and is ranked to be the top most infectious diseases causing deaths.¹¹ In 2020, the Government of India has renamed Revised National Tuberculosis Program (RNTCP) as the National Tuberculosis Elimination Program (NTEP).²²

According to new guidelines on programmatic management of drug resistance TB (DRTB) 2019 of India, DRTB: resistant to any of the anti-TB drugs. Based on the resistance, they are further classified as isoniazid-resistant, rifampicin resistant, poly-drug resistant (other first line drugs), or multidrug-resistant TB (MDRTB) which include first-line and second-line drugs too.¹¹ DRTB is an important concern in India as it contributes to one-fourth of global burden with an incidence of 9.6%.²⁴ DRTB is treated with shorter or
Drug resistance is a challenge, as it reduces the efficacy, increases incidence of treatment failure, relapse, and disease mortality. It is also a huge hindrance in the path to achieve TB elimination by 2025. Severe side effects and ADRs are one of the major reasons for non-adherence and discontinuation of the drug regimen. Withdrawal of drugs even for a short period can increase the resistance against the drug which may further worsen the condition.[7] This is supported by reviews conducted by the World Health Organization (WHO) treatment guidelines for multidrug and rifampicin-resistant TB, 2018 update, which had reported that Grade 3 (severe), Grade 4 (life-threatening or disabling), and Grade 5 (death related to adverse events) has led to the discontinuation of treatment and even stoppage of drug regimen permanently, which further has increased mortality.[8,9]

As there was a dearth of data in this particular area regarding the adverse events following MDRTB and also to assist the NTEP staff to improve the treatment out and maintain the standards of therapy, the present study was undertaken. The primary objective of the study was to estimate the incidence and various types of adverse reactions occurring among DRTB patients and secondary objective was to identify the risk factors associated with adverse reactions in DRTB patients of Northern Karnataka district.

MATERIALS AND METHODS

A prospective observational cohort study was conducted in the Nodal DRTB center of a Northern Karnataka district. The study was conducted after the permission from institutional ethics committee permission (ESICMC/GLB/IEC/13/2021) and also District TB Officer. All diagnosed and treatment initiated DRTB patients in 1st quarter 2021 (January–March) were enrolled in the study, which constituted a total of 70 patients and follow-up for 6 months. All TB case diagnosed of pulmonary DRTB aged ≥18 years of either sex and initiated on treatment and willing to give informed consent were included. Patients with deranged cardiac, liver, and renal function test at baseline or on highly active antiretroviral therapy regimen and pregnant women on DRTB regimen were excluded from the study.

A pre-designed case report form was used to collect details of the DRTB patients’ sociodemographic information, past history, personal history, and drug regimen along with their contact information from the Nodal DRTB center. The patients were counseled regarding the importance of adherence to treatment and common side effects due to anti-TB drugs at Nodal DRTB center. A document was provided to the study participants, containing the information regarding common side effects with pictorial representations of adverse drug events and contact details of investigators. Study participants and their treatment supporters were educated to inform immediately or note it down in case of acceptable ADR and provide the same information to the investigators. Study participants were followed up for 6 months, wherein during the 1st month follow-up was done weekly and later, monthly till 6 months based on the previous study information as most of the adverse reaction appeared during first few months of therapy.[7,10] Information regarding the ADRs among the study participants was shared with District TB officer, in timely manner depending on the severity of the event. ADR management was carried by the District TB officer, as per NTEP guidelines.

Statistical Analysis

All the data were entered in MS Excel and evaluated statistically with the help of SPSS software. The continuous variables were calculated as means and standard deviations and categorical variables were presented as frequencies and percentages. The Chi-square test was used to observe the association between the occurrence of ADRs and the categorical variables of the data. P ≤ 0.05 was considered statistically significant.

RESULTS

A total of 70 participants were enrolled during study period. Male sex was predominant (64%) and the mean age was 36.7 ± 14.5 years. The majority of the study subjects were males with 44(64%) and 26 (36%) were females showing male predominance. Out of 70 patients enrolled, majority were resistant to rifampicin 36 (52%), followed by isoniazid in 17 (24%) and rest 17 (24%) were resistant to isoniazid, rifampicin, and fluoroquinolones as represented in Table 1.

Incidence of ADR among the diagnosed and treated MDRTB patients in the first quarter was 32 (46%) as depicted in Figure 1. Table 2 describes the types and frequency of adverse reactions. The most commonly reported ADR were nausea (30%), gastritis (24%), vomiting (21%) followed by arthralgia (9%) and peripheral neuropathy (9%). However, some minor but important ADR reported includes rash and itching (7%), weakness in 3 (4%), and dizziness in 3 (4%) as shown in Table 2. One patient had severe ADR of vomiting for a month associated with nausea, reduced appetite, and depressive symptoms. Many patients had more than one ADR and these were seen commonly in initially 3 months of the therapy.
Risk factors associated with DRTB: the past history of TB was the major risk factor in development of MDRTB, as 37 (54%) patients were previously treated and showed statistically significant results with $P = 0.009$ and only 32 (46%) patients were newly diagnosed MDRTB cases. History of TB contact was another major risk factor in development of MDRTB, as 11 patient in the present study had history of TB contact, among which 9 (82%) of them had ADR and these results were statistically significant. Regarding the habits, 9 (86%) were alcoholics, 2 (100%) were smokers and 8 (89%) had history of tobacco chewing among the people who developed ADR. About the comorbidities, out of 7 diabetics identified in the study, 4 patients (57%) developed ADR. Among the different regimen, ADR was more common among shorter Injectable MDR regimen 18 (50%), followed by H mono/poly regimen 8 (47%) and all oral longer regimen 6 (35%) as depicted in Table 3.

Causality assessment was done using “Naranjo algorithm” and modified Hartwig and Siegel severity assessment scale was used for severity grading.[10,11] According to “Naranjo algorithm” 79.01% ADR were probable, 14.81% ADR were possible, 0.24% was certain ADR, and 0.37% were doubtful ADR. As per the modified Hartwig and Siegel severity assessment scale 71 (87.65%) ADR were mild and 10 (12%) was moderate ADR.

DISCUSSION

The present study was an attempt to understand the incidence and type of ADR among the patients on DRTB regimen. ADRs were seen in 46% of the treated individuals, and they were the main reason leading to the poor compliance or inappropriate therapy in DRTB treatment patients according to study. We also emphasized the study subjects upon taking the drugs together to prevent resistant during our monitoring visits. All these helped to build confidence and improve patient outcome. Hence, ADR monitoring and treating those ADRs as early as possible is important to make patients complaint and prevent the resistant burden.

The study showed male predominance and the mean age group was 36.7 ± 14.5. In a similar study by Shararo et al. and Patel et al. also, there was male predominance in cobordance with our study and the mean age was 29.58 ± 11.4 and 34.83 ± 12.19 years, respectively.[12,13] These indicated that DRTB is more common during the reproductive age group. Another study done by Ahmed et al., claimed that the mean age of study subjects was 35.86 ± 12.62 years and higher percentage of ADRs was seen in age group of >60 years.[14] Rifampicin resistance was the common type of resistance seen in the present study followed by isoniazid and then combination of rifampicin, pyrazinamide, and fluoroquinolones in that order. In a similar study isoniazid, rifampicin, and fluoroquinolone were the common type of resistance and hence most frequently used treatment regimen was capreomycin, levofloxacin, pyrazinamide, ethionamide/prothionamide, and cycloserin.[12] The incidence of ADR in our study was around 46% patients which is a huge number similar to studies done by Ahmed.
et al., Shararo et al., and Patel et al. with 61%, 59.1%, and 50%, respectively. Around 50–60% of patients on DRTB regimen may get one or the other ADRs. The ADR seen in present study was nausea, gastritis, and vomiting in majority of them and was managed symptomatically but one patient had severe vomiting for a month and required change of regimen. In small number of patients arthralgia, peripheral neuropathy rash, and itching was seen and one patient each had blurring of vision and hearing loss which required medical assistance and expert opinion to prevent future organ damage. A similar study also showed that gastrointestinal symptoms, anorexia, giddiness, and pain at injection site were the common ADRs reported and these ADRs were most commonly reported in the first 3 months of the initiation of therapy similar to the present study. Another similar study of Shararo et al., the most common ADR was nausea and vomiting followed by dyspepsia and abdominal pain and arthralgia and other minor ADRs included headache, insomnia and anorexia, similar to the present study. Another study by Patel et al., more than 50% of them were previous treatment similar to present study. After 6 months of treatment, 48.59% and between 6 and –24 months, 54.93% developed ADRs, and gastrointestinal disturbances was common ADR in both follow-up and other side effects such as headache, arthralgias, decreased hearing, and skin reactions were also reported like that of the present study. Average duration of ADRs was 60–90 days at both the follow-ups and 62.68% of all ADRs were managed by symptomatic treatment and dose reduction was done in 4.47% of the patients in 2nd follow-up. In a retrospective study about spectrum of cutaneous ADRs to anti-tubercular drugs pulmonary TB, maculopapular rash was the most common type of cutaneous eruptions. About 25% patients developed multiple drug hypersensitivity on re-challenging. The past history of TB and history of TB contact were the major risk factor associated with DRTB and also development of ADR in the present study. According to a retrospective study, high-risk factor identified were elderly age, polypharmacy, pre-existing renal disease, diabetes mellitus, smoking, and alcohol intake. Majority of the ADR according to the present study are probably because of the drug and are mild in nature. In a similar 4-year retrospective study by Dela et al., which used WHO causality assessment, 81.5% ADRs were “possible” whereas only 4.7% were “certain.” Severity assessment was done by Hartwig and Siegel scale, majority (77.87%) ADRs were mild to moderate while only 23.12% ADRs were severe.

Strength of the study was that we found that many ADRs were mild and during initial 2 months of therapy, was manageable. Furthermore, early monitoring and patient counseling helped to gain confidence to be adhered and improved patient compliance. The present study was conducted with 6-month duration and did not follow-up the patients till end of the therapy as the duration of the treatment was long. This is the limitation of the study and hence further studies can be conducted with complete duration of therapy.

**CONCLUSION**

To conclude appropriate pharmacovigilance should be encouraged for early recognition and appropriate management.
of these adverse effects which might determine adherence and treatment success. Further studies are required to explore the newer drug in the treatment of DRTB with lesser ADRs.

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