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Original Article

Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis

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ABSTRACT

Background: Multidrug-resistant tuberculosis (MDR-TB) is considered to be a worldwide problem with notoriously difficult and challenging treatment. Adverse events associated with second-line drugs (SLDs) can have severe impact on efficient management.
Objective: To know the frequency of adverse events due to SLDs in patients of MDR-TB.
Design: A prospective cohort analysis of 98 MDR-TB patients enrolled between June 2009 to February 2010 was conducted in Department of Pulmonary Medicine, King George Medical University, Lucknow, India. All the patients were provided standardized regimen. Adverse events associated with treatment were recognized primarily by clinical evidence and/or laboratory investigations that were advised at baseline and whenever clinically indicated during course of treatment. Adverse events were considered major if required permanent discontinuation or substitution of drugs.
Results: 119 adverse events were reported in 46 (46.9%) patients. The grouped adverse events were most commonly gastrointestinal that was observed with a frequency of 48 (40.3%) followed by ototoxicity in 28 (23.6%), and neurological in 21 (17.6%). 17 (17.4%) patients had major adverse events requiring permanent discontinuation or substitution of drugs that included deafness and tinnitus in 5 (5.1%) followed by psychosis in 4 (4.1%). None of the patients stopped complete regimen due to adverse events. The treatment success rate was observed to be 71 (72.4%).
Conclusions: MDR-TB can be cured successfully with appropriate combination of drugs if adverse events associated with them can be managed aggressively and timely. Newer and less toxic drugs are urgently needed to treat MDR-TB patients.

1. Introduction

Multidrug-resistant TB (MDR-TB) is defined as *Mycobacterium tuberculosis* resistant to Isoniazid and Rifampicin with or without resistance to other first-line drugs. The emergence of resistance to drugs used to treat tuberculosis, and particularly MDR-TB, has become a significant public health problem in a number of countries and an obstacle to effective tuberculosis control. Out of the estimated global annual incidence of 9

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million tuberculosis cases in 2011, 2.3 million were estimated to have been reported in India. The prevalence of MDR-TB among notified new and retreatment pulmonary tuberculosis patients are estimated to be 2.1% and 15%, respectively.[1] Patients may present with a variety of adverse events when second-line drugs (SLDs) are prescribed for MDR-TB management. Most of the adverse events are minor and can be managed without discontinuation of treatment. Some adverse events can be life threatening if not recognized and treated promptly. There are major concerns regarding SLDs in that they are expensive, have low efficacy, and more toxic as compared to first-line antituberculosis drugs.[2–4] There may be a severe impact on adherence and higher risk of default and treatment failure affecting outcome overall if such adverse events are not properly managed.[5] Several studies have highlighted regarding high potential of these SLDs to cause adverse events that have led to interruption of treatment in 20–60% of MDR-TB patients.[6–23] Very few have specifically reported frequency of adverse events in India.[24–27] The present study has been designed to know the frequency of adverse events encountered in patients receiving SLDs for treatment of MDR-TB at Lucknow, India.

2. Methods

It was a prospective cohort study performed among 132 consecutive patients of pulmonary tuberculosis referred from various districts of Uttar Pradesh, India between June 2009 and February 2010 in Department of Pulmonary Medicine and Department of Microbiology, King George Medical University, Lucknow, India, which is a WHO-recommended Intermediate Reference Laboratory (IRL) certified by Revised National Tuberculosis Control Programme (RNTCP) of India. The patients included in the study were either new or retreatment cases of pulmonary tuberculosis with proven culture positive for *M. tuberculosis* and resistant to at least Isoniazid and Rifampicin and having age more than 18 years. The retreatment cases received previously multiple courses of antitubercular drugs including five drugs – Streptomycin, Rifampicin, Isoniazid, Ethambutol, and Pyrazinamide (SRHEZ), either daily (unsupervised) or DOTS Category II (supervised). The patients were excluded from the study if they (1) had not confirmed to be MDR-TB according to Drug Susceptibility Testing (DST) results, (2) had taken SLDs more than 1 month before confirmation of diagnosis, (3) had pregnancy, (3) were under 18 years of age, and (4) had concurrent major medical illnesses (chronic kidney disease, decompensated congestive heart failure, fulminant hepatic failure, acute gastritis, and seizure disorder) or major psychiatric illnesses (schizophrenia, depression) at baseline. These exclusions were as per the RNTCP current guidelines at the time of study.[28] All patients provided informed consent before participating in the study. Pretreatment investigations included sputum smear for AFB, culture for *M. tuberculosis* by conventional Löwenstein–Jensen media, DST by proportion method, complete hemogram (hemoglobin, total and differential leukocyte count, platelet count, and peripheral blood smear), chest X-ray, renal and liver function tests, and thyroid profile. All patients were routinely tested for human immunodeficiency virus (HIV) infection before initiation of treatment. All the patients were offered treatment given as per DOTS PLUS Protocol of RNTCP based on World Health Organization (WHO) Guidelines prevailing at that time.[28,29] The standardized regimen consisted of 6–9 months with six drugs – Kanamycin, Ofloxacin, Ethionamide, Cycloserine, Pyrazinamide, and Ethambutol, followed by 18 months Ofloxacin, Ethionamide, Cycloserine, and Ethambutol. The daily dosages prescribed were according to weight band: Kanamycin (500 mg); Ethionamide and Cycloserine (500 mg each); Ofloxacin (600 mg); Pyrazinamide (1250 mg), and Ethambutol (800 mg) for patients having weight less than 45 kg; for patients weighing ≥45 kg, the daily dose of Kanamycin was 750 mg, Ethionamide and Cycloserine was 750 mg, Ofloxacin 800 mg, Pyrazinamide 1500 mg, and Ethambutol 1250 mg. All of the drugs were provided free of cost. Treatment outcome was also defined according to the DOTS PLUS guidelines framed by RNTCP of India, as well as WHO,[28,29] as mentioned in Table 1. Patients were seen by doctors and staffs trained in RNTCP DOTS PLUS guidelines for clinical evaluation at monthly intervals during the intensive phase, and at three monthly intervals during the continuation phase until the end of treatment. Clinical, microbiologic, and radiologic response to treatment, weight, and possible adverse events were assessed at each follow-up visit and recorded in treatment cards. The main outcome variable was the occurrence of adverse events. All patients and their family members were counseled prior to treatment initiation, as well as during all follow-up visits, regarding possible adverse events and encouragement to report such events. Adverse events, if any, were recorded at each visit based on clinical evidence and subsequently managed as per protocol described in Table 2.[28,29] In addition to clinical evidence, certain

Table 1 – Definitions of various clinical outcomes.

Outcomes	Definitions
Cure	Patient of MDR-TB who has completed treatment and has been consistently culture negative with at least 5 consecutive negative results in the last 12–15 months or if one follow-up culture reported positive culture during the same period, and then provided this positive culture is followed by at least 3 consecutive negative cultures, taken at least 30 days apart, with clinical evidence of improvement.
Death	Patient of MDR-TB who dies for any reason during the course of treatment.
Failure	Treatment will be considered to have failed if two or more of the five cultures recorded in the final 12–15 months are positive, or if any of the final three cultures are positive.
Default	A MDR-TB patient whose MDR-TB treatment was interrupted for two or more consecutive months for any reason.
Smear conversion time	Time interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive smears respectively, taken at least 1 month apart.
Culture conversion time	Time to smear and culture conversion was defined as the time interval between the date of MDR-TB treatment initiation and the date of the first of two negative consecutive cultures respectively, taken at least 1 month apart.