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Research Article

Adverse events among patients of multi drug resistant tuberculosis receiving second line anti TB treatment

Kishor B. Rathod, Mangala S. Borkar*, Avinash R. Lamb, Sanjay L. Suryavanshi, Gajanan A. Surwade, Vimlesh R. Pandey

Department of Medicine, Government Medical College, Aurangabad, Maharashtra, India

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***Correspondence:**
Dr. Mangala S. Borkar
E-mail: kargalman@gmail.com

ABSTRACT

Background: As per WHO's "Global Tuberculosis Report, 2012", India accounts for an estimated 64000 patients out of 310000 cases of drug resistant TB estimated to have occurred amongst the notified cases of TB across the globe in a year. MDR-TB is a man-made phenomenon– poor treatment; poor drugs, poor adherence lead to the development of MDR-TB. Treatment of MDR-TB is difficult, much costlier, challenging and needs experience and skills. Reserve drugs are frequently associated with high rates of unacceptable adverse drug reactions, needing change of regimen. Therefore, it is imperative to monitor and treat adverse drug reactions.
Methods: The present prospective observational study was carried out at Drug Resistant Tuberculosis Centre at Govt. Medical College, Aurangabad, Maharashtra, to monitor patients for early detection of adverse events after starting treatment till the patients were admitted and later followed up personally or telephonically at regular intervals.
Results: We observed adverse drug reactions among 90/265 (33.96 %) patients of whom 90/265 (33.96 %) had gastro intestinal ADRs, followed by ototoxicity 15/265 (5.66%), psychiatric manifestations 14/265 (5.28%), injection site pain swelling 13/265 (4.90%), arthralgia 11/265 (4.15%), dermatological ADRs 7/265 (2.64%), peripheral neuropathy 5/265 (1.88%), renal dysfunction 3/265 (1.13%), change of therapy was only required in 13 psychiatric and 12 ototoxic ADRs.
Conclusions: ADRs are more common in MDR TB patients on second line anti tubercular treatment. Good counseling, spacing drugs, high protein diet helps patients to tolerate therapy better and default rate to drop.

Keywords: MDR-TB (Multidrug resistant tuberculosis), ADR (Adverse drug reaction), Second line anti TB drugs

INTRODUCTION

As per WHO's "Global Tuberculosis Report, 2012", India accounts for an estimated 64000 patients out of 310000 cases of drug resistant TB estimated to have occurred amongst the notified cases of TB across the globe in a year.[1] MDR-TB is a man-made phenomenon - poor treatment; poor drugs and poor adherence lead to the development of MDR-TB.

All measures should be taken to persuade and encourage patients not to stop treatment despite all its discomforts to prevent morbidity, mortality and transmission of MDR-TB.[5] Treatment of MDR-TB is difficult, complicated, much costlier, challenging and needs experience and skills. Reserve drugs are frequently associated with high rates of unacceptable adverse drug reactions, needing interruption and change of regimen.[5] Therefore, it is imperative to monitor and treat adverse drug reactions developed by the patients. This approach ensures better

compliance of patients and good treatment outcome. The aim of this study was to assess the adverse drug reactions of second-line anti-tubercular drugs used to treat MDR-TB at Govt. Medical College, Aurangabad, Maharashtra, India.

METHODS

The present prospective observational study was carried out at Drug Resistant Tuberculosis Centre at Govt. Medical College, Aurangabad, Maharashtra with prior approval of institutional ethics committee.

All MDR-TB patients receiving second line anti TB drugs enrolled at Drug Resistance Tuberculosis Centre, during the period of November 2012 to November 2014 were included in the study. This study included all patients diagnosed to have MDR-TB (isoniazid and rifampicin resistance) & rifampicin resistance by CB-NAAT and admitted in Drug Resistance Tuberculosis Centre of our institute. Thorough history was taken and detail examination was carried out.

Pre-treatment investigations done included- sputum for Acid Fast Bacilli (AFB) by smear, culture and Drug Sensitivity Testing (DST), chest X-ray, urine for albumin, sugar and pregnancy test for female patients in child bearing age group, complete haemogram, renal and liver function tests, thyroid function test, psychiatric evaluation and HIV status (as per RNTCP guidelines, every case of TB should be screened for HIV).

The standardized regimen consisted of an intensive phase (IP) of 6-9 months with 6 drugs, namely kanamycin (Km), levofloxacin, ethionamide (Eto), pyrazinamide (Z), ethambutol (E), and cycloserine (Cs) given daily. This was followed by a continuation phase (CP) of 18 months with 4 drugs, namely levofloxacin, Eto, E and Cs.[1] At the end of 6 months of treatment, if the fourth month culture remained positive, the intensive phase regiment was extended for a further 3 months. Doses of the drugs were chosen according the weight bands to which patient belonged. All patients enrolled to the study were treated with a daily supervised regimen.

All patients were monitored daily for adverse drug reactions after starting regimen till the patients were admitted and later followed up personally or telephonically at regular intervals. Health education was given to the patients and other family members by doctors and nursing staff. Follow-up sputum cultures reports were obtained from the register maintained at Drug Resistance Tuberculosis Centre, of our institute. Patients who had adverse drug reactions came to the DOT center in the OPD and were mostly admitted or seen by us on outpatient basis. Treatment outcomes: such as cure, default, failure and death as per the RNTCP definitions were recorded. No statistical test was applied as this was an observational study without controls.

RESULTS

265 patients were studied during the 25 months study period. The age group ranged from 15 years to 70 years (Table1, Figure 1). Maximum number of cases were in the age group 25-34 (28.30%) followed by 15-24 (24.52%). Majority (71.31%) of the patients were in the age group of 15-44 years. The total number of males in the study was 184(69.43%) and females were 81 (30.56%) (Table 1, Figure 2).

Table 1: Demographic profile of MDR TB patients.

Age (years)	0-14	15-24	25-34	35-44	45-54	55-64	65 and above	Total
Male	0	33	47	40	33	22	9	184
Female	0	32	28	09	6	5	1	81
Total	0	65	75	49	40	27	10	265
%	0%	24.52%	28.30%	18.49%	15.09%	10.18%	03.77%	100%

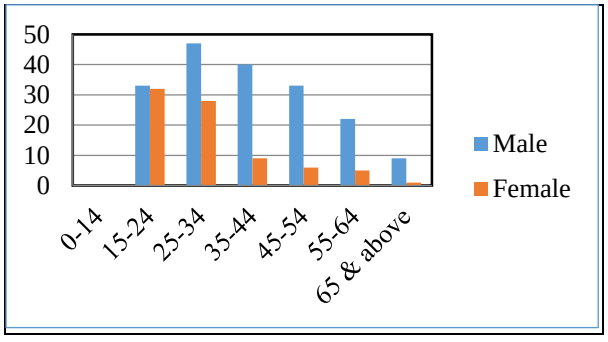

Figure 1: Age distribution.

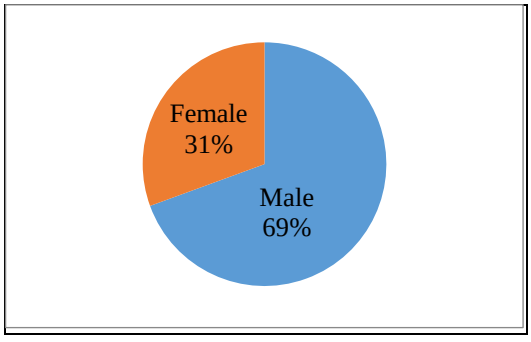

Figure 2: Sex distribution.

Patients of drug resistant tuberculosis presented with weight loss (94% - commonest symptom), cough (88%), fever (82%), breathlessness (74%) and hemoptysis (34%) (Figure 3). In addition, 233/265 (87.92%) patients had anemia, 16 (6.03%) patients had diabetes mellitus, 11 (4.15%) were HIV positive, 6/265 (2.26%) had hypothyroidism, 1 (0.37%) patient had deep venous thrombosis.

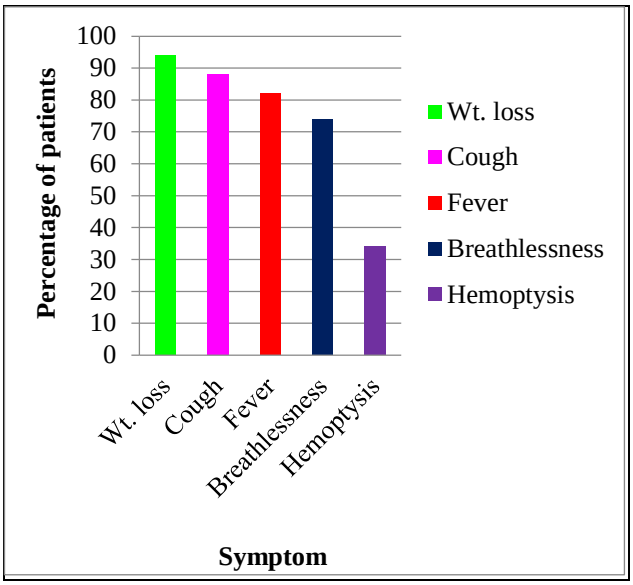

Figure 3: Presenting complaints of MDR-TB patients.

Adverse drug reactions (Figure 4):

We observed the following adverse drug reactions:

1. 90/265 (33.96%) had gastro intestinal adverse drug reactions (nausea, vomiting and anorexia),
2. 15/265 (5.66%) had ototoxicity (hearing loss and tinnitus),
3. 14/265 (5.28%) had psychiatric manifestations (depression, suicidal tendencies, hallucinations, etc.),
4. 13/265 (4.90%) had injection site pain swelling,
5. 11/265 (4.15%) had arthralgia
6. 7/265 (2.64%) had dermatological adverse drug reaction (rash, pruritus)
7. 5/265 (1.88%) had peripheral neuropathy,
8. 3/265 (1.13%) had developed renal dysfunction.

In our study ADRs were observed in 33.96% patients which was less as compared to Singla et al.[6] (58%), Joseph et al.[2] (58%) and Hire R et al.[8] (50%).

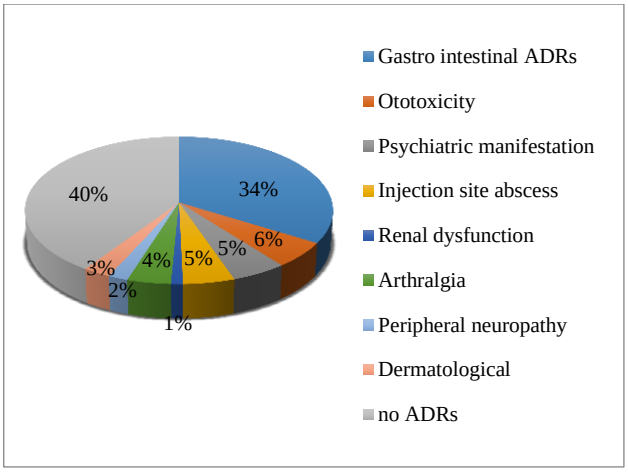

Figure 4: Adverse drug reactions.

DISCUSSION

Gastrointestinal adverse drug reactions

Gastro intestinal ADRs were the commonest adverse reactions observed in 90 out of 265 (33.96%) patients.[8,9,11]

They were mild but required immediate treatment in the form of anti-emetics, H2-blockers or PPI. We also advised the patients to take the pills after some food/embedded in a piece of banana or pedha and spaced at few minutes intervals each. These gastro intestinal symptoms occurred mostly within a week of treatment.

1. Nausea, vomiting and anorexia were most common gastro intestinal ADRs in 81/90(90%) patients.
2. Epigastric discomfort was seen in 7/90 (7.77%) patients.
3. Change of taste was observed in 1/90 (1.11%) patients.
4. Excessive salivation was observed in 1/90 (1.11%) patients.

60/90 (66.66%) gastro intestinal ADRs were observed in the first month of treatment.

11 patients with gastro intestinal ADRs defaulted treatment. These patients had severe disease (pulmonary tuberculosis). No patient required alteration in treatment regimen of DR TB due to gastrointestinal ADRs.

Patients with gastro intestinal ADRs also had associated ADRs such as ototoxicity in 7 patients, psychiatric ADRs in 3 patients, peripheral neuropathy in 2 patients, injection site swelling/pain in 5 patients, pruritis without rash in 2 patients.

Ototoxicity

Ototoxicity was the second most common ADR observed in 15/265 (5.66%) patients, due to kanamycin.[2, 11]

Decreased hearing supported by audiogram report of bilateral sensorineural deafness was seen in 14/15 (93.33%) patients. Two patients of these also had associated tinnitus. One patient had isolated complaint of tinnitus only.

Ototoxicity was seen as early as 2 months and as late as 12 months. 12/15 (80%) patients required withdrawal of Kanamycin from treatment regimen of DR TB. Kanamycin was replaced with PAS (P-aminosalicylic acid).

Psychiatric adverse drug reactions

This is a known ADR of cycloserine, for which one has to be extremely vigilant. Caregivers have to be specially instructed regarding this.[1,6,9,11]

Psychiatric adverse drug reaction were third most common ADR observed in 13/265(4.90%) patients.[6,9,11,12]

Insomnia was observed in 5/13 (38.46%) patients followed by suicidal tendencies in 4/13 (30.76%) patients.

Depression was seen in 3/13 (23.07%) patients. Altered behavior was seen in 2/13 (15.38%) patients. Idea of infidelity and hallucination were seen in 1 (7.69%) patient each.

Four patients had more than one psychiatric manifestation with depression and suicidal tendencies seen in first, while altered behavior and insomnia seen in second, depression and insomnia in third and hallucination and suicidal tendency in fourth.

All patients with psychiatric ADRs required withdrawal of cycloserine which was replaced with PAS. Two patients with psychiatric adverse drug reaction defaulted.

Psychiatric manifestations were seen as early as 7 days and late as 13 months.

Injection site swelling/pain

Injection site swelling was seen in 13/265 (4.90%) patients. All 13 patients developed this at the third to fourth month of therapy. Injection site swelling/pain (4.90%) was fourth common ADR observed in our study. None required withdrawal of injection Kanamycin.

Arthralgia

Arthralgia was observed in 11/265 (4.15%) patients, earliest at 1 month and as late as 10 months.

Arthralgia was seen in 3/11 (27.72%) patients as early as 1 month, in 3/11 (27.72%) at 2 months, 2/11 (18.18%) at 4 months, 2/11 (18.18%) at 6 months and 1/11(9.09%) at 10 months.

None of the patients required withdrawal of drug. All patients responded to NSAIDS (non-steroidal anti-inflammatory drugs). Arthralgia 11/265 (4.15%) was fifth common ADR observed in our study.[8,11]

Cutaneous reactions

Cutaneous reactions were the sixth most common ADR observed in our study, seen in 7/265(2.46%) patients. Pruritis without rash was seen in 6 patients and pruritis with rash was seen in 1 patient. All responded to anti allergic medication (cetrizine), none required withdrawal of drug.

Peripheral neuropathy

Peripheral neuropathy was seen in 5/265(1.88%) patients, earliest at 2 months and as late as at 13 months. Two patients required pyrazinamide withdrawal for this ADR.

Renal dysfunction

Renal involvement was seen in the form of borderline derangement of serum creatinine which improved in few weeks in 3/265 (1.13%) patients and none required withdrawal of injection kanamycin.[7,8,11]

Clinical outcome

During our 2 years study period, 91 patients completed minimum 1 year treatment- of these, 26 patients defaulted treatment, and 23 patients died during the treatment, 4 patients were transferred out to other DR TB Centre.

In our study, the mortality rate was 8.67%. Of these 8.67%; 47.81% patients died within first 6 months and 69.55% within first 9 months of starting treatment.

The shortcoming of our study was that Patients who get admitted to DR TB centre of or hospital come from corporate area or from rural area of our district or other 3 district in our region. The patients who stay in other villages often do not report to us for minor side effects. Though we tried to contact them regularly telephonically they may not have reported minor side effects. However patients with significant ADRs visited our DOTs TU or DR TB ward and these have been recorded

To conclude,

- Gastro-intestinal side effects which were commonest can be largely prevented by proper timing and spacing of drugs with food and if necessary, giving antiemetic, antacids and PPIs or H_2 receptor blockers. These side effects are a common cause of

defaulting and persuasive, sincere counseling is vital to help the patients through this ADR.

- Change of therapy is not needed for gastro-intestinal ADRs but is required in psychiatric and ototoxic ADRs.

- Nutritional advice (high protein diet and timing of food/medicine), encouragement helps in tolerance to drug.

- Good counseling helps patients to tolerate side effects better and default rate can drop. We encouraged patients to come to us when they had any problems and this improved compliance. Counseling should involve patient as well as care-givers and family.

- Not only the treating physicians but also others in the hospital, specially medicine, ENT and psychiatrist needs to be sensitized about extending help, sympathy and admitting cases if needed, if they complain of adverse drug reactions, so that their adherence improves.

- Just as there are counselors in ART, we need dedicated counselors in RNTCP too, which will go a long way in ensuring that the patient completes his treatment. This is important for the patient's survival and well-being as well as to prevent the dangerous illness from spreading in the community.

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Ethical approval: The study was approved by the institutional ethics committee

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