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ADVERSE DRUG REACTIONS AND OUTCOME ANALYSIS OF MDR TB PATIENTS ON DOTS PLUS REGIMEN

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ABSTRACT

Introduction: The emergence of drug resistant mycobacteria has become a significant public health problem world over creating an obstacle to effective TB control. Present study was conducted to evaluate pattern and frequency of adverse drug reactions (ADR) of CAT IV, to analyze demographic, radiological and bacteriological profile and treatment outcome in MDR TB patients.

Method: Total 102 MDR TB patients (with in vitro resistance to Isoniazid and Rifampicin) were analyzed retrospectively who had completed treatment from august 2007 to June 2014. Analysis was made for extent of lung lesion, correlation of sputum smear and culture conversion with clinical and radiological improvement, risk factors for adverse outcome and adverse drug reactions.

Result: Forty six patients (45.09%) were cured/treatment completed, nine patients (8.82%) failed, 21 patients (20.05%) defaulted and 26 patients (25.49%) died of total 102 patients. Mean time for sputum smear and culture conversion were 4.2±2.0 and 4.19±2.3 months, respectively. Advanced lung lesion, cavitations, poor adherence to treatment and BMI less than 18 are variables associated with poor outcome. Fifty (52.94%) patients experienced adverse drug reactions and 42 of them required drug modifications.

Conclusion: The ADRs were more common in the first 60 days of the regimen & in patient with BMI<18. Hence vigilant monitoring is required for these types of patients during the initial period. Sputum smear and culture conversion are very well correlated with clinical and radiological improvement.

Key-words: MDR TB, DOTS Plus, ADR, Cat IV

INTRODUCTION

The emergence of drug resistant mycobacteria has become a significant public health problem world over creating an obstacle to effective TB control. Confirmed Multi Drug Resistant tuberculosis (MDR TB) case is defined as an MDR-TB suspect who is sputum culture positive and whose TB is due to Mycobacterium tuberculosis that are resistant in-vitro to at least Isoniazid (H) and Rifampicin (R).[1] (The culture and Drug Sensitivity Test results are being from an RNTCP accredited laboratory). As per the WHO global TB report 2014, globally, 5% of TB cases were estimated to have had multidrug-resistant TB (MDR-TB) in 2014[2]. Drug resistance surveillance data show that an estimated 480 000 people developed MDR-TB in 2014 and 190 000 people

died as a result of MDR-TB[2]. Extensively drug-resistant TB (XDR-TB) has been reported by 105 countries in 2014[2]. On average, an estimated 9.7% of people with MDR-TB have XDR-TB. In addition to the increased difficulty in treating the disease, the patient remains infectious longer increasing the risk to the public and to healthcare workers.MDR TB entails lengthy and expensive treatment, higher rate of failure and adverse drug reaction as compared to DOTS.[3] Drug resistance arises due to improper use of antibiotics in chemotherapy of drug-susceptible TB patients[3]. This improper use is a result of a number of actions including, administration of improper treatment regimens and failure to ensure that patients complete the whole course of treatment. Essentially, drug resistance arises in areas with weak TB control programmes. The prevalence of MDR-TB mirrors the functional state and efficacy of tuberculosis control programmes in the country. In present study we analyzed different factors affecting clinical and radiological improvement and their correlation and adverse events of second line anti tubercular drugs.

SUBJECTS AND METHODS

Data collection: Data were obtained from medical records like treatment card and registers from August 2007 to June 2014 from southern part of Ahmedabad. History was obtained from patients, health workers, STS, STLS, DOT provider etc. when needed. The details of demographic data, chemotherapy, adverse drug reactions to drugs, regularity of treatment, follow up assessment as well as regular sputum bacteriology and chest radiography results were recorded.

Sputum bacteriology and other investigations (pre treatment evaluation for DOTS Plus therapy): Sputa were collected in sterile Mc cartney bottles containing cetyl pyridinium chloride (CPC) or falcon tubes. All specimens were subjected to culture for mycobacterium tuberculosis and drug susceptibility testing for isoniazide (H), rifampicin (R), ethambutol (E) and streptomycin (S) on Lowenstein Jensen (LJ) medium which were sent in CPC bottle. Specimen collected in falcon tubes were subjected to Line Probe Assay (LPA) [4] to know sensitivity of H and R only. Sputum culture and drug sensitivity results are available after three to four months in LJ media while LPA is a rapid diagnostic test which gives result within few days. Because of this fact RNTCP has adopted LPA method for diagnosis of MDR TB cases after. However LPA is not useful for follow up sputum cultures hence follow up cultures are being done by LJ media.

Prior to starting treatment all patients were underwent detailed clinical, serological, bacteriological, radiological evaluation. Thyroid, hepatic, renal function tests and complete blood counts were done. HIV testing by enzyme linked immunosorbent assay done after pre test counselling and informed consent. All patients were referred to DOTS plus site where after evaluation DOTS plus treatment were started.

DOTS plus regimen: As per RNTCP guidelines this regimen includes six drugs kanamycin (Km), ethambutol (E), pyrazinamide (Z), cycloserine (Cyc), ethionamide (Eto) and ofloxacin (ofx)/ levofloxacin (Lfx). These drugs to be taken daily except Km which is to be taken six days per week. Intensive phase includes all six drugs and continued for six to nine months while continuation phase includes four drugs (Cyc, Eto, E, ofx/lfx) taken for 18 months. PAS (Para amino salisylic acid) is reserved drug for patients who develops adverse drug reaction or who conceives while on therapy.

Patient monitoring: Data was compiled and analysed for different parameters like demographic profile, socio economic status, co morbid conditions, method of diagnosis, drug sensitivity to first line anti tuberculosis drugs, adverse drug reactions, sputum smear and culture conversion, weight gain, radiological improvement. We also analysed correlation of sputum smear and culture conversion with weight gain and radiological improvement.

RESULTS

Demographic and clinical profile: Mean age was 34±11.54 years (range, 16 to 70 years). Sixty one (59.80%) patients were male and 41(40.19%) were female. Mean body weight was 42.80±11.82 kg (range, 20 to 60 kg). Mean body mass index (BMI) was 18.80 (range, 14 to 23.5). Concomitant medical diseases were present in 35 patients (34.31%). These included hypertension, COPD, hyperlipidemia, chronic alcoholic liver disease. Eight (7.84%) patients were immunocompromised, of which three (2.94%) were HIV positive and five (4.90%) were diabetic. All HIV positive patients were already known cases and on anti retroviral therapy. In present study no patient was having thyroid abnormality before initiation of treatment. There was not any female with pregnancy before or after initiation of therapy.

Adherence to therapy: Eighty two (80.39%) patients were regular in therapy. Twenty (19.60%) patients had poor adherence to therapy, which was defined as missing more than 20% of the designated number of doses.

Table 1: Demographic, clinical, bacteriologic and treatment characteristics in MDR TB patients

Variable	Treatment outcome		P value
	Success* (n=46) (%)	Poor outcome# (n=56) (%)	
Age (mean yrs)	33.48	34.05	>0.05
Male sex	31 (67.39)	39 (69.64)	0.98
Presence of cavity/ advanced lung lesion	19(45.23)	41(73.21)	0.002
Initial bacterial load			
3+	16 (34.8)	26 (46.4)	0.42
2+	21 (45.7)	19 (33.9)	
1+/Scanty bacilli	9 (19.6)	11 (19.6)	
Poor adherence	0	20 (35.71)	<0.0001
HIV positivity	1 (2.17)	2 (3.57)	0.68
Diabetes	2 (4.35)	3 (5.35)	0.81
Adverse events which needed drug modifications	15 (32.60)	19 (33.92)	0.89
BMI <18	12 (26.08)	39 (69.64)	<0.0001

*cure/ treatment completed; # Failure or death or default; Figure in parenthesis indicate percentage

Outcome: Forty six patients (45.09%) were cured/treatment completed, seven of the patients who failed therapy were suspected as XDR TB and second line drug sensitivity were sent which revealed non XDR TB (sensitive to ofloxacin) and remaining two patient was XDR TB case. Total 21 patients had defaulted therapy due to social reason, migration to other state or territory and adverse drug reaction. Amongst defaulter 11 patients had defaulted before completion of intensive phase. Five patients had history of defaultation in previous therapy also.

Of the variables that might be associated with the adverse treatment outcome is presence of cavities in chest X ray, BMI< 18, extensive lung lesion and poor adherence to therapy (Table 1).

Adverse drug reactions: Fifty four patients had adverse drug reactions of varying severity. The most common ones were related to gastrointestinal system and central nervous system. Modification of drug regimen required in 42 patients. Cycloserine was terminated after a mean of 3.9± 3.0 months because of depression (n=6), altered behaviour (n=5), suicidal attempt (n=1), insomnia (n=3) and seizure (n=1). Eleven patients required termination of aminoglycosides after a mean of 2.5± 2.1 months because of nephrotoxicity or otovestibular toxicity. Nine patients had severe joint pain and so needed to discontinue pyrazinamide. Three patients developed blurring of vision and so ehambutol was withdrawn from therapy. Two patients had hypothyroidism after commencement of therapy and ehionamide was discontinued. Hypersensitivity was observed in one patient who required stopping ofloxacin. Various adverse drug reactions observed during therapy are depicted in table II.

Table 2: Adverse drug reactions observed

System	Manifestations	Patients(%)	Actions taken for ADR
Gastro intestinal	Nausea, vomiting, epigastric discomfort	25(24.50)	Symptomatic treatment
Central nervous	Insomnia, depression, seizure, suicidal attempt	16(15.68)	Cycloserine stopped in all patients, restarted in 5 patients
Skeletal	Joint pain	9(8.82)	Symptomatic treatment (n=1) Pyrazinamide stopped, para amino salicylic acid added (n=4)
Otovestibular	Giddiness, tinnitus, impaired hearing	7(6.86)	Kanamycin stopped and PAS added (n=5) and kanamycin alternate day (n=2)
Ophthalmic	Visual blurring	3(2.94)	Ethambutol stopped
Endocrinal	Hypothyroidism	2(1.96)	Ethionamide stopped and pyrazinamide added
Renal	Renal function impairment	4(3.92)	Kanamycin stopped and PAS added
Dermatologic	Hypersensitivity, rashes	1(0.98)	Ofloxacin omitted permanently
Hepatobiliary	Jaundice	1(0.98)	Pyrazinamide and ethionamide stopped temporarily

DISCUSSION

In our study younger population with lower weight patients are more affected in contrast to other studies.[5,6,7] While other demographic profile and clinical characteristics were similar to other studies, with male patients' predominance. Among the variables that were found to be independently associated with adverse outcome of patients, the presence of cavitations might affect drug penetration and thus decrease the efficacy of anti-tubercular drugs. It was found that cavitary lesion per Se, irrespective of drug sensitivity pattern was associated with poor treatment outcome[8.] Irregularity of treatment linked with adverse outcome is not unexpected and emphasizes that importance of directly observed therapy in the management of tuberculosis, which should be mandatory for all patients with MDR TB[9]. In our study major cause of irregularity was migration to other territory and alcoholism which is also observed in other study[10]. In a developing country like India malnutrition is a major health problem and very important factor which leads to poor immunity and so associated with adverse outcome as indicated by low BMI (less than 18), which is comparable to one study (unpublished data, DOTS plus pilot project, Gujarat). Similar results were observed in one another study also[11].

Second line anti tubercular treatment adverse events leading to treatment interruption or defaultation was observed in present study. Most common adverse event was related to gastrointestinal which is also seen in other studies[11-14]. Central nervous system related adverse events were second most common which lead to omission of cycloserin in our study.

In this cohort study of MDR TB patients, those who responded achieved sputum culture negativity during early months of therapy, usually within four months. This concurs with a study of HIV negative subjects with MDR TB. In our study sputum culture conversion at three to four month was not predictive of eventual cure, which was shown in other series [15.] The poor cure rate (37.87%) was observed in the current study, is similar to another report from tuberculosis research centre, where only 36% cure rate was observed [14]. Similarly study carried out from Denver in 1993, reported success rate of 56%. Similarly studies from Argentina, Peru and USA have reported positive treatment outcome of around 45%[5,16,17]. The unfavourable outcome shown in these series was strongly associated greater number of drugs received previously and male sex and resistance to more than five drugs. A report from India had shown 68% cure rate [18]. On the contrary to our study other reports from Vietnam, Korea, Netherland and Turkey had shown cure rate of above 75% [7, 19, 21].

In present study poor cure rate was observed mainly due to high default and death rate. Regimens for treatment of MDR tuberculosis are very long (≥20 months), poorly tolerated, expensive, and substantially less effective than first-line treatment of drug-susceptible tuberculosis[22]. WHO reports show that only 48% of the more than 25 000 patients with MDR tuberculosis from 107 countries who started MDR tuberculosis treatment in 2009 completed their treatment successfully because of deaths (15%), treatment interruptions (14%), treatment failure (9%), and insufficient data (14%)[23]. An individual meta-analysis of 9153 patients with MDR tuberculosis from 32 observational cohorts reported similarly dismal findings (success 54%, default 23%, failure or relapse 8%, and death 15%)[24]. Patients with strains of tuberculosis that had acquired additional resistance to second-line injectable drugs, to fluoroquinolones, or both (XDR tuberculosis)[25] had poor outcomes. Health system failures generally underpin the emergence of drug resistance in a population. Factors such as poor diagnostic facilities, insufficient regulation of access to antibiotics, poor implementation of the directly observed treatment short-course programme, and lack of tuberculosis drugs lead to mono therapy and intermittent treatment. In India, huge variations in the quality of management practices in public-sector and private-sector facilities probably play a major part in the emergence of drug-resistant tuberculosis [26]. The highest burden of drug resistance arises in countries that can afford first-line drugs, but have weak health-care systems that are likely to generate MDR and XDR tuberculosis [23]. This situation explains the relative over-representation in Brazil, Russia, India, China, and the emerging economies in the Asia-Pacific region.

This study describes meta-analysis of patients on DOTS plus regimen. Migration to other region or territory, alcoholism and drug toxicity are important factors leading to defaultation or poor treatment adherence and ultimately low cure rate in MDR TB treatment. All patients should be explained and counselled at multiple level regularly to improve adherence to therapy. Low BMI is indicator of poor health status and associated with high mortality so more emphasis should be

given to improve nutritional status of all these patients. Emergence and spread of MDR TB can threaten the global TB control.

CONCLUSION

The treatment of MDR TB is prolonged, expensive, more toxic and often unsuccessful. Hence prevention of MDR TB is more important rather than treatment. Strengthening the program by intensely evaluating treatment regimens, assuring treatment adherence, supporting true DOTS, aggressive and proactive management of adverse events and infection control are very essential.

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