Analysis of Adverse Drug Reactions and Treatment Outcome of DOTS Plus Therapy of MDR-TB Patients at District Tuberculosis Centre

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Abstract: _Background: Expensive and toxic second lines anti tubercular drugs are given under the programme for a longer period of time for the treatment of MDR-TB. However despite being implemented in whole of country, data on programme surveillance is scarce. Adverse drug reactions of second line anti-tubercular drugs affect compliance and thereby treatment outcome. Hence the present study was sought to evaluate the treatment outcome and analyze adverse drug reactions of MDR-TB receiving DOTS plus therapy under programme._ _Methods: Retrospective study of registered MDR TB cases at district tuberculosis center data regarding demoghaphic profile, ADRs, drug adherence, outcome recorded and analysed._ _Results: Majority of ADR were Gastrointestinal (46.36%) followed by generalized weakness (20%), joint pain (11.81%), psychological (6.36%) and others. patients had favorable outcome, amongst them 44 patient were cured and 5 completed treatment. 32 patients had unfavorable outcome, amongst them 19 patients died, 9 became defaulter, 3 became failure to therapy, 1 shifted to bedaquiline based regimen._ _Conclusions: Cure rate was higher in MDR-TB cases with ADRS than MDR-TB cases without ADR and poor treatment adherence have unfavourable outcome._ _Objectives: 1) To Study Adverse drug reactions in MDR TB cases. 2) To evaluate and analyze outcome in MDR TB patients._

Keywords: AKT-anti koch treatment, MDR-TB -multidrug resistant tuberculosis, DOTS- directly observed treatment, short course, PMDT- programmatic management of drug resistant TB

1. Introduction

Currently the WHO estimated incidence of **Rifampicin (R)** and **Multi Drug Resistance (MDR-TB)** in India is around 1, 47, 000, which means around 11 patients per 1 lack population annually as per the global TB report, 2017.

- Treatment of MDR-TB is a major challenge for global tuberculosis control as it requires the use of expensive and toxic second line anti-tubercular drugs for a longer duration.
- **Causes of MDR –TB**: genetic mutation that makes drug ineffective, inadequate and poorly administered treatment regimen, weak TB services, delay in detection of drug resistance, poor adherence to treatment.
- Adverse drug reaction (ADRs) of anti tubercular drugs affects patient's compliance, extension, duration or termination of treatment, drug resistance and treatment failure.
- **Prevention of Drug resistance** : Strong system to detect, successfully treat and ensure long term disease free status of TB patient, are required to prevent emergence of resistance.

2. Methods

It was a retrospective study conducted at Rajkot district tuberculosis centre who were registered between 2016 and 2017 and initiated on cat 4 regimen of RNTCP

Diagnosis of MDR-TB was done at RNTCP accredited Intermediate Reference laboratory using Cartridge based nucleic acid amplification test (CBNAAT) according to standard guidelines. Information on demographic and clinical profiles of patient including smoking and alcohol abuse, comorbidities like diabetes and HIV status, history of previous Antituberculosis treatment and Adverse drug reactions as a part of pretreatment evaluation was extracted from treatment card and patients record available at the district TB centre. Multidrug resistant TB is defined as tuberculosis resistant to both Rifampicin and Isoniazid, first line Anti TB drugs.Different outcomes to category 4v treatment i.e. Treatment default, Cure, Treatment completed, death and Treatment failure were defined as per RNTCP-PMDT guidelines. For analysis successful outcome was represented by cure and completion of treatment

3. Results

Table 1

Age Group (Years)	Number
10-20	10
21-30	28
31-40	24
41-50	12
51-60	10
Above 60	1

A total of 85 cases of CBNAAT confirmed MDR TB cases were included in this study. Though all the group are affected by MDR TB, majority of patients belonged to Age group of 21 to 30 and second is 31 to 40. In our study majority of patients have addiction of either substance but among all addiction tobacco is most one about 34 patient and 14 patient are addicted to smoking and 4 patients are alcoholics. Out of 85 MDR TB cases 83 patients had history of anti Koch treatment and only 2 had no history of AKT.

Out of all MDR TB cases only 1 patient was HIV positive others were negative Out of 85 cases of MDR TB 49 patients had favorable outcome, amongst them 44 patient were cured and 5 completed treatment. 32 patients had unfavorable outcome, amongst them 19 patients died, 9 became defaulter, 3 became failure to therapy, 1 shifted to bedaquiline based regimen, 4 patients were transferred out to other region.

Table 2: Outcome of MDR TB cases

Outcome		No patients
Favorable	Treatment completed	5
	cured	44
Unfavorable	defaulter	9
	died	19
	failure	3
	On bedaquiline	1
Total		81
Transfer out -4		

Table 3 comparison of demographic profil with outcome group

Variables		Favourable outcome	Unfavourable outcome	P value
Age		34.8	34.87	ns
sex	Male (55)	32	23	NS
	Female (27)	17	10	NS
Alcohol addiction		4	4	NS
Tobacco addiction		24	9	NS
DM 2		7	3	NS
h/o akt		47	51	NS
Poor adherence		29	31	HS

In ours study we compared the adverse drug reaction with various variables like age, sex, body mass index, co morbidity, treatment adherence and treatment outcome. We found amongst 85 patients, 74 patients had adverse drug reaction. All age groups male and female were equally affected without relation to co morbidity. There was no significant association between age and ADRs as well as gender and ADR (p>.005). We compared results of ADRs and demographic profile of ours study with DELA A. et al lung India, 2017 vol: 34 (6) pp: 22, it also suggest that treatment outcomes were significantly better among those who experienced ADRs. Majority of patients were in between 21 to 40 age group.

A total of 85 MDR –TB cases were analyzed Among them 87.15% cases were associated with adverse drug reactions while 12.84% cases without adverse drug reaction. Totally 110 ADR reported among 74 cases. Majority of patients within the age group of 21-40 years with mean age 30.24 ± 11.66 Majority of patients 68.23 % were males while 31.77% were females.Among MDR _TB, 97.64% were previously treated cases while 2.36% were naïve patients.All the patients received second anti tubercular drugs (kanamycin [km], Levofloxacin [Lfx], pyrazinamide [Z], ethionamide [Eto], Ethambutol [E], Cycloserine [Cs]Paraaminosalicylic acid [PAS] on the weight basis as per DOTS plus program Majority of ADR were Gastrointestinal (46.36%) followed by generalized weakness (20%), joint pain (11.81%), psychological (6.36%) and others By th WHO casualty assessment majority, 57.27% were possible category whereas only 17.27% probable and 15.45% were certain.Out of 85 patient, 49 had a successful outcome after complete course of AKT, Remaining 32 patients had an unsuccessful outcome and 4 deferred from study.51 patients showed sputum culture conversion at 3 months of AkT, whereas 6 patients converted by 6 months however remaining 14 patients who remain positive, 8 patients died, 2 defaulted, 3 treatment failure and 1 switched to bedaquiline

Table 4 Comparisons of demographic profile and ADRs with DELA. A. all study

	Data of our study		Data of DELA. A. all study	
	Case with ADR (n=74)	Case without ADR (n=9)	Case with ADR	Case without ADR
Age				
12-20	5 (6.7%)	2 (22.22)	4.8%	4.8%
21-40	45 (60.81%)	5 (55.55%)	35.2%	26.4%
41-60	22 (29.7%)	2 (22.22%)	15.2%	10%
61-80	2 (2.7%)	0 (0%)	2.4%	2.7%
Sex				
Male	52 (70.27%)	4 (44.44%)	39.2%	40%
Female	22 (29.7%)	4 (44.44%)	23%	13%
Co morbidity				
HIV	2 (2.7%)	0	4.%	2%
DM2	5 (5.5%)	5 (55.5%)	0%	0%
Treatment adherence				
Yes	51 (68.9%)	2 (22.22%)	45.6%	17.6%
No	23 (31.01%)	6 (66.66%)	15%	31%
Treatment outcome				
Cure	48 (64.84%)	1 (11.11%)	43%	16%
Defaulter/failed	12 (16.21%)	0	4.8%	8.8%
Death	13 (17.57%)	6 (66.66%)	14.94%	27.72%

Table 5: Incidence and characteristic of adverse drug reactions (n =85

	Manifestation	Number of patients	Action taken	Suspected drug
Gastrointestinal	Nausea, vomiting Epigactict discomfort, diarrhoea	51 (46.36%)	Symptomatic treatment	11 (ethionamide) 40 (not mentioned)
Musculoskeletalsystem	Generalized weakness	22 (20%)	Symptomatic treatment	Not mentioned
	Joint pain	13 (11.81%)	Symptomatic treatment Change of AKT in 4 patients	3 (pyrazinamide) 1 (ethambutol)
Ophthalmic	Visual blurring	4 (3.63%)	No need of change in AKT	4 (ethambutol)
Renal	Altered RFT	3 (2.72%)	Symptomatic treatment Temporary discontinuation of AKT	Not mentioned
Psychiatric	Insomnia, depression Seizure, suicidal attempt	7 (6.36%)	Change in AKT of all 7 patients Cycloserine stopped	7 (cycloserine)
Hepato biliary	Altered LFT jaundice	4 (3.63%)	Change in AKT In 3	Not mentioned
Oto vestibular	Hearing loss	6 (5.45%)	Kanamycin stopped (n=5)	Kanamycin (5)

			Cycloserin stopped (n=1)	Cycloserin (1)

Table 6: Comparison between culture conversion and outcome

	Successful Outcome N=49	Unfavorable outcome N=32
Sputum Culture conversion (months)		
3	35 (71.42%)	16 (50%)
>3	10 (20.40%)	10 (31.25%)
Treatment Adherence	43 (87.75%)	20 (62.5%)

Table 7: Causality assessment and severity assessment of adverse drug reacton

Adverse drug reaction	WHO causality assessment		
	Certain	Probable	possible
Nausea/vomiting (51) Diarrhea Abdominal pain	0	16	35
Psychological (7)	7	0	0
Joint pain (13)	0	2	2
Bluring of vision (4)	4	0	0
Hearing loss (6)	6	0	0
Jaundice (4)	0	1	3
Nephrotoxicity (3)	0	0	3
Generalized weakness (22)	0	0	22

4. Discussion

The present study was conducted to evaluate a 2 year retrospective data on treatment outcome and adverse drug reaction in cases of MDR-TB due to second line drugs under programmatic conditions. The study showed convincing result with 60% success rate in treating MDR Tb. Our study achieved a treatment success rate of 60% which is consistent with recently published meta analysis. Though the outcome have improved over a period of time, but they are far from the WHO targets of 75-90% success rate. In spite of treatment, 22.35% of patients died during the course of treatment. 80% of death in our study occurred within 6 month of start of treatment. possible reasons include bilateral extensive disease leading to respiratory failure, adverse drug reactions and superadded infections. Early detection of complications by the DOTS provider and timely referral to DRTB centre might helped in decreasing mortality. Our study showed treatment default rate of 10.58%.Treatment default rate is an important parameter to judge performance of the programme as minimizing it not only improve treatment outcome but also prevent further spread of MDR-TB.Sputum culture conversion is an important indicator of treatment response that also determines the duration of intensive phase. In our study the conversion rate of 83.52% which is comparable to other study around 60%b patient had a sputum culture conversion at 3 months. However 18.82% of them still had unsuccessful end treatment outcome. This emphasizes the need for close monitoring, counseling and care by DOT care provider. Previous studies have shown baseline resistance to fluoroquinolones, baseline sputum smear positivity, previous treatment failure or default and low BMI as predictor of delayed culture conversion. Alcohol abuse has been associated with poor outcome including default and death in previous studies. However the significant difference in alcohol addiction among outcome groups was not seen in our study due to less number of patients with alcohol addiction. Interestingly diabetes has not been seen to impact second line TB treatment outcomes but increases the risk of adverse events to treatment. There were significant (P<0.05) association between cure and ADRs. Treatment outcomes were significantly better among those who experienced ADRs. Possible explanation is those patients who have side effects were followed more closely by TB drug providers and thereby adherent to treatment, thus increasing the likelihood of favourable treatment outcome. In ours study majority of ADRs were gastrointestinal: 51 (46.36%), generalized weakness 22 (20%), Joint pain 13 (11.81%) psychiatrics: 7 (6.36%), otovestibular 6 patients (5.45%). There were no documented ADRs of renal, ophthalmic, endocrinal and hepatobiliary toxicity. Most of the gastrointestinal symptoms were nausea, vomiting, epigastric discomfort which was treated symptomatically. In psychiatric ADRs most of them were Insomnia, depression, seizure. In case of ADRs caused by cycloserin, drug needed to be stopped.

There were 6 patient having hearing loss, among them 5 patients had caused by kanamycine which was stopped and one patient had caused by cyclosporine which was also stopped.

5. Conclusion

Cure rate was higher in MDR-TB cases with ADRS than MDR-TB cases without ADR, Attention needs to be paid for timely recognition and treatment of ADR with minimum of treatment regimen. Present study revealed that the treatment success rates in MDR-TB under programmatic management have shown improvement over the recent years but are still far from targets. The results also suggest measures to ensure treatment adherence might help to improve the performance of programme and treatment success rates

References

[1] World health organization. Global tuberculosis report.2016
[2] Central TB division. Guidelines on programmatic management of deud resistant TB (PMDT) in India
[3] Kibret KT, Moges y, memiah p, biadgilign s. Treatment outcome for multidrug –resistant tuberculosis under DOTS –plus; a systematic review and meta –analysis of published studies. infect dis poverty
[4] Orenstein EW, basu s, shah ns, Andrews jr, friendland GH, mollAP, et all. Treatment outcome among patients with multidrug –resistant tuberculosis ;systematic review and meta –analysis. lancet infect dis 2009:9;153-61