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Adverse Drug Reactions in the Treatment of Drug Resistant Tuberculosis in India

*N T Awad[1] Jairaj P. Nair[2] Ganesh Dhangar[3]
Department of Respiratory Medicine, Lokmanya Tilak Municipal Medical College (LTMMC) & General Hospital, Sion, Mumbai – 22
1 –Professor & Head 2 – Corresponding Author & Associate Professor 3 – Registrar

ABSTRACT:
Drug Resistant Tuberculosis (DR-TB) in India is a major setback to National TB Control Programme and to the socio-economic situation in India. 508 patients of drug resistant TB cases were initiated and followed up over 2 years of DOTS PLUS treatment in Mumbai city. Their demographic profiles were analyzed and their adverse drug reactions were recorded.
DR-TB affected the most economically productive age group (21- 30 yrs) with treatment related side-effects adding to their woes. The most common adverse effects due to DR-TB treatment included gastro-intestinal, neuropsychiatry symptoms and drug induced hypothyroidism. Nutritional deficiencies, addictions and co-existing diseases like diabetes and HIV added to the drug intolerance. This study highlights the need for less toxic drugs and shorter duration of DR-TB treatment.
***Key words**: MDR TB, XDR TB, Outcomes, Co-morbidities, HIV, Diabetes*

I. Introduction:

Drug Resistant Tuberculosis (DR-TB) is a menace to Revised National TB Control Programme in India. The rise in number of cases is due to both incomplete treatment of TB and better diagnostic techniques in DR-TB. Mumbai spearheads the DR-TB cases in India being a densely populated city with migrant population for job opportunities. DOTS PLUS programme was launched in India on pilot basis in 2007 and incorporated in the National Programme in 2010 (DOTS PLUS).[1,2] The treatment of DR-TB is extensive, expensive and associated with side effects to drugs[3]; making it difficult to complete the entire course of treatment. It was necessary to study the demographic profile, co-morbidities and adverse drug reactions in DOTS PLUS treatment.

II. Aims & Objectives:

1) To study the demographic profile of DR-TB patients
2) To study various co-morbidities in DR-TB patients.
3) To study the adverse drug events during the treatment of DR-TB patients.

III. Methodology:

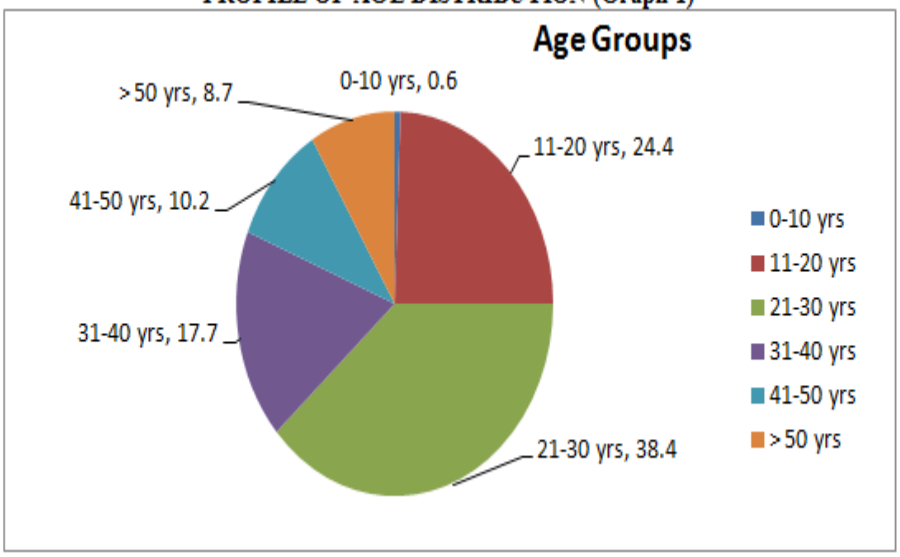
508 patients with DR-TB cases were followed up at DOTS PLUS Site over a period of two years. Their detailed demographic, clinical, radiologic and laboratory data were collected and analyzed. They were followed up periodically for clinical, radiologic and laboratory adverse effects. The data was analyzed using SPSS software programme.

IV. Results & observations:

DEMOGRAPHICAL DATA (Table 1)

No. of cases	508
Age (yrs) Mean Range	30.17 12.54 7.00 – 75.00 yrs
Mean BMI (kg/m^2)	17.38
Gender Males Females	 268 (52.8%) 240 (47.2%)

Profile Of Age Distribution (Graph 1)



The profile showed that **38.4%** of cases belonged to age group of 21 - 30yrs, followed by **24.4%** were in the age group of 11 – 20 yrs followed by **17.7%** were in the age group 31 – 40 yrs and **10.2%** of cases had age 41 - 50yrs. Thus, it is seen that 56.1% of patients belonged to 21-40 years age group which is economically productive age-group. It was seen that 65.1% cases had BMI < 18.5 kg/m^2 (Undernourished) and 34.9% cases had BMI ≥ 18.5 kg/m^2.

Profile of comorbidities (table 2):

Co morbidity	**No. of cases (N=508)**	**% of cases**
Smoking	22	4.33
Alcohol	47	9.25
Diabetes	29	5.7
HIV Status	31	6.1
Hepatitis B	02	0.4
Renal disease	01	0.2

- This table reveals that **13.6%** of cases were smokers & Alcohol consumers. **6.1%** of cases were HIV reactive and **5.7%** cases were Diabetics.

Profile of adverse drug reactions in drug resistant tuberculosis regimen treatment (table 3):

Complications		**(N=508)**		**Intensive Phase**		**Continuation Phase**	
		No	**%**	**No**	**%**	**No**	**%**
Gastro-Intestinal System	Vomiting	**214**	**42.1**	203	40.0	11	2.2
	Nausea	**212**	**41.7**	206	40.6	6	01.2
	Jaundice	**10**	**2.0**	7	1.4	3	0.6
	Abdominal Pain	**48**	**9.4**	37	7.3	11	2.2
	Abdominal discomfort	**27**	**5.3**	20	3.9	07	1.4
	Loose Motions	**54**	**10.6**	50	9.8	04	0.8
	Wt. Loss	**06**	**1.2**	3	0.6	3	0.6
Joint System	Jt. Pain [4,5]	**74**	**14.6**	30	5.9	44	8.7
	Jt. Swelling	**9**	**1.8**	-	-	9	1.8
Peripheral Nervous System	Tingling Sensation	**64**	**12.6**	21	4.1	43	8.5

	Numbness	**22**	**4.3**	8	1.6	14	2.8
Skin system	Itching	**06**	**1.2**	2	0.4	4	0.8
	Reddish discoloration of skin	**06**	**1.2**	1	0.2	5	1.0
	Bleeding from mouth	**02**	**0.4**	1	0.2	1	0.2
ENT System	Loss of hearing	**37**	**7.3**	4	0.8	33	6.5
	Vertigo	**04**	**0.8**	1	0.2	3	0.6
	Tinnitus	**24**	**4.7**	17	3.3	7	1.4
	Giddiness	**05**	**1.0**	2	0.4	3	0.6
Opthalmic System	Blurring of vision	**16**	**3.1**	2	0.4	14	2.8
	Color Blindness	**02**	**0.4**	-	-	2	0.4
Endocrine System	Hypothyroidism	**124**	**24.4**	4	0.8	120	23.6
Neuropsychiatry System	Depression	**81**	**15.9**	47	9.3	34	06.7
	Schizophrenia	**39**	**7.7**	19	3.7	20	03.9
	Psychosis	**14**	**2.8**	8	1.6	6	1.2
	Convulsion	**1**	**0.2**	-	-	1	0.2
	Mania	**3**	**0.6**	1	0.2	2	0.4
	Amnesia	**1**	**0.2**	-	-	1	0.2
	Change of behavior	**10**	**2.0**	5	1.0	5	1.0
	Increase Sleep	**3**	**0.6**	1	0.2	2	0.4
	Anxiety Disorder	**4**	**0.8**	3	0.6	1	0.2

In this study, maximum number of patients had gastro-intestinal intolerance to treatment in form of nausea and vomiting (41.7% & 42.1%) [5]. Therefore, reassurance & continuation of treatment with H_2 antagonist / proton-pump inhibitor + antiemetics helped to improve compliance. Due to these measures, the Adverse Drug Reactions seen in Continuation Phase were much less [6%]. Next common side effect in this study was neuro-psychiatric complaints (depression, anxiety, convulsions, mania, psychosis, sleep disturbances) [26.4%] which were managed with counseling and anti-psychiatry medications and in rare cases Cycloserine was withdrawn. The next common adverse event noted was sub clinical hypothyroidism (elevated TSH) about 25.3% which was managed with thyroid supplementation and follow-up thyroid profile.

Hypothyroidism in DR-TB Treatment:

Serum Thyroid Stimulating Hormone (TSH) among the cases: (Table 4)

Serum TSH level (µIU/ml)	**Baseline (N=427)** **No.** **%**	**II[IP to CP] (N=366)** **No.** **%**	**III[End of treatment] (N=283)** **No.** **%**
< 5	409 95.8	255 69.7	162 57.2
≥ 5	018 04.2	*111 30.3	*121 42.8
p values	NA	*0.001	*0.001

By Chi – Square test *Significant

- According to above study, **4.2%** cases had Serum TSH level ≥ 5 µIU/ml at baseline.
- At Intensive & Continuation phase, proportion of cases with Serum TSH level ≥ 5 µIU/ml showed a statistically significant rise from baseline.(30.3% & 42.8% at Intensive phase and Continuation phase) [6,7]

Association Between Hypothyroidism And Treatment: (Table 5)

Treatment	**No. of cases**	**% of cases with Hypothyroidism**	
		No	**%**
PAS + Ethionamide	14	*09	64.3
Ethionamide	408	115	28.2

By Chi – Square test P= 0.003,*Significant

Above table reveals that, **64.3%** cases treated with combination of PAS & Ethionamide had Hypothyroidism which was significantly more as compared to **28.2%** cases treated with Ethionamide alone.

Liver & Kidney Function Tests on DR-TB Treatment:

Only 0.7% [3 cases] had Serum transaminases (ALT & AST) levels greater than 100 IU/ml at baseline. Of the 3 cases with Serum transaminases level greater than 100 IU/ml at End of Treatment, 2 cases were found to be reactive to Hepatitis B Virus infection; while 1 case had alcoholic liver disease.

At baseline, 3.07% cases had Serum Creatinine levels greater than 1.2mg/dl. No significant changes were noted in these values during the course of treatment.

IV. Conclusions

In our study, as per adverse drug reaction to MDR/XDR-TB treatment, majority of the patients had gastro-intestinal intolerance to treatment in form of nausea, vomiting. Reassurance & continuation of treatment with H_2 antagonist / proton-pump inhibitor + antiemetics helped to improve compliance leading to the reduction of the Adverse Drug Reactions in Continuation Phase to 6%. Next common side effect from our study was neuro-psychiatric complaints [26.4%]. This was followed by sub clinical hypothyroidism about 25.3% seen in regimens containing PAS & Ethionamide.

In all the above cases, common side effects could be treated simultaneously without stoppage of Anti tuberculosis drugs except in extreme cases where modification of regimen may have to be used.

In summary, Drug Resistant Tuberculosis Treatment is associated with adverse drug reactions. Most of these adverse drug events can be managed with counselling and symptomatic treatment. Some of the serious adverse events may require admission and special consultations for symptom management.

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