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Pharmacology

ADVERSE DRUG REACTIONS IN MDR-TB PATIENTS ON CAT IV OF DOTS-PLUS AND THEIR EFFECT ON CULTURE CONVERSION

KEY WORDS: Multi-drug resistant tuberculosis, Adverse Drug Reactions, Culture Conversion.

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ABSTRACT

Background: Multi-Drug resistant tuberculosis, has emerged as a challenge to public health due to long duration of treatment with high pill burden, associated adverse drug reactions. We have thus investigated the adverse drug reactions with MDR-TB Cat-IV regimen under programmatic study settings and analysed the impact of these ADR's on culture conversion.

Methods: This prospective cohort observational study was conducted at DOTS-PLUS site, Amritsar, Punjab (India). Adverse drug reactions reported by Eighty consecutive MDR-TB patients, and recognized by laboratory and/or clinical evidence were recorded after informed consent. The culture conversion rates at 6 months in patients with adverse drug reactions and without adverse drug reactions were compared using Chi2 exact test.

Results: A total of eighty patients reported 76 adverse drug reactions, with a mean age 32.38± 13.60 years, male: female ratio of 5:3. Forty two (52.5%) patients experienced at least one adverse event. The adverse effects warranted discontinuation of the suspected offending medicine in 22(27.5%) patients. The rates of occurrence of ADR's were: Gastrointestinal side effects:31.25%, Ototoxicity:23.75%, psychiatric symptoms:11.25%, arthralgia/ hyperuricemia: 10%, hepatotoxicity: 5%, nephrotoxicity: 5%, injectable related problems: 3.75%, skin rash:2.5%, peripheral neuropathy:2.5%.

The difference in culture conversion rates in patients with ADR's(50%) and without ADR's(52%) was not statistically significant (p value 0.6474, odds ratio 0.75, 95% CI 0.3042 to 1.849)

Conclusion: There is a high frequency of ADR's in MDR-TB cases. When appropriately monitored and managed, ADR's do not effect rates of culture conversion .Newer and less toxic drugs are urgently needed to treat MDR TB patients.

INTRODUCTION:

Drug resistant TB is an emerging public health problem throughout the world. [1] As per the World health organization Global Tuberculosis Report 2014, 9 million people were infected with Tuberculosis worldwide, out of which 4,80,000 were estimated to be infected with multi-drug resistant tuberculosis.[2]

MDR-TB is defined as resistance to Rifampicin and Isoniazid with or without resistance to other drugs. The disease poses difficulties in management due to multidrug treatment for a long duration associated with a wide range of adverse drug reactions.[3,4] An ADR is defined as: any unintended adverse response to a drug occurring at a therapeutic dose and resulting in either death, drug withdrawal, change in the administration of the frequency or dose of the drug, or, that no action is required. The severity of these reactions can range from mild, no intervention required, to the more severe or life-threatening (SADR) where drugs need to be withdrawn, either completely from the regimen or with re-introduction once the SADR has subsided.[5]

Management of ADR's has been recommended as an integral component of MDR-TB management by WHO.[6] The consequences of ADR's in MDR-TB patients and their impact on morbidity, mortality and disease outcomes need to be studied. Adherence to treatment is a critical factor in the management of MDR-TB, and adverse events associated with second line drugs could have a severe impact on adherence. Limited evidence of adverse events is available from resource-limited settings.[7] The present study is an attempt to study the adverse drug reactions in MDR-TB patients and analyse how the ADRs affect the culture conversion at 6 months of therapy.

Subjects And Methods:

This prospective cohort observational study was conducted at District Tuberculosis Centre, Amritsar, Punjab (India). The centre has a DOTS-PLUS site attached to it, where Cat- IV treatment of MDR patients is initiated after pre-treatment evaluation and hospitalization for 7 days. Post-hospitalization, the treatment at DOT centre is initiated and the patient reports monthly for the subsequent follow up examinations to District Tuberculosis Centre. All the patients are given medications free of cost as per DOTS PLUS Protocol of Revised National Tuberculosis Control Programme (RNTCP). During intensive phase, for at least 6 months, patients are given a standard regimen consisting of Kanamycin, Pyrazinamide, Levofloxacin, Cycloserine, Ethionamide, Ethambutol and Pyridoxine. This is followed by continuation phase for eighteen months with Levofloxacin, Cycloserine, Ethambutol and Ethionamide.

The study included 80 consecutive MDR-TB patients, who were treated for at least 6 months between January 2012 to March 2014. The study subjects were initiated on treatment at DOTS-PLUS site Amritsar, and were visiting District TB Hospital for follow up cultures, clinical and laboratory examinations. Before discharge, patients were informed about possible side effects that may occur during MDR-TB treatment. There were no exclusion criteria in the study.

During the monthly follow up visits, the patients were questioned on possible side effects. Symptoms associated with side effects were recorded on a data form prepared for patient follow-up. Informed consent was taken from the patient. Specialist consultation was sought for management of side effects and patients requiring admission were referred to DOTS-PLUS site after recording the adverse effects. Drugs were discontinued whenever ototoxicity, nephrotoxicity, hepatotoxicity, uncontrolled psychiatric disorders, or uncontrolled gastrointestinal disorders developed. The patient was asked to report back after the specialist consultation to the study site. Thus, the ADR's associated with treatment were reported by the patient and recognized by laboratory data and/or clinical evidence. The adverse drug reactions reported by the patient but not defined by laboratory criteria, were considered if the treating TB physician documented the reaction according to his/her clinical criteria The adverse drug reactions were defined as follows:

- Ototoxicity—tinnitus, hearing loss confirmed by audiometry
- Vertigo- presence of disequilibrium
- Psychiatric disorders—presence of depression, anxiety, nightmares or psychotic symptoms

- Gastrointestinal effects—nausea, vomiting, abdominal pain, haematemesis, melena, diarrhoea
- Arthralgia, arthritis—pain or swelling in the joints, limitation of movement
- Hepatotoxicity—any elevation of serum transaminases in the presence of symptoms or Elevation of either serum transaminase or serum bilirubin at least 3 times the upper limit of normal values
- Nephrotoxicity—rise in the serum creatinine of 0.5 mg/dl from baseline at any time during treatment
- Skin Rash- A dermatologic reaction felt to be related to anti-tuberculosis medications, as documented by physician
- Neuropathy- pain or numbness of the distal extremities, as diagnosed by physician.

The culture tests were sent at 3, 4, 5, 6 months of initiation of treatment under the programme, to monitor the culture conversion rates as intermediate outcome and cure rates as the final outcome of Cat IV MDR-TB regimen. The outcome considered in the study was culture conversion after a treatment of at least 6 Months. As per the RNTCP guidelines, the patient was considered culture converted if two consecutive cultures of the patient were negative.[8]

The rate of culture conversion in patients with adverse drug reactions and without adverse drug reactions was calculated and analysed using Chi^2 test.

RESULTS:

Eighty (80) patients were treated for DR-TB during the study period. The number of male patients (50/80, 62.5%) was more than females (30/80, 37.5%). The mean patient age was 32.38± 13.60 (SD) years. The mean baseline Body Mass Index was 17.56 ± 4.1 (SD) kg/ m. Forty two (52.5%) of the eighty patients experienced at least one adverse event. A total of 76 adverse events were reported by these patients. The number of adverse events experienced by an individual patient ranged from one to four.

The characteristics of the two groups, one with adverse effects (42 patients, 52.5%) and other without side effects (38, 47.5%) were compared. **Table1** describes the characteristics of the cohort.

The adverse effects, warranted discontinuation of the suspected offending medicine in 22(52.38%) of the 42 patients experiencing them. The other patients were managed by administering drugs to treat them. Gastrointestinal tract (GIT)-related events (gastritis, nausea, vomiting, abdominal pains, diarrhoea and constipation), hearing loss, tinnitus, vertigo and joint pain were the predominant adverse events. Gastrointestinal side effects were the most common side effect and were detected in 25(32.25%) cases. Proton pump inhibitors, H2 receptor blocker or anti-emetic agents were added to the regimen.

Ototoxicity, presenting as hearing loss, tinnitus and vertigo was detected in 15 cases (18.75%), occurring at a mean of 4.5 months of treatment. Psychiatric symptoms were observed in 9 (11.25%) patients. These included a wide range of symptoms, from mild depression and anxiety to psychosis and suicidal tendency. The disorders were managed by psychiatrist either by regimen modification or with additional medication. Eight (10%) patients complained of arthralgia. Six out of these eight showed uric acid elevation and were managed by non-steroidal anti-inflammatory agents or allopurinol. The description of frequency of adverse drug events is as shown in **Table 2.**

The outcome i.e culture conversion rates of the group with adverse drug events and without adverse drug events (as shown in Fig 1) were compared using Chi^2 test with results p=0.91, RR=1.02, 95% CI=0.66 to 1.58. This shows the adverse events to the MDR-TB treatment do not adversely affect the culture conversion.

On further analysis, students' unpaired 't' test was applied on the data to find if age difference in the two groups was significant. The two tailed P value was 0.0288 considered significant (t=2.227 with 79 degrees of freedom). This shows that the age of patients with adverse drug reactions was higher than those without adverse drug reactions and the age difference is significant statistically. Body mass indices of the patients who showed culture conversion at 6 months were compared with those showing non-conversion or other unfavourable outcomes i.e died, default or transfer out. Average BMI of the culture converted patients was 18.22±4.09 Kg/m^2 while that of the group with unfavourable outcomes was 16.51± 3.84 Kg/m^2. Students' unpaired 't' test showed the difference between the two groups not quite significant. (P value 0.0516, t=1.975 with 83 degrees of freedom).

Amongst the eighty MDR-TB patients in the study group, 41(51.25%) showed favourable outcome i.e culture conversion while 39(48.75%) patients showed unfavourable outcome. Eleven out of eighty patients (13.75%) showed culture non-conversion. Other unfavourable outcomes were twelve out of eighty (15%) default and ten (12.5%) died. Six (7.5%) patients were referred out. A total of twelve patients defaulted; five due to ADR's, two resorted to alternative systems of medicine, two showed lack of trust in treatment due to ignorance and illiteracy, one due to co-morbidities and two due to unknown reasons.

DISCUSSION:

Although there have been studies on epidemiology and outcomes of Multi-drug resistant tuberculosis, adverse drug reactions in MDR-TB patients have seldom been studied.[9]

Adverse drug reactions, particularly GIT-related adverse events, hearing loss, tinnitus, psychiatric symptoms and joint pains were observed in 52.5% of the study subjects. The impact of adverse drug reactions in MDR-TB regimen can be estimated from the findings of the study that ADR's lead to modification of the Cat IV regimen in 52.38% of the patients experiencing them. These findings are in coherence with the previous studies.[10,11,12]

Our study showed a wide range of adverse effects with gastrointestinal adverse effects being the most common followed by a considerable number of patients presenting with ototoxicity and psychiatric manifestations. Although gastrointestinal ADR's were the most common but they did not call for change in treatment regimen in any of the patients.

Ototoxicity, psychiatric symptoms and arthralgia were the side effects that led to alteration in the treatment regimens as in the previous studies. [13] Findings of various other studies have also shown high incidence of ototoxicity to be associated with MDR-TB Regimens[14] This presses upon the need for a baseline and monthly audiology screening for early identification and management of hearing loss. Further research is needed to study alternate regimens for injectable aminoglycosides Vs daily dosing in MDR-TB patients.

The findings of the study press upon the need for adequate training of health professionals for diagnosis and management of these adverse drug reactions concomitantly with administration of treatment regimen. In order to minimize the impact of ADR's on treatment adherence, the MDR-TB patients need elaborate pre-treatment counselling and proper counselling sessions during the treatment also.

The huge burden of ADR'S emphasizes on the need for programmatic availability of drugs for management of ADR's. The ancillary drugs for the management of most common ADR'S should be procured with the second line drugs.

The findings of the study call for development of better and safer drugs through research and development so that better tolerated and shorter drug regimens can be designed for MDR-TB patients.

The study results show that ADR's, if appropriately diagnosed and managed, do not have adverse impact on the outcomes of MDR-TB patients. This is in coherence with a study on adverse drug reactions in MDR-TB in Nigerian population.[15]

The treatment success rate of 51.25% shown by culture conversion is comparable to the global average of 48% as reported by WHO[16] and 52% as shown by the MDR-TB cohort in Vietnam.[17] However some low burden MDR-TB reporting countries like Israel and Dominician Republic have reported comparatively higher success rates of 71% to 75%.[18,19]

The strengths of our study were that the ADR's were patient reported and verified by clinicians and laboratory investigations. The study had limitations of restricting the ADR monitoring to intensive phase of treatment and to the region of Amritsar, though the district catered to almost half of the MDR-TB patients in state of Punjab, being the first of the two DOTS-PLUS centres in the state. In spite of the limitations, our study has generated findings which have important programmatic and clinical implications.

CONCLUSION

The findings of the study depict a huge burden of adverse drug reactions in MDR-TB patients on Cat IV DOTS-PLUS regimen. This emphasizes on intensive training of staff for diagnosis and management of ADR'S aggressively. Pre-treatment counselling and proper intermittent counselling during treatment regarding ADR's could improve psychological well being of the patient and thus treatment adherence. Some ADR's like ototoxicity and psychiatric symptoms call for further research to chalk out shorter and better tolerated regimens and new drugs.

Tables

Table 1. Characteristics And Outcomes Of MDR-TB Patients With ADR'S And Without ADR's

Characteristics	With adverse drug reactions n=42(52.5%)	Without Adverse Drug reactions n=38(47.5%)
Age	36.05±13.42 Years	29.44±13.1 Years
Male Sex	26(62.5%)	28(73.68%)
BMI	18.70±4.35825	16.65± 3.612625
Outcome at 6 months treatment		
Culture Converted	21/42(50%)	20/38(52.63%)
Culture Not Converted	6/42(14.3%)	5/38(13.16%)
Default	8/42(19.05%)	4/38(10.53%)
Died	4/42(9.52%)	6/38(15.79%)
Referred Out/Transfer Out	3/42(7.14%)	3/38(7.89%)

Table 2. Adverse Drug Reactions In MDR-TB Patients

Adverse Drug Reaction	Patients experiencing adverse drug reactions out of 80	Months treatment at presentation (Mean)
Hearing loss	12(15%)	4.5 months
Vertigo	7(8.75%)	4.2 months
Psychiatric disorders	9(11.25%)	3.5 months
Arthralgia	8(10%)	2.2 months
Gastrointestinal adverse effects	25(31.25%)	2 weeks
Hepatotoxicity	4 (5%)	5.2 months
Injectable related problems	3(3.75%)	2.5 months
Nephrotoxicity	4(5%)	4 months
Skin Rash	2(2.5%)	1.2 months
Peripheral neuropathy	2(2.5%)	5.8 months

REFERENCES:

1. World Health Organization. Multi drug and extensive drug resistant TB (M/XDR-TB): 2012 global report on surveillance and response. 2012.
2. World Health Organization (WHO). Global Tuberculosis Report. 2014 Geneva: WHO Press, WHO/HTM/TB/2014.08.
3. Torun T, Gungor G, Ozmen I, Bolukbasi Y, Maden E, Bicakci B, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005; 9:1373–1377. PMID: 16468160
4. Palmero D, Cruz V, Museli T, Pavlovsky H, Fernández J, Waisman J. Adverse drug reactions in multidrug-resistant tuberculosis. Medicina (B Aires). 2010;70 (5): 427-33.
5. Walt MV, Lancaster J, Odendaal R, Davis JG, Shean K, and Farley J. Serious Treatment Related Adverse Drug Reactions amongst Anti-Retroviral Naïve MDR-TB Patients. PLoS One. 2013; 8(4): e5881.
6. World Health Organization. Treatment of tuberculosis guidelines. Geneva: WorldHealthOrganization Press; 2010.
7. Nathanson E, Gupta R, Huamani P, Leimane V, Pasechnikov AD, Tupasi TE, et al. Adverse events in the treatment of multidrug-resistant tuberculosis: results from the DOTS-Plus initiative. Int J Tuberc Lung Dis 8(11): 1382–1384.
8. Central TB Division Directorate General of Health Services, MOH&FW, Nirman Bhawan, New Delhi. RNTCP. Guidelines on Programmatic Management of Drug Resistant TB (PMDT) in India.
9. Kehinde AO, Obaseki FA, Ishola OC, Ibrahim KD. Multi-drug resistance to Mycobacterium tuberculosis in a tertiary hospital. J Natl Med Assoc. 2007; 99:1185–1189.
10. Furin JJ, Mitnick CD, Shin SS, Bayona J, Becerra MC, Singler JM, et al. Occurrence of serious adverse effects in patients receiving community-based therapy for multidrug-resistant tuberculosis. Int J tuberc lung dis 2001; 5(7): 648–55.
11. Torun T, Gungor G, Ozmen I, Bolukbasi Y, Maden E, Bicakci B, et al. Side effects associated with the treatment of multidrug-resistant tuberculosis. Int J Tuberc Lung Dis. 2005; 9:1373–1377.
12. Prasad R, Singh A, Srivastava R, Hosmane GB, Kushwaha RA, Jain A. Frequency of adverse events observed with second-line drugs among patients treated for multidrug-resistant tuberculosis. Indian J Tuberc. 2016 Apr; 63 (2): 106-14.
13. Hire R, Kale AS, Dakhale GN and Gaikwad N. A Prospective, Observational Study of Adverse Reactions to Drug Regimen for Multi-Drug Resistant Pulmonary Tuberculosis in Central India. Mediterr J Hematol Infect Dis 2014, 6(1): e2014061.
14. Modongo C, Sobota RS, Kesenogile B, et al. Successful MDR-TB treatment regimens including amikacin are associated with high rates of hearing loss. BMC Infect Dis. 2014; 14:542.
15. Avong YK, Isaakidis P, Hinderaker SG, Vanden Bergh R, Ali E, Obembe BO, et al. (2015) Doing No Harm? Adverse Events in a Nation-Wide Cohort of Patients with Multidrug-Resistant Tuberculosis in Nigeria. PLoS ONE 10(3): e0120161.
16. World Health Organization. Companion handbook to the WHO guidelines for the programmatic management of drug-resistant tuberculosis. Geneva, Switzerland: WHO; 2015.
17. Islam T, Marais BJ, Nhung NV, Chiang CY, Yew WW, Yoshiyama T, et al. Western Pacific Regional Green Light Committee: progress and way forward. Int J Infect Dis. 2015 Mar; 32:161-5.
18. Mor Z, Goldblatt D, Cedar N, Rorman E, Chemtob D. Drug-resistant tuberculosis in Israel: risk factors and treatment outcomes. Int J Tuberc Lung Dis. 2014; 18:1195–1201.
19. Rodriguez M, Monedero I, Caminero J A. et al. Successful management of multidrug-resistant tuberculosis under programme conditions in the Dominican Republic. Int J Tuberc Lung Dis. 2013; 17:520–525.