ORIGINAL RESEARCH PAPER

Medical Education

EVALUATION OF ADVERSE DRUG REACTIONS IN THE PATIENTS SUFFERING FROM TUBERCULOSIS WITH HIV: A RETROSPECTIVE COHORT STUDY

KEY WORDS: retrospective, anti-TB drugs, HIV positive, chi-square test, adverse drug reaction

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ABSTRACT

TB is a communicable disease, become one of the leading infectious diseases that cause death after HIV. Side effects of the antituberculosis (anti-TB) drugs may be mild as well as serious. Non-adherence to treatment because of adverse drug reactions is one of the major problems in tuberculosis patients. Hence we aim to study the adverse drug reactions and causality assessment in cases receiving anti-TB drugs. An observational retrospective study was used in this study. Patients taken for the study that treated for tuberculosis in the district TB center in Wardha Civil Hospital.TB patients and TB with HIV-reported patients were included in this study while TB with additional illness- was excluded. 2 years of data were collected. A majority of cases reported GIT problems followed by musculoskeletal and skin reactions. Data was scrutinized by using descriptive and inferential statistics using the Chi-square test, Kappa Test and the software used in the analysis were SPSS 27.0 version and Graph-Pad Prism 7.0 version. For the Causality assessment of ADR WHO-UMC was used.

INTRODUCTION

Tuberculosis is an international problem despite advances in the methods of diagnosis and treatment.[1] The World Health Organization (WHO) declared tuberculosis (TB) a public health emergency in 1993. TB remains a significant public health threat and a major cause of death worldwide. Despite the WHO's End TB program, which set aspiring targets for 2020–2035, many regions are not on track to achieving these goals. HIV-positive persons are ten times more likely to develop TB than HIV-negative.[2,3]

Adverse drug reactions (ADRs') to anti-tubercular drugs are quite common as they are being used for longer duration. ADRs may cause associated morbidity and even mortality if not recognized early. It is not sufficient to find out the incidence, nature, and severity of adverse reactions to drugs, though accurate data are obviously useful. It is necessary to evaluate patterns of adverse reactions against each other.[4,5] In countries like India, most clinicians are not adhering to the antibiotics policy and are rampantly using second-line drug treatment even in the absence of sensitivity reports. Such a malpractice may culminate in the outbreak of TB and newer TB strains, viz. XDR-TB strain, etc., beyond control. The emergence of XDR-TB strains is threatening the commitment underlying the DOTS Plus program that intends to provide high-quality service in the diagnosis and treatment of MDR-TB. MDR-TB is not only resistant to quinolones and aminoglycosides but other second-line ATT drugs also. This may be due to the fact that the use of second-line ATT drugs is widespread and unchecked.[6]

Despite greater toxicity and lesser efficacy of second-line drugs compared with first-line therapy MDR –TB treatment programs have achieved cure rates than 80% even in poor patients but show more adverse effects. [7] Active screening should be performed for TB in people living with HIV (PLHIV). A high degree of clinical suspicion for TB is warranted in PLHIV presenting with fever, cough, and unintentional weight loss. HIV-Mycobacterium tuberculosis (MTB) co-infection is often pauci-bacillary, precluding diagnosis by conventional diagnostics and/or smear microscopy/culture. TB- HIV co-infection showed that there was an increase in the co-infection rate, i.e. 15.1% of persons screened in 2010 were positive, this figure reduced to 5.6% in 2011 but raised again to 7.1% in 2012 and so far 32.2% of those screened in 2013 were positive. The rapid increase in co-infection rate indicates that serious measures should be taken by the relevant authorities towards combating this menace.[8,9]

Tuberculosis infection is a result of the interplay between bacterial virulence and host resistance, On the other hand, HIV transmitted primarily through genital fluids, blood, and mucosa interacts with different cells in the body and tends to escape the host immune response against it, resulting in full-blown AIDS disease.[10]

However, more data on the characteristics and management of adverse drug reactions are needed to inform clinicians. In addition, it is important to know whether the occurrence of adverse reactions negatively impacts treatment outcomes.[11]

As TB is a widespread disease in major parts of India, several steps have been taken to eradicate the disease and programs such as RNTCP and DOTS were initiated. [12] The occurrence of ADRs causes discomfort and is one of the main reasons for non-compliance[13]. So monitoring ADRs and increasing awareness of ADR reporting is today's necessary activity to avoid future complications due to ADR and adherence to treatment. The present study aimed to scrutinize the incidence of adverse drug reactions in patients suffering from tuberculosis. in newly diagnosed TB patients and in TB with HIV-positive patients.

MATERIALS AND METHODS[16,17,18]

This was a retrospective experimental study. Two years of 2017 and 2018 data were observed. 2720 patients were registered during these years. Patients diagnosed with TB, (a) evidenced by positive culture, (b) or suspected TB based on their clinical presentation, and (c) documented TB with HIV positive involved in this study. TB with other diseases were excluded except HIV-positive cases. Data of all TB-positive patients used from HIS records of MGIMS and District TB Center, Civil Hospital Wardha after obtaining permission from hospital authority and analyzed. The privacy of the details obtained was confirmed all out the study. Patient's files were sorted and selected according to inclusion and exclusion criteria. Cases of first-line and second-line therapy are identified with the help of medical records. All types of TB patients who were admitted from Jan. 2017 to Dec. 2018 were studied retrospectively. All types of TB patients who were admitted from Jan. 2017 to Dec. 2018 were studied retrospectively. In the hospital patient was diagnosed with TB by examination of morning sputum smears by Zeihl Neelsen staining, for the presence of Acid fast bacilli (AFB), chest radiographs, and for EPTB, pathological investigations were used. Patients were referred to the DOTS clinic where they are registered and treated under National tuberculosis control

programs.

Statistical analysis was done by using descriptive and inferential statistics using the Chi-square test, Kappa Test and relative risk and software used in the analysis was SPSS 27.0 version and GraphPad Prism 7.0 version, and $p<0.05$ is considered as the level of significance. For the Causality assessment of ADRs WHO-UMC was used.

RESULTS

Table – 1 Gender-wise Distribution Of Patients

Gender	Year 2017	Year 2018	Total
Male	795 (63.35%)	903 (61.64%)	1698 (62.42%)
Female	460 (36.65%)	561 (38.29%)	1021 (37.53%)
Transgender	0 (0%)	1 (0.07%)	1 (0.02%)
Total	1255 (100%)	1465 (100%)	2720 (100%)
The chi-square statistic is 0.8001. The p-value is .371072. Not significant at p < .05.			

Table - 2 Distribution Of Patients According To Type Of TB

Type of TB	Year 2017			Year 2018			
	Male	Female	Total	Male	Female	Transgender	Total
Pulmonary	615 (49%)	314 (25.02%)	929 (74.02%)	624 (42.59%)	304 (20.75%)	0 (0%)	929 (63.41%)
Extra Pulmonary	180 (14.34%)	146 (11.63%)	326 (25.98%)	279 (19.04%)	257 (17.54%)	1 (0.07%)	536 (36.59%)
Total	795 (63.35%)	460 (36.65%)	1255 (100%)	903 (61.64%)	561 (38.29%)	1 (0.07%)	1465 (100%)
κ2-value	35.34,p-value=0.0001, Significant						

Table – 3 Association Of Type Of TB With Hiv Status

TB	Year 2017: HIV Status			Year 2018: HIV Status		
	Non Reactive	Reactive	Unknown	Non Reactive	Reactive	Unknown
Pulmonary	813 (64.78%)	32 (2.55%)	84 (6.69%)	816 (55.70%)	45 (3.07%)	68 (4.64%)
Extra-pulmonary	271 (21.59%)	11 (0.88%)	44 (3.51%)	442 (30.17%)	24 (1.64%)	70 (4.78%)
Total	1084 (86.37%)	43 (3.43%)	128 (10.20%)	1258 (85.87%)	69 (4.71%)	138 (9.42%)
κ2-value	5.23, p=0.073, Not Significant			13.12, p=0.0001, Significant		

Table – 4 Association Of Adverse Drug Reaction With Gender

ADR	Year 2017			Year 2018			
	Male	Female	p-value	Male	Female	Transgender	p-value
GIT	507 (63.77%)	308 (66.96%)	1.29 P=0.25,NS	629 (69.66%)	406 (72.37%)	1 (100%)	1.64 P=0.43,NS
Musculoskeletal System	229 (28.81%)	129 (28.04%)	0.088 P=0.77,NS	251 (27.80%)	168 (29.95%)	1 (100%)	1.18 P=0.55,NS
CNS	241 (30.31%)	133 (28.91%)	0.27 P=0.60,NS	257 (28.46%)	172 (30.66%)	1 (100%)	3.21 P=0.20,NS
Urogenital System	662 (83.27%)	379 (82.39%)	0.15 P=0.69,NS	717 (79.40%)	422 (75.22%)	1 (100%)	3.78 P=0.15,NS
Liver	176 (22.14%)	103 (22.39%)	0.01 P=0.91,NS	181 (20.04%)	134 (23.89%)		3.30 P=0.19,NS
Eye	15 (1.89%)	12 (2.61%)	0.72 P=0.39,NS	32 (3.54%)	27 (4.81%)		1.48 P=0.47,NS
Dermatology/ Skin	239 (30.06%)	139 (30.22%)	0.003 P=0.95,NS	290 (32.12%)	186 (33.16%)		0.65 P=0.72,NS
Haematology/ Blood	68 (8.55%)	97 (21.09%)	40.08 P=0.0001,S	205 (22.70%)	132 (23.53%)	1 (100%)	3.47 P=0.17,NS
Total	795	460		903	561	1	

Table – 5 Association Of System Wise Adverse Drug Reactions

System-wise ADRs	Total ADRs with percentage	Male	Female
GIT (Nausea, Vomiting, Diarrhoea)	1851 (100%)	1136 (61.37%)	714 (38.57%)
Musculoskeletal (Generalised weakness, Joint pain, Arthralgia)	778 (100%)	480 (61.39%)	297 (38.17%)
CNS (Sleepiness, Lethargy, Convulsions, Psychosis)	803 (100%)	498 (62.91%)	305 (37.98%)
Urogenital (Orange/Red urine)	2180 (100%)	1379 (63.25%)	80 (36.74%)
Liver (Hepatitis, Increase ALP)	594 (100%)	357 (60.10%)	237 (39.89%)
Eye (Peripheral neuritis, Headache)	86 (100%)	47 (54.65%)	39 (45.34%)
Skin (Cutaneous reactions, Itching, Rashes)	854 (100%)	529 (61.94%)	325 (38.05%)
Blood (Anemia)	502 (100%)	273 (54.38%)	229 (45.61%)

Table- 6 Causality Assessment By Who-umc

Causality Assessment	Year 2017		Year 2018	
	Male	Female	Male	Female
Certain	1408	816	1646	1014
Probable/ Likely	244	141	283	195
Possible	427	236	438	306
Unassessable / Unclassified	68	97	205	132

In the study ADRs were analyzed by using Statistical analysis by using descriptive and inferential statistics using the Chi-square test, Kappa Test and relative risk and software used in the analysis were SPSS 27.0 version and Graph-Pad Prism 7.0 version and $p<0.05$ is considered as the level of significance. For the Causality assessment of ADR WHO-UMC was used.

DISCUSSION

Out of 2720 reported cases, 1255 were found in the 2017 year and 1465 cases were found in 2018 which shows mostly TB-positive cases found in male patients (62.42%) as compared to females (37.53%). One transgender patient (0.07%) was also found in 2018. There were a total of 1858 pulmonary and 862 extra-pulmonary cases reported which is highly significant statistically (Table 2). Out of these total 77(32+45) pulmonary HIV-positive cases and 35 (11+24) extra-pulmonary HIV-positive cases were found (Table 3). Percentage-wise ADR calculations show more in males than in females. This definitely shows tolerance power more in females than males. Most common adverse drug reactions are from GIT like nausea and vomiting. Urogenital reactions like orange color urine. Dermatologically skin rashes and itching are most common which are manageable by symptomatic treatment. (Table 4,5). Himanshu Sharma, Mohammed AQIL, et al reported the same type of reactions in his Pharmacovigilance study. Amongst the organ systems affected, gastrointestinal ADRs constituted a major component (24.7%) followed by skin reactions (22.2%). they suggested that is very necessary to do long-term and more extensive ADR monitoring in the hospital for the promotion of rational prescribing and drug use in the hospital.[10]

Athira mentioned that the establishment of the causal relationship between the drug and its effect is best assessed by using the standard method.[12] The incidence rate of hepatic dysfunction was found to be the most frequent side effect caused by anti-TB drugs in the present study, these results supported the Alisagar study.[13] Due to the antitubercular drug vision problem, anemia was also reported in this study. The majority of ADRs were associated with oral administrations. The frequency of smokers was 18.5% and the most frequent comorbidities in the patients were lifestyle-related problems, hypertension, and cardiac diseases (10.8%), diabetes (8.4%), COPD, and occupational lung diseases (4.6%)., %,) found by Aliasghar Farazi in his study.[13] Rashmi Pusunoori in her study mentioned that socioeconomic factors or social habits like alcohol consumption, smoking, tobacco use, and working environment may provoke to the exposure of tuberculosis. She found patients with habits of alcohol consumption (56%) followed by smokers (27%) and tobacco chewing (4.23%) were more prone to tuberculosis and the development of ADRs.[14] While Mayur P. Shinde et.al coated that Psychosis is an important concern with MDR-TB therapy. It was the second most common ADR in their study.[15]

Drug-induced morbidity is an important cause of hospitalization and is associated with significant morbidity Among TB patients who completed a rifampicin-containing regimen, the recurrence rate is higher in HIV-positive than in HIV-negative TB patients. Post-treatment prophylaxis with isoniazid reduces the risk of TB recurrence in HIV infected.[18] For ADR assessment causality assessment WHO UMC scale was used. More than 50% of patients came under a certain scale, remaining ADRs came under the probable, possible, and unclassified criteria.[19]

CONCLUSION

In this study, it was found that the most common adverse effects are from the gastrointestinal system followed by the musculoskeletal system and hepatotoxicity. In gender-wise study, males are predominant in TB diseases as compared to females, and HIV-positive cases are also more males as compared to females. Most of the ADRs are mild and can be managed with symptomatic treatment without stopping anti-tubercular drugs. Some ADRs can be moderate or severe causing life-threatening exposure that leads to either modification or cessation of regimen and even death if not recognized and treated promptly. Early identification by active supervision and control of these ADRs might improve adherence and treatment success.

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