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"Evaluation of Study Designs In Anti-Tubercular Regimen" – A Review

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Abstract: *Anti-tubercular drugs used in clinical practice, are not free from ADRs. The added problem is that combinations of drugs are always used for prolonged periods of time therefore; it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Moreover, the Adverse Drug Reactions (ADRs) to the drugs used is one of the major reasons for the patient default treatment. Anti-tubercular drugs may result in ADRs involving almost all system in body, including the gastrointestinal tract, liver, skin, nervous system, otovestibular apparatus and the eyes. In this review we analysed various observational researches in TB diagnosed patients on anti TB treatment.*

Keywords: *Anti-tubercular drugs, adverse reactions, observational researches.*

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I. Introduction

Tuberculosis is an infectious disease caused by the bacterium Mycobacterium tuberculosis. One third of the world's population is thought to be infected with TB. Tuberculosis generally affects the lungs, but can also affect other parts of the body. The classic symptoms of active TB are a chronic cough with blood - containing sputum, fever, night sweats and weight loss. Tuberculosis is spread through the air when people who have active TB in their lungs cough, spit, speak or sneeze. Active infection occurs more often in people with HIV/AIDS and in those who smoke. Diagnosis of active TB is based on chest X- rays, as well as microscopic examination and culture of body fluids. Latent TB is diagnosed by tuberculin skin test or blood tests. Treatment requires the use of multiple antibiotics. Resistance is a growing problem with increasing rates of multiple drug resistant tuberculosis (MDR-TB).Therapy is based on onset of infection. In new onset, therapy is about 6 months with a combination of antibiotics containing Rifampicin, Isoniazid, Pyrazinamide and Ethambutol for first 2 months and only Rifampicin and Isoniazid for the last 4 months. Ethambutol is added in last 4 months in case of Isoniazid resistance. In Recurrent disease, testing to the sensitive antibiotic is important before determining treatment. If MDR-TB is detected, treatment with at least 4 effective antibiotics for 18-24 months is recommended. Adverse drug reactions are very common among patients on anti-tubercular treatment alone or in combination with highly active antiretroviral therapy but comparatively studied very less. Anti-tubercular drugs, just like other drugs used in clinical practice, are not free from ADRs. The added problem is that combinations of drugs are always used for prolonged periods of time therefore; it is likely that the adverse reactions of one drug may be potentiated by the companion drugs used. Moreover, the Adverse Drug Reactions (ADRs) to the drugs used is one of the major reasons for the patient default treatment. Anti-tubercular drugs may result in ADRs including gastrointestinal tract, liver, skin, nervous system, otovestibular apparatus and the eyes. Hence, the current study is for evaluating the adverse drug reaction (ADR) profile in patients receiving anti-tubercular treatment (ATT). (1) The Indian government's Revised National TB Control Programme (RNTCP) started in India during 1997. The program uses the WHO recommended Directly Observed Treatment Short Course (DOTS) strategy to develop ideas and data on TB treatment. This group's initial objective is to achieve and maintain a TB treatment success rate of at least 85% in India among new patients. "In 2010 the RNTCP made a major policy decision that it would change focus and adopt the concept of Universal Access to quality diagnosis and TB treatment for all TB patients". By doing so, they extend out a helping hand to all people diagnosed with TB, and in addition, provide better quality services and improve on therapy for these patients.

II. Treatment

Groups of TB Drugs

GROUP 1: First line oral agents
pyrazinamide (Z/Pza)
ethambutol (E/Emb)
rifabutin (Rfb)
Isoniazid (H/Inh)

Group 2: Second line injectable drugs	Group3: Fluoroquinolones	Group4:Oral bacteriostatic second line agents	Group 5: Agents with an unclear role in drug resistant TB
kanamycin (KM)	levofloxacin (Lfx)	para-aminosalicylic acid (Pas)	clofazimine (Cfz)
amikacin (Amk)	moxifloxacin (Mfx)	cycloserine (Dcs)	linezolid (Lzd)
capreomycin(Cm)	ofloxacin (Ofx)	terizidone (Trd)	amoxicillin/clavulanate (Amx/Civ)
streptomycin (S/Stm)		thionamide	thioacetazone
		protionamide (Pto)	imipenem/cilastatin (lpm/Cin)
			high dose isoniazid (H^h)
			clarithromycin (Clr)

III. Adverse Reactions

DRUGS	ADVERSE REACTIONS
Pyrazinamide	Hepatotoxicity(hepatitis), anorexia.
Ethambutol	Retrobulbar neuritis, construction of visual field, GI disturbances.
Rifabutin	GI disturbances, blood disorders, chest pain, reddish colouration of urine.
Isoniazid	Hepatotoxicity,convulsions,pyridoxine deficiency.
Kanamycin	Pain,haematoma at injection site, malabsorption of fat.
Amikacin	Tinnitus, neuromuscular blockae, ataxia, vertigo
Levofloxacin	Nausea,Diarrohea, Occular burning, pain, Pharyngitis.
Moxifloxcin	CNS effects, Hepatitis, HematologicalDistrubences.
Para amino salicylic acid	Abdominal pain, diarrhea, vomiting.
Cycloserine	Dizziness, Anxiety, Convulsions(dose related),Depression, Rashes.
Clofazimine	Diarrhea, vomiting, nausea.
Linezolid	Diarrohea,ReversibleMylosupression, including Anemia, Thrombocytopenia, (< 10-14 days usage).

IV. Review On ADRS In Anti-Tb Regimen By Using Various Studies

Prospective Observational Studies

Shashimarko et al,.(2017)detected and did causality analysis of ADR's of anti-tubercular drugs used in DOTS therapy,In this study they performed causality analysis of ADR's and analysed ADR's according to their information is collected from a DOTS centre. A total of 62 ADR'S were detected from 720 OPD and 100 IPD among them majority of ADR's reported are moderate 33(53.22%) followed by 29(46.77%) mild , no severe ADR were reported maximum AR's are reported within 4 weeks was found to be 50 % possible and 30.64% probable gastritis was the most common ADR Followed by skin rates.[1]**.** Sahithi et al,.(2016) evaluated the incidence and severity of anti-tubercular drugs induced adverse drug reactions in tuberculosis patients,In this observational study studied authors shows that the incidence and severity of ADR's induced by anti-tubercular drugs. For this they involved 116 patients in the study and among them there are 50 newly diagnosed TB patients the results revealed that 48% of ADR's incidence was observed in their study. Among the patients females are mostly accepted along with patients in age group of 41-60 years lowest incidence was in the age groups of (0-20 years). From this they concluded that thus there is need to provide information to reduce ADR's by tubercular regimen.[2]**.** Vaishnaviprasannan et.al,.(2016) conducted event monitoring in patients prescribed with anti-tubercular therapy,to monitor the events associated with ATT in TB patients to achieve better patient outcomes by regular monitoring. They held prospective observational study for 1 year in 175 patients most ADR's are GI problems, skin allergies, most of the events 72% were reported during on investigations. [3]**.** Athira et al,.(2015) studied adverse drug reactions to first line anti-tubercular drugs in DOTS therapy,In this prospective observational study the authors studied on adverse drug reactions to 1st line anti-tubercular drugs in dots therapy. In this study they conduct randomized control trail in total 511 tuberculosis patients who were on DOTS therapy were enrolled for the study. Out of 511 patients, 93 patients (18.20%) developed adverse drug reactions. The higher numbers of ADR's were observed in males (68.81%) and in females (31.18%). Diabetes mellitus (41.02%) was the most common co morbidity. Most of the ADR occurred in the intensive phase (85.71%) of treatment. It was observed that pulmonary TB (55.18%) was more common than extra pulmonary TB. Majority of adverse drug reactions were gastrointestinal (GI) problems (38.09%). The most serious ADR was hepatitis. Isoniazid was the major drug which caused 34.40% of adverse drug reactions. About 17.02% people developed different type of ADR's during the study period. [4]**.** Ashishkumarzala et.al,.(2015) assessed the prevalence of adverse drug reactions in MDR-TB patients at tertiary care hospital in India,In this prospective observational study the main aim is to detect document assess and report suspected ADR's they conducted for 12 months from April 2014 to march 2015on RNTCP, MDR-TB patients. It reveals that detected and suspected ADR's were analysed and preventability by validated scales during this study 121 ADR's detected, documented, assessed and reported of which 23.14% suspected ADR's were severe, 28.29% were moderate in severity 61.1% ADR's were drug related in causality assessment. Majority of patients suffered from ADR's were above 20 yrs and drug associated with ADR is kanamycin. (27%) ototoxicity is common (37%) the results demonstrate and illustrate that preventability of ADR's was assessed and 15.7% ADR's were definitely preventable.[5]**.** Kishore

rathal et.al,.(2015) determined adverse events among patients of multi drug resistant tuberculosis receiving second line anti-TB treatment**.** Present prospective observational study was conducted by the authors to determine the adverse events among patients of multi drug resistant tuberculosis receiving second line anti TB. The results shows ADR's among 90/265 had GI ADR's, followed by ototoxicity 15/265(5.66%), psychiatric manifestations14/265(5.28%) arthralgia 11/265(4.15%), renal dysfunction 3/265(1.13%), peripheral neuropathy 5/265(1.88%). ADR's are more common in MDR TB patients on 2nd anti-tubercular treatment.[6]

Lakshmi sabapathi et.al. (2015) observed adverse events among patients of multi drug resistant tuberculosis receiving second line anti TB treatment,the impact of patient counselling technique and medication adherence for TB patients. Here some standard questionnaires from WHO used to assess and compare patient knowledge about disease and medication before and after patient counselling. Here total 64 patients were included in study over 6 months period. Prospective observational study was carried out from November 2013-april 2014. With this study they have concluded that patient education and medication counselling improved compliance and improved their therapy outcome.[7]. Rohan Hire et al,.(2014) conducted a study of adverse reactions to drug regimen for multi-drug resistant pulmonary tuberculosis in central India,In this study authors want to assess the ADR's of second line anti-TB drugs used to treat MDR-TB in central India on the basis of causality, severity and availability scales. The method they used is prospective observational study in total 110 patients in period of 9 months. After the study they observe 64 ADR's in 55 patients, who are on dots-plus regimen. They observe that ADR's in 55 patients who are on dots-plus regimen. They observe that ADR's were common in patients of MDR-TB on dots-plus regimen due to lack of availability of safer and equally potent drugs in dots-plus regimen.[8]. Shiv kumar et al,.(2014)conducted pharmacovigilance study on drugs used in the treatment of tuberculosis at civil hospital Rohru (Shimla), Himachal Pradesh. There are mainly 3 branches they are 1.Spontaneous reporting 2.Targeted spontaneous 3.Active surveillance. This study was carried in the in patients and out patients' medicine department of a civil hospital in this study they found that the age of patients ranged from 12 to 84 years. Among the 44 TB patients 24(M) and 20(F) They concluded that although 73% of the patients were admitted due to TB for 1st time 19% of cases are due to 2nd attempt, 5.5% cases are third time. Most of admissions are during December maximum incidence was seen in age group of 19-30 years.[9]. Rashmipusunoori et.al,.(2014) conducted a study of adverse drug reactions in tuberculosis patients due to directly observed treatment therapy at government hospital in the city of Warangal, Telangana, India**,** In this prospective -population based study the authors main objective is to determine incidence and prognosis of ADR'S due to DOTs therapy, to evaluate their impact on anti TB treatment in Warangal district. IT was performed from January 2014- august 2014. Patients receiving DOTs therapy were included and 6 months follow up. Suspected ADR's were recorded. A total of 120 tuberculosis patients were included, 70 patients (58.3%),showed at least one ADR due to anti-tubercular regimens. incidence of ADR based on affected organ GI disorders in 35 patients (41.17%), anaemia in 30 patients (42.85%), liver dysfunction in 17 patients (24.94%). no ADR's in CVS . most cases of ADR's (53%) had a good clinical outcome. these ADR's had substantial improve quality of patient care and to control TB safely.[10]. Yugandhra et.al,.(2014) Conducted study on adherence of tuberculosis patients undergoing DOTS plus treatment,among patients underlying dots plus therapy for testing adherence. Total589 patients were studied out of those 28349 (48.45%) were used,6.24% were completed treatment ,23.66%, were completed treatment 23.66%were reported as defaulter,11.67% were died, 5.67% failed to cure,1.88% transferred to other places. They observed that non-compliance of patients was a major cause for the decrease in cure rate of MDR-TB treatment. ADR's long duration for poor outcome results.[11]. Swati mishraet. al,.(2013)studied of anti-tubercular drug induced adverse reactions in patients attending pulmonary medicine department of a tertiary care teaching hospital, in this prospective observational clinical study the author shows the incidence of anti-tubercular drug induced adverse reactions and also assess the causality and severity of reported ADR's patients receiving anti-tubercular drugs for at least 8 month were included , monitored for ADR's during OPD_s and severity by using WHO Uppsala monitoring centre(WHO-UMC) criteria and HARTWIG scale of the 91 TB patients , males were 71%(majority) on evaluation of causality of ADR's majority of them were possible by WHO -UMC and naranjo's causality assessment scale severity of ADR's shows 51% reactions were moderate and 49% were mild.[12]

Mahindra Kumar et al,.(2013) did causality assessment of adverse drug reactions in tuberculosis patients who are on directly observed treatment short course strategy in mysore district,In this prospective observational and active surveillance study the author manifests the causality assessment of ADR's in TB patients who are on DOTS course strategy in Mysore dist. by using naranjo and WHO algorithms. Over a period of 9 months in this study a total of 128 ADR's were identified, in which prevalence of ADR's in female was 31.58% and 29.66% in patients causality assessment naranjo scale showed out of 128 ADR's 128(100%) ADR's wee probable and based on WHO probability assessment scale 119(92.97%) possible whereas 9(7.03%) probable the results shows that (DOT) short course therapy is safer with regular monitoring o ADR's.[13]**.** Xiaozhen et.al,.(2013) In this prospective cohort study the authors aimed to determine the incidence and prognosis of ADR's due to dots therapy in Chinese tuberculosis patients and to evaluate their impact on anti TB

treatment in china during 2007-2008. Sputum smear positive pulmonary patients on DOTS were included and followed up for 6 to 9 months in 52 countries in 4 regions of china. Suspected ADR's were reported. The study was conducted on 4304 TB Patients, of which 649 patients(15.08%) showed at least one ADR based on affected organ-liver dysfunction 6.34%(273),GI disorders 3.79%(161) arthralgia 2.51%(108),allergic reactions2.35% (101),neurological system disorders 2.04% (88),renal impairment 0.07%(3) and others 0.05%(2) most cases of ADR's had a good clinical outcome. Patients with ADR are more likely to have positive smear test results compared with patients without ADR's. So the results shows that incidence of ADR's due to dots therapy was 15.08% and the importance of developing strategies to mitigate ADR's both to improve quality of patient care and to control TB safely.[14]**.** Martha vander Walt et.al,.(2013)conducted research on serious treatment related adverse drug reactions amongst anti-retroviral naïve MDR-TB patients,They used prospective cohort study for 4 years total 2079 patients were enrolled, in analysis, in that 39.1% members are HIV - infected.[15]**.** Dindylpatidaret. al,.(2013) implemented assessment and enhancing adherence to treatment regimen in tuberculosis out patients,in a tertiary care teaching hospital. the aim of this study is to identify most frequent ADR'S recognized by attending physicians, study their nature and to target these ADR's it was conducted over a period of 7 months out of 254 admissions, 32 ADR's in 36 suspected ADR's in 41 patients. Females' predominance was observed that in males in ADR's. Multiple drug therapy accounts 50% of ADR's dermatological ADR's (68.75%)followed by CNS, respiratory and GI ADR's the drug usually involved antibiotics, anti-gut, anti-tubercular agents and NSAIDA out of 32 reported ADR's 50% were probable,46.87%possible and 3.12% definite, by using hartwig and Siegel scale majority of ADR's were mild, moderate and severe reactions. out of all 75%ADR's were recovered. this study indicates that hospital based monitoring is good method to detect links between drug exposure and ADR's.[16]**.** Yin yinxia et al,.(2010)aimed to design the Anti-tuberculosis Drugs induced Adverse reactions in China national tuberculosis prevention and Control Scheme study (ADACS),In this prospective cohort study the authors aimed to explore ADR's incidences, prognoses economical and public health impacts for TB patients and TB control IN this 4488 sputum smears positive pulmonary tuberculosis patients was included, followed up for 6-9 months in 52 countries of 4 regions suspected ADR's should, if the suspected ADR was anti-TB drug induced liver injury(ATLI), a nested case -control study be performed , health economic data of ADR'S would be collected the study gives are overview of anti-TB drugs induced ADR's incidence, prognosis, risk factors , treatments public health impacts for TB patients applying CNTS regimen in china .[17]**.** Kheirollahgholami et al,.(2006) evaluated anti-tuberculosis induced adverse reactions in hospitalized patients,They Conducted study in patients who received therapy from July 2001 to July 2002. They find out 83 patients for study output results are in these 44 members developed at least 1 ADR. Total 81 ADR's was detected. Major ADR's are liver and biliary system (37%), hepatitis (25.3%). More attention is needed to prevent their reactions.[18]

Retrospective Observational Study

Atalsood et al,.(2016) analysed profile of adverse drug reactions in patients on anti-tubercular drugs in a sub himalayan rural tertiary care teaching hospital,Here authors directed retrospective observational study the to show the profile of adverse drug reactions in patients on anti-tubercular drugs in a sub Himalayan rural tertiary care teaching hospital under pharmacovigilence programme of India (PVPI). It was conducted or analysed for 100 anti-tubercular treatment patients, causality assessment was done using WHO scale. Maximum ADR's were reported in adults with a mean age of 40.79 + or - 16.79 years. Males (n=66) outnumbered females (n=34) there were 62%MDR-TB on DOTS - plus regimens followed by 35%on cat 1 ATT ADR's involves GI system 44(44%), CNS 12(12%), psychiatric 0% otovesticular 1(1%).[19]**.** Reenaverma et.al.(2014) evaluated adverse drug reactions associated with first-line anti-tubercular drugs in a tertiary care hospital of central india: a study of clinical presentations, causality, and severity,In this retrospective study the author main objective is to study the ADR's associated with first line anti-tubercular drugs for causality and severity. The study duration of 1 year (may2013-may2014) conducted nearly 118 patients were started on anti-tubercular treatments of first line drugs. Out of these45 patients suffered 1 or more ADR's with a total number of reported ADR's being 91.57% males. most commonly involved system was hepatic and biliary (53.33%), GI system (51.11%),. the most common ADR observed - distributed liver transaminases (33.33%), nausea and vomiting (28.88%). causality assessment by naranjo's scale showed 58.2% ADR's probable 31.86% possible, mild, 31.11% moderate and no case of severe grading was reported. these ADR's occurrences can result in early diagnosis, proper management can be instituted.[20]**.** Atiasghar et al,.(2014) filed adverse reactions to anti-tuberculosis drugs in Iranian tuberculosis patients, In this retrospective cross sectional study a total of 940 TB Patients were included in this study. among the563 ADR's found in the study 82.4% were considered as minor reactions and 17.6% were major reactions no death from anti TB ADR was observed. The results are evaluated through statistical tool p-value. They concluded that the risk of major ADR's was higher in females. This study showed that severe side effects of anti TB drugs are common in patients who have risk factors of ADR's and they should be followed up by close monitoring.[21]

Cross Sectional Study

Medhin et al,.(2015) conducted research study on level of patient adherence to anti-tuberculosis treatment in Mekelle tuberculosis direct observed therapy Centers, tigray, North Ethiopia,In this the study type is descriptive cross sectional study in patients following TB treatment during May to June 2014. Sample size is 162 newly diagnosed TB patients, and the statistical tool used is SPSS version 16. In total 162 members, the overall non adherence for the last 4 days before the survey was about 18%; forgetfulness (43.3%), far distance (33.3%) and travelling to other places(20%) were the most frequent reasons for missing the therapy.[22]**.** Salabuddin Ansari et al,.(2013) studied the contribution of disease and drug related factors to non-compliance with directly observed treatment short-course among tuberculosis patients,The study was conducted on patients who were enrolled for TB treatment at the DOTS centre of LRS-RNCTP defined area. this study focused on finding out the contributing factors to non-compliance with the treatment of TB during specified period of time in different DOTS centres of LRS-RNTCP defined area, 500 and 60 TB patients were enrolled for treatment the results found out of that there was 27% of non-compliance in category I patients, 60% in category II patients and 13% in category III patients the main reason for non-compliance were patient related factors.[23]. Shamiyasadiq et.al,.(2015) conducted study on adverse drug reaction profile in patients on anti-tubercular treatment alone and in combination with highly active antiretroviral therapy,a prospective, cross sectional observational study on 106 patients to observe ADR profile in patients on anti TB treatment alone and in combination with highly active antiretroviral therapy in that 106 patients 74 were on ATT and 32 were on both ATT and HAART. In this comparison they concluded as ADE rate of TB with HIV co-morbid patients was more(55.8%)than TB patients(0.36%). Chi square test was applied to prove their statistical significance with p-vaue≤0.05. For analysis SPSS version 15 is used.[24]**.** Haregewoinbezer et al,.(2014) studied prevalence and risk factors of adverse drug reactions associated multidrug resistant tuberculosis treatments in selected treatment centres in Addis Ababa Ethiopia,In this cross sectional study author illustrates the prevalence and risk factors of ADR's associate multidrug resistant tuberculosis treatments in selected treatment centres in Addis Ababa Ethiopia, conducted between march 2012 and February 2013 it includes 73 MDR TB patients who were on MDR TB treatments, assessed by patients history review and questionnaire of the 72 patients, at least two ADR's were found. the most commonly found ADR's were anorexia 83.3%, nausea and vomiting 82%,gastritis 64%,arthralgia 47%, depression 22.2%, blurred vision 19.4%, alcoholism, AD predictors should be integrated and increase adherence to the treatment .[25]

V. Conclusion

Tuberculosis needs therapy for 6 months to 3 years and adverse drug reactions are observable during the course of time. Study involves evaluation of ADR in different methods like prospective observational study, retrospective observational study and cross sectional study etc. The utilization of study method involves precession, accuracy, and reproducibility of result. In our review we compared the efficacy of retrospective and prospective study in the evaluation of adverse effects of TB treatment. Prospective study is time consuming and expensive method. Hence we conclude that is case of a research performed in academics retrospective observational is more suitable where as in industry prospective study is preferable.

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