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Pulmonary Medicine

A STUDY ON ADVERSE EFFECTS AND OUTCOME OF SHORTER MDR-TB REGIMEN FOR RIFAMPICIN RESISTANT TUBERCULOSIS PATIENTS AT DISTRICT DR-TB CENTRE

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ABSTRACT **INTRODUCTION :-**Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). MDR-TB is still a key challenge in the fight against tuberculosis. In the treatment of MDR-TB, a fast detection of drug resistance and appropriate treatment with more efficient and less toxic regimen is critical. Guidelines on the Programmatic Management of Drug-Resistant TB (PMDT) in India, 2017 version integrated use of the shorter MDR-TB regimen and newer drug containing regimen under RNTCP with a DST guided regimen design.

METHODOLOGY:-Total 75 patients of Rifampicin resistant TB (RR-TB) (69 patients Pulmonary TB & 6 patients EP-TB included 3 lymph node TB, 2 pleural effusion, 1 endometrial TB) diagnosed by CBNAAT of sputum/lymph node aspirate/pleural fluid/endometrial lavage fluid at our lab for implementation of Universal DST were enrolled in this study. After starting shorter MDR-TB regimen by DR-TB committee of our institute these all cases were followed up for adverse effects (as per DAIDS grading) during their treatment course and eventual outcome.

RESULTS :-Shorter MDR-TB regimen was well tolerated with no adverse effect found in the 71 patients (94.67%) & 1 patient (1.33%) had mild skin related side effect of itching (Grade-1). Though 3 patients (4%) suffered serious adverse effects of drug intolerance (nausea, vomiting) (Grade-3). Successful outcome was achieved in 55 patients (73.33%), it includes 49 patients cured of Pulmonary TB and 6 patients completed treatment for extra pulmonary TB. Treatment was failed for 2 patients (2.67%), 9 patients (12%) were lost to follow up and 9 patients (12%) died.

CONCLUSIONS :- Shorter MDR-TB regimen in our study was very well tolerated as most of the patients (more than 95%) had no or mild skin related side effects from the treatment. Successful outcome was achieved in sizeable number of patients (73.3%). Intensive monitoring by local area medical officer and field staff/ASHA/Anganwadi will be helpful to reduce lost to follow up and deaths.

KEYWORDS : PMDT, MDR-TB, DAIDS grading, shorter MDR-TB regimen

INTRODUCTION :-

Tuberculosis (TB) is a communicable disease that is a major cause of ill health, one of the top 10 causes of death worldwide and the leading cause of death from a single infectious agent (ranking above HIV/AIDS). Globally, an estimated 10 million people fell ill with TB in 2019, a number that has been declining very slowly in recent years. There were an estimated 1.2 million TB deaths among HIV-negative people in 2019 (a reduction from 1.7 million in 2000), and an additional 208000 deaths among HIV-positive people (a reduction from 678000 in 2000).[1]

Drug-resistant TB continues to be a public health threat. Worldwide in 2019, close to half a million people developed rifampicin-resistant TB (RR-TB), of which 78% had multidrug-resistant TB (MDR-TB; defined as resistance to rifampicin and isoniazid). The three countries with the largest share of the global burden were India (27%), China (14%) and the Russian Federation (8%). Globally in 2019, 3.3% of new TB cases and 17.7% of previously treated cases had MDR/RR-TB [1].

Estimated number of MDR/RR-TB cases in India is 124000 (9.1/lakh population) [2]. MDR-TB is still a key challenge in the fight against tuberculosis. In the treatment of MDR-TB, a fast detection of drug resistance and appropriate treatment with more efficient and less toxic regimen is critical. Previously, treating drug-resistant tuberculosis with conventional regimen necessitated the administration of a large number of medications (less effective and toxic) over the course of up to two years with unfavorable outcomes. Average success rate of conventional regimen of MDR-TB from 2014 to 2017 was 49%[2].

Guidelines on the Programmatic Management of Drug-Resistant TB (PMDT) in India, 2021 version has introduced shorter oral bedaquiline-containing MDR/RR-TB regimen replacing shorter injection containing regimen for MDR/RR-TB patients. The regimen consists of an initial phase of 4 months that may be extended up to 6 months and a continuation phase of 5 months, giving a total duration of 9–11 months. Bedaquiline is used for a duration of 6 months.

(4-6) Bedaquiline (6 months), Levofloxacin, Clofazimine, Pyrazinamide, Ethambutol, High dose Isoniazid, Ethionamide (5) Levofloxacin, Clofazimine, Pyrazinamide, Ethambutol.[2]

Guidelines on the Programmatic Management of Drug-Resistant TB (PMDT) in India, 2017[3] version integrated use of the shorter MDR-TB regimen and newer drug containing regimen under RNTCP with a DST guided regimen design.

Shorter Mdr-tb Regimen

The shorter MDR-TB regimen is recommended for patients in whom the diagnosis of MDR/RR-TB has been reliably confirmed by molecular (e.g. CBNAAT/ LPA) or phenotypic DST method and are found to be sensitive to both FQ and SLI by SL-LPA. All patients with confirmed R-resistant disease are treated as for MDR-TB and the shorter MDR-TB regimen could be used in these patients too. Children and PLHIV on antiretroviral therapy (ART) could receive the shorter MDR-TB regimen. The following are the features of shorter MDR-TB regimen:

- standardized shorter MDR-TB regimen with seven drugs and a treatment duration of 9-11 months;
- A four-month intensive phase (to be extended upto six months if sputum smear conversion is delayed) containing Moxifloxacin (high dose), Kanamycin/Amikacin, Ethionamide, Clofazomine, Pyrazinamide, High dose Isoniazid, Ethambutol ; followed by a five-month continuation phase containing Moxifloxacin (high dose), Clofazimine, Pyrazinamide, Ethambutol.
- indicated conditionally in MDR-TB or RR-TB, regardless of patient age or HIV status;[3]

EXCLUSION CRITERIA

DST based:

- If DST/DRT result for FQ or SLI is resistant or
- presence of InhA mutation (for Eto) or
- Resistance to Z (whenever available)
- If result for DST (FQ, SLI, Inh A mutation, Cfz* & Z*) is not available, history of use for > 1 month/intolerance to Mfx(h), Km, Eto or Cfz

Non-DST based:

- Pregnancy
- Any extrapulmonary disease in PLHIVDisseminated, meningeal or central nervous system TB
- Intolerance to any drug in the shorter MDR TB regimen or risk of

toxicity from a drug in the shorter regimen (e.g. drug–drug interactions)[4]

Till December-2020, 96913 patients were put on shorter MDR-TB regimen with injectable second-line drugs (SLD) in India. Success rate of patients treated with this shorter MDR-TB regimen with injectable in 2018 was 60%. Preliminary success rates were reported up to 57% in 2019[2].

METHODOLOGY:-

This study was conducted at district DR-TB centre under Department of Respiratory Medicine, medical college, Jhalawar (October 2018 to July2020) after taking ethical committee approval. Here we followed PMDT guidelines 2017 and 2019 versions for our study period.

Total 75 patients of RR-TB (69 patients Pulmonary TB & 6 patients EP-TB included 3 lymph node TB, 2 pleural effusion, 1 endometrial TB) diagnosed by CBNAAT of sputum/lymph node aspirate/pleural fluid/endometrial lavage fluid at our lab for implementation of Universal DST were enrolled in this study. These all patients had undergone pre treatment evaluation as per PMDT guidelines and afterwards all were started on shorter MDR-TB regimen by decision of DR-TB committee of our institute.

All records were maintained in our PMDT register and Nikshay entry. All these patients were followed up telephonically for treatment adherence, support and any adverse effect. Also concerned senior treatment supervisor's (STS) help was taken for their follow up culture deposition.

The DAIDS grading table [5] provides an adverse event severity grading scale ranging from grades 1 to 5 with descriptions for each adverse event based on the following general guidelines:

- Grade 1 indicates a mild event (mild symptoms causing no or minimal interference with usual social & functional activities with intervention not indicated)
- Grade 2 indicates a moderate event (moderate symptoms causing greater than minimal interference with usual social & functional activities with intervention indicated
- Grade 3 indicates a severe event (severe symptoms causing inability to perform usual social and functional activities with intervention or hospitalization indicated)
- Grade 4 indicates a potentially life-threatening event (symptoms causing inability to perform basic self-care functions with interventions indicated to prevent permanent impairment, persistent disability or death
- Grade 5 indicates death

EXCLUSION CRITERIA:-

We had excluded one CNS TB patient, 2 pregnant female patients and 6 patients with additional Fluoroquinolone/second line injectable resistance from our study.

RESULTS :-

In this study we enrolled total 75 patients of RR-TB (69 patients Pulmonary TB & 6 patients EP-TB included 3 lymph node TB, 2 pleural effusion, 1 endometrial TB). Out of these only 1 patient (1.33%) was diabetic and remaining 74(98.67%) were non diabetic. Treatment was started for 42 patients (56%) on OPD basis and for 33 patients (44%) on Indoor basis.

There was no adverse effect found in the 71 patients (94.67%), 3 patients (4%) suffered serious side effects of drug intolerance (nausea, vomiting) (Grade-3) which could not be corrected on OPD basis and required hospitalization; remaining 1 patient (1.33%) had mild skin related side ef fect of itching (Grade-1)(treated on OPD basis). (Figure-1)

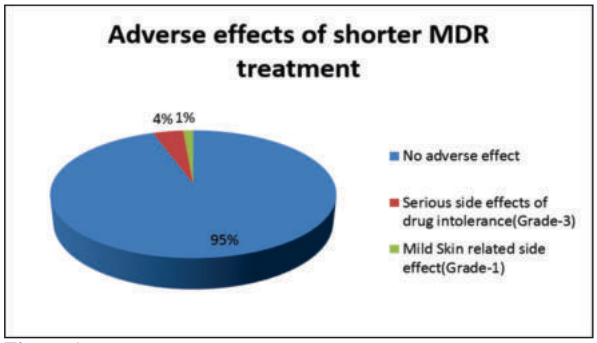

Figure-1

Out of total 75 patients, successful outcome was achieved in 55 patients (73.33%), it includes 49 patients cured of Pulmonary TB and 6 patients completed treatment for extra pulmonary TB. Treatment was failed for 2 patients (2.67%) and 9 patients (12%) were lost to follow up. Worst happened with 9 patients (12%) that they lost their life. (Figure-2)

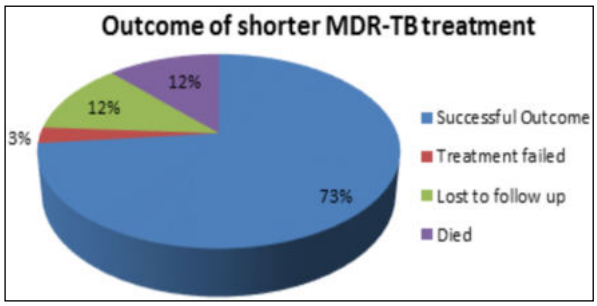

Figure-2

DISCUSSION:-

In our study treatment was started for 42 patients (56%) on OPD basis and for 33 patients (44%) on Indoor basis. So there was a significant proportion of patients which we admitted to start shorter MDR-TB regimen because initially we followed recommendations of PMDT guidelines 2017 version which tells about admitting all drug resistant TB patients to start regimen and later on as per PMDT guidelines 2019 version we admitted only sick patients and stable patients were started on treatment on OPD basis.

In our study no adverse effect was found in the 71 patients (94.67%), 1 patient (1.33%) had mild skin related side effect of itching (Grade-1) (treated on OPD basis). 3 patients (4%) suffered serious side effects of drug intolerance(Grade-3) (required hospitalization). In a study by du Cros P et al.[6] , 14 patients (10.9%) experienced serious adverse events. Thus shorter MDR-TB regimen used in our study caused lesser serious side effects which indicate better tolerance of our regimen. 3 patients who got admitted for drug intolerance were managed at our institute and later they all completed their course successfully with favorable outcome.

Our study shows successful outcome (cure & treatment completed) in 73.33% patients and treatment failure for 2.67% of the patients also 12% patients were lost to follow up and 12% died. Similarly study by du Cros P et al.[6] from Karakalpakstan, Uzbekistan has reported 71.9% (92 out of 128) treatment success rate, 22 (17.2%) treatment failures, 12 (9.4%) lost to follow-up; and 2 (1.5%) deaths. Thus in our study treatment failure was less but more cases of lost to follow up and deaths were recorded which could be attributable to less effective monitoring by field staff causing poor adherence to the treatment and more deaths. Also burden of pills, sense of well being, long duration of injectables could be the possible causes for our patients to interrupt their treatment.

PMDT guidelines 2021 version has replaced shorter injection containing regimen with shorter oral bedaquiline-containing regimen for MDR/RR-TB patients without previous exposure to second-line treatment and without fluoroquinolone resistance. It will solve the issue of daily need of trained staff to give injectables in remote rural areas and adding more efficacious drug like bedaquiline could yield more promising results which will be unfolded by future studies.

CONCLUSION :-

Adverse effects of shorter MDR-TB treatment in our study shows that most of the patients (more than 95%) had no or mild skin related side effects of itching from the treatment. Even serious side effects of drug intolerance were managed successfully with favorable outcome. Similarly, outcome of the MDR-TB treatment shows that the regimen was successful in sizeable number of patients (73.3%), but the results also show that the treatment was failed, patient lost to follow up and patient died are also there. Therefore, stress should be given on more intensive monitoring by local area medical officer and field staff/ASHA/Anganwadi workers to ensure better adherence to the treatment and reduce the casualties due to RR/ MDR- TB.

Conflict of interest: - None.

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