Study of Adverse Effects and Outcome of All Oral Longer Regimen for Drug-Resistant Tuberculosis at Nodal DRTB Center, S N M C, Agra

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Abstract: Introduction and Background: TB was the leading cause of death from a single infectious agent, ranking above HIV/AIDS until the coronavirus (COVID-19) pandemic. In 2021, the estimated proportion of people with TB who had MDR/RR-TB was 3.6% among new cases and 18% among those previously treated. India is one of the nations in the world which has the highest burden of Multidrug-resistant tuberculosis (26%). The estimated number of MDR/RR-TB cases in India is 124,000 (9.1 lakhs population). A total of 109 countries were using all oral longer regimens for the treatment of MDR/RR-TB. Material and Methods: The present study is a hospital-based observational prospective non-randomized without a control group, which was performed at a nodal DRTB center, Department of Tuberculosis & Respiratory Diseases, S. N. Medical College Agra. Results: 140 patients were enrolled on the All-Oral Longer regimen after obtaining informed consent. Among 140 patients 75.6%, 77.6%, 82.4%, 82.4%, and 80.2% were culture negative at the end of 3rd, 6th, 9th, 12th and 18th months respectively. The most common adverse event observed in this group of patients was dermatological events which accounts for 29.2% followed by nervous system (17.8%) and gastrointestinal (15%) events. Among the study population 80.2% (112) were culture negative at the end of treatment, 5.6% died, 7.8% lost to follow up and 6.4% failed. Conclusions: Patients on the All Oral Longer regimen for DRTB have higher and more rapid sputum culture conversion rate, lower mortality, and fewer adverse events which are manageable, which indicates that the All Oral Longer regimen was well tolerated with better compliance in comparison to previous treatment regimens for DRTB.

Keywords: drug-resistant tuberculosis; extensively drug-resistant tuberculosis; national tuberculosis elimination program; AOLR, PMDT

1. Introduction and Background

Globally in 2021, 71% of people (2.4/3.4 million) diagnosed with bacteriologically confirmed pulmonary TB were tested for rifampicin resistance. Among those tested, 141,953 cases of MDR/RR-TB and 25,038 cases of PRE-XDR-TB or XDR-TB were detected, giving a combined total of 166,992. Worldwide, 1,617,462 people with MDR/RR-TB were enrolled on treatment in 2021 (1).

There are five categories of drug-resistant TB used by the national health programs at present: isoniazid (INH)-resistant TB, RR-TB, and MDR-TB (RR and INH resistant), pre-extensively drug-resistant TB (pre-XDR-TB) and XDR-TB. Pre-XDR-TB is TB that is resistant to rifampicin (MDR/RR-TB) and any fluoroquinolone (a class of second-line anti-TB drugs). XDR-TB is TB that is resistant to rifampicin (MDR/RR-TB), plus any fluoroquinolone, plus additional resistance of one of the drugs of Group A either Bedaquiline or Linezolid (2). Outcomes of treatment for drug-resistant tuberculosis are poor globally, with low cure rates and high mortality (4). The duration of treatment is long and many of the drugs are poorly tolerated (5), side effects and adverse events (AEs) are common, and the treatment and management of the cases are expensive and burdensome (6).

Our study with objectives is to determine the 1. Outcome among patients of R/MDR/PRE-XDR/XDR tuberculosis in terms of culture conversion at the 3rd, 6th, 12th, and at 18th month. 2. The adverse effects of all oral longer regimens among patients of R - R/MDR/PRE - XDR/XDR tuberculosis. 3. The radiological patterns among patients of R/MDR/PRE - XDR/XDR tuberculosis. 4. The resistant patterns among patients of RR/M/PRE - XDR/XDR tuberculosis, is an attempt to study and understand the clinical, bacteriological, radiological, and social impact of the regimen and to study the adverse effects in detail so that conclusions of the study can be helpful for the policymakers at any level and thrust to the ongoing existing Tuberculosis eliminating strategies.

2. Material and Methods

It was hospital-based, non-randomized observational prospective study without control group conducted on a cohort of 140 Self-reporting and/or referred R - R/MDR/PRE - XDR/XDR-TB patients registered under the NTEP from January 21 to June 22 at nodal DR-TB centre and Department of Tuberculosis & Respiratory Diseases, S. N Medical College Agra.
Inclusion criteria:
- Persons who could provide written informed consent.
- Patients of age 18 years or older having confirmed pulmonary, R - R/MDR/PRE - XDR /XDR pulmonary tuberculosis and not eligible for the Shorter regimen of DRTB.
- Females who were not pregnant or breast feeding & on non - hormonal - based birth control methods.

Exclusion criteria:
- MDR/XDR TB patient who is/are registered under DOTS outside, during the period of study.
- Extra pulmonary tuberculosis.
- Severe hepatic and renal disease.
- Patients with cardiac abnormalities like uncontrolled arrhythmias, marked prolongation of QT/QTc interval, e. g., repeated demonstration of QTcF (Fredericia correction) interval > 450ms, WPW syndrome, Bundle branch block, II/III heart block, Personal or family history of Long QT Syndrome.

All the study participants have been subjected to a detailed clinical history and examination and information obtained about Age, Sex, Height, Weight, Body Mass Index, Occupation, Income, and Previous history of TB or anti - TB Drug intake (prior exposure to 2nd line injectable drugs), or any preventive therapy and if present the drugs used, etc. The modified Kuppusamy scale of social classification (updated in 2021) has been used to classify the patients into their respective socioeconomic classes.

A detailed pre - treatment evaluation of enrolled included detailed history (including screening for mental illness, seizure disorder, drug/alcohol abuse, known adverse/serious adverse events etc.), Previous history of ATT taken especially SLI/FQ, thorough clinical examination, Weight & height, ECG, Complete blood count with hemoglobin & platelets etc. Blood urea and S. Creatinine to assess renal function, Blood sugar to screen for Diabetes mellitus, UPT (for all women of childbearing age), Chest X - ray. HIV testing and counseling. Hearing evaluation/ Audiogram, Liver function tests, TSH levels to assess thyroid function, Routine Urine examination, Serum electrolytes – potassium, magnesium, calcium, Serum proteins, lipase, amylase, Ophthalmologist opinion to rule out chorioretinitis/uveitis. ECG and QTc interval were measured in lying down position preferably in the morning using a standardized BPL CARDIART 6208 VIEW machine and the QT interval was corrected with the Fridericia formula

\[ \text{QTcF interval} = \frac{Q\text{T}_{\text{F}}}{\sqrt{RR}} \]

Follow - up evaluation of all the eligible study population has been carried out as per the Table 1:
- If Lzd is part of the regimen - rule out bone marrow suppression.
- HBsAG and other viral markers (Hepatitis A, C & E) to be done in case of jaundice.
- In case of baseline ECG abnormality or QTcF ≥450ms with longer oral M/XDR - TB regimen that contains Bdq, Mfx, Cfz or Dlm, ECG must be done on daily basis for initial 3 days or as suggested by cardiologist. Repeat ECG with long II lead after an hour to reconfirm abnormal ECG.
- DST whenever available.
- Cohort event monitoring

<table>
<thead>
<tr>
<th>Regimen Class</th>
<th>Longer Oral M/XDR - TB Regimen</th>
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<tbody>
<tr>
<td>Duration</td>
<td>With culture at the C&amp;DST lab. Conduct SM within 7 days, if any smear at 6 month or later is positive to rapidly ascertain Bacteriological conversion / reversion. LC&amp;C DST lab to update the result on Nikshay and inform the concerned field staff of collection center on same day</td>
</tr>
<tr>
<td>Culture</td>
<td>Monthly from month 3 onwards to end of 6 months or 7 or 8 if the previous month’s culture is +ve. Quarterly month 6 or any time beyond that if the quarter culture is positive, collect one repeat specimen immediately and send it for culture to rapidly ascertain bacteriological conversion / reversion and if the repeat specimen is culture negative, then the subsequent quarterly or</td>
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Each patient was monitored for AEs, clinical and microbiological improvement, and outcomes during treatment.

Statistical analysis of data
For the comparison of categorical variables, significance testing was done by \( \chi^2 \) and if needed then a 2 - sided Fisher exact test will be applied. Associations between selected risk factors with drug resistance will be estimated by computing odds ratios (ORs) and their 95% confidence intervals from an unconditional logistic regression model.

The criterion for significance will be set at \( P<0.05 \) based on a two - sided test. Analyses will be performed with suitable software.
3. Results

Among the cohort of 140 eligible DRTB patients, approximately 62% were males and 38% were females. The mean age of study participants was 31.6 years with the majority of patients being in the younger age group. 58 patients (41.4%) were from rural areas and 82 patients (58.6%) were from urban areas. Among male patients, 50.8% were from urban areas and 49.2% were from rural areas. Whereas the proportion of female patients was more in an urban area (71.6%) as compared to rural areas (28.4%). The majority of the study population was in an upper lower class (IV) 43% and lower class (V) 25.6% as per the modified Kuppuswamy classification. The majority were undernourished with BMI <18.5.

In 40.8% study population personal habits such as tobacco consumption, alcohol consumption, and smoking were present while 59.2% had no habits. 16 had co-morbidities (hypertension, diabetes, thyroid dysfunction) in which diabetes was most common at 6.5% of patients had HIV coinfection. 64% had RR/MDR-TB and 27% had PRE-XDR and 9% had XDR pulmonary TB. Baseline chest x-ray of 64.2% had cavititation and 40.4% had >50% lung involvement. 93% had previous exposure to second-line anti-tubercular drugs either from government institutions or private organizations.

Out of 87 male and 53 female patients initiated on all oral longer regimens, a Baseline QTc interval of <450 ms was in 89.2% of males and <470 ms was in 91.2% of females.

Most of the patients had a duration of illness between 12 - 24 months (47.5%) and 1 - 12 months (42.5%) and only 10% of patients had a duration of illness between 24 - 36 months.

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Among the entire study population 75.6%, 77.6%, 82.4%, 82.4%, and 80.2% were culture negative at the end of 3rd, 6th, 9th, 12th and 18th months respectively.
In our study, we found that the most common adverse events were skin discoloration followed by peripheral neuropathy, and nausea/vomiting after grouping of different adverse events based on body systems involved and their severity according to DAIDS criteria.

It was observed that patients having severe lung damage and cavitation had very low rate of sputum culture conversion. Patients having BMI >18.5 Kg/m2 had high culture conversion rate which was more than those patients who were having low BMI (<18.5 Kg/m2). The resistance pattern does not have any significance on sputum culture conversion. Patients having habit of smoking, tobacco chewing and alcohol intake had low conversion rate in comparison to person with no habit. Patients having HIV co-infection had low sputum culture conversion rate when it compared to person without HIV co-infection. Patients having HIV

### Table 3: Correlation of various factors associated with treatment outcome in DR - TB patients at 3RD month (N=140).

<table>
<thead>
<tr>
<th>Personal habit</th>
<th>Yes</th>
<th>No</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>&gt;18.5</td>
<td>50</td>
<td>7</td>
<td></td>
</tr>
<tr>
<td>&lt;18.5</td>
<td>36</td>
<td>26</td>
<td>0.0081</td>
</tr>
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<table>
<thead>
<tr>
<th>Resistance pattern</th>
<th>RR/MDR</th>
<th>PRE - XDR/XDR</th>
<th>P</th>
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<tbody>
<tr>
<td>Yes</td>
<td>69</td>
<td>21</td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>37</td>
<td>13</td>
<td>0.724</td>
</tr>
</tbody>
</table>

HIV had a lower probability of conversion than patients without HIV similar to our study. 16 patients (12.2%) were found to have co-morbidities in which diabetes was most common (6%). It was similar to the study patients were in the age group of 18 - 25 years while the mean age of the study population was 31.6 years; similar to other studies Norbert Ndjeka et al (median age was 34 years), Rohit Sarin et al (median age was 29.77 years). The high prevalence of DR - TB in the young population is alarming as this would result in considerable health and financial burden on individual families and the country.

Approximately 62% (87) of the patients were males and 48% (53) were females having an increasing male - to-female ratio with respect to age, similar to the study conducted in NITRD, Delhi by Rohit Sarin et al and Norbert Ndjeka et al. It suggests that females are more susceptible to the disease in younger age as compared to the males.

58.4% (82) of the patients were having BMI < 18.5 kg/m2. Low mean body weight and mean BMI indicate that majority of the patients were "undernourished". Studies of Mengqiu Gao et al and V. S. Salhotra et al demonstrated that patients with low body one by Mengqiu Gao et al in China. In our study Presence of comorbidities was associated with poor treatment outcomes in terms of the slow rate of culture conversion. Out of the total no of male patients (87) initiated on all oral longer regimens, The study population was stratified according to the radiographic assessment of lung cavitation and the extent of the disease. Among 140 patients, 90 (64.2%) were having cavitary lung disease, and 57 (40.4%) patients were having >50% lung involvement. A study by Molly F. Franke et al demonstrated that Patients with both cavitary disease and highly positive sputum smear had a lower probability of conversion relative to patients without either, similar to our study.

During our study out of 140 patients, most of the patients had a duration of illness between 12 - 24 months (47.5%) and 1 - 12 months (42.5%), only 10% of patients have duration of illness between 24 - 36 months. Almost all of the patients (93%, 130) previously had exposure of second line anti-tubercular drugs which was more than the study conducted by Alena Skrahina, Hennadz Hurevich et al. This reflects the progressive acquisition of drug resistance mutants during sequential exposure to inadequate treatment leads to RR/MDR, PRE - XDR, and XDR - TB; thereby increasing the risk of DR - TB in treatment - experienced patients.

In the present study, 64% (90) of patients were RR/MDR - TB 27% (38) were PRE - XDR and 9% (12) were XDR PTB. In this study population of XDR - TB patient were lower as compared to the study conducted by Alena Skrahina, Hennadz Hurevich et al, V. S. Salhotra et al, and Norbert Ndjeka et al. According to a study conducted by Mengqiu Gao et al there no significant difference in culture conversion rate among different phenotypes of DRTB patients, similar to our study.

In our study, the outcome of all oral longer regimen was observed in terms of sputum culture conversion rate at the 6th, 9th, 12th, and 18th months which were as follows: Our
The most common body systems showing Adverse Events disability and 2 were life threatening (28.4%), 41 required hospitalizations, 30 had permanent disability, and among the serious adverse events were skin discoloration followed by peripheral neuropathy, and nausea/vomiting, which was different from a study conducted by V. S. Salhotra et al according to their study the most common AEs seen were peripheral neuropathy (21%), vomiting (18%), breathlessness (13%) and thrombocytopenia (11%), and differ from study conducted by Sandip V Barvaliya et al according to their study The most common were gastrointestinal (24, 19.4%) followed by skin and appendages (21, 16.9%) and body as a whole (17%). Vomiting (11, 8.9%) was the most common clinical presentation and also differ from a study conducted by Alena Skrahina, Hennadz Hurevich et al according to their study top five body systems showing Adverse Events were metabolism and nutrition disorders (experienced by 135 patients, hepatobiliary disorders (experienced by 127 patients), cardiac disorders (experienced by 80 patients) and others including gastrointestinal system disorders, blood and the lymphatic system disorders, renal and urinary disorders, nervous system disorders, skin disorders and ear and labyrinthine disorders.

As the occurrence of adverse events will prolong hospitalization and also affect treatment outcome, there is a need to regularly evaluate, monitor and emphasize prevention and management of them. Treatment was overall well tolerated in our cohort. Out of 140 patient 80.2% (112) had favourable outcome in term of culture negative at the end of treatment, and 19.8% patient had unfavourable outcome in term of 5.6% died, 7.8% lost to follow up while 6.4% failed. LTFU in present study was (7.8%, due to occurrence of pandemic COVID - 19 during the study period large number of patients were not accessible to health facility), but it was less as compared to study conducted by Norbert Ndjeka et al.

The study supports that all oral longer regimen shortened the typical time for sputum culture conversion, increased the rate of conversion at follow up and has shown significant benefit in improving survival and treatment outcomes in DR TB patients under clinical and programmatic settings.

5. Conclusions

Despite limitations, we believe that the data generated in our study leads to certain important conclusions. We concluded that All Oral Longer regimen have high and rapid sputum culture conversion rate, low mortality and fewer adverse events which are manageable, which indicates that All Oral Longer regimen was well tolerated with better compliance in comparison to previous treatment regimen for RR/MDR/PRE - XDR/XDR tuberculosis. Further, the outcomes were encouraging in patients having high body mass index due to better nutritional status and immunity. Although All Oral Longer regimen containing Bedaquiline and Delamanid along with concomitant medications has the potential to prolong QTc interval, the benefit certainly
outweighs the risk. It strengthened the DR - TB treatment programme to new lengths. Since DR - TB (RR/MDR/PRE-XDR/XDR) is a major health problem in India and other developing countries, newer drugs like Bedaquiline, Delamanid, Pretomanid and other pipeline drugs under development have the potential of becoming cornerstone drugs for future DR - TB treatment and definitely a game changer.

References