EPIDEMIOLOGY OF ADVERSE DRUG REACTION WITH SECOND LINE DRUGS AMONG PATIENTS TREATED FOR MULTI DRUG RESISTANT TUBERCULOSIS

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ABSTRACT

Multi Drug Resistant Tuberculosis (MDR-TB) is considered to be a global public health problem with notoriously difficult and challenging treatment. Adverse drug reactions (ADRs) associated with Second Line Drugs (SLD’s) can have severe impact on efficient management of patients with MDR-TB. It is necessary to estimate the frequency of ADRs encountered during the treatment with SLD’s. Various studies have reported that gastrointestinal ADRs are most common followed by ototoxicity with more than half of patients requiring either regimen modification or discontinuation. MDR-TB can be cured successfully with appropriate combination of drugs if adverse events associated with them can be can be managed aggressively and timely. There is urgent demand for newer and less toxic drugs to treat MDR TB patients.

KEYWORDS: Adverse Drug Reactions; MDR-TB; Second Line Drugs.

INTRODUCTION

Multi-drug resistant TB (MDR-TB) is defined as M. tuberculosis resistant to Isoniazid and Rifampicin with or without resistance to other first line drugs. It is considered to be a worldwide problem with notoriously difficult and challenging treatment. The emergence of resistance to drugs used to treat tuberculosis, and particularly MDR-TB, has become a significant public health problem in a number of countries and an obstacle to effective tuberculosis control. The prevalence of MDR-TB among notified new and re-treatment pulmonary tuberculosis patients are estimated to be 3.5% and 20.5% respectively.[1] Patients
may present with a variety of adverse drug reactions when Second Line Drugs (SLD’s) are prescribed for MDR-TB management. Most of adverse drug reactions are minor and can be managed without discontinuation of treatment. Some adverse drug reactions can be life threatening if not recognized and treated promptly. There are major concerns regarding SLD’s in that they are expensive, have low efficacy and more toxic as compared to first line anti-tuberculosis drugs.\(^2\)\(^-\)\(^4\) Adverse drug reactions associated with Second Line Drugs (SLD’s) can have severe impact on efficient management. There may be a severe impact on adherence and higher risk of default and treatment failure affecting outcome overall if such adverse drug reactions are not properly managed.\(^5\) This article aims to highlight the prevalence of adverse drug reactions in patients receiving SLD’s for treatment of MDR-TB.

**Prevalence of Adverse drug reactions among patients receiving SLD’s: Global**

The management of MDR-TB patients has been considered to be complicated and challenging reasons being prolonged duration of 24 to 27 months and high toxicity profile of SLD’s. The prevalence of adverse drug reactions observed in various studies conducted worldwide ranged from 69\% - 96\%.\(^6\)\(^-\)\(^{27}\) The reasons for the difference in the prevalence of adverse drug reactions across these studies might be related to several possible factors such as: differences in definitions of adverse drug reactions terminologies as adopted by physicians, whether the adverse drug reactions were reported by patient (subjective) or detected by clinician (objective) on the basis of clinical evidence along with feasibility of monitoring with serial laboratory investigations, whether all or only the major adverse drug reactions were studied, the differences in co-morbidities such as diabetes and other covariates including HIV co-infection and variations in the use of specific anti-tubercular drugs including dosage and also pharmacological interactions with other group of drugs comprising anti-retroviral, oral hypoglycemic agents in case of diabetics and also ancillary medications used for management of adverse drug reactions. The characteristics of various studies showing frequency of adverse drug reactions are shown in Table 1. The observed frequency of specific gastrointestinal adverse drug reactions has been reported in 0.5\% - 100\% patients.\(^7\)\(^,\)\(^9\)\(^-\)\(^{11,13,17,18,22,25,27}\) The high prevalence of gastrointestinal adverse drug reactions in few of the studies was probably due to frequent reporting by patients as compared to other adverse drug reactions leading to subjective variation. Ototoxicity has been reported in 12\% to 70\% patients receiving SLD’s.\(^10\)\(^,\)\(^11,17,20,22\) The frequency of tinnitus has been reported in 5\% to 45\% patients\(^9\),\(^13,18,22\), while that of deafness is reported in 6.7\% - 33\% patients.\(^6\),\(^7,13,18,20,22\) Ototoxicity is predominantly associated with the use of injectable
aminoglycoside (Kanamycin) although there is possibility of additive effects of interaction with other concomitant and potentially ototoxic drugs that were used in the regimen such as Ofloxacin and Cycloserine. This warrants further investigation to uncover the possibility of these interactive effects. Several studies have highlighted regarding high potential of these SLD’s to cause adverse drug reactions that has led to interruption of treatment in 19-60% of MDR-TB patients.\[^{6-23}\] This high prevalence may be due to early identification and aggressive management strategies adopted by DOTS PLUS programme. Baghaei et al. reported deafness and headache/psychosis occurring due to injectable kanamycin and Cycloserine respectively were found to be major adverse drug reactions that required frequent discontinuation and/or substitution.\[^{20}\] MDR-TB patients should be managed aggressively for adverse drug reactions during therapy, especially for ototoxicity and psychiatric disorders.

**Prevalence of Adverse Drug Reactions among patients receiving SLD’s: India**

Very few have specifically reported frequency of adverse drug reactions in India.\[^{24-30}\] A study conducted in Tamil Nadu by Joseph P et. al. reported adverse drug reactions in 86.8% patients.\[^{25}\] Only five patients did not complain of any adverse drug reactions. Adverse drug reactions were considered mild if the patient made 1 or 2 complaints during the 12 month period and only required symptomatic treatment, moderate if the complaint was repeated or of prolonged duration but still could be managed with symptomatic drugs, and severe if either a reduction of dosage or termination of the offending drug(s) was warranted. Severe adverse drug reactions were observed in 58% patients. Of these, 13 had termination of Ethionamide, 4 of ofloxacin, and 1 each had kanamycin, ethambutol, pyrazinamide or cycloserine terminated. In addition, ofloxacin dosage was reduced in 1 patient, pyrazinamide in 2 others, and kanamycin injections changed to 3 days a week for 5 patients.

Another study conducted in Mumbai among 67 HIV/MDR-TB co-infected patients were being treated with anti-TB treatment and anti-retroviral therapy.\[^{27}\] Overall, adverse drug reactions were common in this cohort: 71%, 63% and 40% of patients experienced one or more mild, moderate or severe adverse drug reactions respectively. However, they were rarely life-threatening or debilitating. Adverse drug reactions occurring most frequently included gastrointestinal symptoms (45% of patients), peripheral neuropathy (38%), hypothyroidism (32%), psychiatric symptoms (29%) and hypokalemia (23%). Eleven patients were hospitalized for adverse drug reactions and one or more suspect drugs had to be permanently discontinued in 40% patients. No adverse drug reactions led to indefinite
suspension of an entire MDR-TB or ART regimen. One study conducted at Delhi reported that 40% patients experienced minor adverse drug reactions, defined as those requiring either no discontinuation of a drug or discontinuation for ≤ 1 week and manageable at peripheral level. Twenty-two (18%) patients had major adverse drug reactions requiring treatment modification. PAS was used in 46 patients: 6 (5%) developed simple goitre, which responded to thyroxin replacement therapy with continuation of PAS. In 15 (12%) patients, Cycloserine had to be stopped due to major psychotic reactions varying from major depression, psychosis to violent behaviour. Kanamycin was stopped in five (4%) patients due to hearing loss/giddiness. Ofloxacin and Pyrazinamide were stopped in one patient due to severe arthralgia, and Pyrazinamide was stopped in another patient due to hepatotoxicity. All of these major adverse drug reactions required referral to specialist hospitals. None of the patients required discontinuation of the entire treatment regimen, although two patients defaulted due to adverse drug reactions. No deaths due to drug toxicity were recorded in the cohort. A study was conducted at Lucknow by Prasad et al. among MDR-TB patients treated with second line drugs.

It was observed that 41% patients experienced adverse drug reactions of which seven patients complained of nausea and vomiting. In three patients PAS was stopped after six to eight months of treatment, as it was thought to be the cause. The remaining patients did not require any change of medication. Four patients developed photosensitivity and sparfl Roxacin was replaced in one of the patients by ofloxacin after three months of treatment. In rest of the patients, it did not require any change of medication. Tinnitus and vertigo developed in four patients after one to five months of treatment probably due to kanamycin and it had to be stopped in two of them. Three patients developed depression and abnormal behavior possibly due to cycloserine, which was replaced by a quinolone in two patients.

However, it was continued with anti-psychosis treatment in the remaining patient. A total of 21.1% patients suffered from significant adverse drug reactions, which required stoppage/change of drugs. No other adverse drug reactions, such as arthralgia or cardiotoxicity were observed in any patient. In other study, among 98 MDR-TB patients on standardized treatment, it was observed that 43.9% patients experienced at least one adverse drug reactions.
Table 1: Characteristics of important studies showing frequency of adverse drug reactions due to second line drugs

<table>
<thead>
<tr>
<th>Study Year</th>
<th>Location</th>
<th>Sample Size</th>
<th>Study Period</th>
<th>HIV Prevalence (%)</th>
<th>Age (years)</th>
<th>History of previous treatment</th>
<th>Type of regimen used</th>
<th>Length of treatment (months)</th>
<th>Number of drugs used</th>
<th>Number of patients experiencing Atleast one adverse drug reaction</th>
<th>Adverse Drug Reactions most frequently observed</th>
<th>Incidence of Major Adverse Drug Reactions (%)</th>
<th>Mortality observed due to major adverse drug reactions</th>
</tr>
</thead>
<tbody>
<tr>
<td>Furin (2001)</td>
<td>Peru</td>
<td>60</td>
<td>1996-1998</td>
<td>1.7</td>
<td>26</td>
<td>100 Individualized</td>
<td>Individualized</td>
<td>20 (6-25)</td>
<td>8</td>
<td>60 Gastrointestinal</td>
<td></td>
<td></td>
<td>11.7</td>
</tr>
<tr>
<td>Shin (2007)</td>
<td>Russia</td>
<td>244</td>
<td>2000-2002</td>
<td>NA</td>
<td>32.5</td>
<td>100 Individualized</td>
<td>Individualized</td>
<td>18.5 (1-42.4)</td>
<td>14</td>
<td>73.3 Gastrointestinal</td>
<td></td>
<td></td>
<td>28.7</td>
</tr>
<tr>
<td>Masjedi (2008)</td>
<td>Iran</td>
<td>43</td>
<td>2002-2006</td>
<td>NA</td>
<td>44.4</td>
<td>100 Standardized</td>
<td>Standardized</td>
<td>24</td>
<td>8</td>
<td>25 Gastrointestinal Ototoxicity</td>
<td></td>
<td></td>
<td>46.5</td>
</tr>
<tr>
<td>Seung (2009)</td>
<td>South Africa</td>
<td>76</td>
<td>2007-2008</td>
<td>74</td>
<td>35</td>
<td>97 Standardized and individualized</td>
<td>Individualized</td>
<td>24</td>
<td>6</td>
<td>70 Neurological</td>
<td></td>
<td></td>
<td>Nil</td>
</tr>
<tr>
<td>Singla (2009)</td>
<td>India</td>
<td>126</td>
<td>2002-2006</td>
<td>NA</td>
<td>26</td>
<td>100 Standardized</td>
<td>Individualized</td>
<td>24</td>
<td>6</td>
<td>73 Gastrointestinal</td>
<td></td>
<td></td>
<td>18</td>
</tr>
<tr>
<td>Van Deun (2010)</td>
<td>Bangladesh</td>
<td>427</td>
<td>1997-2007</td>
<td>NA</td>
<td>33.8</td>
<td>87.1 Standardized</td>
<td>Individualized</td>
<td>15 (9-21)</td>
<td>8</td>
<td>47.5 Gastrointestinal</td>
<td></td>
<td></td>
<td>4.2</td>
</tr>
<tr>
<td>Baghaei (2011)</td>
<td>Iran</td>
<td>80</td>
<td>2006-2009</td>
<td>5</td>
<td>40.6</td>
<td>100 Standardized</td>
<td>Standardized</td>
<td>24</td>
<td>6</td>
<td>45 Ototoxicity</td>
<td></td>
<td></td>
<td>Yes</td>
</tr>
<tr>
<td>Joseph (2011)</td>
<td>India</td>
<td>38</td>
<td>2006-2007</td>
<td>NA</td>
<td>30-45</td>
<td>100 Standardized</td>
<td>Individualized</td>
<td>24</td>
<td>6</td>
<td>33 Gastrointestinal</td>
<td></td>
<td></td>
<td>58</td>
</tr>
<tr>
<td>Sagwa (2012)</td>
<td>Namibia</td>
<td>59</td>
<td>2008-2010</td>
<td>53</td>
<td>34.7</td>
<td>92 Individualized</td>
<td>Individualized</td>
<td>24</td>
<td>15</td>
<td>90 Gastrointestinal</td>
<td></td>
<td></td>
<td>73</td>
</tr>
<tr>
<td>Issakidis (2012)</td>
<td>India</td>
<td>67</td>
<td>2007-2011</td>
<td>100</td>
<td>35.5</td>
<td>92.5 Individualized and standardized</td>
<td>Individualized and standardized</td>
<td>10 (1-30)</td>
<td>15</td>
<td>71 (Mild) Gastrointestinal 63 (Mod.)</td>
<td></td>
<td></td>
<td>59.7</td>
</tr>
<tr>
<td>Jacobs (2012)</td>
<td>South Africa</td>
<td>350</td>
<td>2010-2011</td>
<td>72.6</td>
<td>35.7</td>
<td>NA Standardized</td>
<td>Individualized</td>
<td>24</td>
<td>6</td>
<td>282 Ototoxicity</td>
<td></td>
<td></td>
<td>282</td>
</tr>
<tr>
<td>Van der Walt (2013)</td>
<td>South Africa</td>
<td>2079</td>
<td>2000-2004</td>
<td>66.8</td>
<td>36.3</td>
<td>90.6 Standardized</td>
<td>Individualized</td>
<td>19 (16-22)</td>
<td>8</td>
<td>66.8 Ototoxicity</td>
<td></td>
<td></td>
<td>6</td>
</tr>
<tr>
<td>Bezua (2014)</td>
<td>Ethiopia</td>
<td>73</td>
<td>2012-2013</td>
<td>No</td>
<td>28</td>
<td>87.7 Individualized</td>
<td>Individualized</td>
<td>24</td>
<td>6</td>
<td>73 Gastrointestinal</td>
<td></td>
<td></td>
<td>Nil</td>
</tr>
</tbody>
</table>
Adverse Drug Reaction observed most frequently were nausea/vomiting 24(24.5%), hearing disturbances 12(12.3%), dizziness/vertigo 10(10.2%) and arthralgia 9(9.2%). 17(17.4%) patients had major adverse drug reactions requiring change or stoppage of drugs that included ototoxicity (6.1%), headache and psychosis (4.1%), gastrointestinal intolerance and hypothyroidism (3.1%) as well as arthralgia and hepatitis (4.1%). Agents responsible for these adverse drug reactions were Kanamycin (ototoxicity), Cycloserine (headache/psychosis), Ethionamide (gastrointestinal tolerance/hypothyroidism) and Pyrazinamide (arthralgia/hepatitis). At the end of treatment 71(72.4%) patients were treated successfully. There was no mortality due to occurrence of adverse drug reactions. Further studies are required for estimation for prevalence of adverse drug reactions in near future.

CONCLUSIONS
Adverse drug reactions particularly gastrointestinal are most commonly observed during treatment of MDR-TB. Some adverse drug reactions were more prevalent in MDR-TB patients co-infected with HIV. Most adverse drug reactions can be successfully managed on an outpatient basis through a community-based treatment program, even in a resource-limited setting. Concerns about severe adverse drug reactions in the management of MDR-TB patients are justified, however, they should not cause delays in the urgently needed rapid scale-up of second-line anti-TB treatment. MDR TB can be cured successfully with appropriate combination of drugs if adverse drug reactions associated with them can be can be managed aggressively and timely. Newer and less toxic drugs are urgently needed to treat MDR TB patients.

REFERENCES
5. World Health Organization. Guidelines for establishing DOTS-PLUS pilot projects for


