Linezolid is a potentially effective drug for the treatment of patients with drug-resistant tuberculosis. Among 13 patients treated for tuberculosis with linezolid in the present study, nine had treatment success and four remain on treatment. Adverse effects occurred in 11 (85%) patients, of whom three discontinued treatment because of adverse effects. The present study adds to the growing evidence supporting the efficacy of linezolid for tuberculosis, although treatment remains complicated by adverse effects.

**Key Words:** Drug-resistant TB; Linezolid; Toxicity; Treatment outcomes

**METHODS**

All cases of active, culture-confirmed *M tuberculosis* infection treated with a linezolid-containing regimen in the northern Canadian city of Edmonton, Alberta, as well as the rural communities of the province between January 1, 2000 through December 31, 2011 were reviewed. Demographic and clinical data were extracted through retrospective chart review and from the Integrated Public Health Information System for TB. Data review was censured on April 30, 2012.

Treatment outcome of linezolid-containing regimens was defined by clinical, radiographic, and smear and culture results as applicable. For pulmonary cases, treatment success was defined by culture conversion and peripheral and optic neuropathy, have been documented in occurrence of dose- and duration-dependent reversible myelosuppression and peripheral and optic neuropathy, have been documented in the literature. Despite these toxicities, cures have been reported among patients with MDR/XDR-TB treated with a linezolid regimen. The present study aimed to describe outcomes in a case series of TB patients treated with a linezolid-containing regimen.

**RESULTS**

Between January 1, 2000 and December 31, 2011, 13 patients (seven female, six male) with a mean age of 38 years (range 15 to 72 years) with culture-confirmed TB were treated with linezolid as part of their multidrug regimens (Table 1). All patients were foreign-born and one had HIV coinfection. Of the 13 patients, one had a history of previous treatment for TB. Five (38%) patients had pulmonary disease, four (31%) had lymph node disease and one (8%) had spinal disease. Three patients (23%) had pulmonary TB and one other site of disease (Table 1). Of the eight patients with pulmonary TB, one (13%) exhibited cavitary changes on initial chest radiograph or computed tomography and six (75%) had positive sputum smear microscopy results at the time of diagnosis. Drug susceptibility test results are summarized in Table 1. Six patients had MDR-TB. The median number of drugs to which *M tuberculosis* isolates were resistant was five (range zero to seven drugs).

Indications for using linezolid were failure of previous treatment regimens (n=1), presence of extensive drug resistance (n=9) or inability to tolerate other drugs (n=3). One patient (patient 13) had pulmonary TB with a fully susceptible *M tuberculosis* isolate, but developed vertebral TB while in the continuation phase of treatment. Linezolid was thus added to intensify treatment. Patients had been on other drugs for TB for a median of 1.5 months (range zero to 12 months) before starting linezolid (Table 1). The dose of linezolid was always 600 mg once daily. The dose of vitamin B<sub>6</sub> was 25 mg to 100 mg daily. The median number of TB medications used concurrently was three (range one to four [Table 1]). The mean duration of linezolid administration was 8.3 months (range 1.4 to 22 months).

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At data censure, nine (69%) of 13 patients had successfully completed treatment (Table 2) including three patients with MDR-TB. Four patients (31%) were still receiving treatment. Among the eight patients with pulmonary disease, all achieved culture conversion by the time of data censure: five (62%) did so before starting linezolid, while three (38%) did so after starting linezolid (range one to nine weeks). To date, there have been no deaths or unsatisfactory outcomes.

Of the 13 patients, 11 (85%) experienced adverse events attributed to linezolid (Table 2), with 11 experiencing hematological side effects. Adverse events resulted in discontinuation of linezolid therapy in one patient (for gastrointestinal worsening), interruption of linezolid therapy in three patients (for anemia, peripheral neuropathy and rash) and discontinuation of linezolid therapy in 11 patients (1-11). Table 2, with all 11 experiencing hematological side effects. Adverse events resulted in discontinuation of linezolid therapy in one patient (for gastrointestinal worsening), interruption of linezolid therapy in three patients (for anemia, peripheral neuropathy and rash) and discontinuation of linezolid therapy in 11 patients (1-11).

**DISCUSSION**

Treatment outcomes for DR-TB are typically worse because of the lack of potent bactericidal drugs, the duration of treatment, and the side effects and toxicities of second-line medications. Linezolid has been shown to be effective in the treatment of DR-TB in several case series (1-12). A meta-analysis and systematic review of 11 studies (n=148 patients), in which linezolid was used in the treatment of DR-TB, demonstrated a pooled proportion of treatment success of 68% (13). This is comparable with outcomes for MDR-TB treatment in general, with a reported pooled proportion of 62% treatment success (13,14).

A second meta-analysis and systematic review of 12 studies in which linezolid was used in the treatment of MDR-TB (15) found 86 (92.5%) of 93 cases achieved a negative smear and 100 (93.5%) of 107 achieved culture conversion after treatment with individualized regimens containing linezolid. The efficacy of linezolid in the treatment of DR-TB was further demonstrated in the treatment of refractory XDR-TB with the addition of linezolid, resulting in culture conversion within six months (16). In our study, all patients who completed treatment achieved cure and three (38%) of these achieved culture conversion while on linezolid. Furthermore, three of six patients with confirmed MDR-TB achieved cure while the remainder were on treatment at data censure. However, because all patients in our series were receiving multidrug regimens, including eight who were also receiving newer fluoroquinolones, treatment success cannot be attributed solely to the inclusion of linezolid in the regimen.

Several studies have reported toxicities, primarily myelosuppression and neuropathy, to be limiting factors in the use of linezolid. In a meta-analysis (13), the pooled estimate for the frequency of any...
TABLE 2
Treatment outcomes and toxicities

<table>
<thead>
<tr>
<th>Patient</th>
<th>LZD dose, mg</th>
<th>Vitamin B₆ dose, mg</th>
<th>Time to culture conversion on LZD regimen, weeks</th>
<th>Reported toxicity</th>
<th>Reason for discontinuing LZD</th>
<th>Treatment outcome</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>600</td>
<td>100</td>
<td>0</td>
<td>Leukopenia</td>
<td>Completion of therapy</td>
<td>Cure</td>
</tr>
<tr>
<td>2</td>
<td>600</td>
<td>100</td>
<td>1</td>
<td>Rash, anemia</td>
<td>Rash</td>
<td>Continued treatment</td>
</tr>
<tr>
<td>3</td>
<td>600</td>
<td>100</td>
<td>0</td>
<td>Anemia</td>
<td>Completion of therapy</td>
<td>Cure</td>
</tr>
<tr>
<td>4</td>
<td>600</td>
<td>100</td>
<td>9</td>
<td>Anemia</td>
<td>Treatment current</td>
<td>Continued treatment</td>
</tr>
<tr>
<td>5</td>
<td>600</td>
<td>50</td>
<td>4</td>
<td>Leukopenia, neutropenia, thrombocytopenia</td>
<td>LZD interrupted and resumed; completion of therapy</td>
<td>Cure</td>
</tr>
<tr>
<td>6</td>
<td>600</td>
<td>25</td>
<td>N/A</td>
<td>Anemia, nausea, vomiting, hyperpigmentation of oral cavity</td>
<td>Change of recommendation</td>
<td>Cure</td>
</tr>
<tr>
<td>7</td>
<td>600</td>
<td>50</td>
<td>0</td>
<td>Anemia, peripheral neuropathy</td>
<td>Hemolysis (anemia)</td>
<td>Cure</td>
</tr>
<tr>
<td>8</td>
<td>600</td>
<td>25</td>
<td>N/A</td>
<td>Anemia, leukopenia, neutropenia</td>
<td>None</td>
<td>Cure</td>
</tr>
<tr>
<td>9</td>
<td>600</td>
<td>50</td>
<td>0</td>
<td>None</td>
<td>None</td>
<td>Cure</td>
</tr>
<tr>
<td>10</td>
<td>600</td>
<td>50</td>
<td>0</td>
<td>None</td>
<td>Treatment current</td>
<td>Continued treatment</td>
</tr>
<tr>
<td>11</td>
<td>600</td>
<td>50</td>
<td>N/A</td>
<td>Anemia</td>
<td>Treatment current</td>
<td>Continued treatment</td>
</tr>
<tr>
<td>12</td>
<td>600</td>
<td>50</td>
<td>N/A</td>
<td>Anemia</td>
<td>Treatment current</td>
<td>Continued treatment</td>
</tr>
<tr>
<td>13</td>
<td>600</td>
<td>100</td>
<td>0</td>
<td>None</td>
<td>Completion of therapy</td>
<td>Cure</td>
</tr>
</tbody>
</table>

LZD Linezolid; N/A Not applicable

adverse events was 61.5%, with 36.2% discontinuing linezolid due to adverse events. In our small series, 85% of patients experienced adverse events, with only 23% discontinuing because of toxicity. Pooled proportions of the frequency of neuropathy and bone marrow suppression in previous studies were 36.1% and 28.5%, respectively (13). A second meta-analysis reported adverse events in 63 (58.9%) of 107 patients: 54 (68.4%) of 79 were major adverse events including anemia (38.1%), peripheral neuropathy (47.1%), gastrointestinal disorders (16.7%), optic neuritis (13.2%) and thrombocytopenia (11.8%) (15). In our series, hematological side effects represented the most common toxicity, with 85% having anemia. One possibility for the increased rates of bone marrow toxicity observed in our study may relate to varying definitions in definitions and reporting of bone marrow toxicity among studies. Although the incidence of bone marrow toxicity was increased in our study, the number of patients requiring discontinuation of linezolid was low, suggesting that the severity of toxicity was low. Other known toxicities of linezolid, including optic neuropathy, lactic acidosis and serotonin syndrome, were not apparent in our study. It has been suggested that reduced daily doses (<600 mg) may lower the frequency of adverse events without impacting treatment success (1,6,13,15-17).

Our study was limited by the small number of patients and the retrospective nature of our analysis. However, it supports growing evidence that linezolid may be efficacious in the treatment of DR-TB, although treatment is complicated by adverse events. The optimal dose remains to be determined.

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