Short Communication

In Vitro Activity of Linezolid against Mycobacterium tuberculosis Strains Isolated from Western Turkey

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SUMMARY: We investigated the linezolid susceptibility of Mycobacterium tuberculosis strains isolated from a tertiary care hospital in Izmir. A total of 67 M. tuberculosis strains (33 multidrug-resistant [MDR] and 34 non-MDR) were isolated and identified by the Tuberculosis Laboratory, Department of Microbiology and Clinical Microbiology, Faculty of Medicine, Ege University. The activity of linezolid was studied by the standard agar proportion method. For all of the strains, the MIC range was 0.06 - 1 mg/L, and the MIC50 and MIC90 values were 0.5 mg/L. No differences were observed between the MDR and non-MDR isolates. In general, linezolid was found to be effective for both the non-MDR and MDR M. tuberculosis strains.

The increasing prevalence of tuberculosis and problem of multidrug-resistant (MDR) Mycobacterium tuberculosis strains have led to demand for new line antituberculosis drugs such as linezolid (1). The aim of this study was to investigate the in vitro activity of linezolid against both susceptible and resistant M. tuberculosis strains isolated from a tertiary care hospital in Izmir, located in western Turkey. Sixty-seven clinical strains of M. tuberculosis isolated from different patients (29 sputum, 10 bronchial aspirate, 8 abscesses, 5 bronchoalveolar lavage, 5 pleural fluid, 3 urine, 3 biopsies, 2 peritoneal fluid, 2 cerebrospinal fluid) in the Tuberculosis Laboratory, Department of Microbiology and Clinical Microbiology, Faculty of Medicine, Ege University were examined in this study. The drug susceptibility patterns of all isolates were previously detected by the agar proportion method. Of all the strains tested, 33 were resistant to at least isoniazid and rifampicin, and classified as MDR. Thirty-two isolates were susceptible to all first-line drugs, and two strains were resistant to one or two of these agents. The resistance patterns of all MDR and non-MDR strains isolated from first-line drugs are shown in Table 1. Linezolid was provided by Pfizer (Istanbul, Turkey). The agar proportion method was performed as described by Clinical and Laboratory Standards Institute (CLSI) (formerly National Committee for Clinical Laboratory Standards) (2) and H37Rv was used as a control strain. The final concentrations of linezolid were adjusted between 0.06 - 4 mg/L in agar plates. The MIC of each isolate was the lowest concentration of the linezolid that inhibited >99% of the colonies growing on the drug-free control (3).

Of all the MDR M. tuberculosis strains tested, 6 (18%) MDR strains were resistant to isoniazid and rifampicin. In addition to isoniazid and rifampicin resistance, 4 (12%) MDR strains were resistant to ethambutol, 12 (36%) to streptomycin, and 11 (33%) to both ethambutol and streptomycin. For all of the strains, the linezolid MIC range was 0.06 - 1 mg/L, and MIC50 and MIC90 values were 0.5 mg/L. The linezolid MIC for the control strain (H37Rv) was 0.5 mg/L. Both the MDR and non-MDR strains displayed an identical MIC range, and had MIC50 and MIC90 values as mentioned above (Table 1).

The vast majority of the global burden of tuberculosis is borne by developing countries such as Turkey, which is one of the main reasons why only 23% of the prevalent active cases are currently estimated to receive appropriate antituberculosis treatment (4). There is an increasing demand for new drugs that act by different mechanisms and have high levels of bactericidal activity (1). Linezolid, a member of the oxazolidinone class, has been suggested as an alternative treatment for patients infected with MDR M. tuberculosis isolates (5-7).

Until now, several studies have previously assayed the in vitro activity of linezolid against M. tuberculosis isolates. Tato et al. (5) showed that 55 M. tuberculosis isolates, including 10 MDR isolates, were all inhibited by 0.5 mg/L linezolid with the agar proportion method. Zurenko et al. (8) reported good activity of linezolid against five susceptible and five MDR M. tuberculosis isolates. All these isolates were inhibited by a concentration ≤2 mg/L. Alcalá et al. (3) investigated a wide

<table>
<thead>
<tr>
<th>Isolate</th>
<th>No. of isolates</th>
<th>Resistance phenotype</th>
<th>MIC (mg/L)</th>
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<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Range</td>
</tr>
<tr>
<td>Non-MDR</td>
<td>32</td>
<td>Susceptible</td>
<td>0.06 - 1</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>INH</td>
<td>0.25</td>
</tr>
<tr>
<td></td>
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<td>INH, STR</td>
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</tr>
<tr>
<td></td>
<td>Total</td>
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<td>0.06 - 1</td>
</tr>
<tr>
<td>MDR</td>
<td>6</td>
<td>RIF, INH</td>
<td>0.25 - 0.5</td>
</tr>
<tr>
<td></td>
<td>4</td>
<td>RIF, INH, ETB</td>
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<tr>
<td></td>
<td>12</td>
<td>RIF, INH, STR</td>
<td>0.25 - 0.5</td>
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<td></td>
<td>11</td>
<td>RIF, INH, ETB, STR</td>
<td>0.25 - 1</td>
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<tr>
<td></td>
<td>Total</td>
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<td>0.06 - 1</td>
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1) MIC50 and MIC90, MICs for 50% and 90% of the organisms, respectively.
collection of \( M. \) \( \text{tuberculosis} \) isolates, including MDR isolates, and found that all were inhibited at \( \leq 1 \text{ mg/L} \) linezolid.

In our study, the MIC range for all strains was 0.06-1 mg/L. The MIC\(_{50}\) and MIC\(_{90}\) values were 0.5 mg/L. It should be noted that both the MDR and non-MDR \( M. \) \( \text{tuberculosis} \) isolates were inhibited by a concentration of 1 mg/L of linezolid. These findings show that linezolid was effective for both the non-MDR and MDR \( M. \) \( \text{tuberculosis} \) strains investigated in this study.

Although the MIC\(_{50}\) and MIC\(_{90}\) values were the same as those in our study (0.5 mg/L), Huang et al. (9) found that the linezolid MIC range was \( \leq 0.125-4 \text{ mg/L} \) for 199 \( M. \) \( \text{tuberculosis} \) strains and the linezolid MIC value was 4 mg/L in three of these strains. In a study conducted in southeastern Spain (10), 240 \( M. \) \( \text{tuberculosis} \) strains were inhibited by 1 mg/L linezolid, but only three strains had linezolid MIC >16 mg/L.

The results of some studies indicated that elevated MIC values for linezolid were particularly observed in MDR \( M. \) \( \text{tuberculosis} \) strains. In a study conducted in northwestern Turkey, Erturan and Uzun (11) tested a total of 39 MDR \( M. \) \( \text{tuberculosis} \) isolates and determined that all were inhibited between 2 mg/L and 8 mg/L using the radiometric proportion method. The MIC\(_{50}\) and MIC\(_{90}\) values were found to be 4 mg/L and 8 mg/L, respectively. Richter et al. (12) found linezolid resistance in 4 (1.9%) of 210 MDR \( M. \) \( \text{tuberculosis} \) strains.

In general, our findings are in accordance with the results of most studies regarding the in vitro efficacy of linezolid for \( M. \) \( \text{tuberculosis} \) strains. Some studies reported relatively high MIC values for MDR \( M. \) \( \text{tuberculosis} \) strains (9-12). Our MIC values for clinical MDR \( M. \) \( \text{tuberculosis} \) strains were lower than those reported by Erturan and Uzun (11). The dissimilarity between the results could be attributed to using different methods and the fact that the strains were collected from different areas of Turkey. Although there is a general consensus on the in vitro activity of linezolid against MDR strains, there are only a few in vivo studies supporting this data (6,13,14). Further studies to evaluate the in vivo efficiency of this agent in the treatment of MDR tuberculosis are therefore needed.

ACKNOWLEDGMENTS

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REFERENCES