In Vitro Activities of Linezolid against Clinical Isolates of *Mycobacterium tuberculosis* Complex Isolated in Taiwan over 10 Years

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Significant increases in the MIC90s of linezolid in multidrug-resistant *Mycobacterium tuberculosis* isolates were seen between the baseline period of 2001 to 2003 (0.5 µg/ml) and 2004 (2 µg/ml). The MICs were 4 µg/ml in three strains. Both fluoroquinolones (except levofloxacin) and kanamycin were found to have statistically significant degrees of concordance with linezolid.

Tuberculosis (TB) is one of the major causes of death worldwide. The global prevalence of mycobacterial infection has been estimated to be 32% (1.9 billion people), with 8 million new cases of TB diagnosed annually and an average case fatality rate of 23% (11). In the year 2003, the incidence and mortality rate of TB in Taiwan were reported at 62.38 and 5.80 per 100,000 people, respectively (2), and TB is considered a more serious public health problem in southern than in northern Taiwan.

Although TB can be cured with chemotherapy, the treatment is exceedingly lengthy and results in poor patient compliance, which is a frequent cause of selection of drug-resistant and even multidrug-resistant (MDR) *Mycobacterium tuberculosis* complexes. If the treatment fails as a result of drug resistance, treatment with second-line drugs is necessary. In Taiwan, the overall rates of MDR *M. tuberculosis* among new cases and previously treated cases ranged from 1% to 3% and 0.066-4804/08/$08.00+0 doi:10.1128/AAC.00414-07

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TABLE 1. Trends of susceptibility of the *M. tuberculosis* complex to linezolid

<table>
<thead>
<tr>
<th>Yr(s) of isolation</th>
<th>No. of isolates</th>
<th>MIC (µg/ml) range</th>
<th>MIC&lt;sub&gt;50&lt;/sub&gt; (µg/ml)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>MIC&lt;sub&gt;90&lt;/sub&gt; (µg/ml)&lt;sup&gt;a&lt;/sup&gt;</th>
<th>Result with linezolid MIC as independent variable</th>
<th>Goodman and Kruskal tau</th>
<th>P&lt;sup&gt;b&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>1995–1997</td>
<td>34</td>
<td>£0.125–2</td>
<td>0.25</td>
<td>0.5</td>
<td>Susceptible MDR Combination</td>
<td>0.5</td>
<td>0.00</td>
</tr>
<tr>
<td>1998–2000</td>
<td>37</td>
<td>£0.125–4</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
<td>0.5</td>
<td>0.00</td>
</tr>
<tr>
<td>2001–2003</td>
<td>44</td>
<td>£0.125–4</td>
<td>0.5</td>
<td>0.5</td>
<td></td>
<td>0.5</td>
<td>0.00</td>
</tr>
<tr>
<td>2004&lt;sup&gt;c&lt;/sup&gt;</td>
<td>84</td>
<td>£0.125–4</td>
<td>2</td>
<td>0.5</td>
<td></td>
<td>2</td>
<td>0.00</td>
</tr>
</tbody>
</table>

<sup>a</sup> Susceptible, fully susceptible to isoniazid, rifampin, streptomycin, and ethambutol; MDR, resistant to isoniazid and rifampin; Combination, other combination of resistance patterns.

<sup>b</sup> P<sub>chi-square</sub>.

<sup>c</sup> Yr(s) of isolation: 2001 to 2003.

than ours. However, the MIC of strain H37Rv was 1 µg/ml, also 1 dilution higher. In addition, three strains with MICs greater than 16 µg/ml were reported by Rodriguez et al. in 2002 (10).

The MIC<sub>50</sub> and MIC<sub>90</sub> results are similar to previous reports (1, 10). No difference was noted in different susceptibility groups or different periods of time.

The trends in the MIC<sub>90</sub>s of linezolid in the susceptible, MDR, and combination groups during the 3-year periods are shown in Table 1. The only significant increase in MIC<sub>90</sub> was seen for the MDR strains. This was noted between the baseline period of 2001 to 2003 and 2004 when analyzed by the Mann-Whitney test on SPSS version 12 software (SPSS, Inc., Chicago, IL) (P = 0.016). The MIC<sub>90</sub>s were 0.5 µg/ml in 2001 to 2003 and 2 µg/ml in 2004.

All the patients with high linezolid MICs had not been previously treated with linezolid. Therefore, the trend of increasing linezolid MIC is not due to previous exposure to linezolid for treatment of other bacterial diseases in the community.

We examined the correlations of MICs with linezolid MIC as an independent variable by calculating Goodman and Kruskal's measure (4), which is a commonly used measure of ordinal association in the two-way contingency tables in the SPSS version 12.0 software program. With this measure, linezolid showed significant concordance between both fluoroquinolones (except levofloxacin) and kanamycin when the fluoroquinolone MIC was used to predict linezolid MIC, with values of 0.057 (P = 0.000), 0.054 (P < 0.05), 0.059 (P < 0.05), and 0.053 (P < 0.05) for ciprofloxacin, ofloxacin, moxifloxacin, and kanamycin, respectively (Table 2).

It is interesting but unclear how these distinct mechanisms correlate with each other. The effect of efflux pumps remains controversial (3, 10). Future studies are needed to determine if a relation to an elevated linezolid MIC exists and to elucidate the possible mechanism involved in this process.

In the current study, we found that the MICs of linezolid were increased in MDR *M. tuberculosis* isolates in patients with no prior exposure to this antimicrobial agent. The correlation between fluoroquinolones (except levofloxacin) and linezolid may be relevant to the trend of increasing fluoroquinolone resistance (6). Although the increase of MIC does not confer linezolid resistance, it may act additively with another mechanism to achieve clinically significant linezolid resistance through stepwise accumulation of resistance elements and mutations. The correlation between kanamycin and linezolid has not been reported previously.

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REFERENCES


