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Daily 300 mg dose of linezolid for the treatment of intractable multidrug-resistant and extensively drug-resistant tuberculosis

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***Background*: Although previous studies have suggested that linezolid may be effective for treating multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB), the optimal dose of linezolid for intractable MDR/XDR-TB is not clear.**

***Methods*: Twenty-four patients with intractable MDR/XDR-TB were treated with a daily 300 mg dose of linezolid as part of their anti-TB drug regimen.**

***Results*: The patients were treated with linezolid for a median duration of 359 days [interquartile range (IQR) 268–443 days]. Seventeen (71%) patients received 300 mg of linezolid once daily from the beginning of treatment for a median duration of 289 days (IQR 233–405 days). Of these patients, four developed peripheral neuropathy, one of whom discontinued linezolid. In seven (29%) patients, 600 mg/day linezolid was administered initially for a median duration of 104 days (IQR 26–145 days) followed by 300 mg/day linezolid for a median duration of 348 days (IQR 298–427 days). In five of these seven patients, the reason for changing from 600 to 300 mg/day was due to side effects of 600 mg/day linezolid (peripheral neuropathy in four patients and leucopenia in one patient). After reducing the dose to 300 mg/day, linezolid could be continued in six of the seven patients. Negative sputum conversion was achieved in 22 (92%) patients after a median of 89 days from the start of linezolid treatment (IQR 48–160 days).**

***Conclusions*: A daily 300 mg dose of linezolid may be useful for increasing the chances of culture conversion in the treatment of patients with intractable MDR/XDR-TB and might have fewer side effects, especially neurotoxicity, compared with a daily 600 mg dose of linezolid therapy. The present results encourage further research into the use of a 300 mg dose of linezolid for MDR/XDR-TB patients.**

Keywords: MDR-TB, XDR-TB, oxazolidinones, efficacy, tolerability

Introduction

Multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB) is a growing clinical and public health concern.[1] These forms of TB are difficult to treat and are often associated with a poor clinical outcome.[2–4] The key problems are the limited availability of effective drugs, the reduced efficacy of second-line drugs and the increased number of adverse reactions to them, and the long duration of therapy.

Linezolid is a recently approved anti-TB drug belonging to a new class of antibiotics, the oxazolidinones. It has shown good activity against *Mycobacterium tuberculosis*, including resistant strains. Although previous studies have suggested that linezolid (1200 mg/day) may be effective for treating MDR-TB and XDR-TB,[5–9] potential toxicity (e.g. myelosuppression and neurotoxicity) could limit its prolonged use. In recently published studies, a daily half-dose of linezolid (600 mg/day) helped to reduce myelosuppression, but not neurotoxicity, in patients with

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MDR/XDR-TB.[10,11] The optimal dose of linezolid for intractable MDR/XDR-TB is not clear.

In this study, we report our clinical experience with a daily 300 mg dose of linezolid therapy in combination with other anti-TB drugs in patients with intractable MDR/XDR-TB.

Patients and methods

This study included 24 patients with MDR/XDR-TB who had previously failed to respond to treatment with second-line anti-TB drugs. All patients who were given 300 mg/day linezolid orally as part of their anti-TB drug regimen during the period from January 2007 to April 2008 at Samsung Medical Center (n=13) and Asan Medical Center (n=11), in Seoul, South Korea, were included in the analysis. Park *et al.*[10] and Nam *et al.*[11] had found that even a daily 600 mg dose of linezolid therapy was associated with peripheral neuropathy in ~50%–70% of MDR-TB patients. Subsequently, a daily 300 mg dose of linezolid was prescribed from the beginning of treatment of MDR-TB at our institutions. This change of practice occurred from September 2007 in Asan Medical Center and from October 2007 in Samsung Medical Center. This retrospective study was approved by the Institutional Review Board of Samsung Medical Center and Asan Medical Center.

The serum linezolid levels, including C_{min} (trough level) and C_{max} (2 h after the dose), were measured at steady state using an HPLC assay.[12] The MIC of linezolid for *M. tuberculosis* was determined in Middlebrook 7H10 agar using 2-fold dilutions from 0.0625 to 4 mg/L, and MIC_{99} was defined as the lowest concentration for which the growth was <1/100 that of the control.

Drug susceptibility testing (DST) for isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, kanamycin, capreomycin, cycloserine, *p*-aminosalicylic acid, prothionamide, ofloxacin, moxifloxacin and rifabutin was performed at the Korean Institute of Tuberculosis, which is a World Health Organization-designated Supranational Reference Laboratory. DST was not performed for amoxicillin/clavulanate or clarithromycin during the study period. DST for linezolid was determined by the proportion method according to the CLSI (formerly NCCLS)[13] at the Yonsei University College of Medicine.

Results

Twenty-four patients [10 men and 14 women; median age 32 years; interquartile range (IQR) 27–36 years] were included in the study. None of the patients was HIV-positive.

Twenty-three patients had previously failed to respond to treatment including second-line drugs for a median of 48 months (IQR 24–81 months), while one patient with XDR-TB was treated with a linezolid-containing regimen after 4 months of first-line anti-TB treatment. All of the patients had smear- and culture-positive sputum at the start of linezolid treatment, except one patient who had smear-negative and culture-positive sputum. Cavitary disease on chest radiography was present in 23 (96%) patients (Table 1). Three patients had previously undergone surgical resection for MDR/XDR-TB.

The degree of drug resistance was very high at the start of linezolid treatment. The infecting strains of *M. tuberculosis* were resistant to a median of 10 drugs (IQR 8–11). Twelve (50%) patients had XDR-TB. Rates of resistance to ethambutol, pyrazinamide, streptomycin, ofloxacin and moxifloxacin were 92%, 88%, 71%, 100% and 83%, respectively (Table 2).

The median number of drugs, excluding linezolid, given to the patients was 5 (IQR 4–6). However, the median number of drugs to which the *M. tuberculosis* strain was susceptible was only 2 (IQR 2–3), of which the median number of previously unused drugs was 0 (IQR 0–0.5), excluding linezolid (Table 3).

The patients were treated with linezolid for a median duration of 359 days (IQR 268–443 days). Eighteen patients were on the linezolid treatment as of December 2008.

Seventeen (71%) patients received 300 mg of linezolid once daily (a median of 6.4 mg/kg/day, IQR 5.0–7.1 mg/kg/day) from the beginning of treatment for a median duration of 289 days (IQR 233–405 days). Of these patients, four [24%; 95% confidence interval (CI) 7%–50%] developed peripheral neuropathy, three of whom continued linezolid treatment while only one patient discontinued linezolid after 285 days of treatment. No patient developed haematological adverse events.

In seven (29%) patients, 600 mg/day linezolid (a median of 11.1 mg/kg, IQR 10.2–11.8 mg/kg/day) was administered initially for a median duration of 104 days (IQR 26–145 days) followed by 300 mg/day linezolid (a median of 5.6 mg/kg/day, IQR 5.1–5.9 mg/kg/day) for a median duration of 348 days (IQR 298–427 days). In five of these seven patients, the reason for changing from 600 to 300 mg/day was due to side effects of 600 mg/day linezolid, including peripheral neuropathy in four patients (57%, 95% CI 18%–90%) and leucopenia in one patient. After reducing the dosage to 300 mg/day, the leucopenia resolved completely (after the medication was stopped temporally), while the paraesthesiae due to peripheral neuropathy persisted. After reducing the dose to 300 mg/day, linezolid could be continued in six of the seven patients. In one patient,

Table 1. Characteristics of the patients (n=24)

Patient characteristic	Number (%) or median (IQR)
Sex, male	10 (42%)
Age, years	32 (27–36)
Body mass index, kg/m^2	18.8 (17.0–20.9)
Positive sputum smear	23 (96%)
Number of drugs to which the isolates were resistant	10 (8–11)
XDR-TB	12 (50%)
Bilateral disease	20 (83%)
Cavity (or cavities) on chest radiograph	23 (96%)

Table 2. Drug resistance rates

Drug	Resistance rate
Isoniazid	24 (100%)
Rifampicin	24 (100%)
Ethambutol	22 (92%)
Pyrazinamide	21 (88%)
Streptomycin	17 (71%)
Kanamycin	12 (50%)
Capreomycin	7 (29%)
Ofloxacin	24 (100%)
Moxifloxacin	20 (83%)
Prothionamide	17 (71%)
Cycloserine	9 (38%)
p-Aminosalicylic acid	15 (63%)
Rifabutin	18 (75%)

Table 3. Combination drugs

Drug	No. of patients
Ethambutol	0 (0%)
Pyrazinamide	4 (17%)
Streptomycin	2 (8%)
Kanamycin	9 (38%)
Capreomycin	7 (29%)
Amikacin	1 (4%)
Moxifloxacin	17 (71%)
Levofloxacin	4 (17%)
Prothionamide	6 (25%)
Cycloserine	19 (79%)
p-Aminosalicylic acid	7 (29%)
Rifabutin	5 (21%)
Amoxicillin/clavulanate	19 (79%)
Clarithromycin	14 (58%)

600 mg/day linezolid was taken for 238 days; subsequently 300 mg/day was used for 102 days and was then stopped due to persistent neuropathy symptoms.

Of the 24 patients, 10 (42%) had a body mass index of <18 kg/m^2, indicating moderate undernutrition.[14] The occurrence of peripheral neuropathy was not different between patients with a body mass index of <18 kg/m^2 (4/10, 40%, 95% CI 12%–74%) and those with a body mass index of ≥ 18 kg/m^2 (4/14, 29%, 95% CI 8%–58%). Peripheral neuropathy occurred more frequently in patients with diabetes mellitus (2/3, 67%, 95% CI 9%–99%) than in those without diabetes mellitus (6/21, 29%, 95% CI 9%–48%).

Sputum culture conversion, which was defined as two or more consecutive negative cultures taken at least 4 weeks apart, was achieved in 22 (92%, 95% CI 81%–100%) patients after a median of 89 days from the start of linezolid treatment (IQR 48–160 days). One patient had persistent positive sputum despite linezolid therapy (220 days) and one patient died of respiratory failure during linezolid therapy (194 days). Radiographic improvement, including disappearance or shrinkage of cavitary lesion(s) on chest X-ray, was seen in 22 patients with sputum culture conversion after linezolid treatment.

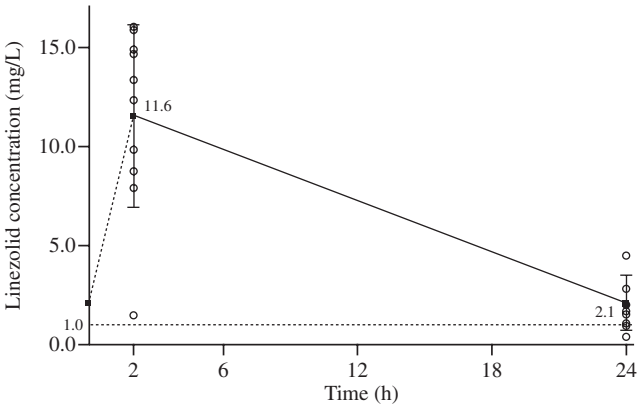

Figure 1. Mean steady-state serum C_{max} and C_{min} of linezolid after the oral administration of 300 mg once daily. The serum linezolid levels were measured before (C_{min}) and 2 h after (C_{max}) the oral administration of linezolid using an HPLC assay at least 7 days after beginning a daily 300 mg dose of linezolid. The broken horizontal line represents the expected MIC (1 mg/L) of linezolid for *M. tuberculosis*.

A patient was classified as cured if they completed treatment and were consistently culture negative (with at least five negative results) during the final 12 months of treatment.[15] Of the 22 patients with sputum conversion, two patients were cured after anti-TB treatment including continued linezolid therapy (550 and 729 days) and two patients were cured despite discontinuing linezolid therapy due to peripheral neuropathy (340 days) or economic reasons (179 days). Another 18 patients were still taking linezolid for a median duration of 350 days (range 284–655 days) with culture conversion. Six patients underwent surgical resection for MDR/XDR-TB during linezolid treatment.

A pharmacokinetic study was performed in 10 patients at least 7 days after beginning a daily 300 mg dose of linezolid (Figure 1). The mean serum C_{min} of linezolid was 2.1 ± 1.3 mg/L (range 0.4–4.5 mg/L) and the mean serum C_{max} was 11.6 ± 4.4 mg/L (range 1.5–15.9 mg/L). In a patient in whom treatment failed, the C_{max} and C_{min} were 13.4 and 1.0 mg/L, respectively. The patient with the lowest linezolid concentration (C_{max}=1.5, C_{min}=0.4 mg/L) was cured after 729 days of linezolid therapy.

The MIC_{99} of linezolid for *M. tuberculosis* was 0.25 mg/L for isolates from three patients and 0.5 mg/L for isolates from seven patients, including a patient in whom treatment failed. The MIC of linezolid was 0.5 mg/L for the H37Rv laboratory control strain.

Discussion

This is the first report on the efficacy and tolerability of a daily 300 mg dose of linezolid for treating MDR/XDR-TB. In this study, 22 of 24 patients with MDR-TB, including 11 out of 12 patients with XDR-TB, achieved sputum culture conversion after daily treatment with 300 mg of linezolid. Our cases had truly 'intractable' MDR/XDR-TB in many respects, including previous long-term treatment with second-line drugs, high rates of resistance to anti-TB drugs, sputum smear status and radiographic findings. These findings suggest that a daily 300 mg dose of linezolid is clinically effective in the treatment of MDR/XDR-TB.

Adverse side effects such as myelosuppression and neurotoxicity are a major problem during the prolonged use of linezolid. A daily half-dose of linezolid (600 mg/day) appears to protect

against myelosuppression, but not neurotoxicity,[10,11] as neurotoxicity is more closely related to the duration of treatment.[16]

The linezolid levels in plasma and epithelial lining fluid are expected to exceed the *M. tuberculosis* MIC (0.5–1 mg/L) during most of the dosing interval following the administration of various oral doses.[17,18] The long-term use of linezolid, even with a daily dose of 600 mg, induces adverse effects, principally neurotoxicity, by inhibiting mitochondrial protein synthesis in a dose-dependent fashion.[19] McKee *et al.*[20] reported that the linezolid concentration inhibiting 50% of mitochondrial protein synthesis (i.e. IC_{50}) in rat and rabbit hearts and in liver mitochondria is 3.37–5.26 mg/L. Therefore, we hypothesized that the serum linezolid concentration after a 300 mg dose would remain above the MIC for *M. tuberculosis*, and yet below the IC_{50} level, permitting efficacy against MDR/XDR-TB without producing serious side effects.

In our previous studies, a daily dose of 600 mg of linezolid therapy was associated with peripheral neuropathy in ~50%–70% of MDR-TB patients, and we found that linezolid treatment should be discontinued in all patients who developed peripheral neuropathy.[10,11] In this study, peripheral neuropathy developed in 4 out of 17 (24%) patients who received 300 mg/day linezolid, while neurotoxicity occurred in 4 out of 7 (57%) patients who were initially given 600 mg/day linezolid. Linezolid had to be discontinued in two patients only, including one patient who was initially prescribed 600 mg/day and had the dose reduced to 300 mg/day. Bone marrow suppression developed in one patient who was initially given 600 mg/day linezolid.

The absorption of linezolid after oral dosing is rapid and C_{max} is achieved 1–2 h after dosing.[17] The oral bioavailability approaches 100%. In addition, linezolid can penetrate bronchial mucosa, alveolar macrophages and epithelial lining fluid well.[18] Our study revealed that both the serum C_{min} and serum C_{max} after oral dosing of linezolid 300 mg/day were higher than the MIC for the infecting *M. tuberculosis* strain.

The present study has several important limitations. This retrospective study included a small group of patients, and this was not a randomized clinical trial including a control group who did not receive linezolid therapy. In addition, the majority of patients were still on treatment at the time the analyses were performed. Therefore, it is hard to conclude anything about cure or the long-term efficacy of a daily dose of 300 mg of linezolid.

In conclusion, a daily dose of 300 mg of linezolid may be enough to keep the serum concentrations of linezolid above the MIC for *M. tuberculosis*, and may be useful for increasing the chances of culture conversion in the treatment of patients with intractable MDR/XDR-TB and possibly reducing or delaying the development of side effects, especially neurotoxicity. The present results encourage further research into the use of a 300 mg dose of linezolid for MDR/XDR-TB patients.

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Transparency declarations

None to declare.

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