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Daily 300 mg dose of linezolid for multidrug-resistant and extensively drug-resistant tuberculosis: updated analysis of 51 patients

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Objectives: Linezolid may be an effective treatment for multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB). The objective was to evaluate the efficacy, tolerability and adverse events of a 300 mg daily dose of linezolid in the treatment of MDR/XDR-TB.

Patients and methods: We retrospectively reviewed the medical records of 51 MDR-TB patients, including 26 patients (51%) with XDR-TB, to evaluate the safety, tolerability and efficacy of therapy with 300 mg/day linezolid. All patients had failed previous treatments with second-line anti-TB drugs.

Results: Patients were treated with linezolid for a median of 413 days (IQR 237–622 days). Favourable treatment outcome (treatment success or still on treatment after culture conversion) was achieved in 40 patients (78%) with culture conversion at a median of 55 days (IQR 41–91 days) from the start of linezolid therapy. Eleven patients (22%) had unfavourable outcomes (treatment failure or death) and 14 (27%) discontinued treatment due to neurotoxicity (peripheral or optic neuropathy) after a median of 278 days (IQR 174–412 days).

Conclusions: Our findings suggest that linezolid at a daily dose of 300 mg is effective against intractable MDR/XDR-TB, and may be associated with fewer neuropathic side effects than a daily dose of 600 or 1200 mg.

Keywords: TB, drug resistance, oxazolidinones, treatment

Introduction

Multidrug-resistant (MDR) tuberculosis (TB), defined as TB with *in vitro* resistance to at least isoniazid and rifampicin, and extensively drug-resistant (XDR)-TB, defined as MDR-TB that is resistant to any fluoroquinolone and at least one of three injectable second-line drugs, are significant public health problems worldwide.[1,2] The key issue is the limited availability of effective drugs.[3] Thus, it is important to assess the clinical efficacy and adverse effects of new anti-TB drugs.

Linezolid, an oxazolidinone antibiotic, has great promise based on initial studies of patients with MDR/XDR-TB.[4–14] However, its potential toxicities (e.g. myelosuppression and neurotoxicity) may limit its widespread use for long-term treatment. Some previous studies indicated that 600 mg of linezolid/day reduced the incidence of bone marrow suppression, although peripheral and optic neuropathy remained serious problems.[5,8,10,13] In addition, we recently found that 300 mg of linezolid/day may increase the rate of culture conversion in patients with MDR/XDR-TB and result in fewer adverse effects, especially neurotoxicity, than 600 mg of linezolid/day.[11] Therefore, the optimal dosing of linezolid for the treatment of MDR/XDR-TB has not yet been established. The major limitation of our previous study was the small study population (17 patients) and the lack of long-term outcomes.[11]

In the present study, we report our further clinical experience with 300 mg of linezolid/day in 51 patients with MDR/XDR-TB. The objective was to evaluate the efficacy, tolerability and adverse events of a 300 mg daily dose of linezolid in the treatment of MDR/XDR-TB.

Patients and methods

Patients

This retrospective study examined the records of 51 patients with MDR/XDR-TB who failed previous treatment with second-line anti-TB

drugs and agreed to use linezolid as part of an anti-TB drug regimen from September 2007 to December 2009 at the Samsung Medical Center ($n=36$) or the Asan Medical Center ($n=15$) in Seoul, South Korea. All patients were given 300 mg of linezolid/day from the beginning of treatment. Vitamin B6 (100–150 mg/day) was given to 41 (80%) patients.

Some clinical data that described the short-term clinical responses of 17 patients to low-dose linezolid were described in a previous publication,[11] and those 17 patients were also included in the present study. This study was approved by the institutional review boards of the Samsung Medical Center and the Asan Medical Center.

Drug susceptibility testing (DST)

DST for all first- and second-line anti-TB drugs was performed using the absolute concentration method with Löwenstein–Jensen medium at the Korean Institute of Tuberculosis, a WHO-designated Supranational Reference Laboratory. The drugs and their critical concentrations for resistance were as follows: isoniazid, 0.2 mg/L; rifampicin, 40 mg/L; ethambutol, 2 mg/L; streptomycin, 10 mg/L; kanamycin, 40 mg/L; capreomycin, 40 mg/L; amikacin, 40 mg/L; ofloxacin, 2 mg/L; moxifloxacin, 2 mg/L; prothionamide, 40 mg/L; cycloserine, 30 mg/L; *para*-aminosalicylic acid, 1 mg/L; and rifabutin, 20 mg/L. DST was not performed for linezolid during the study period.

Evaluation of clinical characteristics

The medical records of all patients were reviewed, including information on patient age, sex, underlying illnesses, history of TB treatment, history of thoracic surgery and results of anti-HIV antibody testing. Sputum smears and culture examinations were performed monthly for the first 6 months after initiation of linezolid and then at 2 month intervals until the end of treatment.

We used the MDR-TB treatment outcome definitions developed by an international expert consensus group.[15] A patient was classified as cured if he or she completed treatment and consistently had negative culture results (with at least five negative results) during the final 12 months of treatment. Patients who completed treatment but who did not meet the definition for cure or who experienced treatment failure were considered to have completed treatment. Treatment failure was defined as two or more positive cultures recorded during the final 12 months or a positive result of any one of the final three cultures. Death was defined as death due to any cause during therapy. Some patients were still on treatment after sputum culture conversion at the time of our analysis. For the purpose of analysis, cure, complete treatment and still on treatment after culture conversion were classified as favourable outcomes, whereas treatment failure and death were classified as unfavourable outcomes.

Peripheral neuropathy, optic neuropathy and myelosuppression were regarded as linezolid related for this analysis. Myelosuppression was assessed by regular blood tests; however, neuropathy was assessed only clinically by attending physicians in most patients. A major adverse event of linezolid was defined as any effect that resulted in temporary or permanent discontinuation of linezolid administration.

Statistical analysis

All statistical analyses were performed using SPSS software (version 12.0; SPSS Inc., Chicago, IL, USA). All results are expressed as numbers (percentages) or medians (IQRs). Categorical variables were analysed by the χ^2 test or Fisher's exact test and continuous variables were analysed by the Mann–Whitney *U*-test. A P value <0.05 was considered statistically significant.

Results

Clinical characteristics of patients

The study included 51 patients with pulmonary MDR/XDR-TB. There were 26 males and 25 females, of median age 33 years (IQR 29–48 years), and all patients were HIV-negative (Table 1). All 51 patients failed to respond to previous treatment with second-line drugs for a median of 40 months (IQR 12–90 months) and had culture-positive sputum when linezolid treatment was initiated. Forty-four patients (86%) had smear positivity and 45 patients (88%) had cavitary disease based on chest radiography. Twelve patients (24%) had resectional surgery for MDR/XDR-TB.

The extent of drug resistance was very high at the initiation of linezolid treatment and the isolated strains of *Mycobacterium tuberculosis* were resistant to a median of 10 drugs (IQR 8–12). Twenty-six patients (51%) had XDR-TB. The rates of resistance to ethambutol, pyrazinamide, kanamycin and ofloxacin were 86%, 88%, 47% and 98%, respectively (Table 2). All patients received linezolid as part of an expanded treatment

Table 1. Characteristics of enrolled patients ($N=51$)

Characteristic	*n* (%) or median (IQR)
Male gender	26 (51)
Age, years	33 (29–48)
BMI, kg/m^2	19.6 (17.5–22.4)
Number of drugs to which isolates were resistant	10 (8–12)
Previous duration of anti-TB drugs (months)	40 (12–90)
XDR-TB	26 (51)
Positive sputum smear at initiation of linezolid	44 (86)
Positive sputum culture at initiation of linezolid	51 (100)
Bilateral disease	40 (78)
Cavity (or cavities) on chest radiography	45 (88)
Previous resectional surgery for TB	12 (24)

Table 2. Resistance rates of *M. tuberculosis* isolates

Drug	Resistance rate
Isoniazid	51/51 (100%)
Rifampicin	51/51 (100%)
Ethambutol	44/51 (86%)
Pyrazinamide	45/51 (88%)
Streptomycin	28/51 (55%)
Kanamycin	24/51 (47%)
Capreomycin	13/51 (25%)
Amikacin	19/47 (40%)
Ofloxacin	50/51 (98%)
Moxifloxacin	45/51 (88%)
Prothionamide	43/51 (84%)
Cycloserine	21/51 (41%)
Para-aminosalicylic acid	33/51 (65%)
Rifabutin	39/51 (76%)

regimen based on individual drug history and the results of recent DST.

Treatment regimens

Linezolid was administered for a median of 413 days (IQR 237–622 days) and a median of 5 anti-TB drugs (IQR 4–6 drugs), excluding linezolid, were given during this time. However, excluding linezolid, the isolated *M. tuberculosis* strains were susceptible to a median of 2 drugs (IQR 1–3 drugs), and there was only a median of 1 previously unused drug (IQR 0–2 drugs).

Nine patients underwent surgical resection for MDR/XDR-TB during linezolid treatment. The median duration of pre-operative linezolid therapy in these patients was 71 days (IQR 20–86 days). The pre-operative sputum cultures were still positive in six of these nine patients.

Adverse events

Fourteen (27%) patients experienced one major adverse event, and none of them resumed linezolid treatment. Peripheral neuropathy that affected the lower limbs occurred in 13 patients (25%) and optic neuropathy developed in 1 patient. These 14 patients discontinued linezolid treatment after a median of 278 days (IQR 174–412 days). Peripheral neuropathy symptoms partially resolved in eight patients, became worse in one patient and did not improve in four patients, after discontinuation of linezolid. The patient with optic neuropathy fully resolved after discontinuation of linezolid. Among these 14 patients, the linezolid treatment duration was longer in 11 patients with successful treatment outcome (median 314 days; IQR 254–414 days) than in 3 patients with unsuccessful treatment outcome (median 156 days; IQR 125–180 days) ($P<0.05$). The clinical characteristics of patients with and without major neuropathy were similar (Table 3). Minor adverse events occurred in 10 patients [8 patients (16%) with leucopenia ($2000/mm^3<$white blood cells$<3000/mm^3$) and 2 patients (4%) with thrombocytopenia ($50\,000/mm^3<$ platelets$<100\,000/mm^3$)] and these patients continued linezolid treatment.

Outcomes

A total of 45 out of the 51 patients (88%) completed their treatment for MDR/XDR-TB. Among these 45 patients with definite treatment outcomes, 33 patients were cured and 1 patient completed therapy. One patient died and 10 patients experienced treatment failure. Six of 51 enrolled patients were still on treatment after sputum culture conversion at the time of our analysis. Therefore, favourable treatment outcomes were achieved in 40 patients (78%) and sputum culture conversion developed after a median of 55 days from the start of linezolid treatment (IQR 41–91 days) in these patients. Eleven patients (22%) had unfavourable treatment outcomes. All of these patients had persistent positive sputum culture despite linezolid therapy and one patient died of respiratory failure 178 days after the start of linezolid treatment.

The culture conversion rate was not significantly different for patients with XDR-TB (81%, 21/26) and non-XDR-MDR-TB (76%, 19/25). Among the 14 patients with major neurotoxicity, 11 (79%) had a successful treatment outcome. Comparison of patients with treatment success and failure indicated that body mass index (BMI) was significantly lower and previous treatment duration was significantly longer in patients with treatment failure (Table 4).

Table 3. Characteristics of patients with and without major neurotoxicity after linezolid treatment

Characteristic	With neurotoxicity ($N=14$), *n* (%) or median (IQR)	Without neurotoxicity ($N=37$), *n* (%) or median (IQR)	*P* value
Age, years	38 (31–49)	33 (29–48)	0.42
Male gender	7 (50)	19 (51)	0.59
BMI, kg/m^2	19.4 (16.7–21.4)	20.1 (17.6–22.8)	0.51
Co-administration of cycloserine	10 (71)	22 (59)	0.53
Use of vitamin B6	9 (64)	32 (86)	0.09

Table 4. Clinical characteristics of patients with treatment success and failure

Characteristic	Treatment success ($N=40$), *n* (%) or median (IQR)	Treatment failure ($N=11$), *n* (%) or median (IQR)	*P* value
Male gender	22 (55)	4 (36)	0.32
Age >45 years	12 (30)	3 (27)	0.59
BMI <18.5 kg/m^2	11 (28)	7 (64)	0.04[a]
XDR-TB	21 (53)	5 (45)	0.74
Duration of previous treatment, months	30 (10–73)	66 (37–120)	0.03[a]
Median no. of drugs to which the isolates were resistant	11 (9–12)	8 (8–13)	0.26
Positive sputum smear	33 (83)	11 (100)	0.16
Cavity (or cavities) on chest radiography	36 (90)	9 (82)	0.39
Bilateral disease	31 (78)	9 (82)	0.59

[a]Statistically significant.

Discussion

The present study is an updated analysis of the safety, tolerability and efficacy of 300 mg of linezolid/day for treatment of MDR/XDR-TB. We previously reported that 300 mg of linezolid/day may be effective in the treatment of MDR/XDR-TB.[11] In that study, we initially administered linezolid at 600 mg/day and then changed to 300 mg/day in many patients and found that many patients did not achieve final treatment outcome because of the short duration of follow-up.[11] In the present study of 51 patients with MDR/XDR-TB, all patients were given 300 mg of linezolid/day from the beginning of treatment and 78% of patients showed a favourable treatment outcome. The results of the present study confirm that low-dose linezolid therapy of patients with

Table 5. Results of previous studies of linezolid treatment for MDR-TB or XDR-TB

First author, year of publication	Country	No. of MDR-TB (no. of XDR-TB)	Initial daily dose of linezolid	No. of successful outcomes[a]	Myelosuppression	Neurotoxicity
Fortun, 2005[4]	Spain	5 (0, 0%)	1200 mg ($n=5$)	5 (100%)	4 (80%)	2 (40%)
von der Lippe, 2006[6]	Norway	10 (1, 10%)	1200 mg ($n=10$)	9 (90%)	5 (50%)	6 (60%)
Park, 2006[5]	Korea	8 (5, 63%)	1200 mg ($n=6$), 600 mg ($n=2$)	8 (100%)	1 (13%)	4 (50%)
Condos, 2008[7]	USA	7 (6, 86%)	1200 mg ($n=7$)	7 (100%)	1 (14%)	2 (29%)
Nam, 2009[8]	Korea	11 (4, 36%)	600 mg ($n=11$)	9 (82%)	2 (18%)	9 (82%)
Migliori, 2009[9]	Belarus, Germany, Italy, Switzerland	85 (10, 12%)	1200 mg ($n=57$), 600 mg ($n=28$)	36/45 (80%)	30/85 (35%)	3/85 (4%)
Koh, 2009[11]	Korea	24 (12, 50%)	600 mg ($n=7$), 300 mg ($n=17$)	22 (92%)	1 (4%)	8 (33%)
Schecter, 2010[13]	USA	30 (3, 10%)	600 mg ($n=28$), 300–450 mg ($n=2$)	22/25 (88%)	2 (7%)	6 (20%)
Anger, 2010[12]	USA	16 (10, 63%)	1200 mg ($n=11$), 400–800 mg ($n=5$)	11 (69%)	13 (81%)	7 (44%)
Udwadia, 2010[10]	India	18 (7, 39%)	600 mg ($n=18$)	11 (61%)	1 (6%)	16 (89%)
Villar, 2011[14]	Portugal	16 (12, 75%)	1200 mg ($n=15$), 600 mg ($n=1$)	8/9 (89%)	2/16 (13%)	1/16 (6%)
Tangg, 2011[20]	China	14 (14, 100%)	600 mg ($n=14$)	14 (100%)	1 (7%)	2 (14%)
Singla, 2011[21]	India	29 (16, 55%)	1200 mg ($n=11$), 600 mg ($n=18$)	21 (72%)	1 (3%)	2 (7%)
Abbate, 2012[22]	Argentina	17 (17, 100%)	1200 mg ($n=17$)	14 (82%)	2 (12%)	3 (18%)
This study	Korea	51 (26, 51%)	300 mg ($n=51$)	40 (78%)	8 (16%)	14 (27%)

[a]Some studies presented efficacy for a limited number of patients due to insufficient treatment duration.

MDR/XDR-TB results in a favourable treatment outcome (40/51, 78%), even though our patients had previously received long treatments with second-line drugs and had high rates of resistance to anti-TB drugs, positive sputum smear status and advanced radiographic findings. However, neurotoxicity was still an obstacle for the long-term use of linezolid, even at a dose of 300 mg/day. Notwithstanding, low-dose linezolid may allow a longer treatment duration than high-dose linezolid.

Previous case series have indicated that linezolid is effective in approximately 60%–100% of cases with MDR/XDR-TB (Table 5).[4–14] However, these published case series are limited by small sample sizes. Our study is one of the largest case series of linezolid treatment of MDR/XDR-TB and reports on the effect of linezolid therapy at 300 mg/day for treatment of MDR/XDR-TB. Our favourable treatment response rate was 78% (40/51); 34 patients successfully completed treatment and 6 patients remained on treatment after successful culture conversion. This is a very promising result, because it indicates the efficacy of low-dose linezolid.

Moreover, a recent study that compared MIC distributions and pharmacokinetic and pharmacodynamic data of linezolid showed that the majority of *M. tuberculosis* strains were covered by an AUC/MIC for the free antibiotic fraction of >200 at a daily dose of 600 mg of linezolid.[16] This means that this value would be >100 at a daily dose of 300 mg of linezolid, implying that the pharmacodynamic target derived from other organisms, such as *Staphylococcus aureus*, is met, although the target for *M. tuberculosis* is unknown so far.[16]

It was necessary, however, to discontinue linezolid therapy due to neurotoxicity in 14 of our patients (27%). Neurotoxicity in particular has been a major obstacle for the use of long-term linezolid therapy of patients with MDR/XDR-TB. Recovery from linezolid-mediated neurotoxicity is limited, even after stopping treatment, so the onset of neurotoxicity warrants immediate cessation of therapy.[17,18] However, in this study, linezolid was administered for a median of 278 days before withdrawal due to adverse events. This long duration of linezolid treatment might have contributed to our successful treatment outcome (78%). In fact, there were no significant differences in the success rates of patients who continued and discontinued linezolid treatment. Many clinicians use linezolid with a 18–24 month regimen for MDR/XDR-TB treatment. However, no definite optimal duration for linezolid usage has been established yet. The results of this study may strengthen the case for reducing the duration of linezolid usage. Further studies about short-term usage of linezolid should be conducted.

Previous studies have reported highly variable incidences of neurotoxicity due to linezolid (Table 5). These findings suggest that ethnicity may affect the frequency of linezolid neurotoxicity. However, other factors, such as nutrition, body weight, previous or concomitant use of neurotoxic drugs or concomitant use of vitamin B6, should also be considered as contributing factors.

In the present study, none of these factors was significantly different in patients with and without major neurotoxicities. Unfortunately, peripheral neuropathy was only assessed clinically in most patients and even though many patients with neurotoxicities were also taking other potentially neurotoxic medications, such as cycloserine (71%, 10/14), all the neurotoxic symptoms were presumed to occur due to linezolid.

The present study had an unfavourable treatment response rate (treatment failure or death) of 22%. The lower BMI and longer duration of previous treatment in patients with unfavourable treatment outcomes might indicate a severe disease or worse health status prior to linezolid treatment. Some of these patients might have been successfully treated by a higher dose of linezolid (600–1200 mg/day). Moreover, the use of low-dose linezolid may lead to more acquired resistance to this drug. We could not confirm the incidence of acquired linezolid resistance in the present study. The dose of linezolid that maximizes efficacy and minimizes toxicity remains to be defined and prospective, randomized trials are needed to resolve this issue. A clinical trial comparing the efficacy and tolerability of 600 and 300 mg of linezolid/day for the treatment of XDR-TB is currently under way in Korea.[19]

In conclusion, our findings suggest that linezolid at a daily dose of 300 mg is effective against intractable MDR/XDR-TB, and may be associated with fewer neuropathic side effects than a daily dose of 600 or 1200 mg.

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Transparency declarations

None to declare.

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