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Efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis

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***Objectives*: Although linezolid has good *in vitro* activity against *Mycobacterium tuberculosis*, its long-term use in the treatment of multidrug-resistant tuberculosis (MDR-TB) may be limited by its cost and serious adverse reactions. We therefore evaluated the efficacy and tolerability of a reduced dose of linezolid, in combination with other anti-TB drugs, in patients with intractable or extensive MDR-TB.**

***Methods*: MDR-TB patients unresponsive to at least three cycles of treatment were treated with daily-half doses of linezolid (600 mg once per day) plus at least four companion drugs.**

***Results*: As of March 2006, eight patients, all HIV-negative, had been treated with linezolid for 3–18 months. Cultures became negative in all patients in an average of 82 days. Four patients developed peripheral neuropathy, two developed optic neuropathy and one developed anaemia. Although optic neuropathy resolved after cessation of linezolid therapy, peripheral neuropathy continued. One patient completed 18 months of linezolid therapy. Two patients, who have taken linezolid for 15–17 months, are still on treatment and remain in culture conversion. Three patients stopped linezolid after 7–9 months, two because of side effects and one for economic reasons, but remain on treatment with other second-line drugs with culture conversion. Two patients died from severe respiratory failure, but both previously had shown culture conversion.**

***Conclusions*: Although daily-half doses of linezolid were effective in patients with intractable or extensive MDR-TB, this dosage regimen did not reduce long-term use-related side effects, such as peripheral and optic neuropathy.**

Keywords: oxazolidinones, *Mycobacterium tuberculosis*, treatment failure, adverse effects

Introduction

In recent years, the epidemiology of tuberculosis (TB) has altered due to the emergence of HIV infection and the propagation of multidrug-resistant (MDR) TB. Treatment failure of MDR-TB can lead to the generation of intractable or extensively drug-resistant (XDR) TB strains, which are resistant to isoniazid, rifampicin and at least three of the six main classes of second-line drugs. This has increased concerns regarding future epidemics of virtually untreatable TB.[1]

Among the drugs that have shown promising activity in the treatment of MDR-TB are two of the newer fluoroquinolones, gatifloxacin and moxifloxacin, as well as experimental compounds (e.g. diaryquinolones) in the same class of agent.[2,3] Many patients, however, have shown cross-resistance within this class, suggesting that previous administration of older fluoroquinolones may have a negative impact on the effectiveness of new compounds. It is therefore of critical importance to assess the efficacy of new anti-TB fluoroquinolones in clinical settings.

Linezolid is a member of the oxazolidinone class of drugs with a mechanism of action involving the inhibition of protein synthesis. It has shown good activity against a variety of Gram-positive organisms, anaerobes and atypical microbes, as well as against *Mycobacterium tuberculosis*, including resistant strains, both *in vitro* and in animal studies.[4] Long-term linezolid use, however, has been associated with myelosuppression and neurotoxicity. Although recent reports of case series have suggested that linezolid may be effective in treating MDR-TB,[5,6] the long-term

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efficacy and tolerability of linezolid requires further evaluation. Due to these serious adverse events, and the slow-growing nature of *M. tuberculosis*, we evaluated the efficacy of daily-half doses of linezolid, in combination with other anti-TB drugs, in patients with intractable or XDR-TB.

Patients and methods

Patient selection and linezolid prescriptions

For inclusion in the present study, patients were required to have microbiologically proven MDR-TB with good adherence to treatment, to have failed at least three previous cycles of treatment and to agree to use linezolid as part of their anti-TB regimen. All patients provided written informed consent, and the study protocol was approved by the Institutional Review Board of Asan Medical Center.

At the commencement of the study, in July 2003, patients were treated with 600 mg of linezolid once daily. Beginning in 2004, patients received 600 mg of linezolid twice daily for the first 2 weeks, followed by once daily thereafter. At the beginning of linezolid treatment, patients were also administered at least four companion drugs, selected according to each patient's drug-use history and the results of recent drug susceptibility tests (Table 1).

Drug susceptibility tests

Drug susceptibility testing (DST) for first- and seven second-line anti-TB drugs was performed on Lowenstein-Jensen media by the method of absolute concentration at the Korean Institute of Tuberculosis, which is taking part in a quality control evaluation of TB laboratories as a WHO Collaborating Center and a WHO/IUATLD designated Supranational Reference Laboratory. MICs of linezolid were measured by the broth dilution method using the manual mycobacteria growth indicator tube (MGIT) 960 system (Becton Dickinson, USA).[7]

Results

Beginning in July 2003, eight patients were included in the study (Table 1). All patients were HIV-negative, two had diabetes mellitus, and two had previously undergone pneumonectomy and lobectomy for TB, respectively. All patients had bilateral pulmonary lesions and seven had cavitary lesions. Linezolid DST was performed in only three patients, with all showing susceptibility (MIC $\leq$ 1 mg/L).

Two patients received 600 mg once daily linezolid from the beginning of treatment; five received 600 mg twice daily for the first 2 weeks and 600 mg once daily thereafter; and one received 600 mg twice daily for 7 weeks due to a prescription error (intended duration was 2 weeks) and 600 mg once daily thereafter (Table 2). Culture conversion was achieved in all eight patients. The mean time from the start of linezolid treatment to culture conversion was 82 ± 47 days (mean ± SD). As of March 2006, patients have been on linezolid for 3–18 months. One patient completed 18 months of linezolid therapy 6 months ago and is now being monitored with no medication. Two patients, who have been taking linezolid for 15–17 months, are still taking the drug and remain in culture conversion. Two patients stopped linezolid after 8–9 months because of optic neuropathy, and one stopped linezolid after 7 months for economic reasons; these three patients have been on second-line therapy for 7–8 months after stopping linezolid, and all have sterile cultures. Two patients (Patients 1 and 2) died from severe respiratory failure, but both were culture negative (Table 2). Patients 3 and 6 underwent thoracic surgery during the course of linezolid treatment, Patient 6 one month after initiation of therapy but 4 months before culture conversion, and Patient 3 after culture conversion.

One patient (Patient 4) developed asymptomatic anaemia (haemoglobin, 9.6 mg/dL) after 7 weeks of 600 mg twice-daily linezolid, but this resolved spontaneously after the linezolid dose was reduced to 600 mg once daily. Peripheral neuropathy affecting the lower limbs was observed in four patients (Patients 3, 5, 7 and 8) at 4, 8, 11 and 5 months, respectively. These patients were treated with amitriptyline, gabapentin and vitamin B6 while taking linezolid. Two of these patients (Patients 5 and 8), however, also developed optic neuropathy, at 9 and 8 months, respectively. After linezolid treatment was stopped, the optic neuropathy fully resolved after 2–3 months in both patients, but neuropathic symptoms continued or improved only marginally.

Discussion

Although this report presents interim results of treatment with daily-half doses of linezolid in a small number of patients, it is the first report on the efficacy and tolerability of reduced dose linezolid for the treatment of intractable or XDR-TB. As compared with two previous published studies,[5,6] our cases were more severe in many aspects, including duration and number of previous treatment, number of previously used drugs for MDR-TB treatment and number of probably active drugs in the combination regimen. In our study, all eight patients had been unresponsive to several cycles of anti-TB treatments, including new fluoroquinolones (seven patients), interferon-γ (four patients) and thoracic surgery (two patients), suggesting all had truly intractable TB. Although three patients were not XDR based on their drug susceptibility tests, all had been unresponsive to the second-line drugs to which they were susceptible *in vitro*. However, all eight patients showed a durable culture conversion in response to linezolid, suggesting that patients with intractable or XDR-TB may benefit from treatment with daily-half doses of linezolid.

Linezolid has an MIC_{90} for *M. tuberculosis* in the 0.5–1 mg/L range, high maximal concentration in serum and an excellent ability to penetrate into bronchial mucosa and bronchoalveolar lavage fluid. AUC_{24}/MIC has been reported to be a key pharmacodynamic parameter for bacteria, and this, along with the slow growth of *M. tuberculosis* and the high concentration achievable in serum and tissues, allowed daily-half dosage of linezolid to be effective. Moreover, the slow replication rate of the bacilli may compensate for the decrease in time above MPC_{90} (MPC: mutant prevention concentration, defined as the capacity to severely restrict the selection of resistant mutants during antibiotic treatment) caused by dose reduction, preventing the selection of linezolid resistant mutants.[8]

In addition to linezolid, all eight patients received at least four other drugs, some of which may be active against *M. tuberculosis.* Most of these drugs, however, had been used in previous treatment regimens without success, and these drugs differed from patient to patient, making it unlikely that they affected treatment outcome (Table 1).

The long-term use of linezolid in treating TB is limited by its toxicity. Clinical trials have shown that 600 mg twice-daily linezolid is safe and generally well tolerated for up to 28 days. However, data on long-term exposure to linezolid are limited.

Table 1. Characteristics of the eight patients treated with linezolid-containing regimens

Patient	Age (year), sex	Underlying diseases	Number of previous treatments	Duration of previous treatment (years)	Previously used drugs for MDR-TB treatment (number)	Recent date of drug susceptibility test	Resistant drugs on drug susceptibility test (number)	Starting date of linezolid-containing regimen	Combination drugs (number)	Probably active drug[a] except LZD
1	36, F	none	4	6.5	AMC, CIP, CLOS, CLR, EMB, INF-γ, KAN, LVX, PAS, PTH, PZA, STR (12)	21 May 2003	INH, RIF, EMB, PZA, OFX (5)	23 July 2003	AMC, CLOS, CLR, IFN-γ, KAN (5)	none
2	17, F	none	5	10	AMC, CLOS, CLR, CPM, IFN-γ, LVX, MXF, PAS, PTH, PZA, RFB, RIF, RXT, STR (14)	7 August 2003	INH, RIF, EMB, CLOS, KAN, OFX, PAS, PTH (8)	13 October 2003	CPM, LVX, RFB, RXT (4)	none
3	36, F	none	3	3.5	AMC, CLOS, CLR, CPM, EMB, IFN-γ, KAN, LVX, OFX, PAS, PTH, RXT (12)	27 October 2003	INH, RIF, EMB, PZA, CLOS, KAN, OFX, PAS, PTH, STR (10)	10 March 2004	CFZ, CLR, CPM, EMB, RFB (5)	CFZ, RFB
4	47, M	none	3	2.5	AMC, CIP, CLOS, CLR, EMB, KAN, OFX, PAS, PTH, PZA, STR (11)	4 March 2004	INH, RIF, EMB, PZA, OFX (5)	4 October 2004	CLOS, CFZ, CPM, PAS, PTH (5)	CFZ, CPM
5	41, F	none	5	11	AMC, CLOS, CLR, EMB, GAT, INH, KAN, OFX, PAS, PTH, PZA, RIF, STR (13)	1 November 2004	INH, RIF, EMB, PZA, CLOS, CPM, OFX, PAS, PTH (9)	1 November 2004	AMC, CLR, EMB, KAN (4)	none
6	41, M	DM	5	12	AMC, CLOS, CLR, EMB, INH, KAN, LVX, OFX, PAS, PTH, PZA, RIF, STR (13)	2 November 2004	INH, RIF, EMB, PZA, CLOS, KAN, OFX, PAS, STR (9)	18 November 2004	CFZ, CPM, MXF, PTH, RFB (5)	CFZ, CPM, MXF, RFB
7	43, M	DM	5	13	AMC, CLOS, CLR, EMB, ENV, GAT, INH, KAN, OFX, PAS, PTH, PZA, RIF, STR, (14)	13 December 2004	INH, RIF, EMB, PZA, CPM, KAN, OFX, PAS (8)	13 December 2004	CLOS, CLR, INH, MXF, PTH, RIF, STR (7)	MXF
8	32, M	none	4	7	AMC, CLOS, EMB, IFN-γ, INH, KAN, LVX, OFX, PAS, PTH, PZA, RXT, STR (13)	27 July 2004	INH, RIF, EMB, PZA, OFX, PTH (6)	23 December 2004	AMC, CLOS, MXF, PAS, PTH (5)	MXF

DM, diabetes mellitus; AMC, amoxicillin/clavulanate; CFZ, clofazimine; CIP, ciprofloxacin; CLOS, cycloserine; CLR, clarithromycin; CPM, capreomycin; EMB, ethambutol; ENV, enviomycin; GAT, gatifloxacin; IFN-γ, interferon-gamma; INH, isoniazid; KAN, kanamycin; LZD, linezolid; LVX, levofloxacin; MXF, moxifloxacin; OFX, ofloxacin; PAS, *para*-aminosalicylic acid; PTH, prothionamide; RFB, rifabutin; RIF, rifampicin; RXT, roxithromycin; STR, streptomycin.

[a]The term 'probably active drug' indicates a drug to which a patient was found not to be resistant in any susceptibility test and was not recycled from a previous failed regimen. Moxifloxacin and rifabutin were considered 'probably active drugs', although the respective organisms were confirmed to be resistant to ofloxacin and rifampicin, respectively.

Table 2. Summary of efficacy and tolerability of daily-half dose linezolid in patients with intractable multidrug-resistant tuberculosis

Patient	Dose of linezolid	Duration of linezolid Tx (months)	Time to smear conversion (days)	Time to culture conversion (days)	Adverse events	Reasons for linezoid discontinuation	Outcome	Follow-up[a] (months)
1	600 mg once daily	3	45	25	none	death	death	NA
2	600 mg once daily	8	179	147	none	death	death	NA
3	600 mg twice daily for 2 weeks, then 600 mg once daily	18	90	27	peripheral neuropathy, headache, nausea, taste alteration	treatment completed	treatment completed	23
4	600 mg twice daily for 7 weeks, then 600 mg once daily	17	45	112	anaemia	on linezolid	on linezolid	14
5	600 mg twice daily for 2 weeks, then 600mg once daily	9	115	115	peripheral & optic neuropathy	optic neuropathy	on 2nd-line therapy	13
6	600 mg twice daily for 2 weeks, then 600 mg once daily	7	30	75	nausea, taste alteration	economic reason	on 2nd-line therapy	13
7	600 mg twice daily for 2 weeks, then 600mg once daily	15	48	115	peripheral neuropathy	on linezolid	on linezolid	11
8	600 mg twice daily for 2 weeks, then 600 mg once daily	8	38	38	peripheral & optic neuropathy, itching, insomnia	optic neuropathy	on 2nd-line therapy	14

NA, not applicable.
[a]Duration: from culture conversion to March 2006.

Haematological adverse events have been reported in more than 50% of patients who used linezolid for more than 14 days.[9] In contrast, we found that only one patient developed asymptomatic anaemia while on standard dose linezolid but recovered soon after dose reduction. These findings suggest that haematological adverse reactions resulting from the prolonged use of linezolid are dose-dependent and that a half-dose regimen may reduce the risk of myelosuppression.

Other adverse events related to the prolonged use of linezolid include peripheral and optic neuropathy. In most patients, optic neuropathy resolved after stopping linezolid, whereas peripheral neuropathy did not resolve or only partially improved.[10] In the present study, four of six living patients developed peripheral neuropathy, and two of these also developed optic neuropathy. This finding suggests that the development of neuropathy may depend on the duration of treatment rather than the dose, although the onset time of neurotoxicity was different in each patient.

Although our follow-up period was not long enough to determine whether the microbiological response is durable, we found that daily-half doses of linezolid were effective in the eradication of tubercle bacilli in patients with intractable or XDR-TB. However, dose reduction did not reduce the risk of neurotoxicity, although it did reduce haematological adverse events and drug cost.

Transparency declarations

We have no financial or any other conflict of interest regarding the contents of this manuscript.

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