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Linezolid for the treatment of multidrug-resistant tuberculosis

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***Objectives*: *In vitro* studies have shown good activity of linezolid against *Mycobacterium tuberculosis*, including multidrug-resistant strains. However, clinical experience with linezolid in tuberculosis is scarce.**

***Methods*: We report our clinical experience with five consecutive patients with multidrug-resistant tuberculosis infection treated with combination regimens that included linezolid.**

***Results*: Two patients had multidrug-resistant *Mycobacterium bovis* infection, with resistance to 12 antituberculous agents (one of them with HIV co-infection and <50 CD4 cells/mm^3). The other three patients were infected by multidrug-resistant *M. tuberculosis* strains, with resistance to all first-line drugs and other second-line drugs. All patients received linezolid in combination with thiacetazone, clofazimine or amoxicillin/clavulanate. Susceptibility tests showed linezolid MIC values ≤0.5 mg/L against all tuberculosis strains tested (standard proportion method, Middlebrook agar 7H10). In all cases, tuberculosis cultures from respiratory samples were sterile after 6 weeks of therapy. Three patients have clinical and microbiological cure of tuberculosis with a combination regimen with linezolid (range: 5–24 months). One patient was lost to follow-up at month 5. The remaining patient has completed 11 months of therapy and is still on treatment. Four patients developed anaemia and needed blood transfusions. In two of these patients, the linezolid daily-dose (600 mg twice a day) was successfully reduced to 50% (300 mg twice a day) to decrease toxicity while maintaining efficacy. Peripheral neuropathy (two patients) and pancreatitis (one patient) were other adverse events observed during linezolid treatment.**

***Conclusions*: In our experience, linezolid has been a valid alternative drug in the management of multidrug-resistant tuberculosis. The prolonged use of linezolid is frequently associated with toxicity, mainly anaemia and peripheral neuropathy, that requires special management.**

Keywords: oxazolidinones, *Mycobacterium tuberculosis*, *Mycobacterium bovis*, MDR-TB

Introduction

Linezolid has been the first oxazolidinone to be developed and approved for clinical use. It is active against a range of bacteria, but its primary clinical role is the treatment of infections caused by aerobic Gram-positive organisms, including resistant strains such as vancomycin-resistant enterococci, methicillin-resistant *Staphylococcus aureus* and penicillin-resistant pneumococci.[1–4]

In vitro studies have shown good activity of linezolid against different species of mycobacteria, including resistant strains. The linezolid MIC_{90} for *Mycobacterium tuberculosis* was in the range 1–2 mg/L.[5] MICs of linezolid against other non-tuberculous mycobacteria are higher than the MIC for *M. tuberculosis*.[6–8] In experimental studies with the murine model of tuberculosis, oxazolidinones have shown an activity similar to isoniazid.[9]

Clinical experience with the use of linezolid in the management of mycobacterial infections is still sparse. Some authors have reported successful results in the treatment of both multidrug-resistant M. *tuberculosis* infections[10] and non-tuberculous mycobacteria infections.[11,12]

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In addition to the lack of information on the efficacy of linezolid in the treatment of tuberculosis, toxicity is a matter of concern when the drug has to be used for long periods. Clinical trials have shown that linezolid (600 mg twice daily in adults) is safe and generally well tolerated for courses of therapy of <28 days,[13–15] but long-term linezolid use has been associated with reversible haematopoietic suppression, primarily thrombocytopenia[13,16,17] and neuropathy.[18–21]

We report our clinical experience with the use of linezolid for multidrug-resistant tuberculosis (MDR-TB) infection in five consecutive patients treated with the drug in an attempt to explore the role of linezolid in the treatment of TB infections.

Patients and methods

The study included all consecutive patients diagnosed with MDR-TB in the period 1999–2004 in our Centre (Ramon y Cajal Hospital, Madrid, Spain) and treated with linezolid as part of the TB regimen. All patients received linezolid as part of a combination regimen and written informed consent was required in all cases.

Diagnosis of TB was confirmed microbiologically by a positive mycobacterial culture in clinical samples. All tuberculosis-resistant strains were identified using DNA probes (AccuProbe; Gen-Probe, San Diego, CA, USA) for *M. tuberculosis* complex. Biochemical and growth testing (and DNA typing, including restriction fragment length polymorphism and spoligotyping in multi-resistant *Mycobacterium bovis*) were used for final identification.

In vitro susceptibility studies to isoniazid, rifampicin, ethambutol, pyrazinamide and second-line drugs were performed as recommended by the NCCLS using the standard proportion method on Middlebrook 7H10 agar medium (Difco, Detroit, MI, USA).[22]

In the agar proportion method, Middlebrook 7H10 agar medium (Difco) with and without antituberculous drugs was dispensed in tubes. With linezolid, final concentrations were as follows: 0.06, 0.12, 0.25, 0.5 and 1 mg/L. The inoculum of each isolate was prepared using 10^{-2} and 10^{-4} dilutions from an initial distilled water suspension equivalent to a 1.0 McFarland standard. From each dilution, 0.1 mL was transferred to different tubes. MICs were read after 3 and 4 weeks. The MIC value was defined as the lowest concentration of drug that inhibited >99% of the bacterial population and results were interpreted according to the NCCLS.[22]

Results

Five patients with MDR-TB were treated with linezolid as part of a combination regimen. Two of them were infected by a species of *M. bovis*, genetically related to the outbreak observed in our Centre during 1993–1995 that caused a fatal infection in 25 HIV-infected patients.[23] This strain was resistant to isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, capreomycin, ofloxacin or levofloxacin, ethionamide or prothionamide, paraaminosalicylic acid and cycloserine, and had intermediate susceptibility to clofazimine and thiacetazone. The other three cases were infected by *M. tuberculosis* strains that were resistant to all first-line drugs and other second-line drugs. Linezolid MICs for all clinical isolates in our patients were ≤0.5 mg/L (between 0.12 and 0.5 mg/L) by the standard 7H10 agar proportion method.

Descriptions of the clinical and microbiological characteristics of the five patients are given below and are summarized in Table 1.

Patient 1 was a 33-year-old male with previous history of drug abuse, negative HIV infection, and with pulmonary TB. During 1993–2000 he had relapses due to a poor adherence to TB treatment, receiving multiple courses and regimens of TB therapy. In March 2000, a pulmonary lobectomy was performed in addition to a TB regimen including paraaminosalicylic acid, clarithromycin, capreomycin, pyrazinamide, clofazimine and prothionamide. In June 2001, he developed positive cultures with an *M. tuberculosis* strain resistant to isoniazid, rifampicin, ethambutol, streptomycin, ofloxacin and cycloserine. He was treated with a regimen including linezolid, thiacetazone, paraaminosalicylic acid, clarithromycin and capreomycin for 24 months, with sterilization of mycobacterial cultures after the second month of treatment. He developed neurosensorial hypoacusia related to aminoglycosides. One year after stopping therapy cultures kept sterile and the patient was asymptomatic. A chest X-ray showed a volume reduction with residual infiltrates in both lungs.

Patient 2 was a 42-year-old man, with a history of insulin-dependent diabetes mellitus, chronic renal failure and inflammatory bowel disease. He was diagnosed with pulmonary TB in 1994, and was initially treated with a 6 month regimen including isoniazid, rifampicin and pyrazinamide. He relapsed in 1998 and was treated with isoniazid, rifampicin, pyrazinamide, ethambutol, cycloserine, paraaminosalicylic acid, minocycline, prothionamide and levofloxacin. In June 2001 he had a second relapse, with a positive culture from a sputum sample with *M. bovis* resistant to isoniazid, rifampicin, pyrazinamide, ethambutol, paraaminosalicylic acid, cycloserine, streptomycin, levofloxacin, clarithromycin and prothionamide. He was treated with a regimen including linezolid (5 months), thiacetazone (18 months), clofazimine (18 months) and amoxicillin/clavulanate (5 months), with sterile mycobacterial cultures from month +1. Anaemia (requiring transfusion on two occasions) and peripheral neuropathy, requiring treatment with amitriptyline and gabapentin, were present in month +5. Linezolid was stopped and haemoglobin levels recuperated to normal levels. Six months after stopping treatment cultures remained sterile.

Patient 3 was a 54-year-old man, with chronic hepatitis C, inflammatory bowel disease and gastrectomy. He was diagnosed with pulmonary tuberculosis in 1980. Since that year, he has been treated many times, but he was a non-compliant patient. In 2001, he had a positive culture for *M. tuberculosis* in a respiratory sample, with a drug susceptibility pattern showing resistance to isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, paraaminosalicylic acid and prothionamide. He was treated with a multidrug regimen including linezolid, thiacetazone, clofazimine and levofloxacin. He had negative cultures 1 month after starting treatment. He developed anaemia as an adverse event related to linezolid and required a blood transfusion on two occasions. He was lost to follow-up 5 months later, because of moving to another city.

Patient 4 was a 29-year-old woman. She had HIV infection, with virological and immunological failure (CD4 count <200/mm^3; HIV viral load >4 log). She developed disseminated TB (pulmonary and splenic). She was an in-house contact of an HIV-positive patient who died in 1997 with a multidrug-resistant *M. bovis* infection. In February 2003, she was diagnosed with TB, with a positive acid-fast bacilli (AFB) sputum sample, yielding *M. bovis* resistant to isoniazid, rifampicin, ethambutol, pyrazinamide, paraaminosalicylic acid, cycloserine, streptomycin,

Table 1. Clinical and microbiological features of 5 cases of MDRTB treated with linezolid-containing regimens

Patient	Age (years), gender	Underlying medical condition	TB location	Previous TB diagnosis and therapeutic regimens	TB identification. MDR-TB pattern	TB regimen including LZD (duration)	Outcome and linezolid-associated adverse events
1	33, male	previous drug user; HIV-	pulmonary	First TB diagnosis: Feb 1993. From Feb 93–Feb 00: multiple and non-completed courses of TB therapy (IZD, RIF, ETB and PZA). Mar 00: pulmonary lobectomy plus new TB regimen (PAS, CLR, CPM, PZA, CFZ and PTH). Jun 01: relapse TB. MDR-TB strain isolated.	*M. tuberculosis*. Resistance to IZD, RIF, ETB, STR, CSN and OFX.	LZD, 600 mg, bid + TCZ, 150 mg, qd + PAS, 4 g, tid + CLR, 500 mg, bid + CPM, 750 mg, 3 times a week (all during 24 months).	month +2: sterile TB cultures. discontinued on month +24.
2	42, male	diabetes, chronic renal failure, inflammatory bowel disease	pulmonary	First TB diagnosis: 1994 (treated with IZD, RIF and PZA). Relapse in 1998 (treated with IZD, RIF, PZA, ETB, PAS, CSN, MIN, PTH and LVX). Jun 01: relapse. MDR-TB strain isolated.	*M. bovis*. Resistance to IZD, RIF, ETB, PZA, PAS, CSN, STR, LVX, CLR and PTH.	LZD, 600 mg, bid (5 months) + TCZ, 150 mg, qd (18 months) + CFZ, 100 mg, qd (18 months) + AMC, 500 mg, tid (5 months).	month +1: sterile TB cultures. month +5: anaemia. month +5: peripheral neuropathy.
3	54, male	gastrectomy, chronic hepatitis C, inflammatory bowel disease	pulmonary	First TB diagnosis: 1980. Non-adherent patient. Multiple relapses. Jun 01: MDR-TB strain isolated.	*M. tuberculosis*. Resistance to IZD, RIF, ETB, PZA, STR, PAS and PTH.	LZD, 600 mg, bid (4 months) + TCZ, 150 mg, qd (5 months) + CFZ, 100 mg, qd (5 months) + LVX, 500 mg, qd (5 months).	month +1: sterile TB cultures. month +3: anaemia. month +5: lost to follow-up.
4	29, female	HIV infection	disseminated (pulmonary and splenic)	In-house contact with HIV patient with multidrug-resistant *M. bovis* infection in 1997. Feb 03: sputum sample with positive AFB smear. Positive spolygotyping for *M. bovis*. Positive mycobacterial culture.	*M. bovis*. Resistance to IZD, RIF, ETB, PZA, PAS, CSN, STR, OFX, CLR and PTH.	LZD (600 mg, bid, 6 months and 300 mg, bid, 8 months) + TCZ 150 mg qd (18 months) + CFZ 100 mg qd (18 months) LZD: 50% daily-dose decrease at month +6. LZD discontinued at month +15.	month +1: sterile TB cultures. month +6: anaemia. month +6: peripheral neuropathy. month +15: optic neuropathy.
5	21, male	none	pulmonary	First TB diagnosis: Nov 03, initially treated with IZD, RIF, PZA and ETB. Dec 03: added KAN, PTH and LVX. Apr 04: sputum sample yielded MDR-TB strain.	*M. tuberculosis.* Resistance to IZD, RIF, ETB, PZA, PTH, STR CSN and PAS.	LZD (600 mg, bid, 2 months and 300 mg, bid, 9 months) + TCZ, 150 mg, qd (11 months) + CFZ, 100 mg, qd (11 months) + LVX 500 mg qd (11 months) (continues on therapy). LZD: 50% daily-dose decrease at month +2.	month +1: sterile TB cultures. month +2: anaemia.

LZD, linezolid; IZD, isoniazid; RIF, rifampicin; ETB, ethambutol; PZA, pyrazinamide; STR, streptomycin; PAS, paraaminosalicylic acid; CLR, clarithromycin; KAN, kanamycin; CPM, capreomycin; MIN, minocycline; CFZ, clofazimine; CSN, cycloserine; PTH, prothionamide; OFX, ofloxacin; LVX, levofloxacin; TCZ, thiacetazone; AMC, amoxicillin/clavulanate; qd, once a day; bid, twice a day; tid, three times a day; AFB, acid-fast bacilli.

ofloxacin, clarithromycin and prothionamide. She was treated with linezolid (14 months), thiacetazone (18 months) and clofazimine (18 months). The antiretroviral regimen was changed to enfurvitide plus lopinavir/ritonavir plus abacavir. She had sterile mycobacterial cultures 1 month after initiating treatment. She developed linezolid-related anaemia, requiring multiple (five) blood transfusions despite a decrease to 50% linezolid daily-dose at month 6. She also developed a sensory–motor neuropathy affecting lower limbs and acute pancreatitis, both events probably associated with linezolid. Fifteen months after initiated treatment, linezolid was discontinued due to toxicity. The rest of the antituberculous drugs were stopped in month +18. Six months later mycobacterial cultures remained sterile.

Patient 5 was a previously healthy 21-year-old man. He was a foreigner, born in Peru. Pulmonary tuberculosis was diagnosed in November 2003 and he was treated with isoniazid, rifampicin, pyrazinamide and ethambutol. In December 2003, kanamycin, prothionamide and levofloxacin were added to the TB regimen. In April 2004, sputum samples still had positive AFB smears and mycobacterial culture. The *M. tuberculosis* strain isolated showed resistance to isoniazid, rifampicin, pyrazinamide, ethambutol, streptomycin, prothionamide, paraaminosalicylic acid and cycloserine. A new TB regimen treatment was initiated in May 2004 with linezolid (600 mg twice a day), thiacetazone (150 mg once a day), clofazimine (100 mg once a day) and levofloxacin (500 mg once a day). Twenty days later, TB cultures became sterile. At month +2, a decrease in haemoglobin level from 14 g/dL (baseline) to 10 g/dL was detected and the linezolid daily-dose was decreased to 600 mg/day. Posterior controls showed haemoglobin levels >14 g/dL. The patient is at month +11 of follow-up. He remains with sterile cultures and drugs are well tolerated since linezolid dose reduction.

Linezolid MICs for all clinical isolates in our patients were ≤0.5 mg/L (in the range 0.12–0.5 mg/L) by the standard 7H10 agar proportion method.

Patients received linezolid for periods in the range 5–24 months. TB cultures were negative after 4–6 weeks of therapy. Mycobacterial cultures from respiratory samples remained sterile during the follow-up period until completion of therapy, although patient 3 was lost to follow-up at month +5.

All patients except patient 1 developed adverse events related to linezolid. Linezolid was discontinued in these four patients due to adverse events. The most frequent toxic side effect was anaemia that was present in four patients. All four patients required multiple blood transfusions and discontinuation or dose reduction of the drug. In all cases, haematological effects related to linezolid were reversible after discontinuation.

Neurological toxicity related to linezolid was observed in two patients (patients 2 and 4). They developed peripheral neuropathy affecting lower limbs. Both of them received treatment with amitriptyline and gabapentin, with poor results. Patient 4 also developed a toxic optic neuropathy at month 15. Formal visual field testing showed patchy field damage, suggestive of drug-induced toxicity. At this time, linezolid was definitely discontinued.

Discussion

The present study confirms that linezolid is a valid alternative in patients with MTD-TB. *In vitro* studies have shown that linezolid has a good activity against *M. tuberculosis*. Recently, Alcala *et al.*[5] evaluated *in vitro* activities of linezolid using the standard and Etest methods against 117 clinical isolates of *M. tuberculosis* with different levels of susceptibility to first-line antituberculous drugs. Linezolid showed high *in vitro* activity, with all the strains inhibited by ≤1 mg/L. Linezolid MICs for clinical isolates in our patients were ≤0.5 mg/L (in the range 0.12–0.5) by the standard proportion method.

Despite high *in vitro* activity of linezolid against clinical strains of *M. tuberculosis*, there are no clinical trials evaluating its *in vivo* efficacy. Clinical experience with the use of linezolid in the management of mycobacterial infections is sparse. Valencia *et al.*[10] reported a case of an HIV-positive patient with multiresistant *M. bovis* infection treated successfully with a combination regimen that included linezolid and five other drugs during an 11 month period.

In our series, all patients received linezolid in combination with other drugs. Most of these antimycobacterial agents had been used in previous regimens without microbiological success. These data support the idea of the great activity of linezolid against these MDR-TB strains, taking into account the poor activity of the other antituberculous agents. However, two patients (3 and 5) received quinolones. Several papers have recognized the role of quinolones in MDR-TB[9,24] including a potential synergy with linezolid.[25]

One of the issues regarding antimycobacterial drugs is the ease for selecting resistant mutant strains during treatment, especially those agents with poor tuberculostatic activities. Preliminary results with linezolid are satisfactory. Rodriguez *et al.*[24] have estimated the mutant prevention concentration (MPC) of different agents against *M. tuberculosis*. Linezolid exhibits excellent activity and an MPC_{90} of 1.2 mg/L. A favourable pharmacodynamic profile with sustained plasmatic and/or intracellular levels above the MPC could potentially delay the appearance of resistance.[25]

The most limiting problem related to the prolonged use of linezolid in MDR-TB is toxicity. Long-term exposure data with linezolid are limited because Phase II and III clinical trials allowed up to only 28 days of therapy. In the pre-license compassionate-use programme, treatment was much more prolonged and some authors have reported haematological and neurological toxicity in patients with linezolid administered for >28 days. Mild and reversible haematological abnormalities are not infrequent.[26,27] In the compassionate-use programme, the most frequent adverse events were thrombocytopenia (7.5%) and anaemia (4%). Risk of myelosuppression is increased with prolonged duration of therapy.[28] All haematological adverse events were reversible after discontinuation.[17,28–30] A reversal of linezolid-associated cytopenia, but not peripheral neuropathy, by administration of vitamin B6 use in these patients has been recently communicated.[31]

Due to the low MICs observed with linezolid in *M. tuberculosis* strains in relation to linezolid serum levels obtained with standard doses, a half dose reduction is plausible, at least in patients in whom toxicity developed. Probably the recommended dose should be 300 mg twice daily, which is preferable to 600 mg once a day, in relation to the time-dependent mode of action of linezolid.[32] In experimental models, the 24 h AUC/MIC ratio required for a bacteriostatic effect with linezolid was, for pneumococci, a half that required for staphylococci, and varied from 22–97 (mean = 48) for pneumococci and from 39–167 (mean = 83) for

staphylococci. Linezolid MICs for *S. pneumoniae* were in the range 0.5–1.0 mg/L, which is similar or higher than MICs for *M. tuberculosis*, and lower than MICs for *S. aureus* (range 1.0–4.0 mg/L).[32]

Duration of therapy is not yet defined in patients with TB who receive linezolid, but our patients receiving linezolid sterilized respiratory samples early after initiating therapy. However, the need for a prolonged intake of antituberculous drugs is not related to the initial clinical and microbiological response but to the long-term sterilizing activity against the sporadically multiplying mycobacteria in caseous lesions. Recent studies have demonstrated excellent activity of linezolid and quinolones in the latent phase of *M. tuberculosis* infection.[33]

Another adverse event related to prolonged use of linezolid is neurotoxicity. Sensory–motor neuropathy and optic toxic neuropathy cases have been reported.[19–21,34] The mechanism of nerve damage is unknown. Mitochondrial toxicity has been proposed as a mechanism.[34,35] In 75% of patients with available follow-up after linezolid discontinuation, peripheral neuropathy did not resolve after months. However, patients with optic neuropathy had at least a partial recovery after linezolid was stopped.[20] In our patients, linezolid-related peripheral neuropathy developed in two patients (patients 2 and 4). Both patients had other concomitant medical problems that could increase or cause peripheral neuropathy (patient 2 was diabetic and patient 4 received antiretroviral therapy, although neurotoxic nucleoside analogues were avoided). The mean duration of treatment in both patients prior to developing neurotoxicity was ~6 months.

Apart from the toxicity related to linezolid, another issue is the cost of the drug: at ~$45 for a single 600 mg tablet, its use could be limited in many countries with high incidences of MDR-TB and low economic resources.

In conclusion, the successful outcome in the reported patients confirms that linezolid could be a valid alternative in patients with MDR-TB. Its antimycobacterial activity sharply increases the efficacy of other second-line therapies in these conditions. The prolonged use of the drug is frequently associated with toxicity, mainly anaemia and peripheral neuropathy. A half-dose reduction is plausible in patients who developed toxicity, due to the low MICs observed with linezolid in *M. tuberculosis* strains in relation to linezolid serum levels obtained with standard doses. This drug should be considered in MDR-TB treatment regimens, although clinical trials are necessary to confirm doses and duration.

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