CASE REPORT

Linezolid in the treatment of multidrug-resistant/extensively drug-resistant tuberculosis in paediatric patients: Experience of a paediatric infectious diseases unit

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Abstract
Linezolid has been used in the treatment of multidrug-resistant/extensively drug-resistant tuberculosis in adults with encouraging results, however experience in children is scarce. We describe our experience with the use of linezolid as part of a multidrug regimen in the treatment of 4 patients who had persistent positive cultures, despite prolonged combined therapy.

Keywords: Linezolid, tuberculosis, multidrug-resistant, extensively drug-resistant, paediatric

Introduction
Tuberculosis (TB) remains one of the major diseases afflicting children throughout the world. The epidemiology of TB in childhood is closely related to TB in adults. Immunological immaturity and social dependence facilitate the spread of infection.

Portugal has the 6th highest TB incidence rate in the European Union [1]. Multidrug-resistant (MDR) TB, defined by the World Health Organization (WHO) as TB with in vitro resistance to at least rifampicin and isoniazid, represents about 1.2% of new TB cases and 7.5% of all retreated patients in our country. Extensively drug-resistant TB (XDR-TB), which is MDR-TB plus resistance to any fluoroquinolone, and to at least 1 of 3 injectable second-line drugs, represents about 25% of all MDR-TB isolates in Portugal. Pre-XDR TB is MDR-TB plus resistance to either a fluoroquinolone or second-line injectable drug. Human immunodeficiency virus (HIV) co-infection and imported cases play a significant part in these numbers (15%).

In Portugal, around 70 TB cases are reported annually in children, but under-notification is likely to occur. More than half of all MDR/XDR cases are diagnosed in the Lisbon and Vale-do-Tejo region [1], where our unit is the reference centre for paediatric TB.

The development of new drugs for TB treatment has been slow. Linezolid, an oxazolidinone antibacterial agent that has inhibitory activity against a broad range of Gram-positive bacteria [2], has shown both in vitro and pharmacological activity against Mycobacterium tuberculosis, including MDR strains, without cross-resistance with standard anti-tuberculous agents [3–6]. It has been used for some time in adults with promising results [4–7]; however experience in children is limited to a few cases [6–8], and most data regarding the pharmacokinetic profile, efficacy, and tolerability are derived from adult studies.

The long-term use of linezolid is associated with myelosuppression (mainly transient thrombocytopenia and anaemia) and neurotoxicity (sometimes irreversible peripheral and optic neuropathy) [2,4,6,9]; these may warrant a reduction in the total dose [9] or even discontinuation of the drug.

We describe the cases of 4 patients with culture-confirmed MDR/XDR-TB still positive despite appropriate therapy, treated with linezolid in combination regimens, in a third-level paediatric infectious diseases unit.
Case reports

Four patients were treated with linezolid in combination regimens. Their demographic data, drug resistance profiles, and the drugs added to their linezolid-containing regimens are summarized in Table I. Patient age at the time of diagnosis ranged from 4 to 17 y. One patient was co-infected with HIV-1 and 1 patient suffered from sickle cell anaemia.

Linezolid was given orally in all except patient 3 (while unstable) and patient 4 (6 months), and was started at a dose of 600 mg twice-daily in patients 1, 2 and 4 and at 10 mg/kg twice-daily in patient 3. Other Anti-TB drugs were chosen according to the drug susceptibilities of the M. tuberculosis isolates.

Case 1

A 14-y-old male was admitted with a diagnosis of pulmonary TB with evidence of cavitation on chest radiograph. The patient’s father had died as a result of infection with the same strain.

During the past year the patient had been on a multidrug regimen containing kanamycin, rifabutin, ofloxacin, clarithromycin and pyrazinamide, in accordance with the susceptibility profile of the sputum isolate. He was discharged after 7 months, as culture conversion occurred, only to be readmitted 3 months later following an episode of haemoptysis and a positive sputum direct exam and culture. The sputum isolate was resistant to all first-line drugs (including rifabutin) and also to the following second-line drugs: capreomycin, amikacin, ethionamide. Due to persistent positive cultures he was started on linezolid 16 months after the initial diagnosis, as part of a combined regimen consisting of pyrazinamide, rifabutin, cycloserine, levofloxacin, kanamycin and para-aminosalicylic acid (PAS).

Cultures were negative after 12 weeks. Linezolid was suspended after 9 months due to severe progressive peripheral neuropathy, which slowly improved. After 2 y of combination therapy and currently almost 4 y without treatment, the patient has been clinically well with persistent negative cultures and no clinical evidence of peripheral neuropathy.

Case 2

Case 2 was a 12-y-old female, born in West Africa, with sickle cell disease. One year before admission she was misdiagnosed with TB infection and was treated with isoniazid, rifampicin and pyrazinamide for 2 months. Four months before admission, after being diagnosed with ‘pneumonia’ and with a positive family history for TB (her sister had died as a
result of pulmonary TB due to the same strain), the patient underwent sputum direct exam, which was positive. She was started on isoniazid, rifampicin, pyrazinamide and streptomycin, which was later changed to ethambutol, rifabutin, clofazimine and amikacin after resistance to all first-line drugs (except ethambutol) and second-line drugs (PAS) was demonstrated in sputum cultures. Due to persistent positive direct exam, PAS and levofloxacin were added 2 weeks before admission. There was marked clinical deterioration with radiological evidence of bilateral involvement, cavitation and endobronchial dissemination. Linezolid was added to the ongoing regimen. Cultures from respiratory specimens were negative after 6 weeks. During treatment the patient developed severe anaemia requiring blood transfusions. This was not attributed exclusively to linezolid, since the patient had sickle cell disease and an ongoing vaso-occlusive crisis. Due to peripheral neuropathy, the daily dose of linezolid was reduced to half after nearly 4 months of combined therapy, and there was progressive improvement. Linezolid was stopped after 6 months and antibacillary therapy was maintained for a total of 2 y. The patient has been off treatment for 3 y with no TB recurrence or clinical evidence of residual neuropathy.

Case 3
A previously healthy 4-y-old girl was admitted with the diagnosis of meningeal TB. The patient was infected with an MDR-TB strain (with additional resistance to streptomycin and ethionamide) identical to her in-household contact (grandmother with pulmonary TB). The patient was started on steroids and the following antibacillary therapy: pyrazinamide, ethambutol and ciprofloxacin, in accordance with the antimicrobial susceptibility profile of the contact’s isolate.

There was no clinical improvement; there was persistent obtundation, no spontaneous speech, and, on day 14, bilateral VI cranial nerve paresis with papilloedema. A computed tomography (CT) scan of the head excluded acute hydrocephalus, and amikacin and linezolid were added to the ongoing regimen. There was progressive neurological recovery and overall clinical improvement.

After the appearance of an urticarial rash attributed to a hypersensitivity reaction, the linezolid dose was reduced to half after 30 days. On control lumbar puncture performed after 3 months, cerebrospinal fluid (CSF) culture was negative. Linezolid was suspended after 6 months and antibacillary therapy after 21 months. The patient has been on follow-up for 2 y since stopping anti-TB treatment and is clinically well.

Case 4
Case 4 was a 17-y-old male who had been living in West Africa until 1 week before admission. The family had immigrated to Europe in order to seek treatment for acquired immune deficiency syndrome (AIDS). He was admitted directly after arrival with the diagnosis of miliary MDR-TB with HIV-1 co-infection, severe malnutrition and immunosuppression (a CD4 T cell count of 19/mm³). He was started on antibacillary therapy with isoniazid, rifabutin, pyrazinamide and ethambutol, which was later changed to rifabutin, pyrazinamide, amikacin, PAS, ethionamide and ciprofloxacin in accordance with susceptibility testing results. Meanwhile highly active antiretroviral therapy (HAART) was started. After 7 months of maintained antibacillary therapy he was readmitted with a retroperitoneal abscess, and underwent surgical drainage. The fluid tested positive for M. tuberculosis. At this time levofloxacin, cycloserine and linezolid were added to rifabutin, ethionamide and PAS due to presumed MDR-TB; rifabutin was stopped after 2 months due to evidence of resistance on additional cultures.

There was progressive clinical improvement with negative cultures after 12 weeks (drainage fluid). The patient was discharged after 5 months. Linezolid was finally stopped after 11 months of therapy (5 months, intravenous) and overall antibacillary treatment after 21 months. No side effects regarding linezolid were reported. The patient has been off TB treatment for 9 months and is currently clinically asymptomatic.

Discussion
The increasing difficulty in treating paediatric TB is an expected reality as more MDR- and XDR-TB cases arise in direct proportion to adult cases.

Linezolid appears to be effective in rescue MDR/XDR-TB treatment in paediatric patients after failure of second-line regimens [6–8]. Additionally it can be administered orally and is generally well tolerated [4–8]. In our series, culture conversion occurred early after initiating therapy and so far seems to be persistent.

The most common side effects described with the use of linezolid in children are gastrointestinal disturbances, thrombocytopenia and cutaneous reactions [2]. There are already some reports arguing that lower dosages than those described for Gram-positive infection can be used in TB, and these still appear to be effective [5,9]. Additionally, there are fewer side effects, and those described are less serious [9]. None of our patients suffered from gastrointestinal disturbances. Two patients developed peripheral neuropathy, which is more commonly
reported in adults [2], and unlike most adult patients, our patients recovered fully.

Two patients underwent dose reduction: 1 early in the treatment course due to a suspected hypersensitivity skin reaction and 1 after 4 months due to suspected myelosuppression and peripheral neuropathy. Another patient suspended linezolid after 9 months due to peripheral neuropathy. We observed an improvement in side effects in all patients, with no relapses.

Safety in children and adequate doses are difficult to establish due to insufficient experience. Although further studies are needed in paediatric patients, the use of half doses from the beginning appears to be safe [9].

The use of linezolid in non-pulmonary TB also appears to be promising [4–7]. As far as we know, we are reporting the first case of meningeal TB treated with linezolid, with excellent results. Linezolid appears to have good penetration into CSF and brain tissue [10]. Although considerable individual variability in serum and CSF concentrations does occur [10], usual doses provide adequate treatment for most Gram-positive pathogens implied in meningitis, and therefore linezolid 10 mg/kg/day was used in patient 3.

Use in chronic disease, such as diabetes and HIV co-infection, has been described [4–7], but the use in other diseases, such as chronic haemolytic anaemia (as in patient 2) is also an option, although some degree of marrow suppression is expected.

As previously argued, new TB drugs are scarce and combination regimens add toxicity and economic constraints. It is also difficult to attribute the success in the treatment outcome to linezolid alone, as it is used in complex combined therapeutic regimens and is often introduced simultaneously with other drugs.

In conclusion, although linezolid is not a first-line TB drug, it is an option to consider in the treatment of refractory MDR- and XDR-TB, although the optimal dose, timing of introduction and associations are yet to be established, especially in younger patients.

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**References**


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