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Successful alternative treatment of extensively drug-resistant tuberculosis in Argentina with a combination of linezolid, moxifloxacin and thioridazine

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Objectives: Current drug choices to treat extensively drug-resistant (XDR) tuberculosis (TB) are scarce; therefore, information on the safety, tolerability and efficacy of alternative regimens is of utmost importance. The aim of this study was to describe the management, drug adverse effects and outcome of alternative combined treatment in a series of XDR-TB patients.

Patients and methods: A retrospective study was performed on 17 non-AIDS, pulmonary adult patients with XDR-TB admitted to a referral treatment centre for infectious diseases in Buenos Aires from 2002 through 2008. Drug susceptibility testing was performed under regular proficiency testing and confirmed at the national TB reference laboratory.

Results: Linezolid was included in the drug regimens of all patients; moxifloxacin and/or thioridazine were included in the regimens of 14 patients. Clinically tractable drug adverse effects were observed in nine patients, the most frequent being haematological disorders and neurotoxicity. In two patients, thioridazine was discontinued. Negative culture conversion was achieved in 15 patients, 11 completed treatment meeting cure criteria, 4 are still on follow-up with good evolution, 1 defaulted treatment and 1 was lost to follow-up.

Conclusions: The combination of linezolid, moxifloxacin and thioridazine is recommended for compassionate use in specialized centres with expertise in the management of XDR-TB.

Keywords: fluoroquinolones, phenothiazines, adverse effects, toxicity, treatment outcome

Introduction

Extensively drug-resistant (XDR) tuberculosis (TB) corresponds to resistance to at least isoniazid, rifampicin, any fluoroquinolone and any of the following injectable agents: capreomycin, amikacin or kanamycin. XDR-TB cases have been documented in many countries worldwide, including Argentina. The magnitude of this problem is increasingly recognized, but is still of an unknown dimension.[1] Although at first it was described as a new phenomenon, it is now known that XDR-TB has been emerging for years and there are indications that ~10% of multidrug-resistant (MDR) TB cases evolve into XDR-TB; MDR-TB corresponds to resistance to at least isoniazid and rifampicin. Understandably, the prognosis of XDR-TB is even worse than that of MDR-TB. Second- and third-line drugs are less effective, more prone to induce severe side effects and considerably more expensive than first-line drugs. Treatment duration is usually extended to ≥2 years, introducing a high social and financial burden. In addition, the transmission of these severe forms of TB has been documented.[2]

In Argentina, 142 cases of MDR-TB occurred in 2008, when the TB incidence was 30/100000. According to the last TB drug resistance survey, performed in 2005, MDR-TB amounted to

Table 1. Demographic and clinical data for 17 HIV-negative patients with XDR-TB treated with compassionate therapy including linezolid

Patient	Gender; age (years)	Comorbid condition	Drugs in failing regimens (years since first treated)	Isolate resistant to IRPES and the following	Treatment regimen	Adverse effect	Treatment adjustment	Days to microscopy/ culture conversion	Outcome
1	M; 40	alcohol abuse	INH/RIF/EMB/STR/ PZA (1)	KAN/OFX/CS/PAS/ ETH	LZD/MXF/TDZ	anaemia, serum transaminase elevation	Vit B+folic acid added	180/270	cured
2	M; 46	alcohol abuse	INH/RIF/EMB/PZA/ PAS/OFX/CS/KAN (2)	KAN/OFX/CS/PAS	LZD/MXF/TDZ	anaemia, leg paraesthesia	Vit B+folic acid added	21/30	cured
3	F; 27	systemic lupus erythematosus	INH/RIF/EMB/STR/ PZA/PAS/ETH (2)	KAN/OFX/CS/PAS	LZD/MXF/TDZ	none	none	35/90	good evolution, still on treatment
4	M; 48	none	INH/RIF/EMB/PZA/ PAS/KAN/ETH (4)	KAN/OFX/PAS/ ETH	LZD/MXF/TDZ	none	none	60/90	lost to follow-up
5	M; 36	none	INH/RIF/EMB/PZA/ ETH/AMK (2)	KAN/OFX/CS/ETH	LZD/MXF/TDZ/ PAS	allergic dermatitis	TDZ discontinued	44/ND	defaulted
6	M; 37	none	INH/RIF/EMB/STR/ PZA/CS/OFX/ KAN/ETH (6)	KAN/OFX	LZD/MXF/TDZ/ CS	optic neuropathy	Vit B+folic acid added, LZD suspended temporarily and reassumed half dose	28/35	cured
7	F; 45	none	PAS/OFX/CS/KAN/ ETH (4)	KAN/OFX/CAP/ ETH	LZD/MXF/TDZ/ PAS/CS	pancytopenia	Vit B+folic acid added, LZD suspended temporarily and reassumed half dose, TDZ discontinued	20/20	cured
8	F; 42	diabetes	INH/RIF/EMB/STR/ PZA/PAS/ETH/ CIP/AMK/AMC (5)	KAN/OFX/PAS/ ETH/CAP	LZD/MXF/TDZ/ PAS/CS	none	none	90/90	good evolution, still on treatment
9	M; 45	diabetes	INH/RIF/EMB/STR/ PZA/CS/PAS/OFX/ ETH/KAN (2)	KAN/OFX/CS/PAS	LZD/MXF/TDZ/ ETH	poly-neuropathy	Vit B+folic acid added, LZD suspended temporarily and reassumed half dose	90/150	cured
10	F; 61	diabetes	ND (3)	KAN/OFX	LZD/MXF/TDZ/ ETH	none	none	90/90	cured
11	M; 24	none	PZA/OFX/ETH/PAS/ KAN (3)	KAN/OFX	LZD/MXF/TDZ/ ETH/PAS/CS	none	none	60/90	good evolution, still on treatment
12	F; 20	none	INH/RIF/EMB/STR/ PZA/CS/PAS/OFX/ ETH (2)	KAN/OFX	LZD/MXF/TDZ/ ETH/PAS/CS	none	none	34/63	cured
13	F; 43	chronic anaemia	INH/RIF/EMB/PZA/ OFX/PROT (6)	KAN/OFX	LZD/MXF/ETH/ PAS/CS	none	none	60/120	cured
14	F; 26	anorexia	NA (0)	KAN/OFX/CAP	LZD/MXF/ETH/ PAS/CS	digestive intolerance	PAS discontinued	360/ND	good evolution, still on treatment
15	M; 32	none	INH/RIF/EMB/STR/ PZA/KAN/OFX (12)	KAN/OFX	LZD/TDZ/CFZ/ PAS/CS	none	none	7/7	cured

16	F; 23	none	INH/RIF/EMB/ STR/PZA/CS/ KAN/ETH (5)	KAN/OFX/CAP/ ETH	LZD/TDZ/PAS	optic neuropathy	Vit B+folic acid added, LZD suspended and later reassumed half dose	14/14	cured
17	F; 55	diabetes, rheumatoid arthritis	INH/RIF/EMB/ PZA/KAN/OFX/ CAP/ETH (5)	KAN/OFX/CAP/ ETH/MXF	LZD/PAS/CS	anaemia	Vit B+folic acid+leucovorin added, LZD suspended temporarily and reassumed half dose	120/150	cured

AMC, amoxicillin/clavulanic acid; AMK, amikacin; CAP, capreomycin; CFZ, clofazimine; CIP, ciprofloxacin; CS, cycloserine; EMB, ethambutol; ETH, ethionamide; INH, isoniazid; KAN, kanamycin; LZD, linezolid; MXF, moxifloxacin; OFX, ofloxacin; PAS, *para*-aminosalicylic acid; PROT, proteonamide; PZA, pyrazinamide; RIF, rifampicin; STR, streptomycin; TDZ, thioridazine; IRPES, isoniazid, rifampicin, pyrazinamide, ethambutol and streptomycin; Vit B, vitamin B complex; M, male; F, female; ND, not determined; NA, not applicable.

2.2% of newly diagnosed and 15.4% of previously treated TB cases. The accumulated number of XDR-TB cases registered from 2002 through 2008 amounted to 50. The present study describes alternative treatments and outcomes of a series of XDR-TB cases diagnosed in that period in a referral treatment centre for infectious diseases in Buenos Aires.

Patients and methods

A retrospective study was undertaken to analyse 17 cases of XDR-TB in adult, HIV-negative patients admitted from January 2002 through December 2008 to the Hospital 'F. J. Muniz', a 400 bed treatment centre where nearly 1000 TB patients are diagnosed every year. The study was conducted in accordance with the Declaration of Helsinki and national and institutional standards, the hospital's Institutional Review Board approved the choice of the drugs included in the treatment, and participants provided written informed consent.

Successful treatment was defined as completion of treatment with clinical recovery, including negative culture conversion with a follow-up period of ≥24 months after culture conversion. Drug susceptibility testing was performed under regular proficiency testing according to WHO guidelines and the results were confirmed at the national TB reference laboratory for *Mycobacterium tuberculosis* drug susceptibility testing.

Results

The patients' mean age was 38 (range 20–61) years; all the patients were seronegative for HIV and had pulmonary disease localization; 16 had a history of TB treatment with a mean of 2.53 (range 2–4) failed treatment courses and an average of 3.76 (range 1–12) years since the first TB diagnosis; and all the patients had acid-fast bacilli smear-positive sputum specimens and their isolates were resistant to all first-line drugs. Table 1 summarizes the main features of the 17 cases.

Drug combination schemes were tailored on the basis of an isolate's drug susceptibility and the patient's drug tolerance. All patients received linezolid, 14 received moxifloxacin and 14 were treated with thioridazine at therapeutic doses, with or without the addition of second-line drugs. All three of linezolid, moxifloxacin and thioridazine were included in the treatment of 12 patients. The patients remained hospitalized for ≥2 months or until bacteriologically negative. In the ambulatory phase, directly observed therapy was not always provided. Ambulatory patients under self-administered treatment were interviewed weekly by a specialized physician in the hospital outpatient XDR-/MDR-TB clinic. Patients who defaulted were contacted by the hospital social service in an attempt to recover them for treatment.

Thioridazine (Meleril®, Roemmers Laboratories, Argentina) was initially administered at a daily dose of 25 mg for 2 weeks; thereafter, the dose was increased by 25 mg weekly until it reached 200 mg/day. This drug was used only in inpatients, initially under strict cardiac monitoring in order to survey for eventual cardiac adverse events.

Combined treatment was continued for ≥12 months after culture conversion, depending on the clinical and radiological evolution. Eleven patients met the recovery criteria, with ≥2 years of follow-up after treatment completion; in these patients, the time to negative culture conversion of sputum ranged from 7 to 270 days. Four patients are considered

recovered, though still on follow-up, 1 defaulted treatment and 1 was lost to follow-up.

Drug adverse effects were observed in nine patients, haematological disorders and neurotoxicity being the most frequent. Other adverse effects were allergic dermatitis, transient mild serum transaminase elevation and digestive intolerance. Optic neuropathy developed in two patients 90 and 100 days after initiating linezolid treatment (600 mg twice daily) and reversed completely 20 and 30 days after stopping it. In these patients, as well as in patients presenting peripheral neurotoxicity or haematological disorders, linezolid was temporarily suspended until neurological signs disappeared or blood values normalized. Thereafter, linezolid was restarted at half the dose (600 mg/day) supplemented with vitamin B complex and folic acid. Thioridazine was discontinued in one patient with pancytopenia and in another with allergic dermatitis.

Discussion

XDR-TB isolates are usually resistant to all first-line drugs, not only to rifampicin and isoniazid. Furthermore, the available treatment options are significantly limited in XDR-TB cases, where neither injectable drugs nor fluoroquinolones can be used, since these bactericidal drugs are the cornerstone of MDR-TB treatment. Therefore, available alternative drugs must be used to face the treatment challenge posed by XDR-TB. This was the case in our series, in which combined therapy including linezolid, moxifloxacin and thioridazine contributed to the cure of 61% of the patients and favourable recovery in 22%, who are still on follow-up. The absence of HIV coinfection is certainly a factor contributing to the high success rate in our series.

The experience in the use of linezolid for the management of MDR- and XDR-TB is exiguous and the results are still controversial.[3,4] In spite of the frequently reported adverse effects, our team had previously administered linezolid to MDR-TB patients with good clinical/bacteriological evolution.[5] In the present XDR-TB patient series, remission of haematological disorders or neurotoxicity attributable to linezolid was achieved after temporary suspension of the drug and subsequent lowering of the dose by half, an alternative already reported by other authors.[4] Promising results are being obtained with structural analogues of linezolid that have a much lower MIC and may cause less adverse effects during prolonged application.[6]

Fluoroquinolones have proved to be highly effective in the treatment of TB. Although cross-resistance among the members of this family has been reported, susceptibility to moxifloxacin is often preserved when *in vitro* resistance to a representative fluoroquinolone is already in evidence. Indeed, experimental as well as clinical data support the use of this newer-generation fluoroquinolone in the treatment of XDR-TB.[7,8] There is reason to infer that the use of moxifloxacin in combined therapy has contributed to the favourable evolution of 12 of 14 patients treated with this drug in our series.

In our series there is also an indication that thioridazine could have contributed to an earlier bacteriological sputum conversion (Table 1). Thioridazine belongs to a family of phenothiazine compounds that were initially developed as antipsychotic drugs and later found to have a remarkable antimicrobial activity. In particular, thioridazine has been found to be active against *M. tuberculosis*, including MDR and XDR strains, *in vitro* as well as in experimentally infected mice.[9] Thioridazine has even been described as a 'salvage drug' for monotherapy of patients with XDR-TB.[10] With the emergence of MDR-TB, this phenothiazine may therefore reappear as an important antimicrobial agent.[10] Although cardiac adverse effects have been reported, no prolongation of the QT interval or any other heart complication was observed in our patients, who were under strict cardiac supervision while receiving thioridazine. Rather, other side effects could have contributed to improve the quality of life of the patients, as shortly after the inclusion of thioridazine in their regimens most of them benefited from a decrease in night sweats, an increase in appetite, a gain of weight and a decreased level of anxiety. Still, as in the UK and other countries, thioridazine is restricted to the therapy of psychosis; well-controlled clinical trials are needed to properly assess its efficacy as an anti-TB agent.

In conclusion, in our study, which was not a clinical trial but one conducted on a compassionate basis, combined therapy including linezolid, moxifloxacin and thioridazine has led to satisfactory evolution and cure free of relapse in most cases. Adverse effects, when they occurred, could be reversed by adjusting drug schemes. These compounds are therefore recommended for the treatment of non-responsive XDR-TB patients in specialized centres with expertise in MDR- and XDR-TB management.

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