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BRIEF COMMUNICATION

Effectiveness and safety of imipenem/clavulanate and linezolid to treat multidrug and extensively drug-resistant tuberculosis at a referral hospital in Brazil

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Abstract Evidence on effectiveness, safety, and tolerability of imipenem/clavulanate (IC) and linezolid containing regimens to treat multidrug-resistant (MDR-) and extensively drug-resistant tuberculosis (XDR-TB) is scarce. The aim of this observational study is to evaluate the therapeutic contribution of IC and linezolid to manage MDR/XDR-TB cases at the reference centre of São Paulo state, Brazil. Twelve patients (9 males, 1 HIV positive in antiretroviral treatment, 4 MDR, 8 XDR) were treated with IC, 11 of them within linezolid-containing regimens. They all were previously treated with treatment failure, for a median (IQR, interquartile range) of 4.5 (2–6.5) times, having a severe resistance pattern (median number of resistances: 7 (5–8)) and being sputum smear and culture positive. IC and linezolid were prescribed at the dose of 1000 mg/day and 600 mg/day, respectively. The overall exposure was (median (IQR)) 419 (375.5–658) days for IC and 678 (392–720) days for linezolid. All of them converted their sputum (time to sputum conversion; 60 (37.5–90) days) and culture (75 (60–135) days), and 7 were cured while 5 are still on treatment with a gradually improving clinical picture.

While no adverse events were reported for IC, 2 minor side effects, only, were attributed to linezolid (17%); in both cases the drug was re-started without further problems. Our study suggests that IC and linezolid-containing regimens can be used safely and with satisfactory outcomes in reference centres to treat MDR/XDR-TB patients.

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Introduction

The World Health Organization (WHO) estimated over 480,000 new multidrug-resistant tuberculosis (MDR-TB) cases with 190,000 deaths occurring in 2014. While overall 9.7% of the MDR-TB strains met the criteria defining extensively drug resistant TB (XDR-TB, e.g. resistance to at least one fluoroquinolone and a second line-injectable drug) in some countries of the former Soviet Union this proportion is much higher (29% in Belarus, 15% in Latvia).[1–3]

Treating MDR- and XDR-TB patients with the drugs available today is known to be long, expensive and complicated, as adverse events (AE) are frequent and often severe.[1–4]

Presently WHO classifies second-line anti-TB drugs into five groups favouring their stepwise use based on decreasing efficacy and safety from Group 1 to 5. Recent new evidence suggests a revision of the present classification might be necessary.[5]

Clinicians treating MDR/XDR-TB cases often face difficulties in identifying at least 4 active drugs which are recommended by WHO to compose an effective multi-drug regimen.[1–5]

Within WHO Group 5, the carbapenems (meropenem, imipenem, ertapenem), are already used to treat MDR/XDR-TB cases, although the evidence available on their efficacy, safety, and tolerability is extremely limited.[1–7]

Linezolid is also used to treat these cases, being considered effective but often difficult-to-manage because of its frequent and severe AE.[8]

Evidence on the combined use of carbapenems and linezolid is anecdotal.[9]

The aim of the present study is to evaluate the potential clinical contribution (effectiveness, safety, and tolerability) of imipenem clavulanate (IC)- and linezolid-containing regimens in treating a cohort of MDR/XDR-TB cases at a referral hospital in Brazil.

Material and methods

The study, observational and retrospective, has been conducted in the São Paulo state reference centre, Brazil, within a joint project of the European Respiratory Society (ERS) and the Brazilian Thoracic Society. The Centre is served by a quality-controlled laboratory belonging to the WHO network.[1] All consecutive MDR-TB cases (TB caused by M. tuberculosis strains phenotypically resistant to at least isoniazid and rifampicin) aged $\geq$15 years and diagnosed from January 2013 to December 2015 were enrolled.

An individualized TB regimen was administered following the results of the drug-susceptibility test (DST).[1]

The attending physician prescribed anti-TB drugs without any compelling criteria of experimental protocols and, consequently, blinding or randomized methods were not followed.

IC was administered at a dose of 1000 mg 1 time per day plus amoxicillin/clavulanic acid 500/125 mg three times a day and linezolid at the dose of 600 mg per day.

A standardized ad-hoc e-form was prepared to collect epidemiological (i.e., duration of hospital stay, age, place of birth, sex, residence, immigration from a TB high-burden country), clinical (i.e., HIV status, administration of HIV drugs, previous TB diagnosis and treatment, previous treatment outcomes, radiological findings, TB therapy and related adverse events, duration of exposure to MC and IC, surgery, sputum smear and culture positivity at the treatment baseline, at 30, 60 and 90 days, time to sputum smear and culture conversion, WHO treatment outcomes), and microbiological (i.e., DST results) information from official medical files.

Ethical approval for the collection and analysis of anonymous and retrospective data and for the compassionate use of the drugs is not necessary according to the Brazilian law.

Results

Twelve patients affected by pulmonary TB were enrolled at a referral hospital in São Paulo state and treated with IC, while 11 of them received also linezolid (Tables 1 and 2).

Nine were males (75%) and 3 females, with a median (IQR) age of 39.5 (27–43) years. A single patient was HIV positive, being in regular antiretroviral treatment with a combination of lamivudine, efavirenz and tenofovir, one had diabetes, one hypertension, 2 were admitted with acute respiratory failure, while 7 were drug abusers and 4 alcohol addicts before admission.

Four cases met the definition of MDR-TB and 8 of XDR-TB.

They all were previously treated (treatment failure being the last outcome), for a median of 4.5 (2–6.5) times.

The cases had a severe resistance pattern (median (IQR) number of resistance 7 (5–8)) and were sputum smear and culture positive when referred to the São Paulo State Secretary of Health. All of them had cavities in the chest radiography, being bilateral in 8 cases (67%).

The overall exposure was (median (IQR)) 419 (375.5–658)) days for IC and 678 (392–720) days for linezolid. They required long hospitalization at the reference Centre (439.5 (403–669.5) days).

All of them converted their sputum (time to sputum conversion: 60 (37.5–90) days) and culture (75 (60–135) days), and 7 (58%) were cured while 5 are still on treatment with a gradually improving clinical picture.

While no adverse events were reported for IC, 2 minor and reversible AEs only were attributed to linezolid (17%): peripheral neuropathy in patient 12 (linezolid was re-started without further problems) and gastro-intestinal disorders in patient 6 (diarrhoea, managed with symptomatic medications without need to stop the anti-TB drugs).

Discussion

This is the first study reporting bacteriological conversion information and treatment outcomes in a Latin American cohort of MDR/XDR-TB cases treated with IC within linezolid-containing regimens. A single patient was prescribed IC but not linezolid to avoid the co-administration with ethionamide due to a prior history of peripheral neuropathy.

The anti-TB regimens have been designed as per WHO guidelines and guided by drug susceptibility testing, taking into account the following: (1) kanamycin was not available in Brazil and capreomycin was available after 2014;

Table 1 Demographic and clinical features in the Brazilian cohort.

Patient	Age at the admission (years)	Gender	Country of birth	HIV-positive (ART)	Previous exposure to anti-TB therapy	Number of times treated >1 month	Pulm/ extrapulm-TB	Radiological findings	Resistances	MDR/XDR-TB
1	43	Male	Brazil	No	Yes	7	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, Z, Ofx, Am, Cm, Km	XDR
2	24	Female	Brazil	No	Yes	6	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, Ofx, Am, Cm, Km	XDR
3	41	Male	Brazil	No	Yes	2	Pulmonary	Cavitary lesions	H, R, S, Z, Ofx, Am, Cm, Km	XDR
4	42	Female	Brazil	No	Yes	10	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, Z, Ofx, Am, Cm, Km	XDR
5	43	Male	Brazil	Yes (Efz + 3Tc + Tdf)	Yes	5	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, Z, Ofx	MDR
6	63	Male	Brazil	No	Yes	2	Pulmonary	Cavitary lesions	H, R, E, Z, Ofx	MDR
7	38	Female	Brazil	No	Yes	2	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, Ofx, Cm,	XDR
8	55	Male	Brazil	No	Yes	7	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, E, Z, Ofx, Am, Cm, Km	XDR
9	27	Male	Brazil	No	Yes	2	Pulmonary	Cavitary lesions	H, R, E, Z, Ofx	MDR
10	18	Male	Brazil	No	Yes	3	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, Ofx, Am, Cm, Km	XDR
11	27	Male	Brazil	No	Yes	4	Pulmonary	Cavitary lesions	H, R, E, Z, Ofx,	MDR
12	34	Male	Brazil	No	Yes	5	Pulmonary	Bilateral pulmonary involvement with cavitary lesions	H, R, S, E, Z, Ofx, Km	XDR

MDR/XDR-TB: multidrug-resistant/extensively drug-resistant- tuberculosis; ART: anti- retroviral therapy; efz: efavirenz; 3tc: lamivudine; tdf: tenofovir. *Drugs*: H: isoniazid; R: rifampicin; S: streptomycin; E: ethambutol; Z: pyrazinamide; Am: amikacin; Cm: capreomycin; Ofx: ofloxacin, Km: kanamycin.

Table 2 Bacteriology, treatment and outcome in the Brazilian cohort.

Patient	Prescribed regimen	Length of hospital stay (days)	Months of treatment after MDR-TB diagnosis	Sputum smear conversion (days)	Sputum culture conversion (days)	Linezolid dose	Interruption of Linezolid due to adverse events	AEs presumably due to Linezolid	Total linezolid exposure (days)	Imipenem dose	Interruption of Imipenem due to AEs	AEs presumably due to Imipenem	Total Imipenem exposure (days)	Treatment outcome
1	Am + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E	720	114	30	40	600 mg/day	No	No	720	1000 mg/day	No	No	720	Cured
2	Cm + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E + Z	720	87	60	60	600 mg/day	No	No	720	1000 mg/day	No	No	720	Cured
3	S + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E	453	40	60	90	600 mg/day	No	No	720	1000 mg/day	No	No	455	Cured
4	Am + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E + Z	227	85	45	15	600 mg/day	No	No	720	1000 mg/day	No	No	227	Cured
5	Am + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E	660	23	180	180	600 mg/day	No	No	638	1000 mg/day	No	No	638	Cured
6	Am + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E + Cfz	415	18	60	60	600 mg/day	No	Gastro-intestinal disorders (reversible)	392	1000 mg/day	No	No	392	Still on treatment
7	S + Mfx + Eto + Ipm + E + Clr + Z	575	39	60	150	–	–	–	–	1000 mg/day	No	No	362	Cured
8	Mfx + Eto + Ipm + Lzd + Clr + E + Z	679	71	30	180	600 mg/day	No	No	678	1000 mg/day	No	No	678	Still on treatment
9	Am + Mfx + Eto + Ipm + Lzd + Z + Cfz	391	7	30	60	600 mg/day	No	No	389	1000 mg/day	No	No	389	Still on treatment
10	Am + Mfx + Eto + Ipm + Lzd + Clr + E + Z + Cfz	419	14	120	120	600 mg/day	No	No	418	1000 mg/day	No	No	418	Still on treatment
11	Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Z	426	44	120	120	600 mg/day	No	No	725	1000 mg/day	No	No	420	Cured
12	Cm + Mfx + Eto + Trd + Ipm + Amx/Clv + Lzd + Clr + E + Z + Cfz	120	46	60	60	600 mg/day	Yes	Peripheral neuropathy (reversible)	105	1000 mg/day	No	No	123	Still on treatment

AE: adverse event. *Drugs*: S: streptomycin; Z: pyrazinamide; E: ethambutol; Am: amikacin; Mfx: moxifloxacin; Eto: ethionamide; Trd: terizidone; Ipm: imipenem; Amx/Clv: amoxicilin/clavulanate; Lzd: linezolid; Clr: claritromycin; Cm: capreomycin; Cfz: clofazimine; Ipm: imipenem.

(2) pyrazinamide was not used when intolerance to it was documented; (3) terizidone is used in Brazil instead of cycloserine; and (4) PAS (para-aminosalicylic acid) has been made available in Brazil after 2014.

The results of our study demonstrate that, in spite of the cases severity, IC within linezolid containing regimens is able to: (1) ensure sputum smear and culture conversion in all the cases of the cohort, with time to bacteriological conversion similar to that recently described by the International Carbapenems Study Group[1–3]; (2) reach a positive treatment outcome in 7 out of 12 cases, while the remaining 5 are improving clinically and radiologically and remain consistently sputum smear and culture negative; and (3) is safe, if managed at reference centre level, with two minor and reversible AEs.

Based on its molecular mechanism of action, imipenem is more active than meropenem.[1,3] However, this does not necessarily translate into better clinical results, as shown in a recent multinational study.[3] Furthermore, the study results confirm the importance of prescribing imipenem in association with clavulanate (a β-lactamase inhibitor) which can inhibit the activity of the potent β-lactamase, encoded by the BlaC gene.[1–3]

The observational and retrospective design of the study has in-built limitations (impossibility to pre-calculate the sample size, to have a control group, to randomize and ensure blindness).

Additional limitations are the small sample size (with limited inclusion of patients with HIV co-infection) and the fact that these patients received several prior anti-TB drugs. However, the study is, as of today, the third in the literature (the first in Latin America) and this anecdotal evidence might be of help.

In conclusion, the study results confirm that IC, within the carbapenems class of drugs might have a role in treating MDR/XDR-TB and that IC and linezolid-containing regimens can be used safely and with satisfactory outcomes in reference centres to treat MDR/XDR-TB patients.[9,10]

Ethical disclosures

Protection of human and animal subjects. The authors declare that no experiments were performed on humans or animals for this study.

Confidentiality of data. The authors declare that no patient data appear in this article.

Right to privacy and informed consent. The authors declare that no patient data appear in this article.

Conflicts of interest

The authors have no conflicts of interest to declare.

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