Rev Port Pneumol. 2016;xxx(xx):xxx–xxx

revista portuguesa de
PNEUMOLOGIA
portuguese journal of pulmonology
www.revportpneumol.org

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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Received 2 May 2016; accepted 29 June 2016

KEYWORDS
MDR-TB;
XDR-TB;
Imipenem;
Linezolid;
Effectiveness;
Safety;
Tolerability

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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http://dx.doi.org/10.1016/j.rppnen.2016.06.006

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;

Please cite this article in press as: Arbex MA, et al. Rev Port Pneumol. 2016. http://dx.doi.org/10.1016/j.rppnen.2016.06.006