



Case report

First Series of Patients With XDR and Pre-XDR TB Treated With Regimens That Included Meropenem-clavulanate in Argentina[☆]



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ABSTRACT

XDR (extensively drug-resistant) and pre-XDR tuberculosis (TB) seriously compromise prognosis and treatment possibilities, and inevitably require the use of group V drugs (World Health Organization). The progress of all patients with XDR and pre-XDR TB seen in a specialized unit during 2012 and 2013 and treated with regimens that included at least 6 months of meropenem-clavulanate (MPC), capreomycin, moxifloxacin, linezolid, clofazimine, high-dose isoniazid, PAS, and bedaquiline in 1 case, were retrospectively analyzed. Ten patients were treated, 9 with an extensive pattern of resistance to at least 6 drugs, and 1 because of adverse reactions and drug interactions leading to a similar situation. Eight of the 10 patients treated achieved bacteriological sputum conversion (2 consecutive negative monthly cultures) over a period of 2–7 months, while 2 died. No adverse reactions attributable to prolonged administration of MPC were observed.

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Primera serie de pacientes con TB-XDR y pre-XDR tratados con esquemas que incluyeron meropenem-clavulanato en Argentina

RESUMEN

La tuberculosis extensamente resistente (TB-XDR) y pre-XDR comprometen seriamente el pronóstico de la enfermedad, y su tratamiento requiere inevitablemente el uso de fármacos del grupo V (Organización Mundial de la Salud [OMS]). Se analizó retrospectivamente la evolución de todos los pacientes con TB pre-XDR y XDR asistidos en un servicio especializado durante 2012 y 2013, medicados con regímenes que incluyeron por lo menos 6 meses de meropenem-clavulanato (MPC), capreomicina, moxifloxacina, linezolid, clofazimina, isoniácida en alta dosis, PAS y en un caso bedaquilina. Fueron tratados 10 pacientes, 9 de ellos con un extenso patrón de resistencia a un mínimo de 6 fármacos y uno por reacciones adversas e interacciones medicamentosas que generaron una situación análoga. Ocho de los 10 pacientes tratados, hicieron la conversión bacteriológica del esputo (2 cultivos mensuales consecutivos negativos) en un lapso de 2 a 7 meses, en tanto que 2 fallecieron. No se observaron reacciones adversas atribuibles a la administración prolongada del MPC.

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Palabras clave:

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Introduction

Extensively drug-resistant tuberculosis (XDR-TB) is caused by *Mycobacterium tuberculosis* strains with resistance to at least

isoniazid (H), rifampicin (R), a fluoroquinolone, and a second-line injectable drug (SLI): kanamycin (Km), amikacin (Amk) or capreomycin (Cm). Pre-XDR-TB denotes resistance to H and R, as well as to at least one FQ or one SLI.¹ The WHO has estimated the worldwide incidence of MDR-TB (multidrug-resistant TB: resistant to at least H and R) to be 480,000 cases in 2013, of which 9% were XDR-TB.² In 2013, Argentina's National Reference Laboratory (ANLIS Malbrán) identified 6 cases of XDR-TB and 18 of pre-XDR.

The WHO divides anti-TB drugs into 5 groups: (1) first-line drugs; (2) FQ (ofloxacin, levofloxacin, moxifloxacin); (3) injectables (kanamycin, amikacin, capreomycin, streptomycin);

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(4) oral bacteriostatic second-line drugs (cycloserine/terizidone, ethionamide/prothionamide, PAS); and (5) anti-TB drugs with limited data on efficacy: clofazimine (Cfz), linezolid (Lzd), amoxicillin/clavulanate (amoxi-clav), carbapenems (imipenem-cilastatin and meropenem) high-dose H, bedaquiline (Bdq) and delamanid (the latter two have been approved for a 6-month course in pre-XDR/XDR-TB). Drugs in groups II to IV (except streptomycin) are considered second-line therapy, while group V drugs are also known as third-line drugs.^{1,3}

Patients with pre-XDR and XDR-TB are usually treated with regimens that include group V drugs, as they are usually resistant to most of the remaining drugs. Treatment given to these patients, therefore, is likely to be less effective. In recent years, studies have shown that meropenem combined with clavulanate (MPC) can have an antimycobacterial and synergic effect.^{4–6} The aim of this study is to show the efficacy, measured in terms of bacteriologic conversion of sputum, of treatment regimens that include combination meropenem-clavulanate given in the initial stage of pre-XDR and XDR-TB therapy.

Methodology

This is a retrospective study of all patients confined to the drug-resistant TB respiratory isolation unit from 1/1/2012 to 12/31/2013 with a bacteriological diagnosis of pre-XDR and XDR-TB, plus 1 case of adverse reaction/drug interaction. The patients were treated with regimens that included at least 5 group 2 to 5 drugs, including MPC, for at least 6 months. In our hospital, we receive patients from Argentina and also immigrants from neighboring countries who have come in search of work. Approximately half of all TB cases diagnosed in Buenos Aires involve recent immigrants from neighboring countries.

The hospital laboratory performed susceptibility testing for H, R, etambutol (E) and streptomycin (S) using quick fluorometric and solid media proportions methods. The ANLIS Malbrán performed susceptibility testing for ofloxacin (Ofx), cycloserine (Cs), ethionamide (Eto), PAS, kanamycin, amikacin and capreomycin using the solid media proportions method; for Cfz, Ldz and moxifloxacin [Mfx] using MIC determination in liquid medium; and for pyrazinamidase (Z) using the pyrazinamidase test.

Indication for MPC was determined empirically. Therapeutic regimens were designed on the basis of previous treatment received and the results of susceptibility testing, when available.

Patients gave a sputum sample for culture each month. Favorable evolution was defined as bacteriologic conversion (negative results from two consecutive monthly cultures) when first negative result occurred before month 6 of treatment.

The results were published following approval by the Independent Ethics Committee of the Instituto Vaccarezza (authorization No. 30/15) (Table 1).

Table 2 shows the drugs and doses given.

Results

A total of 10 patients (5 women) were enrolled in the study, with an average age of 37.5 years. Five had previously received multiple treatment, and 5 had received no treatment.

Radiologically, all showed bilateral involvement with cavitation. Nine cases were diagnosed as pre-XDR or XDR-TB, and 1 received a complicated therapy regimen due to serious adverse reactions and drug interactions (a liver transplant recipient who contracted TB).

Table 2 shows the characteristics and evolution of the 10 patients receiving therapy regimens including MPC. Briefly, 8 patients showed sputum conversion by the end of the follow-up period. These patients continued with a second, 18-month phase of treatment during which only MPC was discontinued. Two patients died during follow-up, 1 due to worsening of TB due to treatment failure, and the other due to respiratory failure secondary to pulmonary destruction, despite good bacterial response. At the date of publication, not all patients have completed their treatment. By way of preliminary data, of the 8 patients that continued to the end of the initial follow-up phase (receiving MPC), 1 died due to hepatic failure not associated with TB (liver transplant recipient), treatment failed in 1 case, with bacteriological reversion after conversion to negative. Of the remaining 6 patients, 3 completed the treatment after meeting WHO "cured" outcome criteria,¹ and 3 continue receiving treatment, with bacteriological conversion at the time of publication.

Discussion

Drug-resistance in TB is a major therapeutic challenge. Standard MDR-TB treatment guidelines have been drawn up, consisting of 2 core drugs, 1 FQ and 1 SLI, combined with 2 oral bacteriostatic agents and pyrazinamide.^{1,3} In the case of pre-XDR and XDR-TB,

Table 1
Drugs and Dosage Used in 10 Patients Receiving Treatment Regimens that Included Meropenem/Amoxicillin-clavulanate.

Drug	Dose and Administration	Most Common Adverse Effects
Amikacin	15 mg/kg/d, IM or IV, diluted	Oto- and nephrotoxicity, electrolyte disorders
Amoxicillin-clavulanate	Amoxicillin 500 mg-clavulanate 125 mg, oral q8 h. Used because clavulanate formulations were not available on the market.	Digestive, hepatic, hyper-sensitivity
Bedaquiline	400 mg/d for 2 weeks, then 200 mg three times weekly for 22 weeks, oral	QTc prolongation, hepatitis, cannot be co-administered with Mfx.
Capreomycin	15 mg/kg/d, IM or IV	Oto- and nephrotoxicity, electrolyte disorders
Clofazimine	100 mg/d, oral	Skin pigmentation, abdominal colic
Cycloserine	15 mg/kg/d in 3 doses, oral	Convulsions, behavioral disorders, depression
Etambutol	100 mg/d, oral	Optic neuritis
Ethionamide	15 mg/kg/d in 3 doses, oral	Metallic taste, toxic hepatitis, hypothyroidism
High dose isoniazid	10 mg/kg/d, oral	Toxic hepatitis, polyneuritis
Levofloxacin	700 mg/d	Tendinitis, toxic hepatitis, neurotoxicity
Linezolid	600 mg/d, oral	Polyneuritis, mononeuritis, optic neuritis, bone marrow depression
Meropenem	2 g IV diluted q8 h until sputum culture is negative, then 1 g q8 h, IV diluted	Inflammation of injection site, digestive, hypokalemia, convulsions, hepatotoxicity
Moxifloxacin	400 mg/d, oral	Tendinitis, toxic hepatitis, neurotoxicity
PAS	15 mg/kg/d in 3 doses, oral	Digestive, hypothyroidism, hepatotoxicity
Pyrazinamide	25 mg/kg/d, oral	Toxic hepatitis, hyperuricemia

IM: intramuscular; IV: intravenous; Mfx: moxifloxacin; QTc: corrected QT interval; PAS: para-aminosalicylic acid.

Table 2
Characteristics of the 10 Patients Receiving Treatment Regimens That Included Meropenem/Amoxicillin-clavulanate.

Case	Age	Sex	Nationality	Previous Treatment	Category	Culture	Resistances ^a	ARs to Anti-TB Drugs	Treatment	Evolution at 6 Months ^b	Comorbidities
1	37	F	Uruguay	No	Pre-XDR (SLI)	C (–) at month 4	S, H, R, E, Z, Km, Cm, Amk	No	Amoxi-clav, MRP, Mfx, Cs, Eto, PAS, Lzd	Favorable	No
2	35	F	Argentina	No	Pre-XDR (FQ)	C (–) at month 4	S, H, R, E, Z, Km, Cm, AMK	Polyneuritis	Amoxi-clav, MRP, AMK, Mfx, Eto, Lzd	Favorable	No
3	26	F	Argentina	Yes	XDR	D (+) C (+)	S, H, R, E, Z, Km, Cm, Ofx, Lfx	No	Amoxi-clav, MRP, Mfx, Cs, Eto, PAS, Lzd	Treatment failure Died	CKF IDU
4	58	F	Peru	Yes	XDR	C (–) at month 4	S, H, R, E, Z, Km, Cs, PAS, Ofx, Lzd, Clf	No	Amoxi-clav, MRP, Mfx, H ^{bd} , Eto, Lzd, CFZ	Favorable	No
5	57	F	Argentina	No (nurse)	Pre-XDR (SLI)	C (–) at month 6	S, H, R, E, Z, Km, AMK	Digestive	Amoxi-clav, MRP, Mfx, Cs, Eto, PAS, Lzd	Favorable	DBT
6	31	F	Argentina	No	Pre-XDR (SLI)	C (–) at month 2	S, H, R, E, Z, Km, AMK	No	Amoxi-clav, MRP, Mfx, Cs, Eto, PAS, Lzd	Favorable	No
7	48	F	Argentina	Yes	RA, R-tacrolimus interaction	C (–) at month 5	H, E, PAS, Cs	Hepatitis	Amoxi-clav, MRP, AMK, Mfx, Lzd	Favorable	CKF DBT Liver transplant
8	24	F	Argentina	Yes	XDR	C (–) at month 6	S, H, R, E, Z, Km, Cs, PAS, Ofx	Digestive	Amoxi-clav, MRP, Mfx, Cm, PAS, Lzd	Favorable	No
9	29	F	Peru	No	Pre-XDR (FQ)	C (–) at month 4	S, H, R, E, Z, Ofx	No	Amoxi-clav, MRP, AMK, Mfx, Cs, Eto, Lzd	Favorable	No
10	30	F	Argentina	Yes	XDR	C (–) at month 4	S, H, R, E, Z, Km, Cm, Ofx, Mfx, Cs, Eto	Digestive Hematologic	Amoxi-clav, MRP, Cm, BDQ, PAS, Lfx	Died ^c	Anorexia nerviosa Diarrhea due to <i>C. difficile</i>

AMK: amikacin; Amoxi-clav: amoxicillin-clavulanate; AR: adverse reactions; Bdq: bedaquiline; Cm: capreomycin; CKF: chronic kidney failure; Clf: clofazimine; Cs: cycloserine; DBT: diabetes; E: etambutol; Eto: ethionamide; FQ: fluoroquinolones; H^{bd}: high dose isoniazid (600 mg/d); IDU: illegal drug user; Km: kanamycin; Lfx: levofloxacin; Lzd: linezolid; MRP: meropenem; Mfx: moxifloxacin; Ofx: ofloxacin; PAS: para-aminosalicylic acid; R: rifampicin; S: streptomycin; SLI: second line injectables; Z: pyrazinamide.

^a Ethionamide susceptibility testing frequently returned un-interpretable results. Resistance to group IV and V drugs was considered approximate due to poor consistency across results.

^b Favorable evolution: bacteriological conversion (2 consecutive negative monthly sputum cultures), the first occurring before the end of the 6-month treatment period.

^c Patient died in hospital due to respiratory failure, despite bacteriological conversion.

treatment consists of the best possible combination of drugs based on susceptibility testing, history of previous treatment regimens, and drug availability. Two important new drugs, bedaquiline and/or delamanid,¹ are currently not available in Argentina in the context of disease management programs.

M. tuberculosis is resistant to beta-lactam antibiotics because it produces an extended-spectrum beta-lactamase (BlaC), which is irreversibly inhibited by clavulanate. Since meropenem is more resistant to BlaC than other beta-lactams, the combination of this drug with clavulanate could be highly bactericidal for both susceptible and resistant strains, including non-replicating strains.⁶

In this patient series we used regimens that included MPC in the initial 6-month phase in hospitalized patients. We observed no adverse reactions associated with MPC. However, the length of time needed to administer the drug is an inconvenience, and 2 patients required implantation of a port device. Eight of our 10 study patients responded well to this initial phase of treatment with Lzd-Mfx-MPC as core drugs.

In conclusion, MPC, however inconvenient due to the route of administration, combined with other group V drugs could be effective as a first-stage treatment strategy for pre-XDR and XDR TB.

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