INT J TUBERC LUNG DIS 16(4):558–560

http://dx.doi.org/10.5588/ijtld.11.0414
Published online 8 February 2012

CASE STUDY

Clinical use of the meropenem-clavulanate combination for extensively drug-resistant tuberculosis

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SUMMARY

Mycobacterium tuberculosis strains resistant to almost all available anti-tuberculosis drugs are an increasing threat to public health worldwide. Among existing drugs with potential antimycobacterial effects, the combination of meropenem with clavulanate has been shown to have potent in vitro bactericidal activity against extensively drug-resistant tuberculosis (XDR-TB). To explore its potential clinical efficacy, a meropenem-clavulanate-containing salvage regimen was started in six patients with severe pulmonary XDR-TB, in association with the only one or two remaining active second-line drugs. Encouraging preliminary data are detailed and discussed.

KEY WORDS: extensively drug-resistant tuberculosis; salvage therapy; carbapenems plus clavulanate

THE EMERGENCE of multidrug-resistant tuberculosis (MDR-TB), and more recently of extensively drug-resistant tuberculosis (XDR-TB), defined respectively as resistance to both isoniazid (INH) and rifampicin, and additional resistance to any fluoroquinolones (FQ) and to at least one of the three injectable second-line drugs (capreomycin [CPM], kanamycin or amikacin), has stressed the need for new therapeutic options. The World Health Organization (WHO) guidelines recommend the use of at least four active drugs based on drug susceptibility testing (DST) results.[1] Some *Mycobacterium tuberculosis* strains with broad-spectrum resistance lack susceptibility to at least four active anti-tuberculosis drugs.[2]

Among drugs with potential antimycobacterial activity, the association of a β-lactam with a β-lactamase inhibitor in the management of MDR-TB led to contrasting results.[3,4] *M. tuberculosis* is intrinsically resistant to β-lactams due to the presence of an extended spectrum β-lactamase, BlaC. The β-lactamase inhibitor, clavulanate, has been shown to irreversibly inhibit *M. tuberculosis* BlaC in vitro.[5] Meropenem, a potent β-lactam antibiotic from the carbapenem class, has recently been found to be an extremely poor substrate for BlaC, with hydrolysis occurring thousands of times more slowly than with ampicillin.[6] The combination of meropenem with clavulanate is highly bactericidal in vitro against drug-susceptible as well as XDR-TB strains, including non-replicative strains, and is able to sterilise cultures in 14 days.[7]

We used the meropenem-clavulanate combination as part of a salvage regimen for the treatment of severe XDR-TB where no alternative drugs could be identified. We report here on the safety, tolerability and potential efficacy of this regimen in six patients. Preliminary data for the four first patients were presented at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy in September 2010.[7]

MATERIALS AND METHODS

The Saint-Pierre University Hospital is a referral centre for MDR-TB in Belgium. Starting in May 2009, we included meropenem-clavulanate as a component of salvage treatment in patients with pulmonary TB for whom no adequate treatment could be identified. All patient samples had second-line DST performed by the National Reference Laboratory of Tuberculosis and Mycobacteria. Unfortunately, in vitro DST for meropenem-clavulanate is not yet available.

In addition to meropenem-clavulanate, patients received all active drugs according to the DST results, as well as pyrazinamide and cycloserine. From May 2010, even where DST showed resistance, moxifloxacin (MXF) was continued because of newly published data suggesting a benefit of second-line regimens that include an FQ.[8] Linezolid was used at a dose of 600 mg daily.[9] Meropenem was administered intravenously at an empirical dose of 2 g thrice daily during hospitalisation and then 2 g twice daily during the continuation phase. Patient 1 started meropenem at a dose of 1.5 g thrice daily due to a very low body mass index (14 kg/m^2).

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Article submitted 16 June 2011. Final version accepted 3 October 2011.

Clavulanate was given in the form of a combination of amoxicillin plus clavulanate (500 mg/125 mg) thrice daily. The safety and tolerability of meropenem-clavulanate were assessed using clinical data (i.e., medical history findings, physical examination findings and serum chemistry levels). Efficacy was evaluated by clinical and radiological improvement and by weekly sputum culture. Culture conversion was defined as the time to first of three consecutive negative weekly sputum cultures.

Ethical approval

The Ethical Review Board of the Saint-Pierre Hospital authorised publication of this paper (Document AK/11-02-24/3132).

RESULTS

Six patients with severe bacteriologically confirmed bilateral pulmonary XDR-TB were treated; their demographic data are summarised in Table 1. All six patients, three women and three men, were from the Russian Federation. Patient age ranged from 14 to 46 years. One patient was co-infected with human immunodeficiency virus (HIV) 1 (CD4 cell count = 316 cells/μl, viral load = 925.000 copies/ml, naïve for antiretrovirals) and two patients had hepatitis C virus. There was no other comorbidity. All had been exposed to second-line drugs. No clinical or bacteriological improvement was observed with empirical treatment that was initiated before obtaining complete DST results, which revealed that all strains had a broad-spectrum resistance profile. DST results, the last failed regimen and salvage treatment are outlined in Table 1. Culture conversion after 8–20 weeks of

Table 2 Mycobacteriology data for six XDR-TB patients treated with M-C

Patients	1	2	3	4*	5	6
Week preceding the start of salvage regimen with M-C						
W-6						
Smear	Not	+	+	+	Not	+
Culture	available	+	+	+	available	+
W-4						
Smear	+	+	+	+	+	+
Culture	+	+	+	+	+	+
W 0						
Smear	+	+	+	+	+	+
Culture	+	+	+	+	+	+
Week following the start of salvage regimen with M-C						
W+4						
Smear	+	+	+	+	+	+
Culture	+	+	+	+	+	+
W+8						
Smear	−	+	+	+	+	−
Culture	+	+	+	−	+	+
W+12						
Smear	−	+	+	−	+	−
Culture	−	+	+	−	−	−
W+20						
Smear	−	+	+	−	−	−
Culture	−	+	−	−	−	−
W+24						
Smear	−	+	−	−	−	−
Culture	−	+	−	−	−	−
W+36						
Smear	−	+	−	−	Not	−
Culture	−	+	−	−	performed	−

*Patient 4 had one positive sputum culture after 15 months of salvage treatment. There was no clinical or radiological worsening. Further monthly sputum cultures have been negative to date (1 August 2011). All other sputum cultures obtained after week 36 were negative, excluding Patient 2.
XDR-TB = extensively drug-resistant tuberculosis; M-C = meropenem-clavulanate; W = week.

Table 1 Demographic and treatment data of six patients with XDR-TB given a salvage regimen including meropenem-clavulanate

Patient no.	Age, years/sex	Comorbid disease/ complications	Resistance to second-line drugs (in addition to all first-line drugs)	Last failing regimen	Salvage regimen	Time to surgery, if any
1	14/Female	None	MFX, AMK, PTH, CS, RBT	MFX, AMK, CS, PTH, PZA, RBT (5 weeks)	PZA, CPM, CS, LZD, CLM, M-C	14 months after culture conversion
2	38/Male	Hepatitis C	MFX, AMK, PTH, CS, RBT, LZD, CLM	RMP, PZA, MFX, CPM, CS, CLM (42 weeks)	RMP, PZA, MFX, CPM, CS, CLM, M-C	No surgery to date
3	27/Female	None	MFX, AMK, CPM, PTH, CS, RBT	PZA, MFX, AMK, PTH, CS, LZD, RBT (6 weeks)	PZA, LZD, CLM, M-C	10 months after culture conversion
4	32/Male	HIV-positive, hepatitis C	MFX, AMK, CPM, PTH, CS, RBT	PZA, MFX, CPM, PTH, CS, LZD, AMX/CLAV (10 weeks)	PZA, LZD, CLM, M-C	No surgery to date
5	46/Male	None	AMK, CPM, PTH, CS, LZD, RBT	AMK, MFX, PTH, CS, PZA (4 weeks)	PZA, MFX, CS, CLM, M-C+LZD after culture conversion	No surgery to date
6	19/Female	None	MFX, AMK, PTH, CS, RBT, CLM	AMK, MFX, CS, PTH, PZA, LZD (6 weeks)	PZA, MFX, CPM, CS, LZD, M-C	No surgery to date

XDR-TB = extensively drug-resistant tuberculosis; MFX = moxifloxacin (400 mg/d); AMK = amikacin (15 mg/kg/d); PTH = prothionamide (750 mg/d [500 mg in Patient 1]); CS = cycloserine (750 mg/d [500 mg in Patient 1]); RBT = rifabutine (300 mg/d in Patient 1, 450 mg/d in Patient 3); PZA = pyrazinamide (35 mg/kg/d); CPM = capreomycin (15 mg/kg/d); LZD = linezolid (600 mg/d); CLM = clarithromycin (500 mg twice daily); M-C = meropenem-clavulanate (2 g thrice daily during the initiation phase and 2 g twice daily during the continuation phase; 1.5 g thrice daily during initiation phase in Patient 1); RMP = rifampicin (10 mg/kg/d); HIV = human immunodeficiency virus; AMX/CLAV = amoxicillin-clavulanate (500/125 mg thrice daily).

salvage treatment was obtained in all but one patient (Table 2). Patients were discharged after three consecutive negative sputum cultures and continued their treatment at home, including meropenem-clavulanate injections. No relapse occurred after culture conversion during a follow-up period of 8–25 months. At month 18 of therapy after culture conversion, Patient 1 was considered cured according to WHO guidelines (at least five consecutive negative cultures from samples collected at least 30 days apart in the final 12 months of treatment).[1] Of note, Patients 1 and 3 underwent pneumectomy after respectively 14 and 10 months of successful treatment.

DISCUSSION

Five of the six patients with bilateral advanced XDR-TB dramatically improved with a salvage regimen containing meropenem-clavulanate. One patient was considered cured.

Contribution of meropenem-clavulanate in an association regimen is difficult to assess. According to the WHO guidelines, all patients had poor prognostic factors: bilateral cavitary lesions in 5 patients, previous exposure to second-line drugs and malnutrition in all 6 patients, and HIV infection in 1 patient. Among the active companion drugs, only CPM ($n = 2$), MFX ($n = 1$) and linezolid ($n = 4$) could have significantly contributed to the successful outcome. However, previous empirical treatment with all available active second-line drugs, including linezolid in three patients, had failed to lead to any improvement. It is therefore likely that meropenem-clavulanate significantly contributed to the favourable outcome of our patients. This potential effect could be supported by the in vitro bactericidal activity against *M. tuberculosis*, including non-replicative forms observed by Hugonnet et al.[5] More recently, a study comparing the activity of carbapenems alone and combined with clavulanate in a murine model of TB showed that the combination of carbapenems plus clavulanate significantly improved survival compared with INH alone.[10]

Long-term treatment was well tolerated. No adverse reaction was attributed to meropenem-clavulanate. The small number of patients, the lack of DST and a relatively short follow-up period are among the limitations of this report.

CONCLUSION

The addition of meropenem-clavulanate to one or two active second-line drugs led to cure in one patient and sputum culture conversion in 4/5 additional cases of severe pulmonary XDR-TB with poor prognostic factors. In view of these encouraging preliminary results, meropenem-clavulanate should be evaluated on a larger scale as a new salvage option against severe XDR-TB where no acceptable alternative exists.

Acknowledgements

The authors thank Dr Blanchard from the Einstein College of Medicine, New York, for reviewing this paper. Preliminary data for this paper were presented at the 50th Interscience Conference on Antimicrobial Agents and Chemotherapy, September 2010, Boston, MA, USA.

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RÉSUMÉ

Les souches de *Mycobacterium tuberculosis* résistantes à l'égard de presque tous les médicaments antituberculeux disponibles constituent une menace croissante pour la santé publique mondiale. Parmi les médicaments existants ayant des effets antimycobactériens, la combinaison du méropénem avec le clavulanate s'est avérée posséder une puissante activité bactéricide in vitro contre les germes de la tuberculose ultra-résistants (TB-XDR). Afin d'étudier son efficacité clinique, un régime de traitement de secours contenant le méropeném et le clavulanate, en association avec les seuls (un on deux) médicaments restants de deuxième ligne, a été initié chez six patients souffrant d'une TB-XDR pulmonaire sévère. Cet article présente et analyse en détail les résultats préliminaires prometteurs de ce traitement.

RESUMEN

Las cepas de *Mycobacterium tuberculosis* que son resistentes a la mayoría de los medicamentos antituberculosos existentes constituyen una amenaza mundial de salud pública. Entre los medicamentos que se encuentran a disposición y que cuentan con posibles efectos antimicobacterianos, se ha demostrado que la asociación de meropenem y ácido clavulánico ejerce in vitro una fuerte actividad bactericida contra las cepas de la tuberculosis extremadamente drogorresistentes (TB-XDR). Con el propósito de investigar su posible eficacia clínica, se inició un tratamiento de rescate que comportaba esta asociación y uno o dos medicamentos adicionales de segunda línea que seguían siendo activos, en seis pacientes portadores de una grave TB-XDR. En el presente artículo se presentan y analizan en detalle los resultados preliminares alentadores de este tratamiento.