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Comparison of effectiveness and safety of imipenem/clavulanate- *versus* meropenem/clavulanate-containing regimens in the treatment of MDR- and XDR-TB

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ABSTRACT No large study to date has ever evaluated the effectiveness, safety and tolerability of imipenem/clavulanate *versus* meropenem/clavulanate to treat multidrug- and extensively drug-resistant tuberculosis (MDR- and XDR-TB). The aim of this observational study was to compare the therapeutic contribution of imipenem/clavulanate *versus* meropenem/clavulanate added to background regimens to treat MDR- and XDR-TB cases.

84 patients treated with imipenem/clavulanate-containing regimens showed a similar median number of antibiotic resistances (8 *versus* 8) but more fluoroquinolone resistance (79.0% *versus* 48.9%, p<0.0001) and higher XDR-TB prevalence (67.9% *versus* 49.0%, p=0.01) in comparison with 96 patients exposed to meropenem/clavulanate-containing regimens. Patients were treated with imipenem/clavulanate- and meropenem/clavulanate-containing regimens for a median (interquartile range) of 187 (60–428) *versus* 85 (49–156) days, respectively.

Statistically significant differences were observed on sputum smear and culture conversion rates (79.7% *versus* 94.8%, p=0.02 and 71.9% *versus* 94.8%, p<0.0001, respectively) and on success rates (59.7% *versus* 77.5%, p=0.03). Adverse events to imipenem/clavulanate and meropenem/clavulanate were reported in 5.4% and 6.5% of cases only.

Our study suggests that meropenem/clavulanate is more effective than imipenem/clavulanate in treating M/XDR-TB patients.

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Introduction

Over 480 000 new multidrug-resistant tuberculosis (MDR-TB) cases and 190 000 deaths were estimated to occur in 2014 by the World Health Organization (WHO), with only one MDR-TB case out of four being currently diagnosed and treated [1]. Half of the 123 000 cases of MDR-TB notified to the WHO in 2014 occurred in India, the Russian Federation and South Africa. Globally, 3.3% of new cases and 20% of previously treated cases of TB harbour MDR-TB strains of *Mycobacterium tuberculosis*. While overall 9.7% of the MDR-TB strains met the criteria defining extensively drug-resistant (XDR)-TB (*e.g.* resistance to at least one fluoroquinolone and a second-line injectable drug), this proportion was much higher in some of the former Soviet Union countries (Belarus 29%, Latvia 15% and Georgia 15%) [1, 2].

Recent evidence shows that treating MDR- and XDR-TB patients with the drugs available today is long, expensive, complicated and associated with frequent adverse events [3–8].

Presently a stepwise approach in the use of second-line anti-TB drugs (which are classified into five groups) is recommended by WHO [7, 9].

The main difficulty faced by clinicians treating MDR- and XDR-TB cases is to identify at least four active drugs which are necessary to design an effective multidrug regimen as per the WHO guidelines [3, 4, 7, 10, 11]. New drugs, such as delamanid, [12–14] and bedaquiline [15–20], and a few repurposed drugs (presently included in WHO Group 5, *i.e.* drugs with unknown/limited evidence on efficacy and/or tolerability) are presently attracting scientific interest [7, 21], among them linezolid [10, 22–28] and carbapenems [29–34]. The carbapenem group of drugs, which includes meropenem, imipenem and ertapenem, are currently used to treat MDR- and XDR-TB cases, although the evidence available on their efficacy, safety and tolerability is extremely limited [29–34].

The effectiveness of β-lactam antibiotics is unfortunately limited, as *M. tuberculosis* is protected through its potent β-lactamase, encoded by the *blaC* gene [35, 36]. Recent studies indicate that clavulanate (a β-lactamase inhibitor) can inhibit the activity of *blaC*-coded products *in vitro* [36]. Meropenem, offering a limited substrate to hydrolysis, has shown high bactericidal *in vitro* activity in association to clavulanate against *M. tuberculosis* (susceptible, MDR- and XDR-TB strains) as well as the *in vivo* ability to sterilise cultures within 2 weeks [37, 38]. Moreover, a study suggested synergy with amoxicillin and meropenem [39]. This has been confirmed in a murine model [40]. Its effectiveness, initially suggested in two case reports of 10 cases or less [30, 41], was then confirmed by two case–control studies. The first, with a limited sample size (37 patients at a single centre), suggested the drug was effective (offering up to

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20–30% sterilising power) and well tolerated [29]. The second, more recent study, was conducted by the International Carbapenems Study Group (ICSG, formerly the European Carbapenems Study Group) in 17 centres and six countries in Europe and Latin America with over 90 cases. It confirmed that meropenem/clavulanate is safe and that the activity of the drug combination is promising, as nondifferent (noninferior) sputum smear conversion, culture conversion and treatment success rates between cases and controls have been identified despite controls having a much less severe resistance pattern than meropenem/clavulanate-treated cases [42].

Evidence on imipenem/clavulanate is even more limited, consisting of a series of 10 patients and one case report [33, 34].

Recently, the TB reference centres belonging to the ICSG [31, 42] conducted a large observational study evaluating the therapeutic contribution of imipenem/clavulanate added to a background regimen (as per the WHO guidelines) when treating MDR- and XDR-TB cases.

The aim of the present study was to compare the effectiveness, safety and tolerability profile of meropenem/clavulanate and imipenem/clavulanate in a large observational cohort of MDR-TB patients.

Material and methods

The methodological characteristics were previously described [42]. MDR-TB reference centres located in European and Southern American countries recruited culture-confirmed MDR-TB patients aged ⩾15 years. An MDR-TB case was defined as an individual with TB caused by *M. tuberculosis* strains phenotypically resistant to at least isoniazid and rifampicin. Patients were consecutively selected on the basis of their exposure to meropenem/clavulanate and imipenem/clavulanate during their intensive and/or continuation phase.

An individualised TB regimen was administered following the results of the drug-susceptibility test (DST) carried out by externally quality-assured laboratories [11]. The attending physician prescribed anti-TB drugs without any compelling criteria of experimental protocols and, consequently, blinding or randomised methods were not followed. Meropenem/clavulanate was administered at a daily dosage of meropenem 1 g three times daily intravenously plus amoxicillin/clavulanic acid 1.2 g three times daily. The only exception was represented by the Belgium centre where meropenem was prescribed at a daily dosage of 2 g three times daily (17/180, 9.4%). Imipenem/clavulanate was administered at a dose of 500 mg imipenem four times daily plus amoxicillin/clavulanic acid as above.

Standardised *ad hoc* E-forms were 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 meropenem/clavulanate and imipenem/clavulanate, 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.

Qualitative and quantitative variables were summarised with percentages and mean±SD or median (interquartile range (IQR)) depending on their normality. The Chi-squared or Fisher's exact and the Mann–Whitney test were adopted to compare qualitative and quantitative variables, respectively. Differences in terms of sputum smear and culture conversions between imipenem/clavulanate and meropenem/clavulanate groups were assessed with a survival analysis and a log-rank test. A p-value <0.05 (two-tailed) was considered statistically significant. Statistical computations were performed with Stata 13.0 (StataCorp, College Station, TX, USA).

Ethical approval for the collection and analysis of anonymous and retrospective data and for the compassionate use of the drugs was obtained by the institutional review boards of the participating institutions as per legislation in force in the different ICSG countries and at the coordinating centre.

Results

180 MDR-TB patients were selected for the analysis: 96 (53.3%) exposed to meropenem/clavulanate and 84 (46.7%) exposed to imipenem/clavulanate (table 1).

The prevalent sex of the cohort was male (105, 58.3%) and the median (IQR) age was 35 (26–45) years (table 1).

Migrants coming from high TB prevalence countries accounted for 100 (55.6%) patients, whereas only a low proportion (5.8%) were HIV-infected. A higher proportion of migrants (76.0% *versus* 32.1%,

TABLE 1 Demographic, epidemiological and clinical characteristics of multidrug- and extensively drug-resistant tuberculosis (MDR- and XDR-TB) patients treated with meropenem/clavulanate (MC)- versus imipenem/clavulanate (IC)-containing regimens

	Total	MC-containing regimen	IC-containing regimen	p-value
Admission year				<0.0001
2005	2/180 (1.1)	0/96 (0.0)	2/84 (2.4)	
2006	3/180 (1.7)	0/96 (0.0)	3/84 (3.6)	
2007	6/180 (3.3)	0/96 (0.0)	6/84 (7.1)	
2008	9/180 (5.0)	2/96 (2.1)	7/84 (8.3)	
2009	11/180 (6.1)	7/96 (7.3)	4/84 (4.8)	
2010	16/180 (8.9)	15/96 (15.6)	1/84 (1.2)	
2011	27/180 (15.0)	26/96 (27.1)	1/84 (1.2)	
2012	20/180 (11.1)	9/96 (9.4)	11/84 (13.1)	
2013	34/180 (18.9)	6/96 (6.3)	28/84 (33.3)	
2014	36/180 (20.0)	25/96 (26.0)	11/84 (13.1)	
2015	16/180 (8.9)	6/96 (6.3)	10/84 (11.9)	
Age at admission years	35 (26–45)	34 (26–43)	36 (27–46)	0.37
Male	105/180 (58.3)	54/96 (56.3)	51/84 (60.7)	0.54
Country of birth				<0.0001
Africa	7/180 (3.9)	5/96 (5.2)	2/84 (2.4)	
Asia	6/180 (3.3)	3/96 (3.1)	3/84 (3.6)	
Europe	110/180 (61.1)	72/96 (75.0)	38/84 (45.2)	
Other	57/180 (31.7)	16/96 (16.7)	41/84 (48.8)	
Migrant	100/180 (55.6)	73/96 (76.0)	27/84 (32.1)	<0.0001
HIV test offered	172/178 (96.6)	88/94 (93.6)	84/84 (100.0)	0.03
HIV-infected	10/173 (5.8)	8/89 (9.0)	2/84 (2.4)	0.10
Exposure to antiretroviral therapy	8/10 (80.0)	6/8 (75.0)	2/2 (100.0)	0.15
Previous exposure to anti-TB therapy	143/179 (79.9)	66/95 (69.5)	77/84 (91.7)	<0.0001
Times treated >1 month	2 (1–3)	2 (1–4)	2 (1–3)	0.98
Surgical treatment	32/176 (18.2)	14/92 (15.2)	18/84 (21.4)	0.29
Prior treatment outcome				0.006
Failed	117/140 (83.6)	49/62 (79.0)	68/78 (87.2)	
Default	11/140 (7.9)	5/62 (8.1)	6/78 (7.7)	
Completed	3/140 (2.1)	2/62 (3.2)	1/78 (1.3)	
Cured	5/140 (3.6)	5/62 (8.1)	0/78 (0.0)	
Transferred out	0/140 (0.0)	0/62 (0.0)	0/78 (0.0)	
Relapse	1/140 (0.7)	1/62 (1.6)	0/78 (0.0)	
Unknown	2/140 (1.4)	0/62 (0.0)	2/78 (2.6)	
Form				<0.0001
New	40/179 (22.4)	32/96 (23.0)	8/83 (9.6)	
Relapse	18/179 (10.1)	13/96 (13.5)	5/83 (6.0)	
Chronic	16/179 (8.9)	15/96 (15.6)	1/83 (1.2)	
Failure	104/179 (58.1)	36/96 (37.5)	68/83 (81.9)	
Unknown	1/179 (0.6)	0/96 (0.0)	1/83 (1.2)	
Pulmonary TB	176/179 (98.3)	93/96 (96.9)	83/83 (100.0)	0.25
Extrapulmonary TB	18/179 (10.1)	14/96 (14.6)	4/83 (4.8)	0.04
Radiological findings				0.01
Cavitary lesions	44/176 (25.0)	16/93 (17.2)	28/83 (33.7)	
Bilateral pulmonary involvement with cavitary lesions	95/176 (54.0)	50/93 (53.8)	45/83 (54.2)	
Bilateral pulmonary involvement	22/176 (12.5)	16/93 (17.2)	6/83 (7.2)	
Noncavitary nonbilateral pulmonary involvement	15/176 (8.5)	11/93 (11.8)	4/83 (4.8)	
Sputum smear-positive	161/180 (89.4)	85/96 (88.5)	76/84 (90.5)	0.67
Sputum culture-positive	174/178 (97.8)	96/96 (100.0)	78/82 (95.1)	0.04
Drug resistance				
Streptomycin	141/155 (91.0)	76/80 (95.0)	65/75 (86.7)	0.09
Ethambutol	140/175 (80.0)	80/95 (84.2)	60/80 (75.0)	0.13
Pyrazinamide	122/159 (76.7)	84/94 (89.4)	38/65 (58.5)	<0.0001
Fluoroquinolone	110/175 (62.9)	46/94 (48.9)	64/81 (79.0)	<0.0001
Ethionamide	111/155 (71.6)	63/86 (73.3)	48/69 (69.6)	0.61
Cycloserine	42/143 (29.4)	15/75 (20.0)	27/68 (39.7)	0.01
Amikacin	67/136 (49.3)	40/82 (48.8)	27/54 (50.0)	0.89
4-Aminosalicylic acid	43/106 (40.6)	23/47 (48.9)	20/59 (33.9)	0.12
Capreomycin	77/142 (54.2)	38/81 (46.9)	39/61 (63.9)	0.04

Continued

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TABLE 1 Continued

	Total	MC-containing regimen	IC-containing regimen	p-value
Kanamicin	84/137 (61.3)	37/75 (49.3)	47/62 (75.8)	0.002
Linezolid	5/83 (6.0)	4/75 (5.3)	1/8 (12.5)	0.41
Rifabutin	37/45 (82.2)	25/26 (96.2)	12/19 (63.2)	0.006
Other	10/18 (55.6)	6/11 (54.6)	4/7 (57.1)	1.00
Antibiotic resistances	8 (6–9)	8 (6–9)	8 (7–8)	0.34
Length of hospital stay days	129 (68–206)	101 (61–172)	164 (110–247)	0.0001
Treatment after MDR-TB diagnosis months	18 (12–24)	18 (18–22)	18 (9–24)	0.24
XDR	104/180 (57.8)	47/96 (49.0)	57/84 (67.9)	0.01
Moxifloxacin	145/179 (81.0)	77/95 (81.1)	68/84 (81.0)	0.99
Levofloxacin	20/180 (11.1)	9/96 (9.4)	11/84 (13.1)	0.43
Linezolid	97/166 (58.4)	50/90 (55.6)	47/76 (61.8)	0.41
Delamanid	1/175 (0.6)	1/95 (1.1)	0/80 (0.0)	1.00
Bedaquiline	16/176 (9.1)	9/95 (9.5)	7/81 (8.6)	0.85

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. Denominators (N) were different among the selected variables because of missing data.

p<0.0001) and of patients born in Europe (75.0% *versus* 45.2%, p<0.0001) was observed in the meropenem/clavulanate-treated group (table 1).

Pulmonary TB was diagnosed in 176 out of 179 (98.3%) cases. The proportion of sputum smear- and culture-positive cases was 89.4% and 97.8%, respectively (table 2).

More than half were affected by XDR-TB (57.8%; 67.9% and 49.0% in the imipenem/clavulanate and meropenem/clavulanate group, respectively, p=0.01), but the median number of drug resistances was similar (8 *versus* 8 in the meropenem/clavulanate and imipenem/clavulanate group, respectively, p=0.34) (table 2).

Over three-quarters of cases were previously treated for drug-susceptible or -resistant TB; however, patients exposed to imipenem/clavulanate-containing regimens had been treated more frequently for a previous TB diagnosis (91.7% *versus* 69.5%, p<0.0001). However, the median (IQR) number of previous anti-TB treatments was similar in the meropenem/clavulanate- and imipenem/clavulanate-treated groups (2 (1–4) *versus* 2 (1–3)) (table 1).

The prevalence of resistance to any fluoroquinolone was significantly higher among the imipenem/clavulanate-treated cases (79.0% *versus* 48.9%, p<0.0001); moreover, a higher prevalence of resistance to capreomycin (63.9% *versus* 46.9%, p=0.04) and kanamycin (75.8% *versus* 49.3%, p<0.002) was observed in comparison with the meropenem/clavulanate-treated group. The prevalence of resistance to amikacin was similar in both groups (50.0% *versus* 48.8%, respectively) (table 1).

Patients were treated with meropenem/clavulanate- and imipenem/clavulanate-containing regimens for a median (IQR) of 85 (49–156) and 187 (60–428) days (table 3). Adjuvant surgical therapy was performed in 18.2% of the cases.

Sputum smear and culture conversion rates were significantly higher in those exposed to meropenem/clavulanate (94.8% and 94.8%, respectively) than in those exposed to imipenem/clavulanate (79.7% and 71.9%, p=0.02 and p<0.0001, respectively). Similar proportional differences for the culture conversion were achieved when subgroup analyses were performed according to MDR/XDR-TB status and the median number of drug resistances (*i.e.* ⩾8 drug resistances) (table 2).

The time to culture conversion was shorter in the meropenem/clavulanate- than in the imipenem/clavulanate-treated group (44 (28–75) *versus* 60 (30–90) days, p=0.05) (table 2 and figure 1).

Overall, cases treated with meropenem/clavulanate achieved higher statistically significant success rates than those treated with imipenem/clavulanate (77.5% *versus* 59.7%, p=0.03) (table 2).

Adverse events were reported only in six (6.5%) meropenem/clavulanate- and three (5.4%) imipenem/clavulanate-treated patients (p=1.0) (table 3).

Discussion

The aim of the present study was to retrospectively compare the effectiveness, safety and tolerability profile of meropenem/clavulanate and imipenem/clavulanate in a large cohort of XDR- and MDR-TB patients.

TABLE 2 Treatment outcomes of multidrug- and extensively drug-resistant tuberculosis (MDR- and XDR-TB) patients treated with meropenem/clavulanate (MC)-*versus* imipenem/clavulanate (IC)-containing regimens

	Total	MC-containing regimen	IC-containing regimen	p-value
Sputum smear conversion	106/122 (86.9)	55/58 (94.8)	51/64 (79.7)	0.02
At 30 days of treatment	89/178 (50.0)	37/94 (39.4)	52/84 (61.9)	0.003
At 60 days of treatment	116/170 (68.2)	59/91 (64.8)	57/79 (72.2)	0.31
At 90 days of treatment	132/165 (80.0)	76/90 (84.4)	56/75 (74.7)	0.12
In patients with <8 resistances	48/51 (94.1)	24/24 (100.0)	24/27 (88.9)	0.24
In patients with ⩾8 resistances	58/71 (81.7)	31/34 (91.2)	27/37 (73.0)	0.07
In MDR-TB patients	49/53 (92.5)	33/33 (100.0)	16/20 (80.0)	0.02
In XDR-TB patients	57/69 (82.6)	22/25 (88.0)	35/44 (79.6)	0.52
Sputum culture conversion	101/122 (82.8)	55/58 (94.8)	46/64 (71.9)	<0.0001
At 30 days of treatment	56/166 (33.7)	30/94 (31.9)	26/72 (36.1)	0.57
At 60 days of treatment	105/169 (62.1)	59/93 (63.4)	46/76 (60.5)	0.70
At 90 days of treatment	123/165 (74.6)	72/91 (79.1)	51/74 (68.9)	0.14
In patients with <8 resistances	46/51 (90.2)	24/24 (100.0)	22/27 (81.5)	0.05
In patients with ⩾8 resistances	55/71 (77.5)	31/34 (91.2)	24/37 (64.9)	0.01
In MDR-TB patients	46/53 (86.8)	33/33 (100.0)	13/20 (65.0)	0.001
In XDR-TB patients	55/59 (79.7)	22/25 (88.0)	33/44 (75.0)	0.23
Time from start of anti-TB therapy to sputum smear conversion days	36 (30–60)	45 (28–68)	30 (30–60)	0.71
Time from start of anti-TB therapy to culture conversion days	52 (30–90)	44 (28–75)	60 (30–90)	0.05
Treatment outcome				<0.0001
Cured	52/180 (28.9)	22/96 (22.9)	30/84 (35.7)	
Treatment completed	37/180 (20.6)	33/96 (34.4)	4/84 (4.8)	
Still on treatment	47/180 (26.1)	24/96 (25.0)	23/84 (27.4)	
Died	25/180 (13.9)	10/96 (10.4)	15/84 (17.9)	
Default	11/180 (6.1)	5/96 (5.2)	6/84 (7.1)	
Failure and died	6/180 (3.3)	1/96 (1.0)	5/84 (6.0)	
Transferred out	2/180 (1.1)	1/96 (1.0)	1/84 (1.2)	
Treatment success[#]	89/128 (69.5)	55/71 (77.5)	34/57 (59.7)	0.03
In patients with <8 resistances	41/60 (68.3)	24/34 (70.6)	17/26 (65.4)	0.67
In patients with ⩾8 resistances	48/68 (70.6)	31/37 (83.8)	17/31 (54.8)	0.007
In MDR-TB patients	45/55 (81.8)	33/37 (89.2)	12/18 (66.7)	0.06
In XDR-TB patients	44/73 (60.3)	22/34 (64.7)	22/39 (56.4)	0.47

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. Denominators (N) were different among the selected variables because of missing data. [#]: denominator includes patients who were successfully treated, died, defaulted or failed.

The results of our study demonstrated that, overall, the meropenem/clavulanate-containing regimens achieved better results than imipenem/clavulanate-containing regimens. In particular, 1) culture conversion rates were statistically higher (both in the whole cohort and in the XDR/MDR-TB subgroups), 2) the time to culture conversion was shorter and 3) the treatment success rates were significantly higher (both in the overall cohort and in the patients with ⩾8 resistances) in the meropenem/clavulanate- than in the imipenem/clavulanate-containing group.

Furthermore, the study demonstrated that both drugs were well tolerated and adverse events were rare (only 6.5% in the meropenem/clavulanate- and 5.4% in the imipenem/clavulanate-containing regimens).

This is, to the best of our knowledge, the first study in the scientific literature describing the efficacy, safety and tolerability of imipenem/clavulanate-containing regimens, and comparing the clinical performances of two of the core carbapenems (*i.e.* imipenem/clavulanate and meropenem/clavulanate) in a large cohort of XDR- and MDR-TB patients.

In a previous study by the same group [42] the performance of the meropenem/clavulanate-containing regimens was compared with a control group. The study results suggested that meropenem/clavulanate is active, as meropenem/clavulanate-containing regimens achieved nondifferent results than the controls in spite of a much more severe resistance profile.

Although it is always difficult to attribute the causality of the results observed to meropenem/clavulanate and imipenem/clavulanate, we can underline that imipenem/clavulanate-containing regimens achieved bacteriological and treatment success rates comparable to those of other cohorts of MDR-TB cases [3, 4],

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TABLE 3 Safety of meropenem/clavulanate (MC)-*versus* imipenem/clavulanate (IC)-containing regimens

	Total	MC-containing regimen	IC-containing regimen	p-value
Interruption of linezolid	39/139 (28.1)	23/90 (25.6)	16/49 (32.7)	0.37
Interruption of linezolid due to adverse events	25/131 (19.1)	14/82 (17.1)	11/49 (22.5)	0.45
Adverse events presumably due to linezolid	48/136 (35.3)	37/89 (41.6)	11/47 (23.4)	0.04
Anaemia	29/141 (20.6)	20/92 (21.7)	9/49 (18.4)	0.64
Leukopenia	6/140 (4.3)	4/91 (53.9)	2/49 (4.1)	1.00
Thrombocytopenia	13/140 (9.3)	11/91 (12.1)	2/49 (4.1)	0.14
Peripheral neuropathy	35 /139 (25.2)	29/91 (31.9)	6/48 (12.5)	0.01
Gastrointestinal disorder	17/140 (12.1)	8/91 (8.8)	9/49 (18.4)	0.10
Reversible adverse events	64/91 (70.3)	44/63 (69.8)	20/28 (71.4)	0.88
Linezolid restarted if interrupted	21/85 (24.7)	19/43 (44.2)	2/42 (4.8)	<0.0001
Total linezolid exposure	239 (92–630)	173 (78–540)	288 (143–670)	0.03
Interruption of MC/IC	67/150 (44.7)	52/94 (55.3)	15/56 (26.8)	0.001
Interruption of MC/IC due to adverse events	12/149 (8.1)	8/94 (8.5)	4/55 (7.3)	1.00
Adverse events presumably due to MC/IC	9/149 (6.0)	6/93 (6.5)	3/56 (5.4)	1.00
MC/IC restarted if interrupted	4/12 (33.3)	4/8 (50.0)	0/4 (0.0)	0.08
Total MC/IC exposure	104 (109–298)	85 (49–156)	187 (60–428)	0.009

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. Denominators (N) were different among the selected variables because of missing data.

while meropenem/clavulanate-containing-regimens had promising results (94.8% sputum smear and culture conversion, and 77.5% treatment success). In order to remove the "background noise" caused by the observational design, the study findings need to be confirmed by randomised controlled clinical trials.

Based on the molecular mechanism of action, imipenem is more active than meropenem [43]. However, this does not necessarily translate into better clinical results. The pharmacokinetic/pharmacodynamic index, as well as the free drug concentration exceeding the minimal inhibitory concentration, could have favoured the group with the meropenem/clavulanate-containing regimens. In addition, synergy with the other anti-TB drugs could have been different for the carbapenems prescribed in this study.

As meropenem/clavulanate appears to be more active against *M. tuberculosis* than imipenem/clavulanate, the former should be favoured in the treatment of MDR-TB. Should meropenem/clavulanate be unavailable, higher doses of imipenem/clavulanate as per *Pseudomonas* infection could probably be administered (*i.e.* 1 g four times daily) given that the drug is well tolerated.

Among the strengths of the study we mention the large size of the imipenem/clavulanate and meropenem/clavulanate cohorts, and the detailed information collected from the participating centres in Europe and Latin America. The drug resistance patterns, number of previous anti-treatment cycles as well as most of the demographic, epidemiological and clinical variables did not differ significantly in the meropenem/clavulanate and imipenem/clavulanate cohorts.

However, the observational and retrospective design of the study determines several interpretational limitations. In particular, we mention the missing pre-study definition of a sample size and the possibility

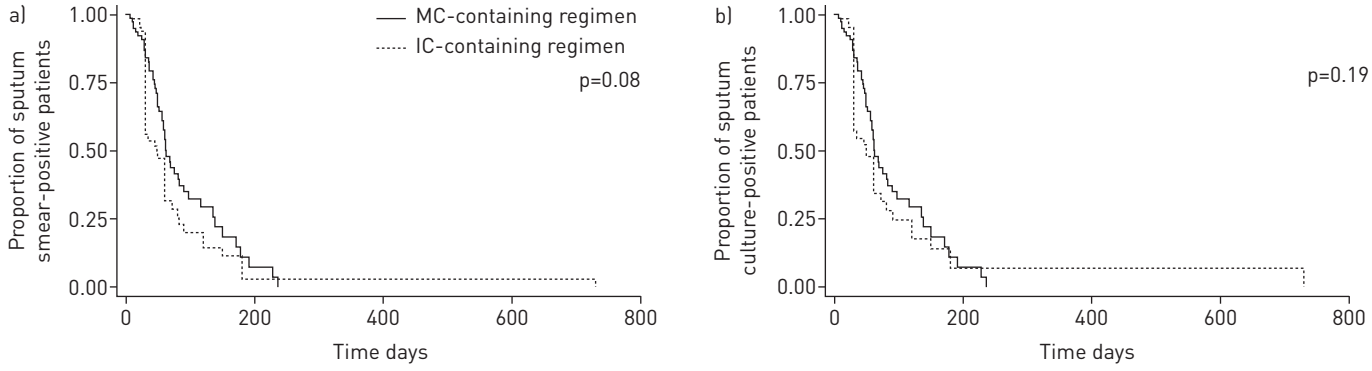

FIGURE 1 a) Sputum smear and b) culture conversion in multidrug- and extensively drug-resistant tuberculosis patients treated with meropenem/clavulanate (MC)-*versus* imipenem/clavulanate (IC)-containing regimens.

to randomise and ensure blindness, which could increase the probability of a selection bias. Furthermore, the latter methodological issue is clearly highlighted by the higher prevalence of resistance to any fluoroquinolone in the imipenem/clavulanate cohort, as well as a higher prevalence of resistance to two out of three second-line anti-TB injectables (kanamycin and capreomycin). Furthermore, exposure to previous anti-TB treatment and the proportion of previous treatment failures was higher in the imipenem/clavulanate cohort.

As meropenem/clavulanate seems to perform better, but imipenem/clavulanate is cheaper and more widely available, economic analyses will be important to finally assess the future role of these compounds. However, the new information provided by this observational study allows clinicians managing difficult-to-treat TB cases to know how to use carbapenems and other repurposed drugs in case the minimum number of active drugs necessary to design an effective regimen is lacking [3, 4, 9, 44–47].

In this context, other second-line drugs such as fluoroquinolones or clofazimine might contribute to cardiologic or other adverse events [48]. Unlike all of the above, the repurposed carbapenems are frequently well tolerated and offer few drug–drug interactions, and should the need arise can replace other TB drugs based on their advantageous safety and tolerability profile. The authors believe that the benefits of β-lactam use for the treatment of TB outweighs the risks of further antimicrobial resistance.

Although new compounds will hopefully appear soon to support the move towards TB elimination [49], the carbapenems are confirmed to have a particular role. The authors would recommend the use of meropenem/clavulanate in the intensive phase of treatment, particularly to manage the most severe cases until bacteriological conversion has been achieved. If active drugs are lacking to design an effective regimen in the continuation phase, ertapenem/clavulanate or faropenem/clavulanate could potentially be considered in the continuation phase. Given the widespread use of amoxicillin/clavulanic acid in the community, DST for meropenem/clavulanate is recommended before using the drug in a regimen.

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