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Efficacy and safety of meropenem–clavulanate added to linezolid-containing regimens in the treatment of MDR-/XDR-TB

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ABSTRACT: Clinical experience on meropenem–clavulanate to treat tuberculosis (TB) is anecdotal (according to case reports on 10 patients). The aim of our case–control study was to evaluate the contribution of meropenem–clavulanate when added to linezolid-containing regimens in terms of efficacy and safety/tolerability in treating multidrug-resistant (MDR) and extensively drug-resistant (XDR) TB cases after 3 months of second-line treatment.

37 cases with MDR-/XDR-TB were prescribed meropenem–clavulanate (3 g daily dose) in addition to a linezolid-containing regimen (dosage range 300–1200 mg·day^{-1}), designed according to international guidelines, which was prescribed to 61 controls.

The clinical severity of cases was worse than that of controls (drug susceptibility profile, proportion of sputum-smear positive and of re-treatment cases). The group of cases yielded a higher proportion of sputum-smear converters (28 (87.5%) out of 32 *versus* nine (56.3%) out of 16; p=0.02) and culture converters (31 (83.8%) out of 37 *versus* 15 (62.5%) out of 24; p=0.06). Excluding XDR-TB patients (11 (11.2%) out of 98), cases scored a significantly higher proportion of culture converters than controls (p=0.03). One case had to withdraw from meropenem–clavulanate due to increased transaminase levels.

The results of our study provide: 1) preliminary evidence on effectiveness and safety/tolerability of meropenem–clavulanate; 2) reference to design further trials; and 3) a guide to clinicians for its rationale use within salvage/compassionate regimens.

KEYWORDS: Efficacy, linezolid-containing regimens, meropenem–clavulanate, multidrug-resistant tuberculosis, safety, tolerability

According to the World Health Organization (WHO), an estimated 650 000 prevalent cases of multidrug-resistant tuberculosis (MDR-TB) occurred globally in 2010 [1–4]. The scale of the problem is alarming, as 12 countries have reported nationwide or sub-national proportions of MDR-TB of ⩾6% among new tuberculosis (TB) cases and five of these countries also reported MDR-TB proportions of ⩾50% among previously treated cases [1–5]. In Minsk, Belarus, over 50% of TB cases are presently affected by MDR-TB [6].

WHO estimated 290 000 new cases of MDR-TB among notified cases of pulmonary TB in 2010, of whom only around 50 000 were reported to have been enrolled on treatment [1–3, 5]. Overall, 5.4% of MDR-TB cases were found to be affected by extensively drug-resistant (XDR)-TB strains of *Mycobacterium tuberculosis* [1–3, 5]. Furthermore, new strains that are resistant to all drugs tested have been described in Italy, Iran and India [7–9], and the international community is still discussing whether the proposed acronym of TDR (totally drug resistant)-TB is adequate to describe the patterns of drug resistance beyond XDR-TB [10].

The difficulty in identifying at least four active drugs, suitable to be included in a multidrug regimen effective against these complicated forms of TB according to WHO recommendations, makes the need for new antibiotics extremely urgent [11]. Preliminary evidence for three new drugs, presently in the development pipeline (delamanid, bedaquiline and PA-824), has been published recently [1, 12, 13].

Delamanid, in combination with a background regimen developed according to the WHO guidelines, is associated with an increase in sputum-culture conversion at 2 months in patients with

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MDR-TB [11, 12]. A recent multiple-agent combination study assessed that the 14-day early bactericidal activity of PA-824+moxifloxacin+pyrazinamide results were significantly higher than those of bedaquiline, bedaquiline+pyrazinamide, PA-824+pyrazinamide and bedaquiline+PA-824, and comparable to those of the standard treatment regimen of isoniazid, rifampicin and pyrazinamide with streptomycin or ethambutol [13].

In parallel with further research on the best way to combine these new drugs into new regimens, additional evidence is necessary to confirm the clinical usefulness of existing drugs presently used ''off label'' to manage difficult-to-treat MDR- and XDR-TB cases. Mounting evidence indicates that the efficacy of linezolid is limited by its toxicity [14, 15].

The association of a β-lactam antibiotic with a β-lactamase inhibitor has been explored recently with apparently sub-optimal results, as *M. tuberculosis* is protected from β-lactams antibiotics through its potent β-lactamase encoded by a gene located in the chromosome and called BlaC [16, 17]. Fortunately, clavulanate (a β-lactamase inhibitor) has demonstrated *in vitro* the capacity to inhibit the activity of BlaC-coded products [18]. Meropenem, a carbapenem offering a limited substrate to hydrolysis, has demonstrated high bactericidal *in vitro* activity when combined to clavulanate against susceptible MDR- and XDR-TB strains of *M. tuberculosis* and the capacity to sterilise cultures *in vivo* within 2 weeks [19, 20].

At present the clinical experience on meropenem–clavulanate is anecdotal and limited to case reports of no more than 10 patients where the drug was prescribed for salvage purposes [16, 19]. Taking advantage of the existing collaboration and established research protocols, based on WHO guidelines, in TB reference centres in Sondalo, Italy, and in Haren, the Netherlands [11, 15], a study was conducted to evaluate the therapeutic contribution of meropenem–clavulanate when added to linezolid-containing regimens during hospital stay in terms of efficacy, as well as safety and tolerability profile in treating MDR- and XDR-TB cases after 3 months of therapy with second-line drugs.

MATERIAL AND METHODS

An observational case–control study was carried out in two centres that specialised in the management of complicated TB cases. Adult patients (*i.e.* aged $\geqslant$15 years) with culture-confirmed MDR-TB (*i.e.* TB caused by *M. tuberculosis* isolates resistant to at least isoniazid and rifampicin) were consecutively selected and enrolled in both centres.

Resistance to first- and second-line anti-TB drugs was assessed by the quality-assured laboratories located in both centres and confirmed by the WHO Supranational Reference Laboratories of Milan, Italy, and the National Tuberculosis Reference Laboratory, National Institute for Public Health and the Environment, Bilthoven, the Netherlands.

On the basis of the drug-susceptibility testing, anti-TB regimens were administered following the WHO recommendations [11]. Both centres pioneered the off-label use of linezolid between 2001 and 2004. Clinicians working in Sondalo started to prescribe meropenem–clavulanate in 2009.

Cases were individuals treated with an anti-TB meropenem–clavulanate-containing regimen, which also included linezolid in all but five patients. The cases were included in the Italian cohort, treated in Sondalo Hospital. The reasons for not prescribing linezolid were the: availability of four effective drugs (n=3); lack of drug-susceptibility testing on linezolid in the presence of four effective alternative drugs (n=1); and concurrent anaemia (n=1).

Controls were treated in Haren Hospital and were subjects whose linezolid-containing regimen did not include meropenem–clavulanate. During hospital admission, meropenem–clavulanate was prescribed intravenously at a dose of 1 g three times a day whereas linezolid was given at a dose ranging from 300 to 1200 mg per day after adjusting the dose based on blood levels. The ratio between cases and controls was 1:2. Drug prescription was not blinded or randomised, following only the drug-susceptibility testing results as per WHO guidelines [11].

Ethical approval for the collection and analysis of anonymous and retrospective data and for the compassionate use of the drugs was obtained by institutional review boards of the participating institutions as per legislation (formal approval not needed in the Netherlands).

Epidemiological, clinical and microbiological information was collected from clinical files on standardised *ad hoc* electronic forms. In particular, the following covariates were recorded: date of admission; date and place of birth; sex; residence and immigration from a high-burden TB country; HIV positivity; exposure to antiretroviral drugs; previous TB diagnoses; previous anti-TB treatments (*i.e.* exposure to anti-TB drugs for >1 month) and previous treatment outcomes; drug-susceptibility testing results, including susceptibility or resistance to the drugs defining XDR-TB (*i.e.* TB caused by *M. tuberculosis* strains resistant to isoniazid, rifampicin, any fluoroquinolones and at least one second-line injectable anti-TB drug (amikacin, capreomycin, kanamycin)); radiological findings; anti-TB regimen administered (including dosage and length of exposure); surgery; duration of exposure to linezolid and meropenem–clavulanate; adverse events potentially ascribed to the study drugs (*i.e.* linezolid and meropenem–clavulanate); management of adverse events; proportion of sputum-smear and -culture positivity at hospital admission and at 30, 60 and 90 days after the prescription of second-line anti-TB drugs; and time to sputum-smear and -culture conversion.

Qualitative and not normally distributed quantitative variables were statistically evaluated with the Chi-squared test and the Wilcoxon Mann–Whitney tests, respectively. Normality distribution of the continuous data was tested with the Shapiro–Wilk test. A p-value >0.05 was considered not statistically significant. All the statistical calculations were performed using the statistical software Stata 9.0 (StataCorp, College Station, TX, USA).

RESULTS

98 MDR-TB patients were enrolled in the study: 37 cases and 61 controls were treated with individualised anti-TB meropenem–clavulanate-containing and -sparing regimens (table 1). The former were managed in the Italian reference centre in Sondalo, and the latter in the Dutch reference centre in Haren.

TABLE 1 Epidemiological and clinical characteristics of 98 multidrug-resistant tuberculosis (TB) cases enrolled in two specialised clinical centres in Italy and the Netherlands

Variables	Total subjects	Italian cohort: cases[#]	Dutch cohort: controls[¶]	p-value
Males	58/98 (59.2)	25/37 (67.6)	33/61 (54.1)	0.19
Age at admission years	30 (24–38)	32 (26–41)	29 (24–35)	0.21
Country of birth				
Europe	48/98 (49)	29/37 (78.4)	21/61 (34.4)	<0.0001
Asia	19/98 (19.4)	2/37 (5.4)	15/61 (24.6)	0.02
Africa	26/98 (26.5)	5/37 (13.5)	21/61 (34.4)	0.02
Other geographical areas	5/98 (5.1)	1/37 (2.7)	4/61 (6.6)	0.40
Migrant	96/98 (98.0)	36/37 (97.3)	60/61 (98.4)	0.72
HIV-positive	8/88 (9.1)	4/37 (10.8)	4/51 (7.8)	0.63
Exposure to ART	6/8 (75)	3/4 (75)	3/4 (75)	
Previous exposure to anti-TB therapy >1 month	41/97 (42.3)	21/36 (58.3)	20/61 (32.8)	0.01
Treated with anti-TB drugs for >1 month	1 (1–2)	1 (0–2)	1 (1–1)	0.99
Sputum-smear positive	50/98 (51.0)	32/37 (86.5)	18/61 (29.5)	<0.0001
Pulmonary TB	89/98 (90.8)	34/37 (91.9)	55/61 (90.2)	0.77
Extrapulmonary TB	12/98 (12.2)	5/37 (13.5)	7/61 (11.5)	0.77
Radiological findings				
Cavitary lesions	17/89 (19.1)	8/34 (23.5)	9/55 (16.4)	0.41
Bilateral pulmonary involvement with cavitary lesions	29/89 (32.6)	11/34 (32.4)	18/55 (32.7)	0.98
Bilateral pulmonary involvement	13/89 (14.6)	6/34 (17.7)	7/55 (12.7)	0.52
Non-cavitary unilateral pulmonary involvement	30/89 (33.7)	9/34 (26.5)	21/55 (38.2)	0.26
XDR-TB	11/98 (11.2)	9/37 (24.3)	2/61 (3.3)	0.001
Resistance				
Ethambutol	66/97 (68.0)	29/37 (78.4)	37/60 (61.7)	0.09
Pyrazinamide	49/90 (54.4)	31/36 (86.1)	18/54 (33.3)	<0.0001
Fluoroquinolones	21/97 (21.7)	15/37 (40.5)	6/60 (10.0)	<0.0001
Ethionamide	33/96 (34.4)	24/36 (66.7)	9/60 (15.0)	<0.0001
Cycloserine	10/73 (13.7)	8/34 (23.5)	2/39 (5.1)	0.02
Amikacin	20/97 (20.6)	10/37 (27.0)	10/60 (16.7)	0.22
Capreomycin	18/61 (29.5)	12/37 (32.4)	6/24 (25.0)	0.53
Kanamycin	23/62 (37.1)	16/37 (43.2)	7/25 (28.0)	0.22
Surgical treatment	12/96 (12.5)	7/35 (20.0)	5/61 (8.2)	0.09
Length of hospital stay days	89.5 (61–153)	81 (60–112)	91 (75–197)	0.03
Exposure to linezolid days	61 (35–117)	79.0 (50.5–133.0)	59.0 (34.0–93.0)	0.08
Exposure to meropenem days		67.0 (46.0–85.0)		

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. For some entries, the total number of subjects may not be 98 due to missing/unavailable data. ART: anti-retroviral therapy; XDR: extensively drug-resistant. [#]: meropenem containing anti-TB regimen; [¶]: meropenem–clavulanate-sparing anti-TB regimen.

Almost 60% were male, with a median (interquartile range (IQR)) age of 30 (24–38) years. Most of them were migrants (96 (98.0%) out of 98), coming from Europe (48 (49%) out of 98), Africa (26 (26.5%) out of 98) and Asia (19 (19.4%) out of 98). The percentage of TB/HIV co-infected patients was <10% and 75% of them were treated with antiretroviral drugs.

No statistical differences between cases and controls regarding social and demographic variables were detected, except for the European origin, being significantly higher among cases treated with a meropenem–clavulanate-containing regimen (29 (78.4%) out of 37 *versus* 21 (34.4%) out of 61; p<0.0001).

The majority showed pulmonary TB disease (89 (90.8%) out of 98), with only 12% affected by an extrapulmonary TB. One-third presented bilateral pulmonary involvement with cavitary lesions, while one-third showed unilateral infiltrates. Half of the patients were sputum-smear positive at hospital admission, with a statistically significant higher prevalence among cases (32 (86.5%) out of 37 *versus* 18 (29.5%) out of 61; p <0.0001). Overall, almost 13% of the cases enrolled underwent surgical intervention. The proportion of patients who were prescribed previous anti-TB treatment was higher among the cases treated with meropenem–clavulanate (21 (58.3%) out of 36) than among the controls (20 (32.8%) out of 61).

Cases treated with a meropenem–clavulanate-containing regimen were infected by *M. tuberculosis* strains showing a worse drug-susceptibility profile, the proportion of XDR-TB cases was significantly higher (nine (24.3%) out of 37 *versus* two (3.3%) out of 61; p=0.001), as was the percentage of those harbouring *M. tuberculosis* strains resistant to pyrazinamide

(31 (86.1%) out of 36 *versus* 18 (33.3%) out of 54; p<0.0001), fluoroquinolones (15 (40.5%) out of 37 *versus* six (10%) out of 60; p<0.0001), ethionamide (24 (66.7%) out of 36 *versus* nine (15%) out of 69; p<0.0001) and cycloserine (eight (23.5%) out of 34 *versus* two (5.1%) out of 39; p=0.02).

In addition, cases were more likely to be previously treated (21 (58.3%) out of 36 *versus* 20 (32.8%) out of 61; p=0.01) and to be born in Eastern European countries (28 (75.7%) out of 37 *versus* 17 (27.9%) out of 61; p<0.0001).

Efficacy analysis

Patients were treated with a linezolid-containing regimen for a median (IQR) time of 61 (35–117) days. Individuals admitted to the Italian hospital (cases) were exposed to a meropenem–clavulanate-containing regimen for a median (IQR) period of 67.0 (46.0–85.0) days. Duration of linezolid and/or meropenem–clavulanate exposure was determined by several parameters, including clinical improvement, sputum-smear and/or -culture conversion and occurrence of life-threatening adverse events. No significant statistical differences were found in the median time to sputum-smear and -culture conversion between cases and controls (46 *versus* 52.5 days and 46 *versus* 42 days, respectively). After 90 days of treatment with second-line drugs the proportion of sputum-smear converters was significantly higher in the meropenem–clavulanate-treated patients (28 (87.5%) out of 32 *versus* nine (56.3%) out of 16; p=0.02), while the percentage of sputum-culture converters reached a borderline statistical significance (31 (83.8%) out of 37 *versus* 15 (62.5%) out of 24; p=0.06) (table 2).

Similar results were obtained after the exclusion of the five meropenem–clavulanate-treated patients not exposed to linezolid (table 3).

A sub-analysis, which excluded the XDR-TB patients (11 (11.2%) out of 98), to partly correct the worse drug-susceptibility testing pattern of cases when compared to controls, showed that a significantly higher percentage of cases exposed to meropenem–clavulanate achieved sputum-culture conversion (p=0.03) (fig. 1).

Safety and tolerability analysis

15 (40.5%) out of 37 cases and seven (11.5%) out of 61 controls experienced adverse reactions following drug prescription (p=0.001). The higher proportion of adverse events among cases was almost entirely related to linezolid (12 (37.5%) out of 32 *versus* seven (11.5%) out of 61; p-value: 0.003) and thought to be the consequence of exposure to a superior dosage (>600 mg·day^{-1}) of linezolid (21 (65.6%) out of 32 *versus* 18 (29.5%) out of 61; p=0.001).

13% (12 out of 93) of the selected patients managed in both centres experienced adverse events potentially caused by linezolid which required interruption of the drug (table 4).

Those treated with a daily linezolid dosage of ⩽600 mg interrupted their regimen less frequently due to adverse effects attributable to linezolid when compared with patients exposed to a daily dosage of >600 mg (three (5.6%) out of 54 *versus* nine (23.1%) out of 39; p=0.01). No statistical differences between patients treated with <600 mg and >600 mg were found with regard to anaemia, leukopenia, peripheral neuropathy and gastrointestinal disorders.

Only five (13.5%) patients out of 37 experienced adverse events potentially attributed to meropenem–clavulanate. In all cases, diarrhoea was present and did not require withdrawal of the drug. In addition, two out of the five cases experienced transient increase of liver function tests. Meropenem–clavulanate was stopped and re-started after 1 week. While in one case meropenem–clavulanate was continued without problems, the other case saw a renewed increase in transaminase levels; the drug was stopped and transaminases normalised rapidly.

DISCUSSION

The aim of our study was to assess the therapeutic contribution of meropenem–clavulanate when added to linezolid-containing regimens during hospital stay in terms of efficacy, safety and

TABLE 2 Treatment outcomes of 98 multidrug-resistant tuberculosis (TB) cases enrolled in two specialised clinical centres in Italy and the Netherlands after 30, 60 and 90 days of treatment

Variables	Total	Italian cohort: cases#	Dutch cohort: controls¶	p-value
Sputum-smear conversion				
At 30 days of treatment	16/50 (32.0)	7/32 (21.9)	9/18 (50.0)	0.04
At 60 days of treatment	27/48 (56.3)	20/32 (62.5)	7/16 (43.8)	0.22
At 90 days of treatment	37/48 (77.1)	28/32 (87.5)	9/16 (56.3)	0.02
Sputum-culture conversion				
At 30 days of treatment	24/66 (36.4)	12/37 (32.4)	12/29 (41.4)	0.45
At 60 days of treatment	37/62 (59.7)	24/37 (64.9)	13/25 (52.0)	0.31
At 90 days of treatment	46/61 (75.4)	31/37 (83.8)	15/24 (62.5)	0.06
Days from start of anti-TB therapy to sputum smear conversion	51 (28.0–75.0)	52.5 (38.5–65.0)	46.0 (6.0–157.0)	0.85
Days from start of anti-TB therapy to culture conversion	42 (16.5–82.0)	42.0 (28.0–65.0)	46.0 (13.0–96.0)	0.96

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. #: meropenem–clavulanate containing anti-TB regimen; ¶: meropenem–clavulanate-sparing anti-TB regimen.

TABLE 3 Treatment outcomes of multidrug-resistant tuberculosis (TB) patients, excluding those not treated with linezolid, enrolled in two specialised clinical centres in Italy and the Netherlands after 30, 60 and 90 days of treatment

Variables	Italian cohort: cases[#]	Dutch cohort: controls[¶]	p-value
Sputum-smear conversion			
At 30 days of treatment	5/28 (17.9)	9/18 (50.0)	0.02
At 60 days of treatment	17/28 (60.7)	7/16 (43.8)	0.28
At 90 days of treatment	24/28 (85.7)	9/16 (56.3)	0.03
Sputum-culture conversion			
At 30 days of treatment	9/32 (28.1)	12/29 (41.4)	0.28
At 60 days of treatment	20/32 (62.5)	13/25 (52.0)	0.43
At 90 days of treatment	26/32 (81.3)	15/24 (62.5)	0.12
Days from start of anti-TB therapy to sputum smear conversion	52.5 (42.0–65.0)	46.0 (6.0–157.0)	0.80
Days from start of anti-TB therapy to culture conversion	42.0 (28.0–77.0)	46.0 (13.0–96.0)	0.79

Data are presented as n/N (%) or median (interquartile range), unless otherwise stated. [#]: meropenem–clavulanate containing anti-TB regimen; [¶]: meropenem–clavulanate-sparing anti-TB regimen.

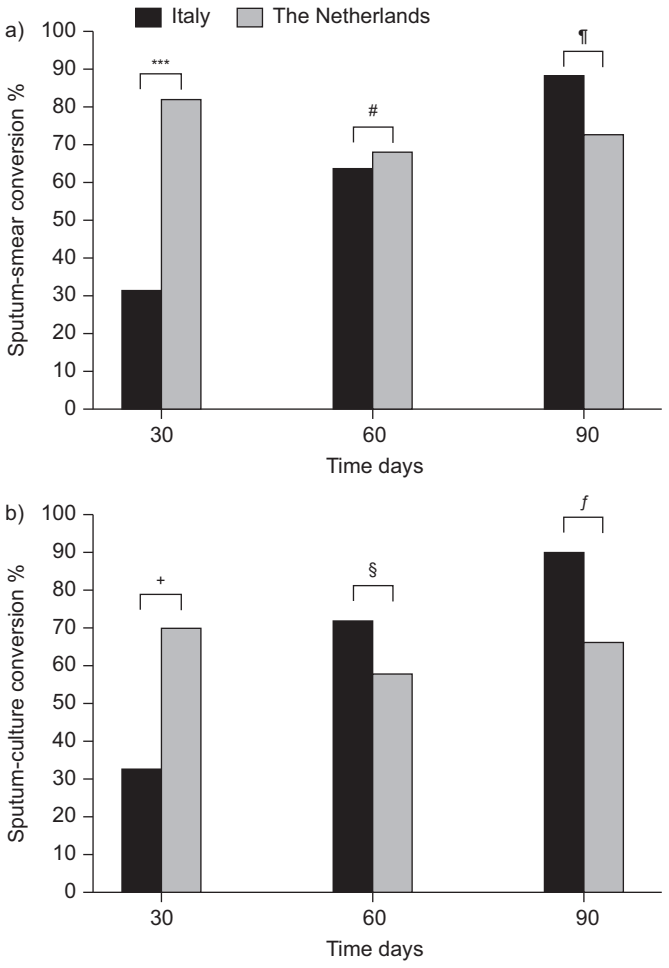

FIGURE 1. a) Sputum-smear conversion and b) culture conversion at 90 days of multidrug-resistant tuberculosis cases, excluding the extensively drug-resistant tuberculosis patients, enrolled in two specialised clinical centres in Italy and the Netherlands. ***: $p<0.001$. [#]: $p=0.71$; [¶]: $p=0.10$; [+]: $p=0.001$; [§]: $p=0.25$; [f]: $p=0.03$.

tolerability in treating MDR- and XDR-TB cases after 3 months of treatment with second-line drugs. To our knowledge, this is the first large study evaluating the added value of meropenem–clavulanate in managing difficult-to-treat MDR-/XDR-TB cases.

In spite of the worse initial clinical severity of cases (in terms of proportion of re-treatment cases, XDR-TB cases, proportion of sputum-smear positive cases and prevalence of resistance to pyrazinamide, fluoroquinolones, ethionamide and cycloserine), meropenem–clavulanate significantly increased the proportion of sputum-smear conversion in the overall sample, including XDR-TB patients, and sputum-culture conversion among MDR-TB cases after 90 days of treatment with second-line drugs.

Furthermore, although the clinical pattern of cases was significantly worse than that of controls (as previously mentioned), the added value of meropenem–clavulanate has already been seen after 60 days of treatment with second-line drugs (with differences not yet significant); although no difference was found in the time to microbiological conversion.

While a comprehensive assessment of culture conversion was performed, unfortunately we could not assess the sputum-smear conversion in all the individuals. This was probably due to a lower pulmonary bacillary load in those with a less severe disease (particularly in the control group) and the effect of previous treatments patients underwent before being admitted to the reference centres.

Importantly, meropenem–clavulanate at an *i.v.* dosage of 1 g three times a day was well tolerated and a single episode of drug withdrawal was recorded over a median hospital exposure time of 67 days.

The clinician's decision to interrupt meropenem–clavulanate (a drug only administered intravenously and needing inpatient care) was related to clinical improvement and microbiological conversion (*e.g.* the conditions allowing hospital discharge) and not to adverse event occurrence in all but one case.

TABLE 4 Safety and tolerability of linezolid in 93 multidrug-resistant tuberculosis cases

Variables	Total	Cohort treated with linezolid ⩽600 mg·day^{-1}	Cohort treated with linezolid >600 mg·day^{-1}	p-value
Subjects n		54	39	
Exposure to linezolid days	61 (35–117)	63.5 (46.0–120.0)	52.0 (30.0–100.0)	0.12
Interruption of linezolid due to adverse events	12/93 (12.9)	3/54 (5.6)	9/39 (23.1)	0.01
Time of occurrence of linezolid-related adverse events days	32.0 (21.5–62.5)	27.5 (15.5–38.0)	53.0 (37.5–83.0)	0.005
Reversible adverse events	13/19 (68.4)	2/6 (33.3)	11/13 (84.6)	0.03
Anaemia	13/56 (23.2)	5/24 (20.8)	8/32 (25.0)	0.72
Leukopenia	4/68 (5.9)	2/35 (5.7)	2/33 (6.1)	0.95
Thrombocytopenia	4/79 (5.1)	1/45 (2.2)	3/34 (8.8)	0.19
Peripheral neuropthy	17/54 (31.5)	8/24 (33.3)	9/30 (30.0)	0.79
Optic neuritis	1/79 (1.3)	1/44 (2.3)	0/35 (0.0)	0.37
Gastrointestinal disorders	5/38 (13.2)	2/12 (16.7)	3/26 (11.5)	0.66

Data are presented as median (interquartile range) or n/N (%), unless otherwise stated.

Our study has provided, for the first time, evidence that meropenem–clavulanate increases the proportion of microbiological converters when added to linezolid-containing regimens, designed according to WHO guidelines [11]. The large sample selected allowed us to obtain more statistical confidence than in previously published case series. In addition, the study was conducted in two specialised centres that had collaborated in the past [15, 21] and shared the same protocol to design linezolid-containing regimens and routinely adjust the linezolid dose based on blood levels [15]. The study protocol allowed collection of quality-assured patient information in both centres, making a comprehensive comparison between cases and controls possible.

A further finding of the study is the possibility to add evidence on safety and tolerability of linezolid, taking advantage of 93 cases not included in a recently published individual meta-analysis [15]. While the proportion of major adverse events was lower than previously reported (12.9%), the study results confirm the better safety/tolerability of the lower dose (⩽600 mg a day) of linezolid [14, 15], prescribed more frequently in the Dutch centre and responsible for the significantly lower proportion of total adverse events observed among controls.

Among the main methodological limitations it is worth mentioning the observational, retrospective nature of the study and the consecutive, not randomised enrolment of patients. In addition, although quality controlled by Supranational Reference Laboratories, and distributed among both cases and controls, drug-susceptibility testing for some of the second-line drugs (*e.g.* cycloserine) needs to be evaluated with caution, given the intrinsic difficulty to perform these tests.

Although the sample size allowed inferential analysis, larger trials will shed further light on the definite role that meropenem–clavulanate might play in treating MDR-/XDR-TB cases (*e.g.* duration of exposure according to clinical severity) when a fourth active drug is needed to design an effective regimen [11].

Although evidence on three new drugs (delamanid, bedaquiline and PA-824) is rapidly accumulating, preceding their market introduction [22], the WHO Group V drugs are still of interest in the management of complicated cases when a fourth active drug is not available either because of the drug-susceptibility testing profile or because of intolerance to active drugs [11]. In addition to continuing research on newly developed drugs and regimens, parallel evidence needs to be raised on existing compounds on which little is proven.

Considering the promising safety/tolerability and efficacy profile of meropenem–clavulanate found in our study, further research on its role and contribution in managing MDR-/XDR-TB cases should be encouraged. Furthermore, the 2012 daily cost of meropenem–clavulanate (a 1-g vial three times a day for *i.v.* use is ~€57 in Sondalo) is substantially similar to that of linezolid (a 600-mg tablet is ~€55 and ~€61 in Sondalo and Haren, respectively) making its use potentially affordable, at least in high-income countries [23, 24].

The results of the present study will provide reference to design trials on meropenem–clavulanate and will guide clinicians for its rationale use within salvage/compassionate regimens [25, 26].

STATEMENT OF INTEREST

None declared.

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