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Ertapenem and faropenem for the treatment of drug resistant tuberculosis

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Background

Carbapenems are a class of beta-lactam antibiotics which include imipenem, meropenem and ertapenem. More recently, a new oral carbapenem (faropenem) have been marketed in a limited number of countries (in particular, India and Japan). Emerging evidence demonstrates that they target the mycobacterial cell wall, providing an alternative treatment for multidrug-resistant (MDR) and extensively drug-resistant (XDR) tuberculosis (TB), where options are limited (**1**). Compared to imipenem and meropenem (both only available as intravenous formulations), ertapenem (once daily administration) and faropenem (oral) are much more attractive alternatives for ambulatory or homecare treatment. However, there is a paucity of data on their efficacy against *Mycobacterium tuberculosis* (**2, 3, 4**).

The aim of this project was to test the in vitro activity of ertapenem and faropenem (with and without the addition of amoxicillin/clavulanate) against different clinical isolates of *M. tuberculosis* and the reference strain H37RV, to better understand their potential role as additional antibiotics in the management of drug resistant TB.

Methods

Twenty isolates in total (19 clinical isolates, including MDR and XDR strains, plus H37Rv) were tested against different concentrations of ertapenem and faropenem (with and without the addition of amoxicillin/clavulanate). Susceptibility testing was performed using two different methods (BACTEC960 and broth microdilution). An ertapenem degradation assay was also performed using a MALDI-MS at timepoints 0, 7 and 50 days.

Strain	Phenotypical resistance profile	Meropenem clavulanate MIC (µg/ml)	Notes
03:013	S	32	
03:039	H	16	
04:018	H,R,clari,ethi	Failed	MDR
05:094	Fully susceptible	8	
07:116	H, ethi	4	
11:136	S,H,R	>32	MDR
11:156	S,H,R	4	MDR
11:191	H	16	
11:368	S,H,R	>32	MDR
324	Fully susceptible	8	
333	S,H,R	2	MDR
346	S,H,R	2	MDR
347	Fully susceptible	>32	
401	H,R	>32	MDR
408	S,H,R	>32	MDR
443	Fully susceptible	>32	
548	N/A*	>32	XDR
421	S,H,R,EMB,CAP,Moxi	>32	XDR
433	S,H,R,EMB,PYR,CAP,Moxi	8	XDR
H37Rv	Fully susceptible	2	Control reference strain

Table 1: List of *M. tuberculosis* isolates tested. S=Streptomycin, H=Isoniazid, R=Rifampicin, Clari=Clarithromycin, Ethi=Ethionamide, EMB=Ethambutol, CAP=Capreomycin, Moxi=Moxifloxacin, PYR=Pyrazinamide. The MIC against Meropenem/clavulanate is also shown. *This isolate was confirmed as XDR by WGS but phenotypical susceptibilities were not performed.

Ertapenem	Ertapenem Clavulanate	Faropenem	Faropenem Clavulanate
µg/ml	µg/ml	µg/ml	µg/ml
16-8-4-2	16-8-4-2 (+2.5 Clavulanate each)	8-4-2-1	8-4-2-1 (+2.5 Clavulanate each)

Table 2: Summary of concentrations used. Four different concentrations of ertapenem (16, 8, 4 and 2 µg/ml) and faropenem (8, 4, 2 and 1µg/ml) were tested with and without the addition of amoxicillin/clavulanate (2.5 µg/ml). These concentrations were selected based on previous pharmacokinetic/pharmacodynamic data (**5, 6, 7**).

Results

Eighteen out of twenty samples were resistant to the highest concentration of ertapenem tested (including the addition of amoxicillin/clavulanate) using the BACTEC960. The number of ertapenem resistant isolates reduced to thirteen when using the broth microdilution method. More than half of the samples tested showed some degree of susceptibility to faropenem, in particular with the addition of amoxicillin/clavulanate. The BACTEC960 and broth microdilution provided 35% concordant results. No ertapenem specific degradation peaks were detected at the timepoints tested for ertapenem incubated at 37C in BACTEC960 MGIT tubes.

	MIC				
Strain	ERT	ERT+C	FAR	FAR+C	MER+C
03:013	>16	>16	8	4	>32
03:039	>16	>16	8	4	16
04:018*	>16	>16	4	4	Failed
05:094	16	16	4	4	8
07:116	16	16	4	1	4
11:136*	>16	>16	8	4	>32
11:156*	>16	>16	8	2	4
11:191	>16	>16	>8	>8	16
11:368	>16	>16	>8	>8	>32
324	>16	>16	>8	>8	8
333*	>16	>16	>8	>8	2
346*	>16	>16	8	8	2
347	>16	>16	>8	8	>32
401*	>16	>16	>8	>8	>32
408*	>16	>16	8	8	>32
443	>16	>16	>8	>8	>32
548*	>16	>16	>8	>8	>32
421*	>16	>16	>8	8	>32
433*	>16	>16	>8	>8	8
H37Rv	>16	>16	>8	>8	2

Table 3: Results of ertapenem and faropenem testing using BACTEC960. An asterisk indicates that the strain is MDR or XDR (n=20). Susceptible concentrations are highlighted in green (ERT=ertapenem, ERT+C=ertapenem plus amoxicillin/clavulanate, FAR=faropenem, FAR+C=faropenem plus amoxicillin/clavulanate, MER+C=meropenem plus amoxicillin/clavulanate). The MIC against meropenem/clavulanate is shown again to facilitate the comparison.

	MIC				
Strain	ERT	ERT+C	FAR	FAR+C	MER+C
03:013	>16	>16	8	8	>32
03:039	>16	>16	16	4	16
04:018*	Failed	Failed	Failed	Failed	Failed
05:094	>16	>16	8	8	8
07:116	16	>16	<1	<1	4
11:136*	>16	>16	8	8	>32
11:156*	>16	>16	2	4	4
11:191	>16	>16	8	8	16
11:368	>16	>16	>8	>8	>32
324	8	16	2	<1	8
333*	8	4	2	<1	2
346*	4	16	1	<1	2
347	>16	>16	>8	>8	>32
401*	>16	>16	>8	>8	>32
408*	>16	>16	>8	>8	>32
443	>16	>16	>8	>8	>32
548*	>16	>16	>8	>8	>32
421*	>16	>16	>8	>8	>32
433*	2	<2	<1	<1	8
H37Rv	8	16	2	4	2

Table 4: Results of ertapenem and faropenem testing using the broth microdilution. An asterisk indicates that the strain is MDR or XDR (n=20). Susceptible concentrations are highlighted again in green (ERT=ertapenem, ERT+C=ertapenem plus amoxicillin/clavulanate, FAR=faropenem, FAR+C=faropenem plus amoxicillin/clavulanate, MER+C=meropenem plus amoxicillin/clavulanate).

Conclusions

The results from this project have highlighted a significant level of in vitro resistance to ertapenem, whilst the clinical isolates have shown different degrees of susceptibility to faropenem. There is also some significant variability in the results depending on the testing method used (only 35% concordance) and further studies are needed to optimize susceptibility testing. Although promising agents (in particular, faropenem), carbapenems will remain a third line choice to be used only in cases of XDR TB. There is currently no evidence to prefer the use of ertapenem despite its once daily administration.

References

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