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 multiderug-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.

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.

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


1. University College London
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3. Imperial College London
4. Royal Free London NHS Foundation Trust