S004

2-hour Symposium

New antibacterial drugs

Which role and indications for new beta-lactams and beta-lactamase inhibitor-combinations?

D. Livermore[1]

[1]*University of East Anglia, Norwich, United Kingdom*

Two new beta-lactamase inhibitor combinations are well-advanced in the regulatory process. Ceftolozane-tazobactam is licensed for complicated urinary and intra-abdominal infections (cUTI, cIAI) by the US FDA, with EMA decisions pending. Ceftazidime-avibactam, also with Phase III trials in cUTI and cIAI, has received a 'positive opinion' from the FDA's advisory panel and awaits a final decision. Also recently licensed in the EU (not the US) is ceftobiprole, for community- and hospital-acquired pneumonia not requiring ventilation.

Ceftolozane has the typical behaviour of an oxyimino-cephalosporin against Enterobacteriaceae, with lability to ESBLs and AmpC enzymes, and to carbapenemases except OXA-48. Tazobactam protects against ESBLs, with efficacy against ESBL producers confirmed in the Phase III trials; efficacy against AmpC hyperproducers is less clear. Ceftolozane's most striking feature, irrespective of tazobactam, is 4-8 fold greater activity than ceftazidime – hitherto the most active antipseudomonal cephalosporin – against *P. aeruginosa*, including strains with derepressed AmpC or upregulated efflux. High-level resistance is largely confined to metallo-carbapenemase producers. The licensing trials were not in settings where *P. aeruginosa* is a prominent pathogen and there is an urgent need for evaluation both in pseudomonal pneumonias and in those chronic respiratory conditions (cystic fibrosis, bronchiectasis and chronic obstructive pulmonary disease) where this pathogen is important and commonly multiresistant.

Ceftazidime-avibactam's Phase III trials will be presented at this ECCMID. Press releases and the FDA panel's response imply results to be positive, as were Phase II trials, but sub-set analysis for different resistance types will be critical In vitro, avibactam inhibits ESBLs, AmpC and KPC enzymes, whilst ceftazidime itself evades OXA-48, leaving metallo-carbapenemase producers as the major resistant group. Animal experiments support efficacy against strains with KPC enzymes. If these results are borne out by experience in humans – and in the lung as well as in cUTI – the combination will fulfil a major need in the growing list of countries where multi-resistant Enterobacteriaceae with KPC enzymes, or OXA-48/ESBL combinations, are proliferating. A concern is the potential for mutational resistance in KPC enzymes, though the clinical risk remains uncertain.

Ceftobiprole's key feature is anti-MRSA activity in the lung, coupled with an anti-gram-negative profile resembling cefepime's, albeit with lower dosages and breakpoints. As with ceftaroline – the other anti-MRSA cephalosporin – there is a need to evaluate efficacy against MRSA in settings where the cidality of beta-lactams has historically been considered an advantage, notable endocarditis, neutropenic fevers and osteomyelitis.