P0329 Evaluation of the efficacy of ceftazidime-avibactam and colistin in carbapenemase-producing Klebsiella pneumoniae experimental osteomyelitis

Azzam Saleh-Mghir, William Mouton, Frédéric Laurent, Laurent Massias, Idir Ghout, Laure Gatín, Pierre Tattevin, Anne-Claude Crémieux

1 UMR U1173 Inserm-Université Versailles St-Quentin, Hôpital Raymond Poincaré, GARCHES, France, Garches, 2 Laboratoire de Bactériologie, Hôpital de la Croix Rousse, Centre National de Référence des Staphylocoques Unité Inserm 851, Faculté de Médecine Lyon Est, 3 Laboratoire de Toxicologie-Pharmacocinétique, Hôpital Bichat-Claude-Bernard, France, 4 Laboratoire de Bio statistiques, Hôpital Ambroise Paré, BOULOGNE-BILLANCOURT, France, 5 Service de Maladies Infectieuses et Réanimation Médicale, Hôpital Pontchaillou, CHU de Rennes, RENNES, France, 6 Hôpital Universitaire Saint-Louis, Université Paris 7, PARIS, France

Background: KPC-producing Klebsiella pneumoniae (KPC-Kp) are responsible for a broad range of invasive infections, including bone infections. Ceftazidime/avibactam (C/A) is active against antibiotic-resistant Gram-negative organisms, including many carbapenem-resistant strains. We evaluated the efficacy of C/A or colistin in vitro and in vivo in a new experimental model of KPC-Kp osteomyelitis.

Materials/methods: KPC-99YC is a clinical strain intermediate to meropenem (MIC, 4 mg/L) and susceptible to C/A (MIC 1.5 mg/L), and colistin (MIC 1 mg/L). Time-kill curves were performed at 4 MICs. Plasma antibiotic concentrations were measured in uninfected rabbits, to select doses equivalent to those used in humans after a 2 g/500 mg C/A iv infusion. An osteomyelitis was induced in rabbits by tibial injection of a sclerosing agent followed by $2 \times 10^8$ CFU/ml of KPC-99YC. Treatment (Tx) started 14 days later, for 7 days, in 3 groups of 11 rabbits: (1) control group (2) C/A 100/25 mg/kg sc tid (3) colistin 150 000 IU/kg im tid (equivalent to 3 M IU tid in Humans). Three days after the end of treatment (D24), rabbits were euthanized, and bones were cultured. Positive cultures were quantified, and screened for strains resistant to C/A, or colistin.

Results: In vitro, C/A and colistin were rapidly bactericidal (i.e., within 3 h), but regrowth occurred after 6 (C/A), or 9 h (colistin), with no emergence of resistant strains. In control rabbits at D24, median and interquartile range (IQR) of bacterial count was 6 (5.7-6.4) log$_{10}$ CFU/g of bone. Rabbits treated with colistin were not different from controls, with 5.5 (4.3-6.2) log$_{10}$ CFU/g at D24, and no rabbit with sterile bone (P=0.106). In contrast C/A was more effective than control, with 3.2 (1.4-3.7) log$_{10}$ CFU/g (P<0.01), and 4/11 (36%) rabbits with sterile bones (P=0.031) and more effective than colistin on bone bacterial counts (P=0.004). No strain resistant to C/A was detected, but strains resistant to colistin were detected in two rabbits (MICs, 64 mg/L).

Conclusions: In this stringent model of KPC producing K. pneumoniae osteomyelitis, C/A was more bactericidal than colistin, with no emergence of resistant strains.