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P2195 Safety and pharmacokinetics of i.v. azidothymidine alone and combined with colistin being developed for the treatment of carbapenem- and colistin-resistant Enterobacteriaceae (phase-1-study)

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Background:

Azidothymidine (AZT) in combination with colistin (COL) has in vitro synergistic activity against COL-susceptible and -resistant and carbapenem-resistant Enterobacteriaceae(CRE), including mcr-1-producing Escherichia coli strains. In this phase-1 study the safety, tolerability and pharmacokinetics of IV-administration of AZT and colistimethate sodium(CMS) alone and co-administered were assessed in healthy male and female volunteers.

Materials/methods:

Twenty-seven subjects were randomized to receive 3 times (q12) 1-h IV-infusions over a 25-h period. Regimen A(n=7): 200, 100 and 100mg AZT co-administered with 4, 2 and 2 MIU CMS; Regimen B(n=3) as A with AZT-placebo; Regimen C (n=4) as A with CMS-placebo; Regimen D (n=6): 180mg AZT co-administered with 1.5 MIU CMS; Regimen E (n=4) as D with AZT-placebo; Regimen F (n=3) as D with CMS-placebo. Plasma and urine were collected in intervals up to 48h after start of first dose. The concentrations of AZT, CMS and free COL were determined by a validated LC-MS/MS method.

Results:

Table 1. Median (range) plasma Cmax and urine concentrations (0-3 h post start infusion) in regimen A/D (combination AZT/CMS). Concentrations of CMS and COL expressed as colistin-base-activity

Regimen	Dosage		Plasma(mg/L)	Urine (mg/L)				
-dose	CMS(MIU) +AZT(mg)	N	CMS	COL	AZT	CMS	COL	AZT
A-1st	4.0MI U +200mg	5	16.7 (14.9 - 19.9)	4.06 (2.83 - 5.19)	1.84 (1.42 - 2,87)	76.4 (38.7 - 149)	106 (55-76)	70.4 (41.2 - 893)
A-3rd	2.0MI U +100mg	5	6.40 (3.34 - 7.41)	2.62 (1.21 - 3.19)	0.68 (0.38 - 1.08)	52.8 (21.5 - 322)	46.9 (14.9 - 217)	39.0 (11.8 - 444)
D-1st	1.5MI U +180mg	6	4.05 (3.48 - 7.71)	1.54 (1.26 - 2.09)	1.30 (1.19 - 1.49)	44.3 (21.0 - 80.9)	70.1 (32.4 - 124)	111 (70.5 - 268)

In regimen A/D median plasma half-life (h) of CMS was 1.11/1.18, of COL 4.96/5.02, of AZT NC/0.73, respectively. Median cumulative renal excretion (% of dose) from 0-48h was in regimen A/D for CMS 12.6/14.2, for COL 25.1/23.0, for AZT 19.8/23.5, respectively.

All treatment emergent adverse events were mild, highest in regimen A after 1st dose and consistent with the prescribing information for CMS and AZT. No renal toxicities were observed.

Conclusions:

Twice daily (BID) doses of AZT 200mg combined with CMS 2.5-3.0 MIU should be tested in a phase-2 study in complicated urinary tract infections. Compared to current CMS loading and daily dosing, this would constitute a low dose regimen.