

P0304

Poster Session I

New therapeutic alternatives

POPULATION PHARMACOKINETICS AND TARGET ATTAINMENT OF THE NEW ANTIPSEUDOMONAL MACROCYCLIC ANTIBIOTIC POL7080

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Objectives

POL7080 is a new macrocyclic antibiotic specifically aimed at *Pseudomonas aeruginosa*. The drug is being developed to treat infections caused by this micro-organism, in particular pulmonary infections (including VAP). A phase 1 trial has been completed in healthy subjects with normal renal function. We describe the results of the phase 1 pharmacokinetic (PK) studies of POL7080 using a population pharmacokinetic model. Furthermore, it was studied whether pharmacodynamic targets (PDT) could be reached using Monte Carlo Simulations (MCS).

Methods

Subjects without renal impairment received a single or multiple doses of POL7080 of 0.05 up to 5mg/kg BID. PK and demographic data from 52 patients were used to construct a population PK model of POL7080 using NONMEM following standard procedures including a bootstrap. Using the population model derived and a protein binding of 40%, MCS were performed for various dosing regimens to determine a probability of target attainment ($fAUC/MIC$) of 30 using 5000 cycles.

Results

A 3-compartment model best fit the data with a correlated coefficient of variability on CL and V1, a coefficient on V2 and V3, and a proportional error with creatinine clearance as covariate on clearance and age on the second peripheral compartment. Estimates for clearance (CL) and the 3 volumes of distribution (V) were as follows: CL 6.72 L/h, V1 8.93 L, V2 6.23 L and V3 13.1 L. For strains with a MIC of 1 mg/L (the upper end of the WT distribution) the PDT at the 95 and 99 percentile were 20.1 and 17.7, 31.1 and 26.9, 41.3 and 37.3 for doses of 5, 7.5 and 10 mg/kg respectively.

Conclusion

A dose of 7.5 mg/kg appears to be adequate to treat infections with strains with a MIC up to 1 mg/L taking into account a PD target ($fAUC/MIC$) of 30. However in severely ill patients a slightly higher dose might be justified in some patients with hyperclearance. POL7080 is a promising new antipseudomonas antimicrobial.