ABSTRACT
Background: Razupenem (PTZ601, RZM) is an investigational parenteral carbapenem with wide in-vitro activity against Gram-negative and Gram-positive pathogens including MRSA. The MIRA MIC is ≤2mg/L. We determined the relationship between razupenem T>MIC and antibacterial effect (AUC) measured by bacterial clearance and emergence of resistance in an in-vitro pharmacokinetic (PK) model. 

Methods: A single compartment open dilutional in-vitro PK model was used. Five strains of MRSA (MIC range 0.25-4mg/L) were employed, inoculum 10^7 CFU/mL. Razupenem was administered 12h/1h. A range of dose simulations (3-4 MIC exposures per strain) produced a range of T>MICs from 0-100%. AB他自己 was assessed by log count in viable count at 24h (d24) and 48h (d48) and area under the bacterial kill curves (AUBKC) at 24h (AUBKC24) and 48h (AUBKC48). Emergence of resistance was assessed by growth on MIC x2 and MIC x4 plates at 24h and 48h.

Results: The T>MIC to produce a 24 hour static effect, -1 log, -2 log or -3 log drops were 6.0±1.4, 7.3±1.3, 9.2±1.4, respectively. The 90% maximum effect using AUBKC24 occurred at 31%. The T>MIC to produce a 48h static effect, -1 log, -2 log or -3 log drops were 5.0±1.4, 6.7±1.5, 9.2±2.1, respectively. The 90% maximum effect using AUBKC48 occurred at 24%.The risk of emergence of resistance as measured by growth on MIC x2 plates was related to T>MIC. At T>MIC in the range 0-100% ABE was assessed by growth on MIC x2 and MIC x4 plates at 24h and 48h.

The 90% maximum effect using AUBKC24 occurred at 31%. The T>MIC to produce a 24 hour static effect, -1 log, -2 log or -3 log drops were 9.2±1.1, 10.3±1.4, 15.0±2.5, respectively. The 90% maximum effect using AUBKC48 occurred at 24%. The T>MIC to produce a 48 hour static effect, -2 log, -3 log or -4 log drops were 5.0±1.4, 6.0±1.3, 7.1±1.4, respectively. The 90% maximum effect using AUBKC48 occurred at 24%.The risk of emergence of resistance as measured by growth on MIC x2 plates was related to T>MIC. At T>MIC in the range 0-100% ABE was assessed by growth on MIC x2 and MIC x4 plates at 24h and 48h.

The aim of this study was using an in-vitro pharmacokinetic model to simulate human serum concentrations associated with 1g by 1.0h infusion every 24h for 7 days. Razupenem was added to T>MIC required for a range of antibacterial effects and emergence of resistance.

RESULTS

In-vitro pharmacokinetic model
A single compartment dilutional in-vitro model was used. 20% Mueller Hinton Broth was pumped from reservoir to the bacterial chamber as a peristaltic pump at a flow rate of 312 ml/h. Razupenem was added at time 0 and 1h, and samples taken hourly for viable count and confirmation of the concentration.

- Five strains of MRSA were used, SMH3922 (RZM MIC 0.09mg/L), SMH6897 (RZM MIC 0.25mg/L), SMH6898 (RZM MIC 1.0mg/L), SMH7720 (RZM MIC 1.0mg/L), SMH3320 (RZM MIC 16mg/L).

- Pharmacokinetics
  - Average Pooled MIC at 24h
    - 0.09 1.4 0.8 2.0 8.0
    - 2.0 4.0 5.0 6.0
  - Average Pooled MIC at 48h
    - 0.09 2.0 5.0 8.0
    - 4.0 6.0 10.0
  - Average Pooled MIC at 72h
    - 0.09 4.0 8.0 12.0
    - 8.0 10.0
  - AUBKC at 24h
    - 0.09 23.5 16.8 13.7 11.8
    - 11.8 7.6 14.7±5.9 14.1
  - AUBKC at 48h
    - 0.09 26.0 23.5 16.8 13.7
    - 14.1 7.6 14.7±5.9 14.1

- Bacteria
  - Five strains of MRSA were used, SMH3922 (RZM MIC 0.09mg/L), SMH6897 (RZM MIC 0.25mg/L), SMH6898 (RZM MIC 1.0mg/L), SMH7720 (RZM MIC 1.0mg/L), SMH3320 (RZM MIC 16mg/L).

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  - Average Pooled MIC at 24h
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    - 4.0 6.0 10.0
  - Average Pooled MIC at 72h
    - 0.09 4.0 8.0 12.0
    - 8.0 10.0
  - AUBKC at 24h
    - 0.09 23.5 16.8 13.7 11.8
    - 11.8 7.6 14.7±5.9 14.1
  - AUBKC at 48h
    - 0.09 26.0 23.5 16.8 13.7
    - 14.1 7.6 14.7±5.9 14.1

- Emergence of resistance occurred mainly at T>MIC ≤ 25%. A T>MIC target of 30-40% is likely to be bactericidal against MRSA while reducing the risk of emergence of resistance.

CONCLUSIONS

- The relationship of T>MIC to AUBKC24 and AUBKC48 is shown in Table 1 and Figures 1a and 1d.

- The results: (a) T>MIC v d24 (all MRSA strains) (b) T>MIC v d48 (all MRSA strains) (c) T>MIC v AUBKC24 (all MRSA strains) (d) T>MIC v AUBKC48 (all MRSA strains) for the averaged and pooled data is shown in Table 1 and Figures 1a and 1c.

Table 1. The relationship to d24 and d48 for the individual strains and the averaged and pooled data is shown in Table 1 and Figures 1a and 1b.

- The relationship of T>MIC to AUBKC48 is shown in Table 1 and Figures 1c and 1d.

- The relationship of T>MIC to AUBKC24 and AUBKC48 is shown in Figure 2a and 2b.

- The relationship of T>MIC to AUBKC24 and AUBKC48 is shown in Figure 2c and 2d.

- The relationship of T>MIC to AUBKC24 and AUBKC48 is shown in Table 1 and Figures 2a and 2b.

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