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Early Bactericidal Activity of Meropenem with & without Rifampin for TB

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BACKGROUND

We conducted a dose finding study to measure the early bactericidal activity (EBA) of Meropenem (Mero) plus Amoxicillin/clavulanate (Amx/clav), with or without Rifampin (Rif), in patients with pulmonary tuberculosis (TB).

METHODS

In this phase IIa trial participants with sputum smear-positive Rif-susceptible pulmonary TB were randomly assigned to one of four treatment Arms consisting of Rif 20mg/kg once daily plus Mero 2g 8 hrly (Arm C), Mero 2g 8 hrly (Arm D), Mero 1g 8 hrly (Arm E), or Mero 3g once daily (Arm F). All Arms received Amx/clav 500/125 mg 8hrly, except Arm F that received 875/125 mg once daily. Participants received 14 consecutive days of study treatment. Overnight sputum was collected on days 0, 1, 2, 3, 4, 6, 8, 10, 12, 14. The mean daily fall in log_{10} CFU of *M.tuberculosis* per mL sputum ($EBA_{0\text{-}14}$CFU) was calculated. Intensive pharmacokinetic (PK) sampling over 8h was performed on Day 13. PK data were analyzed in R and WinNonlin. Adverse events of grade 2 or greater severity were recorded.

RESULTS

Sixty patients were recruited in Cape Town, South Africa. Mean (range) age was 37 years (20-63), 75% were male, and 23% were HIV-positive. Over 14 treatment days, the Mero 6g total daily dose Arms (C & D) showed a significantly higher mean EBA than the 3g total daily doses (Arms E & F) (Table 2). Over the first 2 days of treatment, mean $EBA_{0\text{-}2}$CFU were 0.39; 0.11; 0.14; and 0.02, for Arms C, D, E, & F, respectively. No unexpected adverse events were recorded in any treatment Arms.

Treatment Arm	Mean AUC0-24 (SE) (h*mg/L)	Cmax (SE) (mg/L)
C	573 (35)	133 (10)
D	555 (45)	134 (9)
E	289 (45)	68 (8)
F	314 (20)	179 (12)

Table 1. Mean plasma Mero exposure per treatment Arm

Higher total daily doses of Meropenem plus Amoxicillin/clavulanate (6g vs. 3g daily) showed a significant increase in 14-day bactericidal activity. Addition of Rifampin to Meropenem only modestly increased EBA over 14 treatment days.

Treatment Arm	Daily decrease in log_{10} CFU	95% CI
C	0.172	0.140 – 0.205
D	0.127	0.101 – 0.153
E	0.046	0.017 – 0.074
F	0.058	0.031 – 0.084

Table 2. 14-Day EBA based on the daily rate of change in CFU per treatment Arm

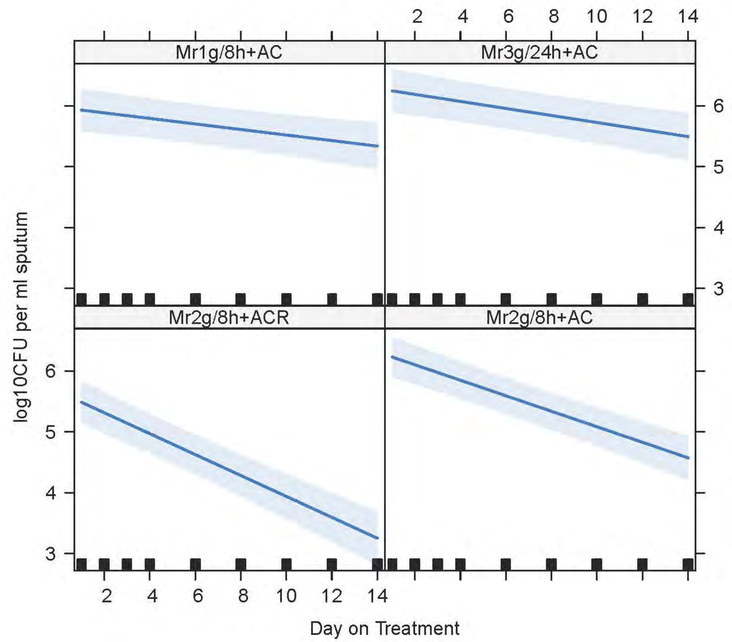

Figure 1. Rate of change in CFU per treatment Arm

CONCLUSIONS

- **Mero exhibits linear dose-dependent PK, and Rif does not impact its exposure.**
- **Addition of Rif to Mero plus Amx/clav increased EBA over the first 2 days, but did not significantly increase 14-day EBA.**
- **14-day EBA was significantly higher with Mero doses of 2g thrice daily (total daily dose of 6g) than with total daily doses of 3g.**
- **With a total daily dose of 3g, 14-day EBA was negligible.**
- **The activity of Mero plus Amx/clav, with and without Rif, against drug-resistant *M.tuberculosis* remains to be explored.**

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