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In vivo Activity of Imipenem/XNW4107 Human-Simulated Regimen against Serine Carbapenemase-Producing *Acinetobacter baumannii* and *Pseudomonas aeruginosa* in the Neutropenic Murine Thigh Infection Model

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ABSTRACT

BACKGROUND

Imipenem (IPM)/XNW4107 is a novel β-lactam/β-lactamase inhibitor with *in vitro* activity against serine carbapenemase-producing *Acinetobacter baumannii*, *Pseudomonas aeruginosa* and Enterobacterales. Herein, we evaluated the *in vivo* activity of an IPM/XNW4107 human-simulated regimen (HSR) against clinical OXA-23- and OXA-24-producing *A. baumannii* as well as KPC- and GES-producing *P. aeruginosa* using a neutropenic murine thigh infection model.

METHODS

Seven *A. baumannii* and 4 *P. aeruginosa* isolates were included. IPM and IPM/XNW4107 MICs (XNW4107 fixed at 8 mg/L) were tested in triplicate by broth microdilution. One thigh of neutropenic ICR mice (6 mice per group) was inoculated with ~10^7 CFU/mL bacterial suspensions. HSR that mimicked the clinical exposures of IPM 500 mg q6h alone or in combination with XNW4107 250 mg q6h each as 1 h infusion were developed in the murine model. In efficacy studies, two hours after inoculation, placebo, IPM 500 mg q6h 1 h infusion HSR, or IPM/XNW4107 500/250 mg q6h 1 h infusion HSR were administered subcutaneously. Efficacy was measured as the change in $\log_{10}$CFU/thigh at 24 h compared with 0 h controls.

RESULTS

Isolates were IPM resistant (MICs 16 - >64 mg/L). IPM/XNW4107 *A. baumannii* and *P. aeruginosa* MIC ranges were 1-16 and 1- 8 mg/L, respectively. Across all examined isolates, 0 h mean ± SD bacterial burden was 5.86 ± 0.32 $\log_{10}$ CFU/thigh. The 24 h increase in bacterial burden was 2.68 ± 0.91 $\log_{10}$ CFU/thigh in the sham controls. IPM HSR monotherapy groups showed mean increase in bacterial burden of 2.34 ± 0.95 $\log_{10}$ CFU/thigh. Bacterial kill with IPM/XNW4107 500/250 mg q6h 1 h infusion HSR ranged from -0.46 ± 1.69 to -3.77 ± 0.15 and -2.33 ± 0.25 to -3.76 ± 0.57 among *A. baumannii* and *P. aeruginosa* isolates, respectively. IPM/XNW4107 500/250 mg q6h 1 h infusion HSR produced >1-log kill against 6/7 examined *A. baumannii* with the exception of *A. baumannii* 160 (IPM/XNW4107 MIC 16 mg/L) and 4/4 *P. aeruginosa* as well as >2-log kill against 4/7 *A. baumannii* and 4/4 *P. aeruginosa*.

CONCLUSION

IPM/XNW4107 500/250 mg q6h 1 h infusion HSR showed potent *in vivo* activity against serine carbapenemase-producing *A. baumannii* and *P. aeruginosa*. These data support the consideration of IPM/XNW4107 for the treatment of serious infections due to these organisms in clinical trials.

INTRODUCTION

- In 2017, the WHO published a list of bacteria for which new antibiotics are urgently needed and named carbapenem-resistant *Acinetobacter baumannii* (CRAB) and *Pseudomonas aeruginosa* among the most critical group (i.e. the highest priority).[1]
- Among the limited armamentarium against CRAB, existing agents such as polymyxin and tetracycline derivatives often have undesirable side effects and are poorly tolerated.[2,3]
- Imipenem(IPM)/XNW4107 is a novel β-lactam/β-lactamase inhibitor (BL/BLI) with *in vitro* activity against serine carbapenemase-producing *A. baumannii*, *P. aeruginosa*, and Enterobacterales.[4]
- XNW4107 is a diazabicyclooctane β-lactamase inhibitor that confers protection against hydrolysis by Ambler Class A, C, and D β-lactamases, including OXA-23 and -24 found in *A. baumannii*.[4]

OBJECTIVE

- Assess the efficacy of a human-simulated regimen (HSR) of imipenem/XNW4107 500/250 mg q6h as a 1 h infusion against serine carbapenemase-producing *A. baumannii*, and *P. aeruginosa*, in the neutropenic murine thigh infection model

METHODS

Animals and Bacterial Isolates

- Specific-pathogen-free, female, CD-1 mice (20-22 g) were obtained from Charles River Laboratories, Inc. (Raleigh, North Carolina, USA).
- 7 *A. baumannii* and 4 *P. aeruginosa* clinical isolates were utilized in these experiments.
- IPM/XNW4107 MICs (XNW4107 fixed at 8 mg/L) were determined in triplicate via broth microdilution to establish a modal MIC value.[5]

Neutropenic Thigh Infection Model

- Mice were rendered neutropenic by administering cyclophosphamide intraperitoneally (IP) as 150 mg/kg and 100 mg/kg four and one day prior to inoculation, respectively.
- A predictable degree of renal impairment was produced using 5 mg/kg of uranyl nitrate administered IP three days prior to inoculation.[6]
- Bacterial suspensions of ~1 × 10^7 colony forming units (CFU)/mL in normal saline were used for the inoculation of left thighs only (injection volume 0.1 mL) 2h prior to antibiotic or placebo administration.

XNW4107 Single-Dose Pharmacokinetic Studies

- Mice were prepared as above and received escalating doses of XNW4107 1 mg/kg, 10 mg/kg, and 20 mg/kg co-administered with the previously established imipenem HSR (500 mg q6h 0.5 h infusion).
- Groups of six mice were sacrificed at predefined time points and cardiac puncture was performed to obtain blood samples.
- Plasma was separated, matched with an equal volume of stabilizing buffer (1:1 50% ethylene glycol/1M pH 6.0 MES buffer), and frozen at -80°C until concentration determination by validated LC/MS-MS.
- A model was fitted to the concentration data using nonlinear least-square techniques with first-order absorption and first-order elimination (Phoenix WinNonlin, Pharsight Corp., Mountainview, CA, USA).

Ex-vivo XNW4107 Plasma Protein Binding Studies

- Utilizing the same dosing scheme as above, groups of 5 mice (3 groups per dose) were sacrificed 0.5h post-dose and their plasma was pooled.
- 0.9mL of each pooled plasma underwent an additional centrifugation process with a Centrifree device to generate an ultrafiltrate.
- XNW4107 concentration determination of both pooled plasma and ultrafiltrate were performed by LC/MS-MS to determine plasma protein binding.
- The protein binding at each dose was calculated using the following formula:
  % Protein Binding = 100 – ($\text{Concentration}_{\text{ultrafiltrate}}$ / $\text{Concentration}_{\text{plasma}}$ × 100)

Human Simulated Regimen Confirmatory Pharmacokinetic Studies

- For the IPM HSR, previously reported murine PK parameters and plasma protein binding[7] were used to establish IPM 500 mg q6h 1 h infusion HSR regimen that approximated the target exposure in critically ill patients.[8]
- For the XNW4107 HSR, murine PK parameters generated during XNW4107 single doses, the protein binding percentage in mice, and protein binding percentage in humans (16.63%) provided by the sponsor were utilized to simulate a dosing regimen that approximated the target exposure found in healthy volunteers after intravenous administration of imipenem/cilastatin/XNW4107 500/500/250 mg q6h as a 1 h infusion.
- Following the mathematical selection of the regimens, confirmatory PK studies were undertaken following the same methodology as outlined above for the HSR regimens as monotherapy and in combination.

Human Simulated Regimen *In vivo* Efficacy Studies

- One group of six mice per isolate was sacrificed at 0h to determine baseline bacterial burden. Additional groups of 6 mice subcutaneously received either IPM 500mg q6h 1h infusion monotherapy HSR, IPM/XNW4107 500/250mg q6h 1h infusion HSR, or vehicle dosed control.
- Following 24h of treatment, the groups were euthanized and inoculated thighs were aseptically harvested.
- Efficacy was assessed as the change in $\log_{10}$ CFU/thigh from the 0h control.

RESULTS

- XNW4107 was best described using a 1-compartment model. The best-fit average PK parameters of XNW4107 in the murine infection model were: V, 4.62 L/kg; first-order absorption rate constant, 7.21 h^{-1}; and overall elimination rate constant, 0.41 h^{-1}. The co-administration of XNW4107 did not alter the exposure profile of the imipenem HSR.
- The average (±SD) murine protein binding across this dose range was 3.53% ± 4.23% and not concentration dependent across the exposures studied
- 0 h mean ± SD bacterial burden was 5.86 ± 0.32 $\log_{10}$ CFU/thigh
- The 24 h increase in bacterial burden was 2.68 ± 0.91 $\log_{10}$ CFU/thigh in the sham controls
- IPM HSR monotherapy groups showed mean increase in bacterial burden of 2.34 ± 0.95 $\log_{10}$ CFU/thigh

Figure 1. XNW4107 Single-Dose Pharmacokinetics

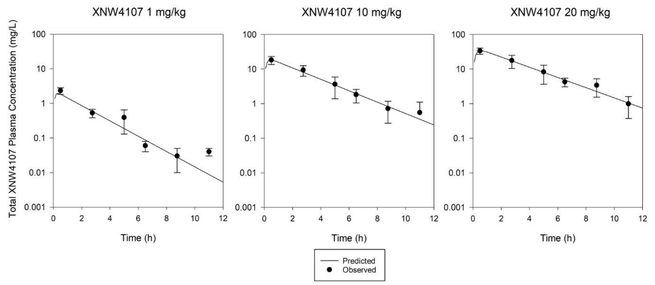

Figure 2. HSR Confirmatory Pharmacokinetics of (a) Imipenem and (b) XNW4107

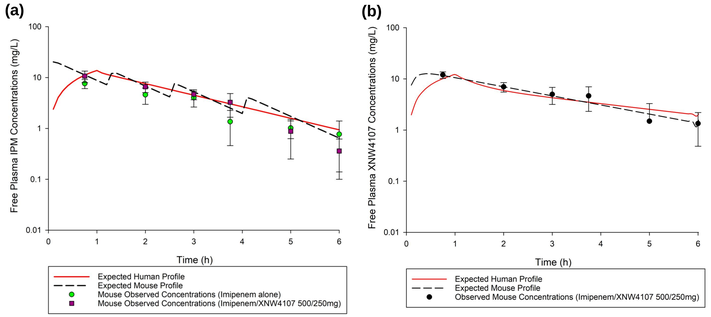

Table 1. Simulated human and murine exposures for IPM and XNW4107

		%*f*T>MIC for a MIC (mg/L) of:								
Regimen	Species	0.5	1	2	4	8	16	32	*f*AUC_{0-24} (mg·h/L)	*f*Cmax (mg/L)
IPM 500 mg q6h	Human	100%	98%	76%	53%	25%	0%	0%	128.0	14.4
	Mouse	100%	92%	78%	55%	28%	6%	0%	146.8	20.9
XNW4107 250 mg q6h	Human	100%	100%	99%	65%	25%	0%	0%	142.7	14.1
	Mouse	100%	100%	86%	57%	29%	0%	0%	142.7	13.9

RESULTS (continued)

Figure 3. IPM/XNW4107 500/250 mg q6h 1h infusion HSR efficacy

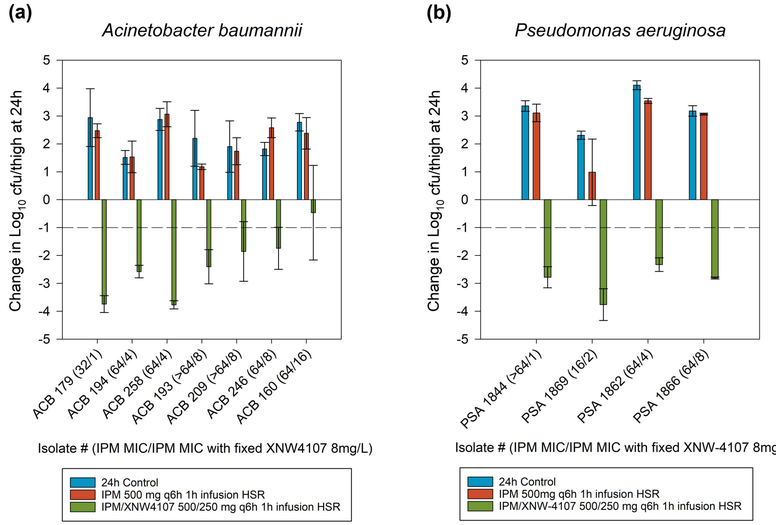

Table 2. *A. baumannii* β-lactamase Profiles

CAIRD Isolate ID	Alternate Isolate ID	β-Lactamase(s) encoded
ACB179	CDC-0296	ADC-25, OXA-23, OXA-223
ACB194	CDC-0311	ADC-25, OXA-23, OXA-82
ACB258	JMI-1043774	ADC-222, OXA-23, OXA-95
ACB193	CDC-0310	OXA-23, OXA-82
ACB209	CDC-0101	OXA-65, OXA-24
ACB246	JMI-990089	ADC-33, OXA-23, OXA-82
ACB160	CDC-0277	OXA-24, OXA-65, TEM-1B

Table 3. *P. aeruginosa* β-lactamase Profiles

CAIRD Isolate ID	Alternate Isolate ID	β-Lactamase(s) encoded
PSA1844	CDC-0356	KPC-2, PDC-42
PSA1869	CDC-0770	GES-19, GES-26
PSA1862	CDC-0763	GES-19, GES-20
PSA1866	CDC-0767	GES-20

OBSERVATIONS AND CONCLUSIONS

- **Imipenem/XNW4107 (500/250 mg q6h as 1 h infusion) showed potent in vivo efficacy against serine carbapenemase-producing *A. baumannii* and *P. aeruginosa* in the neutropenic thigh infection model.**
- **These data support the consideration of this combination and dosage for the treatment of serious infections due to these organisms in clinical trials.**

ACKNOWLEDGEMENTS

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