Poster 734

Modeling the Pharmacokinetics and Pharmacodynamics of Intravenous and Oral Omadacycline With and Without a Loading Dose

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BACKGROUND

- Omadacycline (OMC), a new tetracycline agent, was approved in both oral and intravenous (IV) formulations by the US Food and Drug Administration (FDA) in October 2018 for treatment of acute bacterial skin and skin structure infections (ABSSSI) and community-acquired bacterial pneumonia (CABP) in adults
- In pivotal Phase 3 studies, OMC dosing regimens included a loading dose (100 mg IV every 12 hours [q12h] on Day 1 of therapy for both CABP and ABSSSI, or 450 mg oral daily on Days 1 and 2 of therapy, for ABSSSI only)[1-3]
- However, if the loading dose was accidentally omitted, patients would receive only the maintenance dose, which could adversely affect clinical outcomes
- The objective of this study was to determine the impact of omission of the loading dose on OMC exposure and pharmacodynamics (PD) using known PD thresholds for both stasis and 1_{log} kill for the two most frequently occurring pathogens in CABP and ABSSSI, *Streptococcus pneumoniae* and *Staphylococcus aureus*

METHODS

Pharmacokinetics

- Pharmacokinetic (PK) data from two studies in healthy volunteers were used:
  - One study investigated IV OMC administration (N=20)[4]
  - One investigated oral OMC administration (N=26)[5]
- Extensive PK sampling was performed (13 samples collected over 24 hours in each study)
- Data were fit using noncompartmental methods
  - Area under the concentration–time curve (AUC) was calculated using the linear trapezoidal rule
- PK profiles were simulated on Days 2 and 5, and AUCs were calculated
- The following dose regimens were simulated using actual PK profiles from clinical studies:
  - **IV load:** 100 mg IV q12h on Day 1, followed by 100 mg IV every 24 hours (q24h) on Days 2-5
  - **IV no load:** 100 mg IV q24h on Days 1-5
  - **Oral load:** 450 mg oral q24h on Days 1 and 2, followed by 300 mg oral q24h on Days 3-5
  - **Oral no load:** 300 mg oral q24h on Days 1-5
- AUCs calculated for each subject were corrected for protein binding (20%)[6] to generate free AUCs, and subsequently used in all analyses
- 95% confidence intervals (CI) generated around the mean PK profile were used in subsequent analyses to evaluate the PK/PD target attainment

METHODS

Microbiology

- 2018 SENTRY surveillance program OMC minimum inhibitory concentration (MIC) data obtained for *S. pneumoniae* and *S. aureus*, tested against clinical isolates from the United States and Europe, were utilized in this analysis[7]
- Since OMC activity is not impacted by classical tetracycline resistance mechanisms nor by resistance mechanisms to other classes of antibiotics,[8] isolates with different susceptibility profiles (including multidrug-resistant isolates, penicillin-resistant *S. pneumoniae*, or methicillin-resistant *S. aureus*) were included in these analyses and not analyzed separately

Pharmacodynamics

- The PD parameter associated with efficacy for OMC is AUC/MIC
- *In vivo* PD thresholds for *S. pneumoniae* and *S. aureus* have been reported for stasis and 1_{log} kill in murine pneumonia and murine thigh infection models, respectively (**Table 1**)[9,10]
- Additionally, using Phase 3 data, a PK/PD relationship for clinical response at the early clinical response (ECR) time point was noted among OMC-treated patients with ABSSSI in whom *S. aureus* was identified at baseline
  - At a free plasma AUC/MIC threshold ≥12.5, probability for success exceeded 88.4%[11] with an MIC of 0.5 µg/mL
  - Thus, this threshold was evaluated in addition to AUC/MIC thresholds in animal models to assess the impact of omission of a loading dose
- AUC/MIC ratios were calculated using 24-hour AUCs on Days 2 and 5 for all regimens and the 2018 SENTRY MIC distribution
  - Mean AUC and the AUC for upper and lower bounds of the 95% CI were each used for calculations
  - Given the narrow MIC distributions for both *S. pneumoniae* and *S. aureus*, only MIC_{50} and MIC_{90} values were used

Table 1. *In Vivo* Pharmacodynamic Thresholds for Omadacycline

PD Threshold	*S. pneumoniae* AUC/MIC[9]	*S. aureus* AUC/MIC[10]
Stasis	17.8	21.9
1_{log} kill	17.4	57.7

Data are median values

AUC = area under the concentration–time curve; MIC = minimum inhibitory concentration; PD = pharmacodynamic

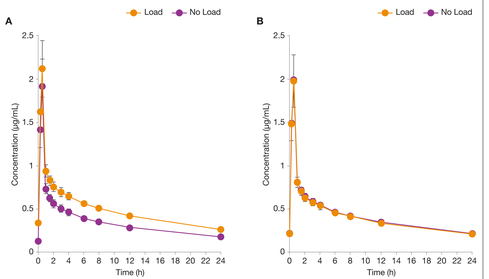
RESULTS

- AUCs on Day 2 for IV and oral no-load regimens were lower than the corresponding loading regimens (72% and 73%, respectively, for IV and oral) (**Fig. 1A**; **Fig. 2A**; **Table 2**)
- However, by Day 5, AUCs for no-load regimens were essentially the same as those for loading dose, for both IV (98%) and oral (97%) regimens (**Fig. 1B**; **Fig. 2B**; **Table 2**)
- OMC displayed potent activity versus both *S. pneumoniae* (MIC_{90} 0.12 µg/mL) and *S. aureus* (MIC_{90} 0.25 µg/mL), with very narrow MIC distributions (**Fig. 3**; **Fig. 4**)

RESULTS

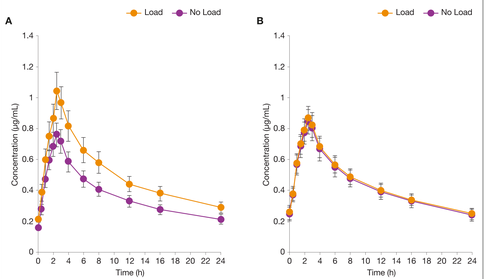
- For *S. pneumoniae*, load and no-load IV and oral regimens exceeded the stasis and 1_{log} kill AUC/MIC thresholds at MIC_{50} and MIC_{90} (**Tables 3** and **4**)
- For *S. aureus*, the AUC/MIC stasis threshold was exceeded for the load and no-load IV and oral regimens on Days 2 and 5 using MIC_{50} and MIC_{90}. However, the 1_{log} kill threshold was only met at MIC_{50} (0.12 µg/mL) for both Days 2 and 5 with the load and no-load regimens (**Tables 3** and **4**)
- Both IV and oral load and no-load regimens on Days 2 and 5 met or exceeded the AUC/MIC threshold associated with clinical success identified from the Phase 3 ABSSSI studies (12.5) for MICs up to 0.5 µg/mL, which is the current susceptibility breakpoint for *S. aureus*

Figure 1. Serum Concentration–Time Profile for IV Omadacycline Dosing With Load vs. No Load: Day 2 (A), Day 5 (B)



IV load: 100 mg IV q12h on Day 1, followed by 100 mg IV q24h on Days 2-5
IV no load: 100 mg IV q24h on Days 1-5
IV = intravenous; q12h = every 12 hours; q24h = every 24 hours

Figure 2. Serum Concentration–Time Profile for Oral Omadacycline Dosing with Load vs. No Load: Day 2 (A), Day 5 (B)



Oral load: 450 mg q24h on Days 1 and 2, followed by 300 mg q24h on Days 3-5
Oral no load: 300 mg q24h on Days 1-5
q12h = every 12 hours; q24h = every 24 hours

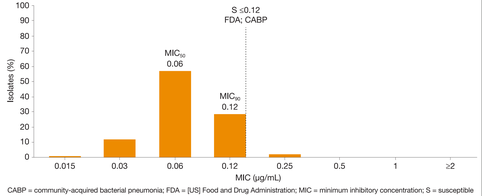
RESULTS

Table 2. Day 2 and Day 5 Free Drug AUC for Load and No-load Dose Regimens

Regimen	Route	Day 2 AUC µg*h/mL (95% CI)	Day 5 AUC µg*h/mL (95% CI)
No load	IV	6.963 (6.415 to 7.652)	7.884 (7.286 to 8.666)
Load	IV	9.615 (8.861 to 10.598)	8.024 (7.406 to 8.811)
No load	Oral	7.092 (6.253 to 8.310)	8.294 (7.249 to 9.839)
Load	Oral	9.682 (8.242 to 12.399)	8.533 (7.486 to 10.090)

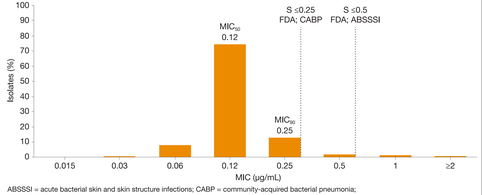
AUC = area under the concentration–time curve; IV = intravenous

Figure 3. MIC Distribution of Omadacycline vs. *S. pneumoniae* Clinical Isolates (N=871) Collected From United States and Europe (2018 Surveillance)[6]



CABP = community-acquired bacterial pneumonia; FDA = [US] Food and Drug Administration; MIC = minimum inhibitory concentration; S = susceptible

Figure 4. MIC Distribution of Omadacycline vs. *S. aureus* Clinical Isolates (N=3,117) Collected From United States and Europe (2018 Surveillance)[6]



ABSSSI = acute bacterial skin and skin structure infections; CABP = community-acquired bacterial pneumonia; FDA = [US] Food and Drug Administration; MIC = minimum inhibitory concentration; S = susceptible

Table 3. AUC/MIC for IV Dosing With and Without Loading Dose Administration for *S. pneumoniae* and *S. aureus*

Therapy	*S. pneumoniae* MIC_{50} (0.06 µg/mL)	*S. pneumoniae* MIC_{90} (0.12 µg/mL)	*S. aureus* MIC_{50} (0.12 µg/mL)	*S. aureus* MIC_{90} (0.25 µg/mL)	*S. aureus* ABSSSI Susc BP[a] (0.50 µg/mL)
Day 2					
No load	111 (107,128)	58 (53, 64)	58 (53, 64)	28 (26, 31)	14 (13, 15)
Load	160 (148, 177)	80 (74, 88)	80 (74, 88)	38 (35, 42)	19 (18, 21)
Day 5					
No load	131 (121, 144)	66 (61, 72)	66 (61, 72)	32 (29, 35)	16 (15, 17)
Load	134 (123, 147)	67 (62, 73)	67 (62, 73)	32 (30, 35)	16 (15, 18)

[a]FDA approved susceptibility breakpoint for *S. aureus* for ABSSSI

Data presented as mean (95% CI)

ABSSSI = acute bacterial skin and skin structure infections; AUC = area under the concentration–time curve; IV = intravenous; MIC = minimum inhibitory concentration; Susc BP = susceptibility breakpoint

RESULTS

Table 4. AUC/MIC for Oral Dosing With and Without Loading Dose Administration for *S. pneumoniae* and *S. aureus*

Therapy	*S. pneumoniae* MIC_{50} (0.06 µg/mL)	*S. pneumoniae* MIC_{90} (0.12 µg/mL)	*S. aureus* MIC_{50} (0.12 µg/mL)	*S. aureus* MIC_{90} (0.25 µg/mL)	*S. aureus* ABSSSI Susc BP[a] (0.50 µg/mL)
Day 2					
No load	118 (104, 139)	59 (52, 69)	59 (52, 69)	28 (25, 33)	14 (13, 17)
Load	161 (137, 207)	81 (69, 103)	81 (69, 103)	39 (33, 50)	19 (16, 25)
Day 5					
No load	138 (121, 164)	69 (60, 82)	69 (60, 82)	33 (29, 39)	17 (14, 20)
Load	142 (125, 168)	71 (62, 84)	71 (62, 84)	34 (30, 40)	17 (15, 20)

[a]FDA approved susceptibility breakpoint for *S. aureus* for ABSSSI

Data presented as mean (95% CI)

ABSSSI = acute bacterial skin and skin structure infections; AUC = area under the concentration–time curve; MIC = minimum inhibitory concentration; Susc BP = susceptibility breakpoint

CONCLUSIONS

- Omadacycline exposure as assessed by AUC was lower early on in therapy (Day 2) for oral and IV regimens when a loading dose was not used. However, exposures on Day 5 were not different and thus were not impacted by the absence of a loading dose
- Despite lower exposures on Day 2 without a loading dose, omadacycline would be expected to meet or exceed PK/PD thresholds associated with stasis for both *S. pneumoniae* and *S. aureus*. The 1_{log} kill threshold was met or exceeded regardless of the use of a loading dose for *S. pneumoniae*; however, for *S. aureus* the 1_{log} kill threshold was met only at MIC values <0.25 µg/mL
- Using the AUC/MIC threshold (12.5) identified in the Phase 3 ABSSSI studies, which correlated with early clinical response, both the IV and oral load and no-load regimens would be expected to exceed this threshold for *S. aureus*, the pathogen most frequently associated with ABSSSI for MICs ≤0.5 µg/mL, which is the FDA susceptibility breakpoint
- Further studies are needed to confirm the clinical impact of omission of a loading dose in patients with CABP or ABSSSI

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