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Post-antibiotic Effect of Omadacycline against Target Pathogens

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ABSTRACT

Background: Omadacycline (OMC) is a new once daily oral and IV aminomethylcycline under phase 3 development for the treatment of serious community-acquired skin and respiratory infections. To better understand the pharmacodynamic properties during dosing, it is important to evaluate the post-antibiotic effect (PAE). In this study, the PAE of OMC, tigecycline (TIG), and linezolid (LZD) was evaluated against target pathogens.

Methods: MICs of OMC, TIG, and LZD were determined in accordance with CLSI M7 against clinical isolates of *S. aureus* (n=2; 1 MRSA), *E. faecalis* (n=1), *E. faecium* (n=1; VRE), *S. pneumoniae* (n=2; 1 PRSP), and *E. coli* (n=1). PAE was evaluated after initial exposure of log-phase bacteria to 5X the MIC of OMC, TIG, or LZD for 1 hr alongside an unexposed control. Post-exposure, the drug was removed by making a 1:1000 dilution into fresh drug free media for 10 hr. Viable bacteria were enumerated at 2 h intervals post-exposure. PAE was calculated as the time it took for bacteria to grow 1-log after initial exposure and drug washout relative to unexposed controls.

Results: The PAE (hr) of OMC, TIG, and LZD after exposure to 5X the MIC is shown in the table below.

Test Agent	*S. aureus* MSSA/MRSA	*E. faecalis* VSE	*E. faecium* VRE	*E. coli*	*S. pneumoniae* PSSP/PRSP
OMC	2.6/2.2	2.0	2.1	1.4	3.3/2.3
TIG	3.9/2.5	3.8	4.4	1.4	3.2/3.6
LZD	1.3/1.0	1.2	1.8	not tested	2.2/1.5

Similar initial exposure concentrations (µg/mL) were used for OMC (1.25 – 5) and TIG (0.6 – 2.5) across isolates except for *S. pneumoniae* (0.15 – 0.3 for OMC and TIG). Initial exposure for LZD was higher (5 – 20 µg/mL). OMC PAEs varied between 1.4 hr (E. coli) and 3.3 hr (*S. pneumoniae*). TIG PAEs were similar to OMC PAEs with the exception of enterococci where the TIG PAE was slightly longer (3.8 – 4.4 hr) compared to OMC (2.0 – 2.1 hr). OMC and TIG PAEs were longer than LZD (PAEs between 1.0 and 2.2 hr) for all organisms tested.

Conclusions: Overall, the PAE of OMC was similar to that of TIG with the exception of the evaluated enterococci where slightly longer PAEs were observed with TIG relative to OMC. Both OMC and TIG exhibited prolonged PAE relative to LZD. These PAE data demonstrate some prolonged activity of OMC and TIG which may provide a benefit in the treatment of serious community-acquired bacterial infections.

BACKGROUND

- Omadacycline (OMC) is an aminomethylcycline currently undergoing phase 3 clinical development by Paratek Pharmaceuticals as a once daily oral or IV treatment of community acquired skin and respiratory infections.
- OMC has potent broad spectrum activity against target skin and respiratory pathogens, including resistant isolates (e.g. MRSA, penicillin-resistant *S. pneumoniae* [PRSP], vancomycin-resistant enterococci [VRE]).
- A persistent suppressive effect or "post-antibiotic effect (PAE)" on bacterial growth can sometimes be observed in vitro after removal of an antibiotic, and such an effect can provide insight into the pharmacodynamics of that agent.
- PAE could be due to either non-lethal damage produced by the antibiotic or the persistence of the antibiotic at bacterial binding sites, either of which may be sufficient for continuation of the bacteriostatic effect following drug removal.
- Studies evaluating the PAE, as determined by monitoring growth of target organisms in vitro after exposure to an antibiotic followed by its subsequent removal[1], are required by the Food and Drug Administration prior to filing for approval[2].

OBJECTIVE

To evaluate the PAE of omadacycline (OMC), tigecycline (TIG), and linezolid (LZD) against *S. aureus* (including MRSA), *S. pneumoniae* (including PRSP), enterococci (including VRE), and *E. coli*.

METHODS

- Clinical isolates (**Table 1**) were evaluated in cation-adjusted Mueller-Hinton broth (CAMHB) or CAMHB supplemented with 3% lysed horse blood (*S. pneumoniae* only).
- MIC values were determined by broth microdilution in accordance with CLSI guidelines[3-4].
- For PAE, log-phase inocula at approximately 5 x 10^6 – 5 x 10^7 CFU/mL were initially exposed at 5X the MIC for 1 hour alongside an unexposed growth control (viable bacteria pre- [T-1] and post-exposure [T0] were quantitated by serial dilution plating in duplicate).
- After exposure, drug was removed by making a 1:1000 dilution into fresh antibiotic-free media, and viable bacteria were quantitated every 2 hr for a total period of 10 hr.
- Viable counts were plotted versus time and the PAE (time for 1-log regrowth post-exposure and removal minus the time for 1-log regrowth of the growth control [GC]) were extrapolated from the resulting graphs.

RESULTS

- MIC values for OMC and the comparators were within the established QC range[4] when tested against *S. aureus* ATCC 29213 and *S. pneumoniae* ATCC 49619 (data not shown).
- Potent activity was observed for OMC and the comparator agents against the evaluated isolates, and this activity was consistent regardless of the resistance phenotype (**Table 1**).
- A summary of PAE as observed with OMC and the comparators after an initial exposure to 5X the MIC for 1 hr is shown in **Table 2**.
- Plots of $\log_{10}$ CFU/mL post-exposure over time are shown by organism in **Figures 1-4** along with the time (hr) for 1-log regrowth in each figure legend.
- OMC and TIG PAEs were generally similar across evaluated isolates, with the exception of enterococci where the TIG PAE was slightly longer (3.8 – 4.4 hr) compared to OMC (2.0 – 2.1 hr).
- OMC and TIG PAEs were longer than those observed with LZD (1.0 – 2.2 hr) across evaluated isolates.

RESULTS

Table 1. MIC (µg/mL) of OMC, TIG, and LZD for the evaluated isolates

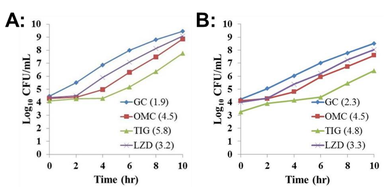
Organism	Isolate	Phenotype	MIC (µg/mL)		
			OMC	TIG	LZD
S. aureus	0753	MSSA	0.5	0.25	4
	2053	MRSA	0.5	0.5	2
S. pneumoniae	7816	PSSP	0.06	0.03	1
	7822	PRSP	0.06	0.06	1
E. faecalis	0796	VSE	0.5	0.25	4
E. faecium	0752	VRE	0.25	0.12	4
E. coli	1316	-	1	0.25	-

Table 2. PAE (hr) of OMC, TIG, and LZD observed with the evaluated isolates

Organism	Isolate	Phenotype	PAE (hr)		
			OMC	TIG	LZD
S. aureus	0753	MSSA	2.6	3.9	1.3
	2053	MRSA	2.2	2.5	1.0
S. pneumoniae	7816	PSSP	3.3	3.2	2.2
	7822	PRSP	2.3	3.6	1.5
E. faecalis	0796	VSE	2.0	3.8	1.2
E. faecium	0752	VRE	2.1	4.4	1.8
E. coli	1316	-	1.4	1.4	-

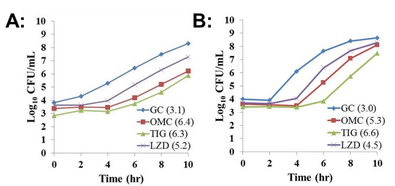
OMC = omadacycline; TIG = tigecycline; LZD = linezolid; MSSA = methicillin-susceptible S. aureus; MRSA = methicillin-resistant S. aureus; PSSP = penicillin-susceptible S. pneumoniae; PRSP = penicillin-resistant S. pneumoniae; VSE = vancomycin-susceptible enterococci; VRE = vancomycin-resistant enterococci

Figure 1. Viable Bacteria Recovered Over Time after Initial Exposure of *S. aureus* (A) 0753 – MSSA and (B) 2053 – MRSA to 5X the MIC of OMC, TIG, and LZD



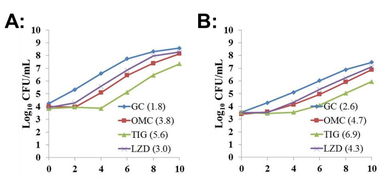
Time to 1-log regrowth (hr) shown in legend in parenthesis

Figure 2. Viable Bacteria Recovered Over Time after Initial Exposure of *S. pneumoniae* (A) 7816 – PSSP and (B) 7822 – PRSP to 5X the MIC of OMC, TIG, and LZD



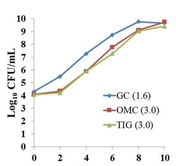
Time to 1-log regrowth (hr) shown in legend in parenthesis

Figure 3. Viable Bacteria Recovered Over Time after Initial Exposure of (A) *E. faecalis* 0796 – VSE and (B) *E. faecium* 0752 – VRE to 5X the MIC of OMC, TIG, and LZD



Time to 1-log regrowth (hr) shown in legend in parenthesis

Figure 4. Viable Bacteria Recovered Over Time after Initial Exposure of *E. coli* 1316 to 5X the MIC of OMC, TIG, and LZD



Time to 1-log regrowth (hr) shown in legend in parenthesis

CONCLUSIONS

- Overall, the PAE of omadacycline was similar to that of tigecycline, excluding enterococci where slightly longer PAEs were observed with tigecycline relative to omadacycline.
- Both omadacycline and tigecycline exhibited a longer PAE relative to linezolid.
- Though the clinical relevance of the PAE observed with omadacycline and tigecycline is unknown, the prolonged activity of omadacycline and tigecycline may provide a benefit in the treatment of serious community-acquired infections.

Acknowledgements

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References

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