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Omadacycline pharmacokinetics and soft-tissue penetration in diabetic patients with wound infections and healthy volunteers using *in vivo* microdialysis

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Objectives: We assessed the plasma and soft-tissue pharmacokinetic exposure of omadacycline in infected patients with diabetic foot infection (DFI) and healthy volunteers using *in vivo* microdialysis.

Methods: Eight patients and six healthy volunteers were enrolled and received an omadacycline IV loading dose (200 mg) followed by two oral doses (300 mg) every 24 h. Microdialysis catheters were placed in the soft tissue near the infected diabetic foot wound (patients) or thigh (healthy volunteers). Plasma and dialysate fluid samples were collected, starting immediately prior to the third dose and continued for 24 h post-dose. Protein binding was determined by ultracentrifugation.

Results: The mean ± SD omadacycline pharmacokinetic parameters in plasma for infected patients and healthy volunteers were: C_{max}, 0.57 ± 0.15 and 1.14 ± 0.26 mg/L; $t_{½}$, 16.19 ± 5.06 and 25.34 ± 12.92 h; and total omadacycline $AUC_{0–24}$, 6.27 ± 1.38 and 14.06 ± 3.40 mg·h/L, respectively. The omadacycline mean plasma free fraction was 0.21 and 0.20 for patients and healthy volunteers, corresponding to free plasma $AUC_{0–24}$ of 1.13 ± 0.37 and 2.78 ± 0.55 mg·h/L, respectively. Omadacycline tissue $AUC_{0–24}$ was 0.82 ± 0.38 and 1.37 ± 0.48 mg·h/L for patients and volunteers, respectively.

Conclusions: The present study describes the plasma and soft-tissue exposure of omadacycline in patients with DFI and healthy volunteers. Integrating these data with the microbiological, pharmacokinetic/pharmacodynamic and clinical efficacy data is foundational to support clinical assessments of omadacycline efficacy specifically for DFI. This, coupled with the once-daily oral administration, suggests omadacycline could be an advantageous translational therapy for the hospital and outpatient setting.

Introduction

Diabetic foot infections (DFIs) are associated with significant morbidity and mortality for patients with diabetes.[1] DFIs account for 10% of all skin and soft tissue infections (SSTIs) and are associated with greater complications compared with SSTI in patients without diabetes.[2] As a result, patients with DFI are more likely to require visits to the emergency department or inpatient admission.[3] The burden of complications from DFI include the need for surgery and potentially amputation.[1] Antimicrobial therapy covering the most likely bacterial pathogens and surgical intervention are the mainstay of therapy for DFI, and novel antimicrobials, especially orally available agents, provide clinicians with alternative treatment options for these complex infections.[4]

Omadacycline is a novel aminomethylcycline approved by the FDA for community-acquired bacterial pneumonia and acute bacterial skin and skin structure infections (ABSSSI).[5] Omadacycline offers a favourable profile for use in DFI due to its microbiological activity against common pathogens associated with DFI, including MRSA and *Streptococcus* spp.[6,7] Additionally, omadacycline offers *in vitro* activity against more challenging DFI pathogens such as *Enterococcus* spp., including vancomycin-resistant isolates that challenge clinicians with limited treatment options.[6,7] Pharmaceutically, omadacycline offers advantages in its once-daily dosing frequency and availability as IV and oral formulations.[5] Phase III randomized controlled trials for ABSSSI have shown omadacycline was non-inferior to linezolid.[8] Collectively, these characteristics of omadacycline suggest it may be a valuable agent in the treatment of DFI.

Physiological changes such as hyperglycaemia and venous/arterial insufficiency in the lower extremities of patents with diabetes predispose patients to impaired wound healing, infection and potentially alterations in the pharmacokinetic exposure of antibiotics at the site of infection.[1,9] Although the pharmacokinetics of omadacycline have been well described in plasma (healthy volunteers and infected patients) and epithelial lining fluid (healthy volunteers), its exposure at the site of infection for ABSSSI has yet to be evaluated.[10,11] *In vivo* microdialysis has been utilized to assess the tissue exposure of antimicrobial agents at the site of infection for ABSSSI.[9] The purpose of the present study was to determine omadacycline exposure in the interstitial fluid of the soft tissue in patients with active DFI and in healthy volunteers.

Methods

Ethics

This study was approved by the Hartford Healthcare Institutional Review Board and written informed consent was obtained for all participants.

Study participants

This present study (NCT04144374) was a single-centre, open-label, observational pharmacokinetic study conducted in eight infected patients with DFI and six healthy volunteers. Infected patients over 18 years old were eligible for inclusion if they had a documented history of type 1 or type 2 diabetes mellitus requiring anti-hyperglycaemic therapy. Inclusion criteria required that patients had an active complicated SSTI as defined by PEDIS Grade 2 or 3 infections.[4] Patients continued their standard-of-care antibiotics to treat the infection during the study period. Additional exclusion criteria for the infected patients included the need for multiple surgical interventions during the study period that could affect the placement of the microdialysis catheter.

For the healthy volunteer cohort, men or women over the age of 18 years were eligible for inclusion. For the healthy volunteers, exclusion criteria included BMI $\geq$35 kg/m^2; serum creatinine >1.5 mg/dL or creatinine clearance <50 mL/min; presence of anaemia, thrombocytopenia or leukopenia (cut-off <75% of the lower limit of normal); AST, ALT or alkaline phosphatase greater than five times the upper limits of normal (ULN); and total bilirubin over three times the ULN. Additionally, healthy volunteers were excluded if they had a positive urine drug screen during screening (<28 days prior to study) or within 24 h of study initiation; regular alcohol use exceeding 7 drinks per week for women or 14 drinks per week for men; or use of any tobacco or nicotine products over 5 cigarettes per day. Participants were not permitted to consume caffeine or any other medications/supplements during the study period except hormonal contraceptives.

Exclusion criteria that applied to both groups were: history of hypersensitivity to any tetracycline antibiotics; history of hypersensitivity to lidocaine; being pregnant or breastfeeding; or receiving concomitant therapy with a tetracycline.

Pre-study, all participants received a physical examination. Clinical laboratory tests, including serum electrolyte panel, serum creatinine, liver function panel, complete blood count with differential, glycosylated haemoglobin (haemoglobin A1c) (infected patients only), albumin and microscopic urinalysis were performed. Urine pregnancy tests were required for women of childbearing potential. A urine sample for screening of common drugs of abuse was collected (healthy volunteers only).

Study medication

Omadacycline was provided by Paratek Pharmaceuticals (Boston, MA, USA). On study Day 1, all participants received a loading dose of omadacycline 200 mg IV as a 60 min infusion.[5] On study Days 2 and 3, participants received omadacycline 300 mg by mouth. All doses were separated by 24 h. Additionally, oral doses were administered after 4 h of fasting and no food or drink except water were consumed for 2 h following administration.[5] No dairy products, antacids or multivitamins were allowed for at least 4 h after taking the oral dose.

Microdialysis procedure

A microdialysis probe (63 MD catheter, M Dialysis Inc., N. Chelmsford, MA, USA) with a membrane length of 30 mm and molecular weight cut-off of 30 kDa was inserted subcutaneously for both inpatients and healthy volunteers. For inpatients, the catheter was inserted into the extravascular subcutaneous tissue of the lower extremity within 10 cm of the margin of the infected wound. For healthy volunteers, the catheter was placed in the subcutaneous tissue of the thigh. Catheters were placed prior to the administration of the third and final omadacycline dose. After catheter insertion, the probe was flushed and then perfused with 0.9% sodium chloride for injection solution at a rate of 2 μL/min. All samples were collected in 200 μL microvials (M Dialysis Inc.) over a period of 1 h.

Sample collection

Sampling was conducted beginning before the third and final omadacycline dose (dosing time considered to be 0 h) and continued for the following 24 h. Plasma samples were collected at 0, 1, 2, 2.5, 3, 4, 6, 8, 12, 16, 20 and 24 h in sodium heparin-containing blood tubes (Becton, Dickinson and Company, Franklin Lakes, NJ, USA). Samples were centrifuged at 2000 **g** for 10 min and separated plasma was stored at −80°C until analysis. Dialysate samples were collected concurrently with blood sampling at 0, 1, 2, 3, 4, 8, 12, 16, 20 and 24 h. Microdialysis samples were stored frozen at −80°C until concentration determination.

Microdialysis probe recovery by in vivo retrodialysis

After dialysate sampling was concluded, the catheter was calibrated by a retrodialysis technique over a 1 h interval to assess recovery of the antibiotic through the dialysis membrane.[9] A calibration standard concentration of omadacycline (100 mg/L in normal saline) served as the perfusate and its rate of diffusion through the membrane determined the recovery rate by obtaining a dialysate sample during this retrodialysis process. Recovery of omadacycline via retrodialysis was calculated and used to correct the omadacycline tissue concertation as determined by the analytical procedure using the following formula:

$$\%\text{Recovery} = 100 - (\text{concentration}_{\text{dialysate}}/\text{concentration}_{\text{perfusate}} \times 100).$$

In vitro microdialysis loss assessment

To assess the potential for omadacycline to adhere to any portion of the microdialysis apparatus or microvials, we conducted an *in vitro* loss experiment. Three replicates of omadacycline solution (0.02 mg/L) were prepared in normal saline and loaded into three different microdialysis syringes. One aliquot of each nominal concentration was frozen to serve as the baseline concentration. A second aliquot was inoculated directly into the microdialysis microvials and frozen until concentration determination. Each omadacycline-containing microdialysis syringe was then perfused through microdialysis catheters and collected in microvials as done *in vivo*. Microvials collected perfusate over 1 h intervals at 1, 2, 3, 4, 6 and 8 h. Samples were stored at −80°C until analysis.

Protein-binding determination and non-specific binding

Protein binding was performed for each participant at the 2.5 h timepoint to correspond with the reported omadacycline peak.[5] At the 2.5 h sampling timepoint, an additional 20 mL of blood was collected. Samples

were centrifuged as described above and one aliquot of plasma was frozen to serve as the total omadacycline plasma concentration for percent protein-binding determination. The remaining plasma was transferred into three Centrifree ultrafiltration devices (Millipore Corporation, Billerica, MA, USA), which were then centrifuged for 45 min at 2000 **g**. Three ultrafiltrate replicates were obtained for each participant and frozen at −80°C until concentration determination. Each ultrafiltrate concentration represented the free plasma omadacycline concentration and the three replicates were averaged for each participant. Omadacycline free fraction was calculated using:

$$\text{Free fraction} = \text{concentration}_{\text{ultrafiltrate}}/\text{concentration}_{\text{plasma}}.$$

The free fraction was then used to calculate unbound plasma omadacycline concentrations for each participant.

To assess the possibility of omadacycline binding to the ultrafiltration devices, non-specific binding was assessed. Three nominal concentrations of omadacycline were made in normal saline (1, 0.1 and 0.02 mg/L). An aliquot of each stock concentration was frozen at −80°C for concentration determination while a second aliquot of 0.9 mL was loaded into one Centrifree ultrafiltration device. All ultrafiltration devices were then centrifuged as described above for the protein-binding samples. The ultrafiltrate was frozen and was compared with the concentration determined in the stock solution aliquot. This procedure was repeated in triplicate on 3 different days.

Omadacycline concentration determination

Omadacycline concentrations were determined using LC-MS/MS (ICPD, Schenectady, NY, USA). Three standard curves were utilized and were linear over the range of concentrations listed: low saline curve (0.005–1 mg/L), high saline curve (5–100 mg/L) and plasma curve (0.02–5 mg/L). The correlation coefficient (r^2) values were 0.9985–0.997, 0.994–0.995 and 0.990–0.994 for each curve, respectively. The interday coefficient of variation values for each curve were 3.45%–6.1%, 1.3%–4.74% and 2.29%–6.03%, respectively.

Pharmacokinetic analysis

Non-compartmental pharmacokinetic analysis was conducted using Phoenix WinNonlin (version 6.4, Pharsight Corporation, Mountain View, CA, USA). Pharmacokinetic parameters for plasma were determined using each individual's plasma concentration–time profile. The C_{max} and T_{max} for each participant were estimated by visual inspection of the concentration–time profiles. The log-linear trapezoidal method was used to determine AUC_{0-24} (plasma) for each participant. The elimination rate constant (K_e) was estimated by the slope of the terminal portion of the concentration–time profile using no less than three concentration timepoints; $t_{½}$ was calculated by $0.693/K_e$. Total plasma clearance (CL/F) was calculated by dose/AUC_{0-24} (plasma). Volume of distribution (*V*d/F) was calculated by CL/F divided by K_e. All microdialysis concentrations were corrected for microdialysis probe recovery before pharmacokinetic analysis as follows:

$$\text{Concentration}_{\text{tissue}} = 100 \times (\text{concentration}_{\text{MicroD sample}}/\%\textit{in vivo}\ \text{recovery}).$$

The AUC_{tissue} was determined using the log-linear trapezoidal rule and ratio of penetration into tissue was calculated as follows: $AUC_{tissue}/fAUC_{plasma}$.

Safety assessment

Participants were monitored for any sign or symptom of adverse events throughout the course of the study. All adverse events requiring medical attention were assessed and treated by the study physician and were recorded. After completion of all sampling and removal of microdialysis catheters, an end-of-study exit evaluation was assessed, including a full physical examination, vital signs, blood testing and urinalysis.

Results

Study participants

Eight inpatients with DFI consented and were enrolled in the study. Pharmacokinetic sampling was completed for six patients. One patient was unable to have the microdialysis catheter placed due to post-surgical anatomical changes to the infected foot. The second inpatient was unable to complete study sampling due to dislodgement of the microdialysis catheter. All eight patients received three doses of omadacycline and were assessed for safety and tolerability.

Six healthy volunteers consented, were enrolled and all received three doses of omadacycline. All six healthy volunteers had microdialysis catheters placed and completed blood and tissue sampling timepoints.

The baseline characteristics of the 12 subjects who underwent the pharmacokinetic analysis are presented in Table 1. Considering baseline characteristics, the healthy volunteers were younger and had lower BMIs, which is expected compared with the cohort of patients with a history of diabetes and active infection. Most participants from each group were male. In the infected patient cohort, the mean haemoglobin A1C was 9% and four of six patients had PEDIS Grade 3 infections. The standard-of-care regimens for the six infected patients with DFI included vancomycin alone ($n=4$), vancomycin and cefepime ($n=1$) and cefazolin alone ($n=1$).

Non-specific binding and in vitro microdialysis

Non-specific binding to the ultracentrifuge devices was not observed as mean recovery rates of 97%, 97% and 98% were detected for the 1, 0.1 and 0.02 mg/L concentrations, respectively.

Table 1. Characteristics of study participants separated by cohort

Characteristic	Infected patients with DFI $N=6$	Healthy volunteers $N=6$
Age, mean (SD)	55 (4)	45 (15)
Male, *n* (%)	5 (83)	4 (67)
Height (cm), mean (SD)	175 (4)	173 (11)
Weight (kg), mean (SD)	93 (18)	79 (16)
BMI (kg/m^2), mean (SD)	30 (7)	26 (3)
Albumin (g/dL), mean (SD)	3.47 (0.7)	4.52 (0.15)
Haemoglobin A1C (%), mean (SD)	9 (1.6)	—
PEDIS infection grade, *n* (%)		
2	2 (33)	—
3	4 (66)	—

Baseline characteristics of infected patient participants and healthy volunteers who completed all pharmacokinetic analyses. PEDIS = perfusion, extent (size), depth (tissue loss), infection, sensation (neuropathy). Grade derived from Lipsky *et al.*[4]

During the *in vitro* loss experiments, all samples that came in contact with the microvials (including those that passed through the catheter and those directly inoculated into the microvials) had lower concentrations compared with the pre-experiment stock (mean 16% lower, range 4%–29%) suggesting binding of omadacycline to the microvial. Based on these data, tissue concentrations were corrected for the average 16% microvial loss.

Plasma pharmacokinetics

The plasma pharmacokinetic parameters from both evaluated cohorts are presented in Table 2. Figure 1 depicts the mean ± SD total omadacycline plasma concentration over the 24 h dosing interval for both infected patients and healthy volunteers. The mean pre-third dose trough and mean post-third dose trough were 0.20 ± 0.06 and 0.16 ± 0.05 mg/L, respectively, for the cohort of infected patients with DFI. For the healthy volunteers, the mean pre-third dose trough and mean post-third dose trough were 0.33 ± 0.06 and 0.36 ± 0.09 mg/L, respectively, suggesting participants reached steady-state. The average calculated $t_{½}$ in the infected patients was 16.19 h compared with 25.34 h in the healthy volunteers. *Vd*/F was higher in the infected patients at 1190.40 compared with 808.38 L, respectively. The total $AUC_{0–24}$ was 6.27 mg·h/L for infected patients and 14.06 mg·h/L for healthy volunteers. Omadacycline free fraction was similar in both cohorts with infected patients having an average free fraction of 0.21 while the healthy volunteers had an average free fraction of 0.20, resulting in plasma $fAUC_{0–24}$ of 1.30 and 2.78 mg·h/L, respectively.

Tissue exposure

In vivo recovery by retrodialysis was 60% ± 14% and 74% ± 16% for infected patients and healthy volunteers, respectively. Following correction for retrodialysis recovery, omadacycline tissue concentrations were corrected for *in vitro* recovery for each subject by 16% due to microvial loss. Mean AUC_{tissue} values were 0.82 and 1.37 mg·h/L for infected patients and healthy volunteers, respectively. Subsequent penetration ratios were 0.66 and 0.54, respectively. The omadacycline tissue concentration–time profiles are presented in Figure 2.

Table 2. Plasma and tissue omadacycline pharmacokinetic parameters from cohort of infected patients with DFI and healthy volunteers after the third dose of omadacycline 300 mg administered orally

Pharmacokinetic parameter, mean (SD)	Infected patients with DFI *N* = 6	Healthy volunteers *N* = 6
Plasma C_{max} (mg/L)	0.57 (0.15)	1.14 (0.26)
Plasma T_{max} (h)	2.75 (0.42)	2.33 (0.26)
Plasma $t_{½}$ (h)	16.19 (5.06)	25.34 (12.92)
Plasma CL/F (L/h)	50.70 (10.32)	22.53 (6.00)
Plasma *Vd*/F (L)	1190.40 (479.07)	808.38 (431.49)
Total plasma $AUC_{0–24}$ (mg·h/L)	6.27 (1.38)	14.06 (3.40)
Free plasma $AUC_{0–24}$ (mg·h/L)	1.30 (0.37)	2.78 (0.55)
Plasma free fraction	0.21 (0.03)	0.20 (0.02)
Tissue $AUC_{0–24}$ (mg·h/L)	0.82 (0.38)	1.37 (0.48)
Tissue penetration	0.66 (0.35)	0.54 (0.30)

Safety and tolerability

Omadacycline administration was generally well tolerated. Four subjects, two subjects in each cohort, experienced an adverse event. For the infected cohort, two participants experienced three adverse events, with one participant experiencing nausea and vomiting, that were treated with ondansetron and considered mild in severity. The second infected patient with a documented adverse event had mild tingling at the site of infusion after the first IV omadacycline dose and this patient tolerated all oral doses.

Of the healthy volunteers, two experienced a total of three adverse events. One healthy volunteer experienced nausea and a mild headache, while the second experienced nausea. No adverse events were noted for any of the other 10 participants who received omadacycline.

Discussion

Due to potent anti-staphylococcal and -streptococcal activity and a once-daily oral formulation, omadacycline represents an attractive therapeutic option for the treatment of patients with DFI. The present study elucidated the plasma and tissue pharmacokinetic profile of omadacycline in both infected patients with DFI and healthy volunteers. Omadacycline concentrations were detectable in the interstitial space of soft tissue in both patients and healthy volunteers. These data must be considered with the microbiological, pharmacokinetic/pharmacodynamic and clinical trial data to determine utility in DFI.

Indeed, the total omadacycline exposure profiles in the plasma of both healthy volunteers and infected patients with DFI were similar to previous pharmacokinetic studies. The average total plasma AUC values in healthy subjects in this study were similar to those from Phase I data who also received the 300 mg oral dosage every 24 h with steady-state total $AUC_{0–24}$ of 14.06 and 11.16 mg·h/L, respectively.[5] A longer $t_{½}$ was found in our healthy subject cohort compared with others (25.34 compared with 15 h, respectively).[5] This finding is likely due to our sampling scheme, which was executed over 24 h, as this study was designed to evaluate the plasma and tissue omadacycline exposure (i.e. AUC) at steady-state over a 24 h dosing interval. Sampling beyond 24 h is needed to more accurately characterize the plasma $t_{½}$. Similarly, plasma samples in the present study were collected at 4 h intervals over the final 12 h of the dosing interval, which may cause differences in $t_{½}$ based on assay variability compared with previous assessments in healthy volunteers having longer intervals between timepoints (i.e. 12 h).[11] The total omadacycline concentration profile in our study was similar to that seen in patients from the clinical trial programme.[10] In these infected patients, a larger *Vd*/F was noted compared with the healthy volunteers and has been well described in the setting of acute infection for numerous antimicrobials including omadacycline.[10] Of note, covariates associated with the pharmacokinetic parameters derived in this study were not undertaken since the present study sought to evaluate the target-site exposure of omadacycline in patients and healthy volunteers. Indeed, a previous evaluation found only sex was a significant covariate identified in previous population analysis.[10]

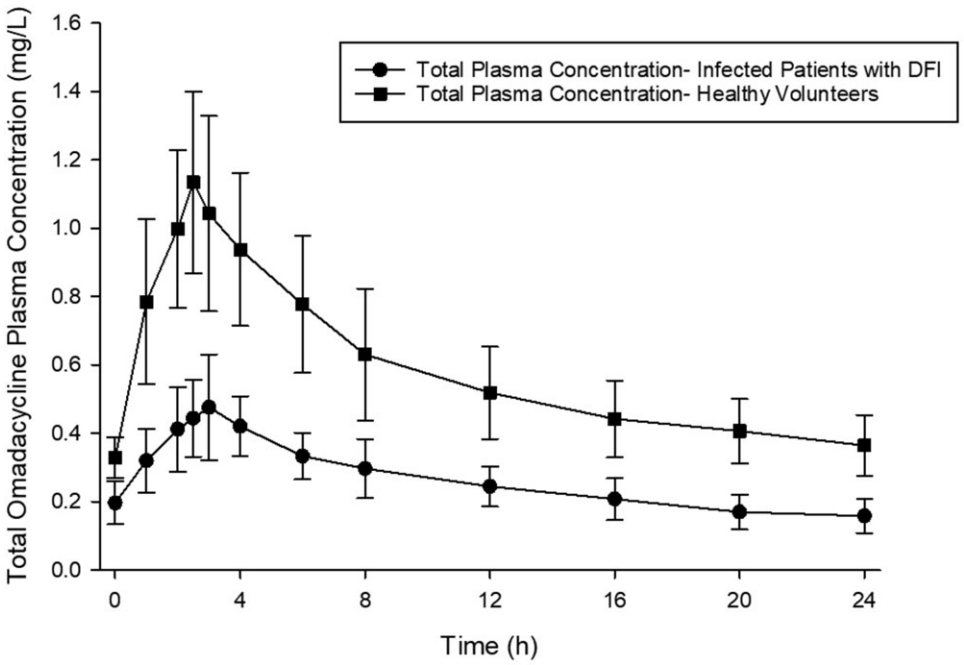

Figure 1. Mean total omadacycline plasma concentrations (±SD) collected over 24 h starting prior to the third of three omadacycline doses (one 200 mg IV and two 300 mg oral).

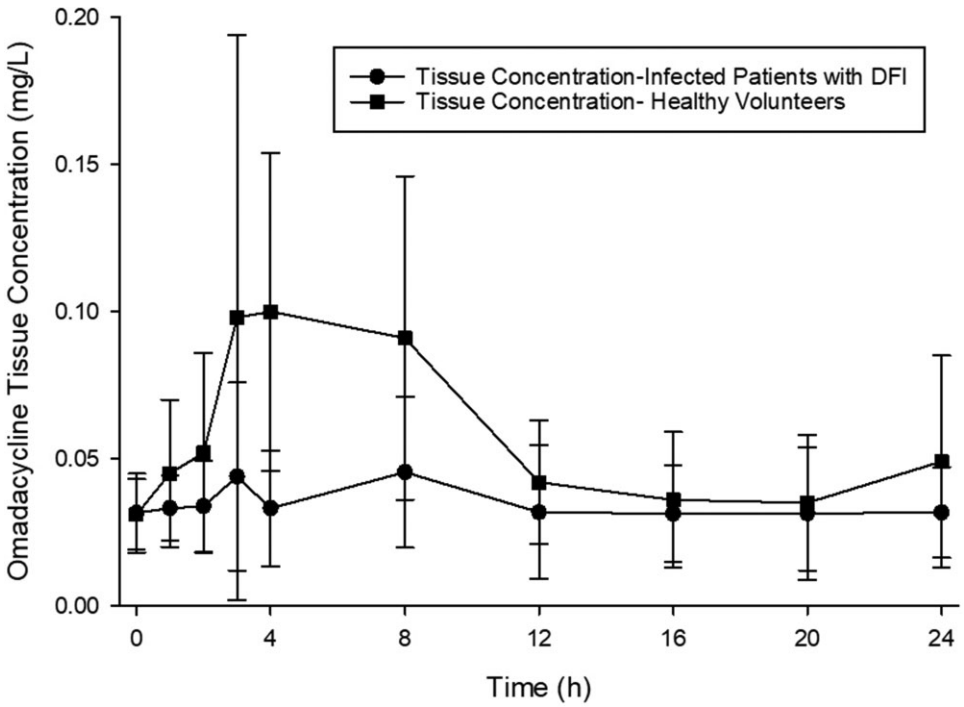

Figure 2. Mean omadacycline tissue concentrations (±SD) collected over 24 h starting prior to the third of three omadacycline doses.

In both our healthy-subject and infected-patient cohorts the free fraction of omadacycline was measured to be 0.20 and 0.21, respectively. These data differ from the previously determined *in vitro* free fraction of ~80%, although the omadacycline protein binding determined in our study cohorts is consistent with other tetracycline agents (doxycycline 82%–93%; minocycline 76%; tigecycline 73%–79%, concentration dependent).[12,13] While we conducted non-specific binding experiments and ruled

out excess binding of omadacycline to the ultrafiltration devices, differences in protein-binding determination methodology, such as our use of fresh whole blood versus the use of pooled human plasma in the previously conducted *in vitro* study, may explain the observed discordance.

It is important to consider the absolute exposure in plasma and tissue rather than penetration ratio in the context of the pharmacokinetic/pharmacodynamic targets relative to the target bacteria for DFI. Lepak and colleagues[14] evaluated the pharmacodynamic targets for *S. aureus* in the neutropenic murine thigh infection model. A median total plasma AUC/MIC target of 21.9 predicted bacteriostasis, an endpoint previously used to predict efficacy in ABSSSI.[14,15] It must be noted the pharmacodynamic targets determined in this study used total plasma omadacycline concentration as a surrogate to predict efficacy as the omadacycline concentrations at the site of infection (i.e. murine thigh muscle) are not practically determined. Using these principles, the total omadacycline plasma concentration in both cohorts achieved the bacteriostasis target for *S. aureus* as determined in the murine model up to the *S. aureus* and *Enterococcus* spp. MIC_{90} of 0.25 mg/L.[6] Notably, this target was met for all six healthy volunteers in the present study. Of the infected patients, three of six met this median $AUC/MIC_{0.25\ mg/L}$ target of 21.9, however; the three patients who did not meet this target had $AUC/MIC_{0.25\ mg/L}$ ratios of 19.7–21.7, and thus all would meet the target for *S. aureus*/*Enterococcus* spp. up to the MIC_{50} and for *S. pyogenes* up to the MIC_{90} of 0.125 mg/L.[6,15] Our use of the *in vivo* microdialysis technique in this infected diabetic patient population has allowed the establishment of the omadacycline concentration–time profile in the interstitial/extracellular space. While the AUC_{tissue}/MIC efficacy target has not been established in man, the resultant infection-site concentrations as reported in the current study appear to be sufficiently high, as Phase III clinical trial data using the same dosing regimen have demonstrated the efficacy of omadacycline in the treatment of ABSSSI, including diabetes patients with lower limb infections.[8,16] Taken collectively, the plasma and tissue exposure data from the present study support the established pharmacokinetic/pharmacodynamic profile of omadacycline and the compound's clinical and microbiological success observed in the clinical trial programme.

In conclusion, total plasma concentrations in both cohorts were similar to that previously seen in infected patients in the Phase III randomized controlled trials and healthy volunteers. Additionally, omadacycline was well tolerated in infected patients with DFI and healthy volunteers. Integrating these findings with the previously established pharmacodynamic and microbiological profiles of omadacycline suggests that the once-daily IV and oral formulations represent a novel option for the treatment of lower-limb ABSSSI in the diabetic population.

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Transparency declarations

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