In Vitro Activity and In Vivo Efficacy of Cefiderocol Against Stenotrophomonas maltophilia

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ABSTRACT

Cefiderocol is a novel siderophore cephalosporin antibiotic with broad coverage against difficult-to-treat Gram-negative bacteria, including those resistant to carbapenems. Its activity against Stenotrophomonas maltophilia was investigated in vitro against clinical isolates and in lung infection models using strains either resistant (SR202006) or susceptible (SR201934, SR200614) to trimethoprim/sulfamethoxazole. Cefiderocol demonstrated potent in vitro activity against all 217 S. maltophilia clinical isolates tested (MIC$_{50}$: 0.063 µg/mL, MIC$_{90}$: 0.25 µg/mL). Cefiderocol also demonstrated low MICs against the trimethoprim/sulfamethoxazole-resistant S. maltophilia strains (i.e. SR202006: MIC=0.125 µg/mL). In a neutropenic mouse lung infection model, cefiderocol (30 mg/kg and 100 mg/kg) demonstrated a significant, dose-dependent reduction in the lung viable bacteria cell count compared with untreated controls in S. maltophilia infection and was the only antibiotic tested to show a similar significant effect in a trimethoprim/sulfamethoxazole-resistant S. maltophilia infection. In immunocompetent rat lung infection models of S. maltophilia, humanized dosing of cefiderocol (2 g every 8 hours) and meropenem (1 g every 8 hours) revealed pharmacokinetic profiles similar to those in human subjects and the humanized cefiderocol dosing significantly reduced the lung viable bacteria cell count compared with baseline controls, which received no intervention. Together, the results from these studies suggest that cefiderocol could provide an effective alternative treatment option for S. maltophilia infections in the lower respiratory tract, particularly strains resistant to empiric antibiotics, such as trimethoprim/sulfamethoxazole or minocycline.
KEYWORDS: cefiderocol, in vitro activity, pharmacodynamics, Stenotrophomonas maltophilia, trimethoprim/sulfamethoxazole
Stenotrophomonas maltophilia is an opportunistic non-fermenter pathogen that causes a variety of different infections (1, 2). In hospitalized patients in the USA, the respiratory tract has been found to be the most frequent site of infection (3). The pathogen’s effects can be particularly problematic in patients who are immunosuppressed and those with indwelling medical devices (2). Many S. maltophilia infections are polymicrobial, common co-pathogens including other non-fermenting Gram-negative bacteria, such as Pseudomonas aeruginosa (4). Mortality rates in patients with S. maltophilia bacteremia vary widely but are in the region of 13–70% (5–7).

S. maltophilia displays resistance to many antibiotics (e.g., carbapenems) (1) by utilizing a number of intrinsic resistance mechanisms. These mechanisms include reduced membrane permeability, multidrug resistance efflux pumps, antibiotic modifying enzymes, such as L1 and L2 β-lactamases, and the quinolone resistance gene Smqnr (1, 8). Recent data have suggested that mutations in the TonB membrane receptor of clinical S. maltophilia isolates are associated with a decrease in the uptake of ceftazidime and may also reduce susceptibility to siderophore antibiotics (9). While trimethoprim/sulfamethoxazole is active against it, S. maltophilia resistance to this antibiotic is growing and appears to be more common among isolates from inpatients compared with outpatients (5, 7). In addition, trimethoprim/sulfamethoxazole is associated with a variety of drug–drug interactions with ligands of CYP2C8, CYP2C9 enzymes or OCT2 transporter, including warfarin, methotrexate, diuretics and several oral hypoglycemics, which may limit its use in some patients (10). Among
patients with bacteremia, a higher Charlson comorbidity index and indwelling venous
catheterization may predispose to infection by quinolone-resistant strains of *S.
maltophilia*, which in turn may be associated with a significant risk of mortality (6).
Thus, antibiotic treatment of respiratory, or other, infections caused by *S. maltophilia*
may be compromised (11).

Cefiderocol is a novel, parenteral siderophore cephalosporin, which is active
against Gram-negative, non-fermenting pathogens, including *S. maltophilia*, even in
the presence of carbapenemases due its stability against these hydrolyzing enzymes
(12). Cefiderocol has shown potent *in vitro* activity against a range of carbapenem-
susceptible and carbapenem-resistant (CR) Gram-negative bacteria collected from
around the world, including *S. maltophilia* strains resistant to other commonly used
antibiotics (13–16). Preclinical studies have already demonstrated that cefiderocol is
effective in murine thigh (17) and rat lung (18) infection models and this *in vivo*
efficacy appears to correspond well with its *in vitro* activity.

The objectives of the series of studies reported here were to characterize the *in
vitro* activity of cefiderocol and its efficacy *in vivo* against various strains of *S.
maltophilia* using animal models of lung infection, including a humanized dosing
regimen in a rat model.

**RESULTS AND DISCUSSION**

*In vitro activity of cefiderocol and comparator agents.* Cefiderocol exhibited
*in vitro* activity in susceptibility tests against 217 *S. maltophilia* clinical isolates
collected over 52 countries from patients with a variety of infections, with MIC\(_{50}\)/MIC\(_{90}\),
0.063/0.25 µg/mL. All *S. maltophilia* isolates were inhibited at cefiderocol MIC ≤2 µg/mL (range 0.004–2.0 µg/mL). Activity against these isolates was also shown by trimethoprim/sulfamethoxazole (European Committee on Antimicrobial Susceptibility Testing [EUCAST]/Clinical and Laboratory Standards Institute [CLSI] susceptibility breakpoints 0.001/2 µg/mL, with resistance ≥4 µg/mL) (MIC$_{50}$ of 0.125/2.375 and MIC$_{90}$ of 0.5/9.5 µg/mL), minocycline (CLSI susceptibility breakpoint 4 µg/mL) (MIC$_{50}$/MIC$_{90}$ of 0.25/1 µg/mL) and tigecycline (EUCAST pharmacokinetic [PK]/pharmacodynamic [PD] susceptibility breakpoint 0.5 µg/mL) (MIC$_{50}$/MIC$_{90}$ of 1/2 µg/mL). All isolates were susceptible to minocycline (range 0.063–4.0 µg/mL [CLSI breakpoint]), 99.1% to trimethoprim/sulfamethoxazole (range ≤0.031/≤0.589–16/304 µg/mL [CLSI breakpoints]) and 73.9% to tigecycline ([0.125–8.0 µg/mL [EUCAST PK/PD] breakpoint]).

Results of activity testing with cefiderocol and other antibiotics against the *S. maltophilia* strains, which were used for *in vivo* studies, from patients with respiratory tract infections are shown in Table 1.

**In vivo mouse lung infection model.** Two isolates were evaluated in a neutropenic mouse lung infection model, which showed different MIC profiles for some antibiotics which were active against *S. maltophilia* (Table 1). *S. maltophilia* strain SR202006 showed relatively high MIC values to trimethoprim/ sulfamethoxazole, minocycline, levofloxacin and ciprofloxacin within the MIC range of each antibiotic. In contrast, *S. maltophilia* strain SR201934 showed MIC values for each of these antibiotics corresponding to concentrations around the MIC$_{50}$ values.
Against both isolates, administration of cefiderocol 30 mg/kg and 100 mg/kg significantly reduced the viable bacterial cell count in the lung by 2- to 4-log_{10} CFU/lung compared with lungs of untreated control animals (Fig. 1, 2). More potent efficacy by administration of minocycline, levofloxacin and ciprofloxacin was observed for strain SR201934 than for strain SR202006, suggesting that the in vivo efficacy reflected well the in vitro activity of these compounds. Of note, efficacy was observed by ciprofloxacin administration for strain SR201934, although a susceptibility breakpoint for this antibiotic has not been defined for S. maltophilia. On the other hand, meropenem, cefepime, ceftazidime and colistin did not show efficacy against these strains (Fig. 1, 2), which was likely due to the high MICs (Table 1). The finding that trimethoprim/sulfamethoxazole was not effective in vivo, despite demonstrating a low MIC against S. maltophilia SR201934 in vitro, may be because infected mice can display increases in the concentration of thymidine (19), high levels of which have been shown to have an antagonistic impact on the activity of trimethoprim/sulfamethoxazole in vitro (20).

**In vivo immunocompetent rat lung infection model.** Humanized doses of cefiderocol and meropenem (both dissolved in 0.9% saline) were tested against two strains of trimethoprim/sulfamethoxazole-susceptible S. maltophilia (SR200614 and SR201934) in the rat lung infection model (Table 1). The plasma concentration-time profiles between the simulated 3-hour infusion of cefiderocol (2 g every 8 hours) and the simulated 0.5-hour infusion of meropenem (1 g every 8 hours) were similar to human PK profiles (Fig. 3). In this rat model, the lungs of untreated animals showed
hemorrhagic inflammation and a 1-log$_{10}$ CFU/lung increase in bacterial numbers over 96 hours. Against both strains of *S. maltophilia*, humanized cefiderocol dosing reduced the viable cell count by 2- to 3-log$_{10}$ CFU/lung compared with baseline controls, which received no intervention (Fig. 4). This suggests that cefiderocol administered according to the approved dosing regimen has the clinical potential to effectively treat respiratory tract infections caused by *S. maltophilia*. As expected from the MIC values (Table 1), meropenem showed no significant activity compared with controls.

We have previously demonstrated the bactericidal activity of cefiderocol *in vivo* against a range of Gram-negative bacteria in murine thigh and rat lung infection models (17, 18, 21, 22), including CR strains of *Klebsiella* spp., *Pseudomonas aeruginosa* or *Acinetobacter baumannii*. In these previous investigations, the *in vivo* efficacy of cefiderocol corresponded well with the *in vitro* activity measured by using iron-depleted cation-adjusted Muller-Hinton broth based on CLSI recommendation, an observation confirmed by the current series of experiments against *S. maltophilia* strains, which were either susceptible or resistant to trimethoprim/sulfamethoxazole.

The cefiderocol dosing regimen (100 mg/kg) selected for the murine lung infection model has been shown to achieve approximately 54% fT>MIC against four strains of *S. maltophilia*, with cefiderocol MIC values of 0.125 and 0.25 µg/mL (17). In the previously described rat model, the %fT>MIC for cefiderocol 2 g once every 8 hours infused over 3 hours was 100% for *A. baumannii* and *P. aeruginosa* strains with MICs of ≤4 µg/mL (18). In a neutropenic murine thigh infection model, infected by *S.
maltophilia strains, cefiderocol demonstrated bactericidal efficacy in vivo and reduced the bacterial burden against 87.5% of the tested strains (22).

In summary, the excellent in vitro activity of cefiderocol against a global collection of S. maltophilia isolates in surveillance studies (14) was shown to extend to trimethoprim/sulfamethoxazole-resistant strains and the in vivo efficacy of cefiderocol in murine and rat models was associated with its in vitro activity against these isolates. Other β-lactam agents were inactive against the S. maltophilia isolates and concentration-dependent effects were demonstrated with levofloxacin, ciprofloxacin and minocycline. The findings indicate that cefiderocol could provide an effective alternative treatment option for S. maltophilia infections in the lower respiratory tract, particularly against strains resistant to empiric antibiotics such as trimethoprim/sulfamethoxazole or minocycline. However, evidence from clinical studies is required to confirm its place in clinical practice for the management of patients with respiratory tract infections.

MATERIALS AND METHODS

Agents. The following antimicrobial agents were tested: cefiderocol, cefepime, ceftazidime, ciprofloxacin, colistin, meropenem, minocycline, tigecycline, levofloxacin and trimethoprim/sulfamethoxazole. In in vivo studies, meropenem was administered with cilastatin at the same dosage to minimize meropenem degradation by murine dihydropeptidase-1 (DHP-1). Cefiderocol was synthetized by Shionogi & Co. Ltd (Osaka, Japan) for both in vitro and in vivo studies. For the in vitro and/or in vivo studies, cefepime, ceftazidime, ciprofloxacin, colistin, meropenem, cilastatin,
minocycline, tigecycline, and levofloxacin were obtained from commercial sources, and trimethoprim/sulfamethoxazole was synthesized by Shionogi & Co., Ltd (Osaka, Japan). For the in vivo studies, ceftazidime was obtained from GlaxoSmithKline K.K. (London, UK), meropenem from Dainippon Sumitomo Pharma Co., Ltd. (Osaka, Japan), minocycline from Pfizer Inc. (New York, USA), and trimethoprim/sulfamethoxazole from Taiyo Pharma Co., Ltd., Tokyo, Japan.

**S. maltophilia test strains.** All three of the *S. maltophilia* strains were collected from patients with respiratory tract infections in the SIDERO-CR surveillance study (14). Strains SR202006 (South Africa) were trimethoprim/sulfamethoxazole resistant and SR201934 (Japan) and SR200614 (USA) were trimethoprim/sulfamethoxazole susceptible.

**In vitro studies.** Full details of the susceptibility testing methodology have been published previously (13,14). It was complemented by testing with tigecycline, minocycline and trimethoprim/sulfamethoxazole at Shionogi & Co., Osaka, using CLSI standard methods. BBL cation-adjusted Mueller-Hinton broth (CAMHB) (Becton-Dickinson, Sparks, MD, USA) was used for all antimicrobial susceptibility testing. For cefiderocol, iron-depleted CAMHB (ID-CAMHB) (at final iron concentration of \( \leq 0.03 \mu g/mL \)) was used, and prepared according to CLSI Subcommittee on Antimicrobial Susceptibility Testing-approved methodology (14).
**In vivo studies.** Full details of the methodology for the neutropenic murine lung infection model (17) and the immunocompetent rat lung infection model (18) have been published previously. All studies with animals were approved by the Institutional Animal Care and Use Committee of Shionogi & Co., Ltd. The *S. maltophilia* strains used in the *in vivo* studies were subjected to multilocus sequence typing (MLST), using the PubMLST typing database (23). Direct sequencing of polymerase chain reaction (PCR) products was performed by Eurofins Genomics (Tokyo, Japan).

SR201934 was characterized as belonging to the *S. maltophilia sensu stricto* complex (Sm6). The strain ST types were confirmed by sequencing seven housekeeping genes (*atpD, gapA, guaA, mutM, nuoD, ppsA, recA* of *S. maltophilia*). For two strains, SR200614 and SR202006, it was not possible to confirm the sequencing typing number, the fact that all three strains were human-derived and were found to harbour L2 beta-lactamase genes, strongly suggests that all were from the *S. maltophilia sensu lato* lineage (24).

**Neutropenic murine lung infection model.** Briefly, for the neutropenic murine lung infection model, male Jcl:ICR mice (weighing 17–20 g [CLEA Japan, Inc., Tokyo, Japan]) were rendered neutropenic by two doses of intraperitoneal cyclophosphamide prior to the experiment (150 mg/kg on day −4 and 100 mg/kg on day −1). Anesthetized mice were inoculated with 3 to 5 x 10⁶ CFU of *S. maltophilia*. Antibiotics (in a 0.9% saline vehicle) were administered subcutaneously at 2, 5 and 8 hours post infection (5 animals/dosing group). Control mice were not treated with antibiotics and received either no intervention (untreated) or vehicle (vehicle-treated). Following the initial
infection, mice were euthanized at 2 hours (untreated controls) or 24 hours (antibiotic-treated animals or vehicle-treated controls), lungs were excised and the numbers of viable cells in lung tissue were counted. Dunnett’s multiple comparison test was used to test differences between active treatment and untreated baseline control groups in the number of viable cells following treatment. Welch’s t-test was used to compare differences between comparator antibiotics cefiderocol at the same doses. The \( P \) value for significance in both tests was <0.05.

**Immunocompetent rat lung infection model.** Specific-pathogen-free, 5-week-old, male Sprague-Dawley rats (weighing approximately 150 g; Charles River Laboratories Japan, Inc., Kanagawa, Japan) were anesthetized before being infected via an intratracheal route with 0.1 mL of \( 3 \times 10^7 \) CFU/mL inoculum with molten nutrient agar. Cefiderocol or meropenem was administered via an inferior jugular vein cannula, implanted 3 to 6 days prior to the initiation of treatment, according to schedules designed to mimic their PK profiles at the approved doses in healthy human subjects: 2 g cefiderocol every 8 hours as a 3-hour infusion and 1 g meropenem every 8 hours as a 0.5-hour infusion (18). The PK profiles were adjusted according to the protein binding ratios in humans and rats taken from the literature (18, 25), and the resulting profiles represent free-drug plasma concentrations. Antibiotic treatment was initiated 2 hours post infection and was continued for 96 hours for the recreated human PK profile (3–6 rats/dosing group). In a control group, infected animals received saline vehicle at a constant flow rate of 0.4 mL/hour (3–6 rats/dosing group). At 96 hours after treatment initiation, rats were anesthetized and, after exsanguination, lungs were
collected and the numbers of viable cells in lung tissue were counted. Five additional infected rats had their organs harvested at the initiation of dosing without any treatment and were used as baseline controls. Welch’s t test was used to compare differences in bacterial density at 96 hours between the treatment and baseline controls, and between the cefiderocol and meropenem treatment groups. The P value for significance was <0.05.

Measurement of cefiderocol and meropenem concentrations in rat experimental model recreating human pharmacokinetics. Cefiderocol concentration in rat plasma has been described elsewhere (18). In brief, rats were treated with cefiderocol and on the second day of dosing, blood samples were collected at various times after the start of the infusion. Cefiderocol concentrations in plasma were determined by the validated liquid chromatography-tandem mass spectrometry (LC–MS–MS) method.

For measurement of meropenem plasma concentrations, rats were treated with meropenem as described above and blood samples were collected and centrifuged. This was followed by a collection of 10 µL aliquot of each plasma sample that was frozen immediately on dry ice and stored at ~20°C prior to analysis. Concentrations of the drug in plasma were determined by LC–MS–MS method. Samples were de-proteinated with acetonitrile–0.1% formic acid (v/v). For plasma calibration, appropriate concentrations of meropenem were spiked into rat plasma to give eight standards from 0.1 to 300 µg/mL. Quality control (QC) samples were prepared by spiking rat plasma with meropenem to achieve final concentrations of 0.3 (low QC), 10
(medium QC), and 300 (high QC) µg/mL. The LC–MS-MS system comprised a Shimadzu Corporation HPLC system (LC-20A) in tandem with an API 5000 triple-quadrupole MS in electrospray ionization mode. Chromatographic separation was performed using an Acquity C18 column (inside diameter: 2.1 mm; length: 50 mm; particle size: 1.7 µm) with a gradient using mobile phases of 0.1% formic acid and acetonitrile–0.1% formic acid at a flow rate of 0.4 mL/min. Meropenem concentrations were obtained using LC–MS-MS monitoring the product ion transitions of m/z 384.2 and m/z 141. The analysis run time was 2.4 min.

DATA AVAILABILITY

All data obtained in these experiments are included in the manuscript.

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AUTHORS CONTRIBUTION

All authors contributed to the conceptualization of the study, obtaining and analyzing the data, writing and approving the final version of the manuscript.

CONFLICT OF INTEREST

All authors are employees of Shionogi & Co., Ltd., Osaka, Japan.
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Tables and Figures

FIG 1 In vivo efficacy of cefiderocol in a neutropenic murine lung infection model caused by *S. maltophilia* strain SR201934.

FIG 2 In vivo efficacy of cefiderocol in a neutropenic murine lung infection model caused by *S. maltophilia* strain SR202006.

FIG 3 Pharmacokinetic profiles of humanized doses of cefiderocol 2 g every 8 hours (simulated 3-hour infusion) and meropenem 1 g every 8 hours (0.5-hour infusion) recreated in immunocompetent rats.

FIG 4 In vivo efficacy of cefiderocol and meropenem recreating human plasma pharmacokinetics in an immunocompetent rat respiratory-infection model caused by the *S. maltophilia* strains SR200614 and SR201934.
TABLE 1 MIC of experimental *S. maltophilia* strains isolated from patients with respiratory tract infections

| Antibiotic            | MIC (µg/mL) | *S. maltophilia* SR200614 | *S. maltophilia* SR201934 | *S. maltophilia* SR202006 |
|-----------------------|-------------|---------------------------|---------------------------|---------------------------|
| Cefiderocol           | 0.063       | 0.5                       | 0.125                     |
| Cefepime              | 32          | 64                        | 32                        |
| Ceftazidime           | 128         | 128                       | 64                        |
| Meropenem             | 64          | >64                       | >32                       |
| Ciprofloxacin         | 2           | 2                         | 32                        |
| Levofloxacin          | 2           | 1                         | 16                        |
| Minocycline           | 0.125       | 0.25                      | 2                         |
| Tigecycline           | 0.5         | 0.5                       | 4                         |
| Trimethoprim/sulfamethoxazole | 0.125/2.375 | 0.125/2.375 | 16/304                   |
| Colistin              | >8          | 8                         | >32                       |

NT, not tested.
**FIG 1** *In vivo* efficacy of cefiderocol in a neutropenic murine lung infection model caused by *S. maltophilia* strain SR201934.

CAZ, ceftazidime; CIP, ciprofloxacin; CS, cilastatin; CST, colistin; FEP, cefepime; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; SXT, trimethoprim/sulfamethoxazole.

Data are expressed as mean ± SD. Five mice/group were tested. For controls, the number of viable bacterial cells in the lung was determined at 2 hours after inoculation for untreated control mice (light grey bar) and at 24 hours for vehicle-treated control mice (black bar).

* Significant reduction (*P*<0.05) vs untreated control (2h), Dunnett’s multiple comparison test.

† Significant difference (*P*<0.05) vs same dose of cefiderocol in favor of comparator, Welch’s t-test.

^ Significant difference (*P*<0.05) vs same dose of cefiderocol in favor of cefiderocol, Welch’s t-test.
FIG 2 In vivo efficacy of cefiderocol in a neutropenic murine lung infection model caused by *S. maltophilia* strain SR202006.

CAZ, ceftazidime; CIP, ciprofloxacin; CS, cilastatin; CST, colistin; FEP, cefepime; LVX, levofloxacin; MEM, meropenem; MIN, minocycline; SXT, trimethoprim/sulfamethoxazole.

Data are expressed as mean±SD. Five mice/group were tested. For controls, the number of viable bacterial cells in the lung was determined at 2 hours after inoculation for untreated control mice (light grey bar) and at 24 hours for vehicle-treated control mice (black bar).

* Significant reduction (*P*<0.05) vs untreated control (2h), Dunnett’s multiple comparison test.

† Significant difference (*P*<0.05) vs same dose of cefiderocol, Welch’s t-test.

^ n=4 (the dose of 30 mg/kg showed toxicity in mice).
FIG 3 Pharmacokinetic profiles of humanized doses of cefiderocol 2 g every 8 hours (simulated 3-hour infusion) and meropenem 1 g every 8 hours (0.5-hour infusion) recreated in immunocompetent rats. Data points are expressed as mean ± SD of three readings/rat. Data for cefiderocol were adapted from (18).
FIG 4 In vivo efficacy of cefiderocol and meropenem, recreating human plasma pharmacokinetics in an immunocompetent rat respiratory-infection model caused by the S. maltophilia strains SR200614 and SR201934.

Data are expressed as mean ± SD. 3–6 rats/group were tested. The number of viable cells in lungs was determined 96 hours after infection.

*Significant reduction (P<0.05) vs baseline control value, Welch’s t-test.
†Significant difference (P<0.05) vs meropenem, Welch’s t-test.

S. maltophilia SR200614:  
- Cefiderocol MIC: 0.063 µg/mL
- Meropenem MIC: 64 µg/mL

S. maltophilia SR201934:  
- Cefiderocol MIC: 0.5 µg/mL
- Meropenem MIC: 128 µg/mL
