In Vitro Activity of Doripenem (S-4661) against Multidrug-Resistant Gram-Negative Bacilli Isolated from Patients with Cystic Fibrosis

Yunhua Chen,¹ Elizabeth Garber,¹ Qiuqu Zhao,¹ Yigong Ge,² Matthew A. Wikler,²
Koné Kaniga,² and Lisa Saiman^{1*}

Department of Pediatrics, Columbia University, New York, New York,¹ and Peninsula Pharmaceuticals, Inc., Alameda, California²

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Doripenem 50% inhibitory concentrations (MIC₅₀) and 90% inhibitory concentrations (MIC₉₀) for multidrug-resistant strains of mucoid *Pseudomonas aeruginosa* (n = 200 strains), nonmucoid *P. aeruginosa* (n = 200), and *Burkholderia cepacia* complex (n = 200) isolated from patients with cystic fibrosis were 8 and 32, 8 and 64, and 8 and 32 µg/ml, respectively. Doripenem had somewhat better activity than established antimicrobial agents.

Patients with cystic fibrosis (CF) can be chronically infected with several pathogens, including *Staphylococcus aureus*, non-typeable *Haemophilus influenzae*, and *P. aeruginosa*; by 18 years of age, 80% of patients are infected with *P. aeruginosa* (3). With time, *P. aeruginosa* converts to a mucoid phenotype which often heralds deterioration in respiratory status. Approximately 4% of patients in the United States become infected with *Burkholderia cepacia* complex, which can be particularly virulent and is associated with increased mortality (4).

The aggressive use of oral, intravenous, and aerosolized antibiotics has substantially contributed to the increased life expectancy for patients with CF. Several classes of intravenously administered agents are available to treat patients with CF experiencing acute pulmonary exacerbations. However, there is a need for additional therapeutic agents, particularly for the treatment of multidrug-resistant gram-negative pathogens (8). Multidrug resistance in CF strains is defined as resistance to all of the agents in two of three classes of antibiotics, i.e., quinolones, aminoglycosides, and beta-lactam agents, including monobactams and carbapenems (9).

Doripenem is a carbapenem in clinical development for serious bacterial infections. It has potent in vitro activity against a wide range of gram-positive and gram-negative clinical isolates (2, 5, 11) and in vivo efficacy in various animal models (10). We studied the in vitro activity of doripenem against 600 multidrug-resistant clinical strains of *P. aeruginosa* and *B. cepacia* complex isolated from patients with CF and compared its activity with seven other conventional antipseudomonal antibiotics.

These isolates were sent to the CF Referral Center at Columbia University, which has established a large collection of multidrug-resistant isolates from patients with CF in the United States. In all, 200 mucoid *P. aeruginosa*, 200 nonmucoid *P. aeruginosa*, and 200 *B. cepacia* complex strains isolated from 2001 through 2003 (each from a unique patient with CF) were tested in this study. Antimicrobial susceptibility testing was performed using a commercially prepared (TREK Diagnostic Systems, Cleveland, OH) broth microdilution assay (6). The

studies were not performed in replicate. Interpretative criteria for susceptibility breakpoints for non-*Enterobacteriaceae*, including *P. aeruginosa* and *B. cepacia*, were used and are shown in Table 1 (7). The breakpoint for imipenem was used tentatively for doripenem for comparative purposes, because National Committee for Clinical Laboratory Standards susceptibility criteria for doripenem are not yet available (7).

The activity of the eight antimicrobial agents against these clinical isolates is shown in Table 1. Overall, doripenem exhibited the lowest 50% inhibitory concentration (MIC₅₀) and lowest 90% inhibitory concentration (MIC₉₀) values (8 and 32 µg/ml for mucoid *P. aeruginosa*, 8 and 64 µg/ml for nonmucoid *P. aeruginosa*, and 8 and 32 µg/ml for *B. cepacia* complex strains). The proportions of *P. aeruginosa* isolates susceptible to doripenem and tobramycin were comparable (40% versus 49% of mucoid and 33% versus 34% of nonmucoid strains, respectively). Less than one-third of the *P. aeruginosa* strains were susceptible to imipenem (26%), aztreonam, piperacillin, ceftazidime, and cefepime. Ceftazidime and doripenem were the two most active agents against *B. cepacia* complex strains, inhibiting 43% and 25%, respectively.

In addition, we assessed cross-resistance between doripenem and tobramycin among *P. aeruginosa* strains, as tobramycin is frequently used for patients with CF. In all, 43% (173 of 400) of *P. aeruginosa* strains were resistant to tobramycin (MIC ≥ 16 µg/ml) and of these 173 strains, 54% were susceptible or intermediately susceptible to doripenem (MIC ≤ 8 µg/ml). Similarly, 49% (197 of 400) of strains were resistant to doripenem and of these 197 strains, 59% were susceptible or intermediately susceptible to tobramycin.

The selected strains represent problematic clinical isolates for patients with CF, as therapeutic options are limited because of multidrug resistance. These strains were obtained from patients across the United States, which supports the notion that multidrug resistance is widespread in this patient population. While accurate rates for multidrug-resistant strains of *P. aeruginosa* and *B. cepacia* complex are unavailable, from 1996 to 2003 the CF Referral Center (<http://synergy.columbia.edu>) processed approximately 20,000 strains from 6,700 patients from 140 CF care centers in the United States.

Over the past several years, there has been increasing clin-

* Corresponding author. Mailing address: Columbia University, 622 West 168th St., PH4W-470, New York, NY 10032. Phone: (212) 305-9446. Fax: (212) 305-9491. E-mail: LS5@columbia.edu.

TABLE 1. Activity of doripenem compared with conventional agents against 600 multidrug-resistant strains of *P. aeruginosa* and *B. cepacia* complex isolated from patients with cystic fibrosis

Organism ^a	Antimicrobial agent	MIC range (μg/ml) ^b	MIC (μg/ml) breakpoint interpretation ^c			No. (%) of strains ^c			MIC ₅₀ (μg/ml)	MIC ₉₀ (μg/ml)
			S	I	R	S	I	R		
<i>P. aeruginosa</i> (mucoid; n = 200)	Doripenem ^d	0.25–512	≤4	8	≥16	81 (40)	21 (11)	98 (49)	8	32
	Imipenem	0.5–512	≤4	8	≥16	60 (30)	12 (6)	128 (64)	32	128
	Tobramycin	0.25–>512	≤4	8	≥16	98 (49)	33 (16)	69 (35)	8	64
	Aztreonam	0.25–>512	≤8	16	≥32	40 (20)	17 (9)	143 (71)	64	>512
	Piperacillin	0.5–>512	≤64 ^e	N/A	≥128	54 (27)	N/A	146 (73)	512	>512
	Ceftazidime	0.5–>512	≤8	16	≥32	49 (24)	11 (6)	140 (70)	64	>512
	Cefepime	2–>256	≤8	16	≥32	27 (13)	30 (15)	143 (72)	64	256
<i>P. aeruginosa</i> (nonmucoid; n = 200)	Levofloxacin	0.25–512	≤2	4	≥8	67 (33)	40 (20)	93 (47)	16	128
	Doripenem ^d	0.25–512	≤4	8	≥16	66 (33)	35 (18)	99 (49)	8	64
	Imipenem	0.5–512	≤4	8	≥16	43 (21)	19 (10)	138 (69)	32	64
	Tobramycin	0.5–>512	≤4	8	≥16	68 (34)	28 (14)	104 (52)	16	256
	Aztreonam	0.25–>512	≤8	16	≥32	31 (15)	10 (5)	159 (80)	128	>512
	Piperacillin	1–>512	≤64 ^e	N/A	≥128	40 (20)	N/A	160 (80)	512	>512
	Ceftazidime	1–>512	≤8	16	≥32	32 (16)	17 (8)	151 (76)	128	>512
<i>B. cepacia</i> (n = 200)	Cefepime	4–>256	≤8	16	≥32	21 (10)	22 (11)	157 (79)	64	256
	Levofloxacin	0.25–512	≤2	4	≥8	29 (14)	52 (26)	119 (60)	16	128
	Doripenem ^d	0.5–256	≤4	8	≥16	50 (25)	53 (26)	97 (49)	8	32
	Imipenem	0.25–256	≤4	8	≥16	18 (9)	14 (7)	168 (84)	32	128
	Tobramycin	0.25–>512	≤4	8	≥16	4 (2)	4 (2)	192 (96)	256	>512
	Aztreonam	4–>512	≤8	16	≥32	15 (7)	10 (5)	175 (88)	>512	>512
	Piperacillin	1–>512	≤16 ^e	32–64	≥128	38 (19)	36 (18)	126 (63)	256	>512
<i>B. cepacia</i> (n = 200)	Ceftazidime	1–>512	≤8	16	≥32	86 (43)	30 (15)	84 (42)	16	>512
	Cefepime	2–>256	≤8	16	≥32	21 (10)	17 (9)	162 (81)	256	>256
	Levofloxacin	0.25–512	≤2	4	≥8	46 (23)	16 (8)	138 (69)	16	128

^a Numbers in parentheses represent the number of strains.^b The range of MICs tested for all agents was 0.25 to 512 μg/ml, except for cefepime (0.25 to 256 μg/ml).^c Abbreviations used in table: S, susceptible; I, intermediate; R, resistant; N/A, no intermediate range for *P. aeruginosa*.^d Breakpoint for imipenem was used tentatively for doripenem, as NCCLS susceptibility criteria for doripenem are not yet available.^e ≤64 for *P. aeruginosa*, ≤16 for *B. cepacia*.

ical experience with carbapenem antibiotics for patients with CF. Much of this interest has focused on meropenem for management of acute pulmonary exacerbations, in part because of its superior activity against *B. cepacia* complex and because of its activity against multidrug-resistant strains of *P. aeruginosa* (1). Overall, we have noted that 40% of multidrug-resistant strains of *P. aeruginosa* and 29% of *B. cepacia* complex strains processed by the CF Referral Center are susceptible to meropenem (L. Saiman, unpublished data). In this study, comparable proportions of *P. aeruginosa* (37%) and *B. cepacia* complex strains (25%) were susceptible to doripenem.

In conclusion, doripenem exhibited somewhat better in vitro activity against multidrug-resistant strains isolated from patients with CF than other conventional antipseudomonal agents. Future studies of doripenem should assess the inhibitory effect of CF sputum on doripenem's potency, the pharmacokinetics of doripenem in patients with CF, and the concentration of doripenem achievable within the lung following intravenous administration. Such studies would support the potential role of doripenem for treatment of acute pulmonary exacerbations associated with *P. aeruginosa* and *B. cepacia* complex, particularly when combined with another effective agent.

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