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In Vitro Activities of CG400549, a Novel FabI Inhibitor, against Recently Isolated Clinical Staphylococcal Strains in Korea▽

Jong Hwa Yum,[1,2,3] Chang Ki Kim,[1,2] Dongeun Yong,[1,2,3] Kyungwon Lee,[1,2,3]* Yunsop Chong,[1,2] Cheol Min Kim,[4] Jeong Mi Kim,[4] Seonggu Ro,[4] and Joong Myung Cho[4]

Department of Laboratory Medicine,[1] Research Institute of Bacterial Resistance,[2] and BK21 Project for Medical Sciences,[3] Yonsei University College of Medicine, and CrystalGenomics, Inc.,[4] Seoul, Korea

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The in vitro activities of CG400549, a novel FabI inhibitor, were compared to those of linezolid and commonly used antimicrobials against recent bacterial isolates. CG400549 had an MIC_{90} of 0.5 μg/ml for *Staphylococcus aureus* strains and was more potent than either linezolid or vancomycin.

Various antimicrobial resistances among clinical isolates have become a major problem in recent years. Of particular concern has been the increasing incidence of methicillin-resistant *Staphylococcus* spp., vancomycin-resistant *Enterococcus* spp., and penicillin-resistant *Streptococcus pneumoniae* (7). The recent introduction of the oxazolidinone class of antimicrobials into clinical practice represents an important advance in therapy for infections caused by gram-positive organisms of multiple antibiotic-resistant strains (3).

The bacterial enoyl-ACP reductase (FabI) is an enzyme essential for the survival of certain kinds of bacteria (5). Because FabI shows low overall sequence homology with mammalian enzymes, it is a potential target for selective antibacterial action (5, 11). A FabI inhibitor could possess antibacterial activity against those pathogens in which FabI is the sole enoyl-ACP reductase (e.g., *Staphylococcus aureus*, *Haemophilus influenzae*, *Moraxella catarrhalis*, and *Escherichia coli*), but not against *S. pneumoniae*, enterococci, or *Pseudomonas aeruginosa*, which utilize either FabK or both FabI and FabK (10).

CG400549 (M.W. 340; CrystalGenomics, Inc., Seoul, Korea) is an inhibitor of FabI (Fig. 1). Therefore, CG400549 could have antibacterial activities against organisms dependent only on FabI. An animal study showed that it has potential for the treatment of staphylococcal infections in mice and rats (4). In this study, the in vitro activities of CG400549 were compared with those of other antimicrobial agents against recent clinical staphylococcal isolates.

(This study was presented in part at the 46th Interscience Conference on Antimicrobial Agents and Chemotherapy, San Francisco, CA, 27 to 30 September 2006 [12].)

Nonduplicate clinical isolates were collected in 2005 and 2006 from patients at a Korean tertiary-care hospital. The species were identified by conventional methods (1) or by using the Vitek system (bioMerieux SA, Marcy l'Etoile, France). Staphylococcal strains for which the MIC of CG400549 was ≥2 μg/ml were reidentified by using a Vitek GPI kit (bioMerieux SA) and/or 16S rRNA gene sequencing (8).

The antimicrobial susceptibilities were tested by using the CLSI agar dilution method or broth microdilution method, depending on the species (2, 9). CG400549 was provided by CrystalGenomics, Inc. The agents used in the comparison were oxacillin, penicillin G, erythromycin, and tetracycline (Sigma Chemical Co., St. Louis, MO), gentamicin (Chong Kun Dang Pharmaceutical Co., Seoul, Korea), clindamycin (Korea Upjohn, Seoul, Korea), sulfamethoxazole and trimethoprim (Dong Wha Pharmaceutical Co., Seoul, Korea), vancomycin and tobramycin (Daewoong Pharmaceutical Co., Seoul, Korea), levofloxacin (Daiichi Pharmaceutical Co., Tokyo, Japan), linezolid and amikacin (Dong-A Pharmaceutical Co., Seoul, Korea), cefoxitin and imipenem (Merck Sharp & Dohme, Rahway, NJ), ciprofloxacin (Bayer Korea Co., Seoul, Korea), clarithromycin (Hanmi Pharmaceutical Co., Seoul, Korea), and doxycycline (Pfizer Korea, Seoul, Korea). *Staphylococcus aureus* ATCC 29213 and *Enterococcus faecalis* ATCC 29212 were used as controls in each plate.

In our preliminary study, CG400549 had no activity against gram-positive bacteria, such as streptococci, enterococci, *M. catarrhalis*, *Listeria monocytogenes*, *Nocardia* spp., and nontuberculous mycobacteria, and gram-negative bacteria, such as *E. coli*, *Klebsiella pneumoniae*, *Enterobacter cloacae*, *Citrobacter freundii*, *Serratia marcescens*, *Morganella morganii*, *Acinetobacter baumannii*, *P. aeruginosa*, *Aeromonas* spp., *Vibrio* spp., *H. influenzae*, *Campylobacter fetus*, *Helicobacter pylori*, and *Neisseria gonorrhoeae* (data not shown).

In many Korean hospitals, the methicillin resistance rates of *S. aureus* isolates in 1998 were approximately 70% (6). In the present study, all isolates of *S. aureus* were inhibited by ≤4 μg/ml of vancomycin and linezolid and the MIC_{90}s for these agents were 1 μg/ml and 2 to 4 μg/ml, respectively (Table 1). However, all isolates of methicillin-resistant and methicillin-susceptible *S. aureus* were inhibited by ≤1 μg/ml of CG400549.

The majority of the methicillin-resistant, coagulase-negative

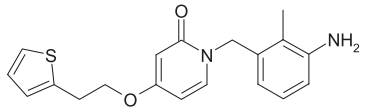

FIG. 1. Structure of CG400549, a FabI inhibitor.

* Corresponding author. Mailing address: Department of Laboratory Medicine, Yonsei University College of Medicine, 134 Shinchon-dong, Seodaemunku, Seoul 120-752, Korea. Phone: 82-2-2228-2446. Fax: 82-2-313-0908. E-mail: leekcp@yumc.yonsei.ac.kr.

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TABLE 1. Comparative in vitro activities of CG400549 and other antimicrobial agents against clinical staphylococcal isolates

Species (no. of isolates tested) and antimicrobial agent	MIC (μg/ml)			Susceptibility (%)[a]		
	Range	50%	90%	S	I	R
Methicillin-resistant *S. aureus* (60)						
CG400549	0.12–0.5	0.5	0.5	—	—	—
Linezolid	1–2	2	2	100	—	—
Erythromycin	0.25–>128	>128	>128	5	0	95
Clindamycin	≤0.06–>128	>128	>128	12	0	88
Cotrimoxazole	≤0.06–64	≤0.06	16	67	—	33
Gentamicin	0.5–>128	>128	>128	10	2	88
Levofloxacin	0.25–>128	16	>128	7	0	93
Tetracycline	0.12–>128	64	128	25	0	75
Oxacillin	32–>128	>128	>128	0	—	100
Vancomycin	0.5–2	1	1	100	0	0
Methicillin-susceptible *S. aureus* (60)						
CG400549	0.12–1	0.5	0.5	—	—	—
Linezolid	2–4	4	4	100	—	—
Erythromycin	0.25–>128	0.5	>128	88	0	12
Clindamycin	≤0.06–0.12	0.12	0.12	100	0	0
Cotrimoxazole	≤0.06–0.25	≤0.06	0.12	100	—	0
Gentamicin	0.12–>128	0.5	128	83	3	13
Levofloxacin	0.12–0.5	0.25	0.5	100	0	0
Tetracycline	0.12–64	1	32	88	0	12
Oxacillin	≤0.06–2	0.5	0.5	100	—	0
Vancomycin	0.5–2	1	1	100	0	0
Methicillin-resistant, coagulase-negative *Staphylococcus* spp. (97)						
CG400549	0.12–16	0.5	4	—	—	—
Linezolid	0.5–4	1	2	100	—	—
Erythromycin	≤0.06–>128	128	>128	20	0	80
Clindamycin	≤0.06–>128	>128	>128	44	2	54
Cotrimoxazole	≤0.06–128	4	16	40	—	60
Gentamicin	≤0.06–>128	64	>128	20	7	73
Levofloxacin	0.12–>128	4	32	35	5	60
Tetracycline	0.12–>128	2	128	67	2	31
Oxacillin	0.5–>128	32	>128	0	—	100
Vancomycin	0.5–16	1	2	99	1	0
Methicillin-susceptible, coagulase-negative *Staphylococcus* spp. (36)						
CG400549	0.5–8	0.5	8	—	—	—
Linezolid	0.5–2	1	2	100	—	—
Erythromycin	0.12–>128	0.25	128	78	6	17
Clindamycin	≤0.06–>128	0.12	0.25	97	0	3
Cotrimoxazole	≤0.06–0.5	≤0.06	0.25	100	—	0
Gentamicin	≤0.06–>128	0.25	32	69	6	25
Levofloxacin	0.12–1	0.25	0.25	100	0	0
Tetracycline	0.12–>128	0.5	64	78	0	22
Oxacillin	≤0.06–0.25	0.12	0.25	100	—	0
Vancomycin	0.5–2	1	2	100	0	0

[a] S, susceptible; I, intermediate; R, resistant; —, CLSI breakpoint is not available.

Staphylococcus (MRCNS) isolates were also resistant to most of the antimicrobial agents tested. All MRCNS and methicillin-susceptible, coagulase-negative *Staphylococcus* (MSCNS) isolates were inhibited by ≤16 μg/ml of vancomycin and ≤4 μg/ml of linezolid. The MIC range and MIC_{90} of CG400549 for MRCNS isolates were 0.12 to 16 μg/ml and 4 μg/ml, respectively, and for MSCNS isolates, they were 0.5 to 8 μg/ml and 8 μg/ml, respectively.

The MRCNS isolates with high CG400549 MICs included five *S. hominis* (4 to 16 μg/ml), three *S. epidermidis* (4 to 8 μg/ml), two *S. haemolyticus* (2 to 16 μg/ml), one *S. saprophyticus* (8 μg/ml), and one *S. sciuri* (4 μg/ml) isolate; the MSCNS isolates with high CG400549 MICs included three *S. simulans* (4 to 8 μg/ml), two *S. haemolyticus* (2 to 4 μg/ml), two *S. hominis* (4 μg/ml), and one *S. epidermidis* (8 μg/ml) isolate.

In conclusion, CG400549 is a FabI inhibitor with high in vitro activity against both methicillin-susceptible and -resistant *S. aureus* strains, including multidrug-resistant strains.

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