BMS284756 Potency And Spectrum Tested Against Over 10,000 Bacterial Blood Stream Infection Isolates from the SENTRY Antimicrobial Surveillance Program (2000)

K.A. Gordon, M.A. Pfaller, R.N. Jones, H.S. Sader, D.J. Biedenbach, M.L. Beach, and the SENTRY Participants Group.

University of Iowa, Iowa City, Iowa, USA; and The JONES Group, North Liberty, Iowa, USA.

Ronald N. Jones, M.D.
The JONES Group / JMI Laboratories
345 Beaver Kreek Centre, Suite A
North Liberty, Iowa 52317
Phone: 319.665.3370
Fax: 319.665-3371
ronald-jones@jonesgr.com

ABSTRACT

Purpose: To determine the in vitro activity of BMS284756 against bacterial (BSI) isolates from the SENTRY Antimicrobial Surveillance Program, 2000.

Methods: Isolates were tested against BMS284756, gatifloxacin, ciprofloxacin, and levofloxacin in a central reference laboratory by reference, NCCLS broth microdilution methods. Over 10,000 bacterial BSI isolates were obtained from SENTRY Antimicrobial Surveillance Program participants in North America, Latin America, and Europe from January through December, 2000. The top 12 pathogens accounted for 9,632 isolate episodes and included: *S. aureus* (2,555 isolates), *E. coli* (1,866), coagulase -negative staphylococci (CoNS; 1,234), *Klebsiella* spp. (884), *Enterococcus* spp. (878), *P. aeruginosa* (556), *Enterobacter* spp. (437), *S. pneumoniae* (393), β-haemolytic streptococci (BHS; 303), *Acinetobacter* spp. (210), viridans group streptococci (VGS; 164), and *Serratia* spp. (152).

Results: By comparison with gatifloxacin, levofloxacin, and ciprofloxacin, BMS284756 was the most active agent against *S. aureus* (MIC_{50}, 0.03 vs. 0.12 - 0.5 μg/ml), VGS (MIC_{50}, 0.06 vs. 0.25 - 1 μg/ml), CoNS (MIC_{50}, 0.12 vs. 0.25 - 1 μg/ml), BHS (MIC_{50}, 0.06 vs. 0.25 - 0.5 μg/ml), , and *S. pneumoniae* (MIC_{90}, 0.06 vs. 0.25 - 1 μg/ml). BMS284756 was less active than the other fluoroquinolones against *E. coli* (MIC_{90}, 0.5 vs. ≤0.25 μg/ml), *Enterobacter* spp. (MIC_{90}, 4 vs. 1 - 2 μg/ml), *Klebsiella* spp. (MIC_{90}, 1 vs. 0.5 μg/ml), *Serratia* spp. (MIC_{90}, > 4 vs. 1 - 2 μg/ml) and *P. aeruginosa* (MIC_{50}, 2 vs. ≤0.25 - 1 μg/ml) or *Acinetobacter* spp. (MIC_{90}, > 4 μg/ml). However, at a proposed susceptible breakpoint (≤4 μg/ml) for newer des-fluoro quinolones, these agents such as BMS284756 should have more equivalent spectrums.

Conclusions: BMS284756 was the most potent and demonstrated the broadest spectrum of activity of the fourquinolones tested against the Gram-positive cocci causing BSI. In contrast, BMS284756 was less potent against the enteric Gram-negative bacilli and *P. aeruginosa* BSI isolates. None of the tested fluoroquinolones was active against *Enterococcus* spp. or *Acinetobacter* spp. We anxiously await the results of clinical trials.

INTRODUCTION

As a class, quinolone compounds have wide therapeutic spectrum of activity against Gram-positive and -negative organisms; however, differences in potency among the marketed fluoroquinolones can occur. Although the newer fluoroquinolones generally have increased activity against Gram-positive and fastidious pathogens, they are no more active than ciprofloxacin and levofloxacin against many enteric and non-enteric Gram-negative species. In previous studies, BMS284756 (formerly T-3811), a novel des-F (6)-quinolone (Figure 1), has shown favorable pharmacokinetic properties and good activity against methicillin -resistant *Staphylococcus aureus*, penicillin-resistant *Streptococcus pneumoniae*, β *Streptococcus* spp. and *Enterococcus faecalis*. BMS284756 was determined to have greater oral bioavailability compared to ciprofloxacin, and was less toxic (both acute and chronic) than levofloxacin in animal models.

The purpose of this study was to determine the in vitro activity of BMS284756 against bacterial blood stream infection (BSI) isolates from the 2000 SENTRY Antimicrobial Surveillance Program. The potency and spectrum of BMS284756 was compared to that of other quinolones including ciprofloxacin, gatifloxacin, and levofloxacin.

MATERIALS AND METHODS

A total of over 10,000 bacterial BSI isolates were obtained from participant laboratories in North America, Latin America, and Europe from January through December 2000 as part of the SENTRY Program. The top 12 occurring pathogens accounted for 9,632 isolate episodes during this time period and were as follows: *S. aureus* (2,555 isolates), *Escherichia coli* (1,866), Coagulase-negative staphylococci (CoNS; 1,234), *Klebsiella* spp. (884), *Enterococcus* spp. (878), *P. aeruginosa* (556), *Enterobacter* spp. (437), *Streptococcus pneumoniae* (393), *b*-haemolytic streptococci (303), *Acinetobacter* spp. (210), viridans group streptococci (164) and *Serratia* spp. (152). This rank order was very similar to the rank order in previous SENTRY Program years since 1997, with *Serratia* spp. replacing *P. mirabilis* in the top 12 pathogens for 2000 SENTRY in the United States (US) and Canada. Likewise, the rank order of pathogens from Latin America was similar to previous years.

The study protocol dictated that each medical center collect the first 20 consecutive clinically significant BSI isolates (one per patient episode) per month and forward them to the reference laboratory for susceptibility testing (University of Iowa, US). All isolates were tested, utilizing NCCLS reference broth microdilution methods, against a panel of antimicrobial agents including BMS284756, ciprofloxacin, levofloxacin, and gatifloxacin. Isolates were identified using Vitek System (bioMerieux Inc., Hazelwood, MO) supplemented with conventional tests as needed. Stock cultures of all isolates were kept at –80°C or stored in double distilled sterile water at room temperature (*Pseudomonas* spp.). Quality control (QC) was performed using the following strains recommended by NCCLS: *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212. *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49766 and 49247, *E. coli* ATCC 25922 and 35218, and *P. aeruginosa* ATCC 27853.

RESULTS

- Among the four quinolones tested, BMS284756 was the most active compound tested against *S. aureus* (MIC_{50} ≤0.03 μg/ml), CoNS (MIC_{50}, 0.12 μg/ml), viridans gr and β-haemolytic streptococci (MIC_{50}, 0.06 μg/ml), and *S. pneumoniae* (MIC_{50}, 0.06 μg/ml).
- As noted in Table 1, none of the tested fluoroquinolones were very active against enterococci with MIC_{50} of 1-2 μg/ml and percent susceptible rates ranging from 40% (ciprofloxacin) to 76% (BMS284756).
- Using the proposed susceptible breakpoint of ≤4 μg/ml, 96-97% of the staphylococcal isolates, regardless of oxacillin susceptibility, were considered susceptible to BMS284756. The remaining quinolones had decreased activity against staphylococci ranging in percent susceptibility from 68% (ciprofloxacin) to 79% (gatifloxacin) for *S. aureus*, and 51% (ciprofloxacin) to 90% (gatifloxacin) for CoNS (Table 1).
- Although the tested fluoroquinolones were very active against the viridans group streptococci (98-100% susceptible) and β-haemolytic streptococci (99-100%), BMS284756 was at least 4-fold more potent (MIC_{90} value of 0.12 μg/ml versus 0.5-1 μg/ml) than the other quinolones. Against *S. pneumoniae* BMS284756 (MIC_{90}, 0.06 μg/ml) was 16-fold more potent than levofloxacin (MIC_{90}, 1 μg/ml).
- Levofloxacin (99% susceptible), gatifloxacin (99% susceptible), and BMS284756 (100% susceptible) were all very active against *S. pneumoniae* at their respective breakpoint concentrations.
- BMS284756 was generally two-to-four fold less potent than the other tested quinolones against the Enterobacteriaceae with MIC_{90}s ranging from 0.5 μg/ml to > 4 μg/ml (see Table 2).
- At the proposed or recommended NCCLS breakpoints, BMS284756 was comparable to the other agents against *E. coli* (92% susceptible versus 91-92%), *Enterobacter* spp. (91% versus 90-92%), and *Klebsiella* spp. (95% versus 93-95%), but was less active against *Serratia* spp. (88% versus 92-97%).
- As a group, the four quinolones were only marginally active against *P. aeruginosa* (MIC_{90}s, > 4 μg/ml; 71 to 74% susceptible) and *Acinetobacter* spp. (MIC_{90}s, > 4 μg/ml; 45 to 55% susceptible). BMS284756 was the least active agent against BSI isolates of *P. aeruginosa* (MIC_{50}, 2 μg/ml; 71% susceptible) but was the most active drug against *Acinetobacter* spp. (MIC_{50}, 4 μg/ml; 55% susceptible).
- The overall potency and spectrum profiles show that BMS284756 maintains activity against several common enteric bacilli and *P. aeruginosa*, and has enhanced potency of *Staphylococcus* spp. and *Streptococcus* spp.

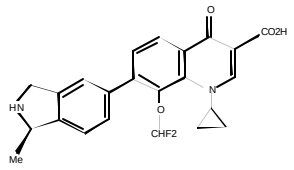
RESULTS (continued)

TABLE 1:
In vitro susceptibility of 5,527 Gram-positive blood stream infection isolates from North America, Latin America, and Europe to BMS284756, gatifloxacin, ciprofloxacin, and levofloxacin: SENTRY, 2000.

		MIC (μg/ml)		% susceptible at (μg/ml):				
Organism (no. tested)	*Antimicrobial agent*	*50%*	*90%*	*0.25*	*0.5*	*1*	*2*	*4*
S. aureus (2,555)	BMS284756	≤0.03	4	69	70	78	89	97[a]
	Gatifloxacin	0.12	4	68	69	70	79[a]	91
	Ciprofloxacin	0.5	>2	47	66	68[a]	68	NT[b]
	Levofloxacin	0.25	>4	67	68	69	70[a]	79
Coagulase-negative staphylococci (1,234)	BMS284756	0.12	4	52	55	68	86	96[a]
	Gatifloxacin	0.25	2	51	52	58	90[a]	96
	Ciprofloxacin	1	>2	44	48	51[a]	52	NT
	Levofloxacin	0.5	>4	48	51	52	58[a]	72
Enterococcus spp. (878)	BMS284756	1	>4	38	50	51	62	76[a]
	Gatifloxacin	1	>4	14	45	51	54[a]	56
	Ciprofloxacin	2	>2	1	8	40[a]	51	NT
	Levofloxacin	2	>4	1	8	43	53[a]	54
b-haemolytic streptococci (303)	BMS284756	0.06	0.12	98	98	99	99	100[a]
	Gatifloxacin	0.25	0.5	88	98	99[a]	99	99
	Ciprofloxacin	0.5	1	10	58	92	96	NT
	Levofloxacin	0.5	1	8	75	96	99[a]	99
viridans group streptococci (164)	BMS284756	0.06	0.12	98	99	99	100	100[a]
	Gatifloxacin	0.25	0.5	75	98	99[a]	99	100
	Ciprofloxacin	1	>2	6	20	52	84	NT
	Levofloxacin	1	1	8	38	92	98[a]	99
S. pneumoniae (393)	BMS284756	0.06	0.06	99	99	99	100	100[a]
	Gatifloxacin	0.25	0.5	88	99	99[a]	99	99
	Ciprofloxacin	1	2	2	19	79	98	NT
	Levofloxacin	1	1	1	42	99	99[a]	99

a. Percent susceptible at NCCLS breakpoint concentration. A breakpoint of ≤4 μg/ml has been proposed by Fung-Tomc et al. (AAC 44:3351-3356, 2000).
b. NT = concentration not tested.

FIGURE 1: Chemical Structure of BMS284756



•CH3 SO3H•H2O

RESULTS (continued)

TABLE 2:
In vitro susceptibility of 4,105 Gram-negative blood stream infection isolates from North America, Latin America, and Europe to BMS284756, gatifloxacin, ciprofloxacin, and levofloxacin: SENTRY, 2000.

		MIC (μg/ml)		% susceptible at (μg/ml):				
Organism (no. tested)	*Antimicrobial agent*	*50%*	*90%*	*0.25*	*0.5*	*1*	*2*	*4*
E. coli (1,864)	BMS284756	≤0.03	0.5	89	91	91	91	92[a]
	Gatifloxacin	≤0.03	0.25	90	91	92	92[a]	95
	Ciprofloxacin	≤0.25	≤0.25	91	91	91[a]	92	NT[b]
	Levofloxacin	≤0.03	0.25	90	91	91	92[a]	94
Enterobacter spp. (437)	BMS284756	0.12	4	79	82	86	88	91[a]
	Gatifloxacin	≤0.03	1	84	87	90	92[a]	94
	Ciprofloxacin	≤0.25	2	85	88	90[a]	92	NT
	Levofloxacin	≤0.03	2	84	87	90	92[a]	93
Klebsiella spp. (884)	BMS284756	0.12	1	83	88	91	93	95[a]
	Gatifloxacin	≤0.03	0.5	87	91	93	95[a]	97
	Ciprofloxacin	≤0.25	0.5	88	92	93[a]	94	NT
	Levofloxacin	≤0.03	0.5	87	91	93	94[a]	97
Serratia spp. (152)	BMS284756	1	>4	7	20	53	80	88[a]
	Gatifloxacin	0.25	2	76	81	90	97[a]	99
	Ciprofloxacin	≤0.25	1	82	85	92[a]	95	NT
	Levofloxacin	0.12	1	80	84	93	97[a]	99
P. aeruginosa (556)	BMS284756	2	>4	3	10	39	62	71[a]
	Gatifloxacin	1	>4	10	45	62	72[a]	77
	Ciprofloxacin	≤0.25	>2	64	71	74[a]	77	NT
	Levofloxacin	0.5	>4	25	57	67	74[a]	78
Acinetobacter spp. (210)	BMS284756	4	>4	43	45	46	48	55[a]
	Gatifloxacin	4	>4	43	45	47	48[a]	61
	Ciprofloxacin	>2	>2	40	43	45[a]	46	NT
	Levofloxacin	4	>4	43	44	47	49[a]	61

a. Percent susceptible at NCCLS breakpoint concentration. A breakpoint of ≤4 μg/ml has been proposed by Fung-Tomc et al. (AAC 44:3351-3356, 2000).
b. NT = concentration not tested.

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