Activity and Spectrum of BMS 284756 Tested Against 3546 Strains of Ciprofloxacin-Resistant Gram-Positive Cocci

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ABSTRACT

Background: BMS 284756 (BMS) is a novel des-fluoro quinolone with an expanded potency versus Gram-positive pathogens and described low risks of clinical toxicity. This study examines a subset of ciprofloxacin-resistant (CIPRO-R) Gram-positive cocci within the experience of the global SENTRY Antimicrobial Surveillance Program (1999).

Methods: More than 24,000 isolates were screened for CIPRO-R (MIC, ≥2 µg/ml) strains. Among 3,541 CIPRO-R strains, the most prevalent species were: *S. aureus* (SA; 1,623), coagulase-negative staphylococci (CoNS; 787), enterococci (726), *S. pneumoniae* (SPN; 197), other streptococci (148) and representatives of 15 other species.

Results: The % of isolates inhibited by BMS at ≤1/2/4 µg/ml (% ≤1 for trovafloxacin [TROVA]) were as follows: SA-43/72/93 (53), CoNS-39/67/92 (38), enterococci-28/38/65 (21), SPN-99/100/100 (99) and other strep-96/99/100 (92). Other resistant features of collection included: SPN penicillin-resistance at 32.0%, oxacillin resistance at 94.9/91.7% for CoNS/SA, and vancomycin resistance at 1.7/43.7% for *E. faecalis/E. faecium*. BMS potency and spectrum most approximated that of TROVA among the previously available fluoroquinolones (FQ), but it was 2- to 4-fold more potent against the CIPRO-R SPN isolates. *Corynebacterium* spp. strains were generally less BMS-susceptible (MIC, ≥4 µg/ml). In contrast, *B. cereus*, lactobacilli, *Listeria monocytogenes, Micrococcus* spp. and *Rhodococcus equi* strains were BMS-susceptible (≤2 µg/ml).

Conclusions: BMS demonstrated potent residual activity/spectrum against Gram-positive cocci proven resistant to ciprofloxacin. Potential use of BMS against some MRSA, VRE and FQ-resistant streptococci was apparent and clinical trials are encouraged to address the possibility.

INTRODUCTION

Fluoroquinolones have broad spectrums of antimicrobial activity that often includes important Gram-positive pathogens such as *Staphylococcus aureus*, coagulase -negative staphylococci (CoNS), *Enterococcus* spp. and streptococci. Many clinical strains, however, have emerged that appear refractory to commonly used agents in this class (ciprofloxacin, levofloxacin), leading to the development of quinolones with expanded potency against Gram-positive cocci and some anaerobes. Of particular concern have been the oxacillin-resistant staphylococci (ORS), glycopeptide-resistant enterococci (VRE), and β-lactam- or macrolide-resistant streptococci. BMS284756 (formerly T-3811 ME), 1-cyclopropyl-8-(difluoromethoxy)-7-[(1R)-(1-methyl-2, 3-dihydro-1H-5-isoindolyl-4-oxo-1, 4-dihydro-3 quinolinecarboxylic acid methasulfonate monohydrate, is a novel des-F(6)-quinolone that has shown excellent potency against a broad spectrum of pathogens including commonly encountered bacterial respiratory tract pathogens (*H. influenzae, M. catarrhalis, S. pneumoniae*) and some atypical organisms such as Mycobacterium, *Mycoplasma, Legionella,* and *Chlamydia*. To critically assess the BMS 284756 activity against contemporary clinical isolates, a collection of isolates was tested against numerous antimicrobial agents after selection for ciprofloxacin MIC results of ≥ 2 µg/ml, non-susceptible by National Committee for Clinical Laboratory Standards (NCCLS) criteria. BMS284756 was compared directly to gatifloxacin and trovafloxacin using reference broth microdilution tests.

From a collection of nearly 25,000 clinical isolates derived from patient infections in medical centers in the Americas (United States, Canada, Latin America) and Europe, all Gram-positive species strains with a ciprofloxacin MIC of ≥ 2 µg/ml were tested for potency against BMS 284756, gatifloxacin, trovafloxacin, and numerous other antimicrobials. The strains were from the SENTRY Antimicrobial Surveillance Program (1999), a global study for the determination of pathogen frequency and surveillance of antimicrobial/antifungal resistance.

MATERIALS AND METHODS

Each drug was tested in validated broth microdilution trays prepared by TREK (Cleveland, OH) using cation-supplemented Mueller-Hinton broth (PML Microbiologics, Wilsonville, OR). A total of 10 or 11 additional drugs were processed for this report. Concurrent quality control with *S. aureus* ATCC 29213 and *E. faecalis* ATCC 29212, consistently produced results within NCCLS published ranges for each studied compound. The organisms included *Corynebacterium* spp. (27 strains), enterococci (726 strains; two major species), *staphylococci* (2,410 strains), *Micrococcus* spp. (seven strains), *Bacillus* spp. (one strain, *Lactobacillus* spp. (one strain), *L. monocytogenes* (two strains), and *R. equi* (one strain). Results were presented as MIC_{50}, MIC_{90}, percent inhibited at various fluoroquinolone concentrations including the breakpoint (NCCLS). Breakpoints for drugs failing to have NCCLS published criteria for these species had breakpoint concentrations assigned based on the pharmacodynamic principles of the "usual" dose (example: 200 mg/d for trovafloxacin).

RESULTS AND CONCLUSIONS

- BMS 284756 possesses enhanced Gram-positive activity and maintains potential potency against man strains resistant to ciprofloxacin. If a susceptible breakpoint of ≤ 4 µg/ml were applied for BMS 284756 the following percentages of ciprofloxacin-resistant species would remain treatable by BMS 284756 (or gatifloxacin) pending clinical trial results:
  - *S. aureus* at 93% (46%)
  - CoNS 92% (80%)
  - Enterococci at 65% (24%)
  - *S. pneumoniae* at 100% (98%)
  - β-haemolytic streptococci at 100% (94%)
  - viridans group streptococci at 100% (93%)
  - *S. bovis* at 100% (100%)
- Rarer Gram-positive species that were resistant to earlier fluoroquinolones generally were susceptible to BMS 284756 (except *Corynebacterium* spp.).
- Desfluoro compounds in the quinolone class may have the ability to be dosed at higher levels to expand the spectrum. If this proves true for BMS 284756, its Gram-positive spectrum could be useful to address emerging resistances to earlier members of the fluoroquinolone class and expand the treatment options for emerging resistant Gram-positive pathogens.

TABLE 1
Comparative antimicrobial activity of BMS 284756 tested against 3,502 strains of Gram-positive cocci having elevated MICs to ciprofloxacin (MIC, ≥ 2 µg/ml).

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	MIC (µg/ml) 90%	% inhibited at: ≤0.5	≤1	≤2	≤4	At the breakpoint[b]
S. aureus (1,623)	BMS284756	2	4	13	43	72	93	-
	Gatifloxacin	4	>4	5	10	46	82	45.6
	Trovafloxacin	1	>4	12	53	72	84	53.2
	Ampicillin	>16	>16	3	4	5	7	2.1
	Oxacillin	>8	>8	6	8	8	9	8.3
	Linezolid	2	2	<1	18	95	100	100.0
	Vancomycin	1	1	9	90	99	99	99.9[e]
CoNS[c] (787)	BMS284756	2	4	8	39	67	92	-
	Gatifloxacin	2	4	3	19	80	94	80.3
	Trovafloxacin	2	>4	7	38	56	70	38.2
	Ampicillin	16	>16	5	7	13	25	3.2
	Oxacillin	>8	>8	6	7	11	17	5.1
	Linezolid	1	2	4	78	99	100	100.0
	Vancomycin	2	2	1	29	99	100	100.0
Enterococcus faecalis (346)	BMS284756	2	>4	26	30	52	86	-
	Gatifloxacin	>4	>4	18	28	29	31	29.2
	Trovafloxacin	>4	>4	26	28	30	41	27.5
	Ampicillin	1	2	3	53	92	98	99.1
	Oxacillin	>8	>8	0	<1	<1	<1	0.6
	Linezolid	2	2	<1	41	100	-	100.0
	Vancomycin	1	2	1	78	97	98	97.7
E. faecium (222)	BMS284756	>4	>4	1	2	12	30	-
	Gatifloxacin	>4	>4	1	5	14	21	14.4
	Trovafloxacin	>4	>4	1	9	16	25	9.0
	Ampicillin	>16	>16	1	3	5	7	7.7
	Oxacillin	>8	>8	0	0	1	2	-
	Linezolid	2	2	<1	25	98	100	98.2
	Vancomycin	1	>16	14	53	56	56	56.3

a. Breakpoint concentrations for susceptibility are underlined in the table [NCCLS, 2000], where established. BMS 284756 does not have a published breakpoint. For trovafloxacin ≤ 1 µg/ml was used and for linezolid, the FDA-product package insert guidelines were followed.
b. MICs at or below the established breakpoint listed to the tenth of one percent.
c. One strain was noted with a vancomycin MIC of 8 µg/ml (VISA).
d. CoNS = coagulase-negative staphylococci.
e. Susceptibility rate determined from the penicillin MIC results (32.0% non-susceptible at ≥ 0.12 µg/ml).

TABLE 1 (continued)
Comparative antimicrobial activity of BMS 284756 tested against 3,502 strains of Gram-positive cocci having elevated MICs to ciprofloxacin (MIC, ≥ 2 µg/ml). (continued)

Organism (no. tested)	Antimicrobial agent	MIC (µg/ml) 50%	MIC (µg/ml) 90%	% inhibited at: ≤0.5	≤1	≤2	≤4	At the breakpoint[b]
All enterococci (726)	BMS284756	4	>4	17	20	38	65	-
	Gatifloxacin	>4	>4	12	20	24	27	24.0
	Trovafloxacin	>4	>4	18	21	25	36	21.2
	Ampicillin	2	>16	3	36	60	64	64.7
	Oxacillin	>8	>8	<1	<1	1	2	-
	Linezolid	2	2	<1	35	99	100	99.4
	Vancomycin	1	>16	6	68	80	82	82.0
Streptococcus pneumoniae (197)	BMS284756	0.06	0.12	99	99	100	-	-
	Gatifloxacin	0.5	0.5	98	98	98	99	98.0
	Trovafloxacin	0.25	0.25	98	99	99	99	98.5
	Ampicillin	≤0.12	2	83	87	93	100	68.0[e]
	Oxacillin	≤0.06	8	78	80	82	86	-
	Linezolid	1	1	24	93	100	-	100.0
	Vancomycin	0.25	0.5	99	100	-	-	100.0
β-haemolytic streptococci (17)	BMS284756	0.12	0.25	94	94	94	100	-
	Gatifloxacin	0.5	0.5	94	94	94	100	94.1
	Trovafloxacin	0.5	1	88	94	94	94	94.1
	Ampicillin	≤0.12	≤0.12	100	-	-	-	100.0
	Oxacillin	0.25	0.5	100	-	-	-	-
	Linezolid	1	1	6	94	100	-	100.0
	Vancomycin	0.5	0.5	94	100	-	-	100.0
viridans group streptococci (131)	BMS284756	0.12	0.25	92	96	99	100	-
	Gatifloxacin	0.5	1	89	93	95	97	93.1
	Trovafloxacin	0.12	0.5	92	92	94	96	92.4
	Ampicillin	≤0.12	1	88	93	95	96	83.2
	Oxacillin	≤0.06	1	87	95	97	99	-
	Linezolid	1	1	14	95	100	-	100.0
	Vancomycin	0.5	1	88	100	-	-	100.0
S. bovis (21)	BMS284756	0.12	0.12	100	-	-	-	-
	Gatifloxacin	0.5	0.5	100	-	-	-	100.0
	Trovafloxacin	0.25	0.5	100	-	-	-	100.0
	Ampicillin	≤0.12	≤0.12	100	-	-	-	100.0
	Oxacillin	0.25	0.25	100	-	-	-	-
	Linezolid	1	2	10	57	100	-	100.0
	Vancomycin	0.5	0.5	100	-	-	-	100.0

a. Breakpoint concentrations for susceptibility are underlined in the table [NCCLS, 2000], where established. BMS 284756 does not have a published breakpoint. For trovafloxacin ≤ 1 µg/ml was used and for linezolid, the FDA-product package insert guidelines were followed.
b. MICs at or below the established breakpoint listed to the tenth of one percent.
c. One strain was noted with a vancomycin MIC of 8 µg/ml (VISA).
d. CoNS = coagulase-negative staphylococci.
e. Susceptibility rate determined from the penicillin MIC results (32.0% non-susceptible at ≥ 0.12 µg/ml).

TABLE 2
BMS 284756 MIC values for 39 strains of unusual bacterial species.

Organism (no. tested)	BMS 284756 MIC in µg/ml (occurrences)
Bacillus spp. (1)	0.5 (1)
Corynebacterium spp. (27)[a]	0.5 (2), 2 (1), 4 (5), >4 (19)
Lactobacillus spp. (1)	2 (1)
Listeria monocytogenes (2)	0.25 (1), 0.5 (1)
Micrococcus lutens (1)	0.5 (1)
Micrococcus spp. (6)	0.25 (1), 0.5 (5)
Rhodococcus equi (1)	2 (1)

a. Includes 11 strains of C. jeikeium (all were resistant to fluoroquinolones). Other species included: C. amycolatum (one strain), C. auris (one strain), C. bovis (one strain), C. pseudodiphtheritum (one strain), C. striatum (three strains), C. urealyticum (one strain), and unspecified coryneba cteria (eight strains).

REFERENCES

1. **Hayashi K, Todo Y, Hamamoto S, Ojima K, Yamada M, Kito T, Takahata M, Watanabe Y, Narita H.** 1997. T-3811, a novel des-F(6)-quinolone: Synthesis and in vitro activity of 7-(isoindolin-5-yl) derivatives, abstr. F158, p. 173. In: Program and Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, DC.
2. **Hori R, Takahta M, Shimakura M, Sugiyama H, Yonezawa M, Todo Y, Minami S, Watanabe Y, Narita H.** 1998. Efficacy of T-3811ME, a novel des-F(6)-quinolone, against experimental meningitis in rabbits caused by penicillin-resistant *Streptococcus pneumoniae*, abstr. F-78. In: Program and Abstracts of the 38th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, DC.
3. **Nagai A, Takahata M, Miyazaki M, Kawamura Y, Kodama T, Todo Y, Watanabe Y, Narita H.** 1997. T-3811, a novel des-F(6)-quinolone: Toxicological evaluation, abstr. F162, p. 173. In: Program and Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, DC.
4. **Takahata M, Mitsuyama J, Yamshiro Y, Araki H, Yamada H, Hayakawa H, Todo Y, Minami S, Watanabe Y, Narita H.** 1997. T-3811, a novel des-F(6)-quinolone: Study of pharmacokinetics in animals, abstr. F160, p. 173. In: Program and Abstracts of the 37th Interscience Conference on Antimicrobial Agents and Chemotherapy. American Society for Microbiology, Washington, DC.
5. **Takahata M, Mitsuyama J, Yamashiro Y, Yonezawa M, Araki H, Todo Y, Minami S, Watanabe Y, Narita H.** 1999. In vitro and in vivo antimicrobial activites of T-3811ME, a novel des-F(6)-quinolone. Antimicrob Agents Chemother 43:1077-1084.