Geographic Variations in BMS 284756 Activity Against Pathogens Associated with Skin and Soft Tissue Infections: Report from the SENTRY Antimicrobial Surveillance Program (2000)

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AMENDED ABSTRACT

Purpose: To geographically compare the activity of BMS 284756, a desfluoroquinolone (formerly T-3811), when tested against isolates from skin and soft tissue infections (SSTI) in the SENTRY Program (2000).

Methods: Over 2,500 SSTI isolates were tested against BMS 284756, ciprofloxacin (CIP), gatifloxacin (GATI) and levofloxacin (LEVO) using NCCLS microdilution methods. A central laboratory tested isolates from Europe (EU), Latin America (LA) and North America (NA); potency and spectrum of activity were examined from each region. The rank order of the 7 most frequent pathogens (85% of 2,537 isolates) was *S. aureus* (SA; 1,013 isolates), *P. aeruginosa* (PSA; 307), *E. coli* (EC; 246), *Enterococcus* spp. (ESP; 195), *Klebsiella* spp. (KSP; 147), *Enterobacter* spp. (EBS; 141), coagulase-negative staphylococci (CoNS; 107).

Results: Against SA, the predominant pathogen isolated from SSTI in each region, BMS 284756 was the most active agent using a proposed susceptibility breakpoint of ≤4 µg/ml (Fung-Tomc et al. AAC 44:3351-3356, 2000). BMS 284756 exhibited ≥4-fold superior potency compared to LEVO (MIC50, ≤0.03 µg/ml vs 0.12-0.25 µg/ml) and a 23% higher susceptibility rate compared to CIP for all regions. The rate of oxacillin-resistant SA (MRSA) isolates did not vary significantly between regions with EU being lowest at 22% and NA highest at 29%. Among the MRSA, LEVO and CIP intermediate resistance was high (>81%). In contrast, BMS 284756 was active against 97% of all SA strains regardless of oxacillin resistance. Against CoNS strains, BMS 284756 (MIC_{50}, 0.12 µg/ml) had a 2- to 4-fold greater potency vs LEVO with higher MICs noted in EU (MIC_{50}, 1 vs 4 µg/ml). GATI was most like BMS 284756 against staphylococci. ESP showed a greater BMS 284756 spectrum (85.1% susceptibility) and potency compared to LEVO or CIP (MIC_{50}; 0.5 vs 2 µg/ml). This new desfluoroquinolone was less active against Enterobacteriaceae compared to LEVO (MIC_{50} values at 2- to 4-fold lower) for KSP and EBS. Utilizing the NCCLS breakpoint interpretive criteria or defined BMS 284756 breakpoint (≤4 µg/ml), the percent susceptibility rates for PSA were similar for all four tested compounds (65-70%). Susceptibility patterns were similar in every region except LA where ESP were more susceptible and PSA or EBS isolates were more resistant.

Conclusions: BMS 284756 demonstrated increased potency and spectrum against staphylococci and other Gram-positive cocci. With the potential for increased des-fluoro quinolone dosages and susceptibility breakpoint criteria, comparable spectrums among quinolone compounds should be achieved.

INTRODUCTION

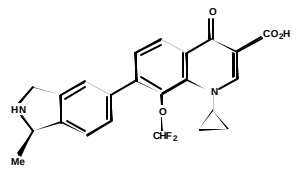
The introduction of quinolones dates back to the 1963 Food and Drug Administration (FDA) approval of a non-fluorinated quinolone, nalidixic acid. Used primarily for urinary tract infections, it possessed limited spectrum and efficacy against the emergence of increasing antimicrobial resistance. Structural modification to this compound, specifically the addition of a fluorine at C-6 and a piperazine ring at C-7 along with additional side chain substitutions, yielded several second-generation and third-generation quinolones (ciprofloxacin and levofloxacin). These fluoroquinolones exhibit increased activity against Gram-positive organisms as well as extended Gram-negative spectrum. Other benefits noted were increased effectiveness against a wide variety of clinical infections, higher intracellular drug levels, longer serum half-lives and a lower protein binding affinity.

The present study involves an expanded spectrum quinolone, BMS 284756. This novel des-fluoro(6)-quinolone differs from earlier quinolones in that it lacks a fluorine atom at the C-6 position, but has an isoindolin-5-yl substitution at the 7 position. BMS 284756 has reportedly shown increased activity compared to other quinolones against Gram-positive organisms including methicillin-resistant staphylococci and *Enterococcus* spp. Broader anti-anaerobic coverage and superior activity against fastidious organisms has also been described. Toxicological findings rate BMS 284756 as excellent by having low chondrotoxicity in juvenile rats making it a viable therapy for children and adolescents.

In the ongoing SENTRY Antimicrobial Surveillance Program (2000), BMS 284756 and several other investigational antimicrobials were tested against 2,537 skin and soft tissue (SSTI) isolates from 59 medical centers world-wide. This study was initiated in January 2000 and included participants from the United States (US; 25 centers), Canada (five centers), Latin America (10 centers) and Europe (19 centers). A proposed breakpoint of ≤ 4 µg/ml was used in evaluating and comparing BMS 284756 performance. Geographic analyses were divided into three regions (North America, Latin America and Europe).

The intent of this report is to present results of the 2000 SENTRY Antimicrobial Surveillance Program focusing on hospitalized patients with community-acquired, as well as, nosocomial (SSTIs) in all three regions. The most common pathogens associated with SSTIs are examined, as well as, potency and spectrum of selected antimicrobial agents. Included are regional patterns of antimicrobial susceptibility for comparison to locally and regionally derived data, as well as, with other multi-center investigations. Statistical data from a large number of isolates like those tested by the SENTRY Program are powerful tools in determining emerging resistance patterns and current antimicrobial susceptibilities.

FIGURE 1: Chemical Structure of BMS 284756



$\cdot CH_3SO_3H \cdot H_2O$

FIGURE 2: MIC distribution of Streptococcus spp. from SSTI (all regions, SENTRY Program, 2000)

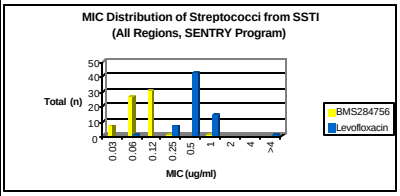


TABLE 1: Rank order of skin and soft tissue infection (SSTI) isolates from medical centers in North America, Latin America and Europe

Rank	*Organism*	*Number of organisms tested (%) in 2000*			
		North American	*Latin America*	*Europe*	*Total*
1	*S. aureus*	645 (45.9)	152 (34.9)	216 (31.0)	1,013 (39.9)
2	*P. aeruginosa*	152 (10.8)	58 (13.3)	97 (13.9)	307 (12.1)
3	*E. coli*	98 (7.0)	54 (12.4)	94 (13.5)	246 (9.7)
4	*Enterococcus* spp.	115 (8.2)	29 (6.7)	51 (7.3)	195 (7.7)
5	*Klebsiella* spp.	71 (5.1)	36 (8.3)	40 (5.7)	147 (5.8)
6	*Enterobacter* spp.	81 (5.8)	20 (4.6)	40 (5.7)	141 (5.6)
7	CoNS	48 (3.4)	25 (5.7)	34 (4.9)	107 (4.2)
8	*Proteus* spp.	45 (3.2)	18 (4.1)	31 (4.4)	94 (3.7)
9	*Streptococcus* spp.	38 (2.7)	8 (1.8)	19 (2.7)	65 (2.6)
10	*Acinetobacter* spp.	23 (1.6)	11 (2.5)	21 (3.0)	55 (2.2)
11	*Serratia* spp.	28 (2.0)	7 (1.6)	15 (2.2)	50 (2.0)
12	*Citrobacter* spp.	19 (1.4)	3 (0.7)	11 (1.6)	33 (1.3)
13	Other species	41 (2.9)	15 (3.4)	28 (4.0)	84 (3.3)
TOTAL		**1,404**	**436**	**697**	**2,537**

TABLE 2: *In vitro* activity of BMS 284756 and three comparator quinolones tested against SSTI isolates from the SENTRY Program centers in the Americas and Europe

Organism (n) / quinolone	*MIC (µg/ml)*							
	North American		*Latin America*		*Europe*		*All Regions*	
	50 / 90	*% Susc.*[a]	*50 / 90*	*% Susc.*[a]	*50 / 90*	*% Susc.*[a]	*50 / 90*	*% Susc.*[a]
S. aureus								
oxacillin -resistant (275)								
BMS 284756	2/>4	87.9	1/2	97.3	2/4	95.8	2/4	90.5
Ciprofloxacin	>2/>2	18.4	>2/>2	8.1	>2/>2	4.2	>2/>2	14.5
Gatifloxacin	4/>4	36.8	2/4	70.3	2/4	56.3	4/>4	44.7
Levofloxacin	>4/>4	21.1	4/>4	10.8	4/>4	12.5	>4/>4	18.2
oxacillin -susceptible (736)								
BMS 284756	≤0.03/0.06	99.8	≤0.03/≤0.03	100.0	≤0.03/ ≤0.03	100.0	≤0.03/0.06	100.0
Ciprofloxacin	≤0.25/0.5	95.1	≤0.25/0.5	98.3	≤0.25/0.5	95.2	≤0.25/0.5	95.7
Gatifloxacin	0.06/0.12	98.0	0.06/0.12	100.0	0.06/0.12	98.8	0.06/0.12	98.5
Levofloxacin	0.12/0.25	96.5	0.12/0.25	100.0	0.12/0.25	97.6	0.12/0.25	97.3
CoNS								
oxacillin -resistant (81)								
BMS 284756	1/4	97.0	1/4	100.0	1/4	93.1	1/4	96.3
Ciprofloxacin	>2/>2	45.5	>2/>2	36.8	>2/>2	34.5	>2/>2	39.5
Gatifloxacin	2/4	87.9	1/4	84.2	2/4	82.8	1/4	85.2
Levofloxacin	4/>4	48.5	2/>4	63.2	4/>4	34.5	4/>4	46.9
oxacillin -susceptible (25)								
BMS 284756	0.06/0.06	93.3	0.06/0.06	100.0	≤0.03/4	100.0	0.06/0.06	96.0
Ciprofloxacin	≤0.25/≤0.25	93.3	≤0.25/≤0.25	100.0	≤0.25/>2	75.0	≤0.25/ ≤0.25	92.0
Gatifloxacin	0.12/0.12	93.3	0.12/0.12	100.0	0.12/2	100.0	0.12/0.12	96.0
Levofloxacin	0.25/0.25	93.3	0.25/0.25	100.0	0.25/>4	75.0	0.25/0.25	92.0
Enterococcus spp. (195)								
BMS 284756	0.5/>4	84.3	0.25/4	100.0	1/>4	78.4	0.5/>4	85.1
Ciprofloxacin	2/>2	44.3	1/>2	65.5	2/>2	39.2	2/>2	45.6
Gatifloxacin	1/>4	55.7	0.5/>4	79.3	1/>4	64.7	0.5/>4	62.1
Levofloxacin	1/>4	54.8	1/>4	75.9	2/>4	60.8	2/>4	60.0
E. coli (246)								
BMS 284756	≤0.03/>4	87.8	≤0.03/>4	81.5	≤0.03/>4	87.2	≤0.03/>4	85.8
Ciprofloxacin	≤0.25/>2	87.8	≤0.25/>2	81.5	≤0.25/>2	87.2	≤0.25/>2	85.8
Gatifloxacin	≤0.03/>4	88.8	≤0.03/>4	81.5	≤0.03/4	88.3	≤0.03/4	87.0
Levofloxacin	≤0.03/4	88.8	≤0.03/>4	81.5	≤0.03/4	87.2	≤0.03/4	86.2
Enterobacter spp. (141)								
BMS 284756	0.12/2	91.4	0.5/>4	70.0	0.12/0.25	100.0	0.12/4	90.8
Ciprofloxacin	≤0.25/0.5	96.3	≤0.25/>2	65.0	≤0.25/≤0.25	100.0	≤0.25/0.5	92.9
Gatifloxacin	≤0.03/0.5	97.5	0.12/>4	70.0	≤0.03/0.06	100.0	≤0.03/1	94.3
Levofloxacin	≤0.03/0.5	97.5	0.06/>4	70.0	≤0.03/0.06	100.0	≤0.03/1	94.3
Klebsiella spp. (147)								
BMS 284756	0.12/2	95.8	0.12/1	97.2	0.12/1	92.5	0.12/2	95.2
Ciprofloxacin	≤0.25/2	88.7	≤0.25/>1	91.7	≤0.25/0.5	90.0	≤0.25/2	89.8
Gatifloxacin	0.06/2	90.1	0.06/1	97.2	≤0.03/2	90.0	0.06/2	91.8
Levofloxacin	0.06/2	90.1	≤0.03/1	97.2	≤0.03/1	90.0	≤0.03/2	91.8
P. aeruginosa (307)								
BMS 284756	2/>4	67.8	4/>4	53.4	2/>4	68.0	2/>4	65.1
Ciprofloxacin	≤0.25/>2	74.3	0.5/>2	51.7	≤0.25/>2	73.2	≤0.25/>2	69.7
Gatifloxacin	1/>4	67.8	2/>4	50.0	1/>4	69.1	1/>4	64.7
Levofloxacin	0.5/>4	69.7	2/>4	51.7	0.5/>4	72.2	0.5/>4	67.1

[a] Using proposed susceptibility breakpoint of ≤ 4 µg/ml [Fung-Tomc et al., 2000]. All other quinolones follow NCCLS 2000 guidelines for susceptibility breakpoints.

MATERIALS AND METHODS

Organisms tested: A total of 59 medical centers from 20 different countries in North America, Latin America and Europe submitted isolates for study. Participants were instructed to collect isolates from 50 consecutive SSTIs meeting that centers' criteria for clinical significance. Nosocomial, as well as, community-acquired infections were permitted as long as the patient required hospitalization due to the infection. Primary identification of each organism occurred at the participating medical center using their own routine methodology. A total of 2,537 isolates encompassing more than 62 different bacterial strains were submitted to the monitor. Confirmation of species identification was performed by Vitek (bio Merieux Vitek, St. Louis, MO) as deemed necessary.

Susceptibility test methods: All strains were tested and interpreted at a central monitoring laboratory using reference broth microdilution methods as described by the NCCLS. Quality control (QC) was achieved by regular performance testing of the following ATCC strains: *Escherichia coli* ATCC 25922, *Staphylococcus aureus* ATCC 29213, *Pseudomonas aeruginosa* ATCC 27853, *Streptococcus pneumoniae* ATCC 49619 and *Enterococcus faecalis* ATCC 29212 and others. Antimicrobials were obtained from US manufacturers and included 28 investigational and clinical agents for Gram-positive isolates and 31 drugs for Gram-negative isolates. Suspected ESBL-producing phenotypes of Enterobacteriaceae were screened by observing increased minimum inhibitory concentrations (MIC) for ceftazidime or ceftriaxone or aztreonam of ≥ 2 µg/ml. Confirmation of these isolates was performed by using ESBL Etest strips (AB BIODISK, Solna, Sweden) which exhibit a greater than four-fold decrease in MICs for ceftazidime when in the presence of 2 or 4 µg/ml clavulanic acid.

RESULTS AND CONCLUSIONS

- BMS 284756 was the most active agent against oxacillin-susceptible *S. aureus* exhibiting potency two- to eight-fold greater compared to gatifloxacin or levofloxacin or ciprofloxacin (MIC_{90}, 0.06 vs. 0.12, 0.25 and 0.5 µg/ml, respectively). All quinolones were active against this sub-population in all regions (> 95% susceptibility).
- Among MRSA isolates, levofloxacin and ciprofloxacin resistance was very high (> 81%), and < 50% of isolates were susceptible to gatifloxacin. In contrast, BMS 284756 was active against > 90% of all MRSA and against 97% of all *S. aureus* strains tested regardless of oxacillin susceptibility pattern.
- BMS 284756 (MIC_{90}, 0.06 µg/ml) exhibited an overall four-fold greater potency compared to levofloxacin (MIC_{90}, 0.25 µg/ml) and ciprofloxacin (MIC_{90}, ≤ 0.25 µg/ml) against oxacillin-susceptible coagulase-negative staphylococci (CoNS). The potency of gatifloxacin and BMS 284756 was most equivalent against oxacillin-resistant CoNS. ≥ 96% of all CoNS strains were inhibited by BMS 284756 regardless of oxacillin susceptibility pattern.
- BMS 284756 showed similar potency to gatifloxacin (MIC_{50}, 0.5 µg/ml) and a four-fold greater activity versus ciprofloxacin (MIC_{50}, 2 µg/ml) and levofloxacin (MIC_{50}, 2 µg/ml), as well as the highest susceptibility rate (85.1% vs. 45.6 - 60.0%) against *Enterococcus* spp. Latin American strains were more susceptible to the quinolones compared to other regions.
- Against *Streptococcus* spp., BMS 284756 exhibited an eight-fold greater potency compared to levofloxacin (MIC_{50}, 0.06 vs. 0.5 µg/ml) and was very active against all streptococcal strains tested (data not shown). Figure 2 shows a four-fold higher modal MIC for levofloxacin with MIC ranges for BMS 284756 of ≤ 0.03 - 1 mg/ml and levofloxacin of 0.06 - > 4 mg/ml.
- For the combined regions, all four quinolone compounds displayed more similar activity and spectrums against *E. coli*: 85.8 - 87.0%, *Enterobacter* spp.: 90.8 - 94.3%, *Klebsiella* spp.: 89.8 - 95.2%, and *P. aeruginosa*: 64.7 - 69.7%. Significant regional variations were, however found only among Latin American Enterobacter spp. isolates, which were significantly more resistant to all listed agents.

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