Geographic Variations in BMS284756 Activity and Spectrum Tested Against Common Respiratory Tract Pathogens: Report from the SENTRY Antimicrobial Surveillance Program (2000)

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ABSTRACT

Purpose: To determine the in vitro activity of BMS284756 a novel desfluoroquinolone , tested against three bacterial species causing community-acquired respiratory tract infections (CARTI). Geographic variation among the isolates from Europe (EU), North (NA) and Latin America (LA) were assessed for the year 2000.

Methods: A total of 844 *Moraxella catarrhalis* (MCAT), 1,788 *Streptococcus pneumoniae* , and 2,066 *Haemophilus influenzae* (HI) isolates were obtained from participants in the SENTRY Antimicrobial Surveillance Program (2000). Each isolate was tested against BMS284756, ciprofloxacin (CIP), gatifloxacin (GATI), moxifloxacin (MOXI) and levofloxacin (LEVO) using the reference broth microdilution method (NCCLS). The geographic regions consist of NA (30 sites), LA (10 sites) and EU (18 sites). The resistance demographics of the collections were: penicillin susceptibility among SPN (65.9% [NA] to 73.8% [LA]), β-lactamase production in MCAT (95.5% [EU] to 97.1% [LA]) and β-lactamase activity in HI (10.3% [LA] to 27.5% [NA]).

Results: Comparing all regions for the activity of BMS284756 to CIP, GATI, MOXI and LEVO showed that BMS284756 was equally active for HI (MIC_{90}, ≤0.03 versus ≤0.015 - ≤0.03 µg/ml) and MCAT (MIC_{90}, ≤0.03 versus ≤0.03 - 0.06 µg/ml), but more potent for SPN (MIC_{90}, 0.06 versus 0.25 - 2 µg/ml). The three regions (NA, LA, and EU) did not significantly differ in the potencies of each drug versus the monitored pathogens. Fluoroquinolone -resistant strains of HI (2 with CIP MICs at >0.12 µg/ml) and SPN (12 with LEVO MICs at >4 µg/ml; 0.9% overall) were noted in NA only. Also the rate of CIP resistance (MIC, >2 µg/ml) in SPN was greatest in NA (3.5%) > LA (2.7%) > EU (1.5%). BMS284756 was active against 11 of 12 LEVO-resistant SPN strains at ≤1 µg/ml. Resistance rates in SPN for NA was ≤0.2% for GATI and MOXI.

Conclusions: BMS284756 showed that it possesses similar effectiveness against HI and MCAT (MIC_{90}, ≤0.03 µg/ml) while it was more active than CIP (32-fold), GATI (8-fold) and MOXI (4-fold) versus 1,788 SPN strains isolated in 2000. BMS284756 potency did not vary between NA or LA or EU regions although quinolone resistance seems to be emerging more rapidly in NA, even among the fastidious Gram-negative species. The role of BMS284756 against strains resistant to previously available quinolones awaits wide spread clinical investigations.

INTRODUCTION

BMS284756, formerly T-3811, was developed to provide enhanced potency for a wide range of bacteria including: Gram-positive cocci (staphylococci, enterococci , streptococci), Enterobacteriaceae and non-fermentative Gram-negative bacilli (Figure 1). Recent and on-going studies have found that BMS284756 is active against numerous bacterial species including strains from the genera *Mycobacterium*, *Mycoplasma* and *Chlamydia*.

The purpose of this study was to evaluate the potency of BMS284756 against *Streptococcus pneumoniae*, *Haemophilus influenzae* and *Moraxella catarrhalis* isolated from patients with community-acquired respiratory tract infections (CARTI). This study also compared the potency of BMS284756 on the isolates from three geographical regions, North America (NA), Latin America (LA) and Europe (EU).

MATERIALS AND METHODS

Bacterial strains: A total of 2,066 *H. influenzae* , 844 *M. catarrhalis*, and 1,788 *S. pneumoniae* isolates were tested from the SENTRY Antimicrobial Surveillance Program (2000). The isolates were from patients with CARTI. The three geographical regions sampled consist of NA (30 sites), LA (10 sites) and EU (18 sites). The resistance demographics of the isolates were: penicillin susceptibility among pneumococci ranged from 65.9% (NA) to 73.8% (LA), and β-lactamase production in *M. catarrhalis*, 95.5% (EU) to 97.1% (LA), β-lactamase production in *H. influenzae*, 10.3% (LA) to 27.5% (NA). All isolates were tested at the monitoring laboratory at the University of Iowa College of Medicine (Iowa City, Iowa, USA).

Susceptibility testing: The minimum inhibitory concentrations (MICs) were performed on each isolate using the broth microdilution method as outlined by the National Committee for Clinical Laboratory Standards (NCCLS). Only the results of the quinolones; BMS284756, ciprofloxacin (CIPRO), gatifloxacin (GATI), moxifloxacin (MOXI) and levofloxacin (LEVO), were compared for this report. Quality control strains of *H. influenzae* ATCC 49247, *S. pneumoniae* ATCC 49619, *Staphylococcus aureus* ATCC 29213, *Enterococcus faecalis* ATCC 29212 and *Escherichia coli* ATCC 25922 were tested.

TABLE 1: Antimicrobial Activity of BMS284756 and Four (4) Quinolones Tested Against *H. influenzae* Isolates in Three Geographic Regions (SENTRY Antimicrobial Surveillance Program, 2000)

	NA (n = 1,194)			LA (n = 195)			EU (n = 677)		
Quinolone	MIC_{90}	*Range*	*% Susc.*	MIC_{90}	*Range*	*% Susc.*	MIC_{90}	*Range*	*% Susc.*
BMS284756	£0.03	£0.03-2	100.0 [a]	£0.03	£0.03-0.06	100.0 [a]	£0.03	£0.03-0.25	100.0 [a]
CIPRO	£0.016	£0.016->2	99.8	£0.016	£0.016-0.03	100.0	£0.016	£0.016-0.12	100.0
GATI	£0.03	£0.03-1	100.0	£0.03	£0.03	100.0	£0.03	£0.03-0.12	100.0
MOXI	£0.03	£0.03-2	100.0	£0.03	£0.03-0.06	100.0	£0.03	£0.03-0.25	100.0
LEVO	£0.03	£0.03-2	100.0	£0.03	£0.03-0.06	100.0	£0.03	£0.03-0.12	100.0

a. Where interpretive criteria do not exist, the criteria of £ 4 mg/ml were used for comparison purposes only [Fung-Tomc et al., 2000].

TABLE 2: Antimicrobial Activity of BMS284756 and Four (4) Quinolones Tested Against *M. catarrhalis* Isolates in Three Geographic Regions (SENTRY Antimicrobial Surveillance Program, 2000)

	NA (n = 524)			LA (n = 34)			EU (n = 286)		
Quinolone	MIC_{90}	*Range*	*% Susc.*	MIC_{90}	*Range*	*% Susc.*	MIC_{90}	*Range*	*% Susc.*
BMS284756	£0.03	£0.03-0.06	100.0 [a]	0.06	£0.03-0.12	100.0 [a]	£0.03	£0.03-0.06	100.0 [a]
CIPRO	£0.016	£0.016-0.12	100.0	0.06	£0.016-0.06	100.0	0.06	£0.016-0.06	100.0
GATI	£0.03	£0.03-0.12	100.0	£0.03	£0.03-0.06	100.0	£0.03	£0.03-0.06	100.0
MOXI	0.06	£0.03-0.12	100.0	0.06	£0.03-0.06	100.0	0.06	£0.03-0.12	100.0
LEVO	£0.03	£0.03-0.25	100.0	£0.03	£0.03	100.0	£0.03	£0.03-0.06	100.0

a. Where interpretive criteria do not exist, the criteria of £ 4 mg/ml were used for comparison purposes only [Fung-Tomc et al., 2000].

TABLE 3: Antimicrobial Activity of BMS284756 and Four (4) Quinolones Tested Against *S. pneumoniae* Isolates in Three Geographic Regions (SENTRY Antimicrobial Surveillance Program, 2000)

	NA (n = 1,103)			LA (n = 149)			EU (n = 536)		
Quinolone	MIC_{90}	*Range*	*% Susc.*	MIC_{90}	*Range*	*% Susc.*	MIC_{90}	*Range*	*% Susc.*
BMS284756	0.06	£0.03-4	100.0 [a]	0.06	£0.03-0.25	100.0 [a]	0.06	£0.03-1	100.0 [a]
CIPRO	2	£0.016->2	96.5	2	£0.016->2	97.3	2	£0.016->2	98.5
GATI	0.5	£0.03->4	99.8	0.5	£0.03-1	100.0	0.5	£0.03-1	100.0
MOXI	0.25	£0.03->4	99.9	0.25	£0.03-0.5	100.0	0.25	£0.03-0.5	100.0
LEVO	1	£0.03->4	98.9	1	£0.03-2	100.0	1	£0.03-2	100.0

a. Where interpretive criteria do not exist, the criteria of £ 4 mg/ml were used for comparison purposes only [Fung-Tomc et al., 2000].

FIGURE 1: Chemical Structure of BMS284756

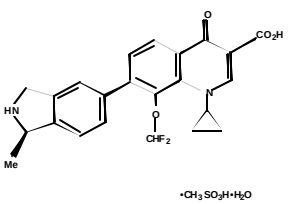

TABLE 4: Regional Trends in Quinolone Resistance in *S. pneumoniae* (SENTRY Antimicrobial Surveillance Program, 2000)

	% Resistant Strains		
Quinolone	*NA*	*LA*	*EU*
BMS284756	0.0	0.0	0.0
CIPRO	3.5 (n = 39) [a]	2.7 (n = 4) [a]	1.5 (n = 8) [a]
GATI	0.3 (n = 2)	0.0	0.0
MOXI	0.1 (n = 1)	0.0	0.0
LEVO	1.1 (n = 12)	0.0	0.0

a. Resistance criteria of Chen et al. [1999].

RESULTS

- In all three regions, BMS284756, CIPRO, GATI, MOXI and LEVO all had similar potencies for each of the drugs when tested against the reported CARTI isolates; ***no geographic variations!***
- For *M. catarrhalis* (all three regions), BMS284756 proved to have equal activity when compared to CIPRO, GATI, MOXI and LEVO (MIC_{90}, ≤ 0.03 versus ≤ 0.03 - 0.06 µg/ml).
- For *H. influenzae* (all three regions), BMS284756 proved to have equal potency when compared to CIPRO, GATI, MOXI and LEVO (MIC_{90}, ≤0.03 versus ≤ 0.015 - ≤0.03 µg/ml).
- For *S. pneumoniae* (all three regions), BMS284756 demonstrated a greater potency when compared to CIPRO, GATI, MOXI and LEVO (MIC_{90}, 0.06 versus 0.25 - 2 µg/ml).
- In NA, BMS284756 was active against the two detected quinolone -resistant strains of *H. influenzae* (CIPRO MIC, > 0.12 µg/ml) and the 12 strains of *S. pneumoniae* (LEVO MIC, > 4 µg/ml).
- CIPRO-resistant *S. pneumoniae* (MIC, ≥ 4 µg/ml) was more prevalent in NA (3.5%) versus LA (2.7%) or EU (1.5%); however, BMS284756 inhibited all CIPRO-resistant strains at ≤ 4 µg/ml (MIC_{100}s, 0.25 - 4 µg/ml; greatest in NA).

CONCLUSIONS

- Overall, BMS284756 had similar high activity against the Gram-negative CARTI pathogens, but possessed greater in vitro effectiveness than CIPRO (32-fold), GATI (eight-fold) and MOXI (four-fold) for pneumococci.
- BMS284756 proved to be active against the emerging quinolone -resistant strains of *H. influenzae* and *S. pneumoniae* at ≤ 2 and ≤ 4 µg/ml, respectively.
- The role of BMS284756 against these monitored CARTI pathogens, especially quinolone -resistant strains, should be explored further.

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