Comparative Activity Of BMS284756, A Novel Desfluoroquinolone, Against Streptococci, Including Initial *In Vitro* Test Development

R.N. Jones, M.A. Pfaller, M.L. Beach, and D.J. Biedenbach

University of Iowa College of Medicine, 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

MODIFIED ABSTRACT

Purpose: To assess the activity and inter-method quantitative accuracy of BMS284756 when testing *Streptococcus pneumoniae* (SPN), viridans gr. streptococci (VGS) and β-haemolytic streptococci (BHS).

Methods: A total of 668 strains from the SENTRY Antimicrobial Surveillance Program (2000) were tested by reference broth microdilution and standardized disk diffusion (5-μg) methods of the NCCLS, as well as Etest (AB BIODISK, Solna, Sweden). Isolates were fresh and 12 representative pneumococcal strains resistant to levofloxacin (MIC, ≥8 μg/ml) and with documented QRDR mutations were also assessed.

Results: For 164 and 177 VGS and BHS, respectively, the BMS284756 MIC_{50} and MIC_{90} was 0.06 and 0.12 μg/ml. Etest MIC results correlated well (99.7% ± one log_2 dilution) with reference MIC values, and BMS284756 5-μg disk zone diameters were generally greater than 20 mm. For the 327 SPN isolates (40% penicillin non-susceptible) the $MIC_{50/90}$ was also 0.06/0.12 μg/ml. Etest/NCCLS reference MIC correlations were very acceptable (r=>0.90) and all results were within ± one log_2 dilution. For levofloxacin-resistant strains, BMS284756 MICs varied between 0.5 and 4 μg/ml with zone diameters of 15 to 27 mm. Comparison levofloxacin $MIC_{50/90}$ values were 1 and 2 μg/ml, 16-fold greater than BMS284756 MIC values.

Conclusions: BMS284756 a novel des-fluoroquinolone, was more potent than comparison agents versus all tested streptococci; had excellent quantitative correlations among *in vitro* test method results; and appears usable clinically against contemporary levofloxacin-resistant streptococcal isolates at a projected breakpoint of ≤4 μg/ml (Gajjar et al. 40th ICAAC abstr. #2259; Toronto, 2000). These results confirm earlier reports by Fung-Tomc et al. (AAC 44:3351, 2000).

INTRODUCTION

Infections caused by Gram-positive cocci, especially streptococci, are a major problem world-wide among community-acquired cases. Quinolones are used widely for both empiric and directed oral therapy due to their excellent spectrum and potency enhanced by favorable pharmacokinetics. Newer advanced generation fluoroquinolone derivatives (gatifloxacin, gemifloxacin, moxifloxacin) with expanded activity against Gram-positive pathogens are being introduced in an effort to meet the ever increasing challenge of resistance in these species.

BMS284756 (formerly T-3811) is a novel des-fluoro(6)-quinolone. These des-fluoro compounds have been shown to have lower cerebral toxicity in mice. Previous studies have demonstrated comparable *in vitro* activity to that of gatifloxacin and trovafloxacin, even against anaerobic species. As the newer, more potent quinolones become available for respiratory tract infection therapy, it is important to develop *in vitro* susceptibility testing criteria for the streptococci.

This study compares the activity of this new desfluoroquinolone and other selected quinolones against the three most commonly isolated groups of streptococci (*S. pneumoniae*, viridans group streptococci and β-haemolytic species) hospitalized and community-acquired patient infections. The results obtained from disk diffusion and Etest (AB BIODISK, Solna, Sweden) methods were also compared to those produced by the reference broth microdilution method described by the National Committee for Clinical Laboratory Standards (NCCLS).

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 (SENTRY Antimicrobial Surveillance Program, 2000). The organisms were derived from community-acquired respiratory tract infections, patients hospitalized with pneumonia, blood stream infections and skin/soft tissue infections. A total of 668 strains were tested: 327 *S. pneumoniae* (60% susceptible to penicillin; ≤ 0.06 μg/ml), 164 viridans group streptococci and 177 β-haemolytic streptococci. Twelve pneumococcal strains were selected for the test development phase that possessed levofloxacin MICs of ≥ 8 μg/ml (resistant). Also the entire *S. pneumoniae* collection from the year 2000 for Europe, Latin America and North America was presented to illustrate comparative activity of BMS284756 versus three selected quinolones (ciprofloxacin, levofloxacin, moxifloxacin).

Susceptibility testing methods: All organisms were tested by reference broth microdilution method and the standardized disk diffusion test. The broth microdilution trays were produced by TREK Diagnostics, Inc. (Westlake, OH) and were validated to be equivalent to NCCLS tests. The BMS284756 5-μg disks were made by BD Microbiology Systems (Cockeysville, MD). Etest (AB BIODISK) were performed as described in the manufacturer product package insert. The reference broth microdilution results were compared to the Etest results. Inter-method essential agreement was defined as the Etest result (MIC) being within ± two log_2 dilution of the reference result for ≥ 90% of strains. The disk diffusion tests were compared using the proposed susceptibility breakpoint of ≤ 4 μg/ml, although no isolates were identified that would be considered resistant to BMS284756 by these criteria. Linear regression statistics and the determination of potential interpretive errors were used to assess diagnostic accuracy applying M23-A2 criteria.

FIGURE 1: Scattergram comparison BMS284756 MIC and zone diameter (5-μg disk) results for 327 *S. pneumoniae*

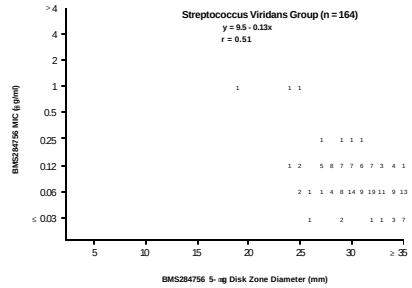

FIGURE 2: Scattergram comparison BMS284756 MIC and zone diameter (5-μg disk) results for 164 viridans group streptococci

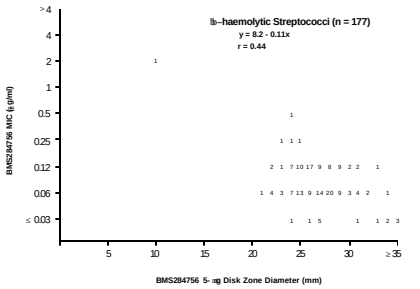

FIGURE 3: Scattergram comparison BMS284756 MIC and zone diameter (5-μg disk) results for 177 β-haemolytic streptococci

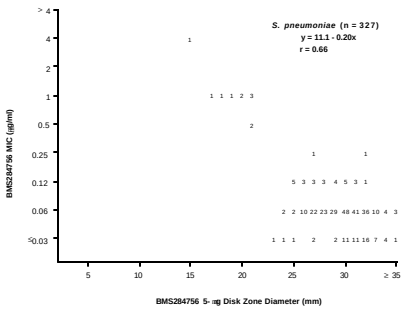

FIGURE 4: Comparison of BMS284756 MIC results obtained with the Etest and the reference NCCLS method for all streptococci tested (668 strains). Only two of 674 strains varied beyond ± one log_2 dilution (99.7% agreement between methods)

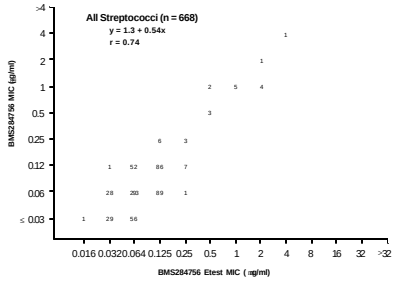

TABLE 1: Antimicrobial activity of BMS 284756 and three comparison quinolones tested against 1,788 *S. pneumoniae* strains from Europe, Latin America and North America (SENTRY Program, 2000)

Quinolone	MIC (μg/ml)		
	50%	90%	Range
BMS284756	0.06	0.06	≤0.03-4
Ciprofloxacin[a]	1	2	≤0.016->2
Levofloxacin[b]	1	1	≤0.03->4
Moxifloxacin[c]	0.12	0.25	≤0.03->4

[a] % of strains with MICs ≥4 μg/ml varied from 1.5% in Europe to 3.5% in North America
[b] Resistance rate was 0.7%, highest in North America at 1.1%
[c] Resistance rate was 0.6%, highest in North America at 1.0%

RESULTS

- BMS284756 potency (MIC_{90}, 0.06 μg/ml) against *S. pneumoniae* was two- to four-fold greater than moxifloxacin and 16- to 32-fold greater than either ciprofloxacin or levofloxacin (Table 1; 1,788 strains).
- Similar activity was observed for BMS284756 against viridans group streptococci (MIC_{90}, 0.12 μg/ml; Figure 2) and β-haemolytic streptococci (MIC_{90}, 0.12 μg/ml; Figure 3).
- Comparisons of BMS284756 MICs and zone diameters for *S. pneumoniae* (Figure 1) displays a slightly elevated MIC_{90} (0.12 μg/ml) due to the 12 levofloxacin-resistant strains added to the collection. However, good linear correlation was observed and only one strain had a BMS284756 MIC of > 1 μg/ml (4 μg/ml).
- Comparisons of BMS284756 MICs and zone diameters for other streptococcal groups (Figures 2 and 3) were similarly acceptable with the vast majority of strains highly susceptible (MICs at ≤ 0.25 μg/ml; zones at > 20 mm). Only five strains (1.5%) had BMS284756 MICs at ≥ 0.5 mg/ml.
- Figure 4 illustrates the excellent correlation of Etest and reference broth microdilution test results. Among 668 strains tested, 99.7% of results were within ± one log_2 dilution. In fact, 63.0% of MIC results were identical for each method.

CONCLUSIONS

- BMS284756, a novel desfluoroquinolone, has a potency against streptococci exceeding that of currently available drugs in its class.
- *In vitro* test development awaits final breakpoint selection, but disk diffusion tests for BMS284756 (Figures 1-3) show little potential for false-susceptible or resistant determinations.
- Alternative MIC systems such as the Etest performed very well, producing results comparable to the reference NCCLS microdilution method.

SELECTED REFERENCES

Fung-Tomc JC, Minassian B, Kolek B, Huczko E, Aleksunes L, Stickle T, Washo T, Gradelski E, Valera L, Bonner DP. 2000. Antibacterial spectrum of a novel des-fluoro(6) quinolone, BMS284756. Antimicrob Agents Chemother 44:3351-3356.

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.

Hori R, Takahata M, Shimakura M, Sugiyama H,Yonezawa M, Todo Y, Minami S, Watanabe Y, Narita H, 1998. Efficacy of T-3811, 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.

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.

National Committee for Clinical Laboratory Standards. 2000. Methods for dilution antimicrobial susceptibility tests for bacteria that grow aerobically. Document M7-A5. Wayne, PA:NCCLS.

National Committee for Clinical Laboratory Standards. 2001. Performance standards for antimicrobial susceptibility testing. Supplement tables, M100-S11. Wayne, PA:NCCLS.

Takahata M, Mitsuyama J, Yamashiro Y, Araki H, Yamada H, Havakawa 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.

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 activities of T-3811ME, a novel des-F(6)- quinolone. Antimicrob Agents Chemother 43:1077-1084.