Comparative Antimicrobial Spectrum and Activity of BMS 284756 (T-3811; A Desfluoroquinolone) Against Streptococci, Including *In Vitro* Test Comparisons and Development

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AMENDED ABSTRACT

Purpose: To assess the activity and inter-method quantitative accuracy of BMS284756 when testing three groups of streptococci.

Methods: Nearly 700 SENTRY Antimicrobial Surveillance Program (2000) streptococci isolates were tested by reference broth microdilution, standardized disk diffusion (5-µg) and Etest (AB BIODISK, Solna, Sweden) methods. Isolates were current and 12 representative pneumococcal strains resistant to levofloxacin (MIC, ≥8 µg/ml) were also assessed.

Results: Among 164 and 177 viridans group and β-haemolytic streptococci, respectively, the BMS284756 MIC_{50} and MIC_{90} was 0.06 and 0.12 µg/ml. Etest results correlated well (99.4% ± one log_2 dilution) and 5-µg disk zones were generally more than 20 mm. For the 327 *S. pneumoniae* isolates (40% penicillin non-susceptible) the $MIC_{50/90}$ was also 0.06/0.12 µg/ml. Etest/reference MIC correlation was acceptable (r=>0.90) and all results were ± one log_2 dilution. For levofloxacin-resistant strains, BMS284756 MICs varied between 0.5 and 4 µg/ml with zone diameters of 15-27 mm. Comparison levofloxacin $MIC_{50/90}$ values were 1 and 2 µg/ml, 16-fold higher than BMS284756.

Conclusions: BMS284756, a new des-fluoroquinolone, was more potent than comparison agents versus all tested streptococci; had excellent quantitative correlations among in vitro test methods; and appears usable versus contemporary levofloxacin-resistant streptococcal isolates at a projected breakpoint of ≤4 µg/ml.

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*

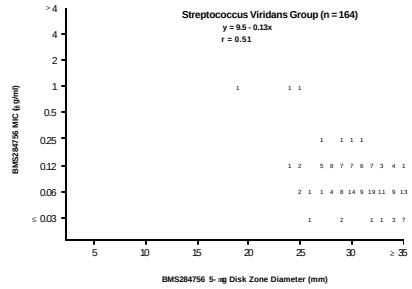

FIGURE 2: Scattergram comparison BMS284756 MIC and zone diameter (5-µg disk) results for 164 viridans group streptococci

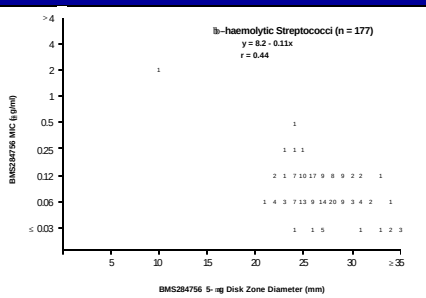

FIGURE 3: Scattergram comparison BMS284756 MIC and zone diameter (5-µg disk) results for 177 β-haemolytic streptococci

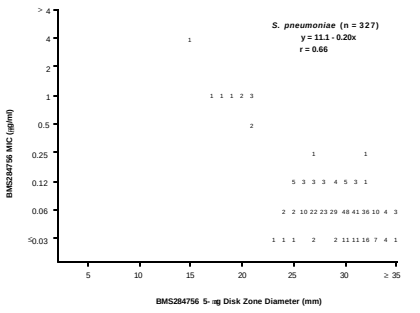

FIGURE 4: Comparison of BMS284756 MIC results obtained with the Etest and the reference NCCLS method for all streptococci tested (668 strains). Only two of 674 strains varied beyond ± one log_2 dilution (99.7% agreement between methods)

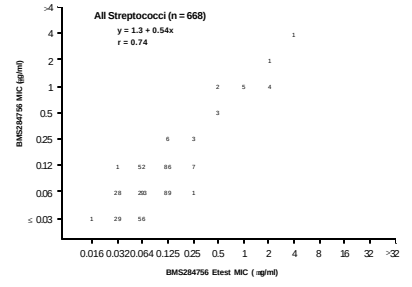

TABLE 1: Antimicrobial activity of BMS 284756 and three comparison quinolones tested against 1,788 *S. pneumoniae* strains from Europe, Latin America and North America (SENTRY Program, 2000)

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 viridansgroup streptococci (MIC_{90}, 0.12 µg/ml; Figure 2) and β-haemolytic streptococci (MIC_{90}, 0.12 mg/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/m; zones at > 20 mm). Only five strains (1.5%) had BMS284756 MICs at ≥ 0.5 µg/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.

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