ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Jan. 2002, p. 234–238 Vol. 46, No. 1
0066-4804/02/$04.00+0 DOI: 10.1128/AAC.46.1.234–238.2002

Antimicrobial Activities of BMS-284756 Compared with Those of Fluoroquinolones and β-Lactams against Gram-Positive Clinical Isolates

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Received 27 April 2001/Returned for modification 30 July 2001/Accepted 5 October 2001

The in vitro antibacterial activity of BMS-284756 was compared to those of ciprofloxacin, gatifloxacin, moxifloxacin, ceftriaxone, imipenem, piperacillin-tazobactam, and amoxicillin-clavulanic acid against 492 gram-positive clinical isolates. BMS-284756 was the most-active agent against *Streptococcus pneumoniae*, *Streptococcus viridans*, beta-hemolytic streptococci, methicillin-sensitive and -resistant *Staphylococcus aureus*, methicillin-sensitive and -resistant coagulase-negative staphylococci, and enterococci.

The fluoroquinolones have considerable antimicrobial activity against most gram-negative bacilli and cocci (15). However, ciprofloxacin and other early fluoroquinolones provide limited activity against most gram-positive organisms (1). The synthesis of newer fluoroquinolones has focused on overcoming the limitations of the early fluoroquinolones by expanding their spectrum of activity with regard to gram-positive organisms (2, 5, 8, 9, 13). Serious infections due to *Streptococcus pneumoniae*, viridans group streptococci, and enterococci have become major treatment problems because of their resistance to several, if not most, currently available antimicrobial agents (8, 9, 14).

BMS-284756 is a novel des-fluoro(6) quinolone that differs from the fluoroquinolones in that it lacks a fluorine molecule at the C-6 position. BMS-284756 has a broad spectrum of antimicrobial activity, including activity against gram-positive bacteria (6, 10). A potential advantage of the des-fluoro(6) quinolone derivatives are that they show less acute toxicity in mice than the fluorinated quinolone compounds and may therefore have the potential of an improved toxicity profile in humans as well (K. Hayashi, Y. Todo, S. Hamamaoto, K. Ojima, M. Yamada, T. Kito, M. Takahata, Y. Watanabe, and H. Narita, Abstr. 37th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F-158, 1997).

In the present study, the in vitro activity of BMS-284756 was tested and compared to those of ciprofloxacin, gatifloxacin, moxifloxacin, ceftriaxone, imipenem, piperacillin-tazobactam, and amoxicillin-clavulanic acid against 492 gram-positive clinical isolates from Yale-New Haven Hospital. A total of 145 streptococcal isolates (65 *Streptococcus pneumoniae*, 38 *Streptococcus viridans*, 17 *Streptococcus pyogenes*, 15 *Streptococcus agalactiae,* and 10 group G streptococci), 297 staphylococcal isolates (175 *Staphylococcus aureus* and 122 coagulase-negative staphylococci, including 45 *Staphylococcus epidermidis*), and 50 enterococcal isolates (25 *Enterococcus faecalis* and 25 *Enterococcus faecium*) were tested. *S. aureus* ATCC 29213, *E. faecalis* ATCC 29212, and *S. pneumoniae* ATCC 49619 were used as control strains.

BMS-284756 E-test was obtained from Bristol-Myers Squibb, Princeton, N.J. The E-test strips for the other antibiotics were obtained from AB Biodisk North America Inc., Piscataway, N.J. All organisms were tested using the E-test methodology for susceptibility testing (4, 11). Specifically, 2 ml of tryptic soy broth was inoculated with organisms to a density of a 0.5 McFarland standard from a freshly grown subculture (grown overnight) and applied to a 150-mm-diameter Mueller-Hinton agar plate for testing of staphylococci and enterococci and to Mueller-Hinton agar supplemented with 5% sheep blood for testing of streptococci. E-test strips were applied following the manufacturer's recommendations. Staphylococci and enterococci were incubated at 37°C in an ambient air incubator, and streptococci were incubated in a 5% CO_2 incubator at 37°C. The plates were examined after 16 to 20 h of incubation. The lowest concentration of drug inhibiting visible growth was used as the MIC. All tests were performed, and susceptibility data were evaluated using the criteria of the National Committee for Clinical Laboratory Standards (12). An MIC of ≤0.5 μg/ml was used to determine the susceptibility of *S. pneumoniae* to amoxicillin-clavulanic acid (]February 1996 package insert supplement for E-test amoxicillin-clavulanic acid; AB Biodisk). Susceptibility breakpoints for BMS-284756 have yet to be determined.

The susceptibility testing results are summarized in Table 1. BMS-284756 demonstrated excellent activity against all streptococcal species tested (MIC at which 90% of the isolates tested are inhibited [MIC_{90}] ≤ 0.25 μg/ml). Ciprofloxacin (MIC_{90}, 4 μg/ml) was the least-active agent against penicillin-susceptible *S. pneumoniae*, while BMS-284756 (MIC_{90}, 0.12 μg/ml) was the most-active agent. BMS-284756 was also the most-active agent against penicillin-nonsusceptible *S. pneumoniae* (MIC_{90}, 0.12 μg/ml), followed by moxifloxacin (MIC_{90}, 0.25 μg/ml). Other studies have shown that BMS-284756 and newer fluoroquinolones maintain activity against penicillin-intermediate and -resistant strains of *S. pneumoniae* (6, 13, 16). The most-active agents against *S. viridans* were BMS-284756, moxifloxacin, and imipenem, with MIC_{90}s of 0.12, 0.25, and

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TABLE 1. Antimicrobial activity of BMS-284756 compared to those of other antibiotics tested by reference methods (12) (E-test; AB Biodisk) against streptococci, staphylococci, and enterococci[a]

Organism and antibiotic	No. of organisms tested	MIC (μg/ml)			% Susceptible
		MIC_{50}	MIC_{90}	Range	
S. pneumoniae, penicillin susceptible	43				
BMS-284756		0.12	0.12	0.03–4	
Moxifloxacin		0.25	0.25	0.12–2	98
Gatifloxacin		0.25	0.5	0.12–1	100
Ciprofloxacin		2	4	0.25–16	
Ceftriaxone		0.03	0.25	0.002–0.5	100
Imipenem		0.03	0.12	0.002–0.5	95
Piperacillin-tazobactam		0.03	1	0.03–2	79
Amoxicillin-clavulanic acid		0.03	0.25	0.03–0.5	100
S. pneumoniae, penicillin nonsusceptible	22				
BMS-284756		0.06	0.12	0.06–0.12	
Moxifloxacin		0.25	0.25	0.12–0.25	100
Gatifloxacin		0.25	0.5	0.12–4	95
Ciprofloxacin		2	4	0.5–>32	
Ceftriaxone		1	2	0.25–4	14
Imipenem		0.25	0.5	0.25–1	0
Piperacillin-tazobactam		2	4	1–16	0
Amoxicillin-clavulanic acid		1	2	1–16	0
S. pyogenes	17				
BMS-284756		0.12	0.25	0.06–0.25	
Moxifloxacin		0.25	0.25	0.12–0.5	100
Gatifloxacin		0.25	0.5	0.25–1	100
Ciprofloxacin		0.5	1	0.25–4	
Ceftriaxone		0.03	0.12	0.002–0.25	100
Imipenem		0.008	0.03	0.002–0.12	100
Piperacillin-tazobactam		0.06	0.12	0.03–1	88
Amoxicillin-clavulanic acid		0.03	0.03	0.03–0.25	100
S. agalactiae	15				
BMS-284756		0.12	0.25	0.06–0.5	
Moxifloxacin		0.25	0.25	0.25–0.5	100
Gatifloxacin		0.5	0.5	0.25–2	100
Ciprofloxacin		1	2	0.5–>32	
Ceftriaxone		0.06	0.12	0.03–1	87
Imipenem		0.03	0.06	0.008–0.12	100
Piperacillin-tazobactam		0.25	0.25	0.12–0.5	33
Amoxicillin-clavulanic acid		0.06	0.06	0.03–0.25	100
Group G streptococci	10				
BMS-284756		0.12	0.12	0.06–0.12	
Moxifloxacin		0.25	0.25	0.12–0.25	100
Gatifloxacin		0.25	0.5	0.25–0.5	100
Ciprofloxacin		0.5	2	0.5–2	
Ceftriaxone		0.015	0.06	0.004–0.06	100
Imipenem		0.008	0.03	0.002–0.03	100
Piperacillin-tazobactam		0.06	0.12	0.03–0.25	90
Amoxicillin-clavulanic acid		0.03	0.03	0.03–0.03	100
S. viridans	38				
BMS-284756		0.12	0.25	0.06–0.25	
Moxifloxacin		0.25	0.25	0.12–0.5	100
Gatifloxacin		0.25	0.5	0.06–0.5	100
Ciprofloxacin		2	4	0.25–8	
Ceftriaxone		0.25	1	0.015–>32	87
Imipenem		0.12	0.25	0.03–2	100
Piperacillin-tazobactam		1	4	0.06–8	18
Amoxicillin-clavulanic acid		0.25	1	0.03–4	58
S. aureus, methicillin and penicillin sensitive	60				
BMS-284756		0.06	0.06	0.015–0.06	
Moxifloxacin		0.12	0.25	0.06–0.5	100
Gatifloxacin		0.12	0.25	0.06–0.25	100
Ciprofloxacin		0.25	0.5	0.12–0.5	100

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TABLE 1—*Continued*

Organism and antibiotic	No. of organisms tested	MIC (μg/ml)			% Susceptible
		MIC_{50}	MIC_{90}	Range	
Ceftriaxone		4	4	0.03–4	100
Imipenem		0.06	0.06	0.008–0.06	100
Piperacillin-tazobactam		2	2	0.06–4	100
Amoxicillin-clavulanic acid		1	1	0.03–1	100
S. aureus, methicillin sensitive, penicillin resistant	20				
BMS-284756		0.06	0.06	0.008–2	
Moxifloxacin		0.12	0.25	0.06–2	100
Gatifloxacin		0.12	0.25	0.06–4	95
Ciprofloxacin		0.25	0.5	0.25–>32	95
Ceftriaxone		4	4	4–>32	95
Imipenem		0.06	0.06	0.03–0.12	100
Piperacillin-tazobactam		2	2	1–4	100
Amoxicillin-clavulanic acid		1	1	0.5–2	100
S. aureus, methicillin resistant, ciprofloxacin sensitive	10				
BMS-284756		0.03	0.12	0.03–0.12	
Moxifloxacin		0.12	0.25	0.06–0.25	100
Gatifloxacin		0.12	0.25	0.12–0.25	100
Ciprofloxacin		0.5	1	0.25–1	100
Ceftriaxone		>32	>32	2–>32	20
Imipenem		0.5	4	0.03–>32	90
Piperacillin-tazobactam		8	64	1–>256	50
Amoxicillin-clavulanic acid		8	16	0.5–32	40
S. aureus, methicillin resistant, ciprofloxacin resistant	85				
BMS-284756		2	4	0.12–16	
Moxifloxacin		4	8	0.5–32	36
Gatifloxacin		8	16	0.5–>32	14
Ciprofloxacin		>32	>32	4–>32	0
Ceftriaxone		>32	>32	12–>32	0
Imipenem		16	>32	0.25–>32	36
Piperacillin-tazobactam		64	>256	2–>256	12
Amoxicillin-clavulanic acid		16	32	2–64	15
S. epidermidis, methicillin sensitive	20				
BMS-284756		0.12	2	0.03–8	
Moxifloxacin		0.12	1	0.06–4	95
Gatifloxacin		0.25	4	0.06–4	85
Ciprofloxacin		0.25	16	0.25–>32	85
Ceftriaxone		2	>32	0.5–>32	60
Imipenem		0.06	0.25	0.008–0.25	100
Piperacillin-tazobactam		0.5	2	0.03–2	100
Amoxicillin-clavulanic acid		0.25	4	0.03–4	100
S. epidermidis, methicillin resistant	25				
BMS-284756		2	4	0.03–16	
Moxifloxacin		4	8	0.12–16	44
Gatifloxacin		2	8	0.06–16	56
Ciprofloxacin		>32	>32	0.25–>32	28
Ceftriaxone		>32	>32	4–>32	12
Imipenem		4	>32	0.06–32	64
Piperacillin-tazobactam		2	64	0.06–>256	68
Amoxicillin-clavulanic acid		2	16	0.25–32	64
Coagulase-negative staphyloccoci, methicillin sensitive	37				
BMS-284756		0.06	0.12	0.015–4	
Moxifloxacin		0.12	0.25	0.06–4	97
Gatifloxacin		0.25	0.25	0.12–4	97
Ciprofloxacin		0.25	0.5	0.25–>32	95
Ceftriaxone		2	16	0.25–>32	86
Imipenem		0.06	0.12	0.008–1	100
Piperacillin-tazobactam		0.5	2	0.03–4	100
Amoxicillin-clavulanic acid		0.25	1	0.03–2	100
Coagulase-negative staphylococci, methicillin resistant	40				
BMS-284756		0.12	4	0.03–8	

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TABLE 1—*Continued*

Organism and antibiotic	No. of organisms tested	MIC (μg/ml)			% Susceptible
		MIC_{50}	MIC_{90}	Range	
Moxifloxacin		0.25	4	0.06–32	77
Gatifloxacin		0.25	4	0.12–>32	70
Ciprofloxacin		0.25	>32	0.25–>32	60
Ceftriaxone		>32	>32	0.5–>32	7
Imipenem		>32	>32	0.03–>32	37
Piperacillin-tazobactam		4	128	0.25–>256	82
Amoxicillin-clavulanic acid		4	16	0.25–64	57
E. faecalis	25				
BMS-284756		0.25	0.5	0.12–4	
Moxifloxacin		0.5	0.5	0.25–>32	96
Gatifloxacin		0.5	1	0.25–>32	96
Ciprofloxacin		2	2	1–>32	32
Ceftriaxone		>32	>32	>32	0
Imipenem		2	2	1–8	96
Piperacillin-tazobactam		4	4	2–8	100
Amoxicillin-clavulanic acid		1	1	0.5–1	100
E. faecium	25				
BMS-284756		4	32	0.25–>32	
Moxifloxacin		2	>32	0.12–>32	64
Gatifloxacin		2	>32	0.25–>32	64
Ciprofloxacin		4	>32	0.5–>32	4
Ceftriaxone		>32	>32	>32	0
Imipenem		>32	>32	1–>32	24
Piperacillin-tazobactam		>256	>256	0.5–>256	12
Amoxicillin-clavulanic acid		32	128	0.5–>256	36

[a] Breakpoints approved by the National Committee for Clinical Laboratory Standards are currently not available for BMS-284756.

0.25 μg/ml, respectively. BMS-284756, imipenem, amoxicillin-clavulanic acid, ceftriaxone, and piperacillin-tazobactam were the most-active agents against the beta-hemolytic streptococci.

A total of 297 staphylococcal strains were tested. BMS-284756 was the most-active agent against methicillin-susceptible *S. aureus* and coagulase-negative staphylococci, with MIC_{90}s of 0.06 and 0.12 μg/ml, respectively. All the agents tested, with the exception of ceftriaxone, demonstrated excellent activity against methicillin-susceptible *S. aureus*, regardless of penicillin susceptibility. Ciprofloxacin had good activity against methicillin-sensitive *S. aureus* (MIC_{90}, 0.5 μg/ml), but the MIC_{90} for BMS-284756 was threefold lower (MIC_{90}, 0.06 μg/ml). BMS-284756 was the most-active agent against methicillin-resistant, ciprofloxacin-sensitive *S. aureus*, with an MIC_{90} of 0.12 μg/ml. BMS-284756 was the most-active agent against methicillin- and ciprofloxacin-resistant *S. aureus*, with an MIC_{90} of 4 μg/ml.

Imipenem (MIC_{90}, 0.25 μg/ml), moxifloxacin (MIC_{90}, 1 μg/ml), BMS-284756 (MIC_{90}, 2 μg/ml), and piperacillin-tazobactam (MIC_{90}, 2 μg/ml) had good activity against methicillin-sensitive *S. epidermidis*. BMS-284756 had the lowest MIC_{90} (4 μg/ml) against methicillin-resistant *S. epidermidis*. Of the methicillin-sensitive and -resistant coagulase-negative staphylococci tested, BMS-284756 was the most-active agent (MIC_{90}s of 0.12 and 4 μg/ml, respectively). Overall, BMS-284756 was the most-active agent against methicillin-resistant staphylococci. Previous experience with ciprofloxacin and levofloxacin has shown that quinolone resistance among staphylococci can develop, particularly among methicillin-resistant organisms, with widespread use of these agents (3, 7). Whether this will also occur with the newer fluoroquinolones or BMS-284756 is unknown and will require further clinical studies.

A total of 50 enterococcal isolates were tested. BMS-284756 and amoxicillin-clavulanic acid were the most-active agents against *E. faecalis.* Ciprofloxacin demonstrated the least activity against *E. faecalis* and *E. faecium*. Although the MIC_{90} for BMS-284756 against *E. faecium* was 32 μg/ml, it was nevertheless the most-active agent against this organism. Ten enterococcal strains, 6 *E. faecium* and 4 *E. faecalis* strains, were vancomycin resistant, and the MIC_{50} and MIC_{90} for BMS-284756 were 4 and 16 μg/ml, respectively. Overall, BMS-284756 showed in vitro effectiveness against *E. faecalis*; however, it was less active against *E. faecium*, as are most antibiotics.

This study illustrates the superior activity of BMS-284756 against gram-positive organisms compared to those of other fluoroquinolones and beta-lactam antimicrobial agents. The enhanced gram-positive bacterial activity of BMS-284756 and the advantages of the quinolone class of antibiotics, which include excellent oral bioavailability, convenient dosing schedules, and favorable adverse event profiles, should make this new agent a good alternative for treatment of many types of infections, including those caused by organisms resistant to currently available antimicrobial agents.

This study was supported in part by a grant from Bristol-Myers Squibb, Wallingford, Conn.

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