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In Vitro Activity of ABT-773, a New Ketolide, against Recent Clinical Isolates of *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*

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The in vitro activity of ABT-773 was evaluated against *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis* isolates. ABT-773 was the most active antimicrobial tested against *S. pneumoniae*. ABT-773 and azithromycin were equivalent in activity against *H. influenzae* and *M. catarrhalis* and more active than either clarithromycin or erythromycin.

ABT-773 (A-195773) is a new ketolide having a potent antibacterial spectrum including activity against penicillin- and macrolide-resistant gram-positive bacteria. Its chemical name is 11-amino-11-deoxy-3-oxo-5-*O*-desosaminyl-6-*O*-[1′-(3′-quinolyl-2′-propenyl)] erythronolide A 11,12-cyclic carbamate (Fig. 1). This investigation assessed the in vitro activity of ABT-773 against three common bacterial respiratory tract pathogens, *Streptococcus pneumoniae*, *Haemophilus influenzae*, and *Moraxella catarrhalis*. These three organisms are the most frequent causative agents of acute otitis media, acute maxillary sinusitis, and acute purulent exacerbation of chronic bronchitis. The first two organisms are also major causes of community-acquired pneumonia.

The organisms examined in this study included isolates of *S. pneumoniae* (n = 1,601), *H. influenzae* (n = 1,529), and *M. catarrhalis* (n = 726) all collected as part of a large, prospective national surveillance study conducted from 1 November 1997 through 30 April 1998. Thirty-four medical centers contributed isolates. Details of this study have been reported previously (1, 5). Prior to testing, organisms having been stored at −70°C using an absorbent bead system (ProLab Diagnostics, Austin, Tex.), were subcultured twice. MICs of ABT-773, erythromycin, azithromycin, and clindamycin were determined by broth microdilution susceptibility testing according to the recommendations of the National Committee for Clinical Laboratory Standards (3, 4). The following media were used: *S. pneumoniae*, cation-adjusted Mueller-Hinton broth plus 3% lysed horse blood; *H. influenzae*, haemophilus test medium; and *M. catarrhalis*, Mueller-Hinton broth. The following control strains were tested on a daily basis: *S. pneumoniae* ATCC 49619 and *H. influenzae* ATCC 49247; *H. influenzae* ATCC 49247, 49766, and 10211; and *Escherichia coli* ATCC 25922 and *Staphylococcus aureus* ATCC 29213. Antimicrobials were provided by their respective manufacturers. A final inoculum concentration of ca. 5×10^5 CFU/ml per well was employed; microdilution trays were incubated for 24 h at 35°C in ambient air before MICs were determined visually.

Results of MIC determinations for *S. pneumoniae* are listed in Table 1. ABT-773 was the most active of the seven antimicrobials tested: 78.9% of *S. pneumoniae* isolates were inhibited by ABT-773 at a concentration of ≤0.008 μg/ml. The MIC at which 90% of the isolates were inhibited (MIC_{90}) was 0.03 μg/ml. The highest ABT-773 MIC was 0.5 μg/ml (n = 3). When isolates were sorted according to penicillin susceptibility category, the ABT-773 MIC_{90}s were as follows: penicillin susceptible (penicillin MIC, ≤0.06 μg/ml), ≤0.008; penicillin intermediate (penicillin MIC = 0.12 to 1 μg/ml), 0.03; and penicillin resistant (penicillin MIC, ≥2 μg/ml), 0.12 μg/ml. Comparison compounds included the macrolides erythromycin, clarithromycin, and azithromycin and a lincosamide, clindamycin. The MIC_{50}s and MIC_{90}s and ranges of MICs obtained with these agents were 0.06, 8, and ≤0.03 to >64; ≤0.03, 4, and ≤0.03 to >64; 0.12, 16, and ≤0.03 to >64; and 0.06, 0.06, and ≤0.008 to >8 μg/ml, respectively.

Table 2 depicts the relationship between ketolide and erythromycin MICs. *S. pneumoniae* has two principal mechanisms of macrolide resistance, efflux and constitutively expressed macrolide-lincosamide-streptogramin B resistance as a result of ribosomal alterations (2, 6). Efflux, the result of expression of the *mefE* gene, usually results in erythromycin MICs of 1 to 32 μg/ml and clindamycin MICs of ≤0.25 μg/ml (1). Altered ribosomal targets as a consequence of *ermAM* gene-mediated

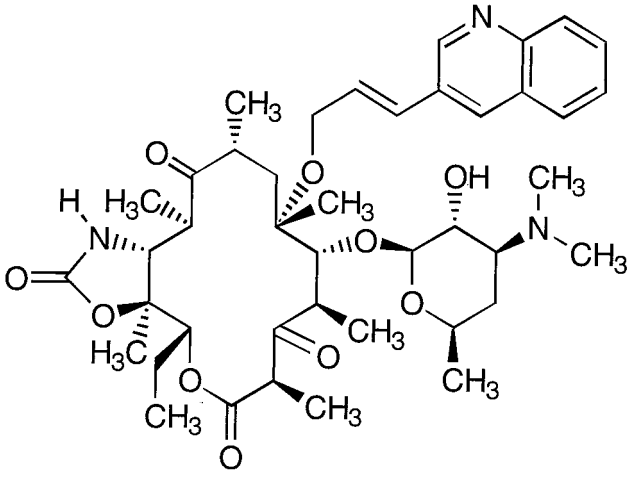

FIG. 1. Chemical structure of ABT-773 (A-195773).

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TABLE 1. Comparison of the in vitro activities of five antimicrobial agents against 1,601 isolates of *S. pneumoniae* by penicillin category[a]

Antimicrobial	Penicillin-susceptible strains (n = 1,127)					Penicillin-intermediate strains (n = 278)					Penicillin-resistant strains (n = 196)					All strains (n = 1,601)				
	MIC_{50}	MIC_{90}	MIC range	% I	% R	MIC_{50}	MIC_{90}	MIC range	% I	% R	MIC_{50}	MIC_{90}	MIC range	% I	% R	MIC_{50}	MIC_{90}	MIC range	% I	% R
ABT-773	≤0.008	≤0.008	≤0.008–0.5			≤0.008	0.03	≤0.008–0.5			0.015	0.12	≤0.008–0.25			≤0.008	0.03	≤0.008–0.5		
Clarithromycin	≤0.03	≤0.03	≤0.03–>64	0.5	5.2	≤0.03	>64	≤0.03–>64	2.2	35.3	2	>64	≤0.03–>64	3.6	64.8	≤0.03	4	≤0.03–>64	1.2	17.7
Erythromycin	0.06	0.06	≤0.03–>64	0.3	5.7	0.06	>64	≤0.03–>64	0.7	37.4	4	>64	≤0.03–>64	0.5	68.4	0.06	8	≤0.03–>64	0.4	18.9
Azithromycin	0.06	0.12	≤0.03–>64	0.2	5.6	0.12	>64	≤0.03–>64	0.7	37.8	8	>64	≤0.03–>64	1.5	67.3	0.12	16	≤0.03–>64	0.4	18.7
Clindamycin	0.06	0.06	≤0.008–>8	0.1	1.1	0.06	>8	≤0.008–8	0.0	12.9	0.06	>8	≤0.008–>8	0.5	21.4	0.06	0.06	≤0.008–>8	0.1	5.6

[a] Penicillin susceptible, MIC ≤ 0.06 μg/ml; penicillin intermediate, MIC of 0.12 to 1 μg/ml; penicillin resistant, MIC ≥ 2 μg/ml. % I, percent intermediate; % R, percent resistant. MICs are expressed as micrograms per milliliter.

TABLE 2. Comparison of ABT-773 MICs for isolates of *S. pneumoniae* by erythromycin categories[a]

MIC (μg/ml)	No. of strains	No. of strains (%) for which erythromycin MIC (μg/ml) is:		
		≤0.5	1–32	≥64
≤0.008	1,318	1,263 (95.8)	40 (3.0)	15 (1.1)
0.015	99	29 (29.3)	44 (44.4)	26 (26.3)
0.03	79	2 (2.5)	62 (78.5)	15 (19.0)
0.06	48	4 (8.3)	34 (70.8)	10 (20.8)
0.12	41	1 (2.4)	33 (80.5)	7 (17.1)
0.25	13		8 (61.5)	5 (38.5)
0.5	3		1 (33.3)	2 (66.7)

[a] Strains for which erythromycin MIC is ≤0.5 μg/ml are erythromycin susceptible or intermediate; strains for which erythromycin MIC is 1 to 32 μg/ml and clindamycin MIC is ≤0.25 have the efflux phenotype; strains for which erythromycin MIC is ≥64 μg/ml and clindamycin MIC is ≥8 μg/ml have the *ermAM* genotype.

methylation typically result in erythromycin MICs of ≥64 μg/ml and clindamycin MICs of ≥8 μg/ml. In the current study, 222 of 302 (73.5%) macrolide-resistant *S. pneumoniae* strains displayed the efflux phenotype and 80 of 302 (26.5%) macrolide-resistant *S. pneumoniae* strains were characterized by the *ermAM* phenotype. Among the macrolide-resistant *S. pneumoniae* strains with the efflux phenotype, for 82.0% (n = 182) the ABT-773 MICs were ≥0.015 μg/ml. Similarly, among the *S. pneumoniae* strains with the *ermAM* phenotype, for 81.3% (n = 65) the ABT-773 MIC was ≥0.015 μg/ml. In other words, higher ketolide MICs were noted with *S. pneumoniae* isolates harboring either efflux or *ermAM*-mediated resistance determinants. Studies aimed at further evaluating this relationship are in progress.

The activity of ABT-773 against *H. influenzae* and *M. catarrhalis* was also evaluated and compared to that of the macrolides (Table 3). ABT-773 and azithromycin had identical activity against *H. influenzae*, with MIC_{50}s and MIC_{90}s of 2 and 4 μg/ml, respectively. ABT-773 and azithromycin were fourfold more active against *H. influenzae* than were erythromycin and clarithromycin, whose MIC_{50}s and MIC_{90}s were also identical at 8 and 16 μg/ml, respectively. The rate of beta-lactamase production was 31.1% among these isolates of *H. influenzae*. No differences in susceptibility were seen between beta-lactamase-positive and beta-lactamase-negative strains.

ABT-773 was considerably more active against *M. catarrhalis* than against *H. influenzae*. The MIC_{50} and MIC_{90} of ABT-773 for *M. catarrhalis* were 0.06 μg/ml. This was nearly identical to the activity of azithromycin, twofold more active than clarithromycin, and fourfold more active than erythromycin. The MIC_{50}s and MIC_{90}s of those agents were as follows: 0.06 and 0.12, 0.12 and 0.12, and 0.25 and 0.25 μg/ml, respectively. Nearly all *M. catarrhalis* strains produced beta-lactamase (94.6%). ABT-773 was consistently twofold less active against beta-lactamase-negative than against beta-lactamase-positive strains. No differences between beta-lactamase-positive and -negative strains were seen with any of the macrolides.

The results of the current study indicate that ABT-773, a new ketolide antimicrobial agent, has potent in vitro activity against recent clinical isolates of *S. pneumoniae*. Although the drug is less active against *H. influenzae* and *M. catarrhalis*, the overall activity of ABT-773 against these three pathogens would be sufficient to warrant performance of clinical trials with patients with respiratory tract infections due to these organisms, assuming acceptable pharmacokinetic and toxicity profiles.

TABLE 3. Comparison of the in vitro activities of ABT-773 and the macrolides against 1,529 isolates of *H. influenzae* and 726 isolates of *M. catarrhalis*[a]

Organism	Antimicrobial agent	Value for strain type:									
		Beta-lactamase positive					Beta-lactamase negative				
		MIC_{50}	MIC_{90}	MIC range	% I	% R	MIC_{50}	MIC_{90}	MIC range	% I	% R
H. influenzae	ABT-773	2	4	0.12–>8			2	4	0.06–>8		
	Azithromycin	2	4	0.25–64			2	4	≤0.12–>256		
	Clarithromycin	8	16	0.5–128	26.9	6.5	8	16	≤0.12–>256	29.1	3.1
	Erythromycin	8	16	0.25–64			8	16	≤0.12–>256		
M. catarrhalis	ABT-773	0.06	0.06	≤0.004–0.12			0.12	0.12	0.008–0.12		
	Azithromycin	0.06	0.12	0.03–0.25	0.0	0.0	0.06	0.12	0.06–0.25	0.0	0.0
	Clarithromycin	0.12	0.12	≤0.015–0.5	0.0	0.0	0.12	0.12	0.03–0.12	0.0	0.0
	Erythromycin	0.25	0.25	0.06–1	0.0	0.0	0.25	0.25	0.06–0.25	0.0	0.0

[a] For beta-lactamase-positive strains, $n = 476$ for *H. influenzae* and 687 for *M. catarrhalis*; for beta-lactamase-negative strains, $n = 1,053$ for *H. influenzae* and 39 for *M. catarrhalis*. MICs are expressed as micrograms per milliliter. % I, percent intermediate; % R, percent resistant.

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