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-oxa-10-cyclic carbamate (Fig. 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 (MIC₉₀) 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 MIC₉₀ values 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 MIC₉₀ and MIC₉₀ ≤ values 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

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**FIG. 1.** Chemical structure of ABT-773 (A-195773).
methylation typically result in erythromycin MICs of $\geq 64$ μg/ml and clindamycin MICs of $\geq 8$ 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 $\geq 0.015$ μg/ml. Similarly, among the *S. pneumoniae* strains with the ermAM phenotype, for 81.3% ($n = 65$) the ABT-773 MIC was $\geq 0.015$ 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 2. Comparison of ABT-773 MICs for isolates of *S. pneumoniae* by erythromycin categories

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

* Strains for which erythromycin MIC is $\leq 0.008$ μg/ml are erythromycin susceptible or intermediate; strains for which erythromycin MIC is 1 to 32 μg/ml and clindamycin MIC is $\leq 0.25$ have the efflux phenotype; strains for which erythromycin MIC is $\geq 64$ μg/ml and clindamycin MIC is $\geq 8$ μg/ml have the ermAM genotype.
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REFERENCES


