ANTIMICROBIAL AGENTS AND CHEMOTHERAPY, Apr. 2000, p. 1112–1113 Vol. 44, No. 4
0066-4804/00/$04.00+0

In Vitro Activity of ABT 773, a New Ketolide Antibiotic, against *Chlamydia pneumoniae*

SEBASTIAN STRIGL, PATRICIA M. ROBLIN, TAMARA REZNIK, AND MARGARET R. HAMMERSCHLAG*

Division of Infectious Diseases, Department of Pediatrics, State University of New York Health Science Center at Brooklyn, Brooklyn, New York 11203-2098

Received 11 October 1999/Returned for modification 23 December 1999/Accepted 15 January 2000

The in vitro activities of ABT 773, telithromycin (HMR 3647), azithromycin, clarithromycin, erythromycin, and levofloxacin were tested against 20 strains of *Chlamydia pneumoniae*. The MIC at which 90% of the isolates were inhibited and the minimal bactericidal concentration at which 90% of the isolates were killed by ABT 773 were 0.015 μg/ml (range, 0.008 to 0.015 μg/ml). ABT 773 was the most active antibiotic tested in this study.

The ketolides are a new class of macrolide antibiotics with a keto group replacing the L-cladinose moiety in position 3 and an alkyl-aryl extension at positions 11 and 12 of the lactone ring. The ketolides are acid stable and have activity against a broad range of respiratory pathogens, including multiresistant pneumococci, *Haemophilus influenzae*, *Legionella* species, and *Mycoplasma pneumoniae* (1, 2, 3, 5, 8). *Chlamydia pneumoniae* is an important cause of community-acquired respiratory infection in adults and children worldwide. Clinically, these infections cannot be readily differentiated from those caused by other "atypical" pathogens, such as *M. pneumoniae*. Data on the activity of ketolides against *C. pneumoniae* are limited; only the activity of telithromycin (HMR 3647) and HMR 3004 (RU 64004) has been evaluated so far (5, 10; F. Haider, F. Eb, and J. Orfila, Abstr. 35th Intersci. Conf. Antimicrob. Agents Chemother., abstr. F165, 1995). Therefore, we compared the in vitro activity of ABT 773 (a new ketolide antibiotic), telithromycin, azithromycin, clarithromycin, erythromycin, and levofloxacin against 20 isolates of *C. pneumoniae*.

Isolates of *C. pneumoniae* tested included two reference strains, TW 183 (ATCC VR-2282) and AR39 (ATCC 53592), an isolate from a child with pneumonia from Japan, J21 (ATCC 1435), W 6805, an isolate from an adult with pneumonia from Wisconsin, and 16 isolates from a large United States multicenter treatment study of adults with community-acquired pneumonia. ABT 773, telithromycin, azithromycin, erythromycin, clarithromycin, and levofloxacin were provided as powders and solubilized according to the instructions of the manufacturers. Susceptibility testing of *C. pneumoniae* was performed with cycloheximide-treated HEp-2 cells grown in 96-well microtiter plates (7). Each well was inoculated with 0.1 ml of the test strain diluted to yield 10^3 to 10^4 inclusion-forming units per ml; the plates were centrifuged at 1,700 × *g* for 1 h and incubated at 35°C for 1 h. Wells were then aspirated and overlaid with medium containing 1 μg of cycloheximide per ml and serial twofold dilutions of the test drug. After incubation at 35°C for 72 h, cultures were fixed and stained for inclusions with fluorescein-conjugated antibody to the chlamydial lipopolysaccharide genus-specific antigen (Pathfinder; Kallestad Diagnostics, Chaska, Minn.). The MIC was the lowest antibiotic concentration at which no inclusions were seen. The minimal bactericidal concentration (MBC) was determined by aspirating the antibiotic-containing medium, washing wells twice with phosphate-buffered saline, and adding antibiotic-free medium. The infected cells were frozen at −70°C, thawed, passed onto new cells, incubated for 72 h, and then fixed and stained as described above. The MBC was the lowest antibiotic concentration which resulted in no inclusions after passage. All tests were run in duplicate.

The results are shown in Table 1. The MIC at which 90% of the isolates are inhibited (MIC_{90}) and MBC_{90} of ABT 377 were 0.015 μg/ml (range, 0.008 to 0.015 μg/ml). The MIC_{90}s for azithromycin, clarithromycin, erythromycin, telithromycin, and levofloxacin were 0.125, 0.06, 0.06, 0.06, and 0.25 μg/ml, respectively. ABT 773 was at least fourfold more active in vitro against *C. pneumoniae* than the other ketolide and macrolides tested. The MICs of ABT 773 were very consistent from isolate to isolate, varying by only one dilution. This is especially impressive in view of the wide geographical distribution of the isolates tested.

The available data on the activity of ketolide antibiotics against *Chlamydia* species are limited. The only other agents that have been tested in vitro are telithromycin and RU 64004 (HMR 3004). Haider et al. (35th ICAAC) found the MICs of RU 64004 against two reference strains of *C. pneumoniae*, TW 183 and IOL 207, to be 0.01 and 0.05 μg/ml, respectively. Boswell et al. (5) found the MIC and MBC of telithromycin against one isolate of *C. pneumoniae*, TW 183, to be 0.06 and 0.12 μg/ml, respectively. Robin et al. (9) tested 19 isolates of *C. pneumoniae*, including TW 183, and 9 recent clinical isolates from children and adults with community-acquired pneumonia against telithromycin. The MIC_{90} and MBC_{90} were 0.25 μg/ml. The MICs ranged from 0.031 to 2 μg/ml. The MIC for TW 183

TABLE 1. Activities of ABT 773 and other antibiotics against 20 isolates of *C. pneumoniae*

Drug	MIC (μg/ml)			MBC (μg/ml)	
	Range	50%	90%	Range	90%
ABT 773	0.008–0.015	0.015	0.015	0.008–0.015	0.015
Telithromycin	0.015–0.25	0.03	0.06	0.015–0.25	0.06
Azithromycin	0.015–0.125	0.06	0.125	0.015–0.125	0.125
Clarithromycin	0.015–0.125	0.03	0.06	0.015–0.125	0.06
Erythromycin	0.015–0.06	0.03	0.06	0.015–0.06	0.06
Levofloxacin	0.125–0.25	0.25	0.25	0.125–0.25	0.25

* Corresponding author. Mailing address: Department of Pediatrics, Box 49, SUNY Health Science Center at Brooklyn, 450 Clarkson Ave., Brooklyn, NY 11203-2098. Phone: (718) 245-4075. Fax: (718) 245-2118. E-mail: mhammerschlag@pol.net.

was 0.125 μg/ml, which was the same as the MIC of telithromycin in the present study. Telithromycin was 10-fold more active against the recent clinical isolates of *C. pneumoniae* than older isolates, such as T2023 and AR 39, that have been passaged extensively in vitro (9). In the present study, the MICs of telithromycin against recent clinical isolates ranged from 0.015 to 0.06 μg/ml compared to 0.03 to 0.25 μg/ml for older laboratory isolates. However, in contrast, this dichotomy was not observed with ABT 773.

In vitro activity may not necessarily predict efficacy in vivo, especially for *C. pneumoniae*. Although clarithromycin is 2- to 10-fold more active in vitro against *C. pneumoniae* than erythromycin (10), it was not more effective than erythromycin in eradicating *C. pneumoniae* from the nasopharynx of children with community-acquired pneumonia (4). Further studies of the safety and efficacy of ABT 773 in vivo by using culture for the detection of *C. pneumoniae* in order to evaluate eradication are warranted.

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