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IN VITRO ACTIVITY OF TELITHROMYCIN AND OTHER ANTIBACTERIAL AGENTS AGAINST *STREPTOCOCCUS PNEUMONIAE*, *HAEMOPHILUS INFLUENZAE*, AND *MORAXELLA CATARRHALIS* IN GERMANY

Brauers J, Bagel S, Kresken M

Antiinfectives Intelligence GmbH, Bonn, Germany

Johannes Brauers
Antiinfectives Intelligence GmbH
Immenburgstrasse 20
53121 Bonn
Germany
Tel: +49 228 444 70612
Fax: +49 228 444 70616
Email: johannes.brauers@antiinfectives-intelligence.de

REVISED ABSTRACT

Background: Telithromycin is the first in a new class of antibacterial agents — the ketolides. The aim of this multicenter study comprising 18 laboratories was to compare the *in vitro* activity of telithromycin with that of other antibacterial agents against three major bacterial respiratory pathogens.

Methods: Organisms were recovered from outpatients during the winter season 2000–2001. MICs were determined by the broth microdilution method according to NCCLS in a central laboratory.

Results: MIC_{50}s and MIC_{90}s (mg/L) are given in the table below.

Antibacterial agent	*S. pneumoniae* (n=595) MIC_{50}/MIC_{90}	*H. influenzae* (n=434) MIC_{50}/MIC_{90}	*M. catarrhalis* (n=242) MIC_{50}/MIC_{90}
Telithromycin	≤0.06/≤0.06	1/2	≤0.06/≤0.06
Erythromycin A	≤0.125/≥32	4/8	0.25/0.25
Roxithromycin	≤0.25/≥64	8/16	≤0.25/≤0.25
Clarithromycin	≤0.25/32	8/8	≤0.25/≤0.25
Penicillin G	≤0.06/0.125	0.25/1	4/8
Amoxicillin	≤0.06/≤0.06	0.25/2	2/4
Amoxicillin–clavulanate	≤0.06/≤0.06	0.25/0.5	≤0.06/0.125
Cefuroxime	0.25/0.5	0.5/1	0.5/1
Cefpodoxime	≤0.06/0.125	≤0.06/≤0.06	0.25/0.5
Levofloxacin	1/1	≤0.06/≤0.06	≤0.06/≤0.06

Telithromycin showed potent activity against all isolates including all macrolide-resistant *S. pneumoniae*.

Conclusions: Telithromycin represents an important new option for the treatment of community-acquired respiratory tract infections, especially in areas of increasing resistance to macrolides.

INTRODUCTION

Streptococcus pneumoniae, *Haemophilus influenzae*, and *Moraxella catarrhalis* are among the leading pathogens causing community-acquired infections of the upper (ear, nose, and throat) and of the lower respiratory tract. Increasing antibiotic resistance among these pathogens is a major problem worldwide, especially penicillin G resistance and/or macrolide resistance among *S. pneumoniae* and β-lactamase production in *H. influenzae* and *M. catarrhalis*.[1–4]

High rates (30–70%) of penicillin resistance among *S. pneumoniae* have been reported in several countries including Spain, France, the USA, and Japan.[2] In Germany, penicillin G resistance among *S. pneumoniae* remains relatively low: only 5–10% of strains are penicillin G intermediate with a minimum inhibitory concentration (MIC) of 0.125–1 mg/L, and <1% of strains are penicillin G resistant (MIC ≥2 mg/L).[5,6] However, macrolide resistance among *S. pneumoniae* appears to be increasing and the German National Reference Center for Streptococci found that macrolide resistance among invasive isolates of *S. pneumoniae* increased from 3% in 1992 to 15.3% in 2000.[5]

Telithromycin is the first member of a new class of antibacterial agents — the ketolides — designed specifically for the treatment of community-acquired upper and lower respiratory tract infections (RTIs). It has a similar a mode of action to other macrolide, lincosamide, and streptogramin (MLS) antibacterials: inhibition of bacterial protein synthesis by interacting with the 50S ribosomal subunit and prevention of translation. However, due to novel structural modifications, telithromycin binds more tightly to bacterial ribosomes (by interacting with two different domains on the bacterial ribosome), does not induce cross-resistance to MLS antibacterials, and retains activity against MLS-resistant pneumococci.[7] Telithromycin has an optimal spectrum of activity for community-acquired upper and lower RTIs, possessing good activity against all relevant pathogens, including *S. pneumoniae*, *Streptococcus pyogenes*, *Staphylococcus aureus*, *H. influenzae*, and *M. catarrhalis*, as well as atypical/intracellular pathogens (*Chlamydophila* [*Chlamydia*] spp., *Mycoplasma* spp., and *Legionella* spp.).[8–13] Telithromycin shows excellent activity against both macrolide-susceptible and macrolide-resistant (methylation [*erm*(B)] as well as efflux-mediated [*mef*(A)] resistance) pneumococci,[14] and is more active than clarithromycin and erythromycin A against *H. influenzae* and *M. catarrhalis*.[15]

This multicenter study compared the *in vitro* activity of telithromycin and nine commonly used antibacterial agents against *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* isolated from outpatients with community-acquired upper and lower RTIs in Germany during the winter season 2000–2001.

MATERIALS AND METHODS

Study design

- Two prospective multicenter *in vitro* studies were performed during the winter season 2000–2001. The sampling period of Study I was from November 2000 to January 2001, and that of Study II was from February 2001 to May 2001. A total of 18 centers participated in this project: 8 in Study I and 10 in Study II (Figure 1).
- Each participating center was requested to randomly collect up to 80 fresh clinical isolates of *S. pneumoniae*, *H. influenzae*, and *M. catarrhalis* from outpatients with acute community-acquired upper and lower RTIs. Duplicate strains were not included in the analyses.
- All isolates were identified locally and subsequently reidentified by the central reference laboratory. Pneumococcal isolates were tested for optochin susceptibility. *H. influenzae* strains were tested for factor X (hemin) and factor V (nicotinamide adenine dinucleotide) dependency.
- Isolates were tested for their susceptibility to the following antibacterial agents: telithromycin, erythromycin A, roxithromycin, clarithromycin, penicillin G, amoxicillin, amoxicillin–clavulanate, cefuroxime, cefpodoxime, and levofloxacin.

FIGURE 1. GEOGRAPHIC DISTRIBUTION OF PARTICIPATING LABORATORIES IN GERMANY.

In vitro susceptibility testing

- MICs were determined in the reference laboratory by broth microdilution in accordance with the methods of the National Committee for Clinical Laboratory Standards (NCCLS).[16] Tests were performed in microdilution trays containing dried antibacterial agents (Merlin Diagnostika, Germany).
- As there are no recommended NCCLS breakpoints for *M. catarrhalis*, those recommended for *S. aureus* were applied.
- The following reference strains were included for quality control: *S. pneumoniae* ATCC 49619, *H. influenzae* ATCC 49247, *H. influenzae* ATCC 49766, *S. aureus* ATCC 29213, and *Escherichia coli* ATCC 35218.

RESULTS

- A total of 1271 clinical isolates were collected (*S. pneumoniae*, n=595; *H. influenzae*, n=434; *M. catarrhalis*, n=242) and tested for their susceptibility to a panel of antibacterials.
- Pathogens were isolated predominantly from specimens obtained from the nose (39.8%, n=506), throat (23.3%, n=296), sputum (14.4%, n=183), and ear (10.3%, n=131) (Figure 2).
- Patients of all ages were included in the study — mean age 24.4 years; median age 10 years; range <1–99.5 years. Isolates were obtained most frequently from children aged 2 to 9 years (37.7% of cases), followed by patients aged ≤1 year (16.1% of cases) and 20 to 39 years (13.9% of cases) (Figure 3).

In vitro susceptibility

- The MIC distributions, the MICs that inhibited 50% and 90% of the organisms tested (MIC_{50} and MIC_{90}, respectively), and the percentages of susceptible, intermediate, and resistant strains are presented for *S. pneumoniae* (Table 1), *H. influenzae* (Table 2), and *M. catarrhalis* (Table 3).

Streptococcus pneumoniae

- In total, 18.0% of *S. pneumoniae* strains were penicillin G intermediate with MICs ranging from 0.125 to 0.5 mg/L. No resistant strains (MIC ≥2 mg/L) were detected (Table 1).

FIGURE 2. DISTRIBUTION OF ISOLATES BY SPECIMEN SOURCE.

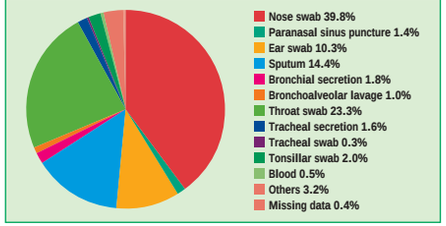

FIGURE 3. DISTRIBUTION OF ISOLATES BY PATIENT AGE GROUP.

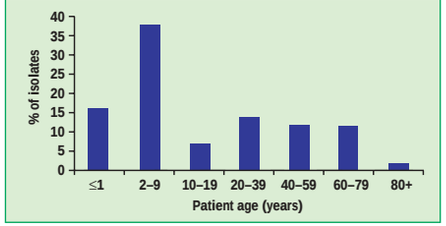

TABLE 1. MINIMUM INHIBITORY CONCENTRATIONS OF ANTIBACTERIAL AGENTS AND PERCENTAGES OF SENSITIVE, INTERMEDIATE, AND RESISTANT ISOLATES OF *STREPTOCOCCUS PNEUMONIAE* (n=595)

	Minimum inhibitory concentration (mg/L)													% Susceptibility		
Antibacterial agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	MIC_{50}	MIC_{90}	S	I	R
Telithromycin	594	1	0	0	0	0	0	0	0	—	—	≤0.06	≤0.06	NA	NA	NA
Erythromycin A	—	510	1	0	0	3	3	1	11	66	—	≤0.125	≥32	85.9	0.0	14.1
Roxithromycin	—	—	511	0	0	1	2	3	1	3	74	≤0.25	≥64	NA	NA	NA
Clarithromycin	—	—	512	2	3	3	2	3	4	13	53	≤0.25	32	86.1	0.3	13.6
Penicillin G	488	75	31	1	0	0	0	0	0	—	—	≤0.06	0.125	82.0	18.0	0.0
Amoxicillin	572	21	2	0	0	0	0	0	0	—	—	≤0.06	≤0.06	100	0.0	0.0
Amoxicillin–clavulanate	573	21	1	0	0	0	0	0	0	—	—	≤0.06	≤0.06	100	0.0	0.0
Cefuroxime	—	—	514	80	0	1	0	0	0	0	0	0.25	0.5	99.8	0.2	0.0
Cefpodoxime	489	56	33	16	1	0	0	0	0	—	—	≤0.06	0.125	99.8	0.2	0.0
Levofloxacin	0	0	3	249	341	2	0	0	0	—	—	1	1	100	0.0	0.0

Intermediate Resistant Minimum inhibitory concentration ≥ concentration given Abbreviations: I, intermediate; NA, no NCCLS breakpoints available; S, susceptible; R, resistant.

TABLE 2. MINIMUM INHIBITORY CONCENTRATIONS OF ANTIBACTERIAL AGENTS AND PERCENTAGES OF SENSITIVE, INTERMEDIATE, AND RESISTANT ISOLATES OF *HAEMOPHILUS INFLUENZAE* (n=434)

	Minimum inhibitory concentration (mg/L)													% Susceptibility		
Antibacterial agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	MIC_{50}	MIC_{90}	S	I	R
Telithromycin	8	7	1	85	248	85	0	0	0	—	—	1	2	NA	NA	NA
Erythromycin A	—	3	1	2	9	15	200	198	6	0	—	4	8	NA	NA	NA
Roxithromycin	—	—	4	2	1	6	59	226	127	9	0	8	16	NA	NA	NA
Clarithromycin	—	—	5	0	5	41	142	216	25	0	0	8	8	94.3	5.7	0.0
Penicillin G	103	110	123	36	24	5	2	4	27	—	—	0.25	1	NA	NA	NA
Amoxicillin	77	40	177	79	10	19	6	3	23	—	—	0.25	2	NA	NA	NA
Co-amoxiclav	80	52	192	68	22	19	0	1	0	—	—	0.25	0.5	99.8	NA	0.2
Cefuroxime	—	—	196	173	27	28	10	0	0	0	0	0.5	1	100	0.0	0.0
Cefpodoxime	415	15	2	2	0	0	0	0	0	—	—	≤0.06	≤0.06	100	NA	NA
Levofloxacin	434	0	0	0	0	0	0	0	0	—	—	≤0.06	≤0.06	100	NA	NA

Intermediate Resistant Minimum inhibitory concentration ≥ concentration given Abbreviations: I, intermediate; NA, no NCCLS breakpoints available; S, susceptible; R, resistant.

TABLE 3. MINIMUM INHIBITORY CONCENTRATIONS OF ANTIBACTERIAL AGENTS AND PERCENTAGES OF SENSITIVE, INTERMEDIATE, AND RESISTANT ISOLATES OF *MORAXELLA CATARRHALIS* (n=242)

	Minimum inhibitory concentration (mg/L)													% Susceptibility		
Antibacterial agent	≤0.06	0.125	0.25	0.5	1	2	4	8	16	32	64	MIC_{50}	MIC_{90}	S	I	R
Telithromycin	240	2	0	0	0	0	0	0	0	—	—	≤0.06	≤0.06	NA	NA	NA
Erythromycin A	—	35	196	11	0	0	0	0	0	0	—	0.25	0.25	100	0.0	0.0
Roxithromycin	—	—	239	2	1	0	0	0	0	0	0	≤0.25	≤0.25	NA	NA	NA
Clarithromycin	—	—	239	2	1	0	0	0	0	0	0	≤0.25	≤0.25	100	0.0	0.0
Penicillin G	32	2	2	5	16	52	54	64	15	—	—	4	8	14.0	NA	86.0
Amoxicillin	34	0	8	24	50	55	56	15	0	—	—	2	4	NA	NA	NA
Amoxicillin–clavulanate	198	40	4	0	0	0	0	0	0	—	—	≤0.06	0.125	100	NA	0.0
Cefuroxime	—	—	34	116	82	8	2	0	0	0	0	0.5	1	100	0.0	0.0
Cefpodoxime	28	40	108	65	1	0	0	0	0	—	—	0.25	0.5	100	0.0	0.0
Levofloxacin	233	9	0	0	0	0	0	0	0	—	—	≤0.06	≤0.06	100	0.0	0.0

Intermediate Resistant Minimum inhibitory concentration ≥ concentration given Abbreviations: I, intermediate; NA, no NCCLS breakpoints available; S, susceptible; R, resistant.

- Resistance to macrolides was observed in about 14% of *S. pneumoniae* isolates (erythromycin A, 14.1%; clarithromycin, 13.6%) and MIC_{90} values for erythromycin A, roxithromycin, and clarithromycin were ≥32 mg/L, ≥64 mg/L, and 32 mg/L, respectively (Table 1). Resistance to amoxicillin, amoxicillin–clavulanate, cefuroxime, cefpodoxime, and levofloxacin was not observed.
- Telithromycin exhibited excellent activity against all pneumococcal isolates including penicillin G-intermediate and macrolide-resistant isolates ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L). All strains were susceptible to ≤0.125 mg/L of telithromycin (Table 1).

Haemophilus influenzae

- When the NCCLS breakpoints for ampicillin were applied to amoxicillin (susceptible, ≤1 mg/L; intermediate, 2 mg/L; resistant ≥4 mg/L), 19/434 (4.4%) strains of *H. influenzae* were amoxicillin intermediate and 32/434 (7.4%) strains were amoxicillin resistant. Amoxicillin–clavulanate ($MIC_{50/90}$ 0.25/0.5 mg/L), cefuroxime ($MIC_{50/90}$ 0.5/1 mg/L), cefpodoxime ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L), and levofloxacin ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L) all showed good activity against *H. influenzae* (Table 2).
- The *in vitro* activity of telithromycin ($MIC_{50/90}$ 1/2 mg/L) against *H. influenzae* was superior to that of erythromycin A ($MIC_{50/90}$ 4/8 mg/L), roxithromycin ($MICs_{50/90}$ 8/16 mg/L), and clarithromycin ($MIC_{50/90}$ 8/8 mg/L) (Table 2).

Moraxella catarrhalis

- Resistance to penicillin G was observed in 86% of the *M. catarrhalis* strains tested (Table 3). As expected, *M. catarrhalis* strains showed increased MICs for amoxicillin ($MIC_{50/90}$ 2/4 mg/L).
- Telithromycin displayed excellent activity against strains of *M. catarrhalis* ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L) (Table 3).
- Good activity was also observed with amoxicillin–clavulanate ($MIC_{50/90}$ ≤0.06/0.125 mg/L), cefuroxime ($MIC_{50/90}$ 0.5/1 mg/L), cefpodoxime ($MIC_{50/90}$ 0.25/0.5 mg/L), the macrolides ($MIC_{50/90}$ ≤0.25/≤0.25 mg/L for all three), and levofloxacin ($MIC_{50/90}$ ≤0.06/≤0.06 mg/L) (Table 3).

CONCLUSIONS

- A total of 18% of *S. pneumoniae* isolates were penicillin G-intermediate. This rate is much higher than the rates of 4–8% reported from other previously conducted resistance surveys in Germany.[6,17] However, penicillin G-resistant strains were not detected.
- Approximately 14% of *S. pneumoniae* isolates showed reduced *in vitro* susceptibility to macrolides (erythromycin A and clarithromycin). This rate is similar to that reported by other investigators for Germany.[17,18]
- Telithromycin exhibited excellent activity against all pneumococcal isolates, including penicillin G-intermediate and macrolide-resistant strains.
- The *in vitro* activity of telithromycin against *H. influenzae* was superior to that of the macrolides erythromycin A, roxithromycin, and clarithromycin.
- Telithromycin is highly active against *M. catarrhalis*.
- Telithromycin represents an important new option for the treatment of community-acquired upper and lower RTIs, especially in areas of increasing macrolide resistance.

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