PR024

Evaluation of Tigecycline and Comparators Against Multi-Drug Resistant (MDR) Streptococcus pneumoniae in the United States

D. Hoban[1], M. Renteria[1], J. Johnson[1], R. Badal[1], S. Hawser[1], M. Hackel[1], S. Bouchillon[1], B. Johnson[1], M. Dowzicky[2]

[1]International Health Management Associates, Inc., Schaumburg, IL, USA
[2]Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
Fax: 847.303.5601

Revised Abstract

Objectives: Although overall rates of non-susceptibility to penicillin seem to have leveled off in the U.S., there is evidence of increasing resistance to macrolides. Multi-drug resistant (MDR) *Streptococcus pneumoniae* strains are not uncommon. Tigecycline, a new glycylcycline, offers the potential of enhanced activity against MDR *S. pneumoniae*. The Tigecycline Evaluation Surveillance Trial (T.E.S.T.) evaluated the activity of tigecycline and comparators to MDR *S. pneumoniae* isolated in the U.S. **Methods**: Between 2004 and 2008, 3739 *S. pneumoniae* isolates were collected in 460 U.S. sites. MICs were determined at each site using broth microdilution panels and results interpreted as specified by CLSI. *S. pneumoniae* strains were categorized into groups according to the number of drug classes to which they were resistant (MDR groups 0 to 5). **Results**: MIC_{90} of tigecycline and comparators to MDR groups 0 to 5 are shown in the table below:

	MIC_{90} (mcg/ml) MDR Group[1]					
	Group 0 (n=3,002)	Group 1 (n=370)	Group 2 (n=231)	Group 3 (n=96)	Group 4 (n=33)	Group 5 (n=7)
Tigecycline	0.06	0.06	0.06	0.12	0.06	0.12
AmoxClav	0.25	4	4	8	8	>8
Ceftriaxone	0.25	1	1	4	8	4
Imipenem	0.25	1	2	2	1	*
Levofloxacin	1	1	1	1	1	1
Linezolid	1	1	1	1	1	≤0.5
Meropenem	≤0.12	0.5	1	2	2	2
Penicillin	0.25	4	4	4	8	8
Vancomycin	0.5	0.5	0.5	0.5	0.5	0.5

[1] MDR Group is defined as resistant to 0, 1, 2, or 3 or more CLSI drug classes
*None tested

Conclusions: Among nine antimicrobials tested, tigecycline exhibited the lowest MIC_{90} for *S. pneumonia* strains isolated in the U.S. that were resistant to one or more drug classes. The high level of in vitro activity was maintained by tigecycline even against strains with resistance to multiple drug classes.

Introduction

Tigecycline is a member of a new class of antimicrobial agents, the glycylcyclines. This synthetic analogue of the tetracyclines exhibits antibacterial activity that is both bacteriostatic and, in certain instances, bactericidal with killing activity that is as much as fourfold better than vancomycin and daptomycin [1, 2] against certain pathogens. The development of tigecycline is important in that it and other glycylcyclines are active against bacterial strains carrying either or both of the two major forms of tetracycline resistance: efflux and ribosomal protection. A single chemical modification of tigecycline overcomes the two molecularly distinct forms of resistance while maintaining activity against susceptible gram-positive, gram-negative, aerobic, and anaerobic bacteria [3].

Infections due to *S. pneumoniae* continue to evolve worldwide and are a major cause of morbidity and mortality. Resistance in *S. pneumoniae* not only to penicillin but also to cephalosporins, macrolides, TMP-SMX, fluoroquinolones and tetracycline is well documented. New guidelines for the management of in-patient and out-patient community acquired pneumonia have recently been published [4].

This study was undertaken to document the in vitro activity of tigecycline against multidrug resistant *Streptococcus pneumoniae* in a diverse population from multiple investigative sites in the United States. This study is part of the larger ongoing global Tigecycline Evaluation and Surveillance Trials (T.E.S.T.) program.

Materials & Methods

- All isolates were derived from blood, CNS, respiratory, sinuses, sputum, middle ear, and other defined sources. Only one isolate per patient was accepted into the study.
- Clinical isolates were collected and tested between January 2004 and December 2008 from 460 investigative sites in the United States. Isolates were identified to the species level and tested at each site by the participating laboratory.
- Organism collection, transport, confirmation of organism identification, and development and management of a centralized database were coordinated by Laboratories International for Microbiology Studies (LIMS), a division of International Health Management Associates, Inc. located in Schaumburg, IL, USA.
- All organisms were deemed clinically significant by local participant criteria. Isolate inclusion was independent of medical history, antimicrobial use, age or gender. All sites identified each study isolate utilizing local laboratory site criteria.
- Minimum inhibitory concentrations (MICs) were determined by the CLSI recommended broth microdilution testing method [5]. Tigecycline was supplied by Wyeth Pharmaceuticals (Collegeville, PA, USA). All other agents were supplied by the panel manufacturers, MicroScan (Dade Behring Inc., West Sacramento, CA, USA) and Trek (TREK Diagnostic Systems, Cleveland, OH). The following antimicrobial agents were included on the panels with their dilution ranges (expressed in mcg/ml): amoxicillin/clavulanic acid (0.12/0.06-32/16); ampicillin (0.06-16); ceftriaxone (0.06-64); imipenem (0.06-16); linezolid (0.5-8); levofloxacin (0.008-8); meropenem (0.12-16); minocycline (0.5-16); tigecycline (0.008-16); penicillin (0.06-8); piperacillin/tazobactam (0.06/4-128/4) and vancomycin (0.12-32). MIC interpretive criteria followed published guidelines established by the Clinical and Laboratory Standards Institute [6], where applicable. There are currently no breakpoints defined for tigecycline against *S. pneumoniae* species.
- Quality controls (QC) were performed by each testing site on each day of testing using *S. pneumoniae* ATCC 49619. Results were included in the analysis only when corresponding QC isolates tested within the acceptable range according to CLSI (2008) guidelines [6].

References

1. Hoellman, D.B., et al., *Antipneumococcal activities of GAR-936 (a new glycylcycline) compared to those of nine other agents against penicillin-susceptible and -resistant pneumococci.* Antimicrob Agents Chemother, 2000. **44**(4): p. 1085-8.
2. Labthavikul, P., P.J. Petersen, and P.A. Bradford, *In vitro activity of tigecycline against Staphylococcus epidermidis growing in an adherent-cell biofilm model.* Antimicrob Agents Chemother, 2003. **47**(12): p. 3967-9.
3. Projan, S.J., *Preclinical pharmacology of GAR-936, a novel glycylcycline antibacterial agent.* Pharmacotherapy, 2000. **20**(9 Pt 2): p. 219S-223S; discussion 224S-228S.
4. Mandell, L.A., et al., *Infectious Diseases Society of America/American Thoracic Society Consensus Guidelines on the Management of Community-Acquired Pneumonia in Adults*. CID, 2007. **44**: p. S27-72.
5. Clinical Laboratory Standards Institute, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Seventh Edition*, in *Document M7-A7*. 2007: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
6. Clinical Laboratory Standards Institute, *Performance Standards for Antimicrobial Susceptibility Testing*, in *Document M100-S18*. 2008: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.

Acknowledgements

This study was sponsored by a grant from Wyeth Pharmaceuticals. We gratefully acknowledge the contributions of all investigators, laboratory personnel and from the entire 364 current members of the Tigecycline Evaluation Study Trials program group.

Results

The results of this study are presented in the following tables:

Table 1. Distribution of *S. pneumoniae* and multidrug resistant strains in the population sample according to body source.

Source	Total Number *S. pneumoniae* from all Sources	% from All Sources	Total Number of MDR Strains	% MDR
Blood	1177	31.5	25	18.4
Central Nervous System	44	1.2	2	1.5
Gastrointestinal	8	0.2	0	0
Genital/Urinary	18	0.5	0	0
Other	240	6.4	8	5.9
Respiratory	2210	59.1	101	74.3
Skin and Skin Structures	42	1.1	0	0
Totals	**3739**	**100**	**136**	**100**

Multidrug resistance is defined as resistance to three or more CLSI drug classes.

Table 2. In vitro activity of tigecycline and comparators against 136 multidrug resistant isolates of *S. pneumoniae* from the population sample.

				MIC (mcg/mL)		
Drug	**%Sus [a]**	**%Int**	**%Res**	**MIC_{50}**	**MIC_{90}**	**Range**
Tigecycline	na	na	na	0.03	0.12	≤0.008 - 0.12
AmoxClav	16.7	13.5	69.8	8	8	≤0.03 - >8
Ceftriaxone	40.6	36.5	22.9	1	4	0.06 - >64
Imipenem	16.7	6.7	76.7	1	2	≤0.12 - 2
Levofloxacin	97.9	0	2.1	1	1	0.25 - 8
Linezolid	100	0	0	≤0.5	1	≤0.5 - 1
Meropenem	4.5	6.1	89.4	1	2	≤0.12 - 4
Penicillin	1.0	4.2	94.8	4	4	≤0.06 - 8
Vancomycin	100	0	0	0.25	0.5	≤0.12 - 1

Multidrug resistance is defined as resistance to three or more CLSI drug classes.
[a] Interpretive criteria as defined by CLSI, M100-S18 (2008), where available.

Table 3. In vitro activity (mcg/mL) of tigecycline and comparators at each grouping of resistant drug classes for 3,739 *S. pneumoniae* isolates.

	MIC_{50} / MIC_{90} (mcg/ml)					
Drug	**Resistant to 0 Drug Classes (n=3,002)**	**Resistant to 1 Drug Class (n=370)**	**Resistant to 2 Drug Classes (n=231)**	**Resistant to 3 Drug Classes (n=96)**	**Resistant to 4 Drug Classes (n=33)**	**Resistant to 5 Drug Classes (n=7)**
Tigecycline	0.03 / 0.06	0.03 / 0.06	0.03 / 0.12	0.03 / 0.12	0.03 / 0.06	0.12 / 0.12
AmoxClav	≤0.03 / 0.25	1 / 4	2 / 4	8 / 8	8 / 8	8 / >8
Ceftriaxone	≤0.03 / 0.25	0.5 / 1	1 / 1	1 / 4	4 / 8	2 / 4
Imipenem	≤0.12 / 0.25	0.5 / 1	1 / 2	1 / 2	1 / 1	na
Levofloxacin	0.5 / 1	0.5 / 1	1 / 1	1 / 1	1 / 1	1 / 1
Linezolid	≤0.5 / 1	1 / 1	0.5 / 1	≤0.5 / 1	≤0.5 / 1	≤0.5 / ≤0.5
Meropenem	≤0.12 / ≤0.12	0.25 / 0.5	1 / 1	1 / 2	1 / 2	1 / 2
Penicillin	≤0.06 / 0.5	2 / 4	2 / 4	4 / 4	4 / 8	4 / 8
Vancomycin	0.25 / 0.5	0.25 / 0.5	0.25 / 0.5	0.25 / 0.5	0.25 / 0.5	0.25 / 0.5

na = none tested

Conclusions

- Tigecycline had an in vitro MIC_{90} of 0.12 mcg/ml against all multidrug resistant strains of *S. pneumoniae*. This value was 8- to 16-fold lower than amox/clav, imipenem, levofloxacin, ceftriaxone and linezolid and 4-fold lower than vancomycin.
- Tigecycline inhibited all multidrug resistant (resistant to three or more drug classes) *S. pneumoniae* strains at a MIC of ≤0.12 mcg/mL.
- The MIC_{50} and MIC_{90} values of some study drugs increased as *S. pneumoniae* species became resistant to more drug classes.
- The in vitro activity of tigecycline was superior to imipenem, amox/clav, ceftriaxone, levofloxacin, linezolid and vancomycin against all *S. pneumoniae* resistant to three or more drug classes.
- The in vitro activity of tigecycline in this study suggests that tigecycline is a potent antimicrobial agent that may be beneficial in the treatment of infections due to difficult to treat drug resistant and multidrug resistant *S. pneumoniae*.