Activity of Tigecycline Against Minocycline Resistance Pathogens: A Global Perspective

#909

S. Hawser[2], M. Hackel[1], D. Hoban[1], S. Bouchillon[1], M. Renteria[1], B. Johnson[1], R. Badal[1], J. Johnson[1], M. Dowzicky[3]
[1]International Health Management Associates, Inc., Schaumburg, IL, USA
[2]IHMA Europe Sàrl , Epalinges, Switzerland
[3]Wyeth Pharmaceuticals, Collegeville, PA, USA

IHMA, Inc.
2122 Palmer Dr.
Schaumburg, IL
60173
Tel: 847.303.5003
www.ihmainc.com

Revised Abstract

Background: Cross-resistance between tetracyclines such as minocycline (MIN) and tigecycline (TIG) has generally been reported to be low. In order to more precisely define cross-resistance rates, large scale surveillance studies are useful. This report documents the activity of TIG against MIN- resistant isolates collected worldwide from January 2004-March 2009, as part of the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) study. **Methods**: 102,524 clinical isolates of which 67,956 and 34,568 were Gram-negative and Gram-positive, respectively, were used in this study analysis. MICs were performed and interpreted according to CLSI and FDA guidelines. **Results**: The table below illustrates the incidence of MIN vs. TIG resistance in selected isolates.

Organism	Total	MIN^R	% MIN^R	% TIG^R
Gram-negative				
Acinetobacter baumannii	8702	365	4.2	NC*
Enterobacter cloacae	11927	1444	12.1	1.0
Escherichia coli	18614	2096	11.2	0.01
E. coli ESBL	1784	448	25.1	0.05
Klebisella oxytoca	3313	159	4.8	0.2
K. oxytoca ESBL	158	24	15.2	0.6
K. pneumoniae	14448	2236	15.5	0.6
K. pneumoniae ESBL	2490	755	30.3	1.0
Serratia marcescens	6520	392	6.0	0.6
Gram-positive				
Enterococcus faecalis	7592	1711	22.5	0
E. faecium	2762	355	12.9	NC*
Staphylococcus aureus	17040	109	0.6	0
S. aureus MRSA	7174	93	1.3	0

MIN^R, minocycline-resistant isolates; NC*, no clinical indication or breakpoint are available for this species; TIG^R, tigecycline resistant isolates.

Conclusions: Taken together, the data show that 4 – 30% and 0.6-22.5% of Gram-negatives and Gram-positives, respectively, exhibited resistance to MIN over the period 2004 - 2009. However, there was no cross-resistance between TIG and MIN in Gram-positives and in Gram-negatives cross-resistance was very low (≤1%).

Introduction

Tigecycline is approved in the United States for the treatment of complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infections (cIAI), and recently approved for the treatment of community acquired bacterial pneumonia (CABP), including pneumococcal bacteremia.

Although resistance to minocycline has increased markedly over the last decade, resistance to tigecycline, which was first introduced in the healthcare setting in 2005, appears to remain low in Gram-negatives and non-existent in Gram-positives[1]. This report documents the activity of tigecycline against minocycline- resistant isolates collected worldwide from January 2004-March 2009, as part of the Tigecycline Evaluation Surveillance Trial (T.E.S.T.) study.

Materials & Methods

- ► Clinical isolates were collected and tested between January 2004 and March 2009 from a cumulative total of 1,258 investigative sites from Africa (21), Asia/Pacific (98), Europe (425), Latin America (149), Middle East (33) and North America (532). Isolates were identified to the species level and tested at each participating laboratory. 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 criteria.
- ► Minimum inhibitory concentrations (MICs) were determined using plates manufactured by Trek in line with Clinical and Laboratory Standards Institute (CLSI) recommended broth microdilution testing method [2]. Interpretive breakpoints were used as defined the CLSI [3] or by the FDA for tigecycline [4].

References

1. Nicolau DP. *Management of complicated infections in the era of antimicrobial resistance: the role of tigecycline*. 2009. Expert Opin. Pharmacother. 10: 1213-1222
2. CLSI, *Methods for Dilution Antimicrobial Susceptibility Tests for Bacteria That Grow Aerobically; Approved Standard—Sixth Edition, in Document M7-A7. 2006*: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
3. CLSI, *Performance Standards for Antimicrobial Susceptibility Testing, in Document M100-S19. 2009*: Clinical Laboratory Standards Institute (CLSI), 940 West Valley Road, Suite 1400, Wayne, Pennsylvania 19087-1898 USA.
4. Tygacil®, FDA approved Product Information. 2005: Wyeth Pharmaceuticals, Inc., Philadelphia, PA, 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

Table 1. Numbers and cumulative totals of investigator sites.

Region	2004	2005	2006	2007	2008	2009	Grand Total
Africa	1	4	6	6	3	1	21
Asia / Pacific Rim	9	11	30	31	16	1	98
Europe	40	38	82	103	142	20	425
Latin America	12	16	36	40	37	8	149
Middle East	3	5	8	11	5	1	33
North America	91	136	122	120	56	7	532
Grand Total	**156**	**210**	**284**	**311**	**259**	**38**	**1258**

Table 2. Total numbers of isolates by geographic region.

Organism	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Grand Total
Acinetobacter baumannii	169	608	2852	1038	122	3704	209	8702
Enterobacter cloacae	202	682	4173	1287	154	5116	313	11927
Enterococcus faecalis	167	338	2398	843	106	3526	214	7592
Enterococcus faecium	14	204	926	225	28	1307	58	2762
Escherichia coli	301	1026	6114	2063	297	8341	472	18614
Escherichia coli, ESBL	12	235	678	523	41	272	23	1784
Klebsiella oxytoca	37	79	1506	177	23	1386	105	3313
Klebsiella oxytoca, ESBL	4	6	59	31	1	55	2	158
Klebsiella pneumoniae	282	934	4293	1689	238	6667	345	14448
Klebsiella pneumoniae, ESBL	135	230	730	649	49	665	32	2490
Serratia marcescens	108	352	2110	674	83	3012	181	6520
Staphylococcus aureus	298	909	5278	1835	247	8044	429	17040
Staphylococcus aureus, MRSA	89	440	1350	841	67	4283	104	7174
Grand Total	**1818**	**6043**	**32467**	**11875**	**1456**	**46378**	**2487**	**102524**

Table 3. Numbers of minocycline-resistant isolates by geographic region.

Organism	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Grand Total
A.baumannii	47	38	67	55	7	145	6	365
E. cloacae	39	101	461	283	14	504	42	1444
E. faecalis	37	88	795	252	32	420	87	1711
E. faecium	2	18	147	56	1	120	11	355
E. coli	53	191	732	476	59	539	46	2096
E., ESBL	3	47	152	159	14	68	5	448
K. oxytoca	5	10	93	19	0	29	3	159
K.oxytoca, ESBL	2	0	11	8	0	2	1	24
K. pneumoniae	78	144	865	390	57	670	32	2236
K. pneumoniae, ESBL	41	63	290	176	18	156	11	755
S. marcescens	4	25	152	84	5	113	9	392
S. aureus	2	45	40	8	0	13	1	109
S. aureus, MRSA	2	44	32	6	0	8	1	93
Grand Total	**315**	**814**	**3837**	**1972**	**207**	**2787**	**255**	**10187**

Table 4. Numbers of tigecycline-resistant isolates by geographic region.

Organism	Africa	Asia	Europe	Latin America	Middle East	North America	South Pacific	Grand Total
E. cloacae	3	5	0	7	2	101	5	123
E. coli	0	0	1	1	0	0	0	2
E. coli, ESBL	0	0	0	1	0	0	0	1
K. oxytoca	0	0	4	0	0	3	0	7
K. oxytoca, ESBL	0	0	1	0	0	0	0	1
K. pneumoniae	4	2	22	14	0	38	2	82
K. pneumoniae, ESBL	3	1	8	8	0	7	0	27
S. marcescens	0	5	10	5	0	20	0	40
Grand Total	**10**	**13**	**46**	**36**	**2**	**169**	**7**	**283**

Table 5. Number and percent of minocycline-resistant and tigecycline-resistant isolates.

	All Isolates	MIN-R	% MIN-R	TIG-R	% TIG-R
Organism	N	N	%N	N	%N
A.baumannii	8702	365	4.2	na	na
E. cloacae	11927	1444	12.1	123	1
E. faecalis	7592	1711	22.5	0	0
E. faecium	2762	355	12.9	na	na
E.coli	18614	2096	11.2	2	0.01
E.coli, ESBL	1784	448	25.1	1	0.05
K. oxytoca	3313	159	4.8	7	0.2
K. oxytoca, ESBL	158	24	15.2	1	0.6
K. pneumoniae	14448	2236	15.5	82	0.6
K. pneumoniae, ESBL	2490	755	30.3	27	1.1
S. marcescens	6520	392	6	40	0.6
S. aureus	17040	109	0.6	0	0
S. aureus, MRSA	7174	93	1.3	0	0
Grand Total	**102524**	**10187**	**9.9**	**283**	**0.3**

MIN-R, minocycline-resistant isolates; TIG-R, tigecycline-resistant isolates ; na = FDA breakpoints not available for this species.

Table 6. Cumulative percent frequency of tigecycline MICs against minocycline-resistant isolates.

		Tigecycline MIC (mcg/ml)												
Organism	N	≤0.004	0.008	0.015	0.03	0.06	0.12	0.25	0.5	1	2	4	8	16
A. baumanii	365	0	0	0	0.3	0	1.4	3.8	15.6	53.7	82.2	92.9	99.2	100
E. cloacae	1444	0	0	0.1	0	0	0.4	4.8	22.9	42	66.2	90	99.5	100
E.faecalis	1711	0	0	0.1	0.5	10.2	60.6	99.8	99.8	100	0	0	0	0
E.faecium	355	0	0.3	0	2.8	31.5	76.6	100	0	0	0	0	0	0
E.coli	2096	0	0	0.1	0	1.5	30.2	71.3	89.7	96.7	99.7	99.9	100	100
E.coli, ESBL	448	0	0	0	0	0.4	21.7	64.3	87.5	97.3	99.8	0	0	100
K.oxytoca	159	0	0	0	0	0	1.9	19.5	36.5	59.1	85.5	96.9	100	0
K.oxytoca, ESBL	24	0	0	0	0	0	4.2	20.8	41.7	62.5	83.3	95.8	100	0
K.pneumoniae	2236	0	0	0	0.1	0.2	0.9	11.7	39.2	60.7	79.3	96.6	100	0
K.pneumoniae, ESBL	755	0	0	0	0	0	0.5	10.6	34.3	62.9	83.6	96.6	100	0
S.marcescens	392	0	0.3	0	0.5	0	0.8	1	5.1	25.3	67.9	92.6	99	100
S.aureus	109	0	0	0	0	0.9	15.6	55	100	0	0	0	0	0
S.aureus, MRSA	93	0	0	0	0	0	14	51.6	100	0	0	0	0	0

Values represent the cumulative frequency (percent) of isolates by MIC.
Values in orange shading are indicative of the MIC_{90} of tigecycline against minocycline-resistant organisms.

Table 7. Susceptibilities of minocycline-resistant isolates to tigecycline and comparators.

	Percent Susceptibility (%)								
Organism	Amikacin	Cefepime	Ceftazidime	Ceftriaxone	Imipenem	Levofloxacin	Linezolid	Tigecycline	Vancomycin
A.baumannii	47.12	12.05	8.77	7.4	71.43	8.77	NB	NB	NB
E.cloacae	87.95	72.92	28.46	31.93	99.2	48.41	NB	66.2	NB
E.faecalis	NB	NB	NB	NB	NB	65.17	97.49	99.77	98.54
E.faecium	NB	NB	NB	NB	NB	23.1	91.27	100	63.1
E.coli	94.18	79.68	75.95	69.23	99.68	35.4	NB	99.71	NB
E.coli, ESBL	87.28	33.04	35.04	7.59	99.23	9.38	NB	99.78	NB
K.oxytoca	88.05	77.36	66.04	50.31	97.22	50.94	NB	85.53	NB
K.oxytoca, ESBL	83.33	50	20.83	4.17	92.86	50	NB	83.33	NB
K.pneumoniae	87.57	65.74	53.67	54.52	99.53	56.26	NB	79.34	NB
K.pneumoniae, ESBL	76.56	33.51	10.33	9.93	100	29.67	NB	83.58	NB
S.marcescens	80.36	79.59	70.15	65.56	100	67.86	NB	67.86	NB
S. aureus	NB	NB	NB	17.43	18.18	14.68	100	100	99.08
S.aureus, MRSA	NB	NB	NB	3.23	NB	3.23	100	100	98.92

Values represent the percent susceptibility of isolates to tigecycline (FDA breakpoints) and comparators (CLSI breakpoints).
Values in grey shading represent percent susceptibilities of ≥90%.

Conclusions

- ► Up to 30% and 22.5% of Gram-negatives and Gram-positives, respectively, exhibited resistance to minocycline over the period 2004 - 2009.
- ► However, there was no cross-resistance between tigecycline and minocycline in Gram-positives whereby 100% were susceptible to tigecycline.
- ► Gram-negative cross-resistance was very low (≤1%); for those pathogens showing cross resistance, tigecycline susceptibilities ranged between 66% and 85%.