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Tigecycline (GAR-936) Activity Against 848 Bloodstream Infection (BSI) Isolates of Viridans Group Streptococci

RN JONES, TR FRITSCHE, HS SADER
JMI Laboratories, North Liberty, IA

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JMI Laboratories
North Liberty, IA, USA
www.jmilabs.com
319.665.3370, fax 319.665.3371
ronald-jones@jmilabs.com

ABSTRACT

Background:
Viridans group streptococci (VGS) including *S. gallolyticus (bovis)* represent serious invasive pathogens often associated with endocarditis or sepsis among immunocompromised or cancer patients. Tigecycline (TIG), the first clinically studied glycylcycline, has a potent Gram-positive spectrum, potentially applicable to VGS infections.

Methods:
The VGS collection of 848 strains included 100 isolates each of *S. anginosus, S. constellatus* (SCON), *S. intermedius, S. mitis, S. oralis, S. salivarius, S. sanguis* (SSAN) and *S. gallolyticus* (98 strains); and 50 *S. mutans* strains. These VGS were isolated from patients on 3 continents in the SENTRY Antimicrobial Surveillance Program and susceptibility (S) tested and interpreted by CLSI broth microdilution methods/criteria. S for TIG was defined as a MIC at ≤ 0.25 µg/ml, as recently approved by the US-FDA.

Results:
Penicillin-S rates for the entire collection varied from 61% (SSAN) to 98% (SCON), and macrolide-S was also compromised (49 - 88% S; average 69%). The TIG-S rate was 100%, in contrast to tetracycline resistance of 8 - 66%, highest for *S. gallolyticus* (see Table below):

	MIC (µg/ml)			
Species	50%	90%	Range	% S
S. anginosus	≤0.06	≤0.06	≤0.06	100.0
S. constellatus	≤0.06	≤0.06	≤0.06	100.0
S. gallolyticus	≤0.06	≤0.06	≤0.06	100.0
S. intermedius	≤0.06	≤0.06	≤0.06-0.25	100.0
S. mitis	≤0.06	≤0.06	≤0.06-0.12	100.0
S. mutans	≤0.06	≤0.06	≤0.06	100.0
S. oralis	≤0.06	≤0.06	≤0.06-0.25	100.0
S. salivarius	≤0.06	≤0.06	≤0.06-0.25	100.0
S. sanguis	≤0.06	0.12	≤0.06-0.25	100.0

Linezolid (LZD), quinupristin/dalfopristin and vancomycin (VAN; 94 - 100% S) were also very active against these VGS species.

Conclusions:
TIG was quite active against BSI isolates of VGS and *S. gallolyticus* with an overall MIC_{90} at ≤ 0.06 µg/ml; highest MIC only 0.25 µg/ml. This potency was 8- to 16-fold greater than LZD or VAN, and indicates possible therapeutic utility for these troublesome species in systemic infections.

INTRODUCTION

Viridans group streptococci are components of the normal flora, but these species are recognized pathogens in immunocompromised patients. Neutropenic cancer patients are especially prone to bacteremia caused by viridans group streptococci. In contrast to non-neutropenic patients, these patients are more likely to develop serious complications from viridans group streptococcal bacteremia. Antimicrobial resistance in viridans group streptococci has further complicated patient management, with resistance to penicillin, other ß-lactam agents and macrolides being especially problematic.

Tigecycline (formerly GAR-936) spectrum of activity includes many Gram-positive multidrug-resistant (MDR) strains for which there are few therapeutic alternatives, including vancomycin-resistant enterococci, methicillin- or oxacillin-resistant *Staphylococcus aureus* (MRSA) and penicillin-resistant streptococci. The United States Food and Drug Administration (US-FDA) recently approved categorical breakpoints for staphylococci, streptococci (other than *S. pneumoniae*) and *Enterococcus faecalis* for tigecycline at ≤ 0.5, ≤ 0.25 and ≤ 0.25 µg/ml, respectively; these criteria are pending presentation and approval by the Clinical and Laboratory Standards Institute (CLSI; formerly the NCCLS). Here we report on the susceptibility profiles using breakpoint criteria promulgated by the tigecycline package insert (Table 1) for each of eight species of viridans group streptococci and *Streptococcus gallolyticus (bovis)* tested against this new glycylcycline.

MATERIALS AND METHODS

The study collection of 848 streptococci (target ≥ 100 strains per species) recovered from bloodstream infections included strains of *S. anginosus* (100 strains), *S. constellatus* (100 strains), *S. intermedius* (100 strains), *S. mitis* (100 strains), *S. mutans* (50 strains), *S. oralis* (100 strains), *S. salivarius* (100 strains), *S. sanguis* (100 strains) and *S. gallolyticus* (98 strains). All isolates were non-duplicate, clinical isolates collected as part of various international surveillance studies by JMI Laboratories (North Liberty, Iowa, USA). Twenty-one additional bacteremic strains of *S. mutans* were kindly provided by Dr. M.J. Ferraro (Massachusetts General Hospital, Boston, MA).

All strains were tested using Mueller-Hinton broth supplemented with 2 - 5% LHB according to the NCCLS M7-A6 reference broth microdilution method. Tigecycline and eight comparator agents including penicillin (0.008 - 16 µg/ml), erythromycin (0.008 - 16 µg/ml), clindamycin (0.008 - 16 µg/ml), vancomycin (0.06 - 2 µg/ml), linezolid (0.12 - 16 µg/ml), quinupristin/dalfopristin (0.06 - 8 µg/ml), minocycline (0.5 - 8 µg/ml) and tetracycline (1 - 8 µg/ml) were tested in reference frozen-form broth microdilution panels manufactured by TREK Diagnostics Systems (Cleveland, Ohio, USA).

An ATCC QC strain (*S. pneumoniae* ATCC 49619) was processed in parallel and all susceptibility test results were within published ranges for the MIC method. The modal MIC results for the QC strain were: tigecycline (0.06 µg/ml), penicillin (0.25 µg/ml), erythromycin (0.06 µg/ml), clindamycin (0.06 µg/ml), linezolid (1 µg/ml), quinupristin/dalfopristin (0.25 µg/ml), vancomycin (0.12 µg/ml), minocycline (≤ 0.5 µg/ml) and tetracycline (≤ 1 µg/ml). Tigecycline was tested in "fresh" lots of Mueller-Hinton broth.

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RESULTS

- The results of testing 848 streptococci by reference NCCLS MIC methods against tigecycline and eight comparison agents are summarized in Table 1. Tigecycline MIC values ranged from ≤ 0.016 to 0.25 µg/ml. The least tigecycline-susceptible species were *S. intermedius, S. mitis, S. oralis, S. salivarius* and *S. sanguis* (MIC_{90}, 0.12 µg/ml).

- All strains of viridans group streptococci were observed to be susceptible to vancomycin at ≤ 1 µg/ml. The MIC_{50} and MIC_{90} was generally 0.5 µg/ml (except *S. bovis* MIC_{50}, 0.25 µg/ml) and only *S. constellatus* and *S. mutans* strains had a vancomycin MIC_{90} of 1 µg/ml (breakpoint concentration). The penicillin MIC results ranged from ≤ 0.008 to > 16 µg/ml, and susceptibility rates widely varied (61.0 - 98.0%) by species. *S. sanguis* isolates were least penicillin-susceptible (61.0%) and *S. constellatus* isolates were highly susceptible (98.0%) at current CLSI breakpoints.

Table 1. In vitro activity of tigecycline (GAR-936) and eight comparison agents tested against viridans group streptococci and *S. bovis* isolates (848 strains).

	MIC (µg/ml)			% by category[a]
Organism (no. tested)/antimicrobial agent	50%	90%	Range	Susceptible/resistant
S. anginosus (100)				
Tigecycline	≤0.06	≤0.06	≤0.06	100.0/-[b]
Tetracycline	≤1	>8	≤1->8	72.0/26.0
Minocycline	≤0.5	8	≤0.5->8	-/-
Clindamycin	0.03	0.03	≤0.008->16	94.0/6.0
Erythromycin	0.03	1	≤0.008->16	88.0/12.0
Linezolid	1	1	0.25-2	100.0/-
Penicillin	0.03	0.12	≤0.008-2	94.0/0.0
Quinupristin/Dalfopristin	0.5	1	≤0.06-1	100.0/0.0
Vancomycin	0.5	0.5	0.25-1	100.0/-
S. constellatus (100)				
Tigecycline	≤0.06	≤0.06	≤0.06	100.0/-
Tetracycline	≤1	>8	≤1->8	79.0/19.0
Minocycline	≤0.5	8	≤0.5->8	-/-
Clindamycin	0.03	0.06	≤0.008->16	93.0/7.0
Erythromycin	0.016	2	≤0.008->16	86.0/14.0
Linezolid	1	1	≤0.12-1	100.0/-
Penicillin	0.03	0.06	≤0.008->16	98.0/1.0
Quinupristin/Dalfopristin	0.25	0.5	0.12-1	100.0/0.0
Vancomycin	0.5	1	0.25-1	100.0/-
S. intermedius (100)				
Tigecycline	≤0.06	≤0.06	≤0.06-0.25	100.0/-
Tetracycline	≤1	>8	≤1->8	75.0/22.0
Minocycline	≤0.5	8	≤0.5->8	-/-
Clindamycin	0.016	0.03	≤0.008->16	92.0/8.0
Erythromycin	0.03	2	≤0.008->16	80.0/19.0
Linezolid	1	1	0.25-2	100.0/-
Penicillin	0.06	0.5	≤0.008-16	88.0/3.0
Quinupristin/Dalfopristin	0.5	0.5	0.12-2	99.0/0.0
Vancomycin	0.5	0.5	0.25-1	100.0/-
S. mitis (100)				
Tigecycline	≤0.06	≤0.06	≤0.06-0.12	100.0/-
Tetracycline	≤1	>8	≤1->8	65.0/31.0
Minocycline	≤0.5	8	≤0.5->8	-/-
Clindamycin	0.016	4	≤0.008->16	89.0/11.0
Erythromycin	0.25	4	≤0.008->16	52.0/43.0
Linezolid	1	1	≤0.12-2	100.0/-
Penicillin	0.12	2	≤0.008->16	68.0/8.0
Quinupristin/Dalfopristin	0.25	0.5	≤0.06-1	100.0/0.0
Vancomycin	0.5	0.5	0.12-0.5	100.0/-
S. mutans (50)				
Tigecycline	≤0.06	≤0.06	≤0.06	100.0/-
Tetracycline	≤1	≤1	≤1->8	92.0/8.0
Minocycline	≤0.5	≤0.5	≤0.5->8	-/-
Clindamycin	≤0.008	0.06	≤0.008->16	96.0/4.0
Erythromycin	0.016	1	≤0.008->16	84.0/16.0
Linezolid	1	1	≤0.12-2	100.0/-
Penicillin	0.016	0.12	≤0.008-4	90.0/4.0
Quinupristin/Dalfopristin	0.25	1	0.12-1	100.0/0.0
Vancomycin	0.5	1	0.12-1	100.0/-
S. oralis (100)				
Tigecycline	≤0.06	≤0.06	≤0.06-0.25	100.0/-
Tetracycline	≤1	>8	≤1->8	71.0/28.0
Minocycline	≤0.5	>8	≤0.5->8	-/-
Clindamycin	0.016	>16	≤0.008->16	84.0/15.0
Erythromycin	0.5	>16	≤0.008->16	49.0/47.0
Linezolid	1	1	0.25-2	100.0/-
Penicillin	0.06	4	≤0.008-16	67.0/16.0
Quinupristin/Dalfopristin	0.5	1	≤0.06-1	100.0/0.0
Vancomycin	0.5	0.5	0.25-0.5	100.0/-
S. salivarius (100)				
Tigecycline	≤0.06	≤0.06	≤0.06-0.25	100.0/-
Tetracycline	≤1	>8	≤1->8	71.0/25.0
Minocycline	≤0.5	>8	≤0.5->8	-/-
Clindamycin	≤0.008	0.03	≤0.008->16	92.0/7.0
Erythromycin	0.016	8	≤0.008->16	65.0/35.0
Linezolid	1	1	0.25-2	100.0/-
Penicillin	0.06	0.5	≤0.008-4	75.0/1.0
Quinupristin/Dalfopristin	0.5	1	0.12-1	100.0/0.0
Vancomycin	0.5	0.5	0.25-1	100.0/-
S. sanguis (100)				
Tigecycline	≤0.06	0.12	≤0.06-0.25	100.0/-
Tetracycline	≤1	>8	≤1->8	68.0/29.0
Minocycline	≤0.5	8	≤0.5->8	-/-
Clindamycin	0.016	>16	≤0.008->16	88.0/12.0
Erythromycin	0.016	>16	≤0.008->16	63.0/34.0
Linezolid	1	1	0.25-2	100.0/-
Penicillin	0.12	2	≤0.008->16	61.0/3.0
Quinupristin/Dalfopristin	0.5	1	0.12-1	100.0/0.0
Vancomycin	0.5	0.5	0.25-1	100.0/-
S. gallolyticus (bovis) (98)				
Tigecycline	≤0.06	≤0.06	≤0.06	100.0/-
Tetracycline	>8	>8	≤1->8	33.7/66.3
Minocycline	8	>8	≤0.5->8	-/-
Clindamycin	0.03	>16	≤0.008->16	73.5/26.5
Erythromycin	0.03	>16	≤0.008->16	53.1/45.9
Linezolid	1	1	0.5-2	100.0/-
Penicillin	0.03	0.06	≤0.008-1	96.9/0.0
Quinupristin/Dalfopristin	0.5	1	0.12-4	93.9/3.1
Vancomycin	0.25	0.5	0.12-0.5	100.0/-

a. Susceptibility criteria of the CLSI or US-FDA (tigecycline).
b. - = indicates no interpretive criteria have been established.

- Macrolide (erythromycin) susceptibility was lowest among *S. oralis* strains (49.0%), whereas *S. anginosus* strains were more susceptible (88.0%). Another MLS_B-class agent, clindamycin, had a greater level of activity against these tested viridans group streptococci. Clindamycin susceptibility rates ranged from 73.5 - 96.0%. The streptogramin combination, quinupristin/dalfopristin, was very potent (99.0 - 100.0% susceptible) against all species except *S. gallolyticus*, (93.9% susceptible).

- Tetracycline, representing the class, had quite variable activities when tested against these viridans group streptococci and only tetracycline among the many tetracycline derivatives has CLSI susceptibility interpretive criteria, although minocycline appears to be more potent overall.

- Linezolid showed excellent potency versus these streptococci. MIC_{50} and MIC_{90} results were all 1 µg/ml and the linezolid-susceptible rate was 100.0%.

CONCLUSIONS

- Tigecycline was very active against bloodstream isolates of viridans group streptococci and *S. gallolyticus* (*S. bovis*) with an overall MIC_{90} at ≤ 0.06 µg/ml.

- The highest MIC was 0.25 µg/ml, with 100.0% of isolates being susceptible at the recently approved, US-FDA breakpoint of 0.25 µg/ml.

- The potency of tigecycline was eight- to 16-fold greater than linezolid or vancomycin, indicating possible therapeutic utility for these troublesome species in systemic infections.