B-046

Efficacy of Tigecycline and Vancomycin in a Rat *Staphylococcus aureus* Endocarditis Model

51st ICAAC Meeting
Chicago, IL
September 17-20, 2011

W. J. WEISS*, M. PULSE, P. NGUYEN, J. PIERCE, P. RENICK, D. VALTIERRA, J. W. SIMECKA
Pre-Clinical Services at UNT Health Science Center, Ft. Worth, TX

* Contact Information:
UNT Health Science Center
3500 Camp Bowie Blvd.
Fort Worth, TX 76107-2699
william.weiss@unthsc.edu
www.hsc.unt.edu/preclinical

Abstract

Background: Infective endocarditis (IE) is an increasing problem in the hospital and health-care related area of clinical importance due in part to its high rate of mortality. Changes in the epidemiology and subsequent therapy of endocarditis infections have been recently described. The current study was performed to evaluate the efficacy of Tigecycline (TIG) and Vancomycin (VAN) in a rat model of IE with a native valve endocarditis *S. aureus* clinical isolate.
Methods: A polyethylene catheter was surgically inserted through the carotid artery into the left ventricle of male Sprague-Dawley rats and secured in place. Rats were infected intravenously with 10^5 CFU of *S. aureus* NRS234 at 48 hrs after catheter insertion. TIG (1., 5, 7.5, 12.5 mg/kg) and VAN (20, 30, 40 mg/kg) were administered subcutaneously 24 hrs post-infection and continued twice daily (bid) for 3 days. Hearts, kidneys and spleens were removed 24 hrs after the last dose for bacterial CFU counts.
Results: MICs of TIG and VAN for NRS234 were 0.125 ug/mL and 0.5 ug/mL, respectively. Mean bacterial titers in the heart, kidneys and spleen of untreated controls were 9.2, 8.7 and 7.2 $\log_{10}$ CFU/tissue. TIG administration at 1, 5, 7.5 and 12.5 mg/kg bid resulted in $\log_{10}$ CFU reductions of 0.95, 0.43, 1.99 and 2.17 in cardiac vegetations, 3.69, 2.91, 5.26 and 5.79 in the kidneys and 3.1, 1.9, 4.13 and 3.86 in the spleen, respectively. VAN administration was less effective with $\log_{10}$ reductions of 0.4, 0.91 and 0.35 at 40 mg/kg bid and 0.2, 0.48 and 0.36 at 30 mg/kg bid for the heart, kidneys and spleen, respectively. In addition to CFU reduction, TIG enhanced overall survival (<25% mortality) at all doses tested as compared to VAN (30 – 75% mortality).
Conclusion: Efficacy in IE requires an antibiotic to penetrate the cardiac vegetation and elicit a response that depends on the activity of the agent, diffusion into the site and pharmacodynamic (PD) parameters required for efficacy. TIG, with its antimicrobial profile and favorable *in vivo* PD properties, was more effective than VAN and is an excellent candidate for the treatment of this serious life threatening infection.

Introduction

Endocarditis has many underlying causes, including complications from intravenous drug use, prosthetic valves, and nosocomial bacteremia, leading to extended hospital stays and high mortality rates. Streptococci, staphylococci, and enterococci are considered the three leading causes of infective endocarditis. It is recognized as a difficult infection to treat and presents a therapeutic challenge, especially when caused by methicillin-resistant *Staphylococcus aureus*. Treatment of resistant strains is limited, involving removal of the vegetation or associated device, constant infusion of effective antibiotics, or synergistic combinations of two or more antibacterial agents. Animal models of infective endocarditis have been shown to be useful for the study of the human disease by examination of dosing regimens, bactericidal effect, relapse, and antibiotic penetration into the vegetation. The current study was performed to evaluate the efficacy of Tigecycline, Daptomycin and Vancomycin in a rat model of experimental endocarditis involving a clinical isolate of *S. aureus* associated with native valve endocarditis.

Methods and Materials

Organism: *Staphylococcus aureus* NRS234 was obtained through the NARSA program: supported under NIAID, NIH Contract No. HHSN272200700055C. The isolate was associated with native valve endocarditis.
In vitro: MICs / MBCs and time-kill curves were performed in accordance with CLSI guidelines.
Animals: Male Sprague-Dawley rats, 200 – 250 gm.
Endocarditis: Gas anesthesia was induced with 4% isoflurane and 5 L/hour of oxygen, and maintained at 3.5% isoflurane and 5 L/hour of oxygen. The ventral cervical area was shaved and de-germed with 3 applications of betadine scrub and 70% ethanol. A 2-cm incision was made within the area from a cranial to caudal aspect, parallel to the midline and just to the right of the pharnyx. Underlying tissues were blunt-dissected away beneath the incision in order to expose the right carotid artery. A pre-sealed polyethylene catheter (PE10) was surgically inserted through the carotid artery into the left ventricle and secured in place with surgical glue/ suture. Rats were infected intravenously with ~10^5 CFU of *S. aureus* NRS234 at 48 hrs after catheter insertion.
Treatment: Compounds were administered subcutaneously, Tigecycline and Vancomycin twice-a-day (bid) and Daptomycin once-a-day (qd), for three days starting 24 hours post-infection.
Sampling: Hearts (including catheter), kidneys and spleens were removed 24 hrs after the last administered dose, placed in sterile saline, homogenized then serially diluted and plated for the determination of bacterial counts.

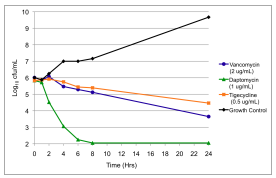
Panel 1. Minimum Inhibitory and Bactericidal Concentrations (MIC / MBC) of Selected Agents against *S. aureus* NRS234

Compound	MIC (ug/mL)	MBC (ug/mL)	MBC/MIC Ratio
Vancomycin	0.5	2.0	4
Daptomycin	0.25	0.25	1
Tigecycline	0.125	1.0	8

Compound	MIC (ug/mL)	CLSI Interpretation
Oxacillin	1.0	S
Penicillin	> 2.0	R
Ciprofloxacin	0.5	S
Erythromycin	1.0	I
Teicoplanin	0.5	S
Linezolid	2.0	S

- MBC / MIC ratios (fold increase in MIC value) were 4, 1 and 8 for Vancomycin, Daptomycin and Tigecycline, respectively.

Panel 2. Time-Kill Curves for Tigecycline, Daptomycin and Vancomycin vs *S. aureus* NRS234



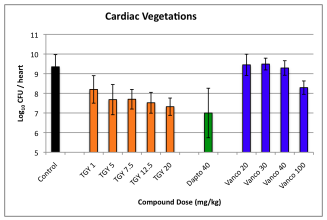
- Time-kill study was performed at 4xMIC of Vancomycin, Daptomycin and Tigecycline.
- Limit of Detection (LOD) = 2.0 $\log_{10}$ CFU/mL.

Panel 3. Survival of Sprague-Dawley Rats in the *S. aureus* NRS234 Endocarditis Infection Model

Treatment	Dose (mg/kg)	Survival (S/T)
Control	na	3/13
Tigecycline	1	3/4
	5	4/4
	7.5	4/4
	12.5	4/4
	20	4/4
Daptomycin	40	4/4
Vancomycin	20	1/3
	30	1/4
	40	2/4
	100	3/4

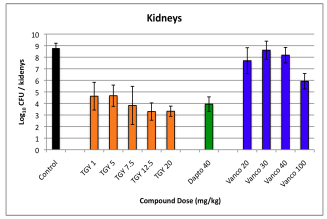
Day 1	Day 2	Day 3	Day 4	Day 5	Day 6	Day 7
Implant	–	Infection	Treatment	Treatment	Treatment	Sample

Panel 4. Efficacy of Selected Treatments in Cardiac Vegetations



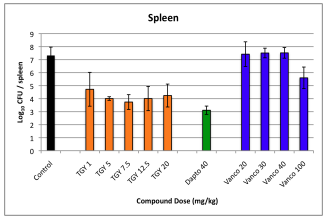
Treatment	Dose (mg/kg)	$\log_{10}$ CFU/heart	Std. dev.	$\log_{10}$ CFU reduction	p-value vs control
Control	na	9.35	0.62	--	--
Tigecycline	1	8.20	0.70	1.15	0.580
	5	7.68	0.77	1.67	0.279
	7.5	7.70	0.50	1.65	0.0002
	12.5	7.52	0.53	1.83	0.0001
	20	7.32	0.44	2.03	0.0004
Daptomycin	40	7.00	1.26	2.35	0.0103
Vancomycin	20	9.45	0.54	-0.10	0.456
	30	9.49	0.30	-0.14	0.1413
	40	9.29	0.37	0.06	0.3914
	100	8.29	0.34	1.06	0.0034

Panel 5. Efficacy of Selected Treatments in Kidneys



Treatment	Dose (mg/kg)	$\log_{10}$ CFU/kidney	Std. dev.	$\log_{10}$ CFU reduction	p-value vs control
Control	na	8.79	0.42	--	--
Tigecycline	1	4.63	1.20	4.16	0.0192
	5	4.67	0.92	4.12	0.084
	7.5	3.83	1.65	4.96	0.0002
	12.5	3.30	0.75	5.49	0.00001
	20	3.33	0.44	5.46	0.00001
Daptomycin	40	3.94	0.63	4.85	0.0001
Vancomycin	20	7.70	1.12	1.09	0.523
	30	8.61	0.78	0.18	0.2294
	40	8.18	0.67	0.61	0.0237
	100	5.92	0.67	2.87	0.0005

Panel 6. Efficacy of Selected Treatments in Spleens



Treatment	Dose (mg/kg)	$\log_{10}$ CFU/spleen	Std. dev.	$\log_{10}$ CFU reduction	p-value vs control
Control	na	7.32	0.64	--	--
Tigecycline	1	4.72	1.30	2.60	0.139
	5	4.01	0.14	3.31	0.0002
	7.5	3.74	0.57	3.58	0.00002
	12.5	4.01	0.93	3.31	0.00004
	20	4.24	0.88	3.08	0.0004
Daptomycin	40	3.11	0.32	4.21	0.00001
Vancomycin	20	7.42	0.95	-0.10	0.356
	30	7.51	0.37	-0.19	0.1071
	40	7.52	0.41	-0.20	0.1374
	100	5.60	0.83	1.72	0.0053

Summary and Conclusions

- MICs / MBCs for Tigecycline, Vancomycin and Daptomycin against *S. aureus* NRS234 were 0.125 / 1.0 ug/mL, and 0.5 / 2.0 ug/mL and 0.25 / 0.25 ug/mL, respectively.
- Time-kill studies at 4xMIC exhibited the bactericidal (≥ 3-log reduction) activity of Daptomycin within 4 hours of exposure and an overall 1.5 - 2.3 $\log_{10}$ CFU reduction achieved by Tigecycline and Vancomycin over 24 hours.
- Mean bacterial titers in the heart, kidneys and spleen of untreated controls reached 9.2, 8.7 and 7.2 $\log_{10}$ CFU/tissue, respectively.
- Tigecycline doses of 1 - 20 mg/kg bid resulted in $\log_{10}$ CFU reductions of up to 2.03 in cardiac vegetations, 5.49 in kidneys and 3.58 in the spleens of infected animals.
- Daptomycin at 40 mg/kg qd demonstrated bacterial reductions of 2.35, 4.85 and 4.21 $\log_{10}$ CFU in cardiac vegetations, kidneys and spleens, respectively.
- Vancomycin administration was the least effective treatment with a reduction of only 1.06 $\log_{10}$ CFU in cardiac vegetations at the 100 mg/kg bid dose.
- Tigecycline and Daptomycin exhibited comparable efficacy at the total daily dose of 40 mg/kg.
- In addition to reduction of bacterial tissue titers, overall survival of infected animals was enhanced by Tigecycline and Daptomycin at all doses tested as compared to Vancomycin.

References

1. Kaatz, G. W., S. M. Seo, V. N. Reddy, E. M. Bailey, and M. J. Ryhak. 1990. Daptomycin compared with teicoplanin and vancomycin for therapy of experimental *Staphylococcus aureus* endocarditis. Antimicrob. Agents Chemother. 34:2081-2085.
2. Jacqueline, C., N. Asseray, E. Batard, V. Le Mabecque, M. F. Kergueris, L. Dube, D. Bugnon, G. Potel, and J. Caillon. 2004. In vivo efficacy of linezolid in combination with gentamicin for the treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. Int. J. Antimicrob. Agents 24:393-396
3. Chiang, F. Y., and M. Climo. 2003. Efficacy of linezolid alone or in combination with vancomycin for treatment of experimental endocarditis due to methicillin-resistant *Staphylococcus aureus*. Antimicrob. Agents Chemother. 47:3002-3004
4. Santoro, J., and M. E. Levison. 1978. Rat model of experimental endocarditis. Infect. Immun. 19:915-918
5. Murphy, T.M., J. Deitz, P. Petersen, S. Mikels, and W. J. Weiss. 2000. Therapeutic Efficacy of GAR-936, a Novel Glycylcycline, in a Rat Model of Experimental Endocarditis. Antimicrob. Agents Chemother. 44: 3022 - 3027.

Acknowledgments

The authors would like to acknowledge the technical assistance of Kim Cavanaugh, Maciej Kukula and Kelly Peterson of the UNT Health Science Center.