B-050

Comparative Efficacy of TR-701 (Prodrug of Torezolid), Vancomycin (Vanco) and Daptomycin (Dapto) in a Rabbit Model of Methicillin-Resistant *Staphylococcus aureus* (MRSA) Endocarditis

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Abstract

Background:
Torezolid (TR-700), the active metabolite of the prodrug TR-701 (TOR), is an investigational oxazolidinone that is 8-10x more potent than linezolid against *S. aureus* in vitro. To determine whether this potency translates into a bactericidal effect in vivo TOR was compared to Vanco and Dapto in a rabbit model of aortic valve endocarditis caused by the MRSA strain COL.

Methods:
A catheter was positioned across the aortic valve of the rabbit and left in place. 48h later infection was established by IV injection of 10^7 CFU of COL (MICs of 0.125 mg/L, 1mg/L and 1mg/L for TR-700, Vanco and Dapto respectively). ~18 h later untreated controls were sacrificed and remaining rabbits were treated either with TOR (15 mg/kg IV bid), Vanco (30 mg/kg IV bid) or Dapo (18 mg/kg IV once daily) for 4 days. Rabbits were sacrificed the following day and vegetations, spleen and kidney were quantitatively cultured.

Results:
Mean plasma concentrations (mg/L) at 1h were 9.7±1.8 (TR-700), 34±10 (Vanco) and 93±13 (Dapto) and at 9h were 5.8±2.2 (TR-700). Mean±SD log10 CFU/g tissues were as follows:

	Treatment Groups			
Tissues	Control (n=9)	TOR (n=14)	Vanco (n=16)	Dapto (n=16)
Vegetation	7.7±1.2	6.0±2.0	5.5±2.6	3.5±2.6
Spleen	4.6±0.7	3.0±1.4	3.2±1.5	2.3±1.5
Kidney	3.5±1.3	2.5±1.1	2.6±1.2	2.2±1.0

TOR significantly decreased the numbers of bacteria in each target tissue compared to untreated control ($p<0.05$). Dapto was more effective than TOR in reducing cfu in ($p=0.05$). TOR, Vanco and Dapto were similarly effective in reducing cfu in spleens and kidneys.

Conclusion:
The efficacy of TOR was comparable to that of Vanco, each producing about a 2 log10 cfu/g kill, and slightly less than that of Dapto in the model.

Objective

The purpose of these studies was to determine whether Torezolid (TR-700), the active metabolite of the prodrug TR-701 (TOR) that is 8-10 x more potent in vitro than linezolid, has bactericidal activity against *S. aureus* in vivo

TOR was compared to two standard agents, Vanco and Dapto, in a rabbit model of aortic valve endocarditis

Methods

Microbiology
- COL, a homogeneous highly methicillin-resistant strain, was used to establish infection
- MICs were determined according CLSI guidelines

Treatment Regimen
- Antibiotic regimens were given IV for 4 days:
  - TR-701: 15mg/kg twice daily
  - Vancomycin: 30 mg/kg twice daily
  - Daptomycin: 18 mg/kg once daily
- Antibiotics were started 16-18h after infection
- Blood was obtained 1h (all drugs) and 9h (TR-701 dosed animals only) after IV injection to determine serum concentrations
- All animals were sacrificed at day 5; vegetations, spleens and kidneys were quantitatively cultured

Endocarditis Model
- 2.5-3 kg New Zealand White male rabbits
- Endocarditis was established by standard method
- 48h post-surgery, a 1ml suspension of $3.7x10^7$ (±1.9) CFU of MRSA strain COL was injected intravenously
- 16h-18h after infection, untreated controls were sacrificed and the hearts, spleens and kidneys were harvested to determine pretreatment bacterial counts

Statistical Analysis
- Results were expressed as log 10 cfu/g of tissue
- The lower limit of detection was 1 CFU/tissue sample weight in grams
- Statistical analysis was determined by student's paired t-test without adjustments for multiple comparisons.

Results

Vegetation Titers

Treatment	Mean Organism Titer (log_{10} CFU/g) ± SD	P value for the comparison btw TOR and other groups	P value for the comparison btw control and other groups
Control (n=9)	7.7 ± 1.2	0.03	ref
TOR (n=14)	6.0 ± 2.0	ref	0.03
Dapto (n=16)	3.5 ± 2.0	0.003	<0.001
Vanco (n=16)	5.5 ± 2.6	0.599	0.024

Spleen Titers

Treatment	Mean Organism Titer (log_{10} CFU/g) ± SD	P value for the comparison btw TOR and other groups	P value for the comparison btw control and other groups
Control (n=9)	4.6 ± 0.7	0.004	ref
TOR (n=14)	3.0 ± 1.4	ref	0.004
Dapto (n=16)	2.3 ± 1.5	0.12	<0.001
Vanco (n=16)	3.2 ± 1.5	0.743	0.013

Kidney Titers

Treatment	Mean Organism Titer (log_{10} CFU/g) ± SD	P value for the comparison btw TOR and other groups	P value for the comparison btw control and other groups
Control (n=9)	3.5 ± 1.3	0.066	ref
TOR (n=14)	2.5 ± 1.1	ref	0.066
Dapto (n=16)	2.2 ± 1.0	0.478	0.012
Vanco (n=16)	2.6 ± 1.2	0.767	0.109

Mean Plasma Concentration

	Mean Plasma Concentrations (mg/L)	
Antibiotic	1 hour	9 hour
Torezolid	9.7±1.8	5.8±2.2
Vancomycin	34±10	N/A
Daptomycin	93±13	N/A

Minimum Inhibitory Concentrations

Antibiotic	MIC *S. aureus* COL
Torezolid	0.125mg/L
Vancomycin	1mg/L
Daptomycin	1mg/L

Findings

- TOR treatment significantly lowered the bacterial burden in vegetations compared to controls with a 1.7 log_{10} CFU/g decrease.
- TOR was not significantly different from Vancomycin.
- Daptomycin was superior to both TOR and Vancomycin in the treatment of aortic valve endocarditis with a 2.5 and 2.0 log_{10} decrease, respectively.

- TOR treatment significantly lowered the bacterial burden in spleen compared to controls with a 1.6 log_{10} CFU/g decrease.
- TOR was similarly effective in lowering bacterial burden in the spleen compared to Daptomycin and Vancomycin.

- TOR treatment significantly lowered the bacterial burden in kidneys compared to controls with a 1.0 log_{10} CFU/g decrease.
- TOR, Daptomycin and Vancomycin were similarly effective in reducing CFU in the kidneys.

Conclusion

- Daptomycin was the most effective antibiotic in reducing bacterial counts in vegetations.

- TOR, Daptomycin, and Vancomycin were similarly effective in reducing bacterial counts in the spleen and kidneys.

- TOR was as effective as Vancomycin.

- Doses used produced serum concentrations of torezolid projected to be similar to an 800 mg twice daily oral dose in humans.