Activity of Exebacase Against Methicillin-Resistant *Staphylococcus aureus* (MRSA) Biofilms on Orthopedic Kirschner Wires

Poster Number 712

Melissa J. Karau, M.S.[1], Suzannah M. Schmidt-Malan, M.S.[1], Jayawant Mandrekar, Ph.D.[2], Dario Lehoux, Ph.D.[4], Raymond Schuch, Ph.D.[4], Cara Cassino, M.D.[4] Robin Patel, M.D.[1,3]

[1]Division of Clinical Microbiology, [2]Division of Biomedical Statistics and Informatics, [3]Division of Infectious Diseases, Mayo Clinic, Rochester, MN

[4]Contrafect, Yonkers, NY

Contact Information:
Robin Patel, M.D.
Division of **Clinical Microbiology**
Division of Infectious Diseases
Mayo Clinic, Rochester, MN
Email: patel.robin@mayo.edu

Background

***Prosthetic Joint Infection (PJI)*[1,2]**

- *Staphylococcus aureus* most common cause of PJI
- Forms biofilms → evades antimicrobials and immune system
- Surgical intervention and long term antibiotic therapy
- Increase in multi-drug resistance

Exebacase

- Phage derived lysin, recombinantly produced as purified cell wall hydrolase enzyme
- Hydrolyzes cell wall of *S. aureus* and associated biofilms
- Rapidly bactericidal, synergistic activity with daptomycin and vancomycin[3-4]
- Bone levels ~15% plasma levels after single dose of 10 mg/kg
- Mouse bacteremia and rat osteomyelitis showed decrease in infection with single dose[3,5]
- Phase 2 clinical trial on bacteremia demonstrated 43% higher clinical response rates *versus* standard therapy alone against MRSA[6]

Treatment

Treatment Groups

- 20mM L-histidine, 5% D-sorbitol (exebacase vehicle)
- Saline (daptomycin vehicle)
- Exebacase 0.098 mg/ml
- Exebacase 0.98 mg/ml
- Exebacase 9.8 mg/ml
- Daptomycin 0.098 mg/ml
- Daptomycin 0.098 mg/ml
- Daptomycin 0.098 mg/ml
- Daptomycin 0.098 mg/ml
- Daptomycin 0.098 mg/ml
- Exebacase and daptomycin each at 0.098 mg/ml

Treatment Durations

- 2 hours
- 4 hours
- 8 hours
- 12 hours

Methods

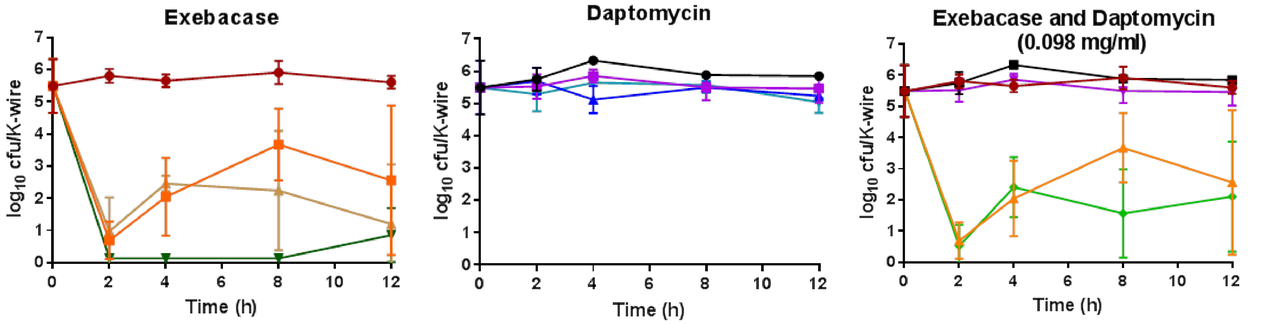
- MRSA (IDRL-6169) from patient with PJI; minimum inhibitory concentration is 0.5 µg/ml for both daptomycin and exebacase
- Biofilms grown on 5 mm stainless steel threaded Kirschner wires (K-wires) in 40 µl of 10^6 cfu/ml in typtic soy broth (TSB) for 10 hours
- Wires removed from growth media → placed in 40 µl of treatment solution
- After specified time, K-wires removed from solution and dipped in sterile saline to remove remnant treatment
- K-wires placed in 0.5 ml sterile saline, vortexed 30 seconds, sonicated (40 kHz, 0.22 W/cm^2) 5 minutes, vortexed additional 30 seconds
- Resultant sonicate fluid cultured using 1:10 dilutions in saline, 100 µl of each dilution plated on sheep blood agar → 37ºC for 48 hours
- TSB placed into sonicate fluid and also incubated
- Colonies counted or growth from broth only assigned 0.65 $\log_{10}$ cfu/K-wire; negative broth cultures assigned 0.13 $\log_{10}$ cfu/K-wire
- Results reported as $\log_{10}$ cfu/K-wire reduction relative to vehicle alone
- 3-$\log_{10}$ cfu/K-wire reduction considered bactericidal
- Testing performed in triplicate; P-values calculated using Kruskal Wallis

Results

Mean $\log_{10}$ cfu/K-wire reduction compared to carrier solution

	Daptomycin (DAP)			Exebacase (EXE)			Daptomycin + Exebacase
	Concentration in mg/ml						
Hours of Treatment	0.098	0.98	9.8	0.098	0.98	9.8	0.098
2	0.23	0.06	0.46	**5.12**	**4.83**	**5.68**	**5.29**
4	0.48	1.21	0.68	**3.60**	**3.20**	**5.52**	**3.24**
8	0.39	0.39	0.31	2.24	**3.67**	**5.78**	**4.34**
12	0.38	0.61	0.81	**3.05**	**4.41**	**4.76**	**3.50**

Bold values considered bactericidal



Conclusions

- Exebacase showed rapid activity against MRSA biofilms on orthopedic K-wires
- Exebacase had superior performance to daptomycin
- The local application of exebacase could be a treatment option for the treatment of biofilm related device infections

References

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