ARE *STAPHYLOCOCCUS AUREUS* PVL TOXIN-POSITIVE ISOLATES CAUSING ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) ASSOCIATED WITH MORE SEVERE PRESENTATION OR WORSE OUTCOME?

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ABSTRACT

Objective: To determine if the presence of PVL toxin in *Staphylococcus aureus* isolates influences the presentation or clinical course of patients with ABSSSI.

Methods: Dalbavancin is a lipoglycopeptide antibiotic with activity against Gram-positive pathogens and a long half-life allowing for weekly dosing. DISCOVER 1 and 2 were identically designed, double-blind, double-dummy trials comparing dalbavancin with a regimen of vancomycin and an option to switch to oral linezolid in the treatment of ABSSSI. Panton-Valentine leukocidin (PVL) toxin analysis was performed on baseline *S. aureus* isolates. The size of the erythema associated with ABSSSI lesions was measured by ruler.

Results: Of 1312 patients enrolled in the DISCOVER program, 513 had *S. aureus* recovered from a baseline culture, of which 391 were tested for the presence of the PVL toxin.

Table 1. Area of Erythema Associated with *S. aureus* ABSSSI by PVL Toxin Production

Measured Area of Cellulitis	PVL Toxin Positive	PVL Toxin Negative
N	219	172
Mean (cm^2)*	362.5	312.2
SD	317.68	177.77
Median (cm^2)	262.5	276.3
Min, Max	79, 2150	80, 1058

*p value 0.467

Table 2. Systemic Signs of Infection by PVL Toxin Production in Patients with *S. aureus* ABSSSI

Systemic Signs	PVL Toxin Positive n/N (%)	PVL Toxin Negative n/N (%)	p value
Temperature ≥38°C	158/219 (72.1)	155/171 (90.6)	<0.001
WBC >12,000 Cells/mm^3	88/214 (41.1)	53/165 (32.1)	0.073
Elevated HS C-reactive Protein (mg/L)	194/219 (88.6)	149/172 (86.6)	0.559

Table 3. Response to Treatment

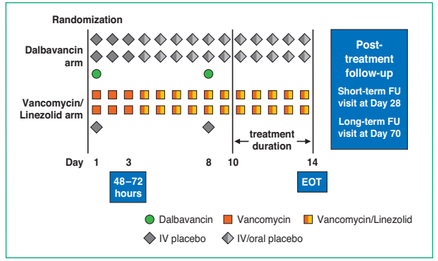
Clinical Response	PVL Toxin Positive n/N (%)	PVL Toxin Negative n/N (%)	p value
Early Response at 48–72 hours (ITT*)	179/220 (81.4)	155/172 (90.1)	0.018
Clinical Status at End of Treatment (ITT)	189/220 (85.9)	154/172 (89.5)	0.212

*Intention-to-treat analysis population

Conclusions: PVL toxin-positive *S. aureus* isolates are not associated with greater areas of erythema at baseline in patients with ABSSSI. Patients with a PVL toxin-positive isolate had lower rates of fever than those with a PVL toxin-negative isolate but had a higher frequency of leukocytosis. Early clinical response rates were lower for patients with PVL toxin-positive isolates. Patients with an ABSSSI due to a PVL toxin-positive *S. aureus* may respond more slowly to treatment than those with a PVL toxin-negative strain.

METHODS

Figure 1. Study Design: Studies DUR001-301/302



- Patients had:
  - Cellulitis, abscess or wound infection with erythema >75 cm^2 and
  - Either a fever, an elevated white blood cell count >12k cells/mm^3 or immature neutrophils >10%
- Patients received:
  - Dalbavancin 1 gram IV over 30 minutes on Day 1 and 500 mg IV on Day 8, or
  - Vancomycin 1 gram (or 15 mg/kg) IV every 12 hours (q12h) for at least three days with an option to switch to oral linezolid 600 mg q12h to complete 10–14 days of therapy.
- The primary endpoint was measured at 48–72 hours of therapy with success requiring both cessation of spread of the lesion and complete resolution of fever.
  - Secondary endpoints included an investigator assessment of outcome at Day 14 and Day 28
  - Efficacy results from both trials were pooled
- Data was analyzed for patients with *Staphylococcus aureus* isolated at baseline by the presence or absence of PVL toxin.

RESULTS

Table 1. PVL Toxin Status

	Staphylococcus aureus	
	PVL Positive n/N (%)	PVL Negative n/N (%)
Staphylococcus aureus	220/392 (56.1)	172/392 (43.9)
MSSA	92/259 (35.5)	167/259 (64.5)
MRSA	128/133 (96.2)	5/133 (3.8)

Table 2. Demographics for Patients with *Staphylococcus aureus* at Baseline

Category	PVL Positive N=220	PVL Negative N=172	p value
Mean Age (years)	41	51	<0.01
Male Gender, n (%)	143 (65.0)	108 (62.8)	0.65
Race, n (%)			
White	191 (86.8)	163 (94.8)	0.01
American Indian or Alaska	2 (0.9)	1 (0.6)	
Asian	2 (0.9)	2 (1.2)	
Black or African American	22 (10.0)	4 (2.3)	
Native Hawaiian or Other	1 (0.5)	1 (0.6)	
Other	2 (0.9)	1 (0.6)	
Region, n (%)			<0.01
North America	157 (71.4)	68 (39.5)	
Europe/Asia	63 (28.6)	104 (60.5)	
Location of Treatment, n/N (%)			<0.01
Inpatient	71/174 (40.8)	103/159 (64.8)	
Outpatient	103/174 (59.2)	56/159 (35.2)	
CrCl<30 mL/min, n/N (%)	0	2/169 (1.2)	
Mean BMI, (kg/m^2)	29.5	27.5	0.003
Elevated fasting glucose at baseline, n (%)	48 (21.8)	70 (40.7)	<0.01
History of Diabetes mellitus at baseline, n (%)	21 (9.5)	23 (13.4)	0.23
Met SIRS Criteria, n/N (%)	98/219 (44.8)	73/172 (42.4)	0.65
History of intravenous drug use, n (%)	49 (22.3)	54 (31.4)	0.04
Median lesion size (cm^2)	262.5	276.3	
Mean lesion size (cm^2)	362.5	312.2	0.47
Sub-type of Infection, n (%)			
Cellulitis	67 (30.5)	57 (33.1)	0.57
Major Abscess	115 (52.3)	55 (32.0)	<0.01
Wound Infection	38 (17.3)	60 (34.9)	<0.01

Table 3. Mean Scores of Local Signs of Infection

	PVL Positive		PVL Negative	
Local Signs	Mean Score*	Patients with Local Sign n (%)	Mean Score*	Patients with Local Sign n (%)
Erythema	2.5	218 (99.1)	2.5	171 (99.4)
Fluctuance	1.2	128 (58.2)	1.1	89 (51.7)
Heat/localized warmth	2.4	217 (98.6)	2.5	171 (99.4)
Purulent discharge	1.4	158 (71.8)	1.4	110 (64.0)
Tenderness to palpation	2.6	217 (98.6)	2.6	171 (99.4)
Pain Score	7.7	218 (99.1)	7.5	171 (99.4)

Scoring system for local signs except pain: Absent=0; Mild=1, Moderate=2, Severe=3

Table 4. Systemic Signs of Infection

Systemic Signs	PVL Toxin Positive n (%)	PVL Toxin Negative n (%)	p value
Temperature ≥38°C	158/219 (72.1)	155/171 (90.6)	<0.001
WBC >12,000 cells/mm^3	88/214 (41.1)	53/165 (32.1)	0.073
Bands ≥10%	23/177 (13.0)	35/153 (22.9)	0.019
Elevated HS C-reactive Protein (mg/L)	194/219 (88.6)	149/172 (86.6)	0.559

Table 5. Mean Duration of Antibiotic Therapy (days)

Study Drug Therapy	PVL Positive N=219	PVL Negative N=172	p value
Total Drug (days)	10.9	10.8	0.96
Oral Drug (days)	6.5	5.7	0.04
IV Drug (days)	3.6	4.5	0.01

Table 6. Clinical Success in Patients with *S. aureus* at Baseline by Presence of PVL Toxin

	PVL Toxin Positive			PVL Toxin Negative			Difference for "All" category (95% CI)
Timepoint	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	All n/N (%)	Dalbavancin n/N (%)	Vancomycin/ Linezolid n/N (%)	All n/N (%)	
Clinical response at 48–72 hours	96/120 (80.0)	83/100 (83.0)	179/220 (81.4)	71/79 (89.9)	84/93 (90.3)	155/172 (90.1)	−8.8 (−15.6, −1.7)
≥20% reduction in lesion size at 48–72 hours	113/120 (94.2)	90/100 (90.0)	203/220 (92.3)	76/79 (96.2)	89/93 (95.7)	165/172 (95.9)	−3.7 (−8.5, 1.3)
Investigator assessment of Success at Day 14	109/112 (97.3)	82/85 (96.5)	191/197 (97.0)	71/72 (98.6)	85/88 (96.6)	156/160 (97.5)	−0.5 (−4.4, 3.6)
Investigator assessment of Success at Day 28	92/95 (96.8)	72/75 (96.0)	164/170 (96.5)	67/68 (98.5)	83/85 (97.6)	150/153 (98.0)	−1.6 (−5.8, 2.5)

DISCUSSION

- Virtually all of the MRSA isolates and about a third of the MSSA isolates were PVL toxin producing strains.
- As compared with patients with a PVL toxin-negative strain, patients with a PVL toxin-producing *S. aureus* strain were more likely to be:
  - Younger
  - Enrolled in N. America
  - Have major abscess as sub-type of infection
- No difference in lesion size, frequency or severity of local signs of infection noted at baseline between the two groups.

CONCLUSIONS

- PVL toxin-positive *S. aureus* isolates are not associated with greater areas of erythema at baseline in patients with ABSSSI.
- Patients with a PVL toxin-positive isolate had lower rates of fever than those with a PVL toxin-negative isolate but had a higher frequency of leukocytosis.
- Early clinical response rates were lower for patients with a PVL toxin-positive strain. However, similar proportions of patients in the two groups achieved ≥20% reduction in lesion size at 48–72 hours.
- Patients with an ABSSSI due to a PVL toxin-positive *S. aureus* may have slower resolution of fever than those with a PVL toxin-negative strain.
- Additional work is needed to understand the effect of PVL toxin production on the clinical presentation and outcomes of ABSSSI.

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