

CLINICAL PRESENTATION OF ACUTE BACTERIAL SKIN AND SKIN STRUCTURE INFECTIONS (ABSSSI) BY BASELINE PATHOGEN IN THE DISCOVER PROGRAM

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ABSTRACT

Objective: To describe the clinical presentation of ABSSSIs caused by *Staphylococcus aureus* versus those caused by streptococcal spp. in patients enrolled in the dalbavancin phase 3 clinical trials.

Methods: DISCOVER 1 and DISCOVER 2 were double-blind, double-dummy, pharmacist-unblinded randomized trials that enrolled patients with cellulitis, abscess or wound/surgical site infection with erythema >75 cm² and either a fever, an elevated white blood cell count >12k cells/mm³ or immature neutrophils >10%. Eligible patients were randomized to receive dalbavancin 1 g IV on Day 1 and 500 mg on Day 8 or Vancomycin with an option to switch to oral linezolid to complete 10–14 days of therapy. Analyses were performed using pooled data from the two trials. Physical signs and symptoms were scored on a scale of 0–3 as absent, mild, moderate or severe; pain was measured on a scale of 1–10.

Results:

Demographics	<i>S. aureus</i> N=405	Streptococci N=73	p value
Mean Age, years	45.4	47.5	0.263
Male Gender, N (%)	256 (63.2)	38 (52.1)	0.072
Race, N (%)			
White	363 (89.6)	66 (90.4)	0.840
Black or African American	30 (7.4)	2 (2.7)	—
Asian	4 (1.0)	4 (5.5)	—
Geographic Region, N (%)			
North America	235 (58.0)	25 (34.2)	<0.001
Europe/Asia	170 (42.0)	48 (65.8)	—
Infection Type			
Cellulitis	131 (32.3)	32 (43.8)	0.057
Major Abscess	176 (43.5)	22 (30.1)	0.034
Wound Infection	98 (24.2)	19 (26.0)	0.738

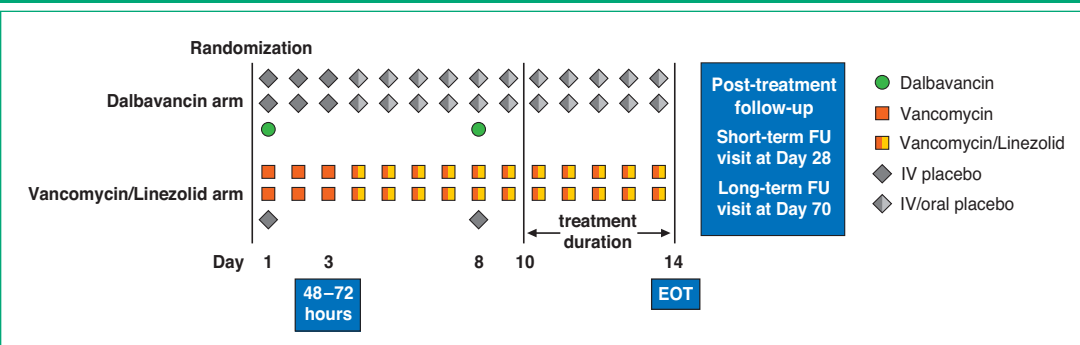
Systemic Sign of Infection	<i>S. aureus</i> n/N (%)	Streptococci n/N (%)	p value
Temperature ≥38°	326 (80.9)	53 (73.6)	0.157
WBC count >12,000 cells/mm ³	145 (37.0)	40 (59.7)	<0.001
Bands ≥10%	59 (17.4)	18 (32.1)	<0.001
Systemic Inflammatory Response Syndrome	178 (44.1)	39 (53.4)	0.140

Local Sign/Symptom	<i>S. aureus</i>	Streptococci
Erythema	2.5	2.5
Fluctuance	1.1	1.1
Heat/localized warmth	2.4	2.6
Purulent discharge	1.4	1.1
Tenderness to palpation	2.6	2.5
Pain score	7.6	7.4
Lesion size (cm ²)*	339.2	650.4

Conclusions: In the DISCOVER ABSSSI trials, a streptococcal etiology was more common in Europe/Asia than in North America. As compared with staphylococcal infection, streptococcal infection was associated with larger skin lesions and was more likely to be accompanied by leukocytosis, >10% band forms and SIRS criteria.

METHODS

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



- Patients had:
 - cellulitis, abscess or wound infection with erythema >75 cm² and
 - either a fever, an elevated white blood cell count >12k cells/mm³ 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 by pathogen isolated at baseline.

RESULTS

Characteristic	<i>Staphylococcus aureus</i> N=405 n (%)	Streptococcus species N=73 n (%)	p value
Mean Age (years)	45.4	47.5	0.263
Male Gender	256 (63.2)	38 (52.1)	0.072
Race			
White	363 (89.6)	66 (90.4)	0.84
American Indian or Alaska	3 (0.7)	1 (1.4)	—
Asian	4 (1.0)	4 (5.5)	—
Black or African American	30 (7.4)	2 (2.7)	—
Other	5 (1.2)	0	—
Region			
North America	235 (58.0)	25 (34.2)	<0.001
Rest of World	170 (42.0)	48 (65.8)	
Sub-type of Infection			
Cellulitis	131 (32.3)	32 (43.8)	0.057
Major Abscess	176 (43.5)	22 (30.1)	0.034
Wound Infection	98 (24.2)	19 (26.0)	0.738
Diabetes Mellitus			
History	44 (10.9)	8 (11.0)	0.981
Elevated fasting glucose*	121 (29.9)	27 (37.0)	0.227
History of IVDU	106 (26.2)	14 (19.2)	0.205
Met SIRS criteria	178 (44.0)	39 (53.4)	0.140

*Diagnostic of prediabetes/diabetes

Local Signs	<i>Staphylococcus aureus</i>	Streptococcus species
Erythema (mean score*)	2.5	2.5
Fluctuance (mean score*)	1.1	1.1
Heat/localized warmth (mean score*)	2.4	2.6
Purulent discharge (mean score*)	1.4	1.1
Tenderness to palpation (mean score*)	2.6	2.5
Mean pain score	7.6	7.4
Mean lesion size (cm ²)**	339.2	650.4

*Absent=0, Mild=1, Moderate=2, Severe=3; **p<0.001

Systemic Sign	<i>Staphylococcus aureus</i> n/N (%)	Streptococcus species n/N (%)	p value
Temperature ≥38°C	326/403 (80.9)	53/72 (73.6)	0.157
WBC >12,000 cells/mm ³	145/392 (37.0)	40/67 (59.7)	<0.001
Bands ≥10%	59/340 (17.4)	18/56 (32.1)	<0.001

	<i>Staphylococcus aureus</i> N=405 N (%)	Streptococcus species N=73 N (%)	p value
Elevated ASO ¹	117 (28.9)	34 (46.6)	0.003
Elevated DNase	94 (23.2)	36 (49.3)	<0.001
Elevated either DNase/ASO	167 (41.2)	50 (68.5)	<0.001
Elevated ASO and DNase	44 (10.9)	20 (27.4)	<0.001

¹ Elevated ASO titre was defined as a value of ≥200 kIU/L or a 4 fold elevation from baseline

Timepoint	<i>Staphylococcus aureus</i>			Streptococcus species			Difference for "All" category (95% CI)
	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	172/208 (82.7)	170/197 (86.3)	342/405 (84.4)	30/39 (76.9)	24/34 (70.6)	54/73 (74.0)	10.5 (0.9, 22.1)
≥20% reduction in lesion size at 48–72 hours	196/208 (94.2)	183/197 (92.9)	379/405 (93.6)	33/39 (84.6)	27/34 (79.4)	60/73 (82.2)	11.4 (3.8, 21.9)
Clinical Success at EOT	172/191 (90.1)	164/177 (92.7)	336/368 (91.3)	35/38 (92.1)	28/31 (90.3)	63/69 (91.3)	0.0 (–5.8, 9.3)
Investigator assessment of Success at EOT	187/191 (97.9)	171/177 (96.6)	358/368 (97.3)	37/38 (97.4)	29/31 (93.5)	66/69 (95.7)	1.6 (–2.0, 9.4)
Investigator assessment of Success at SFU	164/169 (97.0)	159/164 (97.0)	323/333 (97.0)	31/32 (96.9)	26/28 (92.9)	57/60 (95.0)	2.0 (–2.1, 10.8)

CONCLUSIONS

- In the DISCOVER ABSSSI trials, a streptococcal etiology was more common in Europe/Asia than in North America, presumably due to more cellulitis in Europe.
- As compared with staphylococcal infection, streptococcal infection was associated with larger skin lesions; was more likely to be accompanied by leukocytosis, left shift, elevation of ASO/DNase titres; and had lower early response rates.
- Similar clinical success rates for the treatment of staphylococcal and streptococcal ABSSSI were seen with dalbavancin and comparators at 48–72 hours, end of treatment and short-term follow-up.

