Methicillin-Resistant *Staphylococcus aureus* Epidemiology and Clinical Response in Tigecycline Clinical Trials

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ABSTRACT (REVISED)

Background: Methicillin-resistant *Staphylococcus aureus* (MRSA) is one of the most common pathogens causing skin infections. Tigecycline (TGC) is an expanded broad-spectrum glycylcycline approved for the treatment of complicated skin and skin structure infections (cSSSI) excluding diabetic foot infection (DFI). The current investigation examined the infection epidemiology and clinical response of patients with MRSA cSSSI or diabetic foot infection (DFI) within the TGC clinical trials.

Methods: Data from patients hospitalized with a cSSSI or DFI and with a baseline MRSA infection from six TGC clinical trials were pooled and examined. Baseline MRSA isolates from cSSSI and DFI were characterized by staphylococcal cassette chromosome *mec* (SCC*mec*) type and Panton-Valentine leukocidin (PVL) status. The epidemiology of infections associated with SCC*mec* type IV (i.e. community-associated MRSA [CA-MRSA]) vs. other SCC*mec* types (non–CA-MRSA) was compared.

Results: 378 MRSA skin infections were identified, including 79 DFI (65.9% type IV, 33.6% other types, missing 0.5%). Subjects with CA-MRSA compared with non–CA-MRSA were younger (48.0 vs. 54.7), and more likely to be male, and reside in the USA (65.1% vs. 32.3%). Clinical infections with CA-MRSA were more likely to be spontaneous infections (43.4% vs. 23.6%) resulting in major abscesses (37.0% vs. 13.4%), carry the PVL gene (65.1% vs. 3.9%), and less likely to be polymicrobial (23.7% vs. 40.9%). Therapy duration (9.0 vs. 10.5 days) and length of stay (12.7 vs. 21.9 days) were shorter in CA-MRSA cSSSI but not in CA-MRSA DFI versus non–CA-MRSA DFI infections. Clinical efficacy between evaluable TGC and comparator (COM) subjects was similar for MRSA (TGC 76.0% and 75.0%), for CA-MRSA (70.9% vs. 74.7%) and MRSA/PVL+ status (74.2% vs. 76.5%).

Conclusions: CA-MRSA clinical presentations were different from infections with other SCC*mec* types; however, TGC was effective in the treatment of MRSA infections regardless of SCC*mec* type or PVL status.

INTRODUCTION

- Most skin infections are caused by *Streptococcus pyogenes* or *Staphylococcus aureus*, including the now epidemic community-associated methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[1]
- Tigecycline is a broad-spectrum glycylcycline approved for the treatment of complicated skin and skin structure infections (cSSSI), including those caused by MRSA.[2]
- Tigecycline did not meet the primary efficacy endpoints in a trial of diabetic foot infection (DFI) and it is not approved for this indication.[2-4]
- Recently updated clinical practice guidelines for the treatment of MRSA infection do not include the use of tigecycline for the treatment of CA-MRSA skin infections due to: (1) the increased all-cause mortality observed across all phase 3 and 4 clinical trials in tigecycline-treated patients versus comparator-treated patients; and (2) the available alternatives to treat MRSA infections.[2,5]

OBJECTIVE

- To examine the infection epidemiology and clinical response of patients with MRSA cSSSI or DFI within the tigecycline clinical trials.

METHODS

Study Design and Treatment

- A pooled analysis was conducted with patients hospitalized with a MRSA cSSSI or DFI from 6 phase 3 and 4 global trials conducted from 2002 through 2008 (**Table 1**).[3,4,6-9]

Table 1: Description of trials included in analysis

Study name (reference)	Design (total no. of treated patients)	Tigecycline regimen	Comparator regimen	Comments
300[4]	Phase 3, randomized, double-blind (N=573)	100 mg then 50 mg every 12 hours for ≤14 days	Combination of vancomycin 1 g + aztreonam 2 g every 12 hours for ≤14 days	Aztreonam could be discontinued after 48 hours according to the investigator's clinical judgment
305[3]	Phase 3, randomized, double-blind (N=543)	100 mg then 50 mg every 12 hours for ≤14 days	Combination of vancomycin 1 g + aztreonam 2 g every 12 hours for ≤14 days	Aztreonam could be discontinued after 48 hours according to the investigator's clinical judgment
307[7]	Phase 3, randomized, double-blind, resistant pathogen study (MRSA, n=156) (VRE, n=15)	100 mg then 50 mg every 12 hours for ≤28 days	Vancomycin 1 g every 12 hours (with dose adjustment allowed) for ≤28 days	Hospitalized patients were randomized in a 3:1 ratio to either tigecycline or vancomycin
309[8]	Phase 3, open-label, noncomparative, resistant pathogen study of select Gram-negative resistant pathogens (N=112)	100 mg then 50 mg every 12 hours for ≤28 days	—	Subjects coinfected with MRSA were included in this analysis
319[9] (DFI study)	Phase 3, randomized, double-blind (N=944)	150 mg every 24 hours for ≤28 days	Ertapenem 1g/24 hours for ≤28 days; adjunctive therapy with vancomycin, administered according to the package insert, could be provided for the treatment of MRSA in the ertapenem treatment group	Only patients without osteomyelitis were included in this analysis
900[6]	Phase 4, randomized, open-label (N=531)	100 mg then 50 mg every 12 hours for ≤14 days	Ampicillin-sulbactam 1.5–3.0 g every 6 hours or amoxicillin clavulanate 1.2 g every 6–8 hours plus adjunctive vancomycin 1 g every 12 hours for ≤14 days	Dose adjustment of all test articles was allowed

MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; DFI, diabetic foot infection

Analysis Populations

- All patients with a MRSA infection who received ≥1 dose of study medication in the modified intent-to-treat study population were used to describe demographic variables.
- Microbiologically evaluable patients with a MRSA infection met all prespecified evaluability criteria for the respective study protocols including met all inclusion/exclusion criteria, had a test of cure response of cure or failure, and had MRSA isolated from skin or blood cultures at baseline.

Microbiologic Assessments

- Blood cultures and aerobic and anaerobic cultures from the primary site of infection, where appropriate, were collected at baseline.
- Isolate identification was performed at Covance Central Laboratory Services.
- Staphylococcal cassette chromosome *mec* (SCC*mec*) and Panton-Valentine leukocidin (PVL) typing was determined by multiplex polymerase chain reaction.
- CA-MRSA was defined in this study as the presence of SCC*mec* type IV.

Statistical Analysis

- To assess statistical differences in the distribution of baseline characteristics between treatment groups, one-way analysis of variance was used for continuous variables and Fisher exact test or chi-square test, as appropriate, was used for categorical variables.
- *P* values <0.05 (2-sided) were considered statistically significant.
- For analysis of clinical outcomes, risk difference and 95% confidence intervals were calculated for the difference between treatment groups. 95% confidence intervals were calculated by using the Wilson score method corrected for continuity.

RESULTS

- We identified 378 patients with MRSA skin infections, including 79 patients with a DFI.
- Approximately three-quarters of this subgroup (287 of 378 patients with MRSA; 75.9%) were included in the microbiologically evaluable population, including 217 of 299 patients with cSSSI (72.6%) and 70 of 79 patients with DFI (88.6%).
- 65.9%, 33.6%, and 0.5% of MRSA were CA-MRSA, non–CA-MRSA, or unknown.

Demographics and Patient Characteristics

- Relative to patients with non–CA-MRSA infections, patients with a CA-MRSA infection were younger, male, and resided in the United States (**Table 2**).
- Patients with a CA-MRSA infection were more likely to have spontaneous infections with major skin abscesses, a monomicrobial infection, and a MRSA isolate that was PVL positive than patients with a non–CA-MRSA infection.
- Diabetes and peripheral vascular disease were more common in patients with non–CA-MRSA infections.

Table 2: Demographic and baseline characteristics of the modified intent-to-treat population

Characteristic	CA-MRSA (N=249)	Non–CA-MRSA (N=127)	*P* value
Mean age ± SD, y	47.98 ± 15.94	54.67 ± 15.90	<0.001
Male gender, n (%)	165 (66.27)	70 (55.12)	0.035
Ethnic origin, n (%)			<0.001
White	165 (66.27)	107 (84.25)	
Black	44 (17.67)	3 (2.36)	
Hispanic	22 (8.84)	7 (5.51)	
Asian	10 (4.02)	5 (3.94)	
Other	8 (3.21)	5 (3.94)	
Mean body mass index ± SD, kg/m^2	28.69 ± 7.58	30.15 ± 10.76	0.130
Infection type, n (%)[a]			<0.001
Deep or extensive cellulitis	81 (32.53)	41 (32.28)	
Major abscesses	92 (36.95)	17 (13.39)	
Diabetic foot infection	44 (17.67)	35 (27.56)	
Infected ulcers	14 (5.62)	17 (13.39)	
Burns	5 (2.01)	4 (3.15)	
Cause of the original infection, n (%)[a]			<0.001
Spontaneous infection	108 (43.37)	30 (23.62)	
Previous surgery	20 (8.03)	36 (28.35)	
Trauma	37 (14.86)	12 (9.45)	
New/acute onset	26 (10.44)	18 (14.17)	
Worsening of prior infection	18 (7.23)	17 (13.39)	
Therapy duration, cSSSI			
N	205	92	
Mean days ± SD	9.02 ± 4.25	10.49 ± 4.25	0.006
Therapy duration, DFI			
N	44	35	
Mean days ± SD	14.55 ± 8.33	12.97 ± 6.79	0.369
Protocol, n (%)			<0.001
300	69 (27.71)	11 (8.66)	
305	19 (7.63)	9 (7.09)	
307	49 (19.68)	46 (36.22)	
309	3 (1.20)	3 (2.36)	
319	44 (17.67)	35 (27.56)	
900	65 (26.10)	23 (18.11)	
Country, n (%)[a]			<0.001
United States	162 (65.06)	41 (32.28)	
Romania	4 (1.61)	12 (9.45)	
Ukraine	12 (4.82)	4 (3.15)	
Bulgaria	1 (0.40)	14 (11.02)	
Russian Federation	9 (3.61)	4 (3.15)	
Mean creatinine clearance ± SD, mL/min	119.19 ± 50.59	103.13 ± 49.21	0.004
Diabetes, n (%)	90 (36.14)	68 (53.54)	0.001
Peripheral vascular disease, n (%)	19 (9.31)[b]	19 (20.65)[c]	0.007
Prior antibiotic failure, n (%)	123 (50.62)[d]	73 (59.35)[e]	0.114
Mono- or polymicrobial infection, n (%)			<0.001
Monomicrobial	190 (76.31)	75 (59.06)	
Polymicrobial	59 (23.69)	52 (40.94)	
PVL, n (%)	162 (65.06)	5 (3.94)	<0.001
Bacteremia, n (%)	9 (3.61)	7 (5.51)	0.389
Length of stay in hospital, cSSSI			
N	192	92	
Mean days ± SD	12.67 ± 12.51	21.87 ± 16.70	<0.001
Length of stay in hospital, DFI			
N	44	35	
Mean days ± SD	19.00 ± 13.88	15.69 ± 8.39	0.218

[a] Only the 5 most frequent categories shown; *P* value was calculated based on all categories
[b] N=204, [c] N=92, [d] N=243, [e] N=123
Missing values were not included in the analysis
CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; SD, standard deviation; cSSSI, complicated skin and skin structure infection; DFI, diabetic foot infection; PVL, Panton-Valentine leukocidin

- For the different indications, therapy duration (9.0 vs 10.5 days; *P*=0.006) and length of stay (12.7 vs 21.9 days; *P*<0.001) were shorter in CA-MRSA cSSSI (but not in CA-MRSA DFI vs non–CA-MRSA DFI infections).
- In patients with DFI, no baseline differences were detected between patients with CA-MRSA and non–CA-MRSA, except that patients with CA-MRSA had a higher incidence of PVL-positive isolates (31.8% vs 5.7%; *P*=0.0004).

Efficacy

- Tigecycline and comparator had similar clinical cure rates for MRSA skin infections overall (76.0% vs 75.0%, respectively) and by indication (cSSSI and DFI) (**Table 3**).
- Tigecycline and comparator had similar clinical cure rates for MRSA skin infections by CA-MRSA infections, PVL status, and CA-MRSA/PVL status (**Table 4**).

Table 3: Clinical cure rates at the test of cure visit in the ME population

	Treatment					
	Tigecycline		Comparator		Treatment difference	
Population	n/N (%)	95% CI[a]	n/N (%)	95% CI[a]		95% CI[b]
Total ME	133/175 (76.0)	57.0 to 82.0	84/112 (75.0)	56.3 to 81.3	1.0	–9.3 to 12.0
cSSSI	104/131 (79.4)	59.5 to 84.5	67/86 (77.9)	58.4 to 83.4	1.5	–9.9 to 13.8
DFI	29/44 (65.9)	49.4 to 74.4	17/26 (65.4)	49.0 to 91.3	0.5	–22.5 to 25.3

[a] 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson
[b] 95% CI for differences between treatment groups is calculated by using the Wilson score method corrected for continuity
CI, confidence interval; ME, microbiologically evaluable; cSSSI, complicated skin and skin structure infection; DFI, diabetic foot infection

Table 4: Clinical cure rates at the test of cure visit stratified by MRSA infection type in the ME population

		Treatment					
		Tigecycline		Comparator		Treatment difference	
Status		n/N (%)	95% CI[a]	n/N (%)	95% CI[a]		95% CI[b]
CA-MRSA							
Yes		73/103 (70.9)	53.2 to 78.2	56/75 (74.7)	56.0 to 81.0	–3.8	–17.2 to 10.5
No		60/72 (83.3)	62.5 to 87.5	26/35 (74.3)	55.7 to 93.6	9.0	–7.7 to 28.4
PVL+							
Yes		46/62 (74.2)	55.6 to 80.6	39/51 (76.5)	57.4 to 82.4	–2.3	–18.8 to 15.1
No		87/113 (77.0)	57.7 to 82.7	43/59 (72.9)	54.7 to 79.7	4.1	–9.7 to 19.3
CA-MRSA	PVL+						
Yes	Yes	43/59 (72.9)	54.7 to 79.7	38/50 (76.0)	57.0 to 82.0	–3.1	–20.1 to 14.7
Yes	No	30/44 (68.2)	51.1 to 76.1	18/25 (72.0)	54.0 to 93.0	–3.8	–25.8 to 21.3
No	Yes	3/3 (100)	25.0 to 100	1/1 (100)	25.0 to 100	0.0	–69.0 to 94.5
No	No	57/69 (82.6)	62.0 to 87.0	25/34 (73.5)	55.1 to 93.4	9.1	–8.2 to 28.8

[a] 95% CI for individual treatment groups is calculated by using the methods of Clopper and Pearson
[b] 95% CI for differences between treatment groups is calculated by using the Wilson score method corrected for continuity
ME, microbiologically evaluable; CI, confidence interval; CA-MRSA, community-associated methicillin-resistant *Staphylococcus aureus*; PVL, Panton-Valentine leukocidin

Safety

- Six tigecycline patients and 1 comparator patient with baseline MRSA died during the clinical trials (*P*=0.248).
- Adverse events with an outcome of death reported in the patients who died are listed in **Table 5**.

Table 5: Number of patients reporting adverse events with an outcome of death in the modified intent-to-treat population

Adverse event Preferred term(s)	Tigecycline	Comparator
Deaths	6	1
Carcinoma	1	0
Coronary artery disorder	1	0
General physical health deterioration	1	0
Heart arrest	1	0
Hypotension	1	0
Pulmonary embolus, shock	1	0
Chronic obstructive airway disease	0	1

CONCLUSIONS

- CA-MRSA presentations were different from infections caused by non–CA-MRSA.
- Tigecycline was effective in the treatment of MRSA infections regardless of SCC*mec* type or PVL status.
- Tigecycline deaths in patients with baseline MRSA were generally unrelated to the primary infection under study.

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