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Extended-Spectrum Beta-lactamase Infections and Clinical Response in Tigecycline Clinical Trials

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ABSTRACT (REVISED)

Background: Tigecycline (TGC) is an expanded broad-spectrum antibiotic with in-vitro activity against Gram-negative pathogens, including extended-spectrum beta-lactamase (ESBL)-producing organisms. It is approved in the US for the treatment of complicated skin and skin structure infection (cSSSI), complicated intra-abdominal infection (cIAI) and community-acquired bacterial pneumonia (CABP). In addition to the approved indications, TGC has been studied in clinical trials in patients with hospital-acquired pneumonia (HAP) and diabetic foot infection (DFI). The purpose of this current analysis was to compare the efficacy of TGC versus comparators (COM) in treating infections caused by ESBL-producing organisms in clinically evaluable (CE) subjects from multinational phase 3–4 clinical trials.

Methods: Hospitalized subjects enrolled in phase 3–4 trials of TGC and infected with ESBL-producing organisms at baseline were identified. Clinical and microbiological characteristics of infections were summarized and clinical response by indication was analyzed.

Results: 219 (TGC 123; COM 96) subjects with baseline ESBL infections were identified in the TGC trials, of which 162 (TGC 89; COM 73) were clinically evaluable. 92.2% of ESBL infections occurred outside of North America with India contributing 32.9%. The infections were most commonly identified in cIAI (35.6%) and in HAP (32.9%) clinical trials. More TGC subjects were prior antibiotic failures (45.5% vs. 25.0%) and had concomitant baseline bacteremia (16.3% vs. 8.3%). Clinical efficacy by indication is shown in **Table 3**. No decrease in the rate of cure was found in organisms with increasing TGC minimum inhibitory concentrations (MICs).

Conclusions: Tigecycline demonstrated similar efficacy vs comparators in patients with two approved indications (cIAI and cSSSI) due to ESBL+ *Enterobacteriaceae* but had lower efficacy in trials that did not meet their primary endpoints (HAP, DFI) in subjects with ESBLs.

INTRODUCTION

- Extended-spectrum beta-lactamases (ESBL)–producing organisms, including cefotaxime-resistant, have spread globally and infections with these organisms often result in delayed effective therapy and increased mortality.[1]
- Tigecycline is a broad-spectrum glycylcycline with in vitro activity against Gram-positive, Gram-negative, and anaerobic organisms, including Gram-negative resistant pathogens producing ESBL.[2]
- Tigecycline is approved for the treatment of complicated skin and skin structure infections (cSSSI), complicated intra-abdominal infection (cIAI), and community-acquired bacterial pneumonia (CABP).[3]
- Tigecycline did not meet the primary efficacy endpoints in trials of hospital-acquired pneumonia (HAP) and diabetic foot infection[4,5] and is not approved for these indications.

OBJECTIVE

- The purpose of this current analysis was to compare the efficacy of tigecycline versus comparator in treating serious infections caused by ESBL-producing organisms.

METHODS

Study Design and Treatment

- A pooled analysis was conducted of patients hospitalized with an infection caused by an ESBL-producing organism at baseline who were included in phase 3 and 4 studies (**Table 1**).[4-16]

Analysis Populations

- All patients with an ESBL infection at baseline who received ≥1 dose of study medication were included in the modified intent-to-treat (mITT) study population.
- Clinically evaluable (CE) patients with an ESBL infection were those who met all prespecified evaluability criteria for the respective studies including met all inclusion/exclusion criteria, had response of cure or failure at the test-of-cure visit, and had an ESBL-producing pathogen isolated from the primary site of infection or blood cultures at baseline.
  - Clinical efficacy was determined at the test-of-cure visit as defined in each of the individual studies.

Microbiologic Assessments

- Culture collection was performed as defined in the individual study protocol.
- Isolate identification was performed at Covance Central Laboratory Services.
- ESBL detection was performed by antimicrobial agar diffusion using E-test ESBL strips.
- Superinfection was defined as on-therapy emergence of a new isolate at the site of the infection with emergence or worsening of signs and symptoms of infection (ie, deemed a clinical failure).

Statistical Analysis

- To assess statistical differences in the distribution of baseline characteristics between treatment groups in the mITT population, 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.

Table 1: Description of trials included in the ESBL analysis

Study name (reference)	Design (total no. of treated patients)	Tigecycline regimen	Comparator regimen	Comments
cSSSI				
300[6]	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[7]	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
900[8]	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
RP				
307[9]	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[10]	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	—	—
DFI				
319[4]	Phase 3, randomized, double-blind (N=944)	150 mg every 24 hours for ≤28 days	Ertapenem 1 g every 24 hours for ≤28 days; adjunctive therapy with vancomycin, administered according to the package insert, could be provided for adjunctive therapy for the treatment of MRSA for the ertapenem treatment group	Only patients without osteomyelitis were included in this analysis
cIAI				
301[11]	Phase 3, randomized, double-blind (N=825)	100 mg then 50 mg every 12 hours for ≤14 days	Imipenem 500 mg every 6 hours for ≤14 days	Imipenem dose adjusted based on weight and creatinine clearance
306[12]	Phase 3, randomized, double-blind (N=817)	100 mg then 50 mg every 12 hours for ≤14days	Imipenem 500 mg every 6 hours for ≤28 days	Imipenem dose adjusted based on weight and creatinine clearance
315[13]	Phase 4, randomized, open-label (N=467)	100 mg then 50 mg every 12 hours for ≤14 days	Ceftriaxone 2 g/d + metronidazole 1–2 g/d for ≤14 days	Metronidazole given in divided doses
400[14]	Phase 4, randomized, open-label (N=467)	100 mg then 50 mg every 12 hours for ≤14 days	Ceftriaxone 2 g/d + metronidazole 1–2 g/d for ≤14 days	Metronidazole given in divided doses
CABP				
308[15]	Phase 3, randomized, double-blind (N=418)	100 mg then 50 mg every 12 hours for ≤14 days	Levofloxacin 500 mg daily	—
313[16]	Phase 3, randomized, double-blind (N=428)	100 mg then 50 mg every 12 hours for ≤14 days	Levofloxacin 500 mg daily or twice daily	—
HAP				
311[5]	Phase 3, randomized, double-blind (N=934)	100 mg then 50 mg every 12 hours for ≤14 days	Imipenem 500–1000 mg every 8 hours	Ceftazidime and an aminoglycoside were allowed as adjunctive therapy in the tigecycline patients, and vancomycin and an aminoglycoside were allowed as adjunctive therapy in comparator patients

cSSSI, complicated skin and skin structure infections; RP, resistant pathogen; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant enterococci; DFI, diabetic foot infections; cIAI, complicated intra-abdominal infections; CABP, community-acquired bacterial pneumonia; HAP, hospital-acquired pneumonia

- To assess clinical responses, the rates of cure and 95% confidence intervals (CIs) were calculated in the CE population. The method used to compute the 95% CIs for an individual treatment group was the "exact" method of Clopper and Pearson. The method used to compute the 95% CIs for the difference between treatment groups was Wilson score method corrected for continuity.

RESULTS

- We identified 219 patients (tigecycline, 123; comparator, 96) with baseline ESBL infections in the phase 3 and 4 tigecycline clinical trials.
- Of these patients, 162 (74%) were clinically evaluable, including 89 tigecycline-treated patients (72%) and 73 comparator-treated patients (76%).

Demographics and Patient Characteristics

- Baseline demographics and clinical characteristics were mostly well balanced between the treatment groups of the mITT and CE populations (**Table 2**).
- The mean therapy duration was approximately 11 days (**Table 2**).
- 92.2% of ESBL infections occurred outside of North America, with India contributing 32.9%.

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

Characteristic	Tigecycline (N=123)	Comparator (N=96)	*P* value
Mean age ± SD, y	52.28 ± 17.85	51.55 ± 17.84	0.763
Gender, n (%)			0.473
Male	90 (73.17)	66 (68.75)	
Ethnic origin, n (%)			0.783
White	54 (43.90)	38 (39.58)	
Asian	13 (10.57)	12 (12.50)	
Hispanic	8 (6.50)	9 (9.38)	
Oriental (Asian)	8 (6.50)	4 (4.17)	
Black or African American	4 (3.25)	1 (1.04)	
Asian Indian	2 (1.63)	1 (1.04)	
Other	34 (27.64)	31 (32.29)	
Mean weight ± SD, kg	68.59 ± 18.25	69.08 ± 17.11	0.840
Infection type, n (%)			0.067
Complicated intra-abdominal infection	39 (31.71)	39 (40.63)	
Hospital-acquired pneumonia	38 (30.89)	34 (35.42)	
Complicated skin and skin structure infection	25 (20.33)	7 (7.29)	
Diabetic foot infection	17 (13.82)	15 (15.63)	
Bacteremia	3 (2.44)	0	
Community-acquired bacterial pneumonia	1 (0.81)	1 (1.04)	
Mean therapy duration ± SD, d	10.66 ± 5.37	11.10 ± 5.65	0.552
Country, n (%)[a]			0.273
India	36 (29.27)	36 (37.50)	
Ukraine	21 (17.07)	17 (17.71)	
China	7 (5.69)	4 (4.17)	
Mexico	7 (5.69)	3 (3.13)	
Romania	5 (4.07)	5 (5.21)	
Russian Federation	6 (4.88)	4 (4.17)	
South Africa	6 (4.88)	3 (3.13)	
United States	4 (3.25)	2 (2.08)	
Prior antibiotic failure, n (%)	56 (45.53)	24 (25.00)	0.002
Mono- or polymicrobial infection, n (%)			0.185
Monomicrobial	43 (34.96)	42 (43.75)	
Polymicrobial	80 (65.04)	54 (56.25)	
Bacteremia, n (%)	20 (16.26)	8 (8.33)	0.081

[a] Countries shown are United States and those that included ≥4% of the total population; *P* value was calculated based on all countries in the analysis
SD, standard deviation

Efficacy

- Clinical efficacy for tigecycline and comparator for each of the indications is shown in **Table 3**.
- Thirty-three tigecycline-treated patients (27%) and 15 comparator-treated patients (16%) discontinued therapy (*P*=0.050).
  - No significant differences between groups were found for discontinuation due to any reason, including efficacy (6% vs 4%; *P*=0.759) and adverse event (11% vs 7%; *P*=0.361).
- Clinical success rates by infection type and pathogen are shown in **Table 4**.
- Clinical efficacy did not decrease with increasing minimum inhibitory concentration of the pathogens (data not shown).
- Tigecycline cured 10/15 (67%) of patients with baseline bacteremia compared with 4/4 (100%) comparator patients (**Table 5**).
- Superinfection occurred in 5 tigecycline-treated patients (2 HAP; 1 each cIAI, cSSSI, and diabetic foot infection) and 2 comparator-treated patients (both HAP).

Table 3: Clinical success rates by infection type in the clinically evaluable population

Infection type, n/N (%)	Tigecycline (N=89)	Comparator (N=73)	Treatment difference	95% CI
Community-acquired bacterial pneumonia	1/1 (100.0)	1/1 (100.0)	0	−94.5 to 94.5
Complicated intra-abdominal infection	22/28 (78.6)	26/31 (83.9)	−5.3	−27.7 to 16.8
Complicated skin and skin structure infection	8/10 (80.0)	5/7 (71.4)	8.6	−34.2 to 52.9
Diabetic foot infection	4/11 (36.4)	9/14 (64.3)	−27.9	−60.3 to 15.1
Hospital-acquired pneumonia	13/20 (65.0)	19/20 (95.0)	−30.0	−54.5 to −1.2
Resistant pathogen[a]	13/19 (68.4)	NA	NA	NA

[a] From the noncomparative 309 study
CI, confidence interval; NA, not available

Table 4: Clinical success rates by infection type and pathogen in the clinically evaluable population

Infection type	Pathogen	Tigecycline, n/N (%)	Comparator, n/N (%)
Bacteremia	*Klebsiella pneumoniae*	1/2 (50.0)	—
Community-acquired bacterial pneumonia	*Klebsiella pneumoniae*	1/1 (100)	1/1 (100)
Complicated intra-abdominal infection	*Acinetobacter calcoaceticus*	—	2/2 (100)
	Citrobacter freundii complex	—	1/2 (50.0)
	Escherichia coli	10/18 (55.6)	15/19 (78.9)
	Klebsiella pneumoniae	13/14 (92.9)	8/8 (100)
	Proteus mirabilis	1/2 (50.0)	—
Complicated skin and skin structure infection	*Acinetobacter calcoaceticus*	—	1/1 (100)
	Acinetobacter haemolyticus	1/1 (100)	—
	Acinetobacter johnsonii	1/1 (100)	—
	Acinetobacter lwoffii	1/1 (100)	—
	Enterobacter cloacae	2/2 (100)	—
	Escherichia coli	5/7 (71.4)	3/4 (75.0)
	Klebsiella pneumoniae	6/7 (85.7)	1/2 (50.0)
	Proteus mirabilis	4/4 (100)	—
Diabetic foot infection	*Escherichia coli*	2/6 (33.3)	5/7 (71.4)
	Klebsiella pneumoniae	1/4 (25.0)	3/5 (60.0)
	Proteus mirabilis	1/1 (100)	1/2 (50.0)
Hospital-acquired pneumonia	*Escherichia coli*	6/8 (75.0)	9/9 (100)
	Klebsiella pneumoniae	9/14 (64.3)	9/10 (90.0)
	Proteus mirabilis	—	1/1 (100)

Table 5: Clinical success rates in patients with bacteremia by primary infection type in the clinically evaluable population

Primary infection type	Tigecycline, n/N	Comparator, n/N
Bacteremia	1/2	—
Complicated intra-abdominal infection	2/4	1/1
Complicated skin and skin structure infection	5/5	—
Hospital-acquired pneumonia	2/4	3/3

CONCLUSIONS

- Infections with ESBL-producing pathogens in tigecycline clinical trials were most common in patients with cIAI and HAP and mostly observed outside North America.
- The efficacy of tigecycline in patients with ESBL pathogen infections was similar to comparator for its approved indications but was lower for indications for which it did not meet its primary endpoints in clinical trials.

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