Journal of Microbiology, Immunology and Infection (2011) 44, 116—124

available at www.sciencedirect.com

ScienceDirect

journal homepage: www.e-jmii.com

ORIGINAL ARTICLE

Efficacy and safety of tigecycline monotherapy compared with vancomycin-aztreonam in the treatment of complicated skin and skin structure infections in patients from India and Taiwan

Yin-Ching Chuang [a,*], Chia-Ming Chang [b], Sacchidanand Aradhya [c], Bheerappa Nagari [d], Vishwanath Pai [e], Nathalie Dartois [f], Sylvie Jouve [f], Angel Cooper [g]

[a] *Chi Mei Medical Center, Department of Internal Medicine, Yung Kang Dist., Tainan City, Taiwan*
[b] *National Cheng Kung University Hospital, Department of Internal Medicine, Tainan City, Taiwan*
[c] *Victoria Hospital, Department of Dermatology, Bangalore Medical College Fort, Bangalore, Karnataka, India*
[d] *Nizam's Institute of Medical Sciences, Department of Surgical Gastroenterology, Panjagutta, Hyderabad, Andhra Pradesh, India*
[e] *Sri Ramachandra Medical College and Research Institute, Department of Surgery, Porur, Chennai, Tamil Nadu, India*
[f] *Wyeth Research, Coeur Défense—Tour A, Paris la Défense Cedex, Paris, France*
[g] *Wyeth Research, Collegeville, PA, USA*

Received 4 September 2009; received in revised form 4 May 2010; accepted 16 May 2010

KEYWORDS
Complicated skin and skin structure infections;
Efficacy;
India;
Taiwan;
Tigecycline

Background: To compare the monotherapy of tigecycline with vancomycin-aztreonam in hospitalized patients from India and Taiwan with complicated skin and skin structure infections (cSSSIs).
Methods: Safety and efficacy data were analyzed for Indian ($n = 86$) and Taiwanese ($n = 41$) patients hospitalized with cSSSIs who participated in two international Phase 3, randomized, double-blind studies.
Results: Patients were treated for 5—14 days. Cure rates at the test-of-cure assessment (12—92 days post-therapy) were generally similar between tigecycline and vancomycin-aztreonam in the clinically evaluable populations (India, 83.3% *vs.* 75.8%; Taiwan, 78.6% *vs.* 90%) and in the clinical modified intent-to-treat populations (India, 78.6% *vs.* 66.7%; Taiwan, 73.3% *vs.* 75.0%). Nausea and vomiting occurred more frequently with tigecycline, but overall safety and tolerability were comparable between the two treatments.

* Corresponding author. Chi-Mei Medical Center, 901 Chung-Hua Rd, Yung-Kang Dist., Tainan City 710, Taiwan.
E-mail address: chuangkenneth@hotmail.com (Y.-C. Chuang).

doi:10.1016/j.jmii.2010.04.002

Conclusions: Tigecycline monotherapy is a safe and effective therapy for cSSSIs in geographically distinct populations in Asia.

Introduction

Skin and skin structures are frequent sites of bacterial infection, which can range from superficial, easily treated local eruptions to deep aggressive infections that can become life threatening.[1] Complicated skin and skin structure infections (cSSSIs) are considered to be those that involve deep soft tissues, require surgical intervention, or occur in patients with comorbidities such as diabetes, peripheral neuropathy, and peripheral vascular disease.[2,3] cSSSIs often develop during hospitalization for surgery or trauma, and place patients at risk for not only wound infection but also pneumonia and sepsis. These infections prolong hospital stays, increase morbidity and mortality, and increase the cost of patient care.[2]

The agents most frequently implicated in cSSSIs include gram-positive organisms such as *Staphylococcus aureus* and *Streptococcus pyogenes*, as well as Enterobacteriaceae and aerobic nonfermenters such as *Pseudomonas aeruginosa* and *Acinetobacter* spp. Mixed infections that include gram-negative bacilli and anaerobic bacteria are often encountered in complicated cases. Although there has been little change in the incidence and distribution of pathogens isolated from cSSSIs, international surveillance data document an increase in resistance worldwide among both gram-positive and gram-negative organisms to a variety of antimicrobial classes.[4,5] Methicillin-resistant *S aureus* (MRSA) in particular is of increasing concern, as up to 21% of skin infections are now caused by this agent.[2] MRSA infection has usually been associated with exposure to health care settings, but community-associated MRSA with unique virulence and clonal characteristics has now become a widespread cause of skin and soft tissue infections.[6,7]

Tigecycline is an expanded broad-spectrum glycylcycline antibiotic that was designed to overcome the two major determinants of tetracycline resistance, drug efflux, and ribosomal protection.[8–10] As a single antimicrobial agent, tigecycline offers broad antibiotic coverage against many pathogens associated with cSSSIs, including MRSA and many species of multidrug-resistant gram-negative bacteria,[11,12] although it provides no coverage against *P aeruginosa*.

Two independent global Phase 3 trials, as well as a pooled analysis of the trials, have demonstrated that monotherapy with tigecycline is as effective as the combination of vancomycin and aztreonam for treating hospitalized patients with cSSSIs.[13–15] The North American/South American study was conducted in the Americas and India, whereas the worldwide study was conducted in Europe, Asia, Australia, and South Africa. In these Phase 3 studies, only patients from the Asia-Pacific countries of India and Taiwan were enrolled, and this article focuses on these two geographic subpopulations of patients separately, to avoid potential confounding by racial factors, while detailing the efficacy of tigecycline in treating cSSSIs in patients from these countries.

Methods

The study design and methods for the two original clinical trials were similar and have been described in detail elsewhere.[13–15] A brief summary is presented here.

Study design

Two Phase 3 multicenter, randomized, double-blind studies were conducted in hospitalized patients with cSSSIs. The North American/South American study was conducted between August 2001 and February 2004 at 89 sites in 8 countries, including 9 sites in India. The worldwide study was conducted between November 2002 and December 2003 at 65 centers in 21 countries, including 3 sites in Taiwan. The studies were approved by the Institutional Review Board or Ethics Committee at participating institutions and were conducted according to the recommendations of the Declaration of Helsinki. All patients gave written informed consent to participate in the study.

Patients were randomly assigned (1:1) to receive either tigecycline [initial intravenous (IV) dose of 100 mg in 250 mL saline followed by 50 mg IV every 12 hours] or IV vancomycin-aztreonam (1 g vancomycin in 250 mL saline followed by 2 g aztreonam in 100 mL saline, each every 12 hours). Patients treated with tigecycline also received a 100-mL infusion of normal saline placebo after infusion of tigecycline to maintain study blinding. The duration of treatment was 5–14 days unless a patient was deemed a clinical failure after receiving at least four doses of study drug. The test-of-cure assessment was made 12–92 days after the last dose was administered. Wound irrigation with antiseptics and other standard treatment measures was allowed, but other systemic or topical antibiotics or steroids were not permitted.

Patients

The eligible population included hospitalized patients $\geq$18 years of age with cSSSIs that involved deep soft tissue, required surgical intervention (including extensive cellulitis of at least 10 cm in width or length), or were associated with significant underlying disease (diabetes mellitus, peripheral vasculopathy, peripheral neuropathy, or lower venous insufficiency). Furthermore, patients had to exhibit two of the following signs and symptoms of infection: drainage or discharge, fever, erythema, swelling, localized warmth, pain, or white blood cell count $>10 \times 10^9$/L. Patients were excluded if they had necrotizing fasciitis, gangrene, osteomyelitis, required plasmapheresis, or hemoperfusion, had neutropenia, severely impaired arterial supply that would predict amputation within 1 month, or any condition that could impair eradication of infection. Patients with severe hepatic disease or hypersensitivity to the study drugs were excluded.

Populations analyzed

Patients who met eligibility criteria were randomly assigned to treatment and comprised the intent-to-treat (ITT) population. The modified ITT (mITT) (safety) population consisted of patients who received at least one dose of study medication. Patients in the mITT population who had clinical evidence of cSSSI by meeting the minimal disease criteria were included in the clinical mITT (c-mITT) population. Patients in the c-mITT population were considered to be clinically evaluable (CE) if they met inclusion and exclusion criteria, did not have *P aeruginosa* as a sole baseline isolate, received no concomitant antibiotic after the first dose of study medication, received appropriate and sufficient treatment to determine cure or failure, remained blinded, and had an assessment of "cure" or "failure" at the test-of-cure (TOC) visit 12–92 days after the last dose of study medication. The microbiologically evaluable (ME) population consisted of CE patients who had at least one identifiable baseline isolate that was susceptible to both study medications and who had a microbiologic outcome (eradication, persistence, superinfection) at the TOC visit.

Assessments

The primary efficacy endpoint was the clinical response in the coprimary CE and c-mITT populations at the TOC visit (12–92 days after therapy). An investigator blinded to treatment assessed drainage or discharge, fever, erythema, swelling or induration, pain or tenderness to palpation, extent of infection, and localized warmth. Based on these assessments, the clinical outcome was designated as "cure", "failure", or "indeterminate". A patient was considered cured if symptoms resolved or improved so that no further antibacterial therapy was required. An outcome was designated a failure if additional antibacterial therapy or an unplanned surgical intervention for this infection was required or if a patient died from infection >2 days after randomization, discontinued therapy because of treatment-related adverse events, or received >120% of the prescribed treatment doses. The outcome was considered indeterminate if death occurred within 2 days of randomization or was not related to infection before the TOC visit, or if no evaluation was possible.

The clinical response (cure or failure) by baseline isolate and type of infection (monomicrobial *vs.* polymicrobial) was a secondary endpoint and was evaluated with data from the ME population.

Microbiologic efficacy was evaluated at both the patient level (eradication, persistence, superinfection, or indeterminate) and the pathogen level (eradication, persistence, or indeterminate) for baseline isolates. Skin cultures were the principal source of the baseline isolates. All recovered isolates were subcultured and sent to a central laboratory for confirmation. Furthermore, to evaluate the sensitivity of isolates to tigecycline, vancomycin, and aztreonam, minimum inhibitory concentrations (MICs) were determined using procedures published by the Clinical and Laboratory Standards Institute (formerly National Committee for Clinical Laboratory Standards).[16–18]

The safety population comprised all patients who received at least one dose of study drug, that is, the mITT population. Safety assessments included a physical examination and 12-lead electrocardiogram at baseline. Vital signs were recorded daily; hematologic, blood chemistry, and coagulation parameter evaluations were performed at baseline, at regularly scheduled visits during treatment, and at the TOC visit. Adverse events were recorded throughout the study period.

Statistical analyses

In the main Phase 3 studies, the noninferiority of tigecycline compared with vancomycin-aztreonam was evaluated for clinical and microbiologic responses with a two-sided 95% confidence interval for the true difference in efficacy. Noninferiority was concluded if the lower limit of the two-sided 95% confidence interval was no lower than −15%. The efficacy analysis plan was based on a sample size of at least 300 CE patients to allow a 90% probability of detecting a true difference in efficacy of not less than 15% between treatment groups. However, the current analysis of patients from India and Taiwan was a retrospective post hoc analysis and because of insufficient numbers of patients enrolled in both countries, no formal statistical inference could be used to evaluate the efficacy of tigecycline. Hence, findings from these two countries were reviewed mainly for consistency with the results from the respective overall studies.

Results

Table 1 shows the distribution of patients in the various analysis populations for both India and Taiwan. Of 596 subjects randomized to treatment in the main North American/South American study, 86 were from India and all received at least one dose of study drug (mITT population). Of these, 63 patients met the clinical evaluability criteria (CE population) and 37 of these patients were considered ME. The worldwide study randomized 546 patients, of which 42 were from Taiwan; 41 Taiwanese patients received at least one dose of study drug (mITT population). The CE and ME populations consisted of 24 and 8 patients, respectively. The numbers of patients in the two treatment groups were similar within each subpopulation.

Baseline clinical and demographic characteristics were generally well-matched between the two treatment groups in both Indian and Taiwanese patients (Table 2). Compared with the overall worldwide study population, patients from Taiwan were older (median age, 52 years *vs.* 49 years) and had lower body weights (median, 74.5 kg *vs.* 79.0 kg). Furthermore, in comparison with their respective overall trial populations, Taiwanese patients had a higher incidence of deep soft tissue infection (95.1% for Taiwanese patients *vs.* 58–61% in the larger trial population), and patients from India had a higher frequency of diabetes mellitus (41.9% for patients from India *vs.* 29–31% in the overall trial population).

Clinical and microbiologic responses

Indian patients

In the Indian subpopulation, clinical responses in the coprimary CE and c-mITT populations were higher in the tigecycline group than in the vancomycin-aztreonam group

Table 1 Patient disposition

Population	India			Taiwan		
	Tigecycline	Vancomycin-aztreonam	Total	Tigecycline	Vancomycin-aztreonam	Total
	n (%ITT)	*n* (%ITT)	*n* (%ITT)	*n* (%ITT)	*n* (%ITT)	*n* (%ITT)
Screened			95			42
Screen failures			9			0
Intent-to-treat (ITT)	44	42	86	20	22	42
Modified ITT (mITT)	44 (100)	42 (100)	86 (100)	19 (95.0)	22 (100)	41 (97.6)
Clinical mITT (c-mITT)	42 (95.5)	42 (100)	84 (97.7)	15 (75.0)	16 (72.7)	31 (73.8)
Clinically evaluable (CE)	30 (68.2)	33 (78.6)	63 (73.3)	14 (70.0)	10 (45.5)	24 (57.1)
Microbiologically evaluable (ME)	17 (38.6)	20 (47.6)	37 (43.0)	3 (15.0)	5 (22.7)	8 (19.0)

cSSSI = complicated skin and/or skin structure infection; c-mITT = mITT subjects with evidence of cSSSI. ITT = all randomized subjects; mITT = ITT subjects who received at least one dose of study drug.

at the TOC visit (Table 3). Cure rates in the CE population were 83.3% (25/30 patients) with tigecycline, compared with 75.8% (25/33 patients) with vancomycin-aztreonam; in the c-mITT population, cure rates with tigecycline were 78.6% (33/42 patients) versus 66.7% (28/42 patients) with vancomycin-aztreonam. The noninferiority of tigecycline among Indian patients could not be evaluated statistically because of insufficient sample size.

Tables 4 and 5 present clinical and microbiologic responses in the ME population at the TOC visit for selected

Table 2 Baseline demographic and clinical characteristics (mITT population)

Characteristics	India		Taiwan	
	Tigecycline ($n = 44$)	Vancomycin-aztreonam ($n = 42$)	Tigecycline ($n = 19$)	Vancomycin-aztreonam ($n = 22$)
Age (yr)	50.8 ± 14.9	51.1 ± 17.1	53.0 ± 19.9	55.3 ± 20.3
Male sex	31 (70.5)	32 (76.2)	14 (73.7)	11 (50.0)
Female sex	13 (29.5)	10 (23.8)	5 (26.3)	11 (50.0)
Weight (kg)	63.4 ± 11.3	62.5 ± 15.5	75.7 ± 16.2	71.7 ± 13.3
Creatinine clearance (mL/min)	81.6 ± 31.2	78.4 ± 36.7	93.7 ± 31.6	81.8 ± 30.4
Primary clinical diagnosis				
Deep soft tissue infection	20 (45.5)	24 (57.1)	19 (100.0)	20 (90.9)
Cellulitis	19 (43.2)	20 (47.6)	19 (100.0)	20 (90.9)
Complicated underlying disease	4 (9.1)	9 (21.4)	4 (21.1)	8 (36.4)
≥10 cm (where anatomically applicable)	19 (43.2)	18 (42.9)	18 (94.7)	17 (77.3)
Requiring surgery/drainage	7 (15.9)	10 (23.8)	5 (26.3)	6 (27.3)
Wound infection	1 (2.3)	4 (9.5)	0	0
Major abscesses	17 (38.6)	13 (31.0)	0	1 (4.5)
Infected ulcers	6 (13.6)	4 (9.5)	0	1 (4.5)
Other	1 (2.3)	1 (2.4)	0	0
Comorbid conditions				
Diabetes mellitus	18 (40.9)	18 (42.9)	3 (15.8)	6 (27.3)
Peripheral vascular disease	0	0	1 (5.3)	4 (18.2)
Cause of infection				
Trauma	8 (18.2)	13 (31.0)	4 (21.1)	6 (27.3)
Spontaneous	32 (72.7)	23 (54.8)	13 (68.4)	16 (72.7)
Bite (human, insect, animal)	1 (2.3)	1 (2.4)	1 (5.3)	0
Surgery	0	4 (9.5)	1 (5.3)	0
Other	3 (6.8)	1 (2.4)	0	0

Data are presented as mean ± standard deviation or *n*(%).
mITT = modified intent-to-treat; SD = standard deviation.

Table 3 Cure rate at the test-of-cure visit in patients from India and Taiwan (CE and c-mITT populations)

	India				Taiwan			
	Tigecycline		Vancomycin-aztreonam		Tigecycline		Vancomycin-aztreonam	
	n/*N*	% (95% CI)	*n*/*N*	% (95% CI)	*n*/*N*	% (95% CI)	*n*/*N*	% (95% CI)
CE population	25/30	83.3 (65.3—94.4)	25/33	75.8 (57.7—88.9)	11/14	78.6 (49.2—95.3)	9/10	90.0 (55.5—99.7)
c-mITT population	33/42	78.6 (63.2—89.7)	28/42	66.7 (50.5—80.4)	11/15	73.3 (44.9—92.2)	12/16	75.0 (47.6—92.7)

CE = clinically evaluable; CI = confidence interval; c-mITT = clinical modified intent-to-treat.

isolates of clinical interest. The number of isolates was small and no definitive inferences are possible. However, tigecycline demonstrated antimicrobial efficacy against isolates commonly linked to cSSSIs, including *Enterococcus faecalis*, *Escherichia coli*, *S aureus*, and *Streptococcus agalactiae*, both as monomicrobial and polymicrobial infections. There were no MRSA isolates among the Indian patients. Of six patients from whom *S aureus* (non-MRSA) was isolated as part of a polymicrobial infection, the one patient treated with tigecycline was cured, compared with two cured out of the five placed on vancomycin-aztreonam (Table 5). For methicillin-susceptible *S aureus*, the tigecycline MIC_{90} value was 0.25 μg/mL (range, 0.12—0.25 μg/mL) compared with a MIC_{90} value of 1.0 μg/mL for vancomycin (range, 1.0—2.0 μg/mL). MIC ranges for *E coli* (0.12—0.50 μg/mL) and *E faecalis* (0.06—0.25 μg/mL) isolates were also lower for tigecycline than for vancomycin (128.0 μg/mL and 2.0 μg/mL, respectively) or aztreonam (0.12 μg/mL and 128.0 μg/mL, respectively).

Taiwanese patients

Among Taiwanese patients, cure rates in the CE population were lower with tigecycline (78.6%, 11/14 patients) than with vancomycin-aztreonam (90.0%, 9/10 patients), whereas there was no difference in cure rates between the two treatments in the c-mITT population [tigecycline, 73.3% (11/15 patients); vancomycin-aztreonam, 75.0% (12/16 patients)]. The sample size was too small to be able to draw any conclusions.

Clinical responses and microbiologic eradication rates for selected isolates in the Taiwanese ME population are shown in Tables 4 and 5. There were few isolates available for analysis. One patient had an MRSA infection, which responded to tigecycline. The MIC of tigecycline against this MRSA isolate was low (0.25 μg/mL), as were the MICs to methicillin-susceptible *S aureus* (0.12 μg/mL) and *E faecalis* (0.12 μg/mL); these isolates displayed higher MICs to vancomycin, of 2.0 μg/mL, 1.0 μg/mL, and 1.0 μg/mL, respectively.

Safety

Data from patients in the mITT populations (86 patients in India and 41 in Taiwan) were analyzed for safety and tolerability (Table 6). Patients in India received treatment with tigecycline or vancomycin-aztreonam over a median of 7.0 days (range, 1—15 days), whereas the median duration of treatment was 11 days (range, 1—14 days) for patients in Taiwan.

Indian patients

In India, the overall frequency of adverse events was significantly higher among tigecycline-treated patients (90.9%) than among vancomycin-aztreonam-treated patients (73.8%) ($p = 0.048$). Tigecycline was associated with a significantly

Table 4 Clinical and microbiologic responses by selected baseline isolate in the microbiologically evaluable population in India and Taiwan

Isolate	Tigecycline 50 mg		Vancomycin[a]		Aztreonam[b]	
	Clinical cure (*n*/N)	Microbiological eradication (*n*/N)	Clinical cure (*n*/N)	Microbiological eradication (*n*/N)	Clinical cure (*n*/N)	Microbiological eradication (*n*/N)
India						
Enterococcus faecalis (non-VRE)	1/1	1/1	2/3	2/3	2/3	2/3
Staphylococcus aureus (MSSA)	1/1	1/1	2/5	3/5	2/5	3/5
Escherichia coli	1/2	1/2	0/0	0/0	0/0	0/0
Streptococcus agalactiae	1/1	1/1	0/0	0/0	0/0	0/0
Taiwan						
S aureus (MRSA)	1/1	1/1	0/0	0/0	0/0	0/0
S aureus (MSSA)	0/0	0/0	2/2	2/2	2/2	2/2
E faecalis	0/0	0/0	1/1	1/1	1/1	1/1

[a] Includes subjects who received vancomycin.
[b] Includes subjects who received aztreonam.
MRSA = methicillin-resistant *S aureus*; MSSA = methicillin-susceptible *S aureus*; VRE = vancomycin-resistant Enterococcus.

Table 5 Clinical and microbiologic responses by selected baseline isolate and MIC values in microbiologically evaluable subjects in India and Taiwan

Isolate	MIC (μg/mL)	Tigecycline		Vancomycin[a]		Aztreonam[b]	
		Clinical cure (*n*/*N*)	Microbiological eradication (*n*/*N*)	Clinical cure (*n*/*N*)	Microbiological eradication (*n*/*N*)	Clinical cure (*n*/*N*)	Microbiological eradication (*n*/*N*)
India							
Enterococcus faecalis (non-VRE)	0.25	1/1	1/1	0/0	0/0	0/0	0/0
	2	0/0	0/0	2/3	2/3	0/0	0/0
	128	0/0	0/0	0/0	0/0	2/3	2/3
	Total	1/1	1/1	2/3	2/3	2/3	2/3
Escherichia coli	0.12	1/1	1/1	0/0	0/0	0/0	0/0
	0.5	0/1	0/1	0/0	0/0	0/0	0/0
	Total	1/2	1/2	0/0	0/0	0/0	0/0
Staphylococcus aureus (MSSA)	0.12	1/1	1/1	0/0	0/0	0/0	0/0
	1	0/0	0/0	2/5	3/5	0/0	0/0
	128	0/0	0/0	0/0	0/0	2/5	3/5
	Total	1/1	1/1	2/5	3/5	2/5	3/5
Streptococcus agalactiae	0.06	1/1	1/1	0/0	0/0	0/0	0/0
	Total	1/1	1/1	0/0	0/0	0/0	0/0
Taiwan							
Non-fermentative gram-negative rod	0.5	0/0	0/0	1/1	1/1	0/0	0/0
	1	0/0	0/0	0/0	0/0	1/1	1/1
	Total	0/0	0/0	1/1	1/1	1/1	1/1
E faecalis	1	0/0	0/0	1/1	1/1	0/0	0/0
	128	0/0	0/0	0/0	0/0	1/1	1/1
	Total	0/0	0/0	1/1	1/1	1/1	1/1
S aureus (MSSA)	1	0/0	0/0	2/2	2/2	0/0	0/0
	128	0/0	0/0	0/0	0/0	2/2	2/2
	Total	0/0	0/0	2/2	2/2	2/2	2/2
S aureus (MRSA)	0.25	1/1	1/1	0/0	0/0	0/0	0/0
	Total	1/1	1/1	0/0	0/0	0/0	0/0
Streptococcus dysgalactiae	0.5	0/0	0/0	1/1	1/1	0/0	0/0
	64	0/0	0/0	0/0	0/0	1/1	1/1
	Total	0/0	0/0	1/1	1/1	1/1	1/1

[a] Includes subjects who received vancomycin.
[b] Includes subjects who received aztreonam.
ME = microbiologically evaluable; MIC = minimum inhibitory concentration; MRSA = methicillin-resistant *S aureus*; MSSA = methicillin-susceptible *S aureus*; VRE = vancomycin-resistant Enterococcus.

higher frequency of adverse gastrointestinal events (47.7% *vs.* 16.7%; $p = 0.003$), the most commonly reported gastrointestinal events being vomiting (31.8% *vs.* 9.5%, $p = 0.016$), diarrhea (13.6% *vs.* 0%, $p = 0.026$), and nausea (22.7% *vs.* 7.1%, $p = 0.069$). The incidence of nausea and/or vomiting was 40.9% with tigecycline treatment, compared with 11.9% with vancomycin-aztreonam ($p = 0.003$), and the use of antiemetic or antinausea medication was significantly higher in the tigecycline group (25% *vs.* 7.1%, $p = 0.039$). The majority of cases of nausea or vomiting (approximately 90%) were mild or moderate (Grade 1 or 2). One patient in the vancomycin-aztreonam group discontinued treatment because of nausea, and one patient in the tigecycline group withdrew consent because of vomiting, which he felt was because of test article. Other adverse events that occurred significantly more frequently with tigecycline treatment included coagulation system abnormalities, including prolonged prothrombin time (27.3% *vs.* 7.1%, $p = 0.02$) and prolonged activated partial thromboplastin time (38.6% *vs.* 14.3%, $p = 0.015$). Elevated serum amylase levels were also more frequently associated with tigecycline treatment.

Four deaths occurred among Indian patients, three in the tigecycline group (one was the result of septic shock

Table 6 Safety of tigecycline versus vancomycin + aztreonam in patients from India and Taiwan (mITT population)

	India		Taiwan	
	Tigecycline (n = 44)	Vancomycin-aztreonam (n = 42)	Tigecycline (n = 19)	Vancomycin-aztreonam (n = 22)
Any adverse event	40 (90.9)*	31 (73.8)	18 (94.7)	19 (86.4)
Adverse events differing significantly between groups				
Digestive system	21 (47.7)**	7 (16.7)	14 (73.7)**	6 (27.3)
Anorexia	0	0	7 (36.8)**	0
Diarrhea	6 (13.6)*	0	2 (10.5)	0
Nausea	10 (22.7)	3 (7.1)	8 (42.1)**	1 (4.5)
Vomiting	14 (31.8)*	4 (9.5)	7 (36.8)*	1 (4.5)
Hemic and lymphatic system	25 (56.8)**	11 (26.2)	1 (5.3)	0
Prolonged APTT	17 (38.6)*	6 (14.3)	1 (5.3)	0
Prolonged prothrombin time	12 (27.3)*	3 (7.1)	1 (5.3)	0
Increased serum amylase level	6 (13.6)	0	—	—
Headache	2 (4.5)	0	4 (21.1)*	0
Death	3	1	0	0
Serious adverse events	9 (20.5)	10 (23.8)	2 (10.5)	2 (9.1)
Treatment discontinuation for adverse event	3 (6.8)	6 (14.3)	1 (5.3)	1 (4.5)
Withdrawal from study for adverse event	5 (11.4)	7 (16.7)	0	2 (9.1)

* Significant between group difference at <0.05 level.
** Significant between group difference at <0.01 level.
APTT = Activated partial thromboplastin time; mITT = modified intent-to-treat.

that was present before the study and the other two were caused by a perforated duodenal ulcer and myocardial infarction, respectively), and one in the comparator group (caused by chronic obstructive pulmonary disease). All deaths were considered probably not or definitely not related to the study drugs. Serious adverse event rates were comparable between the two treatment groups, with an overall frequency of 22.1% (19/86 patients).

Adverse events were the main reasons for discontinuation of the study drugs (tigecycline, three patients; vancomycin-aztreonam, 6 patients). No single event predominated with respect to early treatment discontinuation in the tigecycline group, but in the vancomycin-aztreonam group, four patients discontinued treatment because of rash or pruritus. Twelve patients withdrew from the study because of adverse events: five in the tigecycline group and seven in the vancomycin-aztreonam group. The primary events leading to withdrawal were nausea and vomiting in three patients with tigecycline and rash or pruritus in four patients who received vancomycin-aztreonam. No significant changes in laboratory parameters or in vital signs occurred in either treatment group.

Taiwanese patients

In patients from Taiwan, overall adverse event rates were comparable between the tigecycline and vancomycin-aztreonam groups, but patients receiving tigecycline experienced a significantly higher frequency of headache (21.1% *vs.* 0%, $p = 0.038$) and adverse gastrointestinal events (73.7% *vs.* 27.3%, $p = 0.005$). Nausea and/or vomiting occurred in 10/19 patients (52.6%) in the tigecycline group, compared with 2/22 (9.1%) in the vancomycin-aztreonam group ($p = 0.005$), but all cases except one were mild to moderate. Only one patient discontinued treatment because of nausea and vomiting. Anorexia was reported by seven patients who received tigecycline (36.8%) and by none of the patients receiving vancomycin-aztreonam ($p = 0.002$). More patients treated with vancomycin-aztreonam had rash or pruritus (9/22, 40.9% *vs.* 5/19, 26.3%), but this was not a statistically significant difference.

No deaths occurred in Taiwanese patients, and two patients in each group experienced a serious adverse event. One patient in each group discontinued therapy because of an adverse event (nausea and vomiting in a patient treated with tigecycline and pruritus and rash in a patient in the vancomycin-aztreonam group). There were no study withdrawals because of adverse events among tigecycline-treated patients, but two patients in the vancomycin-aztreonam group withdrew because of multiple adverse experiences including pruritus and rash.

Discussion

This subanalysis of the pivotal tigecycline studies shows that monotherapy with tigecycline is a safe and effective treatment of cSSSIs in the subpopulation of hospitalized patients from India and Taiwan. The efficacy of tigecycline in these patients was generally similar to that of the combination of vancomycin and aztreonam. Both treatments were well tolerated and the adverse event profiles of both treatments were similar to those previously reported.

The efficacy results for tigecycline in Indian and Taiwanese patients with cSSSIs are generally consistent with those reported in the overall Phase 3 studies as well as in the pooled efficacy analysis of the Phase 3 studies. In both CE and c-mITT populations in India, clinical cure rates were numerically higher with tigecycline than with vancomycin-

aztreonam. In CE Indian patients, the clinical cure rate was 83.3% with tigecycline and 75.8% with vancomycin-aztreonam. These rates are similar to those reported in the North American/South American study overall, namely, 82.9% with tigecycline and 82.3% with vancomycin-aztreonam.[13] Similarly, in the c-mITT population, the cure rate of 78.6% with tigecycline in India is similar to the rate of 75.5% in the overall study subjects, whereas the cure rate with vancomycin-aztreonam was somewhat lower among Indian patients (66.7% *vs.* 76.9% in the overall study).

The data from Taiwan are based on smaller patient numbers, with only 24 and 31 patients comprising the total CE and c-mITT populations, respectively. Although clinical responses to tigecycline in both the CE (78.6%) and the c-mITT population (73.3%) were lower than those obtained with the larger population in the worldwide trial (89.7% in the CE population and 84.3% in the c-mITT population),[14] the results are generally consistent with those from the pooled analysis of the pivotal Phase 3 studies (86.5% and 79.7% in the CE and c-mITT patients, respectively).[15] The numbers of patients enrolled in both India and Taiwan were insufficient for any statistical inference about the efficacy of tigecycline compared with that of the comparator. In both the North American/South American study and the worldwide study, the efficacy of tigecycline monotherapy was statistically similar to that of vancomycin-aztreonam. The current analysis suggests that, as in the larger studies, the efficacy of tigecycline is comparable to that of vancomycin-aztreonam in patients from India and Taiwan.

No new safety concerns emerged in Indian or Taiwanese patients after treatment with tigecycline, and the findings in general support the safety data from the full Phase 3 studies.[13–15] The main adverse events experienced with tigecycline were nausea and vomiting, which occurred significantly more frequently than with vancomycin-aztreonam. However, these events were mild to moderate, were controlled with appropriate therapy, and rarely resulted in discontinuation of study drug. Other adverse events associated more frequently with tigecycline treatment were an increased incidence of headache among Taiwanese patients and prolongation of prothrombin and activated partial thromboplastin times among Indian patients. These laboratory observations do not appear to be clinically significant as treatment with tigecycline was not associated with an enhanced risk of bleeding or bruising.

All patients receiving vancomycin-aztreonam, and 97% of patients receiving tigecycline were also receiving other medications, including anticoagulants (9.1% of patients treated with tigecycline and 7.1% of patients treated with vancomycin-aztreonam). None of the patients in this report were receiving warfarin.

Adverse events involving the skin, such as pruritus, were observed more frequently with vancomycin-aztreonam. Both treatments were comparable with respect to the incidence of death, serious adverse events, and treatment discontinuation.

IV antibiotics are often used to treat cSSSIs.[19] Vancomycin has historically been considered the agent of choice for treating MRSA, but its efficacy is being challenged by strains with reduced susceptibility, which have been reported worldwide.[20,21] These shifts in susceptibility reduce the ability of clinicians to treat patients appropriately with empiric therapy. For patients with serious infections, the initial choice for empiric therapy with broad-spectrum antibiotics is crucial, as an inappropriate antibiotic may contribute to treatment failure, with serious adverse consequences.[2,22] The increasing loss of broad-spectrum coverage because of emergence of resistance to established therapies for many pathogens has created a critical need for new antimicrobial agents.

In Phase 3 studies, tigecycline demonstrated microbiologic efficacy against many bacterial isolates linked to cSSSIs, and notably, 78% of cSSSIs attributable to MRSA were eradicated with tigecycline (compared with 76% with vancomycin-aztreonam).[15] The excellent broad-spectrum activity of tigecycline against clinical isolates from patients in these cSSSI studies, excluding those patients with *P aeruginosa* as a primary baseline isolate, was confirmed by a susceptibility study *in vitro*, in which tigecycline displayed consistently low MIC_{90} values for the most prevalent pathogens associated with cSSSI.[12] This study, which tested worldwide isolates, found no regional differences in the susceptibility to tigecycline of isolates. Of interest with respect to the current analysis was the demonstration that the MIC_{90} of tigecycline against methicillin-sensitive *S aureus* and *E coli* isolates from India was similar to that for isolates of these pathogens from other countries.

cSSSIs in the hospital are almost always treated with antimicrobial agents, and at least initially, therapy is empiric. However, empiric management decisions are complicated by the diverse bacterial etiology of these infections and the constantly evolving patterns of resistance among the causative pathogens.[23] Because of its expanded spectrum of activity, tigecycline is a promising agent for treating cSSSIs in hospitalized patients, particularly when broad empiric coverage is needed. Unlike vancomycin, which requires additional coverage for gram-negative organisms, tigecycline can be administered as a single agent. Thus, compared with vancomycin-aztreonam, tigecycline monotherapy offers similar efficacy and tolerability with more convenient dosing. This retrospective analysis demonstrates that monotherapy with tigecycline is generally safe, effective, and comparable to vancomycin-aztreonam for treating hospitalized patients with cSSSIs in India and Taiwan.

Acknowledgments

This study was sponsored by Wyeth Research, Collegeville, PA, USA. Nathalie Dartois and Sylvie Jouve are employees of Wyeth Research, France. Angel Cooper is an employee of Wyeth Research, USA. Upside Endeavors, LLC, Sanatoga, PA provided the authors with editorial support for the preparation of this manuscript, on behalf of Wyeth pharmaceuticals.

References

1. Nichols RL, Florman S. Clinical presentations of soft-tissue infections and surgical site infections. *Clin Infect Dis* 2001;**33** (Suppl. 2):S84–93.
2. Lee SY, Kuti JL, Nicolau DP. Antimicrobial management of complicated skin and skin structure infections in the era of emerging resistance. *Surg Infect (Larchmt)* 2005;**6**:283–95.
3. DiNubile MJ, Lipsky BA. Complicated infections of skin and skin structures: when the infection is more than skin deep. *J Antimicrob Chemother* 2004;**53**(Suppl. 2):ii37–50.
4. Gales AC, Jones RN, Pfaller MA, Gordon KA, Sader HS. Two-year assessment of the pathogen frequency and antimicrobial

resistance patterns among organisms isolated from skin and soft tissue infections in Latin American hospitals: results from the SENTRY antimicrobial surveillance program, 1997-98. SENTRY Study Group. *Int J Infect Dis* 2000;**4**:75—84.
5. Jones ME, Schmitz FJ, Fluit AC, Acar J, Gupta R, Verhoef J. Frequency of occurrence and antimicrobial susceptibility of bacterial pathogens associated with skin and soft tissue infections during 1997 from an International Surveillance Programme. SENTRY Participants Group. *Eur J Clin Microbiol Infect Dis* 1999;**18**:403—8.
6. King MD, Humphrey BJ, Wang YF, Kourbatova EV, Ray SM, Blumberg HM. Emergence of community-acquired methicillin-resistant Staphylococcus aureus USA 300 clone as the predominant cause of skin and soft-tissue infections. *Ann Intern Med* 2006;**144**:309—17.
7. Naimi TS, LeDell KH, Como-Sabetti K, Borchardt SM, Boxrud SM, Etienne J, et al. Comparison of community- and health care-associated methicillin-resistant Staphylococcus aureus infection. *JAMA* 2003;**290**:2976—84.
8. Petersen PJ, Jacobus NV, Weiss WJ, Sum PE, Testa RT. In vitro and in vivo antibacterial activities of a novel glycylcycline, the 9-t-butylglycylamido derivative of minocycline (GAR-936). *Antimicrob Agents Chemother* 1999;**43**:738—44.
9. Chopra I. Glycylcyclines: third-generation tetracycline antibiotics. *Curr Opin Pharmacol* 2001;**1**:464—9.
10. Sum PE, Petersen P. Synthesis and structure-activity relationship of novel glycylcycline derivatives leading to the discovery of GAR-936. *Bioorg Med Chem Lett* 1999;**9**:1459—62.
11. Fritsche TR, Sader HS, Stilwell MG, Dowzicky MJ, Jones RN. Potency and spectrum of tigecycline tested against an international collection of bacterial pathogens associated with skin and soft tissue infections (2000-2004). *Diagn Microbiol Infect Dis* 2005;**52**:195—201.
12. Bradford PA, Weaver-Sands DT, Petersen PJ. In vitro activity of tigecycline against isolates from patients enrolled in phase 3 clinical trials of treatment for complicated skin and skin-structure infections and complicated intra-abdominal infections. *Clin Infect Dis* 2005;**41**(Suppl. 5):S315—32.
13. Sacchidanand S, Penn RL, Embil JM, Campos ME, Curcio D, Ellis-Grosse E, et al. Efficacy and safety of tigecycline monotherapy compared with vancomycin plus aztreonam in patients with complicated skin and skin structure infections: results from a phase 3, randomized, double-blind trial. *Int J Infect Dis* 2005;**9**:251—61.
14. Breedt J, Teras J, Gardovskis J, Maritz FJ, Vaasna T, Ross DP, et al. Safety and efficacy of tigecycline in treatment of skin and skin structure infections: results of a double-blind phase 3 comparison study with vancomycin-aztreonam. *Antimicrob Agents Chemother* 2005;**49**:4658—66.
15. Ellis-Grosse EJ, Babinchak T, Dartois N, Rose G, Loh E. The efficacy and safety of tigecycline in the treatment of skin and skin-structure infections: results of 2 double-blind phase 3 comparison studies with vancomycin-aztreonam. *Clin Infect Dis* 2005;**41**(Suppl. 5):S341—53.
16. NCCLS. *Methods for antimicrobial susceptibility testing of anaerobic bacteria: approved standard* [NCCLS document M11-A5]. 5th ed. Wayne (PA): NCCLS; 2001.
17. NCCLS. *Methods for dilution antimicrobial susceptibility tests for microbes that grow aerobically: approved standards*. 6th ed. Wayne (PA): NCCLS; 2003.
18. NCCLS. *Performance standards for antimicrobial disc susceptibility tests: approved standards*. 8th ed. Wayne (PA): NCCLS; 2003.
19. Nichols RL. Optimal treatment of complicated skin and skin structure infections. *J Antimicrob Chemother* 1999;**44**(Suppl. A):19—23.
20. Tenover FC, Biddle JW, Lancaster MV. Increasing resistance to vancomycin and other glycopeptides in Staphylococcus aureus. *Emerg Infect Dis* 2001;**7**:327—32.
21. Song JH, Hiramatsu K, Suh JY, Ko KS, Ito T, Kapi M, et al. Emergence in Asian countries of Staphylococcus aureus with reduced susceptibility to vancomycin. *Antimicrob Agents Chemother* 2004;**48**:4926—8.
22. Falagas ME, Barefoot L, Griffith J, Ruthazar R, Snydman DR. Risk factors leading to clinical failure in the treatment of intra-abdominal or skin/soft tissue infections. *Eur J Clin Microbiol Infect Dis* 1996;**15**:913—21.
23. Doern GV, Jones RN, Pfaller MA, Kugler KC, Beach ML. Bacterial pathogens isolated from patients with skin and soft tissue infections: frequency of occurrence and antimicrobial susceptibility patterns from the SENTRY Antimicrobial Surveillance Program (United States and Canada, 1997). SENTRY Study Group (North America). *Diagn Microbiol Infect Dis* 1999;**34**:65—72.