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

Sarvajna Sacchidananda,*, Robert L. Pennb, John M. Embilc, Maria E. Campod, Daniel Curcoie, Evelyn Ellis-Grossef, Evan Lohf, Gilbert Rosef

a Victoria Hospital, Bangalore Medical College, Fort, Bangalore 560 002, India
b Louisiana State University Health Sciences Center, Shreveport, Louisiana, USA
c University of Manitoba, Winnipeg, Manitoba, Canada
d Hospital de Urgencia Asistencia Publica, Santiago, Chile
e Sanatorio Guemes, Buenos Aires, Argentina
f Wyeth Research, Collegeville, 500 Arcola Road, Collegeville, PA 19426, USA

Received 17 January 2005; received in revised form 19 May 2005; accepted 23 May 2005
Corresponding Editor: Peter Donnelly, Nijmegen, The Netherlands

KEYWORDS
Tigecycline;
Glycylcycline;
Skin-structure infection;
Safety;
Efficacy

Summary

Objectives: To compare the effect of tigecycline monotherapy, a first-in-class, expanded broad spectrum glycylcycline, with the combination of vancomycin and aztreonam (V + A) in the treatment of complicated skin and skin structure infections (cSSSI).

Methods: A phase 3, double-blind study conducted in 8 countries enrolled adults with cSSSI who required intravenous (IV) antibiotic therapy for ≥5 days. Patients were randomly assigned (1:1) to receive either tigecycline or V + A for up to 14 days. Primary endpoint was the clinical cure rate at the test-of-cure visit. Secondary endpoints included microbiologic efficacy and in vitro susceptibility to tigecycline of bacteria that cause cSSSI. Safety was assessed by physical examination, laboratory analyses, and adverse event reporting.

Results: A total of 596 patients were screened for enrollment, 573 were analyzed for safety, 537 were included in the clinical modified intent-to-treat (c-mITT) population,
Introduction

Complicated skin and skin structure infections (cSSSI) are often polymicrobial in origin, occurring in patients with preexisting skin lesions or underlying comorbid conditions. Patients with cSSSI frequently require hospitalization and parenteral antibiotic therapy. With the emergence of multi-drug-resistant organisms during the last decade, therapeutic options have become limited, especially when resistance develops to previously susceptible organisms. Since the early 1980s, the number of newly approved antibacterial agents in the USA has decreased substantially, and relatively few are currently in development. Thus, there is an increasing clinical need for new therapies that are effective against resistant strains of microorganisms.

Tigecycline is a broad spectrum glycyclline antibiotic with potent inhibition of bacterial protein synthesis and cell growth. Tigecycline was designed to circumvent two common drug-resistance mechanisms of bacteria: efflux and ribosomal protection. In vitro studies have demonstrated strong activity against a wide range of Gram-positive and Gram-negative pathogens, including methicillin-resistant and methicillin-susceptible Staphylococcus aureus (MRSA and MSSA, respectively), penicillin-resistant Streptococcus pneumoniae, Escherichia coli, Hemophilus influenzae, Enterococcus faecalis, Enterococcus faecium, Moraxella catarrhalis, Bacteroides spp., and Neisseria gonorrhoeae.

A preliminary, phase 2, randomized study of hospitalized patients with cSSSI demonstrated the clinical and microbiologic efficacy of tigecycline at both 50 mg and 25 mg doses. Further, the phase 2 study showed that tigecycline was well tolerated and had a favorable pharmacokinetic profile. Tigecycline has demonstrated activity against a broad spectrum of pathogens frequently associated with cSSSI, including Gram-positive (Staphylococcus aureus, Streptococcus pyogenes, Enterococcus faecalis) and Gram-negative (E. coli) bacteria.

Methods

Patient population

Men and women ≥18 years of age who required intravenous (IV) antibiotic therapy for ≥5 days for known or suspected cSSSI were eligible for study participation. Complicated SSSI included infections involving deep soft tissue or requiring significant surgical intervention, including extensive cellulitis of at least 10 cm in width or length, or those associated with a significant underlying disease state.
tigecycline monotherapy with the combination of V + A in patients with cSSSI. The trial was conducted at 89 centers in 8 countries in North America, South America, and India (USA, Canada, Argentina, Chile, Guatemala, Mexico, Peru, and India). Each center received approval from its institutional review board or independent ethics committee, and all patients provided written informed consent. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.

Patients were randomly assigned (1:1) to receive either tigecycline with placebo or the combination of V + A intravenously for up to 14 days. The randomization schedule was generated by the Biostatistics Department of Wyeth Research (Collegeville, PA, USA). Study medications were administered in a double-blind fashion or through an unblinded dispenser who did not participate in the direct evaluation of patient efficacy or safety endpoints.

Patients randomly assigned to tigecycline received an initial 100 mg dose, followed by 50 mg twice daily (approximately every 12 h) thereafter, in a volume of 250 mL normal saline infused over a 60 minute period. After each tigecycline infusion, patients received 100 mL normal saline placebo infused over another 60 minute period. Patients randomly assigned to V + A received twice-daily IV administration (approximately every 12 h) of 1 g vancomycin in 250 mL of normal saline over a 60 minute period, followed by 2 g aztreonam in 100 mL normal saline over another 60 minute period. Infusion bags and tubing were covered to obscure the color of tigecycline in solution in order to maintain the blind.

Patients were allowed to receive standard treatment for any stable, acute, or chronic medical condition. Wound irrigation with sterile water or saline solution, or topical antiseptics such as sulfadiazine, mafenide acetate, polyvidone iodine, chlorhexidine, hydrogen peroxide, or Dakin’s solution was permitted. Patients could also receive daily debridements or operative procedures as necessary based on standard of care. However, the use of topical antibacterials, steroids, and any nonstudy antibacterials or other investigational therapies was prohibited.

Populations analyzed

Patients were initially screened for enrollment in the study, and those who met eligibility criteria were randomly assigned to treatment and comprised the intent-to-treat (ITT) population. The modified ITT (mITT) population consisted of patients in the ITT population who received at least one dose of study drug. Patients in the mITT population who had clinical evidence of cSSSI comprised the clinical mITT (c-mITT) population. The microbiologic mITT (m-mITT) population consisted of patients in the c-mITT population who had ≥1 isolate identified at baseline. The clinically evaluable (CE) population consisted of c-mITT patients who did not have *Pseudomonas aeruginosa* as a baseline primary isolate, did not receive concomitant antibiotics after the first dose of tigecycline, and who met criteria for either clinical cure or failure at the test-of-cure visit. The microbiologic evaluable (ME) population consisted of CE patients who had an identifiable primary isolate(s) that was susceptible to both study drugs and who had clinical and microbiologic outcomes (i.e., eradication, persistence, or superinfection) at the test-of-cure visit.

Efficacy endpoints

The primary efficacy endpoint was a clinical response in the CE and c-mITT populations at the test-of-cure visit. Clinical response was defined as (e.g., diabetes, peripheral vascular disease) that complicates response to treatment. Patients were eligible for enrollment if they exhibited at least two of the following signs and symptoms of infection: (1) drainage and/or discharge; (2) fever >37.8 °C (100 °F) within 24 h before enrollment; (3) erythema; (4) swelling and/or induration; (5) localized warmth; (6) pain and/or tenderness to palpation; or (7) white blood cell count >10 × 10⁹/L.

Primary exclusion criteria included pregnant or breastfeeding women, patients with severely impaired arterial blood circulation who were likely to require amputation, those with infected diabetic foot ulcers or decubitus ulcers for >1 week, necrotizing fasciitis or gangrene, uncomplicated SSSI infections (e.g., simple abscesses, folliculitis, impetiginous lesions), and osteomyelitis contiguous to the infected site. Patients with clinical suspicion of ecthyma gangrenosum and those with known or suspected hypersensitivities to tigecycline, tetracyclines, minocycline, vancomycin, aztreonam, or related antibiotics, hepatic disease, neutropenia, calculated creatinine clearance <30 mL/min, and patients receiving any investigational drugs within 4 weeks before study drug administration were also excluded. Patients were excluded if they had a known or suspected concomitant infection requiring treatment with additional antibacterial agents or if their SSSI could be treated by surgery alone.

Study design

This randomized, double-blind, phase 3 trial was designed to compare the safety and efficacy of tigecycline monotherapy with the combination of V + A in patients with cSSSI. The trial was conducted at 89 centers in 8 countries in North America, South America, and India (USA, Canada, Argentina, Chile, Guatemala, Mexico, Peru, and India). Each center received approval from its institutional review board or independent ethics committee, and all patients provided written informed consent. This study was conducted in accordance with the ethical principles of the Declaration of Helsinki.
cure (i.e., resolution or improvement of signs and symptoms of infection to the extent that no further antibacterial therapy was required), failure (i.e., lack of response necessitating additional antibacterial therapy, extiporative surgical intervention, death due to infection >2 days after randomization, discontinuation due to treatment-related adverse event, or receipt of >120% of prescribed treatment), or indeterminate (i.e., lost to follow-up, death <2 days after randomization or death not related to infection before test-of-cure visit, no clinical response at test-of-cure assessment).

Secondary efficacy variables included clinical responses (cure or failure) and microbiologic responses at the patient level (eradication, persistence, superinfection, indeterminate) and isolate level (eradication, persistence, indeterminate) for patients in the ME and m-mITT populations at the test-of-cure assessments.

Bacterial cultures were obtained from the primary site of infection and were sent to local microbiology laboratories for identification. Local laboratories tested aerobic isolates for susceptibility to V + A by their standard techniques and to tigecycline by disk diffusion. All isolates recovered were subcultured and sent to a central laboratory (Covance Central Laboratory Services Inc., Indianapolis, IN, USA) for isolate confirmation. Antimicrobial susceptibility testing was done by both the Kirby–Bauer disk diffusion method and by the microbroth dilution method to determine the minimum inhibitory concentration (MIC) using procedures published by the National Committee for Clinical Laboratory Standards (NCCLS).18–20 Provisional MIC breakpoints for tigecycline were determined from microbiologic samples obtained in previous clinical investigations: ≤2 μg/mL for susceptible, 4 μg/mL for intermediate, and ≥8 μg/mL for resistant. MIC and MIC represent the minimal concentration of antibiotic that inhibited the growth of 50% and 90% of the isolates, respectively. Organisms isolated from baseline cultures were considered to be the primary baseline isolates based on the frequency with which those organisms are identified in the particular disease state.21–25

Safety evaluation

All patients who received at least one dose of study drug (mITT population) were evaluated for safety and were monitored for adverse events. Safety assessments included a physical examination and 12-lead electrocardiograms (ECGs) at baseline. At each scheduled evaluation, vital signs (temperature, heart rate, blood pressure) and clinical laboratory parameters (hematology, serum chemistry evaluations, and coagulation profiles) were assessed. Adverse events (AEs) and treatment-emergent AEs (TEAEs), i.e., AEs that occurred or worsened during treatment, were recorded throughout the study period. Because renal failure is a frequent complication of bacteremia in hospitalized patients,26 vancomycin dosage could be adjusted according to creatinine clearance levels for patients with compromised renal function as suggested by the vancomycin label.16 Serum creatinine levels were determined at baseline, on days 3, 7, and 14, or last day of therapy, and at the test-of-cure visit. There was no requirement for monitoring vancomycin levels. For patients who required vancomycin dose adjustments, an unblinded dispenser, who did not participate in direct evaluation of the efficacy or safety endpoints and did not interact with the patients, performed the adjustments.

Statistical analyses

Clinical and microbiologic responses to tigecycline and V + A were evaluated by using a 2-sided 95% confidence interval (CI) for the true difference in efficacy (i.e., tigecycline response rate minus V + A response rate). Noninferiority was concluded if the lower limit of the 2-sided 95% CI for the difference in efficacy was no larger than −15%. For all subpopulation analyses (e.g., subgroup analyses, monomicrobial versus polymicrobial), an adjusted difference between treatment groups with its 95% CI was calculated from a generalized linear model with a binomial probability function and an identity link (SAS® Proc GENMOD). The method of Wilson27 was used for endpoints involving comparisons of tigecycline and V + A with small sample sizes. The ‘exact’ method of Clopper and Pearson28 was used to compute the 2-sided 95% CI for a single proportion. The level of significance was set at 0.05.

Results

A total of 573 patients received at least one dose of study drug (mITT population) and were evaluated for safety; 292 were randomly assigned to tigecycline and 281 were randomly assigned to V + A (Figure 1). Patients were well matched between groups, and statistically significant differences in demographic characteristics between treatment groups (Table 1) did not exist. In both treatment groups, the predominant clinical diagnosis was deep soft tissue infection (62.0%), followed by major abscesses (28.6%). Overall, 51.7% of infections were spontaneous in nature, 26.9% were caused by
trauma, and 10.8% resulted from surgery. Approximately 30% of patients in each group had diabetes. Significant differences were not observed between groups in the mean number of study drug doses, days on therapy, or mean calculated creatinine clearance values.

Concomitant antibiotics were given to significantly more patients in the V + A group (45 patients, 16.0%) than in the tigecycline group (30 patients, 10.3%; $p = 0.047$). These primarily consisted of beta-lactam antibacterials ($n = 22$, 3.8%) and antibacterials for topical use ($n = 21$, 3.7%). Additionally, 6 patients in the V + A group and none in the tigecycline group received concomitant quinolone antibiotics. The use of concomitant antibiotics was considered before the data were unblinded when determining which patients were clinically evaluable.

### Clinical outcomes

Test-of-cure assessments were performed within 12 to 92 days following the end of treatment. A total of 199 tigecycline-treated patients and 198 V + A-treated patients completed therapy and comprised the CE population. Breaking the blind was the most common reason for exclusion from the CE population (8.9%). However, the blind was not broken for failure to respond.

At the test-of-cure visit, cure rates were not significantly different between treatment groups.
in the CE population (Table 2); 82.9% of patients receiving tigecycline monotherapy were cured by the test-of-cure visit. This success rate was comparable with that in patients treated with the V + A

<table>
<thead>
<tr>
<th></th>
<th>Tigecycline (n = 292)</th>
<th>V + A (n = 281)</th>
<th>Test for differences p-value</th>
<th>Test for noninferiority p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age, years, mean (SD)</strong></td>
<td>49.4 (15.4)</td>
<td>48.4 (16.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Sex, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>180 (61.6)</td>
<td>188 (66.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Women</td>
<td>112 (38.4)</td>
<td>93 (33.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ethnic origin, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>154 (52.7)</td>
<td>149 (53.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Black</td>
<td>28 (9.6)</td>
<td>23 (8.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Asian</td>
<td>1 (0.3)</td>
<td>2 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>54 (18.5)</td>
<td>53 (18.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>55 (18.8)</td>
<td>54 (19.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Weight, kg, mean (SD)</strong></td>
<td>81.5 (22.9)</td>
<td>82.0 (27.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Creatinine clearance, mL/min, mean (SD)</strong></td>
<td>109.5 (47.1)</td>
<td>110.1 (64.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Chief clinical diagnosis, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deep soft tissue infection</td>
<td>174 (59.6)</td>
<td>181 (64.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cellulitis</td>
<td>161 (55.1)</td>
<td>169 (60.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Complicated underlying disease ≥10 cm (where anatomically applicable)</td>
<td>141 (48.3)</td>
<td>145 (51.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Requiring surgery/drainage</td>
<td>73 (25.0)</td>
<td>77 (27.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Wound infection</td>
<td>13 (4.5)</td>
<td>12 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major abscesses</td>
<td>88 (30.1)</td>
<td>76 (27.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected ulcers</td>
<td>17 (5.8)</td>
<td>13 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infected Burns</td>
<td>2 (0.7)</td>
<td>6 (2.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>11 (3.8)</td>
<td>5 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Cause of infection, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Trauma</td>
<td>71 (24.3)</td>
<td>83 (29.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Spontaneous</td>
<td>159 (54.5)</td>
<td>137 (48.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bite (human, insect, animal)</td>
<td>21 (7.2)</td>
<td>17 (6.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Surgery</td>
<td>30 (10.3)</td>
<td>32 (11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Injection</td>
<td>7 (2.4)</td>
<td>8 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>4 (1.4)</td>
<td>4 (1.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Number of doses, mean (SD)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Days on therapy</td>
<td>14.7 (6.4)</td>
<td>15.4 (6.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Connections</strong></td>
<td>8.2 (3.3)</td>
<td>8.6 (3.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Comorbidity conditions, n (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>89 (30.5)</td>
<td>82 (29.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>28 (9.6)</td>
<td>18 (6.4)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
combination (82.3%) and demonstrates that the efficacy of tigecycline monotherapy was statistically noninferior to the combination of V + A (difference tigecycline — V + A % (95% CI) = 0.6% (−7.4, 8.6), p-value for noninferiority <0.001, p-value for differences = 0.9816). Tigecycline also met the statistical criteria for noninferiority to V + A in the c-mITT population (difference tigecycline — V + A % (95% CI) = 1.5% (−9.0, 6.1) p-value for noninferiority <0.001, p-value for differences = 0.7650). Specifically, in the CE and c-mITT populations, the lower limit of the 95% CI for the true difference between

<table>
<thead>
<tr>
<th>Baseline diagnosis</th>
<th>Tigecycline</th>
<th>V + A</th>
<th>Difference (tigecycline — V + A)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N</td>
<td>% (95% CI)</td>
<td>n/N</td>
</tr>
<tr>
<td>Soft tissue infections</td>
<td>109/133</td>
<td>82.0 (74.4, 88.1)</td>
<td>118/141</td>
</tr>
<tr>
<td>Abscesses</td>
<td>43/50</td>
<td>86.0 (73.3, 94.2)</td>
<td>33/41</td>
</tr>
<tr>
<td>Infected ulcers</td>
<td>9/12</td>
<td>75.0 (42.8, 94.5)</td>
<td>7/11</td>
</tr>
<tr>
<td>Burns</td>
<td>0/0</td>
<td>NA</td>
<td>1/1</td>
</tr>
<tr>
<td>Other</td>
<td>4/4</td>
<td>100.0 (39.8, 100.0)</td>
<td>4/4</td>
</tr>
</tbody>
</table>

Comorbidity

| Diabetes          | 39/58      | 67.2 (53.7, 79.0) | 42/58   | 72.4 (59.1, 83.3) | −5.2 (−22.5, 12.5) |
| Peripheral vascular disease | 15/19     | 78.9 (54.4, 93.9) | 11/16   | 68.8 (41.3, 89.0) | 10.2 (−21.3, 40.9) |
| Baseline bacteremia | 5/8       | 62.5 (24.5, 91.5) | 11/14   | 78.6 (49.2, 95.3) | −16.1 (−55.9, 24.3) |

NA: not applicable.

**Table 3** Clinical success rates in the CE population at the test-of-cure visit by baseline diagnosis, and in patients with diabetes, peripheral vascular disease, or baseline bacteremia.

<table>
<thead>
<tr>
<th>Isolatea</th>
<th>Tigecycline</th>
<th>Vancomycin/aztreonam</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>n/N % (95% CI)</td>
<td>n/N % (95% CI)</td>
</tr>
<tr>
<td>Enterococcus faecalisb</td>
<td>5/6</td>
<td>83.3 (35.9, 99.6)</td>
</tr>
<tr>
<td>Escherichia coli</td>
<td>4/6</td>
<td>66.7 (22.3, 95.7)</td>
</tr>
<tr>
<td>Staphylococcus aureus</td>
<td>46/56</td>
<td>82.1 (69.6, 91.1)</td>
</tr>
<tr>
<td>MRSA</td>
<td>16/21</td>
<td>76.2 (52.8, 91.8)</td>
</tr>
<tr>
<td>MSSA</td>
<td>30/35</td>
<td>85.7 (69.7, 95.2)</td>
</tr>
<tr>
<td>Streptococcus agalactiae</td>
<td>3/3</td>
<td>100.0 (29.2, 100.0)</td>
</tr>
<tr>
<td>Streptococcus pyogenes</td>
<td>6/7</td>
<td>85.7 (42.1, 99.6)</td>
</tr>
</tbody>
</table>


a Although *Bacteroides fragilis* was a selected primary pathogen, there were less than five total isolates so data are not given for this organism.

b In this study, all *E. faecalis* primary isolates were susceptible to vancomycin.
treatments was $-7.4\%$ and $-9.0\%$, respectively, at test-of-cure visit. Results in the ME and m-mITT populations were consistent with findings of noninferiority of tigecycline in the CE and c-mITT populations (Table 2).

When analyzed by clinical diagnosis, such as soft tissue infections and major abscesses, cure rates were also comparable between groups (Table 3). Tigecycline monotherapy was comparable with V + A in the subsets of patients with baseline diagnoses of diabetes, peripheral vascular disease, or bacteremia.

**Microbiologic responses**

Eradication rates at the patient level were comparable between treatment groups, demonstrating the noninferiority of tigecycline monotherapy to the combination of V + A in eradicating skin infections in the ME (Table 4) and m-mITT (data not shown) populations. Although differences in eradication rates between groups were adjusted for type of infection, these differences were similar to unadjusted differences. Because of the small sample size, microbiologic response of failures were pooled with a similar phase 3 study and analyzed. The results of this pooled analysis will be summarized in a separate manuscript. Eradication rates of selected primary baseline isolates commonly associated with cSSSI were high in both treatment groups (Table 5); for MRSA, eradication rates were $76.2\%$ for the tigecycline group and $81.0\%$ for the V + A group.

MIC testing was used to evaluate the sensitivity of the selected primary baseline isolates commonly associated with cSSSI and the sensitivity of other isolates to tigecycline, vancomycin, and aztreonam. Over the course of this study, there was no evidence of the development of decreased susceptibility to tigecycline. Although the number of isolates available for analysis was small, bacterial susceptibilities to tigecycline appeared to be consistent with clinical responses. MIC$_{50}$ values for tigecycline monotherapy were uniformly low for the most prevalent isolates, including MRSA and MSSA, compared with the V + A combination (Table 6).

**Safety**

Both tigecycline and V + A were well tolerated and the overall frequency of treatment-emergent adverse events was similar between treatment groups (Table 7). Only a small percentage of patients discontinued treatment because of adverse events: 18 patients ($6.2\%$) in the tigecycline group and 13 patients ($4.6\%$) in the V + A group in the mITT

---

**Table 6.** MIC range, and MIC$_{50}$ and MIC$_{90}$ values of selected primary baseline isolates in the ME population.

<table>
<thead>
<tr>
<th>Isolate</th>
<th>Tigecycline</th>
<th>Vancomycin</th>
<th>Aztreonam</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>MIC Range</td>
<td>MIC$_{50}$</td>
<td>MIC$_{90}$</td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em></td>
<td>12</td>
<td>0.06–0.12</td>
<td>0.12</td>
</tr>
<tr>
<td><em>E. coli</em></td>
<td>10</td>
<td>0.12–1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><em>S. aureus</em> (MRSA)</td>
<td>42</td>
<td>0.12–1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><em>S. aureus</em> (MSSA)</td>
<td>73</td>
<td>0.12–1.00</td>
<td>1.00</td>
</tr>
<tr>
<td><em>S. pyogenes</em></td>
<td>15</td>
<td>0.06–0.12</td>
<td>0.60</td>
</tr>
</tbody>
</table>


*a In this study, all *E. faecalis* primary isolates were susceptible to vancomycin.
population. Nausea was the most common adverse event that led to discontinuation of study therapy among tigecycline-treated patients, whereas pruritis and rash were the most common adverse events that led to discontinuation in the V + A group. Of note, patients receiving V + A had a significantly higher incidence of pruritis, rash, and elevated ALT/SGPT levels compared with patients receiving tigecycline, whereas tigecycline-treated patients had significantly a higher incidence of nausea and vomiting, as well as anorexia and dyspepsia. No tigecycline-treated patient had a positive CLOSTIDIUM DIFFICILE toxin assay, nor developed C. difficile-associated diarrhea.

Five deaths occurred in the tigecycline group: two occurred more than one week after completion of therapy, one resulted from a prestudy condition (sepsis), one from unrelated complications (acute renal failure/cardiogenic shock) that occurred on the first and second day of therapy, and one resulted from a perforated ulcer. One death in the V + A group resulted from chronic obstructive pulmonary disease and congestive heart failure. No deaths were considered to be related to the use of the study drug. There were no clinically important changes from baseline in laboratory parameters, vital signs, or ECGs. Most laboratory changes were small, with means remaining within normal biologic ranges.

Discussion

This phase 3 randomized and double-blind trial demonstrated that the efficacy of tigecycline monotherapy was comparable with that of the combination of V + A in the treatment of patients with cSSSI. Subgroup analyses also found that success rates were similar with tigecycline monotherapy and combination V + A treatment among those patients with underlying diabetes, peripheral vascular disease, and bacteremia. In a previously reported phase 2 trial of hospitalized patients with cSSSI receiving 50 mg of tigecycline, patients had a clinical cure rate of 74% at test-of-cure assessment.12 Although similar to the phase 2 trial results, the cure rate in the present phase 3 study is higher (82.9%) in the clinically evaluable population (Table 2).

Tigecycline monotherapy was statistically noninferior to the combination of V + A, based on the lower boundary of the 2-sided CI (−7.4%) in the CE population for the difference in cure rate. Noninferiority of tigecycline to V + A was demonstrated by cure rates in the CE and c-mITT populations, by microbiologic responses of patients in the ME and m-mITT populations, and by microbiologic efficacy

### Table 7 Treatment emergent adverse events that occurred in ≥3% of patients, number of patients (%).

<table>
<thead>
<tr>
<th>Body system adverse event</th>
<th>Tigecycline V + A</th>
<th>(n = 292)</th>
<th>V + A</th>
<th>(n = 281)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any adverse event&lt;sup&gt;a&lt;/sup&gt;</td>
<td>240 (82.2)</td>
<td>218 (77.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Body as a whole</td>
<td>111 (38.0)</td>
<td>94 (33.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>13 (4.5)</td>
<td>7 (2.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chills</td>
<td>9 (3.1)</td>
<td>3 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fever</td>
<td>11 (3.8)</td>
<td>21 (7.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Headache</td>
<td>36 (12.3)</td>
<td>26 (9.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Infection</td>
<td>7 (2.4)</td>
<td>10 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pain</td>
<td>24 (8.2)</td>
<td>13 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular system&lt;sup&gt;b&lt;/sup&gt;</td>
<td>34 (11.6)</td>
<td>55 (19.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>7 (2.4)</td>
<td>11 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Phlebitis</td>
<td>7 (2.4)</td>
<td>16 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Digestive system&lt;sup&gt;b&lt;/sup&gt;</td>
<td>169 (57.9)</td>
<td>75 (26.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Anorexia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>12 (4.1)</td>
<td>2 (0.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Constipation</td>
<td>8 (2.7)</td>
<td>15 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diarrhea</td>
<td>37 (12.7)</td>
<td>24 (8.5)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspepsia&lt;sup&gt;b&lt;/sup&gt;</td>
<td>16 (5.5)</td>
<td>5 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nausea&lt;sup&gt;b&lt;/sup&gt;</td>
<td>126 (43.2)</td>
<td>31 (11.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vomiting&lt;sup&gt;b&lt;/sup&gt;</td>
<td>78 (26.7)</td>
<td>13 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemic and lymphatic system</td>
<td>49 (16.8)</td>
<td>42 (14.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Activated partial thromboplastin time prolonged</td>
<td>18 (6.2)</td>
<td>8 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hemorrhage</td>
<td>6 (2.1)</td>
<td>11 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prothrombin time prolonged</td>
<td>14 (4.8)</td>
<td>5 (1.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td>11 (3.8)</td>
<td>9 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metabolic and nutritional</td>
<td>61 (20.9)</td>
<td>67 (23.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Amylase increased</td>
<td>9 (3.1)</td>
<td>3 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hyperglycemia</td>
<td>7 (2.4)</td>
<td>11 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypokalemia</td>
<td>7 (2.4)</td>
<td>9 (3.2)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Lactic dehydrogenase increased</td>
<td>9 (3.1)</td>
<td>3 (1.1)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AST/SGOT increased</td>
<td>6 (2.1)</td>
<td>14 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALT/SGPT increased&lt;sup&gt;b&lt;/sup&gt;</td>
<td>3 (1.0)</td>
<td>16 (5.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Musculoskeletal system</td>
<td>12 (4.1)</td>
<td>12 (4.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Nervous system</td>
<td>34 (11.6)</td>
<td>41 (14.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dizziness</td>
<td>14 (4.8)</td>
<td>10 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Insomnia</td>
<td>8 (2.7)</td>
<td>14 (5.0)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Respiratory system</td>
<td>23 (7.9)</td>
<td>32 (11.4)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cough increased</td>
<td>10 (3.4)</td>
<td>8 (2.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dyspnea</td>
<td>5 (1.7)</td>
<td>11 (3.9)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Skin and appendages&lt;sup&gt;b&lt;/sup&gt;</td>
<td>40 (13.7)</td>
<td>69 (24.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pruritus&lt;sup&gt;b&lt;/sup&gt;</td>
<td>13 (4.5)</td>
<td>30 (10.7)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rash&lt;sup&gt;b&lt;/sup&gt;</td>
<td>8 (2.7)</td>
<td>22 (7.8)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Special senses</td>
<td>6 (2.1)</td>
<td>10 (3.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Urogenital system</td>
<td>17 (5.8)</td>
<td>13 (4.6)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Others</td>
<td>16 (5.5)</td>
<td>15 (5.3)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Local reaction to procedure</td>
<td>16 (5.5)</td>
<td>11 (3.9)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup> Patients may have had more than 1 treatment-emergent adverse event.

<sup>b</sup> Significant between-group difference (p < 0.05).
responses of isolates. Further, eradication rates appeared to correlate well with clinical cure rates. Tigecycline demonstrated microbiologic efficacy against a broad spectrum of both Gram-positive and Gram-negative microorganisms commonly identified in patients with cSSSI, including Staphylococcus aureus (MRSA and MSSA), Enterococcus faecalis, E. coli, Streptococcus agalactiae, and Streptococcus pyogenes. Provisional MIC breakpoints for tigecycline were established prior to study start from microbiologic samples obtained in previous clinical investigations. MIC\textsubscript{90} values for tigecycline were uniformly low for the most prevalent isolates, including MRSA and MSSA (MIC\textsubscript{90} = 0.25 \mu g/mL for both). During the study period, there was no evidence of the development of decreased susceptibility to tigecycline.

Tigecycline and V + A were shown to be safe and well tolerated. Patients receiving the V + A combination experienced significantly higher incidences of pruritis, rash, and elevated levels of ALT/SGPT than patients receiving tigecycline monotherapy. Although the incidence of nausea and vomiting was significantly higher in tigecycline-treated patients, the severity was mild to moderate, and most patients did not discontinue treatment because of these events. An earlier report demonstrated that patient tolerance of tigecycline was improved when the drug was administered with food.29

Tigecycline offers potential advantages over other parenterally administered antimicrobial agents because of its expanded spectrum of coverage against Gram-positive, anaerobic, Gram-negative, and multiply antimicrobial resistant microorganisms. The current standard of care for cSSSI may require an approach using either a very broad spectrum antimicrobial agent or multiple agents used in combination in order to provide antibacterial activity against both Gram-positive and Gram-negative isolates.30,31 Unlike vancomycin, tigecycline’s spectrum of antibacterial activity does not cause it to require additional antimicrobial agents for Gram-negative coverage. Since tigecycline monotherapy provides activity against Gram-positive and Gram-negative microorganisms as well as anaerobes and certain antimicrobial resistant pathogens,8,13–15,32–35 only one antimicrobial agent needs to be administered. Compared with the V + A combination treatment, tigecycline monotherapy appears to be safe and efficacious in the treatment of patients with cSSSI and is a promising agent for the treatment of cSSSI. These results were presented in part at the 11th International Symposium on Staphylococci & Staphylococcal Infections, October 24–27, 2004, Charleston, South Carolina, USA, Control #TH-13.

Acknowledgments

We thank the tigecycline 300 study group investigators for their valuable involvement in this study: Marc Alpert, Sacchidanand Aradhya, Eduardo Arathoon, Alfred Augustine, Charles Bailey, Ian Baird, Joaquin Bernmejo, Jack Bernstein, Maria Campos, Nicolas Christou, Nancy Crum, Daniel Curcio, Avinash Deodhar, Francois Duble, John Embil, Joseph Fraize, Bruce Friedman, Marvin Gerson, Donald Graham, Stephen L. Green, Doria Grimard, Kamal Itani, Abel Jasovich, Luis E. Jauregi-Peredo, Robert Jones, Stanley R. Klein, Richard Kohler, Carlos Lovesio, Sreevathsna Maddibande, Abhay Mane, W. Scott McDonald, David McEniry, Bherappa Nagari, Eduardo Rodriguez Noriega, Rebeca Northland, Ciaran O’Hare, Vishwanath Pai, Michael Patzakis, Robert L. Penn, Andre Poirier, Michel Polisson, Mayakonda Krishnamurthy Ramesh, Annette Reboli, Stephen Sanche, Carlos Seas, Leon Smith, Kanchana Sundaramurthy, Osvaldo Teglia, Alan Tice, Dean Tsukayama, Subramanian Vaidyanathan, Walter Vasen, Carlos Rodolfo Mejia Villatoro, Karl Weiss, and David Young.

We thank Wyeth Research employees Patricia Bradford for microbiological analysis and Susan Nastasee and Donna Simcoe for professional medical writing services. Wyeth Research, Collegeville, PA, supported and funded this study. Protocol: 3074A1-300-US/CA.

Conflict of interest: Drs Sacchidanand, Penn, Embil, Campos, and Curcio, are investigators for this tigecycline study sponsored by Wyeth. Drs Ellis-Grosse, Loh, and Rose are employees of Wyeth.

References


Available online at www.sciencedirect.com