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Efficacy and safety of tigecycline compared with vancomycin or linezolid for treatment of serious infections with methicillin-resistant *Staphylococcus aureus* or vancomycin-resistant enterococci: a Phase 3, multicentre, double-blind, randomized study

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***Introduction*: Methicillin-resistant *Staphylococcus aureus* (MRSA) and vancomycin-resistant enterococci (VRE) are causing serious nosocomial infections. Tigecycline was evaluated in hospitalized patients with MRSA or VRE infection.**

***Patients and methods*: A randomized (3:1), double-blind, multicentre, Phase 3 study compared the safety and efficacy of tigecycline with vancomycin or linezolid in hospitalized patients with MRSA or VRE infection, respectively. Patients were treated for 7–28 days and the test-of-cure (TOC) assessment was made 12–37 days after the last dose. The primary efficacy endpoint was the clinical response (cure, failure and indeterminate) in the co-primary, microbiologically evaluable (ME) and microbiologically modified intent-to-treat (m-mITT) populations at the TOC assessment.**

***Results*: For MRSA infection, clinical cure rates in the ME population ($n = 117$) were 81.4% (70 of 86 patients) with tigecycline and 83.9% (26 of 31 patients) with vancomycin. In the m-mITT population ($n = 133$), clinical cure occurred in 75 of 100 tigecycline-treated patients (75.0%) and in 27 of 33 vancomycin-treated patients (81.8%). In patients with complicated skin and skin structure infections caused by MRSA, cure rates were similar with tigecycline or vancomycin (86.4% versus 86.9% in ME population; and 78.6% versus 87.0% in m-mITT population). In patients with MRSA infection, nausea or vomiting occurred more frequently with tigecycline than with vancomycin (41.0% versus 17.9%); most cases were mild, with only three patients discontinuing treatment. In patients with VRE (total enrolment, 15), 3 of 3 and 3 of 8 patients in the ME and m-mITT populations, respectively, were cured by tigecycline, compared with 2 of 3 patients in the ME and m-mITT populations treated with linezolid.**

***Conclusions*: Tigecycline is safe and effective in hospitalized patients with serious infection caused by MRSA. There were too few cases of VRE to draw any conclusions.**

Keywords: antibiotic, glycylcycline, resistant pathogen, antimicrobial resistance, adverse events

Introduction

Gram-positive cocci are a predominant cause of serious nosocomial and community-acquired infections.[1] Intensive use of antibiotics, particularly in the hospital setting, is an important contributing factor to the emergence and spread of drug-resistant variants.[2,3] Antimicrobial susceptibility trends for pathogens causing nosocomial infections in the USA demonstrate a significant increase in the prevalence of methicillin-resistant *Staphylococcus aureus* (MRSA), coagulase-negative staphylococci and vancomycin-resistant enterococci (VRE).[1,2,4,5]

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Infection with MRSA is associated with treatment failure, higher mortality and increased costs.[6,7] MRSA infection was previously associated with exposure to healthcare settings, but community-associated MRSA with particular virulence and clonal characteristics have emerged recently and have been reported across the world.[8–12] Vancomycin was historically the agent of choice for treating MRSA, but strains resistant to this agent are now emerging.[13,14]

Vancomycin-resistant *Enterococcus faecium* and *Enterococcus faecalis* have emerged in the past decade as causes of serious intra-abdominal infections and bacteraemia.[15] Enterococci are a therapeutic challenge because of their intrinsic resistance to many antibiotics. The acquisition of resistance to vancomycin by enterococci has seriously affected the treatment and infection control of these organisms. VRE, particularly *E. faecium* strains, are frequently resistant to all antibiotics that are used effectively for treatment of vancomycin-susceptible enterococci, which leaves clinicians treating VRE infections with limited therapeutic options.[16,17] The risk of death associated with antibiotic-resistant enterococcal bacteraemia is several-fold higher than that associated with susceptible enterococcal bacteraemia.[18]

Tigecycline is a glycylcycline antibiotic that has been approved for the treatment of complicated skin and skin structure infection (cSSSI) and complicated intra-abdominal infection (cIAI). Tigecycline overcomes the two key tetracycline resistance mechanisms (efflux pumps and ribosomal protection) and is unaffected by other bacterial mechanisms of resistance, such as extended-spectrum β-lactamases, limiting the number of antibiotic options available.[19] Tigecycline has *in vitro* activity against a broad spectrum of Gram-positive and -negative bacteria, anaerobes as well as multidrug-resistant pathogens such as MRSA and VRE.[20] The efficacy and safety of tigecycline have been demonstrated in randomized, double-blind, controlled Phase 3 studies.[21–23]

The primary objective of this study was to evaluate the safety and clinical efficacy of tigecycline in patients with selected serious infections caused by VRE or MRSA. An active control arm was used to interpret the clinical response to tigecycline. Vancomycin and linezolid were chosen as comparators for MRSA and VRE infections, respectively, as they are currently indicated for the treatment of serious infections caused by these bacteria. The study was not powered for a statistical comparison between tigecycline and control treatment, but rather was designed to provide contemporaneous clinical data on the activity of tigecycline relative to established therapy in the current era of increasing resistance to antimicrobial agents.

Patients and methods

Study design

This randomized, double-blind, multicentre, Phase 3 study was designed to compare the safety and efficacy of tigecycline monotherapy with vancomycin in hospitalized patients with MRSA infection and with linezolid in patients with VRE infection. The trial was conducted at 50 sites in 14 countries between November 2003 and August 2005. Each study site utilized its own individual recruitment plan for identifying patients, which often involved the assistance of the microbiology laboratory to obtain information on culture-positive MRSA/VRE isolates. 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 with MRSA infection were randomized 3:1 to receive iv tigecycline or vancomycin and those with VRE infection were randomized 3:1 to receive iv tigecycline or linezolid. A 3:1 randomization was chosen in order to obtain maximal experience with tigecycline for the treatment of resistant pathogens, while retaining the active control study design. The duration of treatment was 7–28 days depending on the site and severity of infection and was based on the investigator's judgement. The randomization schedule was generated by the Biostatistics Section of Wyeth Research and accessed through a centralized, computerized randomization system. After a subject was screened and deemed eligible for the study, the unblinded dispenser called the provided telephone number to determine the treatment assignment. Subjects were stratified at the time of randomization by type of infection (VRE or MRSA), site of infection (cSSSI or other infection for patients with MRSA; cIAI or other infection for patients with VRE) and by Acute Physiologic and Chronic Health Evaluation Scale (APACHE II) score (>15 or ≤ 15).

Tigecycline infusions were administered approximately every 12 h (initial iv loading dose of 100 mg followed by 50 mg every 12 h) in 250 mL of normal saline. Patients with MRSA infection who were assigned to vancomycin received a vancomycin infusion (iv dose of 1 g) approximately every 12 h; doses could be adjusted for patients with compromised renal function. Patients with VRE infection who were assigned to linezolid received a linezolid infusion (600 mg) every 12 h. Patients were allowed to receive standard treatment for any stable, acute or chronic medical condition. Patients with suspected polymicrobial infection containing Gram-negative bacteria could receive non-study antibacterial agents or irrigants. Topical antiseptics were permitted. Other agents that were permitted included oral vancomycin (to treat *Clostridium difficile* infections), antifungal agents, aciclovir and ophthalmic aminoglycosides.

The study involved one screening visit 24 h prior to start of therapy, up to 28 days of study drug administration, and one post-therapy visit between 12 and 37 days after the last dose of the study drug for the test-of-cure (TOC) assessment.

Patient populations

Inclusion criteria. Patients were eligible if they were 18 years or older, had a confirmed diagnosis of a serious infection (bacteraemia, cIAI, cSSSI or pneumonia) requiring iv antibiotic therapy and were infected with vancomycin-resistant *E. faecium* or *E. faecalis* or MRSA, isolated alone or as part of a polymicrobial infection.

Patients with bacteraemia were required to have two positive blood cultures as well as one of the following signs and symptoms: fever or hypothermia during the 24 h preceding enrolment; white blood cell (WBC) count $>10 \times 10^3/\mu L$; or immature bands $>15\%$.

Patients with cIAIs should have required a surgical procedure to treat the infection. cIAIs included intra-abdominal abscess; appendicitis complicated by perforation and/or periappendiceal abscess; perforated diverticulitis complicated by abscess formation or faecal contamination; complicated cholecystitis with evidence of perforation or empyema; perforation of the large or small intestine with abscess or faecal contamination; purulent peritonitis or peritonitis associated with faecal contamination; perforated gastric or duodenal ulcer with symptoms exceeding 24 h; or traumatic bowel perforation with symptoms lasting at least 12 h before operation. Additionally, patients had to have one of the following signs and symptoms: fever

or hypothermia during the 24 h preceding enrolment; WBC count $>10 \times 10^3/\mu L$; or immature bands >15%.

cSSSIs included infections involving deep soft tissue, requiring significant surgical intervention or associated with a significant underlying disease state (diabetes mellitus, peripheral vascular disease, peripheral neuropathy or lower venous insufficiency) that complicates response to treatment. In addition to the infection, patients had to have at least two of the following signs and symptoms: drainage or discharge; fever; hypothermia; erythema; swelling; localized warmth; pain; WBC count $>10 \times 10^3/\mu L$; or immature bands >15%. Infection in patients with a diabetic foot ulcer or a decubitus ulcer had to be 1 week or less in duration.

For patients with hospital-acquired pneumonia, radiographic evidence of a new or evolving infiltrate developing 48 h or later after in-patient admission was required, together with onset of symptoms at least 48 h after admission or within 7 days of discharge after an in-hospital stay of at least 3 or more days. Patients had to be in respiratory failure, requiring endotracheal intubation, or have at least two of the following: dyspnoea, tachypnoea or respiratory rate $\geq$30 breaths per minute; cough; pleuritic chest pain; rales or evidence of consolidation; hypoxaemia; or sputum characteristics consistent with bacterial infection. Additional requirements were a WBC count $>10 \times 10^3$ or $<4.5 \times 10^3/\mu L$ or immature bands >15%; fever or hypothermia; an adequate lower respiratory tract specimen with a positive culture.

Patients with community-acquired pneumonia were enrolled if a chest radiograph obtained within 48 h of the first dose of study medication showed a new infiltrate; the WBC count was $>10 \times 10^3$ or $<4.5 \times 10^3/\mu L$ or immature bands were >15%; and fever or hypothermia was present. Additionally, the presence of at least two of the following signs and symptoms was required: dyspnoea or tachypnoea; cough; sputum characteristics consistent with bacterial infection; rales or evidence of pulmonary consolidation; and hypoxaemia.

Exclusion criteria. Patients were not enrolled in the study if the anticipated length of antibiotic therapy was <7 days or if they had any concomitant condition or were taking any medication that precluded evaluation of a response based on the clinical judgement of the principal investigator or made it unlikely that the planned course of therapy would be completed. Primary exclusion criteria included: infection with both VRE and MRSA, colonization with VRE or MRSA, or receipt of >24 h of potentially effective concomitant antibacterial therapy for VRE or MRSA after baseline culture was obtained, but before the first dose of the study drug. Other exclusion factors were diabetic foot ulcer or decubitus ulcer infected for >1 week; necrotizing fasciitis or gangrene or suspicion of ecthyma gangrenosum or crepitant cellulites; preoperative suspicion of spontaneous bacterial peritonitis, simple cholecystitis, gangrenous cholecystitis without rupture, simple appendicitis, acute suppurative cholangitis, pancreatic abscess or infectious necrotizing pancreatitis; hepatic disease; neutropenia (absolute neutrophil count $<500/mm^3$), unless MRSA or VRE was the only causative pathogen; creatinine clearance <30 mL/min; endocarditis; primary urinary tract infection; osteomyelitis; meningitis; septic shock; or septic arthritis. Patients with an APACHE II score >30 or with a life expectancy of <1 month and women who were pregnant or breast-feeding were excluded.

Microbiological analysis

All positive cultures for MRSA and VRE from any clinical specimen (e.g. blood, skin and/or skin structure site, respiratory) were sent to a central laboratory for confirmation by standard laboratory procedures to separate true pathogens from contaminant organisms. Isolates tested at the central laboratory were subsequently reviewed and an evaluation was made to determine whether the isolate was a true pathogen or a contaminant, based on medical judgement and published literature, for what would be considered a causative pathogen for each specific site of infection. All susceptibility testing to study drugs was performed according to the methods of the Clinical Laboratory Standards Institute (formerly the NCCLS).

Populations analysed

Patients were assigned to specific populations as defined by Wyeth Research according to the definitions outlined in the protocol and statistical analysis plan. These assignments were made at the end of the study after the database was finalized.

Patients who were randomized to treatment comprised the intent-to-treat (ITT) population. The modified ITT (mITT) population consisted of ITT patients who received at least one dose of the study drug; all mITT patients were assigned a clinical response (cure, failure and indeterminate) by the investigator. Patients in the mITT population who had clinical evidence of disease by meeting minimal disease criteria (e.g. they satisfied all *a priori* requirements for cSSSIs) and had confirmed VRE or MRSA as a baseline isolate (i.e. repeat-positive-culture required if patients had received a recent antibiotic prior to study entry) comprised the microbiological mITT (m-mITT) population. From this population, the microbiologically evaluable (ME) population was defined as those who met inclusion and exclusion criteria, received no more than one dose of potentially effective concomitant therapy for MRSA or VRE infection after the first dose of the study drug, received no more than 24 h of concomitant therapy between obtaining the baseline culture and starting the study drug, had a clinical response of cure or failure at the TOC assessment, and a pre-therapy culture containing MRSA or VRE that was susceptible to both of the relevant study drugs and microbiological or clinical information to allow classification of a microbiological response at the TOC assessment.

Assessments

The primary efficacy endpoint was the clinical response (cure, failure and indeterminate) in the ME and m-mITT populations (co-primary populations) at the TOC assessment. This assessment was determined by the principal investigator between 12 and 37 days after the last dose of the study drug was administered. Patients' clinical status was recorded at baseline, daily during therapy, on the last day of therapy and at the TOC assessment. These assessments included the presence or absence of the clinical signs and symptoms of infection. 'Cure' was defined as resolution of signs and symptoms or improvement such that no further antibacterial therapy was required. 'Failure' was defined as a lack of response necessitating additional antibacterial therapy, need for unplanned surgical intervention, initial recovery followed by deterioration before the TOC visit and requiring additional antibacterial therapy, death from the infection 2 or more days after randomization or from a treatment-related adverse event (AE), or receipt of >120% of the expected doses of the study drug. A response was deemed 'indeterminate' if the patient was lost to follow-up, death occurred within the first 2 days of receiving the study drug or death occurred from a non-infectious cause or from another infection between study day 2 and the TOC assessment.

All patients who received at least one dose of the study drug (mITT population) were evaluated for safety on the basis of medical history, physical examination, reports of clinical AEs and findings

from serum chemistry, haematology and coagulation tests. AEs and serious AEs, including deaths, were recorded throughout the study period through the TOC assessment (or 14 days after the last dose of the study drug, whichever was greater), with severity and relationship to the study drug determined by the investigator. Safety assessments included a 12-lead electrocardiogram at baseline. Laboratory and microbiological evaluations were performed at baseline, on selected days during treatment, and on the last day of therapy. For patients with pneumonia, chest radiographs were obtained at baseline and at the TOC assessment.

Statistical analyses

Data for MRSA and VRE patients were analysed separately. No formal statistical analyses were planned, but clinical response rates were estimated and 95% confidence intervals (CIs) for the true proportion of favourable responses in each treatment group were calculated. Patients were stratified by type of infection (MRSA or VRE), site of infection (cIAI or other infection for VRE patients; cSSSI or other infection for MRSA patients) and APACHE II score (>15 or ≤ 15). The co-primary efficacy analysis was the clinical response rate for the ME population (cure/failure) and for the m-mITT population (cure or failure/indeterminate) at the TOC assessment.

For MRSA patients, the targeted enrolment was 140 patients, based on an anticipated evaluability rate of 80% and 112 evaluable patients. A 3:1 (tigecycline to vancomycin) randomization scheme lent additional reliability to findings obtained with the study drug, and with an expected cure rate of 80%, the two-sided 95% CI was 0.70–0.88 for the tigecycline group and 0.59–0.92 for the vancomycin group.

The study planned to enrol 208 patients with VRE to allow for 144 evaluable subjects based on an anticipated evaluability rate of 70%. A 3:1 randomization scheme allowed for 108 patients to be assigned to tigecycline and 36 to linezolid, lending additional reliability to findings obtained with the study drug. With a cure rate of 70%, the two-sided 95% CI was 0.61–0.79 for the tigecycline arm and 0.52–0.84 for the linezolid arm. After completion of 24 months of planned recruitment, the VRE arm had enrolled only 15 of the targeted 208 patients because the trial design excluded subjects most at risk of developing VRE. A decision was made to terminate this portion of the study early without accruing the targeted number of patients with VRE.

Results

A total of 157 patients with MRSA infection (Figure 1) and a total of 15 patients with VRE infection (Figure 2) were enrolled

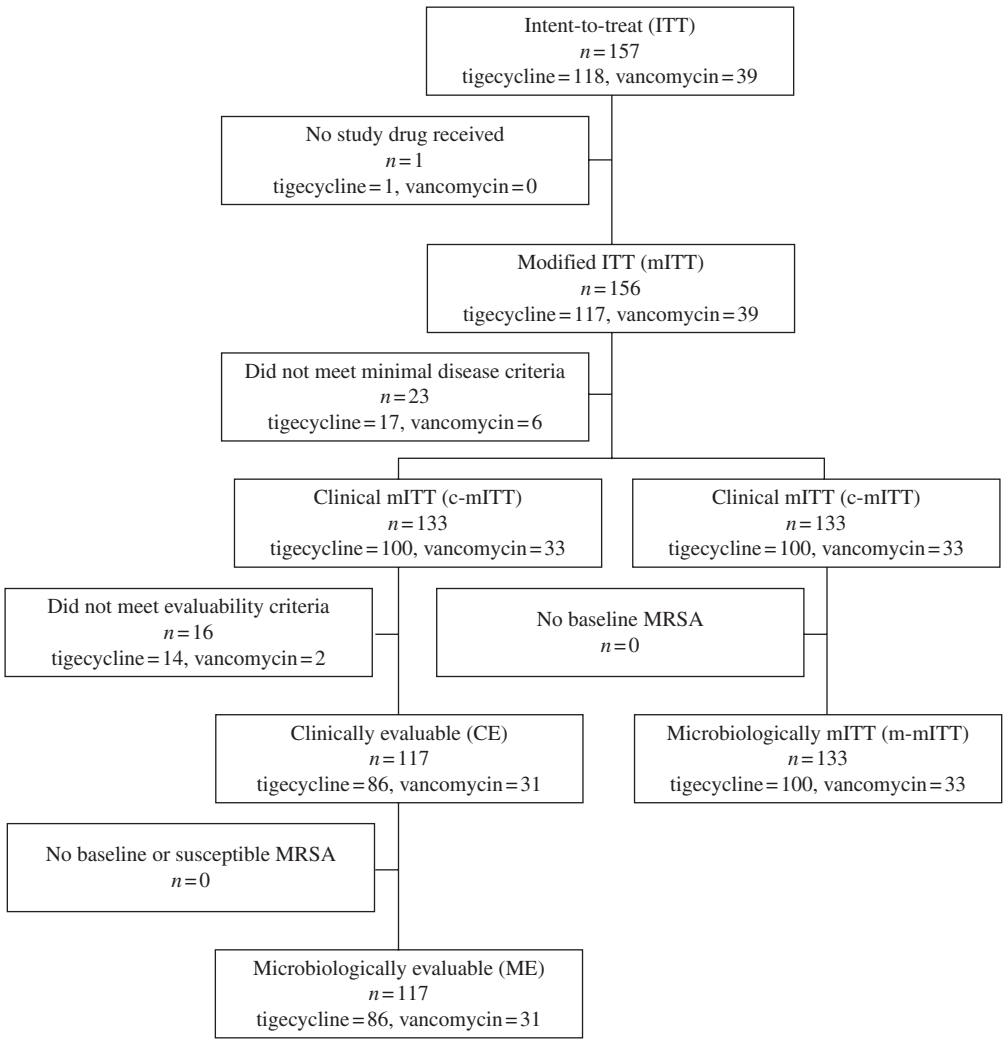

Figure 1. Number of MRSA subjects included in each population.

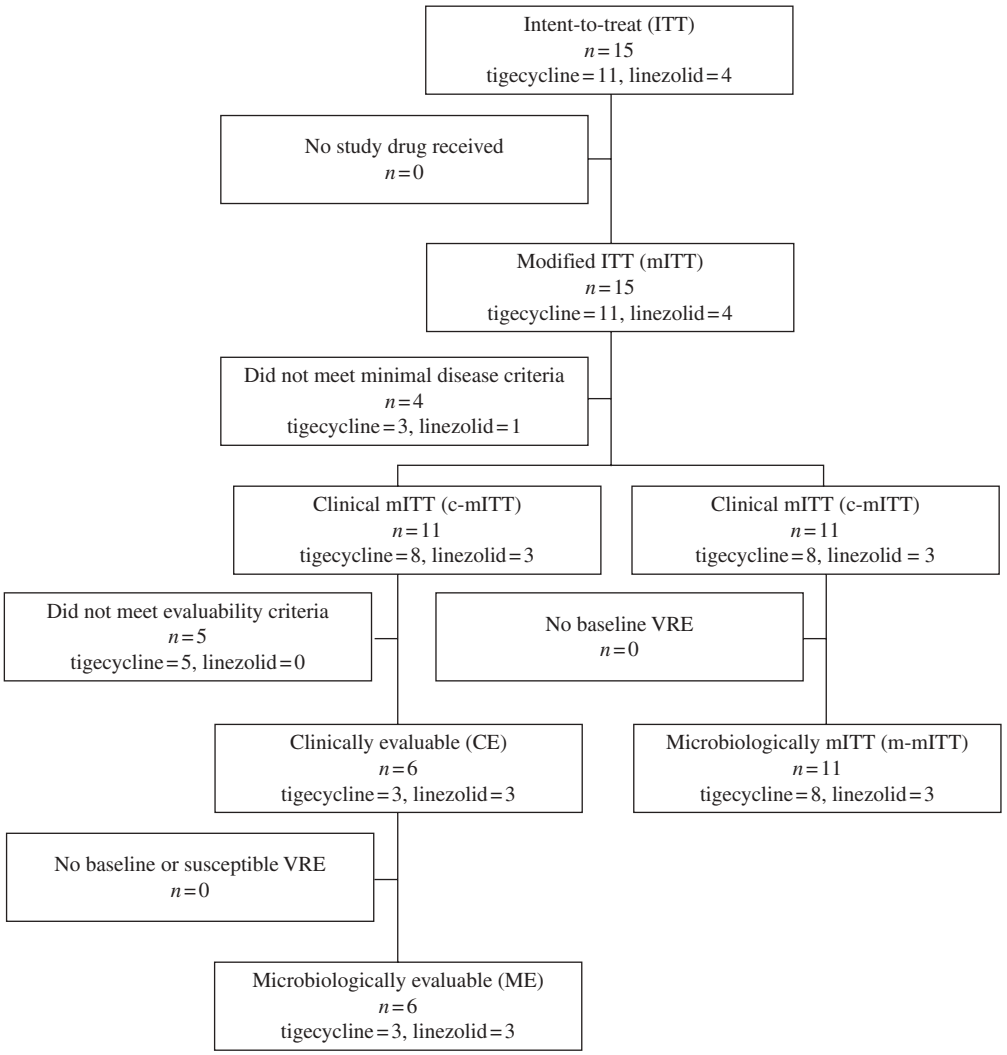

Figure 2. Number of VRE subjects included in each population.

and comprised the ITT populations (Table 1). One hundred and fifty-six MRSA patients received the study drug and hence comprised the MRSA mITT population; all patients with VRE received the study drug. In the MRSA group, 74.5% and 84.7% of patients comprised the ME and m-mITT populations, respectively, and in the VRE group, 40.0% and 73.3% of the patients comprised the ME and m-mITT populations, respectively. Overall, 22 of 156 patients with MRSA (14.1%) and 6 of 15 patients with VRE (40.0%) discontinued study drugs. AEs were the main reason for discontinuing the treatment, with discontinuation rates in the MRSA group of 6.8% for tigecycline and 5.1% for vancomycin. In the VRE group, three patients treated with tigecycline and none treated with linezolid withdrew because of AEs.

Baseline characteristics of the mITT population were similar among the treatment groups (Table 2), with the exception of APACHE II scores, which were generally higher among patients with VRE (mean score, 13.20) than those with MRSA (mean score, 7.87). In the VRE population, APACHE II scores were significantly higher in the tigecycline group compared with those in the linezolid group (14.91 versus 8.50). Patients with MRSA infection were younger than those with VRE infection (median age, 51 years compared with 65 years), and a higher proportion of MRSA patients were male (63.5% for MSRA compared with 46.7% for VRE). Approximately 75% of the study population was white.

The main diagnoses among patients infected with MRSA were cSSSI (69.2%) and cIAI (13.5%). cSSSIs in this population consisted mainly of deep soft tissue infections (37.0%) and major abscesses (32.4%). In VRE patients, the main diagnoses were bacteraemia (40.0%), cSSSI (33.3%) and cIAI (26.7%). In all patients with cSSSI, co-morbid conditions such as diabetes and peripheral vascular disease that predispose to cSSSI were present in 23.1% and 17.6%, respectively, of MRSA patients and 60.0% and 40.0%, respectively, of VRE patients.

The mean time from recruitment to the TOC assessment for the mITT population in patients with MRSA was 27.4 days for tigecycline and 30.8 days for vancomycin. Corresponding mean times for patients with VRE were 18.6 days for tigecycline and 27.3 days for linezolid.

In vitro susceptibility data

For all strains of MRSA tested (ME, $n = 117$ and m-mITT, $n = 133$), low MICs of tigecycline were reported (range 0.12–

Table 1. Study populations analysed

Population	MRSA			VRE		
	tigecycline *n* (%ITT)	vancomycin *n* (%ITT)	total *n* (%ITT)	tigecycline *n* (%ITT)	linezolid *n* (%ITT)	total *n* (%ITT)
Intent-to-treat (ITT)	118	39	157	11	4	15
No treatment received	1	0	1			
Modified ITT (mITT)	117 (99.2)	39 (100)	156 (99.4)	11 (100)	4 (100)	15 (100)
Did not meet minimum disease criteria	17	6	23	3	1	4
Clinical mITT (c-mITT)	100 (84.7)	33 (84.6)	133 (84.7)	8 (72.7)	3 (75.0)	11 (73.3)
Did not meet clinical evaluability criteria	14	2	16	5	0	5
Clinically evaluable (CE)	86 (72.9)	31 (79.5)	117 (74.5)	3 (27.3)	3 (75.0)	6 (40.0)
Microbiologically evaluable (ME)	86 (72.9)	31 (79.5)	117 (74.5)	3	3	6
Microbiological mITT (m-mITT)	100 (84.7)	33 (84.6)	133 (84.7)	8 (72.7)	3 (75.0)	11 (73.3)

ITT, all randomized subjects; mITT, ITT subjects who received at least one dose of study drug; c-mITT, mITT subjects with evidence of disease criteria; m-mITT, c-mITT subjects with identified baseline MRSA or VRE; CE, c-mITT subjects who meet clinically evaluable requirements; ME, CE subjects who meet criteria for microbiological assessment; MRSA, methicillin-resistant *S. aureus*; VRE, vancomycin-resistant *Enterococcus*.

0.50 mg/L). For the few VRE isolates tested (ME, $n = 5$ and m-mITT, $n = 10$), tigecycline MICs ranged between 0.06 and 0.12 mg/L for *E. faecium* and was 0.06 mg/L for one isolate of *E. faecalis*.

Efficacy in MRSA infection

Overall, clinical cure rates in the ME population at the TOC assessment for MRSA infection were 81.4% (70 of 86 patients) with tigecycline and 83.9% (26 of 31 patients) with vancomycin (Table 3). In patients with cSSSIs caused by MRSA, cure rates were similar after treatment with tigecycline (51 of 59 patients; 86.4%) or vancomycin (20 of 23 patients; 86.9%). An APACHE score of >15 was generally associated with a poorer cure rate for MRSA infection with either antibiotic [three of seven patients treated with tigecycline (42.9%) and one of three treated with vancomycin (33.3%)]. However, fewer than 10% of patients in each treatment group had APACHE II scores >15.

Results for the co-primary m-mITT population were similar to those noted in the ME population for infections with MRSA overall and for cSSSIs. At the TOC assessment for the m-mITT population, a clinical cure was achieved in 75 of 100 patients treated with tigecycline (75%) and 27 of 33 patients (81.8%) treated with vancomycin. For patients with cSSSIs in the m-mITT population, 55 of 70 tigecycline-treated patients (78.6%) and 20 of 23 vancomycin-treated patients (87.0%) were cured. In both the treatment groups, fewer patients with higher APACHE II scores responded to therapy [tigecycline, four of nine patients (44.4%); vancomycin, one of four patients (25%)]. In patients with MRSA that had polymicrobial infections (27% and 25% of the ME and m-mITT populations, respectively), a cure rate of at least 80% was noted after treatment with tigecycline.

Findings from an ITT analysis for clinical response supported the co-primary ME and m-mITT population analyses. A clinical cure was achieved in 85 of 118 ITT patients treated with tigecycline (72%) and 29 of 39 ITT patients (74.4%) treated with vancomycin. Microbiological response rates generally paralleled clinical response rates for both the m-mITT and ME populations as the majority of responses were presumed eradications based on clinical cure findings. Within the MRSA ME population, the organisms were eradicated (documented or presumed) in 80.2% (69 of 86) of tigecycline-treated subjects and 83.9% (26 of 31) of vancomycin-treated subjects at the TOC assessment. Within the MRSA m-mITT population, eradication rates for tigecycline and vancomycin were 74.0% (74 of 100) and 81.8% (27 of 33), respectively, at the TOC assessment. Twenty ME patients (14 tigecycline and 6 vancomycin) had MRSA bacteraemia at baseline. Clinical cure and microbiological eradication at the TOC assessment were achieved in 64.3% (9 of 14) of tigecycline-treated patients and 50% (3 of 6) of vancomycin-treated patients.

Efficacy in VRE infection

At the TOC assessment, a clinical cure was obtained in all the three patients in the ME population with VRE infection who were treated with tigecycline and in two of three patients treated with linezolid (66.7%; Table 4). In the m-mITT patients with VRE infection, three of eight patients treated with tigecycline

Table 2. Baseline demographic and clinical characteristics of patients infected with MRSA or VRE (mITT population)

	MRSA			VRE		
Characteristic	tigecycline ($n = 117$)	vancomycin ($n = 39$)	total ($n = 156$)	tigecycline ($n = 11$)	linezolid ($n = 4$)	total ($n = 15$)
Age (median), years	51.00	51.00	51.00	65.00	51.00	65.00
Sex, *n* (%)						
Male	76 (65.0)	23 (59.0)	99 (63.5)	6 (54.5)	1 (25.0)	7 (46.7)
Female	41 (35.0)	16 (41.0)	57 (36.5)	5 (45.5)	3 (75.0)	8 (53.3)
Ethnic origin, *n* (%)						
White	88 (75.2)	31 (79.5)	119 (76.3)	8 (72.7)	3 (75.0)	11 (73.3)
Black	11 (9.4)	3 (7.7)	14 (9.0)	2 (18.2)	1 (25.0)	3 (20.0)
Hispanic	16 (13.7)	4 (10.3)	20 (12.8)	1 (9.1)	0	1 (6.7)
Other	2 (1.7)	1 (2.6)	3 (1.9)	0	0	0
Weight (mean ± SD), kg	80.1 ± 20.8	75.5 ± 20.0	79.0 ± 20.7	76.9 ± 16.9	100 ± 52.5	83.1 ± 30.1
Creatinine clearance (mean ± SD), mL/min	112.1 ± 55.7	116.8 ± 50.2	113.23 ± 54.2	93.01 ± 45.5	120.9 ± 48.8	100.45 ± 46.4
APACHE II score (mean ± SD)	7.9 ± 5.0	7.9 ± 6.3	7.9 ± 5.3	14.9 ± 4.7	8.5 ± 5.6	13.2 ± 5.6
Primary diagnosis, *n* (%)						
Primary bacteraemia	11 (9.4)	4 (10.3)	15 (9.6)	6 (54.5)	0	6 (40.0)
Community-acquired pneumonia	1 (0.9)	1 (2.6)	2 (1.3)	0	0	0
cIAI	15 (12.8)	6 (15.4)	21 (13.5)	3 (27.3)	1 (25.0)	4 (26.7)
cSSSI	81 (69.2)	27 (69.2)	108 (69.2)	2 (18.2)	3 (75.0)	5 (33.3)
Hospital-acquired pneumonia	9 (7.7)	1 (2.6)	10 (6.4)	0	0	0

APACHE, Acute Physiologic and Chronic Health Evaluation; mITT, modified intent-to-treat; MRSA, methicillin-resistant *Staphylococcus aureus*; VRE, vancomycin-resistant *Enterococcus*; cIAI, complicated intra-abdominal infection; cSSSI, complicated skin and skin structure infection.

Table 3. Clinical response (rate of cure) at TOC assessment in patients with MRSA infection

APACHE II Score	Site of infection	Tigecycline		Vancomycin	
		n/N	% (95% CI)	*n/N*	% (95% CI)
ME population					
≤15	cSSSI	50/58	86.2 (74.6–93.9)	19/22	86.4 (65.1–97.1)
	other	17/21	81.0 (58.1–94.6)	6/6	100.0 (54.1–100.0)
>15	cSSSI	1/1	100.0 (2.5–100.0)	1/1	100.0 (2.5–100.0)
	other	2/6	33.3 (4.3–77.7)	0/2	0.0 (0.0–84.2)
overall		70/86	81.4 (71.6–89.0)	26/31	83.9 (66.3–94.5)
m-mITT population					
≤15	cSSSI	54/69	78.3 (66.7–87.3)	19/22	86.4 (65.1–97.1)
	other	17/22	77.3 (54.6–92.2)	7/7	100.0 (59.0–100.0)
>15	cSSSI	1/1	100.0 (2.5–100.0)	1/1	100.0 (2.5–100.0)
	other	3/8	37.5 (8.5–75.5)	0/3	0.0 (0.0–70.8)
overall		75/100	75.0 (65.3–83.1)	27/33	81.8 (64.5–93.0)

APACHE, Acute Physiologic and Chronic Health Evaluation; cSSSI, complicated skin and/or skin structure infection; ME, microbiologically evaluable; m-mITT, microbiological modified intent-to-treat.

Table 4. Clinical response (rate of cure) at TOC assessment in patients with VRE infection

APACHE II score	Site of infection	Tigecycline		Linezolid	
		n/N	% (95% CI)	*n/N*	% (95% CI)
ME population					
≤15	cIAI	1/1	100.0 (2.5–100.0)	0/1	0.0 (0.0–97.5)
	other	2/2	100.0 (15.8–100.0)	1/1	100.0 (2.5–100.0)
>15	cIAI	0/0	NA	0/0	NA
	other	0/0	NA	1/1	100.0 (2.5–100.0)
overall		3/3	100.0 (29.2–100.0)	2/3	66.7 (9.4–99.2)
m-mITT population					
≤15	cIAI	1/2	50.0 (1.3–98.7)	0/1	0.0 (0.0–97.5)
	other	2/3	66.7 (9.4–99.2)	1/1	100.0 (2.5–100.0)
>15	cIAI	0/0	NA	0/0	NA
	other	0/3	0.0 (0.0–70.8)	1/1	100.0 (2.5–100.0)
overall		3/8	37.5 (8.5–75.5)	2/3	66.7 (9.4–99.2)

APACHE, Acute Physiologic and Chronic Health Evaluation; cIAI, complicated intra-abdominal infection; ME, microbiologically evaluable; m-mITT, microbiological modified intent-to-treat.

(37.5%) showed a clinical response, compared with two of three patients treated with linezolid (66.7%). An ITT analysis for the clinical cure at the TOC assessment corroborated these findings: 36.4% (4 of 11) for tigecycline and 75% (3 of 4) for vancomycin.

Within the ME population, the organisms were eradicated (presumed in all cases) in all three (100%) of the tigecycline-treated patients and two of three (66.7%) of the linezolid-treated patients at the TOC assessment. Within the m-mITT population, eradication rates after tigecycline and linezolid were 37.5% (3 of 8) and 66.7% (2 of 3), respectively, at the TOC assessment. One VRE ME tigecycline-treated patient had bacteraemia at baseline. The single blood isolate, a VRE *faecium*, had a tigecycline MIC of 0.12 mg/L; the patient achieved both the clinical cure and microbiological eradication at TOC.

Evaluation of safety

Data from patients in the mITT population with MRSA ($n = 156$) or VRE infection ($n = 15$) were analysed for safety and tolerability (Table 5). For MRSA infection, significantly fewer doses of tigecycline were administered compared with vancomycin (mean, 21.1 doses compared with 24.9 doses), but the mean duration of treatment was similar for the two treatment groups (tigecycline 11.4 days; vancomycin 13.1 days). Except for one patient who received >120% of the expected dose of

Table 5. Safety of tigecycline and vancomycin in patients with MRSA or VRE infection (mITT population)

	MRSA		VRE	
	tigecycline ($n = 117$)	vancomycin ($n = 39$)	tigecycline ($n = 11$)	linezolid ($n = 4$)
Mean duration of therapy (days) ± SD	11.4 ± 4.9	13.1 ± 5.7	11.7 ± 6.7	12.5 ± 4.8
Any treatment-emergent AE, *n* (%)	81 (69.2)	26 (66.7)	10 (90.9)	3 (75.0)
AEs differing significantly between groups, *n* (%)				
digestive system as a whole	58 (49.6)[a]	12 (30.8)	6 (54.5)	2 (50.0)
nausea	42 (35.9)[a]	6 (15.4)	2 (18.2)	2 (50.0)
nausea and/or vomiting	48 (41.0)[a]	7 (17.9)	4 (36.4)	2 (50.0)
ALT increased	1 (0.9)	3 (7.7)*	1 (9.1)	0
AST increased	1 (0.9)	3 (7.7)*	1 (9.1)	0
Death, *n* (%)	6 (5.2)	2 (4.8)	5 (45.5)	0
Serious adverse events, *n* (%)	23 (19.7)	8 (20.5)	7 (63.6)	1 (25.0)
Treatment discontinuation for AE, *n* (%)	8 (6.8)	2 (5.1)	3 (27.3)	0

[a]Significant difference between treatment groups at <0.05 level.

vancomycin, all patients received between 80% and 120% of the expected dosage of the study drug. For VRE infection, the mean number of doses and duration of treatment were similar for patients treated with tigecycline (21.5 doses, 11.7 days) or linezolid (23.3 doses, 12.5 days).

Adverse events

AEs were reported by 113 of the 156 MRSA patients (72%) and 13 of the 15 VRE patients (87%), with a similar frequency among patients treated with tigecycline or the comparator drug. One or more treatment-emergent AEs were reported by 107 (69%) of the 156 MRSA subjects (69% of tigecycline-treated subjects and 67% of vancomycin-treated subjects) and by 13 (87%) of the 15 VRE subjects (91% of tigecycline-treated subjects and 75% of linezolid-treated subjects) (Table 5).

AEs considered by the investigator to be related to study medication (tigecycline or the comparator drug) were reported by 66 (42.3%) of the MRSA patients and 8 (53.3%) of the VRE patients. The frequency of drug-related AEs was similar in patients with MRSA infection receiving tigecycline (45.3%) or vancomycin (33.3%) and in patients with VRE infection receiving tigecycline (54.5%) or linezolid (50.0%). Nausea and vomiting were the most frequently reported drug-related AEs in patients with MRSA infection treated with tigecycline. Nausea was also the most frequently reported drug-related AE for vancomycin-treated subjects. The frequency of drug-related digestive system AEs overall, as well as for nausea and vomiting, in particular, was significantly higher with tigecycline treatment than with vancomycin treatment (35.9% versus 10.3%, respectively, for digestive system; 29.1% versus 7.7%, respectively, for nausea; 18.8% versus 2.6%, respectively, for vomiting). Despite the increased incidence of nausea and vomiting with tigecycline treatment, only three tigecycline-treated MRSA patients discontinued treatment because of these events. Most occurrences of nausea or vomiting were mild to moderate (Grade 1 or 2); two patients reported severe (Grade 3) nausea and one patient reported severe vomiting. Paralleling the increased occurrence of nausea or vomiting was a greater frequency of use of concomitant medications in the tigecycline group to treat these AEs (37.6% versus 17.9%). Metoclopramide was the most frequently administered anti-emetic agent, received by 23% of tigecycline-treated patients and 10% of vancomycin-treated patients.

The only other statistically significant difference for drug-related AEs was for the urogenital system, with significantly more vancomycin-treated subjects reporting AEs under this system (10.3% versus 1.7% for vancomycin- and tigecycline-treated subjects, respectively).

In patients with VRE, two patients in the tigecycline treatment group had drug-related diarrhoea. One of these was considered severe. All of the other AEs occurred in fewer than two subjects in each treatment group and all occurrences were mild.

Thirteen patients died during the study: eight with MRSA infection [six (5.2%) treated with tigecycline and two (4.8%) with vancomycin] and five with VRE infection (all treated with tigecycline). Except for one tigecycline-treated patient with a VRE infection who died of septic shock that was diagnosed 3 days after his last dose of tigecycline, all deaths were considered by the investigator to be unrelated to study drugs [details of the patients are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/)].

A total of 39 patients experienced at least one serious AE during the study: 31 with MRSA [23 (19.7%) treated with tigecycline and 8 (20.5%) treated with vancomycin] and 8 with VRE [7 (63.6%) treated with tigecycline and 1 (25.0%) treated with linezolid]. There was no significant clustering of serious AEs within a single body system or event type for any treatment group among the MRSA and VRE patients.

Of the 171 mITT patients, 13 (7.6%) discontinued the study drug because of AEs. Among the 156 patients with MRSA infection, 10 discontinued treatment [eight in the tigecycline group (6.8%) and two in the vancomycin group (5.1%)]. Among patients with VRE, treatment discontinuation due to AEs occurred in 3 of 11 patients (27.3%) treated with tigecycline and in none of the linezolid-treated patients. AEs leading to discontinuation of tigecycline in MRSA patients included nausea and vomiting (3), new infection (2), hepatic failure (in a patient with a history of liver failure and liver test abnormalities at baseline) (1), abnormal liver function test (1) and embolus (1). One patient each in the vancomycin group discontinued because of

lung oedema or acute renal failure. Among VRE patients, tigecycline was discontinued because of diarrhoea, haemolysis (in a patient with decreased haemoglobin at baseline, receiving iron, taking a blood transfusion 4 days before study start) or pneumonia (one patient each). Overall, all types of AE led to premature discontinuation in both the tigecycline and vancomycin groups.

Among tigecycline-treated MRSA patients, mean BUN/urea values increased during therapy, and the mean change was statistically significantly greater than that in vancomycin-treated patients at different time points during therapy ($P < 0.02$). However, mean serum creatinine decreased and creatinine clearance increased in tigecycline-treated patients, while serum creatinine increased and creatinine clearance decreased in vancomycin-treated patients. The differences in creatinine clearance between the two treatment groups were statistically significant on the last day of treatment ($P < 0.03$).

Discussion

Multidrug-resistant Gram-positive pathogens such as MRSA and VRE are an increasing cause of nosocomial infections such as cSSSI, bacteraemia, cIAI and pneumonia.[5,10,24–26] Inadequate antibiotic management of these infections is often associated with treatment failure, increasing mortality and higher costs.[27,28] The use of tigecycline was therefore evaluated in patients with serious infections caused by MRSA or VRE as the sole pathogen or as part of a polymicrobial infection.

Vancomycin is currently the mainstay antibiotic for treatment of infections caused by MRSA and was therefore used in this study as the active treatment comparator in patients with MRSA infection. Clinical cure rates in patients with serious MRSA infection were comparable for tigecycline and vancomycin. In the ME population, tigecycline led to a clinical cure in 81.4% compared with 83.9% treated with vancomycin. In the m-mITT population, clinical cure rates were 75.0% and 81.8% in subjects treated with tigecycline or vancomycin, respectively. These results, however, assume that the efficacy of either tigecycline or the comparator drugs was not impacted on by variation in the length of time between randomization and evaluation at the TOC assessment, which was not estimated.

In surveillance studies, *S. aureus* is the most commonly isolated organism from patients with cSSSI.[29,30] In the current study, 69% of patients from whom MRSA was isolated had a primary diagnosis of cSSSI. Clinical cure rates to tigecycline and vancomycin were 86.4% and 86.9%, respectively, for the ME population and 78.6% and 87.0%, respectively, for the m-mITT population. The efficacy of both antibiotics was also similarly reduced in patients with a worse clinical condition (APACHE II score of >15) compared with those with less severe illness, primarily patients with cSSSI.

Significantly fewer VRE subjects were enrolled and evaluated than planned, and only 40% of the 15 subjects who enrolled were evaluable. Few conclusions can therefore be drawn about the effectiveness of tigecycline for treating VRE. Tigecycline effected a clinical cure in 3 of 3 ME patients and in 3 of 8 m-mITT patients, and linezolid was effective in 2 of 3 patients in the ME and m-mITT populations. Treatment failure in tigecycline-treated patients with VRE could in part be due to the higher morbidity (higher APACHE II scores) and more serious nature of their infections (high incidence of bacteraemia).

No new safety concerns for tigecycline emerged in this population of seriously ill patients. In agreement with the previously described safety profile of tigecycline, nausea and vomiting were the only AEs that occurred more frequently with tigecycline than with vancomycin. These events were mild to moderate in the majority of cases and led to treatment withdrawal in only three patients. Of the 13 deaths that occurred during the study, only one in a tigecycline-treated patient with VRE infection was considered by the investigator to be possibly related to the study drug; this patient was diagnosed with septic shock several days after tigecycline was discontinued. The frequency of death and serious AEs were consistent with the severity of illness of the patients and the nature of the infections and were similar with tigecycline or vancomycin treatment. The mean changes in BUN/urea that were observed with tigecycline are consistent with its protein-catabolic effects.

cSSSIs and cIAIs are frequent polymicrobial infections that require treatment with a broad-spectrum agent or with a combination of agents.[21,31] In previous Phase 3 studies, monotherapy with tigecycline was as effective as current standard treatment regimens in patients with cSSSIs (vancomycin/aztreonam)[21,22] or cIAIs (imipenem/cilastatin).[31] The current study extends these findings and shows that in patients with serious infections, including cSSSI or cIAI, in which MRSA is also isolated, cure rates with tigecycline are comparable to those with vancomycin. Microbiological responses in these patients with MRSA infections mirrored clinical cure rates, although most of the eradication was presumed, based on clinical response (data not shown). A substantial proportion of patients with MRSA had polymicrobial infection (27% and 25% of the ME and m-mITT populations, respectively); a cure rate of at least 80% was noted in these patients after treatment with tigecycline. This cure rate was similar to that obtained in patients with monomicrobial infection and was also similar to that noted in the vancomycin group (data not shown).

Hospitalized patients are particularly vulnerable to resistant strains, developing infections that are manifested as infected burns, deep abscesses, surgical wound infection perforations or complicated appendicitis, among others. These clinical complications, when added to an already weakened medical condition, cause significant problems in clinical practice and consume substantial hospital resources.[32,33] Antibiotic therapy and surgical intervention are the mainstays of therapy for these infections.[27,28,34,35] Both cSSSI and cIAI are usually polymicrobial infections that are more likely to involve resistant organisms,[36] and the initial selection of empirical antimicrobial therapy for treating these infections is therefore important for a successful outcome.

Tigecycline belongs to a new class of antimicrobial agents and therefore may decrease the epidemiological selection pressure exerted by current antibiotic classes in promoting resistance.[37,38] No other drug to date combines activity against multidrug-resistant Gram-positive bacteria while providing coverage for Gram-negative organisms. *In vitro* studies show that tigecycline has broad-spectrum activity against a variety of Gram-positive, Gram-negative and anaerobic organisms and that it targets common pathogens responsible for cSSSIs and cIAIs.[39,40] The current study further confirms that tigecycline had excellent *in vitro* activity against isolates of MRSA and *Enterococcus* spp.

The ability of tigecycline to kill multidrug-resistant staphylococci and enterococci while maintaining activity against enteric Gram-negative organisms makes it attractive as an empirical

agent in many clinical situations, providing a valuable therapeutic option for hospitalized patients in whom the risk of resistance is highest and who need broad-spectrum coverage.

In summary, monotherapy with tigecycline was observed to be generally safe and well tolerated, and its efficacy was comparable to that of vancomycin in patients with serious infection caused by MRSA, including cSSSI, cIAI and pneumonia. The few subjects with VRE infection responded well to tigecycline, but the results need to be confirmed in a larger patient population.

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Supplementary data

Patient deaths throughout the study period are available as Supplementary data at *JAC* Online (http://jac.oxfordjournals.org/).

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