Tigecycline for the treatment of patients with severe sepsis or septic shock: a drug use evaluation in a surgical intensive care unit

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Objectives: Adequate antimicrobial therapy is crucial for the survival of critically ill patients with severe nosocomial infections. Tigecycline, the first available agent in the new class of glycylcyclines, is active against multiresistant Gram-positive and Gram-negative bacteria. The aim of this observational, retrospective evaluation was to assess tigecycline use patterns in a surgical intensive care unit (SICU) of a tertiary care centre.

Methods: Data from 70 patients receiving tigecycline in the SICU were analysed. We reviewed tigecycline use in terms of demographic data and co-morbidities, disease severity, clinical indication, microbiology, therapy regimens and mortality. A logistic regression analysis was performed to identify prognostic factors for mortality.

Results: The majority of patients had co-morbidities such as cancer (51%) or renal replacement therapy (57%). The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of patients at admission was 27. Intra-abdominal infection was most frequently diagnosed (50% of patients); intra-abdominal infection and pneumonia were diagnosed in 14%. Methicillin-resistant Staphylococcus aureus was found in 16% of patients (colonization; infection: 6%) and vancomycin-resistant enterococci in 27% (colonization; infection: 21%). The mean duration of tigecycline therapy was 9 ± 4 days; 76% of patients received tigecycline in combination, with 64% being treated second line. APACHE score and renal replacement were identified as predictive factors for mortality. SICU mortality was 30%.

Conclusions: Tigecycline treatment of critically ill SICU patients with severe sepsis or septic shock appeared to result in remarkably low mortality. Tigecycline may be an important treatment option for septic patients with infections resistant to other available agents.

Keywords: vancomycin-resistant enterococci, methicillin-resistant Staphylococcus aureus, antibiotic usage, intra-abdominal infections

Introduction

The high incidence of sepsis in critically ill patients in intensive care units (ICUs) is closely linked to ICU mortality.1 Over the last few decades, hospital mortality from sepsis has ranged from 25% to 80%,2 with the reported mortality rates varying by definition and severity of sepsis. Because rapid and adequate antimicrobial therapy is crucial for the survival of critically ill patients with sepsis,3,4 agents that provide broad antimicrobial coverage and effectively overcome resistance mechanisms are urgently required.

Tigecycline, a first-in-class glycylcycline, is approved for the treatment of complicated skin and skin-structure infections and complicated intra-abdominal infection in the USA and...
Europe.5,6 As tigecycline is highly effective against a wide range of clinically important Gram-positive and Gram-negative pathogens, including pathogens causing nosocomial infections such as methicillin-resistant Staphylococcus aureus (MRSA), vancomycin-resistant enterococci (VRE) and extended-spectrum β-lactamase (ESBL)-producing bacteria,7,8 it is an important treatment option, especially when pathogens resistant to other available antimicrobial agents are involved. Resistance to tigecycline by *Pseudomonas aeruginosa* and reduced susceptibility among *Proteus* spp. do occur.9,10

A pooled analysis of two randomized, double-blind, multinational, multicentre Phase III studies demonstrated that tigecycline monotherapy was as effective for the treatment of complicated skin and skin-structure infections in adults as a current standard combination regimen, i.e. vancomycin and aztreonam.7,11 Another pooled analysis of two Phase III double-blind trials of tigecycline versus imipenem-cilastatin in patients with complicated intra-abdominal infection showed that tigecycline was efficacious and well tolerated.12 The mean Acute Physiology and Chronic Health Evaluation (APACHE) II score of tigecycline-treated patients in this study was 6.3.12

The clinical reality in a surgical ICU (SICU) involves severe sepsis patients with substantially higher APACHE II scores than those treated in published clinical trials with tigecycline. Despite promising *in vitro* data,13 tigecycline use has not yet been systematically evaluated in the ICU setting. This observational, retrospective drug use analysis was carried out to review patterns of clinical use of tigecycline in an SICU in terms of demographic data and co-morbidities, disease severity, clinical indication and source of infection, microbiology, therapy regimens and mortality.

### Patients and methods

The current observational, retrospective drug use analysis was carried out in the interdisciplinary SICU of the University Hospital of Heidelberg, Germany, which is a large tertiary care centre. The SICU cares for abdominal, urological, vascular and trauma surgery patients and had gained experience in tigecycline use through participation in pivotal trials of tigecycline.12 The protocol was approved by the Ethics Committee of the University of Heidelberg, Germany.

Record data from all patients with severe sepsis or septic shock, as defined by the American College of Chest Physicians/Society of Critical Care Medicine Consensus Conference,14,15 who received tigecycline between January 2006 and April 2007, were included in this analysis; no further eligibility criteria were applied. We also included patients who were administered off-label tigecycline prior to its European approval in May 2006. Data collection was performed retrospectively by the hospital pharmacy department.

Data recorded on admission included age, sex, admission diagnoses, associated co-morbidities, and surgical procedures preceding admission. MRSA and VRE colonization status was assessed for patients with an estimated ICU stay of ≥24 h. The presence of systemic inflammatory response syndrome criteria, organ failure, and infection was recorded daily, as well as laboratory indices of organ dysfunction/failure (including platelet count, serum total bilirubin, serum creatinine, and serum lactate concentration) and markers of tissue inflammation and infection (including total leucocyte count and C-reactive protein).

According to clinical standard procedures in the SICU, blood cultures were obtained together with specimens from all relevant sites (bronchial aspirates, blood culture, urine, catheter tip, wound swabs and pleural and ascitic fluids) for microbiological studies. The hospital’s microbiology laboratory determined antimicrobial susceptibility of isolates following breakpoints defined by the NCCLS.16 SICU patients with sepsis of unknown aetiology were treated at the attending physician’s discretion, according to the recommendations of the German Paul-Ehrlich-Gesellschaft7,18 and the guidelines of the Infectious Disease Society of America.19 Treatment was defined as empirical when tigecycline was prescribed for signs of infection without prior identification of a responsible pathogen or even a specific localized source of infection. Empirical tigecycline therapies were started according to patients’ risk factors.

Tigecycline was administered according to the recommended dosing schedule:5 the initial dose of tigecycline was 100 mg intravenously (iv), followed by 50 mg iv every 12 h. The duration of tigecycline treatment depended on the site and severity of infection as well as clinical and bacteriological progress. No adjustment was made for patients with renal impairment, patients undergoing haemodialysis, or patients with hepatic impairment.

For the current analysis, the following parameters were evaluated on the basis of the data collected from patients’ records: demographic data and co-morbidities, disease severity, clinical indication and source of infection, isolated pathogen(s), therapy regimens and mortality. The severity of disease was evaluated within 24 h of admission and at the start of tigecycline therapy by the APACHE II score, the Simplified Acute Physiology System (SAPS) score, and the Sequential Organ Failure Assessment (SOFA) score. Duration and choice of previous treatment were also recorded. Mostly descriptive statistics were used. To analyse whether there are any prognostic predictors which lead to a difference in mortality in this specific study population, a multivariate logistic regression for factors which were found to be significantly predictive in preceding univariate analyses was performed (SAS Version 9.1, procedure logistic). *P* values less than 0.05 were considered to indicate statistical significance.

### Results

Data from 70 patients with severe sepsis or septic shock treated with tigecycline were analysed in this assessment.

#### Patient characteristics

Patient demographics, co-morbidities, and disease severity scores within 24 h of admission and at start of tigecycline therapy are shown in Table 1. The majority of the patient population experienced conditions leading to a higher risk of infections with multiresistant bacteria such as cancer, renal replacement therapy, diabetes mellitus or transplantation. The mean APACHE II score at admission was 27.

#### Indications for tigecycline use and isolated pathogens

The most frequent indications were complicated intra-abdominal infection, complicated skin and skin-structure infection, and pneumonia (Table 1). Tigecycline was also used in cases of worsening infection or clinical failure following first- or second-line therapy for urological infection, bone and joint infection, and bloodstream infection. Admission diagnoses were peritonitis, pancreatitis, pancreatic abscess, infected pseudocyst, post-necrotizing pancreatitis, hepatic abscess, cholangitis, bilioma, anastomosis insufficiencies, cirrhosis, perforations and urosepsis.
MRSA colonization was found in 16% of patients, and 27% had VRE colonization. Overall, 59 (84%) of the clinically identified infections were supported by positive cultures. Bacteria isolated from infections are presented in Table 2.

Enterococcus faecium was most frequently found, followed by VRE and Stenotrophomonas maltophilia.

Tigecycline therapy duration and regimens

The mean duration of tigecycline treatment was 9 ± 4 days (range 2–19). Second-line treatment with tigecycline as combination therapy was administered in 45 patients (64%; combination partners are listed in Table 3), and 15 (21%) received tigecycline as an antibiotic monotherapy second line. Eight patients (11%) received tigecycline first line in combination with carbapenem, and two (3%) were treated first line with tigecycline monotherapy according to antibiogram/susceptibility testing results.

Mortality and prognostic predictors

The SICU mortality of tigecycline-treated patients was 30%. Using univariate logistic regression, APACHE II, SOFA and SAPS scores were predictive of mortality, as was renal replacement therapy (Table 4). By multivariate analysis, the APACHE II score [odds ratio (OR) 1.08, confidence interval (CI) 1.01–1.16, \( P = 0.03 \)] and renal replacement therapy (OR 9.99, CI 2.00–49.88, \( P = 0.005\) ) were statistically significant predictors of mortality.

Discussion

We conducted this observational, retrospective analysis to reflect tigecycline use under real-life conditions of daily clinical practice in an SICU of a university hospital providing a full complement of services in medical care.
Table 3. Combination partners for tigecycline in second-line treatment

<table>
<thead>
<tr>
<th>Antibiotic agent</th>
<th>Number of combination therapies with tigecycline</th>
</tr>
</thead>
<tbody>
<tr>
<td>Carbapenem</td>
<td>29</td>
</tr>
<tr>
<td>Acylaminopenicillin</td>
<td>5</td>
</tr>
<tr>
<td>Quinolone</td>
<td>5</td>
</tr>
<tr>
<td>Cephalosporin third</td>
<td></td>
</tr>
<tr>
<td>generation</td>
<td></td>
</tr>
<tr>
<td>Colistin</td>
<td>3</td>
</tr>
<tr>
<td>Amikacin</td>
<td>2</td>
</tr>
<tr>
<td>Tobramycin</td>
<td>1</td>
</tr>
<tr>
<td>Vancomycin</td>
<td>1</td>
</tr>
</tbody>
</table>

Table 4. Results of univariate analysis of predictors of mortality

<table>
<thead>
<tr>
<th>Predictive factor</th>
<th>Odds ratio</th>
<th>95% Confidence interval</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>1.00</td>
<td>0.970–1.04</td>
<td>0.94</td>
</tr>
<tr>
<td>Malignancy</td>
<td>1.39</td>
<td>0.50–3.89</td>
<td>0.53</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>0.87</td>
<td>0.26–2.84</td>
<td>0.81</td>
</tr>
<tr>
<td>Transplantation</td>
<td>1.41</td>
<td>0.37–5.45</td>
<td>0.62</td>
</tr>
<tr>
<td>Empirical therapy</td>
<td>1.38</td>
<td>0.36–5.33</td>
<td>0.64</td>
</tr>
<tr>
<td>Renal replacement therapy</td>
<td>12.67</td>
<td>2.65–60.46</td>
<td>0.002*</td>
</tr>
<tr>
<td>APACHE II score</td>
<td>1.10</td>
<td>1.03–1.18</td>
<td>0.005*</td>
</tr>
<tr>
<td>SOFA score</td>
<td>1.20</td>
<td>1.00–1.44</td>
<td>0.05*</td>
</tr>
<tr>
<td>SAPS score</td>
<td>1.05</td>
<td>1.01–1.08</td>
<td>0.006*</td>
</tr>
</tbody>
</table>

SICU, Surgical Intensive Care Unit; APACHE, Acute Physiology and Chronic Health Evaluation; SAPS, Simplified Acute Physiology System; SOFA, Sequential Organ Failure Assessment. The numbers of patients with carcinoma, diabetes mellitus, transplantation or renal replacement therapy are listed in Table 1. P values less than 0.05 were considered to indicate statistical significance (indicated with an asterisk).

Recently, a prospective, observational, cross-sectional 1 day point-prevalence study analysing the epidemiology of sepsis in German hospitals found ICU and hospital mortality rates of 48.4% for patients with severe sepsis and 55.2% for those with severe sepsis including septic shock. The mortality observed in the current analysis among the SICU patients treated with tigecycline was 30%. Although this result was derived from a relatively small group of patients with specific risk factors and without comparison to a control group, and these limitations should be considered, the mortality rate appears remarkably low.

In a pooled analysis of two Phase III double-blind trials of tigecycline versus imipenem-cilastatin in patients with complicated intra-abdominal infection, the mean APACHE II score of tigecycline-treated patients was 6.3, and only 3.5% of them had an APACHE II score higher than 15; an APACHE II score of more than 30 was an exclusion criterion in those studies. The SICU patient population treated in this analysis mirrors typical intensive care patients with substantially higher APACHE II scores (mean score of 27) and thus higher severities of disease. In addition, the majority of the patient population experienced co-morbidities leading to a higher risk of infections with multi-resistant bacteria.

Our suspicion that tigecycline might be less effective in patients with an impaired immune function was not confirmed: only the APACHE II score and renal replacement therapy were identified as statistically significant predictors of SICU mortality, but not malignancy, transplantation and diabetes mellitus. However, these results should be viewed with care regarding the small sample sizes with which this regression analysis was performed.

In more than half of the patients, complicated intra-abdominal infection was involved, including infections with MRSA and VRE. We observed a remarkably high proportion of enterococcal infections. Among the patients treated first line with tigecycline, the infection rate with enterococci was 40%, rising to 73.3% in the second-line treated patients. This high enterococcal rate could therefore be selected by prior therapy. Additionally, the enterococci rank second of all isolated organisms on this SICU after coagulase-negative staphylococci. The proportion of MRSA among all S. aureus isolates in clinical specimens increased to 30% in 2003 in Germany and to 12.3% in 2004 in the University Hospital of Heidelberg. Although tigecycline has demonstrated potent activity against MRSA and VRE, the label of tigecycline in the USA, unlike the European label, does not include VRE for complicated skin and skin-structure infections and VRE and MRSA for intra-abdominal infection. Improvements in our diagnostic capabilities and more rapid diagnosis of infections regarding these specific multiresistant pathogens may allow for the earlier administration of adequate antimicrobial treatment and a further improvement in clinical outcomes.

The majority of patients received tigecycline in combination with other broad-spectrum antibiotics to expand the range of activity to resistant Gram-positive cocci. Considering the risk of tigecycline-resistant infection with P. aeruginosa or Proteus spp., tigecycline monotherapy should be chosen with care.

The reasons for the use of tigecycline in the SICU were clinical failure, concerns about glycopeptide efficacy in severe intra-abdominal infection and pneumonia as well as a paucity of approved suitable agents, despite there being very few documented experiences with tigecycline treatment in these circumstances. Apart from two case reports, no data have been published yet for patients with septic shock.

**Study limitations**

The results should be viewed as purely descriptive, as this was an observational, retrospective analysis of data from 70 patients who had received tigecycline in our SICU between January 2006 and April 2007. There was no control group of patients not treated with tigecycline analysed in this assessment. Despite these limitations, we think that the reported data of our clinical experience with tigecycline are useful for clinicians considering the lack of data on newly approved antimicrobial agents for critically ill patients.

**Conclusions**

In conclusion, tigecycline treatment of critically ill SICU patients with severe sepsis or septic shock appeared to result in
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a remarkably low mortality. Tigecycline may be an important treatment option for septic patients with infections resistant to other available agents.

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Transparency declarations

None to declare.

References