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CLINICAL AND EPIDEMIOLOGICAL STUDY

Outcomes in patients infected with carbapenem-resistant *Acinetobacter baumannii* and treated with tigecycline alone or in combination therapy

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Abstract
Purpose *Acinetobacter baumannii* is a non-fermenting aerobic gram-negative bacteria and one of the important nosocomial pathogens, especially in intensive care units (ICUs). In recent years, multidrug-resistant (MDR) isolates have been an emerging problem, with limited therapeutic options. Tigecycline is a novel antimicrobial, with its in vitro activity against most gram-positive and gram-negative pathogens.
Methods This is a retrospective study that was conducted in a tertiary care hospital with 550 beds in Ankara, Turkey, from January 2009 to July 2010. Thirty-three patients who had carbapenem-resistant *Acinetobacter* spp. infections and received tigecycline alone or in combination with other antibiotics for at least 3 days were included.
Results The median age of the patients was 62 (18–87) years. All of the patients were diagnosed and treated in the ICU. Clinical responses were observed in 23 patients (69.7%). Ten patients (30%) had clinical failure. There was no significant difference between ventilator-associated pneumonia (VAP) and bloodstream infection (BSI) in terms of clinical or microbiological outcome ($p > 0.05$). The microbiological response rate was 50%. Superinfection was detected in 13 patients (43.3%) and *Pseudomonas aeruginosa* was the most frequently isolated pathogen. The 30-day overall mortality rate and attributable mortality rates were 57.6 and 24.2%, respectively. The attributable mortality rate was higher in the group in which microbiological eradication was not provided.
Conclusions Although it is approved by the Food and Drug Administration (FDA) for the treatment of complicated intra-abdominal infections, complicated skin and soft tissue infections, and community-acquired bacterial pneumonia, emerged resistance of *Acinetobacter* spp. and limited therapeutic options left physicians no choice but to use tigecycline for off-label indications.

Keywords Tigecycline · *Acinetobacter baumannii* · Carbapenem-resistant · Carbapenem-resistant *Acinetobacter baumannii*

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Introduction

Acinetobacter baumannii is a non-fermenting aerobic gram-negative bacteria and one of the important nosocomial pathogens, especially in intensive care units (ICUs) [1]. In recent years, multidrug-resistant (MDR) isolates have been an emerging problem, with limited therapeutic options. This microorganism causes nosocomial pneumonia (especially ventilator-associated pneumonia [VAP]), wound infections, bacteremia, urinary tract infections, and, also, nosocomial meningitis (NM) [2–4].

cTigecycline is a novel antimicrobial agent with in vitro activity against most gram-positive and gram-negative pathogens [5]. Although it is approved for the treatment of complicated intra-abdominal infections, complicated skin and soft tissue infections, and, recently, for community-acquired bacterial pneumonia [5, 6]; because of *Acinetobacter baumannii*'s resistance to most of the antimicrobials, it has become a mandatory option for other nosocomial infections too.

Methods

Patients and study design

A retrospective study was conducted at the Ataturk Education and Research Hospital, a tertiary care hospital with 550 beds in Ankara, Turkey, from January 2009 to July 2010. Thirty-three patients who had carbapenem-resistant *Acinetobacter* spp. infections and received tigecycline alone or in combination with other antibiotics at least for 3 days were included. All patients received an initial dose of 100 mg tigecycline and then 50 mg every 12 h, as approved by the Food and Drug Administration (FDA) [6].

Data collection

General data of the patients, which included age, sex, ICU type, infection site, previous carbapenem and glycopeptide use, length of treatment (LOT) with tigecycline, tigecycline treatment indication, clinical outcome, microbiological response, superinfection, reinfection, and mortality (attributable and crude mortality) rates, were collected from ICU patient charts.

Definitions

The nosocomial infections were diagnosed according to the Centers for Disease Control and Prevention (CDC) definitions [7–9].

Clinical outcome was classified as clinical success (complete resolution of signs and symptoms) and clinical failure (no improvement or deterioration in signs and symptoms of infection).

Microbiological response was defined as the successful eradication of microorganisms during or after the course of tigecycline therapy and, accordingly, microbiological failure was defined as recurrent positive culture with the same microorganism after the 72nd hour of the therapy.

Superinfection was defined as the isolation of bacterial strains other than those causing the primary infection in the presence of infection criteria without any other possible cause.

The 30-day attributable mortality from the start of tigecycline treatment was considered as death occurring without the resolution of signs and symptoms of infection and no other identified cause [10, 11]. The 30-day crude mortality was also recorded from the patient charts.

Microbiological data

Conventional methods and the BBL BD Crystal Enteric/Nonfermenter Identification System (Voigt Global Distribution, Lawrence, KS) were used for microbiological identification. Antimicrobial susceptibility testing was performed by disk diffusion methods and interpreted according to the Clinical and Laboratory Standards Institute (CLSI) criteria [12]. Antimicrobial susceptibility testing for carbapenem, tigecycline, and colistin were performed by both the Etest® (AB Biodisk, Solna, Sweden) and the disk diffusion method. *Acinetobacter* isolates with a minimum inhibitory concentration (MIC) value $\leq$2 mg/L were considered to be susceptible to tigecycline by the Etest® [13]. All isolates were susceptible to tigecycline and resistant to carbapenems.

The collected data were analyzed with SPSS® version 16.0. Group comparisons were done by using the Chi-square test and Student's *t*-test for categorical variables, and significance was defined as $p < 0.05$.

Results

The demographic and clinical data of the patients are shown in Table 1. Clinical response was observed in 21 patients (63.6%). We found no relationship between clinical response and previous usage of carbapenem and/or glycopeptide. There was no significant difference between VAP and bloodstream infection (BSI) in terms of clinical or microbiological outcome ($p > 0.05$). Microbiological outcome was considered in 30 patients; three patients had no follow up cultures during treatment. Only one patient with microbiological success was included in the attributed mortality group due to clinical failure. In terms of attributed mortality, there was a statistically significant difference between microbiological success and failure ($p < 0.05$). We found no relationship between ICU type and clinical or microbiological response ($p > 0.05$). Furthermore, the clinical and microbiological response rates were similar in the age groups $\geq$65 and <65 years.

Superinfection was detected in 13 patients (39.3%). *Pseudomonas aeruginosa*, extended-spectrum beta lactamase (ESBL)-producing *Klebsiella pneumoniae* and *Escherichia coli*, *Enterobacter cloacae*, and *Proteus mirabilis* were isolated from deep endotracheal aspiration and blood cultures during tigecycline treatment. *P. aeruginosa* was the most frequently isolated pathogen. In ten patients, superinfection was established in deep endotracheal aspiration, whereas it was found in two patients in peripheral blood samples and in one patient in both deep endotracheal aspiration and peripheral blood sample. All isolates causing superinfections were susceptible to carbapenem. The vitro activity of tigecycline was not tested against *Enterobacteriaceae* and *P. aeruginosa* isolated from superinfections.

The 30-day overall mortality rate and attributable mortality rate were 57.6 and 24.2%, respectively. The

Table 1 Demographic and clinical data of the patients

Characteristic	Clinical success ($n = 21$)	Clinical failure ($n = 12$)
Demographics		
Sex (M/F)	12/9	6/6
Age, years, median (range)	62 (18–87)	42 (18–87)
Prior antibiotics		
Carbapenem	14 (67%)	4 (33%)
Glycopeptide	8 (38%)	1 (8%)
ICU at onset		
Anesthesia ICU	12	7
NN ICU[a]	10	4
Site of infection		
VAP	13 (62%)	6 (50%)
BSI	6 (29%)	5 (42%)
SSI	2 (10%)	0
NM	0	1 (8%)
Treatment		
Tig[b] + aminoglycoside	15 (71%)	7 (58%)
Tig + cefoperazone sulbactam	6 (29%)	3 (25%)
Tig alone	0	2 (17%)
Duration of treatment, days		
Median (range)	15 (10–21)	14 (3–25)
Microbiologic outcome		
Success	14 (67%)	1 (8%)
Failure	5 (24%)	10 (83%)
Not evaluable	2 (10%)	1 (8%)
Superinfection[c]		
Pseudomonas aeruginosa	5 (24%)	2 (17%)
Klebsiella pneumoniae (ESBL)	3 (14%)	1 (8%)
Escherichia coli (ESBL)	2 (10%)	
Enterobacter cloacae	2 (10%)	
Proteus mirabilis	1 (5%)	
Mortality		
Attributable	0	8 (67%)
Overall (30-day)	9 (43%)	10 (83%)
Time to death, days		
Median (range)	15 (12–18)	12.5 (3–18)

[a] Neurology-neurosurgery intensive care unit (ICU)

[b] Tigecycline

[c] Superinfection was detected in 13 patients. Three of the ventilator-associated pneumonia (VAP) patients had more than one microorganism

attributable mortality rate was significantly higher in the group where microbiological eradication could not be achieved ($p < 0.05$). We found no relation between appropriate empiric treatment and clinical outcome or attributable mortality.

Discussion

MDR *A. baumannii* is an important cause of hospital acquired infection and has been shown in some studies to increase mortality and LOT [14]. The optimal treatment for MDR *A. baumannii* nosocomial infections has not been established. Carbapenems and sulbactam are the basis of treatment in susceptible isolates. Colistin and tigecycline have good in vitro activity and these drugs are the only therapeutic options, especially in MDR isolates.

In our study, we considered the use of tigecycline in patients with VAP, BSI, surgical site infection, and NM caused by carbapenem-resistant *Acinetobacter* spp. In a retrospective study that included 34 patients who received tigecycline for MDR *A. baumannii* or polymicrobial infection involving MDR *A. baumannii*, the positive clinical outcome and microbiological eradication rates were 68 and 29%, respectively [10]. The poor correlation shown between microbiological and clinical outcomes in the aforementioned study was similar to our study. Also, in another retrospective study that included 21 patients, these rates were found to be 81 and 50%, respectively [15]. In a phase 3 open-label, non-comparative study of tigecycline in the treatment of patients with selected serious infections due to resistant gram-negative organisms, a similar difference between clinical and microbiological responses was reported [16]. As seen in different studies, positive microbiological response rates are lower than those of successful clinical outcome. However, clinical success with microbiologic persistence has many possible causes. The most concerning is that the clinical success is, in fact, not attributable to the tigecycline, but represents misdiagnosis or response to other treatments. Although this result can be attributed to the bacteriostatic effect of the tigecycline, it is unclear why microbiological eradication cannot be successfully provided like clinical response. But it is known that, as a single agent, tigecycline does not have sufficient efficacy against BSI and NM.

In one patient, nosocomial meningitis caused by carbapenem-resistant *A. baumannii* emerged in the course of tigecycline and gentamicin combination therapy for VAP caused by the same microorganism. The patient died 3 days after meningitis occurred. Repetitive lumbar punctures for hydrocephalus were thought to be the reason for meningitis in this patient. Although tigecycline has low cerebrospinal fluid penetration, for this patient, no other susceptible antimicrobial agent was used for treatment.

Superinfection was detected in 39.3% of patients in our study and *P. aeruginosa* was the most frequently isolated pathogen. This result may be associated with inherited resistance of *P. aeruginosa* to tigecycline. The resistance of *P. aeruginosa* to tetracyclines in general and tigecycline in particular is almost entirely due to the presence of multiple

efflux pumps. In genetic experiments in which these are knocked out, the organisms are quite susceptible. In a recent retrospective study of 51 patients treated with tigecycline for nosocomial infections due to MDR microorganisms, superinfection was diagnosed in 23.5% of patients. *P. aeruginosa* was the most frequent pathogen as in our study [17]. In another retrospective study, superinfection was detected in 7 of 21 patients and the isolated pathogens were *E. aerogenes*, *K. pneumoniae*, and *P. aeruginosa* [15]. Eight patients (24.2%) died due to clinical failure within 30 days of initiating tigecycline treatment, where the all-cause mortality rate was 57.6%. Although no statistically significant difference was found between tigecycline treatment indication and attributable mortality, in patients with BSI, the attributable mortality rate was higher than patients with VAP (36.4 vs. 15.8%). In different studies, the rate of mortality attributable to *A. baumannii* bacteremia ranges from 22 to 59% [18–20].

Although it is approved by the FDA for the treatment of complicated intra-abdominal infections, complicated skin and soft tissue infections, and community-acquired bacterial pneumonia, emerged resistance of *Acinetobacter* spp. and limited therapeutic options left physicians no choice but to use tigecycline for off-label indications, despite repeated reports showing poor outcomes. Our study has several limitations, such as retrospective design, small number of patients, and, also, tigecycline being used as a part of combination therapy, so it is difficult to attribute clinical response to tigecycline. Because of the small number of patient groups, we could not compare mono or combination therapy. There seems to be a necessity to develop consortiums in order to conduct prospective observational studies in which at least the data collection is complete and standardized with pre-established criteria for case selection and outcomes.

Conflict of interest None.

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