ORIGINAL ARTICLE

EFFICACY OF TIGECYCLINE TREATMENT IN SEVERE AND COMPLICATED *CLOSTRIDIUM DIFFICILE* INFECTION

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Abstract

The aim of this study was to analyse the efficacy of tigecycline compared with the standard therapy (vancomycin plus metronidazole) in adults treated for severe *Clostridium difficile* infection (sCDI). A retrospective cohort study of septic patients, with at least one organ dysfunction and sCDI, hospitalized at Intensive Care Unit of the Clinical Emergency Hospital of Bucharest, Romania, from January to December 2016, was performed. Patients receiving tigecycline plus standard therapy, early or later in the course of the infection, were compared with the standard therapy alone. Outcomes were the clinical recovery, 30-day mortality and complications rate. There were no statistical differences between the groups regarding demographic data, severity score and comorbidity index. The introduction of tigecycline as tardive treatment does not show any major improvement, but survival rate increased from 12.1% with standard therapy to 80% with early administration of tigecycline, without any adverse reactions attributable to tigecycline. Favourable outcomes suggest that tigecycline could be an additional option for treatment of sCDI, but it requires further larger trial studies for support.

Rezumat

Scopul acestui studiu a fost evaluarea eficienței tratamentului cu tigeciclină, comparativ cu terapia standard (vancomicină și metronidazol) în infecțiile severe cu *Clostridium difficile*. S-a efectuat o analiză retrospectivă a cazurilor de *sepsis*, cu cel puțin o disfuncție de organ și infecție certificată cu *Clostridium difficile,* din clinica de terapie intensivă a Spitalului Clinic de Urgență București, din perioada ianuarie - decembrie 2016. S-au comparat pacienții care au primit tigeciclină și terapie standard, tigeciclina administrându-se de la început sau pe parcursul evoluției, cu cei care au primit doar terapie standard. S-au evaluat: răspunsul clinic la tratament, mortalitatea la 30 de zile și rata complicațiilor. Nu au existat diferențe semnificative statistic între grupuri din punct de vedere al datelor demografice, al scorului de severitate și al indicelui de comorbiditate. Tratamentul tardiv cu tigeciclină nu a adus beneficii majore, însă rata de supraviețuire a crescut de la 12,1% cu terapie standard la 80% atunci când tigeciclina a fost introdusă precoce, fără a se constata reacții adverse atribuibile tigeciclinei. Tigeciclina poate fi luată în considerare ca opțiune terapeutică, mai ales în infecțiile severe cu *Clostridium difficile,* fiind însă necesare studii suplimentare pentru validare.

Keywords: *Clostridium difficile*, colitis, diarrhoea, tigecycline

Introduction

Clostridium difficile infection (CDI) is a common cause of nosocomial diarrhoea, with associated substantial morbidity and mortality [1, 2]. *Clostridium difficile* (CD) is one of the pathogens to be classified as an "urgent" threat to public health due to increasing rates of antimicrobial resistance [3]. Current guidelines of the European Society of Clinical Microbiology and Infectious Disease Society of America recommend oral vancomycin, at a dose of 125 mg given 4 times per day and intravenous metronidazole as first-line choices for severe *Clostridium difficile* infection (sCDI) [4, 5]. A major drawback of the oral therapy is that gut motility is often impaired in critically ill patients and the efficacy of oral vancomycin is questionable. In these instances, addition of a retention enema with vancomycin or intravenous metronidazole is recommended, although the delivery of rectal vancomycin may be insufficient and adds the risk for colonic perforation. Guidelines do not provide consensus recommendations concerning the treatment of severe cases being clinically refractory to standard

therapy [26]. There is a need for alternative strategies especially in critically ill septic patients [21].

Tigecycline is the first glycylcycline antibiotic, with a broad-spectrum activity against Gram-positive, Gram-negative and anaerobic bacteria [6]. It is approved by the US Food and Drug Administration for the treatment of complicated skin infections, community-acquired pneumonia, and intraabdominal infections [7]. Tigecycline has proven good activity against *C. difficile*, it is excreted into the gastrointestinal tract with limited disruption of the intestinal flora and also achieves higher faecal concentration in formed stools compared with metronidazole [8-11]. Tigecycline can suppress *in vitro* toxin production and reduce spore production in a dose-dependent manner [24, 25]. These qualities makes it an ideal candidate for the treatment of sCDI, but there is limited clinical data describing its use in the management of CDI [9, 12]. There are limited case reports and case series regarding the use of tigecycline for the treatment of sCDI described in literature [13-18]. Therefore, the objective of this study was to evaluate our experience using tigecycline for the treatment of sCDI.

Materials and Methods

Study design

This is an observational, retrospective cohort study of sCDI treated with standard therapy and/or tigecycline from January through December 2016 within the Clinical Emergency Hospital of Bucharest, Romania. Diagnosis of CDI was confirmed by the presence of diarrhoea plus the qualitative detection of *C. difficile* Toxin A and B in the stool by a rapid chromatographic immunoassay, highly specific (> 99%) and with a highly sensitivity (> 99%) [19]. sCDI was defined as confirmed CDI plus the presence of at least one of the following criteria: hypotension or shock with serum lactate levels > 2.2 mmoll/L, organ failure, WBC $\geq$ 35,000/mm^3 or < 2000/mm^3 [4, 5, 20] or toxic megacolon. Data were collected by review of the electronic medical record, using a data record form. Variables collected included: patient demographics, comorbidities, micro-biological data, laboratory data, vital signs, anti-microbial treatment data, characteristics of current CDI episode (onset, symptoms, findings on physical, laboratory, micro-biological), and adverse reactions of antimicrobial treatments, clinical outcome. To estimate individual comorbidity burden, the Charlson comorbidity index (CCI) was computed for each patient. Additionally, an APACHE II score was calculated for each patient as described by Knaus *et al.* [22].

Due to the retrospective nature of this study, a waiver of informed consent was obtained and approved by the Clinical Emergency Hospital of Bucharest Institutional Review Board.

183 septic patients (pts) with CDI suspicion were screened for inclusion in this study, out of a total of 2049 critically ill patients (8.9%). Of these patients, 43 were confirmed with CDI and 39 (1.9%) included in the study.

Patients were divided into three groups considering anti-CDI antibiotics: group A (n = 17) - standard therapy alone - oral vancomycin (125 mg four times daily) and intravenous metronidazole (500 mg every 8 h), group B (n = 13) standard therapy and administration of tigecycline later, during the course of infection, in clinically refractory case to standard therapy. Group C (n = 9) received standard therapy plus early administration of tigecycline, initiated immediately after definitive diagnosis of CDI. In all cases, tigecycline was administered intra-venously as a 100 mg loading dose, followed by 50 mg twice daily for the subsequent duration of treatment. Treatment was discontinued after the resolution of symptoms and negative bacteriological samples.

Statistical Analysis

Microsoft Office Excel and GraphPad Prism 6 statistic programs were used; the statistical analysis was realized using Students' t test for independent samples or One-Way Anova test in cases which had more than 2 groups of study. $p < 0.05$ was considered as having statistical significance. For the survival analysis Kaplan-Maier test and curves were used. To see if there are any differences in sample negativity we conducted a Chi Square for trend analysis.

Results and Discussion

A summary of patient demographic characteristics, comorbidities, APACHE II severity score, risk factors for CDI and leukocytes at the CDI diagnosis day is presented in Table I.

The mean age for men was 63.59, with a standard deviation (SD) of 3.35, n = 22. The mean age for women was 73.44 with a SD of 3.661, n = 17. For analysing the differences regarding APACHE II score in the groups, we used One-Way ANOVA test, obtaining for the group A a mean APACHE II score of 15.59 ± 1.198, for the group B 18.46 ± 1.845 and for the group C 12.78 ± 1.479. There were no statistical differences between the groups ($p = 0.067$). The APACHE II score has proven its value useful in prediction of critically ill patients' mortality. We applied it to all patients who suffered of CDI, in the moment of diagnose. For developing a Kaplan-Mayer curve we split the whole group in 2 small groups using a cut-off point of 20 points.

Table I

Patients' characteristics

	Group A (n = 17)	Group B (n = 13)	Group C (n = 9)	p value
Age (years)	57.11 ± 5.853	74.62 ± 3.741	68.76 ± 3.390	0.0315
Gender	M = 12, F = 5	M = 5, F = 8	M = 6, F = 3	
APACHE II	15.59 ± 1.198	18.46 ± 1.845	12.78 ± 1.479	0.067
Charlson's index	3.824 ± 0.4475	5.154 ± 0.5644	5.000 ± 0.6667	0.1431
Risk factors for CDI, n (%)				
Antibiotic use in 3 months	16 (94)	12 (92.3)	8 (88.9)	0.8
Hospitalization for > 3 days	16 (94)	12 (92.3)	9 (100)	0.8
Long-term care facility resident	3 (17.6)	2 (15.4)	1 (11.11)	0.42
Leukocytes (elem/mm^3)	10833 ± 2122	10768 ± 1206	10901 ± 1304	0.9835

After this analysis of survival we can say that APACHE II score has been an useful tool in patients who suffer of sCDI (at 10 days patients from the group with APACHE II < 20 were alive in proportion of 75.32%, and those with APACHE II > 20 were alive in proportion of 36.36%), as it is presented in Figure 1.

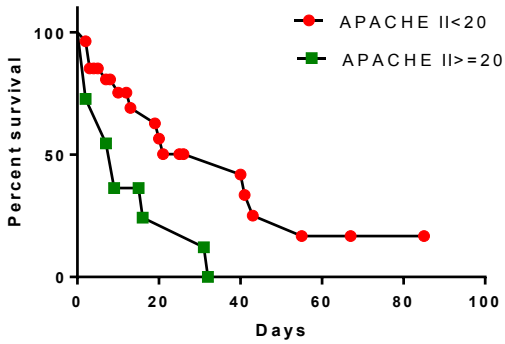

Figure 1.
APACHE II Score and survival
(Chi square 7.496, p value 0.0062)

No statistical differences between the groups regarding Charlson index and leukocytes number were observed (using One-Way ANOVA test, p = 0.1431, respectively 0.0617).

The primary outcome was the clinical recovery, meaning the patient survival and clinical resolution of CDI. The clinical failure was counted as the persistence of CDI symptoms or patient death. Secondary outcomes were 30-day all-cause mortality and complication rates: relapse, colectomy. Overall survival rate was of 38.46% (35.3% in group A, 15.38% in group B, and 77.77% in group C). Colectomy was not performed on any patients from group B or C; 11.76% patients had colectomies in the first group (p = 0.2). Adverse drug reactions attributable to tigecycline treatment were not observed.

The introduction of tigecycline as tardive treatment does not show any major improvement when looking at the survival rate, but it is possible that tigecycline may have some advantages at some sub-set of patients who lived more than 20 days. However, tigecycline is beneficial and significantly rise the survival rate at these patients if it is administrated earlier since the diagnose of sCDI. Median survival for group A was 13 days *vs.* 16 days for group B. The median survival for group C is undefined because it exceeds 50% at the longest time point calculated. The log-rank comparison of curves really does compare entire curves and does not compare only median survival times, so the p value computed by the log-rank test is still valid. But, we observed that the survival in group C at 20 days is very high (almost 80%) as Figure 2 reveals.

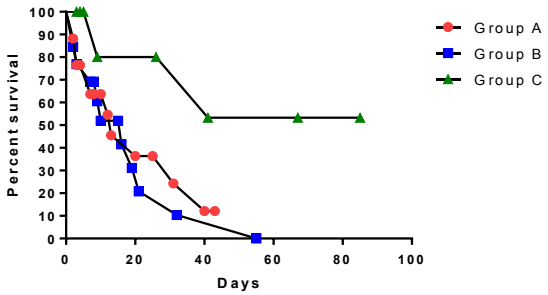

Figure 2.
Comparison of Survival Curves (standard therapy *versus* standard therapy than tigecycline *versus* standard therapy and tigecycline; Log-rank (Mantel-Cox) test, Chi square 6.071, p value 0.0481)

We observed that in the group of patients that have received tigecycline from the beginning no sample was positive at the moment of the death, comparing with the rest of the groups where 5, respectively 2 samples were still positive as it is presented in Figure 3. To demonstrate this statistically, we applied Chi Square test for trend obtaining a p value of 0.0599, which is insignificant. So, in this moment we can acknowledge that there is no difference regarding the bacteriological sample switch according to the treatment, but the results are encouraging and the analysis will be repeated on a larger group of patients, in a prospective, randomized controlled trial.

Over the last few years, treatment options for CDI are no longer limited to metronidazole and oral vancomycin, although this combination, still remain as standard therapy for initial episodes of CDI [4, 5].

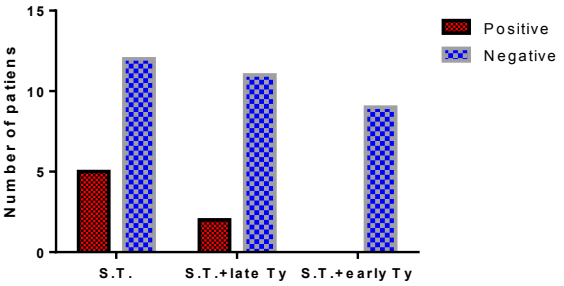

Figure 3.
Bacteriological sample switch
(ST – standard therapy, Ty – tigecycline)

Several published retrospective case reports or case series have also described the successful use of tigecycline for CDI, either as monotherapy or in combination with other agents. There has been only one published case with failure of tigecycline treatment in context of sCDI [23]. Based on the data presented in this study, we depict the successful use of tigecycline for the treatment of sCDI. The limitations of this study may be due to the decision to add tigecycline to metronidazole and oral vancomycin which was strictly of the attending physician. It is possible that more severely ill patients received tigecycline as adjunctive therapy, especially in clinically refractory case to standard therapy, but baseline data (WBC, Charlson index, APACHE II) do not suggest this was the case. As in all retrospective case–control designs, a larger controlled trials are needed to determine the role of tigecycline in *C. difficile* therapy.

Conclusions

The successful use of combined therapy and favourable outcomes with significant improvement of survival, suggest that tigecycline can be an additional option for treatment of sCDI, but it requires further randomized, controlled trials studies for support.

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