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Short Communication

Tigecycline for severe *Clostridium difficile* infection☆

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SUMMARY

Limited data suggest that tigecycline may be of value in the treatment of *Clostridiumdifficile* infection. We reviewed our experience using tigecycline to treat severe *c. difficile* and compared outcomes to similarly ill patients who did not receive tigecycline. We found no difference between the groups. Further study is needed before tigecycline can be recommended for use in severe *C. difficile* infection.

1. Introduction

The incidence and severity of *Clostridium difficile* infections (CDI) have increased over the past decade.[1] Despite the availability of efficacious therapies (vancomycin, metronidazole, fidaxomicin), severe cases occur and often cause severe morbidity or mortality. Oral vancomycin has been the mainstay of current treatment for severe disease, but there are significant limitations to its use in patients with ileus, megacolon, or critical illness.[1]

Herpers et al. suggested that intravenous (IV) tigecycline, an agent with in vitro activity against *C. difficile*, might be useful in severe CDI based on their experience with four patients.[2] Subsequent reports have brought the published cumulative experience to seven total cases, with success in six.[3]

Based on these limited data, some of our clinicians have been using tigecycline in severe cases of *C. difficile*. We review the outcomes and compare tigecycline-treated patients to those with *C. difficile* of similar severity who did not receive tigecycline.

2. Methods

All patients admitted to our 808-bed medical center during 2011 with a diagnosis of CDI were reviewed. A total of 473 inpatient case records of CDI were examined and stratified according to the severity criteria published by Zar et al.[4]

The diagnosis of severe CDI was established in those with a compatible clinical syndrome by positive *C. difficile* toxin B stool PCR (Cepheid GeneXpert). Severe CDI cases were counted as tigecycline-treated if they had received IV tigecycline >48 h as part of their regimen. Observed outcomes included overall survival, rate of colectomy, recurrence, drug adverse effects, and time to resolution of diarrhea. Patients who had received IV tigecycline were further compared to the patient group who had received standard therapy without tigecycline for severe CDI in a retrospective unmatched case–control analysis.

3. Results

Eighteen patients received tigecycline >48 h, in addition to both oral vancomycin and IV metronidazole in 17 patients; the eighteenth patient received fidaxomicin plus tigecycline. Their median age was 55 years and median Charlson score was 4; all fulfilled the highest severity criteria, i.e. severe complicated CDI per the Infectious Diseases Society of America (IDSA) guidelines (hypotension, shock, ileus, or megacolon).[1] Fourteen out of 18 patients survived (78%); four died of multiorgan failure and septic shock. Two of 14 survivors (14%) required an emergent colectomy. The median white blood cell count (WBC) was 11.4 × 10^9/l at the initiation of tigecycline. The median duration to resolution of diarrhea was 4 days. In two out of 18 cases (11%) tigecycline had to be stopped prematurely due to nausea and vomiting; both

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Table 1
Comparison of serious CDI outcomes by tigecycline use[a]

	Tigecycline (n = 18)	Non-tigecycline (n = 26)	p-Value
Age, years	55 years	63 years	
WBC, $\times 10^9$/l	11.4[b]	13.5	0.96
Serum creatinine, mg/dl	1.10[b]	1.15	1.0
Charlson index	4	5	0.23
Survival	14/18 (78%)	21/26 (80%)	1.0
Colectomy (survivors)	2/14 (14%)	3/21 (14%)	1.0
CDI recurrence	2 (14%)	3/21 (14%)	1.0

CDI, *Clostridium difficile* infection; WBC, white blood cell count; NS, not significant.
[a] Results are given as the median or n/N (%).
[b] At the time of tigecycline initiation.

survived. Two out of 14 surviving patients (14%) developed recurrent CDI.

The non-tigecycline severe CDI group of 26 patients had a median age of 63 years and a median Charlson score of 5. All had severe CDI per IDSA guidelines and received both vancomycin and metronidazole therapy. Their median WBC at the time of diagnosis was 13.5 $\times$ 10^9/l. Twenty-one of 26 (80%) survived their severe CDI; five died. Three of 21 survivors (14%) required a colectomy. Three out of 21 surviving patients (14%) developed recurrent CDI.

Table 1 summarizes the relevant data; there were no significant differences between the groups.

4. Discussion

Our tigecycline and non-tigecycline treated patients did not differ with regard to CDI survival, rates of colectomy, or relapse rates. Two patients treated with tigecycline suffered significant gastrointestinal toxicity, and all had the added expense of this broad-spectrum agent. The use of tigecycline did not appear to add benefit, and its use for CDI should be considered unproven. Earlier small reports of efficacy may have suffered from a positive reporting bias.[2,3]

Why tigecycline failed to improve outcomes is unclear. It has reasonable in vitro activity against *C. difficile* and is excreted in the feces.[5] Perhaps its broad anaerobic activity negates its activity against *C. difficile*.

Our retrospective case–control study is subject to multiple limitations. The decision as to whether to add tigecycline to metronidazole and oral vancomycin was strictly at the discretion of the attending physician. It is possible that more severely ill patients received tigecycline adjunctive therapy, but baseline data (WBC, blood pressure, Charlson index, creatinine) do not suggest this was the case. As in all retrospective case–control designs, a controlled trial is needed to definitively determine the role of tigecycline in *C. difficile* therapy. Our preliminary data do not support a role for tigecycline.

Conflict of interest: No conflicts of interest or funding sources to declare.

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