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Original article

Use of intravenous tigecycline in patients with severe *Clostridium difficile* infection: a retrospective observational cohort study

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ABSTRACT

There are only a limited number of antimicrobials for treating severe *Clostridium difficile* infection (sCDI). Tigecycline shows significant *in vitro* effect against *C. difficile* and is approved for management of complicated intra-abdominal infections. Our aim was to analyse the efficacy of tigecycline compared with standard therapy (oral vancomycin plus intravenous metronidazole) in adults treated for sCDI. A retrospective cohort study of such patients hospitalized at our department from January 2014 to December 2015 was performed. Patients receiving tigecycline monotherapy were compared with patients treated with standard therapy alone. Diagnosis and severity of CDI were determined according to guidelines of the European Society of Clinical Microbiology and Infectious Diseases (ESCMID). Primary outcome was clinical recovery, secondary outcomes were in-hospital and 90-day all-cause mortality and relapse, colectomy, and complication rates. Of the 359 patients hospitalized for sCDI, 90 (25.0%) were included, 45 in each group. Patients treated with tigecycline had significantly better outcomes of clinical cure (34/45, 75.6% vs. 24/45, 53.3%; p 0.02), less complicated disease course (13/45, 28.9% vs. 24/45, 53.3%; p 0.02), and less CDI sepsis (7/45, 15.6% vs. 18/45, 40.0%; p 0.009) compared with patients receiving standard therapy. Tigecycline usage was not associated with adverse drug reactions or need for colectomy. Rates of ileus, toxic megacolon, mortality, and relapse were similar between the two groups. Favourable outcomes suggest that tigecycline might be considered as a potential candidate for therapeutic use in cases of sCDI refractory to standard treatment. **B. Gergely Szabo, CMI 2016;22:990**

Introduction

The disease burden of *Clostridium difficile* infection (CDI) is growing in Europe and North America, becoming the most common cause of nosocomial diarrhoea outbreaks among adults over the past decade [1]. Studies have shown that clinically severe CDI and recurrent infections are becoming more prevalent with the emergence of hypervirulent *C. difficile* strains which possess high toxin producing capacity and increased antibiotic resistance [2].

Current guidelines of the European Society of Clinical Microbiology and Infectious Diseases, Infectious Disease Society of America/Society of Hospital Epidemiologists of America, and the American College of Gastroenterology recommend oral vancomycin and intravenous metronidazole as first-line choices for severe CDI (sCDI) [1–3]. However, growing numbers of clinically refractory cases are reported worldwide, which are usually attributed to hypervirulent *C. difficile* strains less susceptible to standard anti-CDI antibiotics [4–6]. Faecal microbiota transplantation has promising advantages for treating recurrent CDI unresponsive to standard treatment, but its exact role in sCDI therapy needs further clinical research [2].

Oral vancomycin is considered the cornerstone of anti-CDI therapy, but the challenge of patients with severe disease or critical illness could greatly limit successful clinical application. Metronidazole administered as an additional drug in severe disease or when oral

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treatment is not possible does not reach high therapeutic levels in the colon and is not tolerated by some patients. There is only scarce evidence supporting routine use of fidaxomicin in sCDI and the use is limited by its high cost [1–3]. Guidelines do not provide consensus recommendations concerning the treatment of severe cases being clinically refractory to standard therapy. Thus, there is a need for alternative strategies driven by increasing failure rates of antibiotics commonly used as initial therapy and lack of other agents.

Tigecycline is a broad-spectrum glycylcycline antibiotic approved in the European Union and the USA for treatment of complicated intra-abdominal infections. Its significant *in vitro* activity against *C. difficile* was proven by studies demonstrating low minimum inhibitory concentrations even for multidrug-resistant human isolates [7–9]. Using *in vivo* gut models it was concluded that tigecycline does not provoke intraluminal *C. difficile* proliferation or toxin production [10,11]. Additionally, tigecycline is excreted into the bile in high concentrations and only minimally disrupts the normal intestinal microbiome [12]. Despite favourable *in vitro* activity against *C. difficile*, the clinical role of tigecycline in the treatment of CDI is not well established as there are only limited data on successful use from case reports and studies including small numbers of patients [13–18]. The current ESCMID guideline only marginally supports recommendation for use of tigecycline as a last resort drug for sCDI (grade C-III evidence). At our institution, we consider applying tigecycline if improvement of laboratory and imaging findings attributable to sCDI fails and the physical status of the patient significantly deteriorates during standard therapy. Our objective was to analyse the efficacy of intravenous tigecycline compared with standard therapy (oral vancomycin plus intravenous metronidazole) in patients with sCDI.

Methods

Patient selection and data collection

We performed a retrospective, observational cohort study of adult (≥18 years) patients hospitalized for sCDI between January 2014 and December 2015 at the 80-bed 1st Department of Infectology of Joined Saint Stephan and Saint Ladislaus Hospital—Clinic (Budapest, Hungary), a tertiary referral center with nationwide accessibility. The study was in accordance with institutional and national ethical standards as well as the Helsinki Declaration (1975, revised in 2000 and 2008). The institutional review board approved the study protocol.

All cases of CDI (International Classification of Diseases, 10th Edition: A0470) were reviewed for eligibility. Patients who were diagnosed with sCDI and treated with tigecycline during their hospitalization were included in the tigecycline therapy group. Patients receiving vancomycin plus metronidazole without tigecycline for sCDI were identified using computer-generated random selection from the same time frame and included in the standard therapy group. Patients were excluded from both groups if anti-CDI antibiotics were given for <48 hours.

Data were collected by reviewing electronic medical records and using a standardized case report form. Data of included patients were followed up for 90 days after hospital discharge. Variables extracted were: 1) age at admittance, gender; 2) comorbidities, such as arterial hypertension, chronic heart, lung or renal disease, diabetes mellitus, malignancy, long-term systemic corticosteroid therapy (≥15 mg/day prednisone or dose-equivalent for ≥3 months), chronic immunosuppression (congenital immunodeficiency, asplenia, HIV infection, solid organ or hematopoetic stem cell transplantation, chemotherapy or immunosuppressive therapy within ≤6 months, autoimmune disease, hepatic cirrhosis), and Charlson index [19]; 3) risk factors for CDI (antibiotic use in ≤3 months, hospitalization for ≥3 days in ≤6 months, long-term care facility resident, multiple CDI recurrences); 4) number and treatment of preceding CDI episodes; 5) characteristics of current CDI episode (onset, symptoms, findings on physical, laboratory, microbiological, imaging and endoscopic examinations, ATLAS score, admission to intensive care unit [ICU], length of stay [LOS]); 6) administration, length, adverse reactions of antimicrobial treatments; and 7) clinical outcomes.

Diagnosis and assessment of severity

Diagnosis of CDI was based on a clinically compatible presentation (diarrhoea, ileus, toxic megacolon, sepsis) and toxin producing *C. difficile* confirmation from unformed stool by enzyme immunoassay detecting glutamate dehydrogenase and toxins A+B (C. Diff Quik Chek Complete, Techlab). Diarrhoea was defined by at least three unformed stools (Bristol stool chart type 5–7) in ≤24 hours for 2 consecutive days [20]. All specimens were processed within 3 hours at Saint Ladislaus Hospital Microbiology Laboratory.

Severe disease (sCDI) was defined as confirmed CDI episode with at least two of the following: fever (core body temperature ≥38.5°C), chills, abdominal pain, respiratory failure (need for ventillatory support), or haemodynamic instability (need for circulatory support), peritonitis (muscle defence, rebound sensitivity), leucocytosis (white blood cell (WBC) count $>15\times10^9$/L), marked left-shift (>20% of band neutrophils), elevated serum creatinine (≥1.5-fold rise compared with premorbid levels), elevated serum lactate (≥5 mmol/L), reduced serum albumin (<30 g/L), colonic distension (>6 cm in transverse width) or wall thickening, ascites, or pseudomembranous colitis.

Complicated disease was defined as sCDI with presence of ileus, toxic megacolon, or sepsis. Ileus was defined as complete absence of intestinal motility (stool, flatulence, bowel sounds) for at least 24 hours, with simultaneous radiological signs of abnormal bowel distension. Toxic megacolon was defined as colonic ileus with radiological signs of extreme large intestinal distension. *C. difficile* sepsis was defined as confirmed CDI with presence of at least two systemic inflammatory response syndrome adult criteria according to the American College of Chest Physicians/Society of Critical Care Medicine definition [21]. Recurrent CDI was diagnosed if there was at least one previously documented CDI with clinical cure before onset of the current episode.

To quantify disease severity, ATLAS score for each patient was calculated at time of diagnosis as described by Miller *et al.* [22]. ATLAS is a validated scoring system predicting the likelihood of patient mortality and clinical responsiveness to anti-CDI antibiotic treatment. The score takes five parameters into account regarding the possible outcome: age of patient, body temperature, WBC count, serum albumin, and the need for systemic antibiotics.

Anti-CDI antibiotics were initiated immediately after definitive diagnosis of CDI. Tigecycline was given intravenously (50 mg twice daily) after a loading dose (100 mg) without other antibiotics. Vancomycin was administered orally (125 mg four times daily) with addition of intravenous metronidazole (500 mg three times daily). Adverse reactions of antibiotics were assessed by daily history and physical examination.

Disease outcome measures

Primary outcome was clinical cure, defined by patient survival and complete resolution of all the following CDI characteristics at the end of treatment without any additional anti-CDI therapy: 1) diarrhoea; 2) abdominal pain; 3) fever; and 4) leucocytosis. Clinical failure was counted as persistence of CDI symptoms, need for introduction of additional anti-CDI therapy, or patient death