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Tigecycline in the management of post-neurosurgical spondylodiscitis: a review of eight cases

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SUMMARY

Background: Tigecycline is a relatively new glycylcycline antimicrobial, active in vitro against a variety of Gram-positive and Gram-negative organisms. In this study we evaluated the outcomes of spondylodiscitis cases treated with tigecycline-including therapies retrospectively.
Methods: All adult (age >18 years) cases with a diagnosis of spondylodiscitis, who were treated with a tigecycline-including therapy between 2007 and 2011, were included in the study. The primary efficacy outcome was clinical success with tigecycline at the end of induction, while the secondary efficacy outcome was maintenance of success through 3 months following completion of induction.
Results: A total of eight spondylodiscitis cases fulfilled the study inclusion criteria. All cases had back pain, restricted mobility, magnetic resonance findings associated with spondylodiscitis, and microbiology or pathological findings related to spondylodiscitis. All had post-neurosurgical spondylodiscitis. In five cases, tigecycline was started in accordance with the antibacterial susceptibility results from intervertebral tissue biopsy cultures, whereas in three it was started empirically. All cases had received several different antibacterials with failure before receiving tigecycline. The mean duration of tigecycline treatment was 37 ± 21 days. One case was lost to follow-up after 2 days of tigecycline. Primary and secondary success was achieved in the remaining seven cases.
Conclusions: These limited data suggest that tigecycline may have a role in the treatment of refractory spondylodiscitis cases.

1. Introduction

Healthcare-associated/nosocomial infections are increasing and important causes of morbidity after spinal surgery in many countries around the world.[1–3] The efficacy of treatment choices is very limited in multidrug-resistant (MDR) *Acinetobacter baumannii*. For example, there is currently no universally effective antibiotic against MDR. Hence, treatment regimens are tailored according to antibiotic resistance patterns and available antibiotics.[4–6]

Tigecycline is a relatively new glycylcycline antimicrobial, active in vitro against a variety of Gram-positive and Gram-negative organisms, including nosocomial MDR pathogens such as methicillin-resistant *Staphylococcus aureus* (MRSA), vancomycin-resistant enterococci (VRE), extended-spectrum beta-lactamase (ESBL) producers, and carbapenem-resistant *A. baumannii*. The US Food and Drug Administration (FDA) has approved tigecycline for the treatment of complicated intra-abdominal infections, complicated skin and skin structure infections, and community-acquired pneumonia (CAP). However, its pharmacological and microbiological profiles have encouraged physicians to use the drug in hospital-acquired pneumonia (HAP), ventilator-associated pneumonia (VAP), and meningitis caused by MDR and tigecycline-sensitive pathogens featuring limited therapeutic options. Nevertheless, data regarding

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the efficacy of tigecycline in spondylodiscitis and vertebral osteomyelitis are very limited.[4–6] In this study we retrospectively evaluated the outcomes of spondylodiscitis cases who were treated with a tigecycline-including therapy.

2. Patients and methods

This study was performed at a tertiary-care general teaching hospital with an infectious diseases ward of 31 beds. All adult (age >18 years) patients with spondylodiscitis who were treated with a tigecycline-including therapy between January 2007 and August 2011 were included in the study. All cases with the following four criteria were accepted as spondylodiscitis: (1) symptoms of back pain and restricted mobility, (2) magnetic resonance imaging (MRI) findings associated with spondylodiscitis, (3) increased erythrocyte sedimentation rate (ESR) and/or C-reactive protein (CRP) levels, (4) intervertebral disc sample culture yielding spondylodiscitis-associated organisms, or pathology result associated with spondylodiscitis.

Demographic, clinical, and laboratory data and predisposing factors, as well as information on response to treatment and outcome were obtained from each patient's hospital records. Intervertebral disc samples were obtained by trucut biopsy and/or during the surgery. Samples were sent routinely in thioglycollate broth, which was incubated for up to 72 h at 37 °C and passaged into eosin–methylene blue agar and 5% sheep blood agar. Bacterial identification was performed with an automated system (VITEK, bioMérieux, Marcy l'Etoile, France).

Antibacterial susceptibility tests were performed by Kirby–Bauer disk diffusion method, as described by the Clinical and Laboratory Standards Institute (CLSI).[7] The FDA clinical minimum inhibitory concentration (MIC) breakpoints for *Enterobacteriaceae* (2 mg/l, sensitive) were used for tigecycline susceptibility in *Acinetobacter spp*. The primary efficacy outcome was clinical success with tigecycline at the end of induction, while the secondary efficacy outcome was maintenance of success through 3 months following completion of induction.

3. Results

A total of eight spondylodiscitis cases (six female, two male, aged 59 ± 11 years; Table 1) had received a tigecycline-including therapy for spondylodiscitis, which was diagnosed according to the criteria above. The ages and characteristics of these eight cases are shown in Table 1.

3.1. Clinical presentation and diagnosis

All but one of the cases had fever on admission. In addition to back pain and restricted mobility, two cases had paraparesis. Four cases had diabetes mellitus as the underlying disease. All had spondylodiscitis secondary to previous spinal surgery: three had a lumbar canal stenosis, two had a lumbar hernia, two had a thoracic canal stenosis, and one had a cervical hernia. The time to spondylitis after surgery was ≤2 months in six cases (Table 1).

Intervertebral disc sample cultures yielded the etiology in five cases (Table 1); the pathology, symptoms, and MRI findings supported the diagnosis in the remaining three cases. Brucellosis serology as well as tuberculosis PCR and culture were negative for all cases. MRI and microbiological cultures, as well as ESR and CRP levels, are shown in Table 1.

3.2. Treatment

All cases had received two to eight different antibacterials with failure before receiving tigecycline (Table 1). Tigecycline was given as a 100-mg loading dose, followed by 50 mg every 12 h in all cases. In five cases, tigecycline was started in accordance with the results of the antibacterial susceptibility testing of intervertebral tissue biopsy cultures, whereas in the remaining cases it was started empirically (Table 1).

Tigecycline was used as monotherapy in four cases, while it was used as a part of combination therapy in the other four (Table 1). No additional therapy was used after tigecycline in five cases, whereas two cases received further therapy (Table 1).

Four cases (Table 1, cases 4–7) underwent additional neurosurgery for the spondylodiscitis during the tigecycline therapy period.

3.3. Clinical efficacy

One case was lost to follow-up after being discharged at her request from our setting. Primary and secondary success was achieved in the remaining seven cases, with a remarkable response, including a decrease in inflammatory parameters (Table 1) and relief of the clinical and radiological findings at the end of the intravenous tigecycline therapy. Despite clinical and radiological improvement, cases 3 and 5 (Table 1) could be mobilized only with support. None of the seven cases with a successful outcome developed relapse during at least 1 year of follow-up.

3.4. Adverse events

Three of eight cases (cases 1, 2, and 5) experienced nausea and vomiting secondary to tigecycline (Table 1). Ondansetron was started as anti-emetic in all of these cases. Despite ondansetron, one of the three cases (case 2) had their treatment switched to another regimen.

4. Discussion

Tigecycline is a semi-synthetic derivative of minocycline and is the first antibiotic in the glycylcycline class. Although it is a bacteriostatic agent, it is used successfully in combination with other agents for the treatment of MDR bacterial meningitis and other infections.[5]

Spondylodiscitis is a rare complication of spinal surgery. However, despite developments in antimicrobial therapy, it may be associated with significant morbidity. The diagnosis depends on the clinical and laboratory findings, as well as MRI and microbiology or pathology.[1–6] In our series, the diagnosis was supported by both MRI and microbiological evidence and/or pathological findings associated with osteomyelitis.

The main risk factors for vertebral osteomyelitis are invasive interventions including neurosurgery, endocarditis, underlying carcinoma, pyelonephritis, and advanced age.[8] All the cases presented here had spondylodiscitis secondary to neurosurgery. In addition five were aged >50 years and four had diabetes mellitus.

Brucellosis and tuberculosis are common etiologic agents of spondylodiscitis in Turkey.[9] Brucellosis serology and bacterial culture, as well as mycobacterial culture and PCR, were negative in all the cases presented.

The recommendation for nosocomial vertebral osteomyelitis is vancomycin.[1–5] All eight cases had received vancomycin or teicoplanin before receiving tigecycline. In addition, since Gram-negative organisms are not rare in our setting, all cases received additional antibiotics against Gram-negative bacteria. However, since they did not have a clinical response to the previous two to eight therapies, tigecycline was started as salvage therapy. In the

Table 1
Age, gender, time to spondylitis after surgery, radiological and microbiological findings, treatment modalities before and after tigecycline, reason for including tigecycline in therapy, pre- and post-treatment ESR and CRP data of the cases

Patient	Age/gender	Time after surgery to spondylodiscitis/ MRI finding	Microbiological results of intervertebral biopsy cultures	Therapy before tigecycline	Reason for tigecycline/ tigecycline-including therapy	Therapy after tigecycline	Admission and discharge ESR (mm/h)/CRP (mg/dl)
1	49/female	15 days/L1–L4 spondylodiscitis and abscess	Methicillin-resistant coagulase-negative staphylococci, *Pseudomonas aeruginosa*, *Klebsiella pneumoniae*	Ceftriaxone (6 days), teicoplanin (6 days), linezolid (45 days), ceftazidime (13 days), meropenem (16 days)	Guided therapy after failure with previous therapies/meropenem (70 days) + tigecycline (70 days) + rifampin (30 days)	Cefixime + amoxicillin/ clavulanate + rifampin (180 days)	51/10 10/0.26
2	64/male	45 days/L3–L4 spondylodiscitis	*Acinetobacter baumannii*	Ceftazidime (9 days), teicoplanin (9 days), piperacillin/ tazobactam (7 days), linezolid (7 days)	Guided therapy/ tigecycline (25 days)	Doxycycline (42 days), netilmicin (25 days) + sulbactam (15 days), 9 months doxycycline monotherapy	63/2.15 19/0.45
3	49/female	60 days/T8–T9 spondylodiscitis	*Salmonella enteritidis*, *Enterobacter cloacae*	Teicoplanin (9 days), linezolid (9 days), doripenem (15 days), ciprofloxacin (32 days)	Guided therapy after failure with previous therapies/ tigecycline (42 days) + meropenem (42 days) + ciprofloxacin (42 days)	No additional treatment	63/8.53 45/0.98
4	50/female	30 days/L4–L5 spondylodiscitis	No pathogen	Ceftriaxone (20 days), teicoplanin (20 days)	Empirical therapy/ tigecycline (42 days monotherapy)	No additional treatment	98/6.5 2/0.5
5	66/male	10 days/L4–L5 spondylodiscitis + paravertebral and epidural abscess	No pathogen	Ceftriaxone (21 days), teicoplanin (21 days)	Empirical therapy, tigecycline (56 days monotherapy)	No additional treatment	95/23 30/0.12
6	52/female	40 days/T7–T8 abscess collection, T7 osteomyelitis	*Acinetobacter baumannii*	Imipenem (3 days), linezolid (3 days)	Guided therapy/ tigecycline (2 days) + netilmicin (2 days)	Lost to follow-up	-/9.27 -/5.76
7	60/female	5.5 years/T7–T8 osteomyelitis	Methicillin-resistant coagulase-negative staphylococci	Teicoplanin (50 days), rifampin (50 days), levofloxacin(30 days), fusidic acid (30 days), linezolid (35 days), daptomycin (44 days), cefepime (9 days), meropenem (14 days)	Guided therapy after failure with previous therapies/ tigecycline (28 days monotherapy)	No additional treatment	80/2.54 65/0.50
8	81/female	6 months/L3–L4 spondylodiscitis + lumbar stenosis	No pathogen	Ampicillin/sulbactam (31 days), ceftriaxone (14 days), teicoplanin (23 days), linezolid (22 days), daptomycin (14 days)	Empirical therapy/ tigecycline (31 days) + rifampin (31 days)	No additional treatment	95/1.49 55/0.38

MRI, magnetic resonance imaging; ESR, erythrocyte sedimentation rate; CRP, C-reactive protein.

cases with available susceptibility patterns, tigecycline was combined with another antibiotic.

Data related to tigecycline in osteomyelitis are very rare in the literature. Tigecycline was reported to have similar antibacterial efficacy as teicoplanin or vancomycin in MRSA osteomyelitis in the rabbit osteomyelitis model.[10,11] Twilla et al.[3] reported a successful outcome of MRSA osteomyelitis with 4 weeks telavancin, 1 week of tigecycline, and 2 weeks of oral linezolid. Polilli et al.[2] reported failure with tigecycline in osteomyelitis in a renal transplant recipient with Anderson–Fabry disease. Kuo et al.[4] reported two cases of osteomyelitis successfully treated with tigecycline. Recently Griffin et al.[6] reported 85% success in 13 osteomyelitis cases (one vertebral osteomyelitis) for the primary efficacy endpoint of clinical success used in our study. Nine of these 13 patients who were treated successfully returned for evaluation at 3 months; 6/9 evaluable patients (67%) attained the secondary endpoint of maintenance of success used in our study. In the presented series, four cases received tigecycline monotherapy, whereas four cases received additional combined antibiotics due to coexisting pathogens. The most common adverse effect was nausea and vomiting, which necessitated drug cessation in one case.

In our series, three cases were started on tigecycline as empirical therapy after failure with at least two antibiotics. We chose tigecycline since the MRSA, carbapenem-resistant Acinetobacter, and ESBL-producing *Klebsiella pneumoniae* and *Escherichia coli* rates are high in our setting. Such MDR infections are quite common in most parts of the world, as well as in our setting.[12] Among all nosocomial infections in the clinics that are under active nosocomial infection surveillance in our setting, the carbapenem-resistant *Acinetobacter spp* rate was 89.6% (189/211), ESBL-producing *K. pneumoniae* rate was 66.1% (111/168), ESBL-producing *E. coli* rate was 60% (120/200), and MRSA rate was 50% (53/106) (Bilgin Arda, unpublished data).

Although this is a limited experience in a small cohort without any comparator agent, our data suggest that tigecycline may have a role in the treatment of refractory spondylodiscitis cases. To our knowledge, this is the largest set of data reported related to

tigecycline in the treatment of spondylodiscitis. A clinical study involving larger osteomyelitis cohorts may increase the evidence related to this problem.

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