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Short communication

Tigecycline-based prolonged salvage therapy in patients presenting with complex bone and joint infection☆

Antibiothérapie de sauvetage à base de tigécycline chez des patients présentant une infection ostéoarticulaire complexe

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Abstract

Objectives. – To assess the clinical experience of tigecycline-based salvage therapy in patients presenting with Bone and Joint Infections (BJI).

Patients and methods. – Multicenter retrospective cohort study in France and Turkey (2007–2014).

Results. – Thirty-six patients (age 58.2 ± 17.8 years; 21 men) were included. The most frequently isolated bacteria were Enterobacteriaceae and staphylococci. Tigecycline (50 mg BID, mainly in combination (69.4%), mean duration of 58 days) was indicated for multidrug resistance (90.6%) and/or previous antibiotic intolerance (36.1%), and/or as second- or third-line therapy (69.4%). Six patients (16.7%) experienced early treatment discontinuation for adverse event (4 severe vomiting, 1 pancreatitis, 1 asymptomatic lipase increase). Clinical success was observed in 23 of 30 assessable patients who completed the tigecycline therapy (mean follow-up: 54.1 ± 57.7 weeks).

Conclusion. – Prolonged tigecycline-based therapy could be an alternative in patients presenting with BJI requiring salvage therapy, especially if multidrug-resistant Enterobacteriaceae and/or staphylococci are involved.

Keywords: Tigecycline; Bone and joint infection

☆ This article has not been submitted or published elsewhere, but part of this study was presented as a poster at the Interscience Conference on Antimicrobial Agents and Chemotherapy, Washington DC, on September 8, 2014.

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Résumé

Objectifs. – Étudier le traitement de sauvetage par tigécycline dans les infections ostéoarticulaires (IOA).

Patients et méthodes. – Étude rétrospective multicentrique en France et Turquie (2007–2014).

Résultats. – Trente-six patients (âge 58,2 ± 17,8 ans, 21 hommes) ont été inclus. Les bactéries les plus fréquemment isolées étaient des entérobactéries ou des staphylocoques. La tigécycline (50 mg, 2×/j, principalement en association (69,4 %), durée moyenne 58 jours) était indiquée pour multirésistance bactérienne (90,6 %), et/ou intolérance à une précédente ligne d'antibiotiques (36,1 %) et/ou comme seconde ou troisième ligne (69,4 %). Six patients (16,7 %) ont arrêté prématurément le traitement pour effet secondaire (4 vomissements sévères, 1 pancréatite, 1 augmentation asymptomatique des lipases). Vingt-trois des 30 patients qui ont complété le traitement ont été guéris (durée moyenne: 54,1 ± 57,7 semaines).

Conclusion. – La tigécycline pourrait être une alternative de sauvetage chez les patients présentant une IOA, notamment si des entérobactéries et/ou des staphylocoques multirésistants sont impliqués.

Mots clés : Tigécycline ; Infection ostéoarticulaire

1. Introduction

Tigecycline is approved by the US Food and Drug Administration (FDA) and by the European Medicines Agency (EMA) for the treatment of adults presenting with complicated intraabdominal infections and complicated skin and skin structure infections, and by the FDA for community-acquired pneumonia. Tigecycline usually shows good in vitro activity against difficult-to-treat Gram-positive and negative aerobic and anaerobic bacteria, including methicillin-resistant staphylococci, extended-spectrum beta-lactamase-producing and carbapenemase-producing Enterobacteriaceae [1]. Consequently, and despite a higher risk of mortality with tigecycline versus comparators highlighted by several meta-analyses, its wide spectrum supports a role as salvage therapy in complex infections [2–4].

Two animal models of methicillin-resistant *Staphylococcus aureus* (MRSA) osteomyelitis in rabbits and rats showed similar high efficacy of tigecycline compared with glycopeptides [5,6]. Though, clinical data in Bone and Joint Infection (BJI) is limited to a few case reports [7–13], case series [14,15], and a negative subgroup analysis of a prospective trial of diabetic foot osteomyelitis [17].

Consequently, this study aimed to assess the clinical experience of tigecycline-based regimens used as prolonged salvage therapy in patients presenting with complex BJI.

2. Patients and methods

This retrospective cohort study included adult patients receiving tigecycline as prolonged salvage therapy for complex BJI (i.e. with multidrug-resistant pathogen and/or history of antimicrobial intolerance and/or clinical failure after a previous antimicrobial therapy) between June 2007 and June 2014 in France (Regional Reference Centers in France also called CRIOAc: Lyon, Garches, Bordeaux, Clermont-Ferrand, Grenoble, Toulouse, and Paris; Peripheral hospitals: Chambery, Contamine-sur-Arves, Chalon-sur-Saône) and Turkey (Ege University, Izmir; Çukurova University, Adana). Previously published case reports from one center (Ege University, Izmir) were excluded [15]. The ethical review board of each hospital approved the study. Tolerability was investigated in patients receiving at least one dose of tigecycline. All adverse events (AEs) mentioned in the medical chart and related to tigecycline prescription were collected. As mild AEs could not always be reported in the medical chart, attention was mainly focused on severe AEs and on AEs that led to treatment discontinuation. AEs were graded using the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 of the National Institutes of Health. Clinical efficacy was considered in clinically evaluable patients, after exclusion of patients who experienced early treatment discontinuation because of AEs. Clinical success was defined as the resolution of symptoms and lack of need of additional antibiotic therapy or surgery until the last follow-up visit. Data was analyzed using descriptive statistics.

3. Results

Thirty-six patients (21 men; 58.3%) with a mean age of 58.2 ± 17.8 years (mean modified Charlson score of 3.8 ± 2.7) were treated with tigecycline (50 mg BID; mean duration of 8.4 ± 7.1 weeks) for BJI, mostly implant-associated (58.3%) (Table 1). Tigecycline was mainly indicated for multidrug resistance (90.6%), but patients also received tigecycline as a second- or third-line therapy after treatment failure (69.4%) and/or because of previous antibiotic intolerance (36.1%). A loading dose of 100 mg was administered in 84.9% of the 33 informed patients.

A total of 18 AEs were reported in 13 patients (36.1%) (Table 2). Seven were classified as severe (CTCAE grade 3). Six patients (16.7%) required early treatment discontinuation due to AEs: four patients experienced severe vomiting (day 1, 9, 17, and 20), one presented with pancreatitis (day 12), and one with asymptomatic lipase increase (day 84). An 82 year-old-woman presented with asymptomatic hypofibrinogenemia (1.2 g/L, $n = 2$-4), which normalized two days after tigecycline cessation. Disseminated intravascular coagulation was ruled out.

Out of the 30 remaining patients, clinical success was achieved in 23 patients (76.7%), with a mean follow-up of 54.1 ± 57.7 weeks. Tigecycline was used against the following bacterial isolates ($n = 36$): Enterobacteriaceae ($n = 19$, including

Table 1
Clinical and microbiological characteristics of patients treated with tigecycline for complex BJI.
Caractéristiques cliniques et microbiologiques des patients traités par tigécycline pour une IOA complexe.

Characteristics	All patients ($n = 36$) Number (%)[a]	Clinically evaluable patients ($n = 30$) Number (%)[a]
Patients		
Age, mean (SD)	58 (17.8)	58 (16.6)
Male	21 (58.3)	19 (63.3)
Cardiovascular disease	12 (33.3)	11 (36.7)
Diabetes mellitus	9 (25.7)	8 (27.6)
Chronic kidney disease	6 (16.7)	6 (20.0)
Modified Charlson score, mean (SD)	3.8 (2.7)	3.9 (2.6)
History of antimicrobial drug allergy	8 (22.2)	6 (20.0)
Infection		
Infection site		
Lower limb	25 (69.4)	20 (66.7)
Rachis	8 (22.2)	7 (23.3)
Other	3 (8.4)	3 (10.0)
Previous infection on the same site	8 (22.2)	6 (20.0)
Route of infection		
Postoperative	15 (41.7)	13 (43.3)
Hematogenous	12 (33.3)	10 (33.3)
Contiguous	5 (13.9)	5 (16.7)
Post-traumatic	4 (11.1)	2 (6.7)
Implant-associated infection	21 (58.3)	16 (53.3)
Abscess	20 (57.1)[b]	16 (55.2)[c]
Fistula	13 (36.1)	10 (33.3)
Microbiology		
Mono-microbial	21 (58.3)	19 (63.3)
Polymicrobial	11 (30.6)	7 (23.3)
No pathogen identified	4 (11.1)	4 (13.3)
Tigecycline		
First-line treatment	11 (30.6)	9 (30.0)
Monotherapy	11 (30.6)	10 (33.3)
Treatment duration (weeks), mean (SD)	8.4 (7.1)	9.0 (7.0)

[a] All values are given as number (% of total patients) unless otherwise specified.
[b] In a total of 35 patients for whom data was available.
[c] In a total of 29 patients for whom data was available.

Table 2
Adverse events reported during tigecycline treatment.
Effets indésirables raportés pendant le traitement par tigécycline.

	All AEs ($n = 13$)	CTCAE grade ≥ 3 ($n = 7$)	AEs requiring discontinuation ($n = 4$)
Nausea/vomiting	9	4	2
Diarrhea	2	0	0
Increased asymptomatic lipase	1	0	1
Clinical pancreatitis	1	1	1
Drug fever	1	0	0
Renal failure	0	/	/
Allergy	0	/	/
Neutropenia	2	1	0
Increased aminotransferase	1	0	0
Decreased fibrinogene	1	1	1[a]

All values are given as number. AE: adverse event; CTCAE: Common Terminology Criteria for Adverse Events.
[a] Treatment was discontinued for severe vomiting.

14 multidrug-resistant isolates among 17 patients), *Staphylococcus epidermidis* ($n = 8$, including 7 methicillin-resistant isolates (MRSE) among 8 patients), *S. aureus* ($n = 1$), *Streptococcus* spp. ($n = 2$), *Enterococcus* spp. ($n = 1$), *Gemella morbillorum* ($n = 1$), *Neisseria* spp. ($n = 1$), *Eikenella corrodens* ($n = 1$), *Mycobacterium abscessus* ($n = 1$), and *M. chelonae* ($n = 1$). Two patients were also infected with *Pseudomonas aeruginosa* and received appropriate companion drugs.

Twenty patients (66.7%) received a companion drug (mainly a carbapenem, 35%). The companion drug was mainly a carbapenem when multidrug-resistant Enterobacteriaceae was involved (7/14 patients). The companion drug (4/7 patients)

varied for MRSE infections (vancomycin ($n = 2$), fosfomycin, daptomycin).

During the mean follow-up of 13.4 months, seven patients experienced clinical failure, including three superinfections involving tigecycline-resistant pathogen in two cases.

4. Discussion

This study provides a retrospective evaluation of the clinical experience of tigecycline in patients presenting with complex BJI. As in most previously published case reports [7–10] and uncontrolled series, [14–16] tigecycline was used to target multidrug-resistant Enterobacteriaceae and staphylococci.

The most frequent AEs were nausea and vomiting (9/13 patients who presented with AEs), as expected from a meta-analysis of 14 clinical trials [3]. No acute pancreatitis was reported in these trials but a retrospective 14-year-analysis (1997–2010) of the FDA's Adverse Event Reporting System identified 62 cases of tigecycline-related pancreatitis, including five patients treated for osteomyelitis [19]. A previous case of coagulation disorder with hypofibrinogenemia (down to 0.28 g/L) was reported during prolonged tigecycline administration, which normalized five days after tigecycline cessation [20]. Despite the retrospective design, patients included in the study were closely followed in each center and it is unlikely that any severe adverse event were not reported or missed in the medical chart.

The clinical success rate of 76.7% observed among the 30 patients who completed tigecycline treatment is highly satisfactory in this setting of difficult-to-treat BJI, mostly using tigecycline as salvage therapy in debilitated patients (mean modified Charlson score of 3.8 ± 2.7) with mostly implant-associated infections (58.3%). Among all 36 patients, clinical success was only 63.8% when considering AE-related early treatment discontinuation as a failure.

Other retrospective cohort studies also assessed clinical success of tigecycline in BJI: it was reported in five of six patients presenting with *S. epidermidis* bone infections [14], seven of eight patients presenting with post-neurosurgical spondylodiscitis [15], and 11 of 13 patients presenting with osteomyelitis [16]. However, in a phase 3 clinical trial comparing tigecycline 150 mg once daily versus ertapenem 1 g ± vancomycin in patients presenting with moderate to severe diabetic foot osteomyelitis, the clinical cure rate was lower in the tigecycline group [17].

Tigecycline was most frequently used in combination (66.7% of 30 clinically evaluable patients), mostly a carbapenem when a multidrug-resistant Enterobacteriaceae was involved (7 of 14 patients). Four of the seven patients presenting with methicillin-resistant *S. epidermidis* received a companion drug, just like in Asseray's case series [14].

In our study, two patients presenting with BJI due to multidrug-resistant rapidly growing mycobacteria (RGM) were successfully treated with tigecycline-based regimen. Treatment duration was 29 weeks for a facet joint infection due to *M. abscessus* (associated with clarithromycin and amikacin) and 17 weeks for postoperative knee infection due to *M. chelonae* (associated with clarithromycin and ethambutol). These case patients are consistent with a large series of mostly pulmonary RGM infections treated with tigecycline-containing regimens, which reported clinical improvement in 48.1% of patients [18], and with case reports [11–13].

5. Conclusion

Despite the intrinsic limits of a retrospective uncontrolled study and the heterogeneity of patients, our study provides important information regarding tolerability of prolonged tigecycline-based regimen. It may support its use as an alternative in patients requiring salvage therapy for complex BJI, especially if multidrug-resistant Enterobacteriaceae and/or staphylococci are involved. Prospective cohort studies and clinical trials are required to determine the role of tigecycline in the management of patients presenting with BJI.

Authors' contributions

TF coordinated the study. JW wrote the first version of the article. All authors contributed to the patient's care and to the improvement and review of the article. Members of the Lyon BJI Study Group contributed to the patient's care.

Disclosure of interest

TF received speaker honoraria from Pfizer.

CC received speaker and chairman honoraria from Pfizer.

The other authors declare that they have no competing interest.

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