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Philippe Montravers
Hervé Dupont
Jean-Pierre Bedos
Philippe Bret
The Tigecycline Group

Tigecycline use in critically ill patients: a multicentre prospective observational study in the intensive care setting

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Take-home message: The efficacy and safety of tigecycline in the treatment of severe infections is consistent with other antibiotics, regardless of disease severity. No particular safety concerns were raised.

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P. Montravers (✉)
Department of Anesthesiology and Surgical Intensive Care, Bichat-Claude Bernard University Hospital Center, Paris Diderot University, Sorbonne Paris-Cité and AP-HP, 46 Rue Henri-Huchard, 75018 Paris, France
e-mail: philippe.montravers@bch.aphp.fr
Tel.: +33 140 25 83 55

H. Dupont
Department of Anesthesia and Critical Care Medicine, Amiens University Hospital Center, University of Picardie Jules Verne, Amiens, France
e-mail: dupont.herve@chu-amiens.fr

J.-P. Bedos
Department of Intensive Care, André Mignot Hospital, Versailles, France
e-mail: jpbedos@ch-versailles.fr

P. Bret
Pfizer France, Paris, France
e-mail: Philippe.Bret@pfizer.com

Abstract *Purpose:* This prospective observational study aimed at describing prescription patterns of tigecycline and patient outcomes in 26 French intensive care units (ICU). *Methods:* Data of consecutive cases of adult patients treated with tigecycline were collected from the initiation until 7 days after the end of treatment. Response to treatment was classified as success, failure or undetermined and analyses were presented according to severity (SOFA score <7 or ≥ 7). Survival was recorded at 28 days. *Results:* A total of 156 patients were included (64 % male, age 60 ± 15 years). At inclusion, 53 % had a SOFA score ≥ 7; 93 % had received prior anti-infective agents. Tigecycline was given as first-line treatment in 47 % of patients, mostly in combination (67 %), for intra-abdominal (IAI 56 %), skin and soft tissue (SSTI 19 %) or other infections. A total of 76 % of the treated infections were hospital-acquired. Bacteraemia was reported in 12 % of patients. Median treatment duration was 9 days. Tigecycline was prematurely stopped in 42 % patients. The global success rate was 60 % at the end of treatment, and significantly higher with treatment duration more than 9 days (76 vs. 47 %, $P < 0.001$). Success rate was 65 % for patients alive at the end of treatment. Success rates tended to decrease with illness severity, immunosuppression, bacteraemia and obesity. Survival rate at day 28 was 85 % in the whole cohort and significantly higher in the less severely ill patients ($P < 0.001$). *Conclusions:* Tigecycline success rates appear comparable to those reported in clinical studies in ICU with severe infections. Tigecycline could be an alternative in ICU patients.

Keywords Tigecycline · Multidrug resistance · Intensive care · Organ failure · Severe infections

Introduction

Tigecycline is one of the scarce available compounds, with a broad-spectrum activity, effective against multidrug-resistant strains including Gram-positive, Gram-negative aerobic, anaerobic bacteria and atypical microorganisms. In randomised controlled trials (RCT), tigecycline was effective in the treatment of complicated

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skin and soft tissue infections (cSSTIs) [1–3], complicated intra-abdominal infections (cIAIs) [4–7] and community-acquired pneumonia (CAP) [8–10]. Additional studies showed that tigecycline was effective in serious infections caused by known resistant pathogens [11, 12].

However, the use of tigecycline in patients with severe underlying diseases is limited, and little is known about its efficacy [13–15]. To date, RCTs included few intensive care unit (ICU) patients. Few data are available for ICU patients with bacteraemia [16].

For these reasons, we carried out a prospective, observational study in the intensive care setting to describe tigecycline prescription patterns and outcomes in critically ill patients from French ICUs. Some of our results were recently published in a series of articles reporting the "real-life" practice gathering five European databases (German, Italian, two Spanish studies and the current cohort). These analyses focused on labelled indications [17–19], global microbiology results [20] and safety issues [21], but did not address several key points, such as off-label indications, bacteraemia, emergence of resistance, superinfections and long-term outcomes; this led us to consider this in-depth analysis.

Materials and methods

Study design and patients

This prospective, multicentre, national observational study included consecutive cases of adult ICU patients treated with tigecycline. The only inclusion criterion was the receipt of tigecycline therapy in any, approved or non-approved, indication as mono- or combination, empiric, documented or rescue therapy for a specific localised source of infection or a specific flora. There was no recommendation on dosage or needed indication for the study protocol.

In accordance with French law, approval of an ethics committee was not required. The protocol was approved by the institutional review board (CEERB, CHU Bichat, Paris). All patients were informed of the data collection and agreed to participate in the study. A scientific committee (the authors) independently designed the study and reviewed all the collected data.

Clinical and microbiological data

Data were collected at ICU admission, at the start and end of tigecycline treatment, and 7 days after the end of treatment (or at hospital discharge if earlier). Clinical data included demographics, underlying diseases [22] (including diabetes mellitus, chronic renal failure, and chronic liver failure assessed using the Child–Pugh score [23]), immunosuppression (defined as steroid therapy or cancer therapy), severity of illness (assessed using the simplified acute physiology score (SAPS) II at ICU admission [24] and the sequential organ failure assessment (SOFA) score at the start of tigecycline treatment [25]), and previous tigecycline therapy.

The tigecycline-treated infection was clinically and microbiologically characterised. cIAIs (localised, generalised peritonitis, etc.) and cSSTI (dermis-hypodermis, fascia, etc.) were detailed as assessed during the surgery. The infection site and hospital- or community-acquired settings were collected.

The results of direct examinations and cultures were recorded. Identification and in vitro sensitivity testing of the pathogens were performed in the microbiology laboratory of each hospital using routine methods. Isolates were classified as susceptible (S), intermediate (I) or resistant (R) to tigecycline according to European Committee on Antimicrobial Susceptibility Testing (EUCAST) methodology. Data concerning persistent and emerging isolates, including *Pseudomonas aeruginosa*, were collected.

Treatment data

The reasons for choosing tigecycline and any anti-infective agents received in the previous 28 days were recorded. The tigecycline regimen (loading dose, maintenance dose and treatment duration) and the associated anti-infective agents were recorded.

Outcomes

Response to treatment was determined as clinical success/failure at the end of tigecycline treatment and 7 days later (or at hospital discharge if earlier). Success was defined by the lack of need to use a new antibiotic or a surgical treatment not initially planned for the initial infection. Criteria for failure were persistence of the initial infection signs requiring a change of antibiotic therapy or a surgical intervention, reappearance of the initial infection signs, infection-related death occurred later than 48 h after the start of tigecycline and/or premature treatment discontinuation due to a tigecycline-related adverse event. Response was classified as undetermined in case of insufficient data (e.g. de-escalation before the fourth day of treatment), death not directly related to the initial infection or occurred within the first 48 h of treatment, or addition of an antibacterial agent for another infection. Survival was recorded 28 days after the end of tigecycline treatment: data were retrieved from the French national epidemiology center for medical causes of death (CépiDc,

Centre d'épidémiologie sur les causes médicales de décès, INSERM).

Statistics

Data were analysed using SAS® 8.2 (SAS Institute Inc., Cary, NC, USA). To describe a characteristic or an event with a 10 % frequency and an accuracy of ±5 % as assessed by the 95 % confidence interval (95 % CI), 150 patients were to be enrolled.

For the purpose of this study, patients' characteristics were stratified for disease severity assessed by SOFA score (<7 or ≥7). Outcomes were stratified for SOFA score, body mass index (BMI ≤35 kg and >35 kg/m^2), immunosuppression, and age groups (<70 and ≥70 years of age).

Variables were expressed as median values and ranges for numerical variables, and as frequencies and percentages for categorical variables. The 95 % CIs of the response rates were calculated. Groups were compared using Wilcoxon signed-rank test for numerical variables, and the Chi square or the Fisher's exact test for categorical variables. Comparisons for success rates were carried out under the worse assumption, i.e. considering undetermined responses as failures. Factors independently associated with success to treatment at 7 days were identified by multivariate stepwise logistic regression among the factors that were statistically significant at the 10 % level in univariate regressions and taking into account significant interactions. The predictive performance of the final multivariate model was evaluated using receiver operating characteristic (ROC) analysis [26]. Survival, defined as the time from the first tigecycline intake to 28 days after last intake (or death), whichever occurs first, was assessed using the Kaplan–Meier method. A log-rank test was performed for subgroup analyses. As day-28 follow-up was not available for 18 patients, their survival time was censored at the time of the last visit in the study. A death recorded after day 28 was censored at the time of day 28. Statistical significance was accepted at the 5 % level.

Results

Patients' clinical characteristics

A total of 156 patients from 26 ICUs were enrolled between September 2008 and April 2010, including 73 patients with a SOFA score <7 and 83 severe cases (SOFA ≥7) (Table 1). Immunosuppression was mainly due to cancer ($n = 29$) and steroid therapy ($n = 16$).

The majority of patients (145/156, 93 %) had received one or more anti-infective agents in the last 30 days before the start of tigecycline [including penicillins (60 %), cephalosporins (42 %), aminoglycosides (39 %), carbapenems (28 %), glycopeptides (26 %) or fluoroquinolones (26 %)].

Infections treated with tigecycline

Tigecycline was given for the treatment of cIAI in 88/156 (56 %) patients, cSSTI in 29 (19 %) and other infections in 56 (36 %) (mainly lung infections, $n = 38$, 24 %) (Table 1). Most of the treated infections were hospital-acquired (131/173, 76 %). A positive blood culture was observed in 17 (12 %) patients. Overall, 17/145 (12 %) patients had secondary bacteraemia, including 9/63 (12 %) patients with a SOFA score ≥7 ($P = 0.963$). Indications for tigecycline were similar in the less and the most severely ill patients.

Microbiological data

Overall, 146 (94 %) patients had at least one microbiological sample at the start of tigecycline [direct examination in 87 (56 %) patients, species identified in 127 (81 %) patients] (Table 2). Infection was polymicrobial in 29 cases. There were no marked differences between the less and the most severely ill patients (data not shown).

Three microorganisms in three patients acquired resistance to tigecycline during the course of treatment (*Escherichia coli*, *Enterobacter cloacae* and *Enterobacter aerogenes*). Sixty-four microorganisms in 41 patients emerged during the course or at the end of treatment: 18 Gram-positive cocci (including 11 staphylococci), 39 Gram-negative bacilli (including 9 *P. aeruginosa*, 6 *Enterobacter* ssp., 3 *Proteus* ssp., and 1 *Morganella morganii*), 4 anaerobic germs and 3 yeasts. A total of 28 microorganisms in 23 patients persisted with no change in susceptibility (both emergence and persistence were observed in 13 of these 23 patients) during the course of tigecycline treatment: 11 Gram-positive cocci (5 enterococci and 6 staphylococci) and 16 Gram-negative bacilli (including 6 *E. coli*, 4 *Klebsiella* spp. and 3 other enterobacteria).

Treatment with tigecycline

Characteristics of treatment are provided in Table 1. The vast majority of patients were given the recommended loading and maintenance doses with an overall median treatment duration of 9 (1–78) days: 8 (1–78) days in the less severely ill, 9 (2–43) days in the most severely ill ($P = 0.499$) patients and 9 days (2–78) in patients alive at the end of treatment. Tigecycline was combined with other anti-infective agents in two-thirds of the patients (101/156, 65 %) (Fig. 1), without statistically significant

Table 1 Treatment with tigecycline: patients' characteristics at baseline, types of infections treated and characteristics of treatment

	SOFA <7 $n = 73$	SOFA ≥7 $n = 83$	Total $n = 156$	*P* value
Patients' clinical characteristics at the start of tigecycline treatment				
Demographics				
Age (years)	61 (19–84)	63 (27–86)	62 (19–86)	0.268
Age ≥70 years	26/52 (50)	26/52 (50)	52/156 (33)	0.362
Male gender	42/73 (58)	58/83 (70)	100/156 (64)	0.109
BMI (kg/m^2)	26 (16–58)	27 (17–51)	26 (16–58)	0.577
BMI >35 kg/m^2	7/64 (11)	10/78 (13)	17/142 (12)	0.731
Severity of disease				
SAPS II on admission in ICU	35 (3–78)	48 (12–99)	42 (3–99)	<0.001
SOFA	3 (0–6)	10 (7–24)	7 (0–24)	<0.001
Hemodynamic failure	4/73 (6)	12/83 (15)	16/156 (10)	
Respiratory failure[a]	9/73 (12)	41/83 (49)	50/156 (32)	
Renal failure[b]	2/73 (3)	26/83 (31)	28/156 (18)	
Underlying disease				0.868
Ultimately fatal	19/73 (26)	21/82 (26)	40/155 (26)	
Rapidly fatal	7/73 (10)	6/82 (7)	13/155 (8)	
Immunosuppression	23/73 (32)	29/83 (35)	52/156 (33)	0.650
Diabetes mellitus	12/73 (16)	18/83 (22)	30/156 (19)	0.771
Chronic renal failure	4/73 (5)	12/83(15)	16/156 (10)	0.110
Chronic liver failure	1/73 (1)	4/83 (5)	5/156 (3)	0.372
Prior anti-infective agents (last 30 days)	68/73 (93)	77/83 (93)	145/156 (93)	0.926
Types of infections treated with tigecycline				
Intra-abdominal infection	37/73 (51)	51/83 (61)	88/156 (56)	0.176
Hospital-acquired	26/37 (70)	35/51 (69)	61/88 (69)	
Localised peritonitis	7/26 (27)	3/42 (7)	10/68 (15)	
Abscess without peritonitis	6/26 (23)	9/42 (21)	15/68 (22)	
Localisation				
Colon	15/37 (41)	25/51 (49)	40/88 (45)	
Small intestine	10/37 (24)	9/51 (18)	18/88 (20)	
Stomach/duodenum	6/37 (16)	5/51 (10)	11/88 (12)	
Other site	10/37 (27)	18/51 (35)	28/88 (32)	
Skin and soft tissues infection	14/73 (19)	15/83 (18)	29/156 (19)	0.859
Hospital-acquired	10/14 (71)	10/15 (67)	20/29 (69)	
Dermohypodermitis	13/14 (93)	15/15 (100)	28/29 (97)	
Localisation				
Abdomen	3/8 (38)	7/9 (78)	10/17 (59)	
Head and neck	4/8 (50)	1/9 (11)	5/17 (29)	
Other infection	26/73 (36)	30/83 (36)	56/156 (36)	0.945
Hospital-acquired	23/26 (89)	27/30 (90)	50/56 (89)	
Lung	17/26 (66)	21/30 (70)	38/56 (68)	
Characteristics of treatment with tigecycline				
Treatment line intended				0.045
Empiric	38/73 (52)	35/83 (42)	73/156 (47)	
Documented[c]	27/73 (37)	45/83 (54)	72/156 (46)	
Reason for choosing tigecycline				
Polymicrobial infection	37/73 (51)	49/83 (59)	86/156 (55)	0.295
Multiresistant bacteria suspected/identified	28/73 (38)	35/83 (42)	63/156 (40)	0.628
Renal failure	7/73 (10)	21/83 (25)	28/156 (18)	0.011
Multiple site infection	8/73 (11)	16/83 (19)	24/156 (15)	0.151
Failure of previous treatment	6/73 (8)	13/83 (16)	19/156 (12)	0.156
Allergy/intolerance to another antibacterial agent	9/73 (12)	6/83 (7)	15/156 (10)	0.281
Rescue treatment	8/73 (11)	5/83 (6)	13/156 (8)	0.266
Other	5/73 (7)	5/83 (6)	10/156 (6)	0.834
Loading dose of 100 mg	70/73 (96)	82/83 (99)	152/156 (97)	0.341
Maintenance dose of 50 mg bid	68/73 (93)	78/83 (94)	146/156 (94)	0.859

Data are median values (range) or *n*/*N* (%) of patients, with *N* = number of available data

BMI body mass index, *ICU* intensive care unit, *SAPS* simplified acute physiology score, *SOFA* sequential organ failure assessment

[a] SOFA subscore of 3 or 4 (on a 0–4 scale)

[b] SOFA subscore of 3 or 4 (on a 0–4 scale); chronic renal failures are not included

[c] Including rescue treatments

Table 2 Number (%) of baseline isolates by sensitivity to tigecycline

	Total isolates	Susceptible[a]	Intermediate or resistant[a]
Total	250 (100)	108 (83.7)	21 (16.3)
Aerobes	221 (88.4)	104 (83.2)	21 (16.8)
Gram-positive cocci	103 (41.2)	50 (96.2)	2 (3.8)
Enterococci	51 (20.4)	29 (93.5)	2 (6.5)
Enterococcus faecalis	16 (6.4)	6 (85.7)	1 (14.3)
Enterococcus faecium	21 (8.4)	12 (92.3)	1 (7.7)
Staphylococci	36 (14.4)	16 (100)	
Staphylococcus aureus	20 (8.0)	10 (100)	
Streptococci	16 (6.4)	5 (100)	
Gram-negative bacilli	118 (47.2)	54 (74.0)	19 (26.0)
Enterobacteriaceae	89 (35.6)	41 (74.5)	14 (25.5)
Escherichia coli	44 (17.6)	23 (95.8)	1 (4.2)
Klebsiella spp.	18 (7.2)	8 (61.5)	5 (38.5)
Enterobacter spp.	14 (5.6)	8 (72.7)	3 (27.3)
Serratia spp.	4 (1.6)	1 (33.3)	2 (66.7)
Citrobacter	2 (0.8)	1 (50.0)	1 (50.0)
Proteus spp.	6 (2.4)		1 (100)
Morganella spp.	1 (0.4)		1 (100)
Non-fermenting Gram-negative bacilli	15 (6.0)	5 (50.0)	5 (50.0)
Pseudomonas aeruginosa	6 (2.4)		1 (100)
Stenotrophomonas maltophilia	8 (3.2)	5 (62.5)	3 (37.5)
Acinetobacter baumannii	1 (0.4)		1 (100)
Other Gram-negative strains	14 (5.6)	8 (100)	
Anaerobes	18 (7.2)	4 (100)	
Bacteroides fragilis	6 (2.4)	1 (100)	
Other anaerobes	12 (4.8)	3 (100)	
Pathogens, no further specified	3 (1.2)		

[a] Percentage of isolates for which the sensitivity to tigecycline was known

difference between groups (64 vs. 65 % for the <70 and ≥70 years age groups, respectively, $P = 0.906$; and 63 vs. 66 % for the SOFA <7 and ≥7 groups, respectively, $P = 0.671$). The aminoglycosides used were amikacin (17 % of all patients) and gentamicin (8 %). The most frequently used penicillin was piperacillin (combined with tazobactam, 11 %).

Tigecycline treatment was prematurely stopped in 66 (42 %) patients, without statistically significant difference according to the illness severity ($P = 0.774$). The reasons were resistant strain included ($n = 11$), clinical failure ($n = 12$), de-escalation ($n = 20$), death ($n = 14$), new infection ($n = 4$), persistent fever of unknown origin ($n = 1$), unjustified antibacterial agent change ($n = 1$) and/or shock probably not of infectious origin ($n = 1$). In the less severely ill patients, the most common reasons were de-escalation (10/37, 33 %) and resistant strain ($n = 8$), whereas in the most severely ill patients they were death (12/36, 33 %) and de-escalation ($n = 10$).

Adverse events were reported in 16 and 29 % of the less and most severely ill patients, respectively (23 % of total patients). Three adverse events were considered as probably/definitely related to tigecycline: drug resistance ($n = 1$), drug inefficacy (death due to septic shock, $n = 1$) and acute renal failure (patient cured with tigecycline, $n = 1$). Irrespective of causality, serious adverse events (fatal or not) occurred in 10 and 23 % of the less and most severely ill patients, respectively (17 % of total patients).

Response to treatment

The overall success rate was 60 % [93/156, 95 % CI (51–67)] at the end of treatment, and 53 % [77/145, 95 % CI (45–61)] 7 days after the end of treatment (Table 3). The difference in success rates between the less and the most severely ill patients was significant at both time points ($P = 0.005$, $P = 0.001$, respectively). The success rate at the end of treatment for patients alive after the last tigecycline uptake was 65 % [92/141, 95 % CI (57–73)]. The causes of failure at the end of treatment are described in Table 3. Table 4 provides the success rates obtained in the patient subgroups of interest, 7 days after the end of treatment.

The success rate at 7 days after treatment was statistically significantly higher when tigecycline treatment duration was longer. In the whole cohort, the success rate was 70 % with a treatment duration >9 days vs. 40 % with a treatment duration ≤9 days ($P < 0.001$). Similarly, it was 80 vs. 55 % ($P = 0.097$) respectively, in the less severely ill patients and 61 vs. 27 %, respectively, in the most severely ill patients ($P = 0.008$). Combination of another antibiotic with tigecycline did not markedly influence the success rate in the whole cohort, in the less and in the most severely ill patients (54 vs. 51 %; 67 vs. 64 %; 42 vs. 39 %, respectively).

A reduced rate, although not statistically significant, was observed with concomitant bacteraemia vs. without

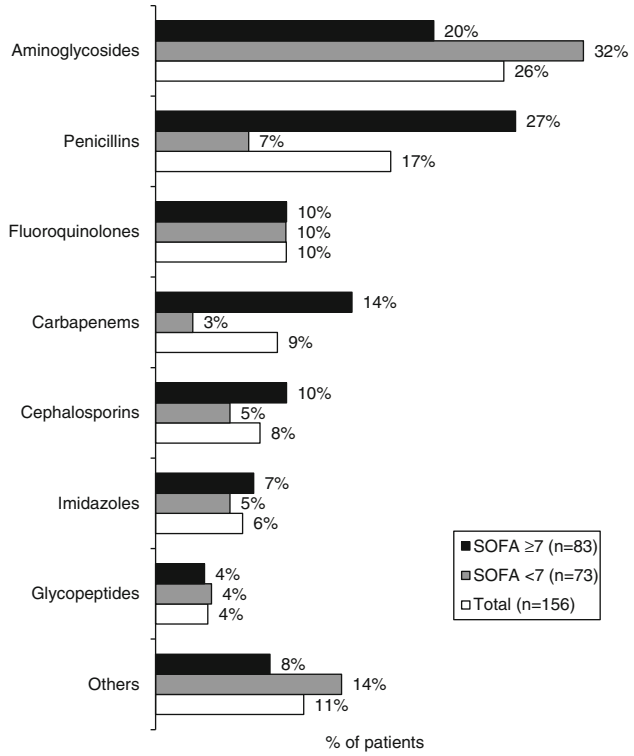

Fig. 1 Anti-infective agents combined with tigecycline

bacteraemia, in the less (62 vs. 74 %) and in the most severely ill patients (33 vs. 54 %).

Univariate regressions identified two factors associated with failure of treatment at 7 days: the SOFA score, either expressed as increasing SD units [OR = 1.72, 95 % CI (1.20–2.50), $P = 0.003$] or a score ≥ 7 [OR = 2.70, 95 % CI (1.39–5.26), $P = 0.004$], and BMI, either expressed as increasing SD units [OR = 9.09, 95 % CI (1.92–50), $P = 0.005$] or a BMI >35 kg/m^2 [OR = 1.39, 95 % CI (0.96–2.00), $P = 0.080$]. The factors associated with failure and identified using the multivariate analysis were an increasing SOFA score [OR = 1.67, 95 % CI (1.12–2.44), $P = 0.010$] and a BMI >35 kg/m^2 [OR = 8.33, 95 % CI (1.82–33.33), $P = 0.007$]. The sensitivity and specificity of this model were 94 % [95 % CI (0.88–1.00)] and 37 % [95 % CI (0.25–0.49)], respectively.

Survival

Global survival at 28 days was 85 % and no statistical difference was observed between age groups (87 vs. 80 % for the <70 and ≥70 years age groups, respectively, $P = 0.408$). Survival at day 28 was higher in patients with a BMI ≤35 kg/m^2 than with a BMI >35 kg/m^2 (87 vs. 63 %,

Table 3 Response to treatment with tigecycline

	SOFA <7 $n = 73$	SOFA ≥7 $n = 83$	Total $n = 156$	*P* value
At the end of treatment				
Success	51/73 (70)	42/83 (51)	93/156 (60)	0.005
Failure	14/73 (19)	14/83 (17)	28/156 (18)	
Persistence of the initial infection signs requiring a change of antibiotic therapy or a surgical intervention	5	7	12	
Infection-related death occurred later than 48 h after the start of tigecycline	1	3	4	
Clinical failure	8	4	12	
Undetermined	8/73 (11)	27/83 (33)	35/156 (22)	
Insufficient data	4	6	10	
Death not directly related to the initial infection or occurred within the first 48 h of tigecycline treatment	1	11	12	
Addition of an antibacterial agent for the treatment of an infection different from the initial one	3	10	13	
7 days after the end of treatment				
Success	46/70 (66)	31/75 (41)	77/145 (53)	0.001
Failure	16/70 (23)	16/75 (21)	32/145 (22)	
Reappearance of the initial infection signs	16	16	32	
Undetermined	8/70 (11)	28/75 (37)	36/145 (25)	
Insufficient data	4	6	10	
Death not directly related to the initial infection	1	11	12	
Addition of an antibacterial agent for the treatment of an infection different from the initial one	3	11	14	

Data are *n*/*N* (%) of patients, with *N* = number of available data
SOFA sequential organ failure assessment

Table 4 Success rate according to the major characteristics of patients, infections and tigecycline treatment

Characteristics	Success rate 7 days after the end of tigecycline	*P* value
Patient		
Age <70 years	50/94 (53)	0.937
Age ≥70 years	27/51 (53)	
Not immunosuppressed	53/94 (56)	0.555
Immunosuppressed	24/51 (47)	
BMI ≤35 kg/m^2	65/116 (56)	<0.001
BMI >35 kg/m^2	2/16 (13)	
Localisation of infection		0.402
cSSTI	17/27 (63)	
cIAI	44/82 (54)	
Pulmonary infection	17/37 (46)	
No concomitant bacteraemia	66/118 (56)	0.492
Concomitant bacteraemia	8/17 (47)	
Species at start of treatment		0.107
Gram-positive cocci	31/64 (48)	
Enterobacteria	37/66 (56)	
Anaerobes	10/11 (91)	
Other bacteria	14/25 (56)	
Tigecycline treatment		
Duration ≤9 days	34/84 (40)	<0.001
Duration >9 days	43/61 (70)	
Monotherapy	23/45 (51)	0.747
Combination	54/100 (54)	
Empiric therapy	38/70 (54)	0.783
Documented therapy	39/75 (52)	

Data are *n*/*N* (%) of patients, with *N* = number of available data
cSSTI complicated skin and soft tissue infection, *cIAI* complicated intra-abdominal infection

$P = 0.003$) and statistically significantly higher in the less than in the most severely ill patients (96 vs. 75 %, $P < 0.001$) (electronic supplementary material). Moreover, patients receiving catecholamines treatment had a statistically significant lower survival rate than those not treated with catecholamines (75 vs. 94 %, $P = 0.001$). Survival at day 28 was 86, 93 and 80 % for the patients initially suffering from IAI, SSTI and other infections, respectively.

Discussion

The efficacy of tigecycline versus other antimicrobial agents for the treatment of cSSTI [1–3] and cIAI [4–7, 27] has been evidenced in several RCTs, demonstrating that tigecycline was as efficacious as the comparators in treating infections, with a comparable safety profile. Three recent meta-analyses evaluating the published data from available RCTs also found no statistically significant difference in treatment success between cIAI patients treated with tigecycline and those treated with comparators [28–30]. However, in both cSSTI and cIAI trials, severe cases were usually excluded from the protocol, leading to insignificant information about these particular cases.

Recently, the US Food and Drug Administration (FDA) and the European Medicines Agency (EMA) issued a warning regarding the risk of increased mortality in patients treated with tigecycline, observed in the clinical trials [31, 32]. In all phase III and IV (cSSTI and cIAI) studies, death occurred in 2.4 % (54/2,216) of patients receiving tigecycline and in 1.7 % (37/2,206) of patients receiving comparator drugs [33]. A number of meta-analyses also reported higher all-cause mortality in patients treated with tigecycline versus comparators in RCTs [28–30, 34, 35]. Taking into account these findings, the EMA Committee for Medicinal Products for Human Use concluded that tigecycline benefits continue to outweigh its risks, but recommended modifications in product information to ensure an appropriate use, by making prescribers aware of the observed increased mortality risk. In addition, they issued a recommendation stating that tigecycline should be used only when other antibiotics are known or suspected to be not suitable [33].

However, clinical trials concerning critically ill patients' management are limited. A few large observational studies have been set up to determine the outcomes of ICU tigecycline-treated patients in clinical practice. The success rates obtained in the current study are in line with those reported in previous registries [13–15, 18] and in the European registry [17–19]. Interestingly, the success rate is also comparable to those reported in RCTs assessing the efficacy of other antibiotics in the ICU setting [36].

RCTs in contrast to registries generally do not reflect the clinical practice and do not represent real-life patients because of stringent selection criteria. This point is of interest particularly in ICU patients, for whom a limited number of trials are conducted only in selected indications. In addition, the evaluation endpoints used here were selected to ensure that the physician's concerns were respected and obviously do not favour the product.

The tigecycline dosage used in this study stands in the conventional range (100 mg daily) in 93–94 % of the cases. Interestingly, a relatively satisfactory success rate was reported in pulmonary infection patients. Similarly to other antibiotic drugs [37], concerns have been raised about the best dose for tigecycline, especially for treatment of pulmonary infections. Recent publications suggest a potential benefit of high dose tigecycline (200 mg daily) in severe/difficult-to-treat infections [38]. Effectiveness and safety of this policy without adding new risk factors for potentially resistant bacteria remain to be confirmed [39].

The never-ending debate on bacteriostatic drugs use for treatment of serious infections was re-triggered with the launch of tigecycline [40]. In many ICUs across the world, physicians dare to prescribe this bacteriostatic agent without having the feeling of putting their patients in jeopardy [13–15]. This point is particularly relevant in patients receiving a monotherapy as a first-line treatment. We, like others, report good results in monotherapy in more than half of patients receiving tigecycline. In contrast to other countries, tigecycline seems to be used in France mainly in combination with agents directed

particularly against Gram-negative microorganisms, and the preferred indications are those of the marketing authorisations. This finding was also reported in the European registries [17–19]. For instance, in a severe ICU population in Germany, tigecycline was also used mostly in combination (76 %), but the therapy frequently targeted Gram-positive cocci (including enterococci) possibly because of the high frequency of vancomycin-resistant strains. In Latin American countries, the tigecycline use in off-label indications appears to be important [41].

Finally, there were no serious adverse events requiring tigecycline discontinuation, and few tigecycline-related adverse events were reported. It is important to note that tigecycline administration in severe ICU patients, particularly in those with multiple organ failure, raised no safety concerns.

Like all observational studies, the limitations of our study included the lack of a control group and randomisation. However, our results contribute to the knowledge about tigecycline use in severely ill patients, a fragile population lacking clinical data. It is interesting that no increased mortality was observed in the cIAI and cSSTI tigecycline-treated patients, as observed in the five different European registries.

From our experience, tigecycline could be proposed as an empiric therapy in low severity cases, non-immunosuppressed or non-bacteraemic infections. In severe infections, immunosuppressed, bacteraemic or obese patients, its use should be cautiously considered, and restricted to documented therapy based on susceptibility testing in difficult-to-treat infections. Other options should be considered for suspected *P. aeruginosa* infections [42, 43].

Conclusions

In this ICU population treated with tigecycline, the success rates were comparable to those obtained in clinical studies analysing severe infections. In contrast to its use in other countries, tigecycline appears to be used mainly in combination with agents directed particularly against Gram-negative microorganisms.

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Conflicts of interest P.M. has received research grant support and consultancy and/or speaker fees from Astellas, AstraZeneca, Gilead, Merck Sharp & Dohme, Pfizer and The Medicine Company. H.D. has received research grant support from Pfizer and consultancy and/or speaker fees from Astellas, Merck Sharp & Dohme and Pfizer. J.P.B. has received consultancy and/or speakers fees from Astellas, Astra-Zeneca, Novartis and Pfizer. P.B. is an employee of Pfizer.

Appendix: List of investigators (France)

Professors/Drs Airapetian (Amiens), Arich (Nîmes), Martin (Marseille), Asehnoune (Nantes), Auboyer (St Priest en Jarez), Bazin (Clermont-Ferrand), Bonneil (Pau), Bruder (Marseille), Bruneel (Le Chesnay), Desmard (Paris), Duranteau (Le Kremlin-Bicêtre), Georges (Toulouse), Ichai (Nice), Jaber (Montpellier), Payen (La Tronche), Perrigault (Montpellier), Plantefeve (Argenteuil), Pottecher (Strasbourg), Poussel (Laquenexy), Riu Poulenc (Toulouse), Samain (Besançon), Schoeffler (Clermont-Ferrand), Seguin (Rennes), Sztark (Bordeaux), Veber (Rouen), Winnock (Bordeaux).

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